Drug Interactions with Antipsychotic Agents
Incidence and Therapeutic Implications

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Summary

Antipsychotics are the mainstay of treatment for psychotic disorders. Both the newer atypical antipsychotics and their more traditional counterparts are subject to drug-drug interactions amongst themselves, with other psychotropics and with agents used in the treatment of various physical ailments. Furthermore, drug interactions have been documented to occur with many agents commonly used in conjunction with antipsychotics such as anticholinergics, anticonvulsants, antidepressants, anxiolytics and lithium.

Different types of drug interaction can occur, including pharmacodynamic, pharmacokinetic and pharmaceutic interactions. Pharmacodynamic interactions occur between agents that have similar receptor site activity.

Pharmacokinetic interactions occur when the combination of drugs results in alterations in the absorption, distribution, metabolism or excretion of either agent. As a group, the antipsychotics are highly protein bound (>90%) and distribute widely into tissues. As a consequence, interactions can arise from combining antipsychotics with other agents that are also highly protein bound. Antipsychotics undergo phase I and II metabolism to more water-soluble compounds to aid
in excretion from the body. Research has dramatically expanded in the area of metabolism by the cytochrome P450 (CYP) system. Most antipsychotics are metabolised by the CYP system and potential drug interactions could occur when they are administered with other agents that affect or are metabolised by the same isozymes. Persons who lack specific CYP isozymes (CYP2D6 or CYP2C19) can be at an increased risk for the development of adverse effects when administered antipsychotics, due to higher than expected plasma concentrations of these drugs.

The anticonvulsants carbamazepine and phenobarbital (phenobarbitone) are enzyme inducers. When these drugs are given concurrently with antipsychotics, decreased plasma concentrations and therapeutic effectiveness of antipsychotics can occur. Tricyclic antidepressants can compete for similar metabolic enzymes with antipsychotics. This can result in an increase in plasma concentrations and a risk of adverse effects of either agent. All clinically available serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors have inhibitory activity at various CYP isozymes and potentially cause increases in plasma concentrations of antipsychotics. Smoking is relatively common in schizophrenic populations and can induce metabolic enzymes, resulting in lower then expected plasma concentrations of several antipsychotics.

Most data on antipsychotic drug interactions come from case reports and limited uncontrolled studies, making assessment of the clinical significance of the interactions difficult. However, with further insight into the metabolic interactions of the CYP isozyme systems through in vitro and in vivo testing, the clinical significance of these drug interactions will become more apparent.

Antipsychotic agents are used for the treatment of schizophrenia and other psychotic disorders. The estimated prevalence of schizophrenia worldwide is between 0.5 and 1.0%.[1]

Antipsychotics have binding affinity at a variety of receptor systems including dopaminergic, serotonergic, cholinoergic, histaminergic and adrenergic. These receptor interactions are responsible for the therapeutic effect of antipsychotics as well as a variety of adverse effects and potential drug-drug interactions.[2] Traditionally, antipsychotics are believed to work through their antagonistic activity at dopamine receptors, most notably the dopamine D2 receptor subtype. Indeed, the antipsychotic potency of these drugs has been measured by their ability to occupy D2 receptors. The use of clozapine and other atypical antipsychotics brought new insight into the pathophysiology of schizophrenia and the treatment of psychotic disease states. New antipsychotics have sparked investigation into the role of other dopamine receptors, most notably D3 and D4.[3] The atypical antipsychotics are so-named because of their ability to treat psychotic symptomatology, both positive and negative, and their minimal potential to cause extrapyramidal symptoms (EPS) or prolonged elevations in serum prolactin levels.[4]

Both the typical antipsychotics and the newer atypical agents are subject to drug-drug interactions. The use of multiple psychoactive agents for patients with treatment-resistant psychiatric illnesses or with comorbid psychiatric or physical disease states has increased the importance of drug-drug interactions in clinical practice. Unfortunately, much of the literature pertaining to drug interactions with antipsychotics comes from empirical case reports and small uncontrolled trials.[5] From these reports, it may be possible to theoretically predict drug-drug interactions based on the pharmacological or pharmacokinetic profiles of these agents. However, without controlled trials, the clinical significance of these drug interactions is questionable.

The aim of this article is to review the available