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CASE REPORT

Potential Effect of Enalapril on Clomipramine Metabolism

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In two patients treated for hypertension with enalapril for more than 12 months, clomipramine was introduced in small to moderate doses for the treatment of dysthymic disorders. Rapid improvement of depressive symptoms was noted, which was followed by signs of antidepressant overdosage. The blood levels of clomipramine and desmethylchlomipramine were high. After reducing the dose, the symptoms resolved and the blood level of antidepressant returned to the usual therapeutic range. Enalapril would appear to reduce the clearance of clomipramine; the association enalapril + clomipramine does not appear to modify blood pressure.

KEY WORDS—Clomipramine, angiotensin converting enzyme, enalapril, drug interaction.

INTRODUCTION

Captopril and enalapril, two angiotensin converting enzyme (ACE) inhibitors have proved useful in the treatment of congestive heart failure and for mild to moderate hypertension (Williams, 1988). ACE inhibitors are well tolerated. Captopril and enalapril have been reported to elevate mood (Zubenko and Nixon, 1984), but further investigations have demonstrated a lower incidence of side-effects (Croog *et al.*, 1986) and failed to demonstrate any intrinsic antidepressant pharmacological effect (Olajide and Lader, 1985; Martin *et al.*, 1990).

Drug interactions with ACE inhibitors have been reported with digitalis, diuretics, salicylates, antidiabetics, non-steroidal anti-inflammatory drugs and lithium (Hansten and Horn, 1989). To our present knowledge, an interaction with tricyclic antidepressants has not been reported.

Two cases of interaction between enalapril and clomipramine, a tricyclic antidepressant, are presented.

CASE 1

A 58-year-old man treated for moderate hypertension with enalapril 20 mg and hydrochlorothiazide 12·5 mg (Co-Reniten®) fives times a week over 2 years presented signs of depression. The diagnosis according to DSM-III-R was dysthymic disorder and clomipramine 25 mg/day was introduced. After 9 days the blood concentrations of clomipramine and its main active metabolite desmethylclomipramine were low–26 and 18 ng/ml respectively. The recommended level is: clomipramine + desmethylclomipramine: 160–450 ng/ml. The clomipramine dosage was increased to 50 mg/day. Ten days later the patient experienced a rapid mood elevation, became progressively euphoric and exalted. Clomipramine+desmethylclomipramine levels were elevated (160 and 104 ng/ml). The dose was reduced to 25 mg/day and the patient became euthymic. Further blood control tests showed that clomipramine+desmethylclomipramine blood levels diminished to 94 and 79 ng/ml and remained within this range. Hepatic function was within normal limits, and oxidation-type debrisoquine showed a metabolic ratio $<0{\cdot}3$, indicating a major metabolizer phenotype (Mahgoub *et al.*, 1977). During the co-administration of enalapril and clomipramine, the blood pressure and heart rate remained unchanged.

CASE 2

In a 54-year-old depressed, alcoholic man treated for hypertension over 1 year with enalapril 20 mg/day (Reniten®), clomipramine was introduced at

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the same time as disulfiram 400 mg/day. Two weeks later the patient became confused and irritable, and he complained of insomnia. The blood concentration of clomipramine and desmethylclomipramine was 252 and 184 ng/ml respectively. Clomipramine was reduced to 50 mg/day with lessening of confusion and irritability. Twenty days later disulfiram was stopped; the patient continued to improve and the clomipramine and desmethylclomipramine blood levels decreased to 78 and 41 ng/ml respectively and remained within this range 3 months later. In this patient hepatic enzymes, (ALAT) and (AZAT) were slightly elevated (ALAT, 7; N: 11–60 u/l. AZAT, 53; N: 14–50 u/l).

DISCUSSION

Clomipramine, a tricyclic antidepressant, is widely used in Switzerland for the treatment of depression (Broadhurst *et al.*, 1977) and was recently introduced in the USA for the treatment of obsessive–compulsive disorders (McTavish and Banfield, 1990). Clomipramine mainly inhibits the reuptake of serotonin while its active metabolite desmethylclomipramine is principally a noradrenaline uptake inhibitor. Clomipramine and desmethylclomipramine are further hydroxylated, then conjugated, before hepatic elimination. There is no correlation between doses and blood level of clomipramine, which has nonlinear kinetics. The steady state of clomipramine is reached after 7–10 days and for desmethylclomipramine after 14–20 weeks (Millet *et al.*, 1977). After oral regimen the clomipramine/desmethylclomipramine metabolic ratio indicating the liver capacity to demethylate clomipramine is < 1 with magnitude of 20 in inter-individual variation (Jones and Luscombe, 1977; Denker and Nagy, 1979; Evans *et al.*, 1980; de Cuyper *et al.*, 1981; Balant-Gorgia *et al.*, 1991).

In our two patients the clomipramine/desmethylclomipramine ratio > 1 during treatment with ACE inhibitor could neither be attributed to excessive alcohol use, alcoholics and smokers having been shown to have clomipramine/desmethylclomipramine ratio < 1 (Vandel *et al.*, 1982) nor to liver dysfunction, AZAT and ALAT being slightly elevated in patient 2. The clomipramine/desmethylclomipramine ratio > 1 could reasonably be explained by inhibition of the demethylation of clomipramine by enalapril, leading to accumulation of clomipramine and the unusual metabolic ratio after oral regimen.

The role of disulfiram in patient 2 is still a matter of debate. Disulfiram seems not to have an effect on the pharmacology of enalapril; blood pressure was within normal limits during the co-administration of enalapril + disulfiram. The inhibition of demethylation of clomipramine by disulfiram in patient 2 seems to be minimal; no relationship between disulfiram and toxicity was established for amitriptyline on other tricyclic antidepressant (Maany *et al.*, 1982). After reducing the daily dosage of clomipramine while taking disulfiram, and at a steady-state level, the metabolic ratio was 1·16. After disulfiram withdrawal and in the same steady-state conditions, the metabolic ratio was 1·90, indicating only a minor effect of disulfiram on clomipramine metabolism.

CONCLUSIONS

We observed that in our two depressed patients ACE-inhibitor enalapril has no effect on mood; ACE-inhibitor enalapril reduces the hepatic clearance rate of clomipramine. The diminished clearance of clomipramine induced by enalapril and the subsequent elevation of blood concentrations of clomipramine + desmethylclomipramine, could explain the rapid mood elevation. Finally, the association enalapril & clomipramine does not affect the control of blood pressure.

More clinical cases would be needed to enable us to confirm our observations.

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