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I ANTI-HIV AGENTS

A. Different combinations of ritonavir-indinavir

In order to suppress HIV, it is necessary to have high levels of anti-HIV drugs in the blood. To accomplish this, doctors sometimes prescribe two protease inhibitors (PIs) together as part of a combination drug regimen. One of the issues involved in taking two drugs simultaneously is that they can interact — raising or lowering levels of each other in the blood. For example, the PI ritonavir (Norvir) can usually boost levels of another PI when the two drugs are taken together. Taking ritonavir together with another PI also helps to maintain high levels of the other PI in the blood. Ritonavir can be used to boost levels of the following PIs:

- amprenavir (Agenerase)
- indinavir (Crixivan)
- lopinavir (in Kaletra)
- saquinavir (Fortovase)

Using ritonavir with these other PIs sometimes results in people with HIV/AIDS (PHAs) having to take fewer pills, thus allowing them to use a twice-daily regimen rather than a three-times-a-day schedule. An example of this is with the PI indinavir. Ordinarily indinavir has to be taken every 8 hours and according to dietary restrictions. But when used with ritonavir, the combination can be taken every 12 hours without dietary restrictions.

A major issue about this ritonavir-indinavir combination is what is the best dose of both drugs that could be used in combination. Some PHAs use a “400-400” dose: 400 mg of ritonavir and 400 mg of indinavir, taken twice daily. However, tolerating this dose of ritonavir isn't easy, so researchers are testing reduced doses of ritonavir in this PI combination.

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A research team working at Merck, the drug company that manufactures indinavir, recently published results from its studies of various combinations of ritonavir-indinavir. Although these experiments were done using HIV negative volunteers, the results may be useful for doctors who prescribe ritonavir-indinavir for their PHA patients.

Study details

Researchers enrolled 73 healthy, HIV negative subjects (44 female, 29 male). Combinations of ritonavir-indinavir that were tested included the following, which were taken every 12 hours:

- ritonavir 100 mg, indinavir 800 mg
- ritonavir 200 mg, indinavir 800 mg
- ritonavir 400 mg, indinavir 800 mg
- ritonavir 400 mg, indinavir 400 mg

Data collected from this study were compared to those from previous studies in which indinavir was taken at a dose of 800 mg every eight hours (without ritonavir). All subjects in the current study were required to drink 1.5 litres of water daily. Subjects took their assigned drugs for 15 days.

Results

As expected, researchers found that ritonavir boosted levels of indinavir. There were no significant differences with regard to indinavir levels when the following combinations were taken:

- ritonavir 200 mg, indinavir 800 mg
- ritonavir 400 mg, indinavir 800 mg

The levels of indinavir in the blood with the combination of twice-daily ritonavir 100 mg and indinavir 800 mg, although high, were not as high as those seen with the two doses listed above.

Keeping it in perspective

In order to suppress production of HIV, PI levels have to be high and remain high for prolonged periods, particularly between doses. When ritonavir-indinavir is taken either at the 200-800 dose or the 400-800 dose, the level of indinavir in the blood 12 hours later (near the time for the next dose) is between 10 to 25 times greater than it would be if indinavir 800 mg without the ritonavir boost was used. Taking ritonavir with indinavir therefore helps keep indinavir levels in the blood within a stable range, making it harder for HIV to develop resistance.

Meals — high and low fat

Researchers also tested the effect of high- and low-fat meals, which they defined as follows:

- high fat: two scrambled eggs, two strips of bacon, two slices of buttered toast, fried potatoes and a glass of whole milk
- low fat: two slices of toast with jelly, a glass of apple juice and a cup of coffee

The researchers found that absorption of indinavir was not affected when indinavir was taken with high- or low-fat meals — as long as subjects also took ritonavir at the same time.

Ritonavir

It is important to remember that in the combinations ritonavir is used as a “booster” and not for its anti-HIV activity. Nonetheless, researchers measured ritonavir levels during the study and found that indinavir raised ritonavir levels when low doses of ritonavir (100 mg or 200 mg) were used. This is not clinically significant. Ritonavir and indinavir levels were not affected by a person’s gender.

Side effects

Although 73 subjects enrolled in the study, only 53 were able to complete the two-week clinical trial. Ten subjects left the study because of side effects and 10 others left for unknown reasons.

In general, the researchers described side effects seen during the study as being “mild to moderate in severity.” Side effects commonly noted during this study included nausea and vomiting. One subject developed kidney stones and two had blood in their urine. Side effects were most common among subjects using the ritonavir-indinavir 400-800 dose. This is likely due to the high level of ritonavir.

Results from this study suggest that a combination of ritonavir 200 mg and indinavir 800 mg, taken twice daily, may be the most useful of the doses tested. Doctors who prescribe this combination need to remind their patients about the importance of drinking at least 1.5 litres of water daily, in addition to all the fluid they usually drink.

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1. Saah AJ, Winchell GA, Nessly ML, et al. Pharmacokinetic profile and tolerability of indinavir-ritonavir combinations in healthy volunteers. *Antimicrobial Agents and Chemotherapy* 2001;45(10):2710-2715.

B. Searching for the right dose of ritonavir-saquinavir

Another combination of protease inhibitors (PIs) that is useful for some PHAs is ritonavir (Norvir) and saquinavir (Fortovase). Some doctors prescribe a combination of 400 mg of ritonavir and 400 mg of saquinavir to be taken twice daily; this is sometimes called “400-400.” This combination is used because ritonavir acts as a “booster,” raising levels of saquinavir in the blood far higher than if saquinavir alone were taken.

Although the 400-400 dose combination is clearly effective against HIV, this high daily dose of ritonavir is not always easy to tolerate. Researchers are therefore testing lower doses of ritonavir with higher doses of saquinavir, in the hope of finding a more tolerable combination with greater anti-HIV activity.

Study details

Researchers in the U.S. recruited 66 healthy, HIV negative adult subjects (9 females, 57 males) for their study. Subjects were confined to a hospital for the two weeks that this study lasted. Different subjects received the following drugs taken 15 minutes after a meal, twice daily:

- saquinavir – 800 mg
- ritonavir – 400 mg
- ritonavir 200 mg, saquinavir 800 mg
- ritonavir 300 mg, saquinavir 600 mg
- ritonavir 300 mg, saquinavir 800 mg
- ritonavir 400 mg, saquinavir 600 mg
- ritonavir 400 mg, saquinavir 800 mg

Although subjects in this study were HIV negative, the results may be useful for physicians who prescribe combinations of ritonavir and saquinavir for their patients.

Results

Analysis of blood samples from subjects showed that in all cases where combinations of ritonavir and saquinavir were used, saquinavir levels were much higher than if saquinavir alone were used. While ritonavir boosted saquinavir levels, saquinavir did not increase (or decrease) ritonavir levels.

Side effects

The researchers described most of the side effects as being “mild” in their severity. Common side effects seen were as follows:

- headache
- nausea
- altered sense of taste

- tingling/numbness around the mouth

Those subjects who received no ritonavir or who received ritonavir 200 mg together with saquinavir 800 mg, both twice daily, reported few side effects.

Two subjects left the study, one because of a severe rash and the other because of nausea and vomiting.

On average, ritonavir-saquinavir 200-800 mg twice daily resulted in a greater increase in saquinavir levels in the blood than when the 400-400 mg combination or saquinavir 1,200 mg three times daily (without ritonavir) was used (according to data from previous experiments). Further testing on HIV positive people to note and compare the effectiveness of ritonavir-saquinavir 200-800 mg twice daily against that of other PI combinations needs to be done.

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1. Buss N, Snell P, Bock J, et al. Saquinavir and ritonavir pharmacokinetics following combined ritonavir and saquinavir (soft gelatin capsules) administration. *British Journal of Clinical Pharmacology* 2001;52:255-264.
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C. Study finds HIV subtly damages vision

In the context of AIDS, when one hears about eye damage the phrase “CMV-retinitis” often comes to mind. In that sight-threatening complication — caused by a virus called cytomegalovirus or CMV — the light-sensitive portion of the eye, known as the retina, is infected and becomes swollen. What some researchers are finding, however, is that people with HIV/AIDS (PHAs) who do not have any obvious inflammation of the retina are developing subtle visual defects, including:

- reduced sensitivity to light
- reduced sensitivity to colour

These defects appear to be caused not by CMV but rather by HIV. Moreover, the usual means of assessing retinal damage — fundus photography — does not appear to be sensitive enough to detect this subtle damage.

Adventures in 3D

Researchers at the University of California at San Diego have been using an instrument called the Heidelberg Retina Tomograph. This device uses a laser beam to produce detailed 3-dimensional images of the retina and optic nerve in PHAs. The researchers found that HIV positive people who did not have any obvious eye disease had significant

damage to the retina and optic nerve. Details about why this occurred appear later in this report.

Study details

Researchers recruited three groups of subjects:

- 17 male subjects who were HIV positive but who did not have the sight-threatening complication CMV-retinitis
- 21 subjects (1 female, 20 male) who had CMV retinitis in at least one eye
- 24 subjects (11 females, 13 males) who were healthy and HIV negative

The researchers did not release information on CD4+ and CD8+ cell counts, viral load or the type of anti-HIV treatment, if any, subjects were taking. All subjects had 3D images of their eyes produced and analysed.

Results

The researchers found that while subjects with CMV retinitis had the most damage to their retinas, HIV positive subjects without this complication also had significant damage to their retina and optic nerve (which carries pictures from the eye to the brain). This research team has previously found that the optic nerve of PHAs who don't have CMV-retinitis can shrink by as much as 50%.

The standard of care for investigating retinal damage in PHAs is for ophthalmologists to use an instrument called a funduscope. However, ophthalmologists would not have been able to detect the damage to the retina documented in this study by using this instrument. The researchers therefore stated that “proper evaluation of HIV-associated damage to the retinal nerve fibre layer may need to include nerve fibre layer photography or confocal imaging techniques.”

Why the subtle eye damage?

The researchers aren't sure exactly how HIV damages the nerves in the eye. They suspect that proteins produced by HIV or HIV-infected cells are toxic to nerves in the eye and cause cells in the retina and optic nerve to commit suicide, a process called apoptosis. This process is similar to the way in which HIV can cause brain cells to die. Hopefully, future studies will examine the impact of therapies, such as HAART and antioxidants like vitamins C and E and zinc, on this subtle damage to vision.

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3. Jiang ZG, Piggee C, Heyes MP, et al. Glutamate is a mediator of neurotoxicity in secretions of activated HIV-1-infected macrophages. *Journal of Neuroimmunology* 2001;117(1-2):97-107.

II IMMUNE BOOSTERS

A. IL-12 may be useful for hepatitis C

Hepatitis C virus (HCV) infects and inflames the liver. In some people, the immune system can bring HCV under control. In other people, the virus cannot be controlled, and over a period of many years, it slowly scars and destroys the liver. Currently available treatments for HCV include interferon-alpha and ribavirin. Even when these two medications are used together, about 50% of treated people fail to recover. These drugs also have unpleasant side effects. Researchers are testing several therapies for use by people with HCV infection, including IL-12 (interleukin-12). They hope that repeated use of this immune booster will be able to strengthen the immune system's ability to fight the virus.

Study details

Researchers enrolled 24 adults (7 females, 17 males) who were positive for HCV, but not HIV, into their study. All subjects had previously received treatment with interferon-alpha, but this failed to help them recover from HCV. The basic profile of subjects was as follows:

- average age – 46 years
- all subjects had liver damage according to analysis of liver biopsy
- all subjects had higher-than-normal levels of the liver enzyme ALT
- 20 subjects had the difficult-to-treat form of HCV called genotype 1

Subjects were randomly assigned to receive one of the three following doses of IL-12 injected under the skin twice weekly for three months:

- 30 nanograms/kg of body weight
- 100 nanograms/kg of body weight
- 300 nanograms/kg of body weight

Results

Although three different doses of IL-12 were used in this study, beneficial effects occurred only in three of six subjects receiving the highest

dose (300 nanograms). At that dose, levels of HCV in the blood of subjects fell to undetectable levels. In two of these three subjects, levels of ALT fell within the normal range during the study. Unfortunately, once subjects stopped taking IL-12, HCV and ALT levels rose.

Side effects

Common side effects experienced by the following proportion of IL-12 users included:

- headache – 100% of subjects
- bone and/or joint pain – 100% of subjects
- muscle pain – 100% of subjects
- lack of energy – 100% of subjects
- fever – 33% of subjects in the lower-dose groups and 100% of subjects receiving the 300 nanogram dose
- swollen, irritated gums – 50% of subjects in the high-dose group developed this problem

Two subjects became depressed and two experienced temporary mild loss of hair.

The results seen in the three responding subjects at the highest dose suggest that IL-12 may be beneficial for some people with HCV infection. But there are at least two hurdles to be faced by people who may, in the future, participate in clinical trials of this drug. First, IL-12 will probably need to be taken for far longer than three months. Second, given the side effects from IL-12, it is not certain that users will be able to tolerate this drug over the long-term. The IL-12 used in this study was made by the Genetics Institute in Cambridge, Massachusetts.

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III SIDE EFFECTS

A. Does efavirenz cause breast enlargement?

The non-nucleoside analogue (non-nuke) efavirenz (Sustiva), although a useful and convenient part of many HIV treatment regimens, has been associated with unusual side effects, particularly those affecting the brain, such as dizziness, intense dreams and hallucinations. Researchers in France and Spain have also reported another unusual side effect of efavirenz — breast enlargement in both men and women.

Reports from France

A team of French doctors reported details on six people with HIV/AIDS (PHAs) aged between 43 and 55 years. The six PHAs had been treated with protease inhibitor (PI)-containing regimens and had developed lipodystrophy. Between one to six months after these PHAs switched from their PI-based regimens to regimens based on efavirenz, painful breast enlargement occurred. Each of these PHAs was using different drug combinations; the only drug that they all used in common when breast enlargement occurred was efavirenz. Technicians tested the blood of the PHAs for levels of many hormones including the following:

- testosterone
- DHEA
- estrogen
- progesterone
- cortisol
- FSH (follicle-stimulating hormone)
- LH (lutinizing hormone)
- TSH (thyroid-stimulating hormone)

All hormone levels were within the normal range.

Doctors continued treatment with efavirenz. In five of the six cases, breast enlargement stabilized. The remaining PHA's breasts partly shrunk over time. The doctors note that breast enlargement has occurred in 8% of their patients who use efavirenz.

Reports from Spain

Doctors in Spain recently reported details on three male PHAs who also developed breast enlargement after using efavirenz. Again, extensive and sophisticated hormonal measurements were done but no abnormalities were detected. The Spanish cases were very similar to the ones from France with one major exception: none of the Spanish PHAs had lipodystrophy before starting efavirenz.

Breast enlargement and female hormones

Breast enlargement usually occurs when testosterone levels fall and estrogen levels rise. As hormonal measurements indicated that this did not apparently happen in the case of all the PHAs reported here, doctors remain puzzled as to why this problem occurred. Perhaps a clue lies in work done by researchers in Turino, Italy. Last year, the Italian researchers found that blood samples from PHAs who took efavirenz appeared to have unusually high levels of the female hormone estradiol. However, when the researchers performed more sophisticated tests, they found that estradiol levels were in fact normal; it was

the presence of efavirenz in the blood samples that had confused the initial test used to measure estradiol. They suspect that this occurred because efavirenz may bind to parts of the test that normally detect estradiol. Thus it is possible that efavirenz may have estradiol-like effects in the human body, fooling it into assuming that this drug is similar to a female hormone and triggering the growth of breast tissue or accumulation of fat in the breasts of some people who take efavirenz.

The reports from France, Spain and Italy underscore the need for long-term monitoring of anti-HIV drugs in general and efavirenz in particular. As well, the manufacturer of efavirenz needs to conduct research into preventing this side effect and other troublesome complications of its drug.

Note: The test used by the Italian researchers that detected falsely high estradiol levels was the AIA 21 made by Tosoh corporation in Tokyo, Japan.

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B. Andractim for HAART-associated breast enlargement

HAART has greatly reduced death rates from complications of AIDS in North America, Western Europe and Australia. But HAART regimens can be complex and have side effects. One of the more rare side effects is breast enlargement (gynecomastia). Although the previous report highlighted the occurrence of breast enlargement in efavirenz-users, readers should note that breast enlargement can occur with other anti-HIV drugs.

Until recently doctors were at a loss for how to relieve this distressing problem. Now researchers in Paris, France, have reported their success in treating breast enlargement with the use of a form of testosterone called DTH (dihydrotestosterone).

The doctors reported on four HIV positive male patients who had been taking various combinations of HAART for several years before they experienced breast enlargement. Technicians analyzed blood samples from the four patients and found normal levels of the following hormones:

- prolactin
- androstenedione (a building block for testosterone)
- testosterone

The doctors prescribed DTH gel, 5 grams daily, applied to the enlarged breasts. In three of the four cases, the breasts returned to their normal size after 10 to 30 days. In the remaining case, although his breast size did decrease, it did not shrink back to its normal size.

Why did breast enlargement occur?

The researchers aren't certain why breast enlargement occurred but they have a theory. They noted that in HIV negative people a similar problem can happen when certain drugs — digitalis, tricyclic antidepressants — are used. In such cases, gynecomastia likely occurs because these drugs somehow mimic the hormone estrogen and/or progesterone or increase the body's production of the hormone prolactin. Since all four men had normal levels of prolactin, the dramatic reduction in breast size associated with the use of DTH reinforces their theory that HAART drugs may somehow mimic the effect of estrogen on breasts.

Further investigation on the reasons for HAART-associated breast enlargement needs to be conducted as the findings from France are preliminary. Another puzzling aspect of this story is why breast enlargement is not a more common side effect of HAART.

A note on DTH

Readers should note that the use of testosterone may be dangerous in men who have prostate cancer or who are at high risk of prostate cancer. The French team noted that what makes DTH different from other forms of testosterone is that it cannot be converted into estrogen by breast tissue. Although DTH is not licensed in Canada, it is available in France and other countries of the European Union. In France, DTH gel is sold under the brand name Andractim and is made by Laboratoires Besins-Iscovesco. Canadian physicians who wish to order non-approved drugs can discuss their request with Health Canada's Special Access Program at 613.941.2108 between the hours of 8:30 am and 4:30 pm Eastern time.

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Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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