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Understanding drug-drug interactions in the management of HIV disease

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Recent technologies within the last decade have resulted in our understanding a huge body of knowledge and information concerning the cytochrome P-450 isoenzymes present in the human body, and thus created an awareness of the many life-threatening interactions with such commonly prescribed drugs as the newer antihistamines and cisapride. A basic knowledge of the substrates, inhibitors and inducers of this enzyme system assists providers in predicting drug interactions that may become clinically significant. Apart from the processes of induction and inhibition, other factors that may affect microsomal drug metabolism include hepatic disease, state of nutrition, age, the presence of some endogenous chemicals, and genetic polymorphism. So far, as many as 30 human cytochrome isoenzymes have been identified. The major ones responsible for a majority of drug metabolism include CYP3A4, CYP2D6, CYP1A2 and the CYP2C subunits. This article, which will be continued in a later edition of this newsletter, will present fundamental concepts necessary for an appreciation of the role of these enzymes in drug-drug interactions as they relate to antiretroviral therapy.

Pharmacologically, there are two broad classes of drug interactions, namely the pharmacokinetic and pharmacodynamic drug interactions. Interactions are described as pharmacokinetic when the action of one drug alters the serum concentration of

another drug by changing any of the following processes: drug liberation, absorption, distribution, metabolism and excretion. Pharmacodynamic interactions are described simply as those interactions that may alter the overall clinical response expected from use of the drugs by altering the efficacy and often toxicity of the drugs. It could be synergistic (mostly positive, i.e., the positive antiretroviral response seen when zidovudine is combined with lamivudine) or it could be negative (antagonistic, i.e., use of zidovudine and ganciclovir causing additive bone marrow suppression or concomitant use of d4T and ddI causing additive neuropathy).

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Neurologic disease in HIV-1 infected children

April Palmer, MD

A Case Report

A 3-year-old black female was reported to be in good health until six weeks prior to her admission to the University of Mississippi Medical Center in Jackson. She initially presented with upper respiratory tract symptoms and was treated twice by her local pediatrician with oral antibiotics. Three weeks prior to admission to our facility, she began having difficulty walking, starting first as a limp which progressively worsened. She was referred to an orthopedic surgeon for evaluation. Physical examination, plain radiographs of the

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Pharmacy

The majority of interactions do not require extensive changes

[Interactions](#), continued from page 1

Defining pharmacokinetics: relationship to drug-drug interactions

Pharmacokinetics is simply defined as the study of the processes of drug action through the various processes of liberation, absorption, distribution, metabolism and excretion, often referred to as the LADME system. As a result of this broad definition and the involvement of several key processes, numerous possibilities abound for potential pharmacokinetic drug interactions. For instance, any circumstance that alters gastric pH can affect the absorption of many drugs. This is particularly important for patients receiving palliative care, many of whom may have hypochlorhydria which is common in advanced HIV disease and AIDS and may lead to suboptimal absorption of pH-dependent medications such as ketoconazole (Nizoral), itraconazole (Sporonox) and indinavir (Crixivan). Since fluconazole (Diflucan) is readily absorbed independent of gastric pH, it is often the azole of choice when an azole antifungal is indicated for the treatment of several opportunistic infections.

Drug-disease interactions

Drug interactions may arise because of changes due to HIV disease itself. As HIV-infected persons advance in their illness, often oral absorption of foods and drugs is compromised due

to changes in gastric pH that accompany HIV enteropathy, a syndrome that describes the effect of advancing HIV disease on the gastrointestinal system. Diarrhea tends to be common in HIV disease and may result from a variety of causes, namely gastrointestinal disturbance following side effects of several of the most commonly used antiretroviral agents, and the presence of concurrent opportunistic organisms, bacterial, protozoal and viral infections that tend to be more common as the disease advances and the immune system weakens. The occurrence of diarrhea, especially if frequent and poorly controlled as in patients with cryptosporidiasis (a disease entity that is almost impossible to eradicate since none of the agents used for symptomatic treatment have shown persistent efficacy in clinical studies), may jeopardize absorption of all drugs because of the decreased transit time and may cause drug regimens to be less efficacious.

This will lead subsequently to less than optimal clinical outcomes and in some instances may predispose the patient to sub-therapeutic drug levels that may herald the emergence of resistant strains of the virus in patients still taking antiretroviral agents.

HIV-infected persons in palliative care are more likely to suffer from an increase in susceptibility to adverse events, such as a higher incidence of

allergic reactions to sulfonamides and other drugs, than patients in the early stages of their disease. Other physiological components of advancing AIDS/HIV disease include the malabsorption which is the hallmark of enteropathy and predisposes the patient to changes in body weight that often reflect changes in volume as well as distribution of both fat and muscle tissue. This in turn may affect the dose-related efficacy of drugs, for example, the agents used in the treatment of tuberculosis and mycobacterial avium complex disease. Also frequently reported at this stage of illness are decreases in serum albumin, which in turn may alter the efficacy of drugs such as phenytoin when used in the management of patients with toxoplasmosis or sulfamethoxazole when used both as treatment and in the prophylaxis of patients with pneumocystis carinii pneumonia.

Other changes also occur in drug metabolism with advancing disease. These include changes due to hepatitis, frequently a co-infection in this population, especially those who were intravenous drug users (IVDUs), as biliary disease makes it necessary to adjust both the doses, and often the dosing intervals, of drugs that are mostly metabolized through the liver such as rifampin, isoniazid, ketoconazole, and to be selective in the choice of such medications. Changes in the renal elimination of drugs also occurs with advancing disease



and can be especially important for renally-cleared antiretrovirals such as zidovudine, lamivudine, didanosine, zalcitabine and stavudine, antiviral agents such as ganciclovir and cidofovir, antifungal agents such as amphotericin B, and antibacterial agents such as the aminoglycosides.

Changes in immune status that may affect drug responses to antimycobacterial medications (such as the tuberculostatics) or management of opportunistic infections (such as mycobacterium avium complex) have frequently been reported in patients with advancing disease. As a general rule, there is an increased incidence of drug toxicity as well as drug sensitivity, for example with use of the neuroleptics (chlorpromazine and prochlorperazine), which may necessitate a decrease in the usually recommended doses in order to avoid undue toxicity.

When to suspect a drug-drug interaction in a patient with HIV disease

As a general rule, patients experiencing exaggerated toxicities on usual doses of medications or manifesting treatment failure, in the absence of factors such as resistance or poor adherence/compliance, may be suffering from an unidentified drug-drug interaction. In order to monitor for such drug interactions, a careful review of the patient's medication profile is necessary. Clinicians should become familiar with the agents most often associated with significant drug-drug interactions and measures to circumvent them

when necessary. Regimens with enzyme inducers such as rifampin or enzyme inhibitors such as ritonavir should be noted and checked against a list of other agents metabolized by those same enzyme pathways.

Fortunately, the majority of drug-drug interactions are minor in nature and do not require extensive changes to the patient's drug regimen. However, the minority population of drug interactions that can be clinically important may offset treatment goals and outcomes in patients when these remain unrecognized or unaddressed, leading to sub-optimal drug levels of various drugs and so to treatment failures, often due to emergence of drug resistant strains of the virus.

Drug-food interactions of clinical significance

It is well established that the presence or absence of food or certain beverages may significantly affect the bioavailability of a number of medications. A variety of mechanisms including changes in pH, formation of unabsorbable cation complexes, increased solubility of drugs, interference with gut metabolism, as well as a decrease in the motility of the gut, may be at play. Table 1 (next page) lists some of the more common food-drug interactions and simple strategies to circumvent them.

Changes in the renal elimination of drugs also occur with advancing disease and HIV-associated nephropathy (HIVAN), which can disproportionately affect male African-Americans with a previous history of IV

drug use. Such changes can be especially important for renally-cleared antiretrovirals such as zidovudine, lamivudine, didanosine, zalcitabine and stavudine; antiviral agents such as ganciclovir and cidofovir; antifungal agents such as amphotericin B; and antibacterial agents such as the aminoglycosides.

A second installment of this article will appear in a future issue of this publication. It will discuss interactions between antiretroviral agents, psychotropic agents and street drugs.❖

See next page for related tables.

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