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Interaction between carbamazepine and dextropropoxyphene

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Summary: Serious side effects may result from the concurrent administration of the usual dosage of carbamazepine and dextropropoxyphene. Three cases are reported and the mechanisms and implications discussed.

Introduction

Carbamazepine and dextropropoxyphene are commonly used drugs and may be prescribed simultaneously in certain medical conditions. We report three Chinese patients who suffered from severe side effects brought about by administering the usual dose of these two drugs concurrently and wish to draw attention to the clinical implications of the pharmacokinetic interaction between them.

Case reports

Case 1

A retired clerk, 70 years old, was admitted because of painful vesicular eruptions over the forehead. Examination revealed a well-built man (55 kg) in distress from florid herpes zoster of the first division of the left trigeminal nerve.

A course of intravenous acyclovir and topical idoxuridine were given. In addition, because of the excruciating pain, he was started on carbamazepine 200 mg twice a day and dextropropoxyphene 32 mg 6-hourly as required. The pain, however, continued unabated for the next 2 days. As no side effects of the medication were observed, carbamazepine was increased to 200 mg three times a day and dextropropoxyphene 32 mg 4-hourly. The pain was partially relieved. Three days later the patient was noted to be drowsy and became comatose within 2 hours. No focal signs were elicited.

The serum carbamazepine level was high at 84 μmol/l (toxic level >64 μmol/l). Electroencephalogram showed bilateral slow activity compatible with a metabolic disturbance and cerebrospinal fluid (CSF) analysis revealed 16×10^6 cells/l (69% polymorphs and 31% lymphocytes) with normal glucose and protein levels. The other investigations, including blood counts, biochemistry and computed tomographic (CT) scan of the brain, were normal.

The diagnosis of carbamazepine intoxication was made. All drugs were stopped and supportive treatment given. His conscious level recovered completely within 5 days, by which time the serum carbamazepine level had fallen to 9 μmol/l. The alternative diagnosis of herpes zoster encephalitis was considered unlikely in view of the course of events. Mild CSF pleocytosis, as present in this case, has been reported in patients with only cutaneous zoster (Gold, 1966).

Case 2

A 69 year old housewife presented with a painful skin rash on her left forehead. She had a history of myelofibrosis and splenectomy, and chemotherapy had been stopped 4 months before admission. Examination revealed a thin lady (37 kg) in severe pain with herpetic lesions at the ophthalmic division of the left trigeminal nerve.

Intravenous acyclovir was given for 5 days. Because of the severe pain, dextropropoxyphene was started at 32 mg 4-hourly on demand and gradually increased to 64 mg 6-hourly. Four days later, this was substituted by carbamazepine 200 mg twice daily to achieve better pain relief. Two days later the carbamazepine was stepped up to 200 mg three times a day and dextropropoxyphene re-started at 32 mg 4-hourly.

On the fifth day of this regime, she fell in the toilet and on that evening, she became drowsy and then comatose. No focal signs were elicited. CT scan, serum electrolytes, and blood sugar were normal. CSF analysis showed 14×10^6 cells/l with 75% lymphocytes and 25% polymorphs. Serum carbamazepine was above toxic level at 70.8 μmol/l.

Carbamazepine intoxication was diagnosed. All medications were stopped and supportive treatment was given. Her conscious level began to improve on

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the second day and she was fully orientated by the fifth day.

Case 3

A 79 year old lady, of medium build (53 kg), was hospitalized because of painful rash and vesicles in the left groin and examination showed herpes zoster at the left L1 dermatome. Dextropoxyphene 64 mg 6-hourly was given for the severe pain. When it was clear after 7 days that the pain was not relieved, carbamazepine 100 mg twice a day was added and then increased to 200 mg twice a day 2 days later with some improvement. However she became confused on the 12th day of hospitalization. Both drugs were immediately stopped and the carbamazepine level was found to be near the toxic range at 60 μmol/l. Her mental confusion subsided in 3 days. The pain was partly relieved by codeine phosphate.

Discussion

Potentiation of the side effects of carbamazepine by dextropropoxyphene was first reported by Dam *et al.* in 1977 and then by Hansen *et al.* in 1980. To our knowledge, no further reports have been published. This drug interaction is mentioned briefly in the British National Formulary, Martindale's Extra Pharmacopoeia and an information brochure on carbamazepine produced by Ciba-Geigy, but is not listed in the data sheet of either drug and many medical practitioners appear unaware of the potentially serious consequences.

Hansen *et al.* (1980) investigated the mechanism of the interaction. The usual dose of dextropropoxyphene was given to epileptic patients who had been stabilized on carbamazepine. In six patients who took both drugs for 6 days, the mean increase of the serum carbamazepine level was 66%, though none was clinically affected. A further patient, however, developed dizziness and nausea with a 49% increase in the serum carbamazepine level on day 1. The protein binding of both drugs was not affected, but there was a concomitant decrease in the serum level of carbamazepine-epoxide, its major metabolite. The authors therefore suggested that inhibition of carbamazepine metabolism by dextropropoxyphene was a likely mechanism and recommended that dextropropoxyphene as an analgesic should be avoided in epileptic patients on carbamazepine therapy even if only for a short period. The same would also apply to patients on long-term carbamazepine for other medical conditions like trigeminal or post-herpetic neuralgia.

Carbamazepine is sometimes used for pain in acute herpes zoster infection. Logan (1963) first described its efficacy in one patient though he mislabelled the condition as post-herpetic neuralgia. Halman (1968) subsequently reported a good response in 18 out of 22 patients. In our three patients, the severity of pain persuaded the doctors-in-charge to use the combination of carbamazepine and dextropropoxyphene. This brought about partial control of pain, but it is probable that a more potent analgesic *per se* would have achieved the same result.

The development of serious side effects in our three cases was probably not due to excessive carbamazepine dosage, since when such doses are prescribed for our epileptic patients, therapeutic levels are achieved without causing side effects. More likely, such side effects resulted partly from the interaction with dextropropoxyphene (as discussed above), and partly from the carbamazepine first dose phenomenon. The latter is probably related to auto-induction of drug metabolizing enzymes in the liver (Bertilsson, 1978). This would explain the observation of Rawlins *et al.* (1975) that the pharmacokinetics of carbamazepine change during long-term therapy: the predicted steady-state concentration of 200 mg three times a day calculated from the parameters of a single oral dose was two to three times higher than that encountered in patients stabilized on carbamazepine at the same dosage. This phenomenon also accounts for the frequent occurrence of side effects at the initiation of carbamazepine treatment which tend to diminish as treatment continues.

Our experience suggests that serious side effects due to interaction of carbamazepine and dextropropoxyphene are not uncommon, particularly during the initial stage of carbamazepine therapy. We propose that the possibility of such an interaction should be stated in the data sheets of both drugs. Under the circumstances, this combination of drugs is best avoided, but if deemed necessary, frequent monitoring of carbamazepine levels is strongly recommended.

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