It is a Risk Prescribe Together Neuroleptics and Benzodiazepines?

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SUMMARY

A brief review of the therapeutic and adverse effect aspects of neuroleptic-benzodiazepine combinations is presented. This combination, which is used relatively frequently in the clinical setting, appears to result in a low incidence of adverse effects, whether as a result of pharmacodynamic or pharmacokinetic interactions. However, several agents from both these classes of drugs are substrates and/or inhibitors of cytochrome P450 isozymes, and the possibility of potential pharmacokinetic drug-drug interactions should be kept in mind. Although such drug-drug interactions have not apparently been a major problem with the neuroleptic-benzodiazepine combinations used to date, it should be remembered that numerous new neuroleptics have just been, or are about to be, introduced. It is important to be cognizant of the metabolic profiles of these new drugs to avoid any possible pharmacokinetic drug-drug interactions.

Key Words: Neuroleptics, benzodiazepine, drug-drug interactions, adverse effects, cytochrome P450 isozymes.
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Coadministration of neuroleptics and benzodiazepines is not unusual in the treatment of schizophrenia, with the benzodiazepines usually added to treat agitation and/or aniety (They may also reduce neuroleptic-induced akathisia) (1). This drug combination could also be used to treat mania. The combination of lorazepam or alprazolam with a strong antipsychotic drug such as haloperidol could reduce agitation more than each of these drugs used by itself. That is may be possible to decrease the neuroleptic dose usually needed to control the patient's behaviour. Parenteral administration of benzodiazepines alone may decrease the intensity of agitation as well as some symptoms of the acute psychotic state.

Because of the frequency of coadministration of benzodiazepines and neuroleptics, it is important to consider possible adverse effects which may result from such combinations.

Adverse effects reported with neuroleptic-benzodiazepine combinations

There are remarkably few reports in the literature of adverse effects resulting from coadministration of neuroleptics and benzodiazepines (2,3). Toxic effects which have been reported upon addition of benzodiazepines to clozapine include sedation, sialorrhea, ataxia, fainting, loss of consciousness and respiratory arrest (2,4), but the incidence of such adverse effects is apparently rare and little is known about the pharmacodynamic and/or pharmacokinetic mechanisms involved. Hypotension, stupor and respiratory distress have been reported when the neuroleptic loxapine and the benzodiazepine lorazepam are combined (5,6), but the precise mechanisms involved are unknown.

Potential Drug-drug Interactions Between Neuroleptics and Benzodiazepines Involving Cytochrome P450 Isozymes

Metabolic drug-drug interactions involving cytochrome P450 (CYP) isozymes have received increased attention in recent years because of the rather potent effects of some of the selective serotonin reuptake inhibitor (SSRI) antidepressants in inhibiting these isozymes, particularly CYP2D6 (7-11). There are now numerous reports of pharmacokinetic interactions between SSRIs and other antidepressants, neuroleptics and benzodiazepines (7-11), but there

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is a paucity of reports of such interactions involving neuroleptics and benzodiazepines. However it is important to remember that most of the neuroleptics and benzodiazepines available are substrates for and(or inhibitors of some CYP isozymes, and the possibility of metabolic drug-drug interactions should at least be considered; this is particularly important since several new neuroleptics have recently been introduced or are about to come on the market imminently.

CYP2D6 has been reported to play an important role in the metabolism of a number of neuroleptics, including perphenazine, thioridazine, clopenthixol, haloperidol, risperidone and loxapine (9). CYP1A2 and CYP3A4 appear to be involved in metabolism of clozapine (12-1), although other CYP isozymes may also play a role. Both CYP1A2 and CYP2D6 seem to play important roles in the metabolism (N-demethylation and 2-hydroxylation, respectively) of a newly introduced neuroleptic, olanzapine (15).

Several neuroleptic, including chlorpromazine, haloperidol, thioridazine and levomepromazine are relatively potent inhibitors of CYP2D6 (7-9), while others, including clothiapine, flupenthixol and pimozide, apparently have little or no effect on this CYP isozyme (16-18).

While CYP2D6 seems to be an important catalyst of metabolic pathways of several neuroleptics and a number of neuroleptics are effective inhibitors of CYP2D6 (as mentioned above), the CYP isozyme 3A4 seems to play a dominant role in metabolism of benzodiazepines, including diazepam, alprazolam, triazolam and midazolam (7,9,19-22). This difference in selectivity for CYP isozymes may explain why there are few reports of pharmacokinetic drug-drug interactions between neuroleptics and benzodiazepines. However, recent studies (12-14, 23) indicate that CYP3A4 contributes to the metabolism of both haloperidol and clozapine, suggesting that more comprehensive studies on metabolic drug-drug interactions with benzodiazepines are warranted. Douyon et al. (24) had previously reported that the addition of alprazolam to stable doses of haloperidol or fluphenazine led to a mean increase in plasma concentrations of these neuroleptics of >20%. Both diazepam and N-desmethyldiazepam are substrates for CYP2C19 (7,9,19), but there is currently limited information available about the involvement of this isozyme in the metabolism of other benzodiazepines (or of neuroleptics).

In summary, metabolic drug-drug interactions seem to be less of a problem with combinations of neuroleptics and benzodiazepines than with some other drug combinations encountered in psychiatry. However, the recent large increase in the volume of psychopharmacology literature describing metabolic drug-drug interactions among psychiatric drugs (7-9) indicates that characterization of future neuroleptics should include a profile of interactions with CYP isozymes to predict if metabolic drug-drug interactions might be a potential problem. Such characterization is particularly important since several new neuroleptics have just been launched or about to come on the market in the near future.

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