New members

To: chap_acpv@yahoogroups.com
Cc: Jessica Burry
Subject: RE: [chap_acpv] New contact member for the listserv

> Welcome, Jessica & Roland, I have added you both to the CHAP listserve.
>
> Roland, can you please send me your complete contact information so I may add it to our contact list?
>
> And this is a rather belated introduction, as I believe many of you met Trish Marr at part of the CHAP meeting this spring.
>
> Trish is covering my maternity leave here at TGH, and is already doing a great job. Trish's hospital e-mail address is:
>
> Patricia.Marr@uhn.on.ca
>
> Alice

Welcome to Jessica and Roland. We look forward to your involvement with our group. Nathalie

Hi all,

Please welcome Elaine to the group. Elaine joins the HIV clinic at Sick Kids and I know she'll be another valuable resource to the group. Alice could you add Elaine to the CHAP list-serve.

Her details are below:

Elaine Lau, BScPhm, PharmD, MSc
Coordinator, Drug Information Service
The Hospital for Sick Children
555 University Ave
Toronto, ON M5G 1X8
Tel (416) 813-6003
Fax (416) 813-7886
Email: elaine.lau@sickkids.ca

Welcome Elaine!

HI ,
We have a new general member (at least for the next 4 months) who is covering for us at my clinic site this summer. He will be added to the list-serve. His name is Mike Thompson.

Mike.Thompson@capitalhealth.ca

Case discussions:

Case # 1

A question from a doc today about a patient who is currently on Atovaquone 1500 mg daily for PCP prophylaxis. The patient is allergic to both septra and dapsone (rash/fever). The atovaquone liquid tastes bad, and the doc was wondering if there is anything on atovaquone 3 times/wk?

Thanks!
Gloria Tsang
Oak Tree Clinic
have never seen any documentation supporting 3 times weekly atovaquone. We never use atovaquone here in Ottawa, so I never had a personnal experience.

We would go for aerosilized pentamidine qmonthly.
pg
agreed, the pentamidine is alot less expensive than atovaquone too. Tastes bad, but at least just once monthly...

jeff

I have never seen this either. Not a very good drug even for PCP tx, therefore I would avoid for px.
Another option is IV pentamidine once monthly 4mg/kg/month IV if the patient refuses the aerosolized form. Depending on how serious the septra allergy is, Septra desensitization is another option.
Michelle

Is this primary prophylaxis? Is the patient currently on suppressive ARV's and do you have a viral load of <50 and signs of immune reconstitution? I know in cases like this, though the perfect world would have us keep the patient on until CD4>200, we would feel comfortable if the above questions are answered "yes" to d/c prophylaxis if the allergy/intolerability is making the patient miserable. If the patient has already suffered from PCP and/or is not on suppressive therapy, that is a different story. We'd offer pentamidine, aerosol.

Linda Robinson BSc.Phm
Thanks everyone for their comments! The patient's viral load is <50 and CD4 is now 170. Will discuss options with the physicians.

I love this group!

Gloria

The VL has been suppressed for quite a while now (few years) but her CD4 has never risen above 200 consistently. We have seen on the rare occasion CD4 going up to 300, then 2 months later dropping down to 120.

GT

> -----Original Message-----
> **From:** chap_acpv@yahoogroups.com [mailto:chap_acpv@yahoogroups.com] **On Behalf Of** Michelle Foisy
> **Sent:** Thursday, May 24, 2007 7:18 PM
> **To:** chap_acpv@yahoogroups.com
> **Subject:** Re: [chap_acpv] Atovaquone 3 times/wk for PCP?
>
> In this case, we would likely just withold px, especially is the CD4 % is > 12-15%. Also like Linda said, if it is primary px, then it would likely be ok. Has the VL been suppressed for some time? Do you anticipate an CD4 rise soon? (or has the patient been suppressed for years, with a slow rise in CD4?
>
> M

Dr Angel did a retrospective study to look at this particular situation. He looked at all the patients in whom we stopped PCP prophylaxis despite a CD4 less than 200 but with VL < 50 copies/mL. He then compared with anticipated rate of relapse from historical data. None of our patients developed PCP after a median follow up of around 1 year (I do not have the exact data with me…) I will provide you with the exact data later. It was presented in IAS in Toronto last year.

In light of these data, I would recommend to stop PCP prophylaxis.

Pg

Case # 2

HI all,
A question from my doc today in a patient who we have just started on TFV 2 days ago and baseline labs have come back with all renal function tests normal but hypophospatemia (0.6mmol/l: range = 0.82-1.59 mmol/l). Her question: Should we give him phophate supplements? So, any thoughts or

experience with this would be greatly appreciated!
1) do any of you supplement?
2) with normal renal function should we just watch , and monitor
3) would anyone suggest to not use TFV?!?

Other labs are normal except for lipids. Patient suffers from mild depression, but is healthy weight and claims he eats well. No c/o diarrhea.

Thanks to all!
Linda R

Hi Linda,

Good question! There is no one answer to your question. Here is though what I belive

1) It looks like your PO4 level is the baseline value. I do not believe that there is a relationship between this hypophosphatemia and tenofovir yet. We may expect that TDF may worsen it though. I would not recommend to make any change for now other than increased PO4 monitoring (and creat, mg, ca)

2) With regards to treatment of low phosphate, the opinions varie depending who you talk to. Even if asymptomatic, 'bone' doctor would recommend to supplement to prevent osteoporosis. At last CHAP, Dr Hladunewich, a nephrologist from Sunnybrook Hospital made the exact same comment. She was not worry from a nephrology perspective, but respects her colleagues opinion for correcting the PO4. Michelle sent guidelines on PO4 replacement lately. Personnally, I would replace with K Phosphate and continue TDF.

pg

Hi

Unless the patient is symptomatic (parestheias, weakness etc, which would be unusual with that phosphate), I would repeat it before deciding to take any action.

Case # 3

Hi guys,
I have forwarded my letter and reply from Merck as an FYI for the group. There is a great article to attach to applications as well as the LB abstract references from CROI. I am applying for raltegravir in 2 incidences, one who is undetectable (3 class resistant) on ENF + DRV + TFv and 3TC but is threatening to stop all because of ENF burnout and the other who is beyond a doubt needle phobic, triple class resistant and desperately needs suppressive therapy. I'll keep the group posted as to my luck.
Linda R
-----Original Message-----
From: Fluckiger, Jean Pierre [mailto:jeanpierre_fluckiger@merck.com]
Sent: Thursday, May 24, 2007 2:01 PM

To: Robinson, Linda
Cc: Tran, Luan
Subject: RE: raltegravir

-----Original Message-----
From: Fluckiger, Jean Pierre [mailto:jeanpierre_fluckiger@merck.com]
Sent: Thursday, May 24, 2007 2:01 PM
To: Robinson, Linda
Cc: Tran, Luan
Subject: RE: raltegravir Good afternoon Linda,

The dose is indeed 400 mg BID. 1 tablet of 400 mg/dose. It comes as clinical supply in 70 bottles counts or a little more than a month. We typically provide 3 bottles per patient.

The SAP for MK-0518 is well known by Health Canada. As participating in a clinical trial you have probably access to the Confidential Investigator Brochure (CIB) You can refer to it as it was provided to the SAP.

You are probably aware that an Expanded Access Protocol(EAP) is available in Canada. You may want to consider the inclusion of your patient(s) into that EAP. Please contact Luan Tran from Clinical Research for further information.

CASE #4

Hi everyone,

An ID physician who I do not work with was looking for a suggestion for once daily ARV therapy for a pregnant patient (~15 weeks). The physician is quite worried about adherence and was hoping to link the antiretrovirals with her methadone. Most recent CD4 690 and VL 57000. I was thinking of Kivexa as the backbone but am not sure what to use with it. Once daily Kaletra is not recommended in pregnancy..Any input appreciated!

Christine
Hi Christine,

That's a good question...but tricky! Do you have access to TDM for this patient? It would make things much easier.

Does this patient have a history of PI failure? What is her resistance profile like?

As I had mentioned at the CHAP meeting in Toronto we have had LPV samples that were undetectable at 12 hours post-dose for pregnant patients in the third trimester so I would be reluctant to start LPV once daily without access to TDM. Saquinavir plasma concentrations seem to be unaffected by pregnancy but the PK studies are in BID dosing only. In the general HIV

population, we have seen a wide variation of results for SQV once daily (undetectable to supratherapeutic). What about once daily nevirapine? (but her CD4 count is so high...). The literature suggests that nevirapine concentrations are unaffected by pregnancy, but again in BID dosing. Nevirapine can also decrease methadone concentrations.

I will let you know if any more thoughts cross my mind...

Niamh

Hi Niamh,

Yes it is tricky! I believe the patient is antiretroviral naive and does not require HIV treatment herself (high CD4). I would be reluctant to use once daily nevirapine due to high CD4 count. Again this is not my patient but would assume she is coinfected with HCV given her drug use history. For what it is worth, apparently she is quite skinny.

We don't have TDM here in Edmonton but can send samples to Ottawa. I had thought about saquinavir once daily but could not find studies in pregnant women. I think this is a risk-benefit situation - once daily may not be ideal but missing a lot of meds is not either....

Other thoughts are welcome!

Christine

Hi Christine,

I agree with Linda to keep Atazanavir as an option. The decision to boost or not is dependant on many other factors (compliance, prior Tx failure, HCV co-infected (levels are higher in co-infected pts)).
Although not indicated as QD regime in pregancy, LPV/r could still be used with TDM support if no prior PI failure. Otherwise, go BID.
My personal expericence is with BID Kaletra because of Combivir co-administration. I know that we would not hesitate to go ATV if needed.

Pierre

From: chap_acpv@yahoogroups.com on behalf of Robinson, Linda
Sent: Thu 05/07/2007 5:49 PM
To: 'chap_acpv@yahoogroups.com'
Subject: RE: [chap_acpv] once daily regimen for pregnant patient

Hi Christine,

Here is a reference to an abstract at CROI 2007 that looked at 33 case reports of atazanavir use in pregnancy in London. The concern of hyperbilirubinemia in the neonate remains, but this summary showed that although many of the babies had mild elevations, they did not require phototherapy and levels resolved on their own. We had one patient last year who we started on nelfinavir at the beginning of 2nd trimester, changed to Kaletra at 1 and 1/2 months because we weren't confident that the VL was going down fast enough. She then developed a rapid increase in LFT's so we put her on ATV 400mg daily wiith CBV for the remainder of pregnancy. We got her to <50 by delivery (and well before) and mom and baby were and still are both fine. I would consider it in this case especially if naive. I'd probably boos for once daily to make sure you get

good levels throughout pregnancy, though in our case we didn't, but she did take CBV bid. I believe ATV has a category B listing in the last DHHS guideline from Oct 2006.Hi Christine,

Here is a reference to an abstract at CROI 2007 that looked at 33 case reports of atazanavir use in pregnancy in London. The concern of hyperbilirubinemia in the neonate remains, but this summary showed that although many of the babies had mild elevations, they did not require phototherapy and levels resolved on their own. We had one patient last year who we started on nelfinavir at the beginning of 2nd trimester, changed to Kaletra at 1 and 1/2 months because we weren't confident that the VL was going down fast enough. She then developed a rapid increase in LFT's so we put her on ATV 400mg daily wiith CBV for the remainder of pregnancy. We got her to <50 by delivery (and well before) and mom and baby were and still are both fine. I would consider it in this case especially if naive. I'd probably boos for once daily to make sure you get good levels throughout pregnancy, though in our case we didn't, but she did take CBV bid. I believe ATV has a category B listing in the last DHHS guideline from Oct 2006.

http://www.retroconference.org/2007/Abstracts/28351.htm

-----Original Message-----

We don't have TDM here in Edmonton but can send samples to Ottawa. I had thought about saquinavir once daily but could not find studies in pregnant women. I think this is a risk-benefit situation - once daily may not be ideal but missing a lot of meds is not either..

Case #5

We have a tx experienced fellow who we had to recently stop all ARVs b/c his Hgb fell to 35!! At the time he was on a very strange combination of Combivir and Nelfinavir plus Delaviridine (the ID doc didn't' want to go with nelfinavir alone or a ritonavir boosted regimen at that time and used the Dec/05 genotyping results to choose this).

Lowest CD4 was 223 in July/98 when he was in the ICU with PCP and very very ill (and dx with HIV), then again in Jan/00 CD4 = 211, but not real compliant with his regimen by then

He had been exposed to the following ARVs:

1997-99: AZT + 3TC + SQV (alone) with grapefruit juice (took about 8 days of ritonavir alone but couldn't tolerate this in 1998

Fe 99 - Dec 00: SQV changed to IDV and AZT was changed to d4t, can't recall why & cont'd 3TC, but he stopped meds on his own x 2_ years

****

CD4=271 (23%): May 02 to Feb/06 on CBV & NVP -- had low level viremia (<1000 copies/mL) on this regimen, but adherence not good

The genotyping done in Dec/05 while on CBV & NVP showed

NRTI mutations 41wt/L, 184V, 215Y

NNRTI mutations 101E, 135wt/T, 179wt/I, 190A

PIs: none, but his could be b/c he had been off any PIs for quite some time prior

Feb 06 - May 07 DLV + NFV + CBV based on genotyping, but stopped all ARVs when Hgb decreased significantly CD4 June/06 = 430 (33%), VL <40 copies/mL

Feb/07 CD4 = 471

Now off meds since May/07 and CD4 = 367 and VL pending

Not sure what ARVs to suggest based on the resistance - likely does have some PI resistance as was on IDV for a while (not sure what the SQV alone would have done?), but not on RTV for enough time I think to develop any signif resistance b/c of that (about 8 days in 1999)

Also not sure of what NRTI combo will have any effect since Dec/05 report suggests:

Resistance to ABC & FTC

Reduced response to AZT, ddI, TDF and minimal to 3TC (and need to avoid AZT & d4T d/t anemia anyway)

Susceptible - ddC

We were considering Truvada with ATZ/r 300mg/100mg once daily, but since we have the m184V mutation, is there any benefit when combining it with tenofovir? Would be nice if we could use a once daily b/c he's not great at twice/day. Thanks.

/Linda

Hi Linda,

One important missing piece in your story is the virologic response in 97-99. If VL was then suppressed and the genotype in 2005 was not showing PI mutations, I would feel confident to restart with a boosted PI. Although not being an expert in resistance, I believe that as long as

there is drug pressure, the PI mutation will remain, even if on a non-PI regime (anyone has data or experience to prove that I am wrong?).

Your patient is definitely NNRTI resistant. He does not have the Y181C mutations, so maybe etravirine (TMC-125) would be an option if you have access to the EAP. NRTI wise, keeping 3tc or FTC is a good idea just for decreasing the replication capacity. TDF is probably your best guess (or ddI if problems with your kidneys). The interpretation for 3TC is wrong... 184V mutation confers absolute resistance to 3TC.

ATV/r, LPV/r are good options. Lately, the TITAN study suggests that DRV/r is also a good option. In theory, FPV/r is also an acceptable alternative... It is not on top of my list though...

If your patient was in Ottawa, he had good chances to be on DRV/r- TMC125 - TDF - 3TC or FTC, regime similar to the DUET studies. And he'd get an adherence talk. :)

Good luck
pg

Thanks Pierre. . His virologic response for the 2 years or so after being on death's door was very good (<40 from Jan/98 to Sept 99 with 2 ?blips Dec 98 = 810 and Ja/99 1900 copies. Then he started the non-adherence stuff. Then in Jan 2000 it went to 260,000, then Feb/01 320,000 off meds.

I wondered about the M184V and 3TC, but also whether or not it was an option then with Tenofovir?? I know it would be with AZT, but not clear on this point and the effects of 3TC resistance with other NRTIs. . I had a slide somewhere that explained this, but can't find it right now. , Thanks again.

/Linda
H Linda,
M184V has these 3 main effects:
1) resistance to 3TC but resulting in a virus with decreased replication capacity
2)the potential to delay the further development of TAMS (1 believe your genotype has only 2 of the TAMS from pathway 1)
3) the ability to hypersensitize or partially reverse some of the resitance to tenofovir that may be present in light of those same 2 TAMS

On that note I would keep the 3TC in the mix to maintain the M184V virus. I would add tenofovir as this would definitely be a useful agent, but we normally would use Combivir/TFV in this case. We do this, because in the presence of AZT, in a patient whose adherence is questionable, K65R does not develop with TFV. If anything the virus will develop more thymdine mutations, which, again may be delayed because of the M184V. The only concern with this is the potential for anemia with AZT. I believe you said that he had this in the past. I agree with Pierre re: the boosted PI's. If anything he probably has the L90M mutation from his SQV days, which, by itself does not render too much problem with boosted PI's such as kaletra or the newer ones.

Linda Robinson.

Case #6

Hello to my Alberta colleagues,
a couple of questions: I have a patient and his partner who are relocating

to Calgary next month. I have given him the name of Dr. Gill and contact information as that is what I had at my disposal. I also have a list of medications that they take and told them that I'd make sure that they would be covered in Calgary. They will have to wait the 3 month period as any other province to province jump so I will send my patient with his 3 month supply of meds. His partner however is from Detroit and I'm not sure how things will work for him. On another note, they will have private coverage through my patient for 80% drug coverage. so....I assume that ARV's will be available to them through Alberta health. Does it cover all ARV's? The list is as follows:

My patient:
Sustiva/Truvada

His partner:
Viread/3TC/Aptivus/Norvir/Fuzeon

Any other tidbits I could advise them with would be greatly appreciated.

Thanks,
Linda R.

Case#7

Hi folks:

We have our first patient to start Fuzeon. I was wondering if there the company is supplying any self-injection teaching materials for training patients? If so, does anyone have a contact person? I don't know who our rep is… they change so much lately! We usually have the same rep as Ottawa and Quebec, if that helps.

Thanks!
Debbie

Hi Debbie,
Yes, Fuzeon comes with extensive self-injection teaching material including a DVD / VHS video.
For Québec, the Roche reps are Nancy Watmore and Claire Perron. I am not

certain which one covers the maritimes. I believe Claire but I might be mistaken. Nancy

Case #8 Deborah

Does anyone have anything to add to the discussion of BCP and ARVs. Using the TGH website, It looks like a patient on Kaletra and Marvelon (Ethinyl estradiol) should also be told to use a condom (which they should use anyway) but is that enough coverage for a teenager or a young 20 year old woman who does not want to get pregnant? Thanks Natalie

[Dayneka, Natalie] -----Original Message-----
From: chap_acpv@yahoogroups.com [mailto:chap_acpv@yahoogroups.com]**On Behalf Of** Dr. Deborah Kelly
Sent: Friday, November 04, 2005 8:01 AM
To: chap_acpv@yahoogroups.com
Subject: RE: [chap_acpv] birth control and nevirapine

> We are also avoiding Depo-Provera due to the concerns about reduced BMD and fractures. We don't have any experience with the newer forms of BC yet… seems when we explain the concerns about DI for oral contraceptives and osteoporosis for Depo-Provera, the couple of ladies we've had have been more convinced to use condoms (I think one may also have gotten a diaphragm too, but I can't remember for certain).
>
> Deb

Here is a table we have been working on for some time- Cara Hills took a lead on it. Take a look here also Natalie- same info basically.
Michelle
Hi Natalie,

That is what I tell our patients. I find this a little redundant as we tell them to use condoms anyway as a measure to avoid spreading the virus. For HIV couples, we recommend to use condoms for transmission of another virus strand.

pg

Oral Contraceptive (OC) and Antiretroviral (ARV) Drug Interactions

Drug	Interaction	Suggestion	Summary
Protease Inhibitors			
Atazanavir (Reyataz®) CYP3A4 substrate Inhibits CYP3A4	In a study of 22 healthy women taking ATV 400mg/day X 2 weeks, ↑ 48% AUC of ethinyl estradiol and ↑ 110% AUC of	Use **lowest effective dose** of each contraceptive component and monitor for side effects (including ↓	**Increase OC levels**

	norethindrone.[1]	HDL and ↑ insulin resistance esp. in diabetic women).[2]	
Darunavir (Prezista®) CYP 3A4 substrate	In study of 18 women on DRV/rtv 600/100mg bid X 2 weeks, ↓ 44% AUC, ↓ 62% Cmin of ethinyl estradiol and ↓ 14% AUC, ↓ C_{min} of norethindrone.[3]	**Use alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy.	**Decrease OC efficacy.**
Fos/amprenavir (Telzir®/Agenerase®) CYP3A4 substrate Inhibits CYP3A4 Induces CYP3A4	↓ 22% AUC, ↓ 20% C_{min} of amprenavir; ↑ 32% C_{min} of ethinyl estradiol and ↑ 45% C_{min}; ↑ 18% AUC of norethindrone with oral contraceptives containing ethinyl estradiol 0.035 mg/norethindrone 1mg.[4] May lead to loss of virologic response and possible resistance to amprenavir.	**Use alternate/ additional methods of contraception** (latex condom) due to potential decrease in amprenavir efficacy.	**Decrease ARV efficacy.**
Indinavir (Crixivan®) CYP3A4 substrate CYP3A4 inhibitor	↑ 24% AUC of ethinyl estradiol, ↑ 26% AUC of norethindrone.[5,6]	**No specific action required.**[6]	**Increase OC levels.**
Lopinavir (Kaletra®) CYP3A4 substrate CYP3A4>2D6 inhibitor Induces: GT and possibly CYP1A2, 2C19, 2C9	↓ 42% AUC, ↓ 41% C_{max}, ↓ 58% C_{min} of ethinyl estradiol; ↓ 17% AUC, ↓ 16% C_{max}, ↓ 32% C_{min} of norethindrone.[7]	Use alternate/ additional methods of contraception (latex condom) secondary to loss of OC efficacy. **Use Progestin based contraceptives (Depo-Provera®)**. However, delavirdine, lopinavir/ritonavir, nelfinavir, and ritonavir might ↑ concentration of progestin-based contraceptives (metabolized by CYP 3A4). Monitor for the development of adverse effects with	**Decrease OC efficacy.**

		Depo-Provera®.[8]	
Nelfinavir (Viracept®) CYP3A4>2C19, 2D6 substrate Inhibits CYP3A4	↓ 47% AUC, ↓ 28% C_{max} of ethinyl estradiol; ↓ 18% AUC of norethindrone. C_{max} norethindrone unchanged.[9]	**See Lopinavir** **See DMPA chart**	**Decrease OC efficacy.**
Ritonavir (Norvir®) Inhibits CYP3A4> 2D6>2C9>2C19>>2A6>2E1. Induces GT, CYP1A2 and possible 2C9, 2C19.	↓ 40% AUC, ↓ 32% C_{max} of ethinyl estradiol.[10]	**See Lopinavir**	**Decrease OC efficacy.**
Saquinavir (Invirase®) CYP3A4 substrate Weak inhibitor of CYP3A4	In 8 healthy women, single dose saquinavir levels were not affected by combined low-dose OC (0.03 mg ethinyl estradiol, 0.075 mg gestodene).[11]	Due to use of saquinavir in combination with ritonavir, use **alternate/ additional methods of contraception** (latex condom).	**Decrease OC efficacy** (due to use with ritonavir).
Tipranavir (Aptivus®) CYP3A4 substrate Induces CYP3A4, GT, Pgp	↓ 50% AUC of ethinyl estradiol.[6]	Use **alternate/ additional methods of contraception** (latex condom) secondary to loss of OC efficacy.[6] *No information on interaction between tipranavir and progestin based contraceptives is currently available. Anticipate a possible loss of efficacy due to the CYP 450 induction by tipranavir.*	**Decrease OC efficacy.**

Case#9 everyone,
I have a couple questions about raltegravir combos:

1) Have you mainly been combining with standard doses of boosted darunavir (vs tipranavir)?

A) what do you make of the intx with TPV/r with lowering of raltegravir levels- are you increasing doses of raltegravir?

B) also, I was unable to find intx data on raltegravir and darunavir/RTV- are you just using standard doses of both?

2) I have a couple pts with NNRTI and NRTI resistance. They are not really interested in enfuvirtide.

A) Do you have any experience with the use of raltegravir and darunavir/RTV **only** as your prime agents (+/- recycled nukes) vs holding out for TMC-125 (etravirine) or maraviroc to add to these 2 active agents?

B) Do any of you have experience with TMC-125 and how effective it is with past NNRTI resistance? Our EAP is still in the works for this agent.

Thanks!

Michelle

Hi Michelle,

My experience so far:

1) Have you mainly been combining with standard doses of boosted darunavir (vs tipranavir)?
-using standard doses of DRV/r; haven't used it with TPV/r

A) what do you make of the intx with TPV/r with lowering of raltegravir
levels- are you increasing doses of raltegravir?
-MRK suggests that dose adjustment not needed since no clinical difference yet seen; maybe since AUC(0-12) was only a 24% decrease

B) also, I was unable to find intx data on raltegravir and darunavir/RTV- are you just using standard doses of both?
-using standard dosing of both

2) I have a couple pts with NNRTI and NRTI resistance. They are not really interested in enfuvirtide.

A) Do you have any experience with the use of raltegravir and darunavir/RTV only as your prime agents (+/- recycled nukes) vs holding
out for TMC-125 (etravirine) or maraviroc to add to these 2 active agents?
-not yet with this combo
-have a raltegravir and TMC-125 (resistent to DRV and T20, dual tropic)
- awaiting results

B) Do any of you have experience with TMC-125 and how effective it is with past NNRTI resistance? Our EAP is still in the works for this

agent.
-have started enrolling in our EAP; awaiting results/follow-up (hoping its as good as the DUET study results; had pts enrolled in DUET at our site with good results - I assume they must have been randomized to active arm); can update you in the near future.

Thanks!

Michelle
Marijuana

Federal paperwork to authorize HIV patients to "legally" obtain & smoke marijuana. As far as I know in Sask. we have very limited physicians who have agreed to do this and we only have 1 patient in our clinic with this "liscence". We have another who is demanding our ID physicians complete this for him, but he doesn't seem to meet the criteria and they are reluctant to get involved in this anyway. Thought it might help if we can tell him the situation in other sites across the country. Thanks.

/Linda

Hi Linda S,

I can't comment on outside of Vancouver, but we do have physicians (even Julio) who are willing to complete the paperwork for this program.

Linda A.
ps. are you on strike???

Hi all,

You have not heard from me before; my name is Mike Thompson and I'm filling in for Michelle Foisy while she's on vacation.

I thought I would reply to this post because I have filled this paperwork out for a patient at our site. The patient failed Nabilone and is now self-treating his nausea with illegal marihuana. After initially giving the green light to the paperwork, the physician is having second thoughts and we are now exploring Sativex as as option before going down the medicinal marihuana path. If carried out, this would be the first time for this doc. I know of no others attempts at this site to provide this treatment.

Mike
Limited in Southern AB - two docs have submitted but are very conservative, and probably less than a half-dozen patients have permits. If your patient decides to move, however, I'm sure he'd be MUCH happier in BC.....

jeff

Hi Linda,

We have done it for our patients here. I do not know the exact number of patients on it but I can guestimate around 5-6.

pg

Dieticians in HIV clinic

HI,
For the Chest, we have Richard Laroche (richard.laroche@muhc.mcgill.ca)
Nancy
Hi,

Hi,

At the Oak Tree Clinic our program dietician is Diana Johansen, djohansen@cw.bc.ca.

Thanks,

Gloria

At the Oak Tree Clinic our program dietician is Diane Johansen, djohansen@cw.bc.ca.

Thanks,
Gloria
Our fabulous HIV dietician is Julie Larocque, JLarocque@cheo.on.ca. I have cc'd her on this email. Natalie
Hi,
Our dietician at the Gilwest Clinic in Richmond Hospital is Michele Blanchet (michele.blanchet@vch.ca).
Ray

DATABASE

I've been trying for some years to get our IT department to assist in getting this set up for our Clinic, however, I'm not really getting anywhere, so thought I would ask if any site has a program that our Region could purchase? It would be nice to be able to start entering our data so we can evaluate our patients over time and for research purposes. Thanks.

/Linda

Linda A. Sulz

We've also been looking into this, but on a local level to be built for our population specifically. Cost has been a barrier, as well as changing clinic staff and need for reeducation, etc. If there are any "ready made" databases out there, I'd be interested to hear more also.
Debbie

Hi,
We have an HIV specific database for the Chest Immunodeficiency Clinic. We now have retrospective data as far back as 1989. We had the original version and have just had a newer version constructed. We are presently ensuring that the data has properly transfered into the new database. I think other HIV clinics in Québec will have the same database named RISQ. I imagine it is possible to purchase it ($$$$).
The person to contact is Richard Lalonde (richard.lalonde@muhc.mcgill.ca)
Good luck with this project
Nancy

Drug	Interaction	Suggestion	Summary
Non-nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (Rescriptor®) CYP3A4>>2D6 substrate Inhibits CYP3A4, 2C9,2C19	Clinically significant interaction is unlikely.[12]	**No specific action required.**	**No change.**
Efavirenz (Sustiva®) CYP3A4, 2B6 substrate Induces CYP3A4 Inhibits CYP3A4, 2C9, 2C19	In study of 13 healthy volunteers, ↑ 37% AUC ethinyl estradiol after 10 days of EFV 400mg.[13,14] However, efavirenz found to interfere with the estradiol ELISA assay. This may artificially elevate estradiol levels if ELISA assay used.[15]	**No specific action required.**	**Increase OC levels.**
Nevirapine (Viramune®) CYP3A4>>2B6 substrate Induces CYP3A4, 2B6	↓ 20 % AUC of ethinyl estradiol; ↓ 19% AUC, ↓ 16% C_{max} of norethindrone.[16]	Use alternate/ additional methods of contraception (latex condom) secondary to loss of OC efficacy. **Use Progestin based contraceptives (Depo-Provera®)**. **See DMPA chart.**	**Decrease OC efficacy.**

Oral Contraceptives

Low Dose OC	**Ingredients**
Alesse®	Ethinyl estradiol 20ug/levonorgestrel 100ug
Minestrin®	Ethinyl estradiol 20ug/norethindrone acetate 1mg
Tri-Cyclen Lo®	Ethinyl estradiol 25ug/ norgestimate 180/215/250ug
High Dose OC	**Ingredients**
Cyclen®	Ethinyl estradiol 35ug/norgestimate 250ug
Ovral®	Ethinyl estradiol 50ug/norgestrel 250ug
Tri-Cyclen®	Ethinyl estradiol 35ug/norgestimate 180/215/250ug
Brevicon 0.5/35®, Ortho 0.5/35®	Ethinyl estradiol 35ug/norethindrone 0.5mg
Brevicon 1/35®, Ortho 1/35®	Ethinyl estradiol 35ug/norethindrone 1mg
Synphasic ®	Ethinyl estradiol 35ug/norethindrone 0.5/1/0.5mg
Ortho 7/7/7®	Ethinyl estradiol 35ug/norethindrone05/0.75/1mg

OC metabolism:
GT, sulphatase, CYP3A4 substrate
Inhibits CYP1A2, 3A

Depo-medroxyprogesterone (DMPA/Depo-Provera®) and Antiretroviral Drug Interactions

Drug	Interaction	Suggestion
Protease Inhibitors		
Nelfinavir (Viracept®) CYP3A4>2C19,2D6 substrate Inhibits CYP3A4	In 20 HIV patients, no change in AUC of nelfinavir 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels.[17]	DMPA appears effective and safe in patients on nelfinavir.[17]
Non-nucleoside Reverse Transcriptase Inhibitors		
Efavirenz (Sustiva®) CYP3A4, 2B6 substrate	In 15 HIV patients, no change in AUC of efavirenz 4 weeks after DMPA administered. After 12 weeks, no	DMPA appears effective and safe in patients on efavirenz.[17]

Induces CYP3A4 Inhibits CYP3A4, 2C9, 2C19	pregnancies, no women appeared to ovulate based on progesterone levels.[17]	
Nevirapine (Viramune®) CYP3A4>>2B6 substrate Induces CYP3A4, 2B6	In 14 HIV patients, small increase in nevirapine AUC 4 weeks after DMPA administered. After 12 weeks, no pregnancies, no women appeared to ovulate based on progesterone levels.[17]	DMPA appears effective and safe in patients on nevirapine. Increased nevirapine levels do not appear to be clinically significant.[17]

DMPA metabolism:
CYP3A4 substrate

Potential side effects of DMPA include:

- Menstrual irregularity occurs most frequently
- Frequent and irregular bleeding are common, while long duration of bleeding episodes and amenorrhea are less likely
- Headache, breast tenderness, nausea, and dizziness are increased among progestin-only oral contraceptive users in some studies
- Androgenic side effects such as acne, hirsutism, and weight gain can occur
- Long-term: decreased bone mineral density

Product information

Some of you may be aware that BMS is no longer selling Videx 4G pediatric powder. However, it may be possible to access it through Health Canada's Special Access Program (SAP). I just got off the phone with BMS drug info and they suggested that if anyone wants to access this product, that they ask the prescribing physician to put in a request to SAP. SAP will then decide whether or not BMS can release the drug.

Linda.

Articles and other infos

: Clinical Care Options
To: Michelle Foisy
Sent: Thursday, May 24, 2007 2:33 PM
Subject: Downloadable Tool for Assessing HIV Drug-Drug Interactions

CLINICAL CARE OPTIONS
HIV

Downloadable Tool Now Av
Drug-Drug Interactio
in HIV-Infected Patie

Downloadable Tool for Mobil
This unique downloadable tool for Pa

Hi guys,

First of all thanks to Tony and Pierre re: phosphate. Also, Pierre, thanks for the contact at Merck. I have forwarded my letter and reply from Merck as an FYI for the group. There is a great article to attach to applications as well as the LB abstract references from CROI. I am applying for raltegravir in 2 incidences, one who is undetectable (3 class resistant) on ENF + DRV + TFv and 3TC but is threatening to stop all because of ENF burnout and the other who is beyond a doubt needle phobic, triple class resistant and desperately needs suppressive therapy. I'll keep the group posted as to my luck.
Linda R

-----Original Message-----

http://www.retroconference.org/2007/Abstracts/30688.htm

RAPID COMMUNICATION

Antiretroviral Activity, Pharmacokinetics, and Tolerability of MK-0518, a Novel Inhibitor of HIV-1 Integrase, Dosed As Monotherapy for 10 Days in Treatment-Naive HIV-1–Infected Individuals

Martin Markowitz, MD,* Javier O. Morales-Ramirez, MD,† Bach-Yen Nguyen, MD,‡ Colin M. Kovacs, MD,§ Roy T. Steigbigel, MD,‖ David A. Cooper, MD, DSc,¶ Ralph Liporace, MD,#
Robert Schwartz, MD,** Robin Isaacs, MD,‡ Lucinda R. Gilde, BS,‡ Larissa Wenning, PhD,‡
Jing Zhao, PhD,‡ Hedy Teppler, MD,‡ and the Protocol 004 Study Team

(J Acquir Immune Defic Syndr 2006;43:509–515)
J Acquir Immune Defic Syndr _ Volume 43, Number 5, December 15, 2006

Atazanavir urinary stones in an HIV-infected patient.
Pacanowski J, **Poirier JM**, **Petit I**, **Meynard JL**, **Girard PM**.
PMID: 17053366 [PubMed - indexed for MEDLINE]
Related Links

- Atazanavir urolithiasis. [N Engl J Med. 2006]
- Acute hepatic cytolysis in an HIV-infected patient taking atazanavir. [AIDS. 2004]
- Rash in an HIV-positive patient. [HIV Med. 2005]
- [Simplified HIV therapy. Atazanavir: the first protease inhibitor with once daily administration] [MMW Fortschr Med. 2004]
- Rescue therapy with once-daily atazanavir-based regimens for antiretroviral-experienced HIV-infected patients. [J Acquir Immune Defic Syndr. 2006]

Hi Christine,

Here is a reference to an abstract at CROI 2007 that looked at 33 case reports of atazanavir use in pregnancy in London. The concern of hyperbilirubinemia in the neonate remains, but this summary showed that although many of the babies had mild elevations, they did not require phototherapy and levels resolved on their own. We had one patient last year who we started on nelfinavir at the beginning of 2nd trimester, changed to Kaletra at 1 and 1/2 months because we weren't confident that the VL was going down fast enough. She then developed a rapid increase in LFT's so we put her on ATV 400mg daily wiith CBV for the remainder of pregnancy. We got her to <50 by delivery (and well before) and mom and baby were and still are both fine. I would consider it in this case especially if naive. I'd probably boos for once daily to make sure you get good levels throughout pregnancy, though in our case we didn't, but she did take CBV bid. I believe ATV has a category B listing in the last DHHS guideline from Oct 2006.

http://www.retroconference.org/2007/Abstracts/28351.htm

-----Original Message-----
From: Hughes, Christine [mailto:chughes@pharmacy.ualberta.ca]
Sent: Thursday, July 05, 2007 10:51 AM
To: chap_acpv@yahoogroups.com
Subject: RE: [chap_acpv] once daily regimen for pregnant patient

Hi Niamh,

Yes it is tricky! I believe the patient is antiretroviral naive and does not require HIV treatment herself (high CD4). I would be reluctant to use once daily nevirapine due to high CD4 count. Again this is not my patient but would assume she is coinfected with HCV given her drug use history. For what it is worth, apparently she is quite skinny.

We don't have TDM here in Edmonton but can send samples to Ottawa. I had thought about saquinavir once daily but could not find studies in pregnant women. I think this is a risk-benefit situation - once daily may not be ideal but missing a lot of meds is not either....

Welcome to Jessica and Roland. We look forward to your involvement with our group.

Natalie, Chair CHAP
Natalie Dayneka, B.Sc.Phm.,Pharm.D.,FCSHP
Clinical Specialist/SpÃ©cialiste clinique
Pharmacy Department/Pharmacie
Children's Hospital of Eastern Ontario
401 Smyth Road
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Fax: 613-738-4206
email: dayneka@cheo.on.ca

-----Original Message-----
From: chap_acpv@yahoogroups.com [mailto:chap_acpv@yahoogroups.com]**On**

Behalf Of Tseng, Alice Dr
Sent: Friday, August 24, 2007 8:48 AM
To: chap_acpv@yahoogroups.com
Cc: Jessica Burry
Subject: RE: [chap_acpv] New contact member for the listserv

Welcome, Jessica & Roland, I have added you both to the CHAP listserve.

Roland, can you please send me your complete contact information so I may add it to our contact list?

And this is a rather belated introduction, as I believe many of you met Trish Marr at part of the CHAP meeting this spring.

Trish is covering my maternity leave here at TGH, and is already doing a great job. Trish's hospital e-mail address is:

Patricia.Marr@uhn.on.ca

Alice

We have a tx experienced fellow who we had to recently stop all ARVs b/c his Hgb fell to 35!! At the time he was on a very strange combination of Combivir and Nelfinavir plus Delaviridine (the ID doc didn't' want to go with nelfinavir alone or a ritonavir boosted regimen at that time and used the Dec/05 genotyping results to choose this).

Lowest CD4 was 223 in July/98 when he was in the ICU with PCP and very very ill (and dx with HIV), then again in Jan/00 CD4 = 211, but not real compliant with his regimen by then

He had been exposed to the following ARVs:

1997-99: AZT + 3TC + SQV (alone) with grapefruit juice (took about 8 days of ritonavir alone but couldn't tolerate this in 1998

Fe 99 - Dec 00: SQV changed to IDV and AZT was changed to d4t, can't recall why & cont'd 3TC, but he stopped meds on his own x 2_ years

****

CD4=271 (23%): May 02 to Feb/06 on CBV & NVP -- had low level viremia (<1000 copies/mL) on this regimen, but adherence not good

The genotyping done in Dec/05 while on CBV & NVP showed

NRTI mutations 41wt/L, 184V, 215Y

NNRTI mutations 101E, 135wt/T, 179wt/I, 190A

PIs: none, but his could be b/c he had been off any PIs for quite some time prior

Feb 06 - May 07 DLV + NFV + CBV based on genotyping, but stopped all ARVs when Hgb decreased significantly CD4 June/06 = 430 (33%), VL <40 copies/mL

Feb/07 CD4 = 471

Now off meds since May/07 and CD4 = 367 and VL pending

Not sure what ARVs to suggest based on the resistance - likely does have some PI resistance as was on IDV for a while (not sure what the SQV alone would have done?), but not on RTV for enough time I think to develop any signif resistance b/c of that (about 8 days in 1999)

Also not sure of what NRTI combo will have any effect since Dec/05 report suggests:

Resistance to ABC & FTC

Reduced response to AZT, ddI, TDF and minimal to 3TC (and need to avoid AZT & d4T d/t anemia anyway)

Susceptible - ddC

We were considering Truvada with ATZ/r 300mg/100mg once daily, but since we have the m184V mutation, is there any benefit when combining it with tenofovir? Would be nice if we could use a once daily b/c he's not great at twice/day. Thanks.

/Linda

Hi Linda,

One important missing piece in your story is the virologic response in 97-99. If VL was then suppressed and the genotype in 2005 was not showing PI mutations, I would feel confident to restart with a boosted PI. Although not being an expert in resistance, I believe that as long as there is drug pressure, the PI mutation will remain, even if on a non-PI regime (anyone has data or experience to prove that I am wrong?).

Your patient is definitely NNRTI resistant. He does not have the Y181C mutations, so maybe etravirine (TMC-125) would be an option if you have access to the EAP. NRTI wise, keeping 3tc or FTC is a good idea just for decreasing the replication capacity. TDF is probably your best guess (or ddI if problems with your kidneys). The interpretation for 3TC is wrong... 184V mutation confers absolute resistance to 3TC.

ATV/r, LPV/r are good options. Lately, the TITAN study suggests that DRV/r is also a good option. In theory, FPV/r is also an acceptable alternative... It is not on top of my list though...

If your patient was in Ottawa, he had good chances to be on DRV/r- TMC125 - TDF - 3TC or FTC, regime similar to the DUET studies. And he'd get an adherence talk. :)

Good luck
pg

Thanks Pierre. . His virologic response for the 2 years or so after being on death's door was very good (<40 from Jan/98 to Sept 99 with 2 ?blips Dec 98 = 810 and Ja/99 1900 copies. Then he started the non-adherence stuff. Then in Jan 2000 it went to 260,000, then Feb/01 320,000 off meds.

I wondered about the M184V and 3TC, but also whether or not it was an option then with Tenofovir?? I know it would be with AZT, but not clear on this point and the effects of 3TC resistance with other NRTIs. . I had a slide somewhere that explained this, but can't find it right now. , Thanks again.

/Linda
H Linda,
M184V has these 3 main effects:
1) resistance to 3TC but resulting in a virus with decreased replication capacity
2)the potential to delay the further development of TAMS (1 believe your genotype has only 2 of the TAMS from pathway 1)
3) the ability to hypersensitize or partially reverse some of the resitance to tenofovir that may be present in light of those same 2 TAMS

On that note I would keep the 3TC in the mix to maintain the M184V virus. I would add tenofovir as this would definitely be a useful agent, but we normally would use Combivir/TFV in this case. We do this, because in the presence of AZT, in a patient whose adherence is questionable, K65R does not develop with TFV. If anything the virus will develop more thymdine mutations, which, again may be delayed because of the M184V. The only concern with this is the potential for anemia with AZT. I believe you said that he had this in the past. I agree with Pierre re: the boosted PI's. If anything he probably has the L90M mutation from his SQV days, which, by itself does not render too much problem with boosted PI's such as kaletra or the newer ones.

Linda Robinson.

Hello to my Alberta colleagues,
a couple of questions: I have a patient and his partner who are relocating to Calgary next month. I have given him the name of Dr. Gill and contact information as that is what I had at my disposal. I also have a list of medications that they take and told them that I'd make sure that they would be covered in Calgary. They will have to wait the 3 month period as any other province to province jump so I will send my patient with his 3 month supply of meds. His partner however is from Detroit and I'm not sure how things will work for him. On another note, they will have private coverage through my patient for 80% drug coverage. so....I assume that ARV's will be available to them through Alberta health. Does it cover all ARV's? The

list is as follows:

My patient:
Sustiva/Truvada

His partner:
Viread/3TC/Aptivus/Norvir/Fuzeon

Any other tidbits I could advise them with would be greatly appreciated.

Thanks,
Linda R.

Hi folks:

We have our first patient to start Fuzeon. I was wondering if there the company is supplying any self-injection teaching materials for training patients? If so, does anyone have a contact person? I don't know who our rep is… they change so much lately! We usually have the same rep as Ottawa and Quebec, if that helps.

Thanks!
Debbie

Hi Debbie,
Yes, Fuzeon comes with extensive self-injection teaching material including a DVD / VHS video.
For Québec, the Roche reps are Nancy Watmore and Claire Perron. I am not certain which one covers the maritimes. I believe Claire but I might be mistaken.
Nancy

Some of you may be aware that BMS is no longer selling Videx 4G pediatric powder. However, it may be possible to access it through Health Canada's Special Access Program (SAP). I just got off the phone with BMS drug info and they suggested that if anyone wants to access this product, that they ask the prescribing physician to put in a request to SAP. SAP will then decide whether or not BMS can release the drug.

Linda.

Our HIV team is looking for a guest speaker to come lecture on the issues around addictions (mainly prescription drug diversion issues vs. IV drug use) and mental health in HIV. Can anyone recommend a good speaker?

Thanks
Debbie

Welcome to Jessica and Roland. We look forward to your involvement with our group.

Natalie, Chair CHAP
Natalie Dayneka, B.Sc.Phm.,Pharm.D.,FCSHP
Clinical Specialist/SpÃ©cialiste clinique
Pharmacy Department/Pharmacie
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario K1H 8L1
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Fax: 613-738-4206
email: dayneka@cheo.on.ca

> -----Original Message-----
> **From:** chap_acpv@yahoogroups.com [mailto:chap_acpv@yahoogroups.com]**On Behalf Of** Tseng, Alice Dr
> **Sent:** Friday, August 24, 2007 8:48 AM
> **To:** chap_acpv@yahoogroups.com
> **Cc:** Jessica Burry
> **Subject:** RE: [chap_acpv] New contact member for the listserv
>
> Welcome, Jessica & Roland, I have added you both to the CHAP listserve.
>
> Roland, can you please send me your complete contact information so I may add it to our contact list?
>
> And this is a rather belated introduction, as I believe many of you met Trish Marr at part of the CHAP meeting this spring.
>
> Trish is covering my maternity leave here at TGH, and is already doing a great job. Trish's hospital e-mail address is:
>
> Patricia.Marr@uhn.on.ca
>
> Alice

How many of you have patients who are allergic to sulfonamides on Darunavir? Any one concerned about this? Natalie

Hi Natalie

This issue came up recently for one of my patients. I could not find case reports of cross-sensitivity between Darunavir and other sulfonamides....Tibotec-Janssen Ortho Incorporated, the manufacturer of Darunavir, confirmed this finding by checking their private files. There is however, a theoretical concern about cross sensitivity between these products as both Darunavir and Septra are sulfonylarylamines (see attached articles - particularly the letter to the editor).

From my clinical experience in HIV (although limited), the few patients who had allergies to Septra (simple rashes) tolerated Darunavir just fine. We did monitor these patients closely for adverse reactions

Hope this helps

Trish

www.theannals.com The Annals of Pharmacotherapy _2005 February, Volume 39 _

The clinical significance of cross-reactivity of medications in a person with a "sulfa" allergy continues to perplex clinicians and complicates decisions regarding patient safety. Historically, the term "sulfa" refers to a derivative of the antimicrobial agent sulfanilamide. More recently, the term has been applied to a diverse group of drugs, all of which contain the sulfonamide chemical structure ($–SO_2NH_2$). Sulfonamides can be divided into 3 distinct groups (Figure 1). The first group has a sulfonamide moiety directly connected to a benzene ring with an unsubstituted amine ($–NH_2$) moiety at the N4 position (sulfonylarylamines); see sulfanilamide in Figure 2. The second group has a sulfonamide moiety connected to a benzene ring or other cyclic structure without the amine moiety at the N4 position (nonsulfonylarylamines). The third group has a sulfonamide moiety not directly connected to the benzene ring. The chemical structure of a drug is one aspect that affects potential adverse reactions. At least 2 types of reactions have been described that are related to the sulfonylarylamine structure.[1-3] The first is an immunologic reaction that requires a 5- or 6-membered aromatic heterocyclic ring at the sulfonamide-N1 position. This reaction is immunoglobulin (Ig) E mediated and presents most commonly

as either a maculopapular eruption or an urticarial rash that develops within 1–3 days of initial medication administration and resolves spontaneously upon discontinuation of the drug. Anaphylaxis may develop with repeat exposure. The second is a hypersensitivity reaction that requires the presence of an amine group at the N4 position. This reaction, usually part of a drug hypersensitivity syndrome, initially presents as a fever and a non-urticarial rash that may progress to erythema multiforme and multi-organ toxicity. The onset is delayed, usually within 7–14 days, and resolves upon withdrawal of the medication. Therefore, based on current understanding of the pathogenesis of sulfonylarylamine adverse reactions, non-sulfonylarylamines and other sulfonamide moiety–containing drugs do not share the same risk on a chemical or metabolic basis even though the clinical presentation may appear to be similar. The purpose of this article is to provide a critical and comprehensive review of the literature, specifically case reports and observational studies that have been used to support the concept of cross-reactivity between sulfonylarylamines and non-sulfonylarylamines.

Data Sources

Sulfonamide Cross-Reactivity: Fact or Fiction?

Kelly K Johnson, David L Green, Jason P Rife, and Lynn Limon

Adverse Drug Reactions

Author information provided at the end of the text.

OBJECTIVE: **To provide a critical and comprehensive review of the literature, specifically case reports and observational studies used to support the concept of cross-reactivity between sulfonylarylamines and non-sulfonylarylamines.**

DATA SOURCES: **A list of medications was formulated from several different review articles. A MEDLINE/PubMed search was conducted (1966–March 2004) using the individual medications and the MeSH terms of drug hypersensitivity/etiology, sulfonamides/adverse effects, and/or cross-reaction.**

STUDY SELECTION AND DATA EXTRACTION: **A critical review of the methodology and conclusions for each article found in the search was conducted. The manufacturer's package insert (MPI) for each drug was examined for a statement concerning possible crossreactivity in patients with a sulfonamide allergy. If indicated, the manufacturers were contacted to obtain any clinical data supporting the statement.**

DATA SYNTHESIS: **A total of 33 medications were identified. Seventeen (51.5%) of the MPIs contained statements of varying degrees concerning use in patients with a "sulfonamide" allergy; 21 case series, case reports, and other articles were found.**

CONCLUSIONS: **After a thorough critique of the literature, it appears that the dogma of sulfonylarylamine cross-reactivity with nonsulfonylarylamines is not supported by the data. While many of the case reports on the surface support the concept of crossreactivity, on closer examination the level of evidence in many of the cases does not conclusively support either a connection or an association between the observed cause and effect.**

KEY WORDS: **cross-reaction, hypersensitivity, sulfonamide.**

***Ann Pharmacother* 2005;39:xxxx.**

Published Online, 11 Jan 2005, *www.theannals.com*, DOI 10.1345/aph.1E350

A list of medications was created using information from several different review articles.[2-8] The sulfonamide moiety–containing agents topiramate, ibutilide, zonisamide, and sotalol were added based upon their chemical structures. A MEDLINE/PubMed search from 1966 to March 2004 was conducted using each medication from the above list and the individual MeSH terms drug hypersensitivity/etiology, sulfonamides/adverse effects, and cross-reaction as separate searches. The purpose of the search was to obtain a list of the primary literature to include studies, abstracts, or case reports. All review articles and foreignlanguage articles were excluded. Also, the reference list of each article was examined for articles not identified in the original search. The manufacturer's package insert (MPI) for each drug was obtained to determine whether a statement concerning possible cross-reactivity in patients with a sulfonamide allergy was included. For MPIs containing such a statement, the manufacturers were contacted to obtain any clinical data supporting the statement. Finally, the chemical structures of the medications were located for reference (Figure 2). Dapsone, sulfamethoxazole, and other sulfanilamide derivatives were excluded since cross-reactivity between these drugs has been well documented.[1,9,10] We use the term sulfonylarylamine to refer to sulfanilamide-derived medications. All other agents are referred to as either non-sulfonylarylamines or sulfonamide moiety–containing drugs depending upon their chemical structure. Since the term sulfonamide is most readily interpreted to mean sulfonylarylamines but is otherwise nonspecific, we place the term sulfonamide in quotation marks when referring to its use in an article or MPI.

Various diagnostic tests were utilized in the studies reviewed including skin tests, lymphocyte transformation tests, lymphocyte toxicity assay, and oral challenges. Review articles providing specific information concerning these tests are available.[11,12]

A total of 33 medications were identified (Table 1).[13-45] Seventeen (51.5%) of the MPIs contained statements of varying degrees concerning use in patients with a "sulfonamide" allergy. The location of the statement in the MPI varied, with 8 (47.1%) listed in the contraindications section, 6 (35.3%) in the warnings section, and 3 (17.6%) in the precautions section.

Carbonic Anhydrase Inhibitors

Four carbonic anhydrase inhibitors (CAIs) were identified during the search. The MPIs for all CAIs contain the warnings, "Fatalities have occurred, although rarely, due to severe reactions to sulfonamides.… Sensitizations may recur when a sulfonamide is re-administered …". These statements are vague, taking advantage of the generic sulfonamide terminology, which results in a wide variety of possible interpretations.

Figure 1. **Classification of sulfonamides. CAIs = carbonic anhydrase inhibitors; COX-2 = cyclooxygenase-2; thiazides = thiazide diuretics and related compounds.**

We found 5 case reports for acetazolamide. Three were excluded because the patients did not have a known sulfonylarylamine allergy and cross-reactivity with non-sulfonylarylamines and sulfonamide moiety–containing medications was not assessed.[46-48] Even so, a connection between the anaphylactic reaction to acetazolamide and "sulfonamides" was postulated in 2 of the case reports.[47,48]

In 1955, Mosely and Baroody[49] reported that a patient with congestive heart failure with a "sulfa" allergy experienced an adverse reaction following administration of oral acetazolamide. The patient developed gait disturbances, vertigo, facial numbness, and generalized paresthesia 20 minutes after the first dose. Upon re-administration of acetazolamide 2 days later, the patient reported "the same sort of reaction," accompanied by respiratory distress and limb edema. The authors concluded that the patient experienced a hypersensitivity reaction to acetazolamide and, since acetazolamide is chemically related to "sulfonamides," patients with a "sulfonamide" allergy should not receive acetazolamide. As mentioned by the authors, acetazolamide adverse reactions include paresthesias, dysthesias, and vertigo related to hypokalemia. Whether this was the cause of the reaction in this case is unknown since a serum potassium concentration was not reported. Stock[50] interpreted this case as being inconclusive, stating that the second episode could have been related to a worsening of the patient's congestive heart failure.

One patient experienced an anaphylactic reaction following administration of a single oral dose of acetazolamide following surgery for glaucoma.[51] Following his recovery, a skin test with a "sulfonamide" solution was administered, which was positive. The authors concluded that the reaction could have been caused by a previously unknown "sulfonamide" allergy and the reaction represented a cross sensitivity to acetazolamide, since acetazolamide is a "sulfonamide" derivative. The authors supported this conclusion by citing a case report[47] that did not assess cross-reactivity and a study[11] that evaluated the lymphocyte toxicity assay in patients with a hypersensitivity to sulfonylarylamines, not acetazolamide. Anaphylaxis to a drug without prior exposure would be unusual.[52] While the authors stated that the patient had not received acetazolamide prior to the event, no other medication history was provided. Likewise, the positive "sulfonamide" skin test would indicate prior exposure to a sulfonylarylamine, possibly several years prior to the positive result.[53] Acetazolamide, a nonsulfonylarylamine, does not have the chemical structure

Figure 2. **Chemical structures of sulfonamides.** (***continued on page xxx***)

necessary to cross-react with an IgE-mediated sulfonylarylamine reaction.[10,53,54] The positive "sulfonamide" skin test in this patient may only represent a concurrent IgE-mediated

sulfonylarylamine allergy unrelated to acetazolamide.

Sulfonylureas

Seven sulfonylureas were identified in the search (Table 1). None of the MPIs[17-23] include a statement concerning their use in patients with a sulfonylarylamine allergy. The literature search revealed 4 articles: 3 case reports and one case series. One case report[55] was excluded because the patient did not have a known sulfonylarylamine allergy and cross-reactivity was not assessed.

Two patients receiving a sulfonylurea developed systemic contact dermatitis following exposure to a sensitizing topical para-amino compound.[56] One patient who had been taking tolbutamide for 6 years was treated with a sulfanilamide vaginal cream for 2 weeks and then developed a severe pruritic, edematous, eczematous eruption of the vulvar area. She had a positive skin test to sulfanilamide. The reaction did not resolve until tolbutamide was discontinued.

Upon rechallenge with a single dose of tolbutamide, the eruption recurred. Therapy was changed to chlorpropamide, which was tolerated without difficulty. The second patient had been taking chlorpropamide for 7 years and experienced severe contact dermatitis following the application of a topical benzocaine preparation. Similar to the first case, the reaction did not resolve until chlorpropamide was discontinued. Evaluation of the reaction in the second patient was limited to a positive skin patch test with chlorpropamide since the patient refused oral rechallenge with either a sulfonylarylamine or sulfonylurea. The authors incorrectly stated that all oral hypoglycemic compounds (chlorpropamide and tolbutamide at the time) are "paraamino sulfonamides" although neither compound is a sulfonylarylamine (Figure 2). The authors concluded that exposure to a sensitizing para-amino compound, sulfanilamide in the first case and benzocaine in the second case, produced the contact dermatitis during concomitant use of a sulfonylurea.

Given this explanation, it is unclear why the patient in the first case could tolerate chlorpropamide but not tolbutamide. In support of their argument, the authors cited an earlier study which showed that the incidence of cross-reactivity between sulfanilamide and sulfonylureas using an oral challenge is lowest with chlorpropamide.[57] Oral challenge tests in this earlier study with other para-amino compounds were all negative. The results of that study would seem to refute the authors' assertion in the second case that exposure to para-amino compounds such as benzocaine would sensitize a patient to either sulfonylarylamines or sulfonylureas.

Figure 2 (continued). **Chemical structures of sulfonamides.** (***continued on page xxx***)

Bukhalo et al.[58] described a patient with a known allergy to sulfamethoxazole who was prescribed glyburide, resulting in a cutaneous rash 2 days later. A skin biopsy showed leukocytoclastic vasculitis (LCV), an immune complex reaction,

[3] **which the authors concluded represented a crossreaction to glyburide. This conclusion is questionable given the data presented. For example, the authors stated that LCV is caused by drugs in only 13% of cases and, in those cases, typically develops 7–10 days after treatment is started. Secondly, the patient was also taking furosemide,**

Figure 2 (continued). **Chemical structures of sulfonamides. COX-2 = cyclooxygenase 2. (*continued on page xxx*)**

which has also been reported to cause angiitis and LCV.[59] **Thirdly, the LCV reaction could have been due to glyburide alone since this reaction has been reported in a patient without a concurrent sulfonylarylamine hypersensitivity.** [60] **Finally, the authors described sulfamethoxazole and glyburide as being structurally similar, when in fact glyburide is not a sulfonylarylamine (Figure 2).**

In a survey of 82 clinic patients taking a sulfonylurea, 34 reported having taken a sulfonylarylamine in the past, with 7 patients reporting an allergic reaction.[61] **Two patients developed a rash following the start of therapy with the sulfonylurea, only one of whom had a previous reaction to a sulfonylarylamine. The authors suggested that precluding the use of sulfonylureas in patients with a "sulfonamide" allergy may not be warranted. Any commentary is limited given the observational design, the low number of patients, and the reliance on self-reporting of allergic reactions.**

Loop Diuretics

Three loop diuretics were identified in the search (Table 1). The MPIs for furosemide[24] **and bumetanide**[26] **contain a statement that patients may also be allergic to these drugs if they are allergic to "sulfonamides." The torsemide MPI lists a contraindication to sulfonylureas but does not mention sulfonylarylamines.**[25] **Conversely, none of the MPIs for the sulfonylureas contains a statement concerning the concurrent use of torsemide. The literature search revealed 2 case reports and one abstract.**

A "sulfonamide"-naïve patient experienced diffuse urticaria, periorbital edema, and hypotension 5 minutes after receiving an intravenous dose of furosemide.[62] **The patient had taken hydrochlorothiazide 5 years prior to the event for an unknown length of time. The hypersensitivity reaction was evaluated using skin prick and graduated intradermal injections of chlorothiazide, ethacrynic acid, furosemide, trimethoprim/sulfamethoxazole (TMP/SMX), and bumetanide with positive and negative controls. The patient had a positive reaction at the most concentrated intradermal dose to all except ethacrynic acid. The authors concluded that sensitization to furosemide occurred during the patient's prior exposure to hydrochlorothiazide and that the positive skin tests suggested a cross-reaction between the 2 compounds since they share the same sulfonamide nucleus (Figure 2). This one case report is the cornerstone of the controversy surrounding the use of furosemide in patients with a sulfonylarylamine allergy.**[3-6,63-65] **Tilles**[4] **described it as an example**

of a patient having a serious adverse reaction to

Figure 2 (continued). **Chemical structures of sulfonamides.**

more than one class of "sulfa" drugs, which was not the case since the patient developed the reaction only following the administration of furosemide and had tolerated hydrochlorothiazide for some time in the past. Patterson et al.[63] cited the case as a reason to question whether cross-reactivity exists, since an oral rechallenge with the possible offending agents was not undertaken. Sullivan[64] also used the same case report to support his conclusion that the absolute risk of cross-reaction is low and that if alternative therapy with structurally unrelated compounds is not possible, patients could be administered these related compounds with appropriate monitoring.

Another case report described a torsemide desensitization protocol for a patient with a history of Stevens–Johnson syndrome while receiving TMP/SMX who developed a rash upon administration of furosemide.[66] While limited information was presented concerning the adverse event during the administration of furosemide, this case would seem to support the concept that cross-reactivity can occur between furosemide and sulfonylarylamines. However, this case describes exactly the type of patient whom others[3-5] have indicated are at increased risk for a hypersensitivity reaction: those with serious allergic reactions to medications and/or multiple drug allergies.

Barrio et al.[67] investigated cross-reactivity between sulfamethoxazole, sulfadiazine, sulfametizole, furosemide, and procaine in 33 patients with a history of either urticaria and angioedema or a fixed drug eruption from a sulfonylarylamine. Using an oral challenge, the authors were unable to elicit a reaction to either furosemide or procaine despite an 85.7% positive response to sulfamethoxazole and a 14.3% positive response to sulfadiazine. The nature of the positive response was not described. The authors concluded that cross-reactivity between sulfonylarylamines and furosemide did not occur.

Thiazide Diuretics and Related Compounds

Thiazide diuretics and other related compounds including indapamide, chlorthalidone, metolazone, and diazoxide were found in the search (Table 1). The MPIs for all of these medications list "sulfonamide-derived" medications in either the contraindication or warning sections[27-32]; however, the only specific drugs mentioned are metolazone and diazoxide, which list thiazide diuretics.[30,32] The manufacturer of metolazone could not provide information

supporting the inclusion of this class of medications. The literature search revealed one case series and 2 case reports, all pertaining to indapamide.

Thirteen patients experienced a skin rash during therapy with indapamide.[68] Eleven of these patients later took chlorthalidone, hydrochlorothiazide, furosemide, epitizide, or clopamide without recurrence of the rash. The authors concluded that the allergic reaction to indapamide was due to a reactive intermediate metabolite unrelated to the sulfonamide side chain, since the patients tolerated other nonsulfonylarylamine compounds.

DeBarrio et al.[69] described a patient without any medication allergy history who developed an intermittent fixed drug eruption (FDE) with indapamide and then underwent an oral chal-

Table 1. **Manufacturer's Package Insert Information for Sulfonamide-Containing Medications**

Drug Class	Presence	Content[a]	Manufacturer's Package Insert Statement Location
Carbonic anhydrase inhibitors			
acetazolamide[13]	**yes**	**A**	**warnings**
brinzolamide[16]	**yes**	**A**	**warnings**
dorzolamide[15]	**yes**	**A**	**warnings**
methazolamide[14]	**yes**	**A**	**warnings**
Sulfonylureas			
acetohexamide[19]	**no**		
chlorpropamide[18]	**no**		
glimepiride[21]	**no**		
glipizide[22]	**no**		
glyburide[23]	**no**		
tolazamide[20]	**no**		
tolbutamide[17]	**no**		
Loop diuretics			
bumetanide[26]	**yes**	**B**	**warnings**
furosemide[24]	**yes**	**B**	
torsemide[25]	**no**	**C**	**precautions**
Thiazide diuretics and related compounds			
chlorthalidone[29]	**yes**	**D**	**contraindications**
diazoxide[32]	**yes**	**D**	**contraindications**
hydrochlorothiazide[27]	**yes**	**D**	**contraindications**
indapamide[30]	**yes**	**D**	**contraindications**
methyclothiazide[28]	**yes**	**D**	**contraindications**
metolazone[31]	**yes**	**D**	**warnings**
5-HT$_3$ receptor antagonists			
naratriptan[34]	**no**		
sumatriptan[33]	**no**		
COX-2 inhibitors			
celecoxib[35]	**yes**	**B**	**contraindications**
rofecoxib[36]	**no**		
valdecoxib[37]	**yes**	**B**	**contraindications**
Other compounds			
amprenavir[38]	**yes**	**B**	**contraindications**
dapsone[44]	**no**		
fosamprenavir[39]	**yes**	**B**	**precautions**
ibutilide[41]	**no**		
probenecid[45]	**no**		
sotalol[42]	**no**		
topiramate[43]	**no**		
zonisamide[40]	**yes**	**B**	**precautions**

COX-2 = cyclooxygenase 2.

[a]**A = Due to severe reactions to sulfonamides, sensitizations may recur when a sulfonamide**

is readministered.
B = Contraindicated in patients with known sulfonamide allergy.
C = Contraindicated in patients with a known hypersensitivity to sulfonylureas.
D = Hypersensitivity to other sulfonamide-derived drugs.

lenge test with sulfamethoxazole, sulfadiazine, and furosemide. The FDE lesion recurred with the 2 sulfonylarylamines. The authors concluded that the reaction was due to a metabolite of indapamide but also advised that all other sulfonylarylamine agents be avoided.

A patient with a known hypersensitivity to "sulfonamides" developed toxic epidermal necrolysis following 16 days of therapy with indapamide.[70] The patient had tolerated hydrochlorothiazide for 16 months without difficulty prior to this event. The authors suggested that molecular differences between hydrochlorothiazide and indapamide increased the hypersensitivity potential of the latter medication in a "sulfonamide"-allergic patient but then went on to state that the reaction may be totally unrelated to the "sulfonamide" allergy.

5-HT_{1D} Agonists

Both sumatriptan and naratriptan are sulfonamide moiety–containing medications (Figure 2). The MPIs for these compounds do not contain any statement about their use in patients with a sulfonylarylamine allergy.[33,34]

Newman et al.[71] conducted a retrospective chart review of 15 patients with prior allergic reactions to a "sulfonamide" who were prescribed sumatriptan. The type of allergic reactions included angioedema, rash, urticaria, fever, photosensitivity, and severe headache. None of the patients reported an adverse event during sumatriptan therapy. The authors concluded that sumatriptan could be used in patients allergic to sulfonylarylamines.

COX-2 Inhibitors

The selective cyclooxygenase 2 (COX-2) inhibitors have generated the largest number of studies concerning their use in patients with a sulfonylarylamine allergy. Only the MPIs for valdecoxib[37] and celecoxib[35] contain a statement concerning their use in patients with a "sulfonamide" allergy.

Celecoxib, rofecoxib, and valdecoxib have all been implicated in at least one case report (Table 2).

A review of the case reports highlights the difficulties in defining cross-reactivity between sulfonylarylamines and COX-2 inhibitors, despite the conclusions of some of the authors. In the first case report, the authors concluded that patients with a celecoxib allergy should avoid sulfonylarylamines, despite skin testing that showed no cross-reaction.[72]

In the second case report, the authors stated that celecoxib and glyburide can illicit a hypersensitivity reaction similar to that caused by sulfonylarylamines because the 3 drugs are structurally related.[73] However, neither celecoxib nor glyburide contains either of the necessary chemical structures for a sulfonylarylamine-related immunologic or hypersensitivity reaction.[1,10] The authors' conclusion that the patient developed a hypersensitivity reaction to celecoxib

Table 2. **Summation of COX-2 Case Reports**

Description	Evaluation	Conclusion
2 pts. with erythematous skin rash scratch tests for celecoxib negative in both pts. who develop a maculopapular rash with following start of celecoxib therapy; pts.; patch test for celecoxib positive in celecoxib should be tested for sulfonamide hyperneither had a past history of ADR to patient A and unknown in patient B; LTT with sensitivity and a drug-specific allergy to celecoxib; sulfonamides[72] celecoxib positive in patient B and unknown pts. with celecoxib allergy should avoid sulfonamides in patient A; scratch and patch for sulfon- and vice versa amides negative in both pts.		
Pt. with "sulfa" allergy experienced IgE 318 U/mL (10–180), normal rheumatoid reaction indicated celecoxib hypersensitivity with erythema multiforme 25 days after factor, complement 3, and complement 4 after subsequent cross-reaction to glyburide introduction of celecoxib; pt. also re- second exposure to glyburide ceiving HCTZ and glyburide; rash recurred on 2 subsequent exposures to glyburide and HCTZ[73]		
Pt. with sulfonamide allergy developed oral provocation test with rofecoxib and TMP/ pts. with FDE to rofecoxib should be tested for FDE on 2 subsequent exposures to SMX at 1/4 usual dose with a positive result drug-specific allergy to rofecoxib and sulfonamides rofecoxib[74]		
Pt. with sulfonamide allergy developed none caution when prescribing valdecoxib in pts. with docu- TEN after 8 days of valdecoxib[75] mented sulfonamide allergy		
Pt. with sulfonamide allergy developed none pancreatitis may have represented an allergic reaction acute pancreatitis 2 days after starting since sulfonamides are known to cause pancreatitis celecoxib[76]		
Pt. with sulfonamide allergy developed none hypersensitivity reaction similar to that seen with sulcholestatic hepatitis 3 wk after starting fonamide-induced hepatitis celecoxib[82]		
Pt. with history of vomiting and vertigo scratch and patch test negative and LTT posi- either independent sensitization to the 2 drugs or a with TMP/SMX experienced vomiting, tive for both drugs; pt. refused oral provocation real cross-reactivity cited as possible causes flushing, shivering, loss of conscious- test ness 30 min after ingestion of celecoxib[78]		

ADR = adverse drug reaction; COX-2 = cyclooxygenase 2; FDE = fixed drug eruption; HCTZ = hydrochlorothiazide; IgE = immunoglobulin E; LTT = lymphocyte transformation test; TEN = toxic epidermal necrolysis; TMP/SMX = trimethoprim/sulfamethoxazole.

because of an underlying sulfonylarylamine hypersensitivity that subsequently sensitized the patient to glyburide assumes many metabolic and immunologic processes that are not supported by data. The authors also did not comment on the fact that the patient experienced the reaction on 2 other occasions while not taking either of the medications.

The third case report also attempts to link concurrent hypersensitivity reactions to rofecoxib and sulfonylarylamines because of similarities in chemical structure.[74] The authors incorrectly stated that rofecoxib has a sulfonamide moiety when, in fact, it is a sulfone (Figure 2). They pointed out that the MPI for rofecoxib does not contain any warning statement concerning administration in patients with a sulfonylarylamine allergy, but then go on to conclude that rofecoxib may be contraindicated in these patients despite a lack of data.[36] The authors of the fourth case, while stating that valdecoxib lacks the sulfonylarylamine group necessary for a hypersensitivity reaction, concluded that such a reaction occurred in their patient.[75] The authors based their conclusion on 2 of the previously discussed case reports[73,74] and the review by Knowles et al.,[3] which does not support the concept of cross-reactivity

between sulfonylarylamines and non-sulfonylarylamines. In the fifth case report, the authors concluded that celecoxib caused pancreatitis because the condition resolved when celecoxib was discontinued and "sulfonamides" are known to cause pancreatitis.[76] The patient was also taking a thiazide diuretic that has a well-known association with acute pancreatitis.[77] The case report does not state whether the thiazide diuretic was continued during the episode.

In a case report of a patient receiving celecoxib, the authors stated that the clinical presentation and biochemical pattern of the observed cholestatic hepatitis was similar to that seen with sulfonylarylamines.[78] Hepatotoxicity from sulfonylarylamines may be a part of the systemic hypersensitivity reaction that is associated with the sulfonylarylamine group that is not present in celecoxib. Also, cholestatic hepatitis due to celecoxib alone has been reported in several patients without a concurrent "sulfonamide" hypersensitivity,[79-81] so their conclusion that a "sulfa" allergy may increase the risk of this type of reaction is questionable. Shuster and Wuthrich[82] admitted that their patient may have had 2 independent hypersensitivities but still caution that patients with a "sulfonamide" allergy should not take celecoxib.

In an effort to quantify the incidence of allergic reactions in patients taking celecoxib, Patterson et al.[63] performed 3 meta-analyses using data from 14 randomized controlled trials involving 11 008 patients. In the first metaanalysis, patients with a reported allergy to sulfonylarylamines and non-sulfonylarylamines, such as furosemide, thiazide diuretics, or sulfonylureas, who received celecoxib (n = 73), a placebo (n = 32), or an active comparator (n = 30) were included. There was no statistically significant difference (Fisher's exact test) between the 3 groups in potential allergic events, pruritus, rash, or skin disorders. The second meta-analysis compared patients taking celecoxib with and without other non-sulfonylarylamines such as loop diuretics, thiazide diuretics, and sulfonylureas. The third meta-analysis evaluated the overall incidence of allergic reactions to celecoxib versus the active comparators in each study and found no statistically significant findings. Based upon the findings of the 3 meta-analyses, the authors concluded that the risk of cross-reactivity between celecoxib and other "sulfonamides" is no greater than that seen with placebo or other comparators.

A prospective study assessed the incidence of cross-reactivity in 28 patients with a self-reported history of sulfonylarylamine allergy who then received celecoxib.[65] The sulfonylarylamine allergy was assessed by either skin prick, intradermal testing, and/or lymphocyte toxicity assay (LTA) using TMP/SMX. Positive reactions occurred in 4 of 28 patients administered a skin test and 2 of 10 patients evaluated by LTA. Patients with a negative skin test (n = 20) received an oral challenge with TMP/SMX. All patients underwent a low- and high-dose oral challenge

test with celecoxib without any adverse events. Follow-up in 25 patients showed that 15 (60%) continued to tolerate therapy with celecoxib, 5 did not take celecoxib after the oral challenge, and 5 discontinued celecoxib therapy secondary to adverse effects. In the 6 patients with a positive skin test, 4 continued to take celecoxib, one discontinued therapy secondary to gastrointestinal adverse effects, and one did not take the drug after the oral challenge upon the advice of the primary care physician. The authors concluded that the risk for cross-reactivity of celecoxib in patients with a sulfonylarylamine allergy is low.

Other Drugs

No studies or case reports concerning the use of amprenavir in patients with a sulfonylarylamine allergy were found during the literature search. The amprenavir[38] and fosamprenavir[39] MPIs contain a precaution that both medications are sulfonamides and that the potential for cross-reactivity with other "sulfonamides" is unknown. The manufacturer reports that 16 patients with a history of "sulfonamide" allergy were prescribed amprenavir during the initial clinical trials. Of these, 5 (31%) experienced a rash, resulting in permanent discontinuation of amprenavir in 2 patients. Concurrent therapy with abacavir may have contributed in 2 of the cases that did not require permanent discontinuation.[83] The manufacturer also cited an abstract by Shelton et al.[84] describing 66 "sulfonamide-experienced" patients who received amprenavir. Nineteen of these patients had a history of a rash with "sulfonamides." Seven (37%) patients developed a rash while receiving amprenavir compared with 10 of 46 (22%) patients with no "sulfonamide" rash history (p = NS). Thirteen of the 17 patients who experienced a rash received concurrent therapy with efavirenz and/or abacavir. The use of amprenavir and a "sulfonamide" concurrently did not appear to increase the risk of rash in clinical trials: 15% compared with 22% incidence of rash in patients receiving amprenavir alone.[83]

No studies or case reports were found during the literature search concerning the use of zonisamide in patients with a sulfonylarylamine allergy. The zonisamide MPI lists

a contraindication in patients with a known hypersensitivity to "sulfonamides."[40] The manufacturer provided 2 references.[85] Ritter et al.[86] reported 8 patients with a sulfonylarylamine allergy who also received zonisamide for up to 29 months. No patient experienced a rash or other hypersensitivity reaction during therapy. No cross-reaction between zonisamide and sulfonylarylamines was identified using a zonisamide graduated skin test in 2 patients with a history of an allergic reaction to TMP/SMX and an unspecified "sulfonamide."[87] It is unknown whether oral challenge with zonisamide was performed. The authors concluded that a previous history of "sulfa" allergies may

not result in zonisamide cross-reactivity.
No studies were found for the other sulfonamide moiety–containing medications listed in Figure 1.

Discussion

The controversy surrounding cross-reactivity between sulfonylarylamines and non-sulfonylarylamines and sulfonamide moiety–containing drugs began with the publication of the first case report involving acetazolamide in 1955[49] and continues 50 years later. After a thorough examination of the literature, we believe that the dogma of sulfonylarylamine cross-reactivity with non-sulfonylarylamines is not supported by the data.

The drug class with the most data, the COX-2 inhibitors, is relatively new. We believe it is noteworthy that, despite this close association, celecoxib and valdecoxib, both nonsulfonylarylamines, do not have data to support a concern for cross-reactivity.

Stock[50] attempted to clarify the issue concerning acetazolamide based upon 2 case reports, neither of which substantiated a concern for cross-reactivity. The sulfonylureas also have inconclusive case reports. The concern for crossreactivity with loop diuretics, as discussed previously, lies with only one case report. In 1983, Schneiweiss[88] evaluated the available data for this drug class and concluded that patients with a sulfonylarylamine allergy could probably receive furosemide with close monitoring. The thiazide diuretics, with the exception of indapamide,[69] do not have data to support a concern for cross-reactivity.

We conclude that, while many of the case reports initially support the concept of cross-reactivity, on closer examination, the level of evidence does not convincingly support an association between the observed cause and effect in many of the cases. This conclusion is supported by the most rigorous study to date, which concluded that a predisposition to allergic reactions is the primary risk factor for the association, not a true cross-reactivity.[5]

Summary

In the past, clinicians have been left with difficult decisions regarding "sulfa" allergy cross-reactivity issues due to vague and inconsistent warning statements found in MPIs, with few data to support those statements. We suggest a new paradigm: patients with a sulfonylarylamine allergy can be administered non-sulfonylarylamine and/or sulfonamide moiety–containing medications with appropriate monitoring if alternative therapy with structurally unrelated compounds is not plausible. The exception is patients with serious allergic reactions and/or multiple medication allergies.

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EXTRACTO

OBJETIVO: **La relevancia de la sensibilidad cruzada entre medicamentos en personas con alergia a sulfamidas dificulta las decisiones clínicas cuando se tiene que considerar la seguridad de los pacientes. El objetivo principal de este artículo es realizar una revisión crítica y amplia de la literatura científica, particularmente de los estudios de casos y los estudios observacionales que apoyan el concepto de la sensibilidad cruzada entre las sulfonilarilaminas y las no-sulfonilarilaminas.**

FUENTES DE INFORMACIÓN: **Se preparó una lista de medicamentos utilizando diferentes artículos de revisión. Se hizo una búsqueda a través de los sistemas MEDLINE/PubMed utilizando la lista individual de los medicamentos y los términos MESH "hipersensibilidad a medicamento/etilogía," "sulfamidas/efectos adversos," y/o "reacción cruzada."**

SELECCIÓN DE ESTUDIOS Y OBTENCIÓN DE LOS DATOS: **Se llevó a cabo una revisión crítica de los métodos y las conclusiones de cada artículo encontrado en la literatura médica. También se evaluó la aseveración sobre posible sensibilidad cruzada en pacientes con alergia a sulfamidas en el prospecto del fabricante (manufacturer's package insert-MPI) de cada medicamento. Si era necesario, se contactaba con el fabricante para obtener información clínica que apoyara dicha aseveración.**

SÍNTESIS DE LOS DATOS: **Se identificaron un total de 33 medicamentos. En 17 (51.5%) de los prospectos, había una afirmación relacionada con el uso del medicamento en pacientes con alergia a "sulfamida." También, se encontraron 21 series de casos, notificaciones de casos, y otros artículos relacionados.**

CONCLUSIONES: **El dogma de una sensibilidad cruzada de sulfonilarilaminas con no-sulfonilarilaminas no se sostiene tras una evaluación completa y crítica de la literatura médica. Los autores concluyen que, aunque muchos de los informes de casos superficialmente apoyan el concepto de sensibilidad cruzada, al realizar una evaluación exhaustiva de los mismos, el nivel de evidencia científica no apoya definitivamente la conexión o asociación entre causa y efecto observado en la mayoría de los casos.**

Mirza D Martinez

RÉSUMÉ

OBJECTIF: **L'importance clinique de la réactivité croisée entre médicaments chez une personne allergique aux sulfamidés continue de rendre les cliniciens perplexe et de compliquer les décisions concernant la sécurité des patients. L'objectif premier de cet article est de faire une révision critique et étendue de la littérature, spécialement des rapports de cas et des études d'observation utilisés pour supporter le concept de réactivité croisée entre les sulfonylarylamines et les nonsulfonylarylamines.**

REVUE DE LITTÉRATURE: **Une liste de médicaments a été formulée à partir de plusieurs articles de revue. Une recherche MEDLINE/Pubmed a été réalisée en utilisant le nom de chacun des médicaments et les termes "drug hypersensitivity/etiology," "sulfonamides/adverse effects," et/ou "cross-reaction."**

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: **Une révision critique de la méthodologie et des conclusions a été réalisée pour chacun des articles retrouvés lors de la recherche. Les monographies de chacune des médications ont été révisées pour déterminer si elles contenaient un avis d'allergie croisée possible chez les patients connus allergiques à un sulfamidé. Si tel était le cas, les manufacturiers étaient contactés pour obtenir les données cliniques supportant cet avis.**

RÉSUMÉ: **Un total de 33 médicaments ont été identifiés. Dix-sept (51.5%) monographies contenaient des avis d'importance variable concernant l'utilisation du médicament chez les patients ayant un antécédent d'allergie aux sulfamidés. Trente et une séries de cas, rapports de cas, et autres articles ont été retrouvés.**

CONCLUSIONS: **Après une revue approfondie de la littérature, il semble que les données ne corroborent pas le dogme de réactivité croisée entre les sulfonylarylamines et les non-sulfonylarylamines. Les auteurs concluent que bien que plusieurs rapports de cas supportent superficiellement le concept de réactivité croisée, un examen plus poussé du niveau d'évidence ne supporte pas de façon concluante un lien ou une association de cause à effet dans la plupart des cas.**

Marie Larouche

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Caspofungin and amphotericin B for disseminated *Fusarium verticillioides* in leukemia

TO THE EDITOR: Disseminated *Fusarium* causes significant morbidity and mortality in patients with hematologic malignancies.[1] Recent clinical and in vitro data suggest caspofungin may have a role in the treatment of refractory *Fusarium* infection.[2,3] As of June 2, 2005, we report the first case of a partial response of disseminated *Fusarium* infection to combination amphotericin B and caspofungin in a patient with refractory acute lymphocytic leukemia (ALL).

Case Report. **A previously healthy 54-year-old male admitted for chemotherapy for ALL first complained of right eye pain 12 days after starting chemotherapy. A subsequent computed tomography (CT) scan revealed acute sinusitis, and antibiotics were initiated. Six days later, the patient experienced photophobia and diplopia, and amphotericin B 0.5 mg/kg was started for presumed fungal sinusitis. One day later, the patient developed subcutaneous nodular skin lesions on his leg. A biopsy revealed *Fusarium* spp., and the amphotericin B dose was increased to 1 mg/kg/day (day 22).**

A bone marrow biopsy 3 weeks after initiation of chemotherapy revealed refractory leukemia, and on day 25, a low-dose salvage chemotherapy regimen was commenced. On day 32, a sinus biopsy revealed inflamed mucosa with rare hyphae consistent with *Fusarium*. Five days later, after 12 days of conventional amphotericin B followed by 8 days of amphotericin B lipid complex (ABLC), the patient was febrile and continued to develop skin lesions. Intravenous caspofungin 50 mg every 24 hours was initiated. After 4 days of combination therapy, the patient defervesced and no new skin lesions appeared. By day 45, he was afebrile and his skin lesions decreased in size despite an absolute neutrophil count of 0.4 · 10^9/L (Figure 1). Subsequently, a 4-day course of granulocyte colony-stimulating factor (G-CSF) was administered. Five days later, the patient's skin lesions continued to decrease in number and he was discharged on ABLC 5 mg/kg and caspofungin 50 mg every 2 days. The skin biopsy culture identified *Fusarium verticillioides* with a minimum inhibitory concentration of amphotericin B of 2 _g/mL. The patient continued to improve and, on day 69, oral voriconazole 200 mg twice daily was started and intravenous therapy was discontinued. Thirteen days later, the patient experienced recurrent sinus pain, and a CT scan showed worsening sinusitis with bony dehiscence. Partial debridement of the sinuses was conducted on day 89. Although the fungal cultures were negative and histology was not performed, alternate-day ABLC and caspofungin were reinstituted. Voriconazole was discontinued. On day 91, circulating blasts were noted and a bone marrow biopsy confirmed progressive ALL. Shortly thereafter, the patient died from progressive ALL and disseminated fusariosis.

Discussion. **Our case highlights 3 important points: (1) our patient's lack of response to single-agent amphotericin B emphasizes the need for new strategies to treat disseminated *Fusarium* infection, (2) his partial response to combination therapy prior to the initiation of G-CSF supports the limited in vitro evidence of synergy between caspofungin and amphotericin B against *Fusarium* as demonstrated by Arikan et al.,[2] and (3) recovery of normal hematopoiesis is critical in the treatment of disseminated fusariosis. We suggest that combination caspofungin and amphotericin**

B therapy may be considered in amphotericin B– refractory fusariosis in patients with hematologic malignancies.

Figure 1. **Peripheral blood cell counts and drug therapy. ABLC = amphotericin B lipid complex; AmB 0.5 = amphotericin B deoxycholate 0.5 mg/kg; AmB 1 = amphotericin B deoxycholate 1 mg/kg; ANC = absolute neutrophil count; Caspo = caspofungin; Fluc = fluconazole; G-CSF = granulocyte colony-stimulating factor.**

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Hemodialysis clearance of metronidazole following overdose

TO THE EDITOR: Hemodialysis clearance of metronidazole following standard therapeutic dosing has been previously described.[1] **Studies have documented hemodialysis clearance rates ranging from 24% to 45% of therapeutic doses of metronidazole administered either orally or intravenously.**[2,3] **Metronidazole pharmacokinetics are favorable for hemodialysis; peak oral absorption occurs within 1–2 hours; volume of distribution is 0.51–1.1 L/kg; protein binding is <20%; the half-life is 6–14 hours; 6–18% is excreted unchanged in the urine; and the molecular weight is 171.**[4] **Metronidazole also undergoes extensive hepatic metabolism, and its kinetics are unaltered in renal disease.**

A MEDLINE search from 1966 to May 2005 using the terms metronidazole, kinetics, dialysis, and related search terms was performed, and no studies or case reports of metronidazole clearance by hemodialysis following acute or acute-on-chronic overdose were found. To our knowledge,

as of May 2005, this is the first reported case showing the hemodialysis clearance of metronidazole after acute-on-chronic overdose.

Case Report. **A 62-year-old, 76-kg man ingested 17 tablets of metronidazole 500 mg (8.5 g) in a therapeutic error. The patient had an extensive past medical history, including end-stage renal disease requiring multiple daily medications and dialysis 3 times per week. The overdose occurred on the morning of his scheduled dialysis. The patient had taken 4 doses of metronidazole over the previous 2 days (one tablet twice a day).**

The poison center was contacted 5 hours after ingestion. No gastrointestinal decontamination was recommended or performed. The recommendation was to continue with routine scheduled hemodialysis. Pre-dialysis blood urea nitrogen was 80 mg/dL, serum creatinine 9.2 mg/dL, and aspartate aminotransferase 21 U/L. It was requested that pre- and post-dialysis serum metronidazole concentrations be obtained to determine the clearance of metronidazole by hemodialysis in the overdose setting. The pre-dialysis venous metronidazole concentration was 120 _g/mL (9.5 h after ingestion). The patient underwent 4 hours of dialysis with a Fresenius 2008H machine at a blood flow rate of 450 mL/min using an Optiflux 200NR dialyzer at a dialysate flow rate of 800 mL/min. The post-dialysis venous metronidazole concentration was 32 _g/mL one hour after dialysis. All drug assays were performed by HPLC. The expected peak concentration following a single 250-mg dose is 5.1 ± 1.7 _g/mL, and the expected concentration following a 2-g dose is 40.6 ± 9.3 _g/mL.[5] The assays of hydroxy and acetic acid metabolites were not determined. The patient was stable the entire time and did not demonstrate any evidence of metronidazole toxicity such as nausea, vomiting, diarrhea, impairment of the central nervous system or peripheral nervous system, or hepatotoxicity.

Discussion. **Previous studies have documented hemodialysis clearance rates of 24– 45% of therapeutic doses of metronidazole administered orally or intravenously.[2,3] Following an 8.5-g acute-on-chronic ingestion of metronidazole, a standard 4-hour dialysis procedure (along with endogenous hepatic metabolism) demonstrated a significant reduction in blood concentrations of 73.3% with an approximate half-life of 2.5 hours. Assuming complete oral absorption, nearly one half-life elapsed prior to dialysis. The patient had a volume of distribution of 0.6 L/kg and steady-state drug concentrations before and after dialysis. The total body metronidazole concentration fell from 5.5 to 1.5 g (4 g) or 47% of the ingested 8.5-g dose. This is within range of therapeutic hemodialysis clearance of metronidazole.[3]**

Hemodialysis is not routinely recommended following metronidazole overdose. We speculate, however, that early hemodialysis in this patient with end-stage renal disease may have prevented neurologic toxicity by avoiding prolonged high concentrations of the potentially neurotoxic hydroxyl metabolite.

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Efficacy and tolerability of levetiracetam treatment in an epileptic patient with SLE

TO THE EDITOR: Systemic lupus erythematosus (SLE) is an autoimmune disease that involves the central nervous system with seizures, stroke, headache aseptic meningitis, transverse myelitis, psychosis, and cognitive dysfunction in 25–75% of patients.[1,2] A higher frequency of adverse reactions in patients with SLE has also been described.[3-5] We report a case of a young woman with SLE and complex partial epileptic manifestations responsive to levetiracetam treatment.

Case Report. **A 28-year-old woman taking prednisone 12.5 mg/day for SLE manifestations was admitted to a Cosenza hospital because she developed 2 episodes per week of mental confusion. There was no history of alcohol or other drug abuse, and there was no significant past medical or surgical history. A 24-hour electroencephalogram (EEG) showed left fronto-temporal spike discharges with contralateral spread. Therefore, the diagnosis of complex partial seizure was made, and oxcarbazepine 300 mg every 12 hours was started. Ten days later, the woman was discharged home on a regimen of prednisone 12.5 mg/day and oxcarbazepine 300 mg every 8 hours.**

Five days after discharge, she was readmitted because of a complex partial seizure. Blood chemical analysis revealed a clinically significant decrease in total white blood cells (from 4.2 to 2.9 · 10^3/mm^3; reference range 4.0–11.0). Oxcarbazepine was promptly discontinued and topiramate 50 mg every 12 hours was initiated. Seven days later, a new blood evaluation revealed a normalization of the white blood cell count (4.1 · 10^3/mm^3). On hospital day 10, the patient was discharged on prednisone 12.5 mg/day and topiramate 100 mg every 12 hours. After 25 days from the beginning of topiramate therapy (final dose 150 mg every 12 hours), an ambulatory follow-up visit documented a remission of the seizure activity, with a normalization of blood chemical findings. About 5 days later, the patient developed drowsiness, irritation, and blurred vision. An ophthalmologic examination showed angle-closure glaucoma with acute myopia and ocular hyperemia; therefore, topiramate was withdrawn. The patient began home treatment with phenobarbital 100 mg every 12 hours and then recovered within 2 days.

Seven days later, a new ambulatory outpatient laboratory analysis showed a decrease in platelet cells (from 165 to 139 · 10^3/mm^3; reference range 150– 450), which prompted discontinuation of phenobarbital with the beginning of levetiracetam treatment (500 mg every 12 hours). After 10 days, we recorded a normalization in the platelet count. During the entire period, prednisone therapy was dosed at 12.5 mg/day. After 7 days with no adverse events, the levetiracetam dosage was increased to 1500 mg/day (1000 mg in the morning, 500 mg at night). Two days later, the dose of levetiracetam was increased to 1000 mg every 12 hours, but 15 days later the development of irritability necessitated a reduction of the levetiracetam to 1500 mg/day.

Neurologic evaluation and blood chemical tests performed 6 months later appeared normal without residual seizure activity and did not require dose adjustments of levetiracetam and prednisone or even drug substitution. At present, the patient has not shown any seizures, and no adverse event associated with levetiracetam has been recorded. The present findings suggest that levetiracetam may be useful in treating seizures in epileptic patients with SLE.

Discussion. **Many common adverse reactions produced by anticonvulsant therapy (eg, glaucoma) may also be induced by corticosteroid treatment.[6] It is possible that, in our patient, prednisone was associated with the adverse events. It is unlikely that the events observed could have resulted from the use of prednisone alone since its dosage was stable during the entire series of drug trials. We suggest that levetiracetam may be useful in treating seizures in epileptic patients with SLE.**

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Aripiprazole prescribing and continuation rates during psychiatric hospitalization

TO THE EDITOR: Aripiprazole is an atypical antipsychotic with a unique mechanism of action. Unlike other antipsychotics that are dopamine D_2 antagonists, aripiprazole demonstrates partial dopamine D_2 receptor agonist activity.[1] It is also a partial agonist for serotonin 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors.[2] Due to its unique mechanism and potential for significant market penetration, we set out to describe the prescribing patterns and continuation rates of aripiprazole in an inpatient setting.

Methods. **This was a retrospective analysis of patients admitted to a universitybased psychiatric hospital treated with aripiprazole during a 6-month period after market approval. Drug use data and diagnoses were collected from pharmacy, admission, and discharge summaries.**

Results. **Aripiprazole was prescribed for 80 patients (mean age 36 y). Forty-nine (61%) patients were female and 54 (68%) were white. Psychiatric**

diagnoses included psychotic disorder (48%), bipolar disorder (28%), depressive disorder (14%), and childhood disorders such as attention deficit hyperactivity disorder and conduct disorder (11%). Seventysix (95%) patients had a history of prior psychiatric admissions, and prior use of atypical antipsychotics was documented in 85% of the patients. Lower mean doses were prescribed in the young and the elderly compared with those aged 18–65 years, although these differences did not reach statistical significance (Table 1). Higher doses were prescribed in patients with psychotic and bipolar disorders. Fifty-seven (71%) patients were continued on aripiprazole until hospital discharge. Treatment continuation rates were 75% for patients <18 years of age, 73% for those aged 18–65 years, and 50% for patients aged >65 years (p = 0.37). Aripiprazole continuation rates were 82% for depression, 79% for psychosis, 59% for bipolar disorder, and 56% for childhood disorders (p = 0.22). Discontinuation due to adverse drug events and lack of efficacy was re-

ported in 4 (5%) and 8 (10%) patients, respectively. Reason for drug discontinuation was not specified in 11 (14%) patients.

Discussion. **Aripiprazole was generally well tolerated, with a treatment continuation rate of 71% in this inpatient psychiatric setting. Adverse effects were reported as the reason for drug discontinuation in only 5% of patients. This reported rate may be an underestimate since the reason for drug discontinuation was not recorded in the discharge summaries of 11 patients. Despite this shortcoming, it is important to determine whether continuation rates observed in controlled clinical trials can be achieved in real-world settings. The rate of drug discontinuation due to adverse effects observed in this naturalistic setting was consistent with that described in prospective studies (7–11%).**[3,4]

This evaluation provides some additional insight on dosing of aripiprazole in a real-world setting. In general, lower doses are being prescribed for children in our setting. Appropriate dosing in children has not been clearly delineated, and weight-based dosing has been proposed. In a case report by Davenport et al.,[5] treatment initiation with a standard adult dose of 15 mg caused excessive sedation in a 9-year-old patient. It is evident that more research should be conducted to determine optimal dosing in children.

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Possible colchicine rhabdomyolysis in a fluvastatin-treated patient

TO THE EDITOR: Colchicine is used for the treatment of acute gouty

arthritis and rarely causes rhabdomyolysis.[1] We recently noted a case of rhabdomyolysis that developed after short-term intake of colchicine for acute gouty arthritis in a patient who had been on fluvastatin therapy for 2 years.

Case Report. **A 70-year-old man with hyperlipidemia and gout was admitted to our hospital for rhabdomyolysis and nonoliguric myoglobinuric acute renal failure. He had been taking fluvastatin 80 mg/day for 2 years, and for 10 days before presentation, he had also been taking colchicine 1.5 mg/day for acute gouty arthritis. Three days after initiation of colchicine therapy, the man started reporting stomach ache and nausea. He later developed increasingly severe pains in his arms and legs as well as weakness.**

One month prior to admission, the patient's laboratory data were as follows: serum urea 38 mg/dL, creatinine 0.9 mg/dL, aspartate aminotransferase 17 U/L, and alanine aminotransferase 24 U/L. On admission, axillary temperature was 36 °C, blood pressure 110/50 mm Hg, and heart rate 84 beats/min. He was clinically dehydrated, and his pupils were reactive. Thoraco-abdominal examination was unremarkable. There was no rash or lymphadenopathy. Neurologic examination showed diffuse muscle tenderness and proximal muscle weakness. Relaxation of deep-tendon reflexes was grossly delayed. Electromyography revealed polyphasic action potentials consistent with myopathy. The initial laboratory evaluation is shown in Table 1. Stool examination was unremarkable, and a culture was nega-

Table 1. **Mean Aripiprazole Doses**

Parameter	Pts. (n)	First Dose (mg)	Last Dose (mg)
Age group (y)			
<18	**12**	**11.9**	**12.3**
18–65	**60**	**14.0**	**15.4**
>65	**8**	**11.3**	**13.8**
Diagnosis group			
childhood	**9**	**11.4**	**12.5**
bipolar	**22**	**13.6**	**15.0**
depression	**11**	**12.7**	**12.7**
psychosis	**38**	**13.9**	**15.8**

Table 1. **Daily Laboratory Findings and Diuresis in a Fluvastatin-Treated Patient**

Parameter	Hospital Day 1	2	3	4	5	6	8	9	10	11	12	13	15	19
Hematocrit (%)	**35.6**	**35.4**	**35.8**	**39.5**	**37.2**	**36.2**	**34.1**	**34.8**	**33**	**30**	**29**	**33**	**33**	**30.5**
Sodium (mEq/L)	**140**	**141**	**137**	**137**	**125**	**134**	**136**	**138**	**140**	**139**	**142**	**143**	**142**	**144**
Potassium (mEq/L)	**6.3**	**5.5**	**4.4**	**4.8**	**4.5**	**3.8**	**3.6**	**3.9**	**4.8**	**4.6**	**4.3**	**5.1**	**5.3**	**4.3**
Urea (mg/dL)	**141**	**160**	**155**	**178**	**181**	**197**	**134**	**132**	**106**	**86**	**74**	**74**	**68**	**25**
Creatinine (mg/dL)	**3.8**	**4.0**	**3.9**	**3.7**	**3.3**	**2.2**	**1.4**	**2.3**	**2.2**	**1.9**	**1.8**	**1.7**	**1.6**	**1.4**
CK (U/L)	**37**	**782**	**31**	**350**	**6785**	**3853**	**2160**	**669**	**390**	**213**	**160**	**127**	**122**	**70**
AST (U/L)	**856**	**691**	**493**	**286**	**157**	**103**	**56**	**45**	**38**	**52**	**57**	**49**	**38**	**30**
Calcium (mg/dL)	**9.4**	**9.2**	**9**	**8.8**	**9.1**	**8.8**	**8**	**8.9**	**9**	**9.8**	**9.2**	**9.6**	**10**	**9.8**
Phosphorus (mg/dL)	**3.4**	**4.1**	**3.4**	**4.3**										
Uric acid (mg/dL)	**10.1**	**10.9**	**10.3**	**5.1**	**6.7**									
Serum myoglobin (ng/mL)	**4375**	**164.4**	**39.9**											
Urine myoglobin (ng/mL)	**110**	**3.9**	**0.0**											
Diuresis (mL/day)	**2100**	**5500**	**4350**	**3900**	**3500**	**4250**	**5500**	**5300**	**6050**	**5400**	**5000**	**6100**	**6500**	**4000**

AST = aspartate aminotransferase; CK = creatine kinase.

tive. Results of thyroid function tests and the levels of creatine kinase (CK)–myocardial band, troponin-T, viral markers, and serologic screening were normal.

The patient was treated with an infusion of NaCl 0.9%. Colchicine and fluvastatin were stopped. Intraarticular steroid was administered for acute gouty arthritis. As the patient's urine output increased, serum creatinine and CK decreased steadily. He was discharged 19 days after admission, feeling well, with CK 70 U/L and creatinine 1.4 mg/dL. Fluvastatin was reinitiated after the CK level was normalized. Renal function of the patient was normal 2 months later.

Discussion. **Two different mechanisms may be responsible for the pathogenesis in our patient. Drug interactions that potentiate adverse effects may occur when colchicine is coadministered with a statin since both drugs are metabolized by cytochrome P450 isoenzymes and myotoxic effects are well known.[2,3] Colchicine and fluvastatin, however, are cleared through 2 different CYP450 isoenzymes. The second possible mechanism is synergistic myotoxicity.[4] Statin therapy is associated with myonecrosis, membranous myeloid bodies, and vacuolization. Finally, statins can disrupt cytoskeletal integrity. In addition to this, colchicine induces myopathy via disruption of tubular function with subsequent vacuolization. Concerning the potential cytoskeletal toxicity of colchicine and statins, it would appear that their combined use produced a synergistic drug-induced myopathy via both pharmacokinetic and related pharmacodynamic mechanisms. According to the Naranjo probability scale,**

our case suggests that rhabdomyolysis was probably related to colchicine.[5]

Patients on colchicine therapy should be informed about the possible muscular and gastrointestinal adverse effects and advised to stop this drug immediately if any symptoms occur. In addition, if colchicine is used together with fluvastatin in renally impaired patients, one should be cautious about myotoxicity.

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A possible case of gynecomastia with fluoxetine

TO THE EDITOR: Selective serotonin-reuptake inhibitors (SSRIs) can be associated with mammary hypertrophy in women.[1] **Benazzi**[2] **described a case of gynecomastia in a man taking fluoxetine; however, the patient was concomitantly treated with risperidone. Boulenger et al.**[3] **reported a case of gynecomastia for which the only triggering factor identified was previous use of fluoxetine. We report a case of gynecomastia in which the only etiologic factor identified was fluoxetine.**

Case Report. **A 49-year-old man was admitted to our clinic in January 2004 with left breast enlargement. He had no remarkable medical history. The enlargement was elastic and painful to palpation. He had no galactorrhea or lymph node enlargement. Results of the rest of the physical examination were normal. Results of all biochemical markers, including renal and liver function tests, ruled out malnutrition and hepatic and renal diseases. Follicle-stimulating hormone, luteinizing hormone, estradiol, human chorionic ®-gonadotropin, ⟨-fetoprotein, prostate-specific antigen, total and unbound testosterone levels, and results of thyroid function tests ruled out gonadal insufficiency, testicular tumors, paraneoplastic syndromes, and hyperthyroidism.**

Ultrasound examination of the testes and computed tomography of the chest showed no signs of testicular or bronchogenic carcinoma. Breast examination, mammography, and ultrasonography confirmed the marked enlargement of the left breast, which showed a retroareloar glandular component. Multiple-site biopsies were performed, and cytologic analysis confirmed the absence of infectious or malignant cells. There was no traumatic (castration, trauma) etiology. The patient had not been taking any other drug or herbal product at the time of onset of gynecomastia except fluoxetine 20 mg/day for depression for 4 months, which was stopped after the onset of gynecomastia.

Discussion. **There are 2 previous reports on gynecomastia in association with SSRIs, but as of this writing, none with fluoxetine alone. Although**

idiopathic gynecomastia could not be ruled out, fluoxetine treatment was considered the cause. Gynecomastia appeared after the onset of fluoxetine therapy and was still present but subsided 10 months after cessation of the drug. We did not readminister the drug or give a placebo to the patient. The patient had had no previous exposure to a similar drug. There are insufficient data about the relationship between fluoxetine blood levels and gynecomastia.

According to the Naranjo probability scale, it was possible that the gynecomastia was fluoxetine-related.[4] Fluoxetine treatment has been reported to cause gynecomastia in combination with risperidone, but there was no clear relationship between prolactin levels and gynecomastia in our patient. Controlled studies are necessary to clarify this adverse effect of fluoxetine. As a result, physicians should take into account SSRIs as a possible cause of gynecomastia.

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Comment: promethazine adverse events after implementation of a medication shortage interchange

TO THE EDITOR: We read with interest the report by Sheth et al.[1] on the adverse events related to administration of promethazine.

Promethazine is an effective antiemetic with a long duration of action. It is used in the treatment of nausea and vomiting from a variety of causes and is particularly effective in the treatment of established postoperative nausea and vomiting (PONV).[2,3] Older reports have suggested that the use of promethazine in the perioperative period is limited by prolonged recovery from anesthesia and delayed recovery room discharge.[4] Recently, the Food and Drug Administration issued a black box warning stating that promethazine should not be used in children <2 years of age because of the potential for fatal respiratory depression. It also recommends that caution should be exercised when administering promethazine to children ≥2 years of age and that the lowest effective dose should be used.[5]

It is likely that the sedative effect of promethazine is dose-dependent. On the other hand, there is no evidence that the antiemetic effect of promethazine is dose-dependent. We recently reported that low-dose promethazine (6.25 mg) was as effective as doses ≥12.5 mg for treatment of established PONV.[6] We have also found that the use of 6.25 mg for PONV prophylaxis is associated with similar efficacy and less sedation

compared with 12.5 mg (unpublished data). In our institution, 6.25 mg is currently the recommended intravenous dose for promethazine, and higher doses are specifically not recommended. We note that all 14 patients reported by Sheth et al. who suffered an adverse event received promethazine >6.25 mg: 8 patients received 12.5 mg and 6 were given 25–50 mg. While we agree with the authors in urging caution with the use of promethazine with other sedatives and narcotics in the elderly and patients with renal impairment, we recommend the use of low doses (6.25 mg) which provides good efficacy and minimizes adverse effects.

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AUTHORS' REPLY: We read with great interest the letter by Habib et al. commening on our article and acknowledge that the adverse effects of promethazine are dose related.

The strategy for combining antiemetic medications with differing chemoreceptor sites of action may have better effectiveness in preventing PONV considering the multifactorial etiology and existence of multiple emetic neuroreceptors. This agrees with the findings of Habib et al.[1] that promethazine was a more effective rescue drug compared with ondansetron for PONV after failure of prophylaxis with ondansetron. The risk of PONV is related to 4 primary patient-related risk factors: (1) female gender, (2) nonsmoking status, (3) postoperative opioid use, and (4) history of PONV/motion sickness.[2] Recent consensus guidelines denote these patient-related factors, plus anesthetic- and surgery-related factors, as necessary for evaluation of PONV risk and recommend prophylaxis for all high-risk patients.[3]

Efficacy of the preventive antiemetic is related to the perioperative administration time, with the goal being near the end of surgery.[4] Promethazine is recommended for PONV rescue in doses of 12.5–25 mg given intravenously, but its use is limited in outpatient settings due to its sedating effects. There have been reports of ineffective prevention of PONV related to promethazine monotherapy in doses of ≥12.5 mg.[5,6] Thus, the

effectiveness of low-dose promethazine for PONV requires further study. Serotonin antagonists alone may not be as effective as older antiemetics in treatment of PONV.[7] However, their safety profile, especially their lack of sedating properties, as well as the limited availability and safety concerns with older antiemetics, has prompted practitioners to use serotonin antagonists preferentially in populations, such as elderly patients, who may be sensitive to oversedation and hemodynamic changes. One study found antihistaminic agents, such as promethazine and hydroxyzine, to be the most frequent inappropriately prescribed drug class in elderly Georgia nursing home residents.[8] Although the promethazine dosing range is not described in that report, the current recommendations cite doses of 12.5–25 mg for adults.[9]

Our report mainly describes adverse promethazine outcomes in medically compromised patients on general patient care units. Such patients are not as closely monitored as are those in the postoperative setting, which was the setting for the study by Habib et al. It is our understanding that most institutions continue to use promethazine doses of ≥12.5 mg in nonmonitored settings for patients with complex comorbidities. We caution against the use of promethazine in elderly patients and in those receiving opioids and/or central nervous system depressants in nonmonitored settings. Until data are available demonstrating the safety and efficacy of doses <12.5 mg in such populations, our adverse event experience prompts us to recommend serotonin receptor antagonists as the safer antiemetic choice in these patients.

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Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.–ED.

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Comment: when does pharmaceutical care impact health outcomes? A comparison of community pharmacy-based studies of pharmaceutical care for patients with asthma

TO THE EDITOR: I congratulate McLean and MacKeigan for their very interesting findings in comparing 4 different pharmaceutical care (PC) studies in community pharmacies for patients with asthma.[1] They addressed the important question of whether some community pharmacy–based interventions have been proven more effective than others and whether "complete" PC has been applied. However, based on the principles of evidence-based medicine, it is likely that not all information regarding a complex study has been published in one article. This holds true, for example, for our study.[2]

Hence, before further conclusions are drawn, at least the following facts should be considered: (1) Besides the 13-hour initial training provided, all pharmacies were closely monitored by a pharmacist (PhD in pharmacology) based in Hamburg and employed for this study.[2] This monitor visited all practice sites regularly to check for compliance with the entire study protocol and the documentation forms for PC, to minimize missing data, and to enhance the documentation of drug-related problems detected and solved (intervention group only). In addition, counseling on-site and via phone/fax was offered from the first day of recruitment until the end of the study. Therefore, assistance from a distant research center was limited to supervision and monitoring the monitor.

(2) Patient satisfaction with healthcare/PC and the pharmacist was evaluated in the intervention group and proved to be extremely high. So far, these data have been presented at meetings[3] or nationally[4] only. A comparison with the control group was considered inappropriate as these patients did not experience elements of PC (usual care).

(3) Additionally, we evaluated physicians' (emergency) visits, hospitalizations, and days off work/school without finding significant differences. This was mainly due to the mild to moderate severity of asthma within our cohort.

(4) We paid a small honorarium of 50 German Marks (€25.60 or $34 US) to pharmacists and physicians, but not patients, in both groups based on data provision at baseline and after 6 and 12 months for each timepoint and patient.

One of the most important elements in our study was the monitor. Visiting all practice sites regularly and offering counseling and advice contributed to favorable outcomes in our study.

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AUTHOR'S REPLY: Thank you for the details on your study. I believe it shows the components of PC that we had assigned. Thank you for your cooperation in providing us with the methodology of your study so that we could publish this comparison.
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Comment: decreased warfarin effect after initiation of high-protein, low-carbohydrate diets
TO THE EDITOR: A recent article described 2 case reports of low-carbohydrate dieters who required a 20–30% increase in warfarin dose to maintain therapeutic anticoagulation.[1] The authors concluded that a likely mechanism was a change in protein binding.
We agree that protein binding can be clinically important in some circumstances. Warfarin, however, is an example of a compound in which protein binding probably has little clinical relevance because it is given orally, has low hepatic extraction, and has a long equilibration time.[2] In these case reports, no measurement of serum protein or albumin was given to specifically implicate protein binding as the cause. Another possible mechanism is that a higher protein intake might induce liver microsomal enzymes and thereby increase warfarin clearance.
A more likely mechanism is an increase in vitamin K intake. In one study that examined micronutrient intake on a low-carbohydrate diet, the vitamin K consumption increased from 36 _g/day at baseline to 77 _g/day.[3] Sources of vitamin K on a low-carbohydrate diet include cauliflower, broccoli, brussels sprouts, spinach, cabbage, liver, and cheese. Many individuals also start taking a multivitamin, which typically includes vitamin K. If the previous diet was replete of snack foods, which are low in vitamin K, then a change to this type of diet consisting of natural foods may accentuate the change in vitamin K intake.[4]

Regardless of the mechanism, these case reports are an important reminder that close anticoagulation monitoring is required with any medication or lifestyle change.
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AUTHORS' REPLY:We appreciate the insightful considerations made by Dr. Kalvass and colleagues. In response, we agree that protein binding may not have been the only factor resulting in the reduction in international normalized ratio (INR) observed in our case report. Since we did not measure serum protein or albumin levels, it cannot be stated that protein binding was the definitive cause of the interaction between warfarin and high-protein, low-carbohydrate diets; however, a partial role in this interaction may be due to a protein-binding interaction. The alternative mechanism suggested by Kalvass et al. involving induction of liver microsomal enzymes was described in our case report as a plausible supplementary mechanism.[1] The possible additive role of these mechanisms was not explicitly discussed in our case report, but may explain the observed early and sustained reduction in INR. Temporally, the protein-binding interaction is expected to be transient and of limited duration (7–10 days).[2] Induction of warfarin metabolism produces a delayed, yet sustained, effect that factors onset of INR changes at 7–35 days.[3] The patients described in the case study experienced a quick reduction in INR (INR decrease of 1.1 in patient 1, 2–4 weeks after starting the diet; decrease of 1.0 in patient 2, 3 weeks after starting the diet), which was sustained while the patients remained on high-protein, low-carbohydrate diets.
The increase in vitamin K intake may also have played a minor role. However, neither patient started taking a multivitamin, often containing vitamin K, during the course of our observation period. Also, each patient was specifically asked about his or her intake of vitamin K–containing foods, including green, leafy vegetables, at every appointment, and each patient claimed that he or she had closely monitored their intake of vitamin K–containing foods while adhering to the diet. Both of these patients had a history of stable INR measurements over the course of at least one year prior to starting the high-protein, low-carbohydrate diets; this consistency suggests that they were knowledgeable about the foods that interacted with warfarin.
The intensity of INR reduction after initiating the high-protein, lowcarbohydrate diets was greater than would be attributed to an increase in vitamin K intake. Khan et al.[4] report that an increase of 100 _g in daily vitamin K intake averaged over 4 days results in a reduction in INR of 0.2. Similarly, Franco et al.[5] describe a reduction in INR from mean ± SD, 3.1 ± 0.8 at baseline to 2.8 ± 0.6 on day 4 of a vitamin K–enriched diet, which provided a 500% increase in dietary vitamin K relative to baseline. These studies support the INR reduction observed to be possibly due in part to changes in vitamin K intake.
We have discussed multiple possible mechanisms of interaction between

warfarin and high-protein, low-carbohydrate diets. Data to support one mechanism over others are not available. However, our experience does support that patients initiating high-protein, low-carbohydrate diets should have their INR monitored soon after beginning the diet to assess for changes in the INR due to one or more of the discussed mechanisms of interaction.

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Comment: sulfonamide cross-reactivity: fact or fiction?

TO THE EDITOR: The article titled "Sulfonamide Cross-Reactivity: Fact or Fiction?" in *The Annals*[1] was a very nice comprehensive review of the evidence and myths of cross-reactivity between sulfonylarylamines, such as the sulfonamide antimicrobials, and sulfonamides, which are nonsulfonylarylamines.[1] However, in Figure 1 and subsequently in the text, some information may have been miscommunicated as to which drugs are truly sulfonylarylamines. The authors need to clarify the structural distinction between a sulfonylarylamine and a nonsulfonylarylamine. Most

of the drugs that the authors describe are nonsulfonylarylamine-containing agents that simply contain the sulfonamide moiety (ie, NH_2S0_2).
In the article, amprenavir and its prodrug fosamprenavir are erroneously represented as nonsulfonylarylamines. Amprenavir shares this sulfonylarylamine structure with another protease inhibitor currently in Phase III studies, TMC-114, and both can be differentiated from the sulfonamide protease inhibitor tipranavir, which is a sulfonamide derivative without the aromatic amine ring.[2] The risk of cross-reactivity between sulfonylarylamines and nonsulfonylarylamines appears to be low and may be predicated on general factors associated with host predisposition to drug reactions rather than chemical structure.[3] The cross-reactivity between drugs that share the sulfonylarylamine structure is largely unknown and would be difficult to measure since reactions to sulfonamide antimicrobials, such as trimethoprim/sulfamethoxazole (TMP/SMX), may not be reproducible within the same patient across time.[4]

However, this issue is of particular relevance to HIV therapeutics since hypersensitivity reactions to sulfonamide antimicrobials such as TMP/SMX are common in this population and decisions have to be made about future use of sulfonylarylamine protease inhibitors, such as amprenavir, fosamprenavir, and TMC-114, in patients who have experienced hypersensitivity or more severe cutaneous reactions associated with TMP/SMX. The putative mechanism by which hypersensitivity to sulfonamide antimicrobials occurs is thought to be in part by the generation of cytotoxic and immunogenic reactive hydroxylamine and nitrosamine metabolites. Oxidative formation of these reactive metabolites is cytochrome P450 mediated and is thought to occur at the N4 arylamine group that sulfonylarylamine drugs share.[5]

In conclusion, although there is limited information as to clinical cross-reactivity between drugs sharing the sulfonylarylamine structure (ie, amprenavir, fosamprenavir, TMC-114), this group should be separated from the nonsulfonylarylamine group drugs in that there is at least, in theory, a risk of clinical cross-reactivity between these drugs and sulfonamide antimicrobials such as sulfamethoxazole.

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AUTHORS' REPLY: We appreciate the comments of Dr. Phillips and Ms. Knowles. They are accurate in pointing out that amprenavir and fosamprenavir should be classified as sulfonylarylamines since these compounds share the same basic structure as sulfanilamide derivatives. Both drugs should be listed under the sulfonylarylamines in Figure 1 of our article with the sulfanilamide derivative antibiotics. Tipranavir was not included in the review since it has not been approved by the Food and Drug Administration.

The clinical information available concerning possible cross-reactivity between these 2 protease inhibitors and other sulfonylarylamines is limited to 2 case series from the manufacturer.[1] These data show that 31% of patients in one group and 37% of patients in another group with a history of a "sulfonamide" allergy or a rash reaction to "sulfonamides" experienced an adverse reaction to amprenavir. However, it was concluded that concurrent therapy with abacavir in 40% of patients in one group and abacavir and/or efavirenz in 76.5% of patients in the other group may have contributed to the adverse reactions.

As discussed in the review, the level of evidence in the case reports of

cross-reactivity between sulfonylarylamines and other medications has been poor due in part to inadequate documentation. Future reports can help delineate cross-reactivity more clearly through a concise description of the reaction, the course of events leading to the reaction, and documentation of any diagnostic tests performed.

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Correction: sulfonamide cross-reactivity: fact or fiction?

In Figure 1 (pg. 291) and throughout the text of "Sulfonamide Cross-Reactivity: Fact or Fiction?", the protease inhibitors amprenavir and fosamprenavir should have been classified as sulfonylarylamines.

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Letters and Comments

Letters are subject to review prior to acceptance. They should address areas related to pharmacy practice, research, or education, or articles recently published. Corrections of previously published material also are accepted. Letters are limited to no more than five authors. In cases where adverse drug effects are described, the Naranjo ADR probability scale should be used to determine the likelihood that the adverse effect was drug-related (Clin Pharmacol Ther 1981;30:239- 45). Text: limit 500 words. References: limit 5. Art: limit 1 table or figure.

Hi Natalie

I met with Eric Lefebvre (scientific affairs at Tibotec) last night and I asked exactly the same question. He told me, with numbers to back it up, that there is no association so far between Septra allergy and darunavir rash. I think the incidence is around 8%.

Pg

> We had a presentation at lunch. Up to now only 2 patients in studies had grade 3-4 rash on darunavir . Most other patients continued through rash without further problem
>
> .

Previous sulfonamide allergy in heir analysis has not comre across as a major contributing factor to rash. It is only a precaution not a contraindication

Marie Courchesne

Thanks to Michelle, Linda and Jeff and Alice (by the way, Alice, hope you are well and do we have any news yet?)
I will forward all comments and suggestions to Merla at BI and will try to keep you all posted with respect to this. Perhaps I will try to come up with a list of possible solutions with them, once I see what their level of committment is, and then send it back out to the group. Is that ok with everyone?
Linda R

-----Original Message-----
From: Michelle Foisy [mailto:michellefoisy@shaw.ca]
Sent: Thursday, September 06, 2007 11:58 PM
To: chap_acpv@yahoogroups.com
Subject: Re: [chap_acpv] beepers

Our patients use a ton of them and our mom's who deliver use them also.... not sure if we can find other companies... will have to look into it. Should we each try to get our own sponsorship, or have it more coordinated via CHAP still?

Michelle

> ----- Original Message -----
>
> **From:** Robinson, Linda
>
> **To:** 'chap_acpv@yahoogroups.com'
>
> **Cc:** 'mrussell@bur.boehringer-ingelheim.com'
>
> **Sent:** Wednesday, September 05, 2007 3:15 PM
>
> **Subject:** [chap_acpv] beepers
>
> Hi everyone,
> I am attaching an email that I received from BI re: the beeper program. I
> promised I would put this out to the group and provide some feedback to
> them. I guess the first thing we have to assess is how often we need/give

out beepers. Secondly, I don't see a problem with asking if other companies
would like to get on board with joint support. I guess BI is open to any
suggestions, as you can see that they do not want to abandon the program.
Please brainstorm and I will forward any and all ideas to them.

Thanks,
Linda R

My message:

Linda
We've some real challenges with the HIV beeper program run out of Toronto
General through Alice Tseng.
Cost for the program has more than doubled as the beepers are now sourced
through a Canadian distributer. Cost was $11.00 when ordered through the
U.S. - it is now $25.00 a beeper and we have spent over $25,000 year to
date.
BI really can't continue to support the program and we are hoping that your
group can come up with a creative answer to the problem of financial support
without BI having to foot the whole bill.
It's a terrific and valuable program and we hate to abandon it - perhaps you
and your group can help us find a solution some way.
Hope to speak with you soon.....Merla
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A 42-year-old man was admitted to hospital with chills and progressive shortness of breath on exertion. He had received an aortic valve replacement 12 years before presentation and had been taking warfarin since that time. A diagnosis of pneumonia caused by Pneumocystis jiroveci was made and was confirmed by Giemsa staining of bronchoscopy specimens. Serologic testing revealed a positive HIV status, with a baseline CD4 cell count of 150 · 10₆/L. The patient's pneumonia was treated with high-dose co-trimoxazole therapy and a tapering course of steroids. In addition, daily fluconazole therapy was initiated for the treatment of candidiasis, and citalopram for the treatment of depression. In the year before he was admitted to hospital, the patient had been taking warfarin (5.5 mg/d) to maintain his international normalized ratio (INR) between 2 and 3. Five days after discharge from hospital, his INR was 4.4. Warfarin was held for 1 dose and was then resumed at an alternating dose of 3 mg/d and 3.5 mg/d. Three days and 2 weeks later the INR was 3.8 and 2.1 respectively. Two weeks after discharge, co-trimoxazole therapy was decreased to a prophylactic dose (1 doublestrength dose daily). One month after discharge, the patient was prescribed antiretroviral therapy (zidovudine, lamivudine and lopinavir/ritonavir). At that time, in addition to warfarin, he was taking co-trimoxazole, fluconazole daily, citalopram, clonazepam, zopiclone and pantoprazole. He was instructed to reduce fluconazole therapy from daily to weekly, and the co-trimoxazole therapy was decreased from double to single strength.

Following initiation of the lopinavir/ritonavir therapy, the patient's INR decreased substantially, with repeated values between 1.1 and 1.3. At a follow-up visit 1 month after initiation of the lopinavir/ritonavir, the patient reported that he had continued taking fluconazole daily despite instructions to decrease it to once weekly. The fluconazole therapy was discontinued at that time, and repeat testing over the next few weeks revealed INR values between 1.0 and 1.3. We ruled out patient nonadherence as well as changes in diet as possible explanations for the continued low INRs. The warfarin dose was titrated by

his family physician over several months to a dose of 11 mg/d. His INR remained subtherapeutic during this period. Six months after fluconazole was discontinued his INR was 2.6. The patient was referred to the anticoagulation management service, and 1 month later his INR had stabilized between 2 and 3 (at a warfarin dose of about 13 mg/d). He continued to take antiretroviral medications, as well as the other prescribed medications, during this period. Seven months after initation of the antiretroviral therapy, the patient's CD4 cell count had risen to 330 · 10_6/L, and his HIV viral load was < 50 copies/mL.

Comments

Lopinavir/ritonavir (a co-formulation of lopinavir and ritonavir) is recommended as a preferred protease inhibitor for the treatment of HIV in patients who have not previously received antiretroviral therapy because it is potent, has a high genetic barrier to resistance and is tolerated by patients.[1] Lopinavir is enzymatically inactivated by the cytochrome P450 (CYP450) 3A4 isozyme; however, ritonavir inhibits CYP3A activity and thus increases the plasma concentration of lopinavir and other CYP3A substrates.[2] These drug interac-

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Interaction between lopinavir/ritonavir and warfarin

Christine A. Hughes PharmD, Andrea Freitas BSc, Lilly J. Miedzinski MD

Case report

Drug interactions involving protease inhibitors are common. Protease inhibitors are well known inhibitors of the 3A4 isozyme of cytochrome P450. Select protease inhibitors, including co-formulated lopinavir/ritonavir, may induce glucuronidation or the activity of other CYP450 isozymes. We describe the case of a patient taking warfarin who experienced a significantly decreased international normalized ratio after the initiation of antiretroviral therapy that included lopinavir/ritonavir. We review the possible mechanisms of this interaction and the reported interactions between warfarin and other protease inhibitors.

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Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/177/4/357/DC1

From the Faculty of Pharmacy and Pharmaceutical Sciences (Hughes, Freitas), and the Division of Infectious Diseases, Department of Medicine (Miedzinski), University of Alberta; and Capital Health (Hughes), Edmonton, Alta.

@ **See related articles pages 347 and 369**

tions are complex, as shown by the ability of lopinavir/ritonavir to induce its own metabolism, as well as to induce the metabolism of other drugs metabolized by CYP450 enzymes

or by glucuronidation.[3] For example, lopinavir/ritonavir reduces the maximum concentration and systemic exposure of methadone and ethinyl estradiol.[2]

Warfarin also has the potential to interact with numerous medications as a result of altered protein binding and metabolism. Available as a racemic mixture, the 2 warfarin enantiomers differ pharmacokinetically and pharmacodynamically.[4] Warfarin is stereoselectively metabolized by hepatic microsomal enzymes.[5,6] S-warfarin, the more potent form, is metabolized primarily by CYP2C9, and the R-isomer is metabolized by CYP1A2 and CYP3A4.[6] Given the potential for drug interactions, close INR monitoring is recommended when lopinavir/ritonavir is taken concurrently with warfarin; however, no specific information about this interaction is available.[2,3] A computerized search of MEDLINE (1950–December 2006) and EMBASE (1988–January 1997) using keywords including lopinavir, ritonavir, HIV protease inhibitors and warfarin did not reveal any clinical reports of this interaction.

We believe, for several reasons, that the precipitous decrease in INR observed in our patient's case was due to an interaction between warfarin and lopinavir/ritonavir. First, previous case reports have described a potential interaction between warfarin and other protease inhibitors (Table 1). In 2 cases, a decrease in INR was observed after administration of ritonavir (400–600 mg twice daily),[7,8] and in one case an increase in INR was observed after ritonavir (400 mg twice/d) was administered in addition to nelfinavir.[9] An increase in INR has also been reported in a patient who received saquinavir therapy.[10] Second, we ruled out patient nonadherence and other potential explanations for the decreased INR, such as changes in diet or addition of other medications. Cotrimoxazole, citalopram and fluconazole have been shown to potentiate the effects of warfarin,[11] and the administration of these drugs probably accounted for the increased INR seen before initiation of the lopinavir/ritonavir therapy. The patient had been taking co-trimoxazole (double strength daily) for about 2 weeks before the initiation of antiretroviral drugs, and his INR had been within the therapeutic range during that time. The co-trimoxazole therapy was reduced to single strength; however, the dose of the patient's other medications remained the same as before the decrease in INR. The warfarin dose that was required to maintain the patient's INR in the therapeutic range after the initiation of the lopinavir/ritonavir therapy was higher than the maintenance dose he had been taking in the year before his HIV diagnosis (about 13 mg v. 5.5 mg). Finally, recent evidence supports a pharmacokinetic basis for the interaction between lopinavir/ritonavir and warfarin and suggests that lopinavir/ritonavir therapy results in modest induction of CYP1A2 and CYP2C9 activity.[12,13] Pharmacokinetic analysis using phenotyping methods in healthy participants found that 10 days of lopinavir/ritonavir therapy resulted in a 43% increase in CYP1A2 activity and a 29% increase in CYP2C9 activity (as measured by S-warfarin exposure).

[12] **The increased enzymatic activity of CYP2C9 and CYP1A2 induced by lopinavir/ritonavir may reduce S- and R-warfarin levels, thus accounting for the reduction in INR and the increased warfarin dose required to maintain the patient's INR in the therapeutic range.**

The decrease in INR and the subsequent need for adjustment of the warfarin dose after initiation of lopinavir/ritonavir therapy suggests that clinicians should be aware of the potential interaction and should closely monitor the patient's INR when these drugs are coadministered. This report highlights the complexity of drug interactions involving protease inhibitors and how our understanding of the differential effects of protease inhibitors on CYP450 isozymes is evolving.

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This article has been peer reviewed.

Competing interests: **None declared for Andrea Freitas and Lilly Miedzinski. Christine Hughes has received speaker fees from Abbott Laboratories and Bristol–Myers Squibb and travel assistance from GlaxoSmithKline and Pfizer.**

Contributors: **Christine Hughes conducted the literature review of warfarin and protease inhibitor interactions. All of the authors were involved in the analysis and interpretation of the literature. Christine Hughes and Andrea Freitas were the principal authors, and all of the authors critically revised the article for important intellectual content. All of the authors approved the final version of the article for publication.**

Table 1: **Reported interactions between warfarin and protease inhibitors**

Report	Warfarin dose before initiation of protease inhibitor	Protease inhibitor, dose at initiation	Effect on INR	Warfarin dose required to maintain therapeutic INR
Knoell et al, 1998[7]	12.5 mg/d	Ritonavir, 400 mg twice daily	Decreased	~ 25 mg/d
Gatti et al, 1998[8]	6.25 mg/d	Ritonavir, 600 mg twice daily	Decreased	8.75 mg/d
Newshan and Tsang, 1999[9]	10 mg/d	Ritonavir, 400 mg twice daily	Increased	Ritonavir discontinued; INR stabilized at warfarin dose of 15 mg/d
Darlington,1997[10]	NA	Saquinavir, 600 mg three times daily	Increased	Warfarin dose decreased by 20%

Note: NA = not available.

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Correspondence to: **Dr. Christine A. Hughes, Faculty of Pharmacy and Pharmaceutical Sciences, 3126 Dentistry/Pharmacy Centre, University of Alberta, Edmonton AB T6G 2N8; fax 780 492-1217; chughes@pharmacy.ualberta.ca**

Hi guys,

In order to avoid reinventing the wheel (and save time !!!), I am wondering if someone already has a document on PEP for a physician/RN audience. I am looking for something specific to drugs (not a protocol on the evaluation of the cases) with details on side effects and precautions (drug interactions, etc).

As an incentive, I will pay a drink of your choice at the next meeting to my rescuer. :)
Thanks.
Pierre

Hi Pierre,
I have one but it is in French with the Québec guidelines. Do you still want it?
Nancy

I have taken the infor leaflets that are available on Kaletra and Combivir from the PSG and adapted them for PEP as I include them in the PEP packs with the drugs. Would you like a copy of them. There are also some info sheets in the sexPEP kit that has just come out of Toronto. Do you have that booklet? Your Sexual Assult Treatment Center will have it if you don't.

P.S. a Southern Comfort Manhattan on the rocks should suffice!
Take care and let me know if you want me to fax anything.
Linda R

While we're adding names, please also welcome Jessica Burry (burryj@smh.toronto.on.ca) who will be covering my mat.leave as of Sept 4.
I believe some of you know Jessica already as she did an HIV rotation with Pierre during her residency.

thanks,
deborah

Welcome, Jessica & Roland, I have added you both to the CHAP listserve.
Roland, can you please send me your complete contact information so I may add it to our contact list?

And this is a rather belated introduction, as I believe many of you met Trish Marr at part of the CHAP meeting this spring.
Trish is covering my maternity leave here at TGH, and is already doing a great job. Trish's hospital e-mail address is:
Patricia.Marr@uhn.on.ca

Alice

Welcome, Jessica & Roland, I have added you both to the CHAP listserve.
Roland, can you please send me your complete contact information so I may add it to our contact list?

And this is a rather belated introduction, as I believe many of you met Trish Marr at part of the CHAP meeting this spring.
Trish is covering my maternity leave here at TGH, and is already doing a great job. Trish's hospital e-mail address is:
Patricia.Marr@uhn.on.ca

Alice

Our HIV team is looking for a guest speaker to come lecture on the issues around addictions (mainly prescription drug diversion issues vs. IV drug use) and mental health in HIV. Can anyone recommend a good speaker?

Thanks
Debbie

Hi Debbie,

Carol Strike is a scientist at CAMH (Centre for Addiction and Mental Health) who has specialized in HIV, addictions and mental health. She is not a pharmacist. She is very pragmatic - I've worked with her and like her. She may be someone to check out. My best to Kevin and the kids (and pets!).

Laura

Hi Debbie,

Carol Strike is a scientist at CAMH (Centre for Addiction and Mental Health) who has specialized in HIV, addictions and mental health. She is not a pharmacist. She is very pragmatic - I've worked with her and like her. She may be someone to check out. My best to Kevin and the kids (and pets!).

Laura

HIV/AIDS • CID 2007:45 (1 October) • **000**

BRIEF REPORT

Outcomes of Dosage Adjustments Used to Manage Antiretroviral Drug Interactions

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Dosage adjustments are often used to manage HIV drug interactions, but little is known about their clinical significance. We examined patients from the Ontario HIV Cohort Study to assess the effects of dosage adjustments on plasma viral load. A significant reduction (0.67 $\log_{10}$ copies/mL) in viral load was associated with adjustments to manage efavirenz-based interactions (95% confidence interval, _1.33 to _0.01) but was not observed after adjustments to manage rifabutin-based (difference in viral load, 0.03 $\log_{10}$ copies/mL; 95% confidence interval, _0.71 to 0.77) or nevirapinebased interactions (difference in viral load, 0.09 $\log_{10}$ copies/mL; 95% confidence interval, _0.83 to 1.01).

The prescribing of antiretroviral medications concurrently with drugs that result in interactions is unavoidable in the treatment of patients with HIV infection [1, 2]. Guidelines often recommend adjusting the dosage of _1 interacting drug to mitigate the potential risks associated with interactions and to maintain drug concentrations at therapeutic levels. However, these guidelines are often based on data from pharmacokinetic studies of varying quality [3–11]. The real consequences for patients, resulting from both the drug interaction and the adjustment, are often unknown.

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We studied antiretroviral drug interactions in an observational cohort study. Our purposes were to determine the frequency with which clinicians adjusted dosages in accordance with guidelines and to assess the impact of dosage adjustments on patient outcomes [1, 2, 12, 13]. We focused on 3 known sets of interactions between drugs commonly used in the treatment of HIV-infected patients.

Methods. **We studied patients enrolled in the Ontario HIV Cohort Study, a longitudinal voluntary database of _3500 HIV-infected patients observed in primary care and**

specialty clinics across Ontario, Canada [14]. Trained abstractors reviewed participants' medical charts every 6 months and recorded clinical data, medication use, and laboratory parameters (including CD4 cell counts and viral loads) [15]. Dates of medication use, dosage information, and reasons for discontinuation of therapy were recorded from the health record. Antiretroviral drugs with missing start and stop dates were imputed from an algorithm that used the start and stop dates of other antiretroviral drugs being received concurrently or health care center visit dates [16, 17].

We identified participants who were prescribed at least 1 of 3 sets of interacting drugs: (1) rifabutin and CYP450 inhibitors (saquinavir, indinavir, nelfinavir, ritonavir, amprenavir, lopinavir plus ritonavir, and delavirdine) or inducers (efavirenz and nevirapine), (2) nevirapine and selected protease inhibitors (PIs; saquinavir, indinavir, and lopinavir plus ritonavir) or ritonavir-boosted PIs; and (3) efavirenz with the same interacting drugs as those for nevirapine. We included drug combinations if the combinations had been taken together for at least 2 days (for interactions involving CYP450 inhibitors) or 1 week (for interactions involving CYP450 inducers).

We defined dosage adjustments from 4 reference Web sites that summarize antiretroviral drug interactions [2, 18–21]. We included any dosage adjustments listed by at least 1 site, although the sources were generally strongly consistent. The exposure group was defined as patients who received at least 1 drug at a recommended adjusted dosage, and the control group was defined as patients who received either unadjusted dosages or nonrecommended adjusted dosages. The study received approval from the research ethics board at St. Michael's Hospital (Toronto, Ontario, Canada).

Our primary clinical outcomes were changes in plasma viral load and frequency of expected adverse events. For each individual, we calculated the difference between the last viral load measured prior to commencing the interacting drug combination and the viral load measured during the 3–6 months after

Table 1. Characteristics of HIV-infected patients and outcomes of adjusted versus unadjusted dosages for each drug combination.

Characteristic or outcome	Rifabutin plus a PI or an NNRTI		Nevirapine plus a PI		Efavirenz plus a PI	
	Adjusted dosage (*n* p 20)	Unadjusted dosage (*n* p 122)	Adjusted dosage (*n* p 61)	Unadjusted dosage (*n* p 49)	Adjusted dosage (*n* p 99)	Unadjusted dosage (*n* p 54)
Age 145 years	13 (65)	70 (57)	30 (49)	30 (61)	65 (66)	36 (67)
Male sex	18 (90)	113 (93)	54 (89)	47 (96)	85 (86)	47 (96)
Cumulative duration of previous antiretroviral therapy, years	2.86 _ 2.36	2.79 _ 2.38	5.10 _ 2.55	4.60 _ 2.78	5.35 _ 2.88	4.98 _ 2.95
Baseline viral load, $\log_{10}$ copies/mL	5.10 _ 5.29	5.12 _ 5.32	5.06 _ 5.21	4.86 _ 5.05	4.96 _ 5.16	4.98 _ 5.26
Baseline CD4 cell count, cells/mm^3	275 _ 270	107 _ 164	232 _ 170	280 _ 274	239 _ 303	267 _ 220
Duration of use of interacting drug combination, no. of days	193 _ 167	224 _ 358	265 _ 301	304 _ 345	310 _ 405	399 _ 449

Dosage adjustment outcome
Change in viral load, log_{10} copies/mL _0.34 _ 1.13 _0.37 _ 0.88 _0.68 _ 1.75 _0.77 _ 1.43 _1.28 _ 1.39 _0.61 _ 1.39
P **.93 .84 .05**
Adverse events 7 (35) 28 (23) 28 (46) 26 (53) 51(52) 26 (48)
P **.25 .46 .40**
NOTE. **Data are no. (%) of patients or . NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor. mean_SD**

initiation of the interacting drug. If viral load had been measured multiple times within the defined time frame, we used the value closest to the end date of the combination drug therapy. Undetectable viral loads were assigned a value of 49 copies/ mL or 499 copies/mL for the Chiron 3.0 and 2.0 tests (Chiron), respectively. The presence of well-described adverse events were identified for each drug and included uveitis, arthralgias, and bone marrow depression for rifabutin and hepatotoxicity, rash, and dyslipidemias for antiretroviral drugs. We used Student's *t* test to assess differences between groups and the x_2 test to assess associations. All analyses were performed using Stata software, version 8.0 (Stata), and SPSS, version 13.0 (SPSS).

Results. **We identified 435 potential participants who were observed from 1995 through 2004, 30 of whom were excluded because of missing data. Of the remaining 405 patients, 142 had received rifabutin therapy with a PI or a nonnucleoside reverse-transcriptase inhibitor, 110 had received nevirapine therapy with an interacting PI, and 153 had received efavirenz therapy with an interacting PI (table 1). Missing day imputations were calculated for 72 patients (17%). No month imputations were required.**

Of 142 patients who received rifabutin therapy with an interacting antiretroviral drug, 20 (14%) received a dosage adjustment, 77 (54%) received unadjusted but not contraindicated drug combinations, and 45 (32%) received unadjusted and contraindicated drug combinations. Of the latter category, the large majority (42 [93%] of 45 patients) received the concomitant prescription of saquinavir prior to the presentation of pharmacokinetic evidence of a detrimental interaction between the 2 agents. CD4 cell count at the time of initiation of the interacting drugs was significantly higher in the group who received dosage adjustments ( ). The mean decrease in *P*p.002 viral load was 0.34 log_{10} copies/mL in the group who received adjusted dosages ( ) and 0.37 log_{10} copies/mL in the *n*p10 group who received unadjusted dosages ( ); the differ- *n*p22 ence in viral load between the groups was 0.03 log_{10} copies/mL (95% CI, _0.71 to 0.77;). Adjusting for baseline dif- *P*p.93 ferences in CD4 cell count resulted in similar results (*P*p). Adverse events were experienced by 35% of the patients .91 who received adjusted dosages and 23% of patients who received unadjusted dosages ( ). The most common ad- *P*p.25 verse events were transaminitis, diarrhea, and hyperlipidemia.

Of 110 patients who received nevirapine with an interacting PI, 61 (55%) received a dosage adjustment. The interacting PI was indinavir in 33 regimens (14 adjusted and 19 unadjusted), lopinavir plus ritonavir in 56 regimens (30 adjusted and 26 unadjusted), and saquinavir plus ritonavir in 21 regimens (17 adjusted and 4 unadjusted). The mean decrease in viral load was 0.68 log_{10} copies/mL in the group who received adjusted dosages ( ) and 0.77 log_{10} copies/mL in the group who *n*p22 received unadjusted dosages ( ); the difference in viral *n*p29 load between the groups was 0.09 log_{10} copies/mL (95% CI,

_0.83 to 1.01;). Adverse events were experienced by *P*p.84 46% of the patients who received adjusted dosages and 53% of patients who received unadjusted dosages (a decrease from baseline of 7%;). The most common adverse events *P*p.25 were transaminitis and rash.

Of 153 patients who received efavirenz therapy with an interacting PI, 99 (65%) received a dosage adjustment. The interacting PI was indinavir in 56 combinations (26 adjusted and 30 unadjusted), lopinavir plus ritonavir in 65 regimens (51 adjusted and 14 unadjusted), saquinavir plus ritonavir in 22 regimens (22 adjusted and 0 unadjusted), and other PIs in 10 regimens. Viral load data were available for 56 patients who received adjusted dosages and 25 patients who received unadjusted dosages. The mean change in viral load was larger in

the group who received adjusted dosages than in the group who received unadjusted dosages (decrease in viral load, 1.28 $\log_{10}$ copies/mL vs. 0.61 $\log_{10}$ copies/mL); the difference in viral load between the groups was 0.67 $\log_{10}$ copies/mL (95% CI, _1.33 to _0.01 $\log_{10}$ copies/mL;). Adverse events were *P*p.05 experienced by 52% of the patients who received adjusted dosages and 48% of patients who received unadjusted dosages (a difference of 4%;). The most common adverse events *P*p.25 were transaminitis, hyperlipidemia, and neuropsychiatric symptoms.

Discussion. **We studied potentially clinically relevant interacting drug combinations in a voluntary observational cohort of patients with HIV infection in Ontario, Canada. Overall, we found that rates of dosage adjustments for interacting drugs were relatively low (15%–65%). Significantly improved viral outcomes were associated with dosage adjustments for management of efavirenz-based interactions, but we did not identify differences in virologic outcomes associated with dosage adjustments for management of rifabutin-based or nevirapinebased interactions.**

We observed more frequent dosage adjustment practices for newer drugs (e.g., efavirenz and nevirapine), compared with an older drug (i.e., rifabutin). A minority (!15%) of patients received dosage adjustments in our analysis of interactions between rifabutin and antiretroviral drugs. In the analysis of interactions between nevirapine and antiretroviral drugs, slightly more than one-half of the patients received dosage adjustments, and almost two-thirds of the patients received dosage adjustments for management of efavirenz-based interactions.

Several limitations of our study deserve to be mentioned. Our analyses were based on a relatively small number of evaluable viral load measurements, reflecting the limited availability of viral load testing during our study period. However, a clinically and statistically significant improvement in viral load (0.67 $\log_{10}$ copies/mL) was observed in participants receiving dosage adjustments for management of efavirenz-based interactions, supporting the importance of such modifications in these cases. Our inability to detect improved virologic outcomes after dosage adjustment in either the rifabutin or nevirapine subgroups may reflect a true lack of clinical effect or the low statistical power of these data.

Another limitation pertains to missing therapy start and stop dates. It is possible that the use of an imputation algorithm introduced biases into the analyses. The imputation algorithm was not previously validated and relied on the assumption that antiretroviral drugs would have been started together or adjusted during health care visits. The magnitude of such biases is likely to be small, however, because we imputed only the day (and not the month or year) that therapy was started and stopped. We also did not externally validate medication data. Specifically, we relied only on clinic charts and did not have access to pharmacy records or direct patient questionnaires to confirm therapy dates. Chart data may be inaccurate if patients started therapy later than was prescribed or if they were not adherent to therapy. Classifying patients who were not adherent to therapy as having a potential interaction would tend to minimize the adverse consequences of receiving interacting drugs; the converse is also true.

Our finding that dosage adjustment did not result in differences in adverse events should be viewed cautiously, because our conclusions were based on relatively few events, and our ability to capture events comprehensively was constrained by the reliance on medical records.We were also unable to measure the severity of adverse events. Thus, we may have missed moderate but clinically important effect sizes for known adverse events or relatively large effect sizes for unrecognized adverse events.

Our study supports the importance of dosage adjustments for management of efavirenz-based induction drug interactions on viral outcomes. Low statistical power precludes us from commenting on whether pharmacokinetic research can predict which drug interactions will be clinically relevant and change virologic and clinical outcomes. Potential reasons for the low adherence to dosage adjustment recommendations could not be identified by this study.

Virologic, clinical, and adverse event outcomes should be further explored in large and more recent observational cohorts to ascertain whether pharmacokinetically guided dosage adjustments improve clinical outcomes. Our finding that some, but not all, adjustments may be important suggests that a randomized controlled trial of dosage-adjusted therapy versus standard of care might be warranted. Finally, further research should examine the reasons some clinicians elect to not adjust dosages of potentially interacting medications.

Acknowledgments

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Potential conflicts of interest. All authors: no conflicts.

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But has subsequently been tested and is negative for HIV at this time. Her partner (father of the baby) has had a relationship with a known HIV +ve women so this is the primary risk factor. . . don't know the HIV status of the father nor whether or not he is still "in the picture".

AZT prophylaxis was initially started on the baby, but in light of the Mom's negative test, do you generally stop the AZT? . we have a difference of opinion here in regards to the possibility the mom is in the "window period" and so prophylaxis for baby should continue (or not). . if that's the case, then we are treating this baby as if they had been exposed to an known HIV +ve mom and don't we have to do all the follow up tests, etc. on the baby which then draws out the process for a negative diagnosis and exposes the baby to meds they may not need????

What is your clinic's general rule on this type of case? I'm kinda thinking if we treat all babies regardless whether or not the Mom turns out +ve or -ve, why bother doing the test at

If the Mom is negative and not involved in any high risk activities during the window period, we would stop the AZT. Often, it is difficult to determine this and we have stopped AZT on babes with only antibody results on mom. Of course, ideally getting the mother's PCR would be the best.

Gloria Tsang
Oak Tree Clinic
I agree with Gloria. You have to assess the risk of the mom to acquire HIV. When was the 'extramarital relationship' of the father and what was the sexual activity of the couple is in the equation. At the end, I would rely on HIV PCR of the mom for stopping or not the prophylaxis.
pg
Hi Everyone,

I just heard that Nelfinavir 625 mg and 250 mg tablets are back-ordered. Pfeizer has no expected release date at this time. Has anyone heard any news as to how long this will last?

Gloria Tsang
Oak Tree Clinic
Vancouver,BC
Production in Canada was shut down while Health Canada was reviewing the manufacturing process (after the kerfuffle in Europe). The review is complete but production hasn't restarted yet, pending permission from Health Canada to go ahead. It's probably going to be on product allocation for some time until they catch up on the backorders.....

jeff

"Tsang,

Very interesting, considering that nelfinavir is manufactured by Roche outside of North America, and by Pfizer here. The two products are not even identical (have different excipients). Funny that I mentioned this to our Pfizer rep last week and he didn't mention anything.
Alice
In case you are interested.
Michelle

From: Donna Brooten [mailto:DonnaB@medactionplan.com]
Sent: Wednesday, August 29, 2007 1:16 PM
To: undisclosed-recipients
Subject: Revised 4.0 Version for MedActionPlan for Antiretroviral Therapy

Announcing the Introduction of MedActionPlan for Antiretroviral Therapy 4.0.

You can now access Version 4.0 at this address.
http://www.medactionplan.com/index.asp All of your records in the current 3.0 version will automatically be transferred over to version 4.0.

MedActionPlan has been expanded to include these helpful functions:

- Schedules include up to 6 time slots. (It shows 5 if you use less than 6)
- Find a Pharmacy
- Separate patients by group
- Quick find patients
- Insulin chart has been expanded
- Appointment Calendar
- Email schedules to patient read access only
- Change password
- Instructions page now includes images of pills
- Print labels for Pack-m-Ups

For more details, see the attachment. For any questions or to schedule an online demonstration for your department, please call or email us.

Take care--Donna

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Our Mission: *To provide the healthcare industry with innovative resources that utilize cutting-edge technology and proven health literacy principles to empower patients to become active partners in their healthcare.*

Hi Everyone

Case:

I am caring for a 20 year old treatment experienced patient with extensive HIV resistance. He is currently receiving TDF, Combivir, and TPV/r. He is failing this regimen. His genotype is pending. Once the results are available we will switch his ARVs.

We may need to switch from TPV/r to LPV/r. Given the strong inductive properties of TPV/r, I am wondering how best to make the switch. I want to minimize the risk of resistance developing to LPV/r.

Last year Nimish Patel, Alice Tseng, Charles la Porte and Nancy Sheehan discussed different ways to address this problem. They developed a protocol that involved giving LPV/r with extra ritonavir for the first 2 weeks (Week 1: ritonavir 200 mg BID; Week 2: ritonavir 100mg BID).

Is anyone using other approaches to address this problem? I would love to hear about your experiences

Thanks in advance

Trish

Patricia Marr
Pharmacist
Immunodeficiency Clinic
Toronto General Hospital
Pager: 416-790-7857

Hello all!

thanks for including me in the group!

I have no real experience yet treating HIV patients, so this comment is really more of a question than a suggestion.

I wonder in this case if it is possible to simply stop all ARVs for 2 weeks to allow the enzyme induction to fade. If all the meds are changing and they are all stopped at the same time, theoretically, further resistance should not develop assuming the half-lives of the agents are ~ equal, should it? Obviously this will depend (at least partly) on the patient's current CD4 count, viral load and whether all or only some of the meds will be switched to an alternative.

All things being equal, are there other dangers to simply holding all meds for 2 weeks between changes?

Sincerely,

Roland Halil, PharmD
Bruyere and Primrose Family Health Team
Ottawa, ON

I tend to agree with Roland (Has he had a preceptorship here in our clinic???). Switching TPV/r in a situation of treatment failure is different than once the patient's viral load is suppressed.

In your situation, you have little to gain by switching to a LPVr regime. In fact, your chances are that your patient's virus is less sensitive to LPVr. I would interrup the treatment for 10-14 days and then resume the new treatment. That treatment interruption should not harm your patient too much.

Pierre

Thanks for the feedback - I really appreciate it!

We had discussed stopping all ARVs for 2 weeks. But decided against this option as the patients last CD4 count had drastically declined (83; Aug 24/07) and we were concerned about opportunistic infections.

We will have to wait to see what the next genotype shows in terms of resistance before making any treatment decisions. Based on the last genotype from 2006, we have very little to choose from. Virus resistant to NNRTIs (NVP, DLV, EFV) and almost all PIs (IDV, NFV, fAPV, ATV, TPV, RTV). The only PIs with some activity on the genotype (reduced response expected) include: APV/r, SQV/r, LPV/r.

Note: The patient had remained on TPV/r despite drug resistance because the viral load was partially suppressed, the CD4 count was reasonable, and most importantly the patient was nonadherent. We didn't want to risk loosing another drug regimen (we have so little to choose from!). The patients adherence to medications has improved lately; his mother is now involved

with monitoring medication administration. We feel it is time to make a regimen change given the decline in CD4 count.

So far we're thinking our best option may be DRV/r, TMC125, Combivir, TDF, Raltegravir. Although not our 1st choice, we thought LPV/r may be an option given that it showed some response on the last genotype. And so this is where my question on how best to switch from TPV/r to LPV/r comes from.

Thanks everyone for the help
Have a great day

Trish
On the other hand, if you are not counting on a whole lot from LPV (the CYP substrate) in the first place and are including agents such as raltegravir and/or enfurvirtide, which do not rely on CYP metabolism, I don't see any reason to wait before starting the new regimen. When we made switches in 2 of our patients from TPV/ to DRV + enfuvirtide, and these patients were suppressed, we had no wash out period. At the time I consulted with Dr. MacArthur in Detroit in light of the induction/resistance development etc. story and he was not offering any washout time for his patients as well.

Linda R

Just nother quick note, be sure to check the newer, last page of the genotype when it comes in as it gives a much more reliable FC evaluation with respect to the usefulness of boosted DRV or TPV. Also don't forget to rely on the information within the actual reported mutations for TPV and (11) for DRV to predict your proposed response to these drugs. NNRTI resistance should help in telling you whether TMC 125 will be very useful or not. Be sure to check previous genotypes when the virus was under NNRTI pressure. If you need any info re: the mutation patterns that appear to be pro or con for TMC 125 we can help with that too. I find with my patients on these newer agents, when they understand that daily injections (if ENF not used yet) are the next and most likely last option for now, they are a little better motivated for adherence. It is also a great time to work with the retail pharmacy and invoke their help in re-iterating adherence counseling. The Ont PSG has been working hard at stressing their complimentary role, esp in Toronto, over the last year. I'm actually off again tomorrow to the OPA conference in Deerhurst to deliver this message, once again to our retail colleagues in the province.

Linda R

Hi everyone,
I am attaching an email that I received from BI re: the beeper program. I promised I would put this out to the group and provide some feedback to them. I guess the first thing we have to assess is how often we need/give out beepers. Secondly, I don't see a problem with asking if other companies would like to get on board with joint support. I guess BI is open to any suggestions, as you can see that they do not want to abandon the program. Please brainstorm and I will forward any and all ideas to them.

Thanks,
Linda1
Hi Linda R,

Re: your question about how often the beepers are used....I can tell you that the BC patients love them. We currently use at least a few hundred a year. I don't have a problem with getting financial support from other companies.

Linda A
I wonder if we lost the cost advantage of bulk purchasing when the distributor changed? We might use 30-50 per year....I'd be happy to privately approach my local reps for support for purchasing for my clinic's patients when I need additional supply - that would also eliminate any hassle on Alice's part as far as storing and shipping beepers to us when we needed more.... Could Merla provide the contact info for the Canadian distributor, in case that's what we need to do?

Jeff Kapler, Pharmacist
Southern Alberta Clinic for HIV/AIDS
#213, 906-8th Ave SW
Calgary, AB
T2P 1H9
Tel: (403) 234-2388
Fax: (403) 531-8052
Email: jeff.kapler@calgaryhealthregion.ca
Our patients use a ton of them and our mom's who deliver use them also.... not sure if we can find other companies... will have to look into it. Should we each try to get our own sponsorship, or have it more coordinated via CHAP still?
Michelle
Making additional arrangements via CHAP is probably a good idea, as Jeff mentioned, to get the "bulk" (hah!) rate - sorry, it still steams me up as to how much the Canadian distributor has jacked up the price, even though they apparently promised the US company to still honor the original arrangement with us.

Merck might be one company to approach - they were the ones that originally sponsored the green ALR beepers.
Alice