Relationship Between the Plasma Concentration of Clomipramine and Desmethylclomipramine in Depressive Patients and the Clinical Response

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Summary. Thirty one in-patients suffering from depression were treated orally with clomipramine (C1) at various dosage, for 28 days, after a “wash-out” period of three days. In 17 patients receiving 75 mg per day of C1, steady state plasma levels of C1 were reached at Day 14, and steady state plasma levels of its active metabolite, desmethylclomipramine (DMCI), were reached at Day 21. In contrast, in 7 other patients receiving a dosage increasing to 150 mg per day at Day 7, mean plasma levels of C1 and DMCI continued to rise during the entire treatment period. At the steady state, a correlation was found between C1 dosage expressed as mg kg body weight and the plasma concentration of C1 and DMCI. Factors such as tobacco and alcohol consumption seem to modify the C1/DMCI ratio. A comparison of clinical response with plasma levels of C1, DMCI and C1 + DMCI showed a significant negative linear correlation.

Key words: clomipramine, desmethylclomipramine, depressive syndrome; plasma level, pharmacokinetics, clinical response, benzodiazepines

It is still a common clinical experience to find that about 30% of depressed patients respond poorly to tricyclic antidepressants (Broadhurst et al. 1977; Buchins and Ananth, 1976). Pharmacokinetic factors may partly explain this failure. Treatment with tricyclic antidepressants (TCA) might be made more effective if more attention were paid to plasma concentrations in individual patients (Sjöqvist 1971). Studies of the relationship between the pharmacokinetic and pharmacological effects of the TCA are therefore important. Once the steady-state is achieved, the plasma concentration of a TCA reflects its concentration at the site of action. The plasma level is thus likely to bear a relationship to clinical effect. Several groups of workers have examined this concept. There have been more studies on the relationship of plasma concentration to clinical response for nortriptyline than any other TCA. (Åsberg et al. 1971; Kragh-Sørensen et al. 1976; Ziegler et al. 1976; Montgomery et al. 1978; Burrows et al. 1974), but there is no general agreement in their results. Most authors now agree that there is a curvilinear relation between nortriptyline plasma level and clinical effect. Concerning other TCAs there are still discrepancies. Studies of two of the tertiary amine tricyclics, imipramine and amitriptyline, have suggested a linear or curvilinear relationship between plasma level and clinical response (Gram et al. 1976; Reisby et al. 1977; Glassman et al. 1977; Olivier-Martin et al. 1975; Braithwaite et al. 1972; Ziegler et al. 1976; Kupfer et al. 1977; Vandel et al. 1978; Montgomery et al. 1979; Perel et al. 1976). In contrast, a collaborative study failed to establish a significant linear correlation between the plasma levels of amitriptyline and clinical response (Coppen et al. 1978). The results of these studies seem to vary somewhat from drug to drug and from group to group. But all the reports have indicated that, for TCA, there is no simple relationship between dosage and plasma level in a patient population. These large interindividual variations in steady-state plasma TCA levels led to the hope, based on the assumption of a therapeutic range of plasma levels, that the monitoring of plasma concentrations would improve the precision with which these drugs can be individually prescribed.

Recent advances in analytical techniques make it possible to devise routine assay procedures capable of measuring therapeutic levels of all TCA in common use, such as clomipramine (C1). The pharmacokinetic profile and clinical pharmacology of C1 have not yet been fully characterized. For this reason, the aim of the present study was to examine the pharmacokinetics of C1 in depressive patients and variations in its biotransformation, and to investigate the relationship between the plasma levels of clomipramine and its active metabolite (DMCI), and the clinical response.
Patients and Methods

Patients

31 in-patients, 13 males and 18 females, aged 21–77 years (mean 44 years), with an endogenous or exogenous depressive syndrome, without delusional pathology (Gurney et al. 1972), participated in the study. Their body weights ranged from 44 kg to 99 kg (mean 61.8 kg). Only patients with a Hamilton rating score higher than 44 were accepted (Hamilton rating scale with 26 items). There were 14 endogenous and 17 neurotic depressives.

No attention was paid to the duration of the recent or earlier depressive periods. Patients with serious physical disorders were not accepted. Data on blood chemistry, in particular protein electrophoresis to show α1-acid glycoproteins, to which clomipramine binds, in all cases were normal, even in smokers and alcoholic patients. There were 7 subjects who smoked more than 20 cigarettes per day (prior and during the study), and 6 non-cirrhotic alcoholic patients. Alcoholic patients drank more than 2 litres of red wine per day during the 6 months prior to their hospitalization. Their blood chemistry findings, in particular transaminases, α-glutamyltransferase and triglycerides, were normal.

Of the 31 patients who started, 28 completed the study. The reasons for the three drop-outs were:
1 – confusion on Day 10
2 – important side effect on Day 7 (dizziness)
3 – discharge from hospital for family reasons on Day 16

Drug Administration

Following a three day “wash out” period, and after randomization, 15 patients were started on oral clomipramine chlorhydrate 75 mg, once daily (6 p.m.), or on three times a day dosing (9 a.m., 12, 6 p.m.), n = 16, during the first 3 days of therapy. 17 patients received a fixed dose of CI 75 mg per day. The dosage was increased to 150 mg for 10 patients and to 225 mg per day for 4 patients, the final dose being dependent upon how well the patient was able to tolerate the drug. 28 patients were treated for 28 days. All patients received benzodiazepines (flunitrazepam 2 mg, clorazepate dipotassium 50–150 mg, oxazepam 50–150 mg, diazepam 10–50 mg, lorazepam 5–7.5 mg) throughout the treatment. Benzodiazepines do not appear to influence plasma clomipramine levels or the clinical efficacy of clomipramine therapy (Luscombe and Jones 1977; Silverman and Braithwaite 1973; Gram et al. 1974; Träskman et al. 1979). Lack of patient compliance cannot be ruled out with certainty, but the patients were always observed to ingest their medicine.

Blood Samples

Plasma concentrations of clomipramine and desmethylclomipramine were determined on Days 0, 7, 14, 21, 28, in blood samples taken 15 h after administration of the evening dose. Plasma was stored frozen at −20 °C until analysed.

Recording of the Effects

Rating of depressive symptoms on the Hamilton rating scale for depression was always performed by the same psychiatrist, who was unaware of plasma level of the drug, on Day 0 at the end of the “wash out” period, and on Days 7, 14, 21, 28 of treatment. Recording of the clinical effect and blood sampling were carried out at the same time of day.

Chemical Analysis

Plasma concentrations of CI and DMC1 were measured at the end of the trial by gas-liquid chromatography with a nitrogen-sensitive detector. These data were not known by the psychiatrists when rating the patients. There was no interference by benzodiazepines with the assay procedure.

The analytical technique used to measure simultaneously the plasma levels of clomipramine and desmethyliclampiramine consisted of simple extraction of the two drugs (n-hexane-isooamylalcohol 98.5 : 1.5 v/v) from alkalinized plasma (2 ml, pH ≈ 12) containing the internal standard (ethanolic solution of cyclobenzaprine). After centrifugation, the organic phase was evaporated to dryness in a water bath at 60 °C under a gentle stream of nitrogen. The residue was dissolved in ethyl alcohol and chromatographed at 260 °C on a Perkin-Elmer 3920 gas-chromatograph equipped with an alkali flame nitrogen-phosphorus detector. The column (2 m × 4 mm ID) was of silanized glass packed with 3% OV 17 on Chromasorb WHP (80–100 mesh).

Plasma standards containing known concentrations (10 to 200 ng · ml⁻¹) of clomipramine and desmethyliclampiramine were analyzed in duplicate concurrently with unknowns. The calibration curves prepared for each series of samples (peak height ratio of clomipramine and desmethylichlampiramine standards to peak height of cyclobenzaprine vs their concentrations per ml plasma) were linear, and the coefficient of variation over this range did not exceed 5% (n = 10 for each concentration). Recoveries were about 70–80%, and the lower limit of accurate determina-