AIDS/HIV: Drugs for Opportunistic Infections

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INTRODUCTION

As outlined in Chapter 3, drug interactions in HIV are encountered frequently, particularly with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). In a retrospective chart review of 165 HIV patients newly prescribed a protease inhibitor, at least one potential drug interaction was identified in 82 (49.7%) patients (1). In total, 111 interactions were identified, but only 22 (19.8%) were recognized at the time of protease inhibitor therapy initiation. An additional 12 drug interactions were later identified at follow-up, but 77 (69.3%) were never recognized. At the time this study was conducted, only three protease inhibitors (saquinavir, ritonavir, and indinavir) were available. With even more agents and drug classes available today, the potential for interactions is likely much higher.

While the overall incidence of opportunistic infections has declined in recent years (2–4), concurrent therapy for prophylaxis, treatment, or suppression of opportunistic infections is often still required (5,6). Thus, polypharmacy remains an important risk factor for multiple and often complex drug interactions. This chapter will focus primarily on drug interactions between antiretroviral medications and agents commonly used for the management of opportunistic infections.

General Approach/Considerations

In general, drug interactions may be considered as either pharmacokinetic or pharmacodynamic in nature. Drug absorption, distribution, metabolism, or elimination may be affected by pharmacokinetic interactions, resulting in an alteration of the amount and/or concentration of one or both agents in the body. Such changes are especially undesirable when the disposition of an agent with a narrow therapeutic index is affected. Pharmacokinetic drug–drug interactions are encountered frequently, particularly with protease inhibitors and NNRTIs. For instance, ritonavir is an extremely potent inhibitor of many cytochrome P450 isoenzymes, including CYP3A, CYP2D6, CYP2C9, CYP2C19, and others, and thus has the potential to interact with a multitude of agents that are metabolized via similar routes (7). Agents such as indinavir, nelfinavir, amprenavir, and delavirdine have moderate inhibitory effects on CYP3A, while...
saquinavir is a weak inhibiting agent. Nevirapine, in contrast, is a moderate inducer of CYP3A, while efavirenz is associated with both enzyme-inducing and -inhibiting properties.

With pharmacodynamic interactions, additive, synergistic, or antagonistic drug combinations may affect pharmacologic parameters, such as efficacy and toxicity. Pharmacodynamic drug–drug interactions are often desirable when agents with complementary mechanisms of action are administered, to enhance clinical efficacy. For example, the combination of zidovudine plus lamivudine has greater effects on improving immunologic and viral markers of HIV disease compared to either agent alone (8). Some drug combinations may be used to reduce patient toxicity. To minimize the risk of isoniazid-induced peripheral neuropathy, pyridoxine can be coadministered. In contrast, certain combinations may be undesirable if antagonism or additive toxicity occurs. For example, lamivudine and zalcitabine share structural similarities, and both are initially phosphorylated by the same enzyme, deoxycytidine kinase. Lamivudine and zalcitabine have been shown to interact negatively in vitro, likely via competition for intracellular phosphorylation (9), and thus should not be coadministered. Similar concern exists regarding the combination of zidovudine and stavudine (10).

The clinical significance of an interaction depends on several factors, including the magnitude of change in pharmacokinetic parameters and the efficacy and toxicity of the affected agent(s). Achieving adequate drug concentrations is a very significant factor in determining the success or failure of current as well as future highly active combination antiretroviral therapies. Many antiretroviral agents, particularly protease inhibitors and NNRTIs, have narrow therapeutic indices, and maintenance of minimum drug concentrations may be necessary in order to achieve optimal therapeutic benefit (11,12). This is of especial concern because within-class cross-resistance is not uncommon (13). Patients who fail therapy with one protease inhibitor often do not experience sustained benefit by switching to another protease inhibitor, even one with different in-vitro resistance mutations (14–17).

Furthermore, interactions may result in excessively elevated drug concentrations, which in turn may be associated with increased toxicity. For example, in a study by Preston et al. (1), 82 of 165 patients (49.7%) had at least one potential drug interaction at the time of protease inhibitor therapy initiation. Of those, 29 (35.4%) had at least one potentially serious/life-threatening interaction, 22 (26.8%) had at least one potentially serious interaction with therapeutic drug monitoring available, and 49 (59.8%) had at least one non-life-threatening interaction. Overall, 42.4% of serious or life-threatening interactions were recognized at the time of protease inhibitor therapy initiation. The researchers concluded that patients who were starting protease inhibitors had a high likelihood of concurrently receiving an agent with a potentially serious drug interaction, and that increased awareness and recognition of potential interactions was needed.

**Predicting Pharmacokinetic Interactions with Antiretroviral Agents**

Since new therapeutic agents are continually being developed, keeping abreast of potential interactions is extremely challenging. Often there are little or no pharmacokinetic interaction data available for certain combinations of drugs. In such situations, familiarity with the basic pharmacokinetic and pharmacodynamic characteristics of the agents involved may help practitioners predict the likelihood of interactions. All pro-