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MULTIPLE DRUG INTERACTION ACROSS MEDICAL SPECIALIZATIONS

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ABSTRACT

An epileptic patient on high dose carbamazepine monotherapy received erythromycin from a physician and ketoconazole from a dermatologist. Carbamazepine neurotoxicity developed as a result of a pharmacokinetic interaction between the three drugs. Precautions are suggested to minimize the risk of such drug interactions that span medical specializations.

Key Words : Carbamazepine, drug interaction, neurotoxicity, erythromycin,ketoconazole, metabolic interactions, pharmacokinetic interactions

Drug interactions are of two types: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions are those which involve drug absorption, protein-binding, distribution, metabolism and excretion; fluoxetine-mediated inhibition of the metabolism of tricyclic antidepressant drugs is an example of a pharmacokinetic interaction. Pharmacodynamic interactions are those which involve physiological effects through receptor or other mechanisms; cyproheptadine-mediated reversal of the antidepressant benefits of fluoxetine is an example of a pharmacodynamic interaction.

Pharmacokinetic interactions are of much importance in psychiatry because many psychotropic and antiepileptic agents commonly induce or inhibit the metabolism of other drugs through their action on the cytochrome P450 hepatic microsomal enzymes. A less common situation is one in which non-psychotropic drugs exert pharmacokinetic effects on psychotropic medications; such interactions are of importance because they span medical specializations, and may arise because the concerned specialists do not take cognizance of interactions across treatment domains.

This report illustrates a multiple drug interaction that arose from independent prescriptions issued by a psychiatrist, a physician and a dermatologist. Suggestions are offered to guard against the occurrence of such situations.

CASE REPORT

Mr. R, a 40 year old epileptic, was fit-free for the past 2 years on monotherapy with carbamazepine 1200 mg/day in 3 divided doses. His carbamazepine blood level was 12mg/l.during January 1999, he consulted a physician for a respiratory infection and was prescribed erythromycin 250 mg four times daily. On the same day, he consulted a dermatologist for a fungal infection, and was prescribed ketoconazole 200 mg/day. On the second day of erythromycin and ketoconazole, he began to experience a squinting sensation. By the third day, he developed diplopia, giddiness, slurring of speech and unsteadiness of gait. Physical examination revealed lateral gaze nystagmus, marked incoordination on various tests, and other cerebellar signs. There were no other abnormal physical findings. Cognition was grossly intact. His 12 hr. carbamazepine level was found to be 25.0 mg/L.

Carbamazepine neurotoxicity was diagnosed, secondary to a multiple drug interaction, and all medication was stopped for a day. The neurotoxicity began to subside. Carbamazepine alone was resumed the next day in a gradually escalating dose. The upward dose titration was based on carbamazepine blood levels which were obtained daily to ensure that these were below toxic (15-20 mg/L) but not below the therapeutic range (6-12 Mg/L). After a week, the original dose and blood level were re-attained, and the patient remained symptom-free.

DISCUSSION

About 98% of carbamazepine is cleared by hepatic metabolism (Ciraulo and Slattery, 1995) through the cytochrome P450 3A3/4 microsomal enzymes (Preskorn, 1996), and this metabolism is inhibited by erythromycin and other macrolide antibiotics; there are several reports on record of the development of carbamazepine neurotoxicity following the administration of a macrolide antibiotic with carbamazepine (Janicak, 1993; Ciraulo & Slattery, 1995). Patients who are on high doses of carbamazepine, such as the patient in the present case report, are therefore especially vulnerable to such interaction- mediated toxicity.

Ketoconazole, a broad-spectrum anti-fungal agent, is also a potent inhibitor of the 3A3/4 enzyme system (Greenblatt, 1993). Being a relatively new drug, there are few reports of its effects on carbamazepine levels; in one such report, Spina et al. (1997) demonstrated that ketoconazole 200 mg/day increased plasma carbamazepine (but not its epoxide metabolite) concentrations by about 25%.

It is therefore likely that the patient in the present report developed carbamazepine neurotoxicity as a combined pharmacokinetic interaction between carbamazepine on the one hand and erythromcin and ketoconazole on the other.

It is suggested that treating doctors neec to be aware of psychotropic - medical drug interactions such as that between carbamazepine and erythromycin or ketoconazole. Psychiatrists also need to routinely warn patients about specific hazardous interactions between psychotropic and medical drugs; for example the patient can be given a short list of drugs that are best avoided. Such a precaution is especially important when patients are on high doses of psychotropic medication. It is not prudent to assume that the patient will discuss his psychotropic prescription with physicians from other specialization, nor is it prudent to assume that other specialists will be aware of all interactions between medical and psychotropic agents.

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