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Clinical Response and Tricyclic Plasma Levels During Treatment with Clomipramine

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SUMMARY Fifty depressed in-patients at two psychiatric units, one in Italy the other in England, were treated with clomipramine, either orally, or intravenously and orally. A comparison of clinical response with plasma levels of clomipramine and its metabolite, desmethylclomipramine, showed clear relationships especially in the case of desmethylclomipramine. In the intravenously-treated group this was linear, in the orally-treated group it was curvilinear. Plasma levels of desmethylclomipramine and administered clomipramine correlate highly.

These findings, together with the fact that significant clinical improvement was observed in only 55 per cent of the patients, suggest that titration of the administered dose to obtain more effective plasma levels of the metabolite might improve the clinical response to the drug in some patients.

Introduction

It has been shown that a proportion of depressed patients do not respond to tricyclic drugs (Medical Research Council, 1965), and this present study was designed to examine this fact and to suggest an explanation and possibly a remedy.

Studies on the relationship between clinical effect and plasma levels for various types of tricyclic antidepressants have yet to produce conclusive results. The disparities in various findings undoubtedly reflect the great methodological problems encountered. Since the introduction of sensitive, specific and reproducible methods of analysis of plasma concentrations, therapeutic response and plasma level have been studied most frequently in patients treated with nortriptyline (Åsberg *et al*, 1971; Burrows *et al*, 1972; Kragh-Sørensen *et al*, 1973; Burrows *et al*, 1974; Ziegler *et al*, 1976; Ziegler *et al*, 1977), amitriptyline (Braithwaite *et al*, 1972; Ziegler *et al*, 1977; Kupfer *et al*, 1977; Coppen *et al*, 1978) or imipramine (Gram *et al*, 1976; Glassman *et al*, 1977; Reisby *et al*, 1977).

However, the pharmacokinetic profile of clomipramine, despite its wide use in the treatment of depressive illness, has not yet been fully characterized.

In the present study plasma levels of clomipramine (CI) and its metabolite desmethylclomipramine (DMCI) were measured and assessed against clinical response. There were two groups of patients, making a total of 50 in all, who underwent the different dosage regimes (intravenous, oral) of CI, which represent accepted clinical practice with this drug.

Although the two groups of patients were followed up in two different clinics, one in Italy and the other in England, a comparison of the results was made possible by a standardization of methods; the same criteria in patient selection and clinical assessment were followed in both clinics, and plasma levels were measured in the same laboratory by the same analytical technique.

The study has enabled an examination of a relatively large numbers of patients, and apart from the examination of clinical response the

method allowed a reassessment of the well-known variability in plasma level for differing drug dosages and also presented an opportunity to examine the relative activity of CI and its major metabolite DMCI.

Methods

This study was conducted on 50 in-patients suffering from depressive illness severe enough to warrant admission to one of two similar psychiatric clinics, one in the University of Florence, Italy (UF) and the other in the West Suffolk Hospital, Bury St Edmunds, England (WSH). All patients were of similar age group and satisfied the Feighner criteria (Feighner *et al*, 1972) for diagnosis of primary depressive illness. These are—for primary depression—a dysphoric mood accompanied by at least five of the following criteria for a 'definite' diagnosis (i) poor appetite or weight loss exceeding 2 lb per week or 10 lb per year (ii) sleep difficulties (iii) loss of energy (iv) agitation or retardation (v) decrease in sexual drive or activity (vi) feelings of self-reproach or guilt (vii) complaints in difficulty in thinking or concentration (viii) recurrent thoughts of suicide. A final requirement is that no other psychiatric illness pre-exists within a month of the depressive disorder.

There were 20 patients in the UF group, 7 male and 13 female, whose ages ranged from 32 years–78 years (mean 51.5 years) and whose weights ranged from 47 Kg–75 Kg (Mean 63.9 Kg). The WSH group consisted of 13 male and 17 female patients whose ages ranged from 23 years–73 years (Mean 51.0 years) and whose weights ranged from 37 Kg–88 Kg (Mean 63.2 Kg). There were no significant differences in age or weight when male and female patients were compared.

These two groups entered a different treatment schedule, the UF patients underwent a mixed intravenous-oral CI treatment while WSH patients were treated exclusively with oral CI.

Dosage regimen

After recruitment to the study a 'wash-out' period of three days was allowed. During this period and the subsequent period of treatment the patients were given no other drugs except benzodiazepines.

(i) Intravenous-oral treatment of UF patients

The UF patients were started on clomipramine hydrochloride (Anafranil), administered intravenously, immediately after the 'wash-out' period. The CI regime initially consisted in increasing the intravenous dose which was then tailed off and replaced by oral administration (Fig 1). The daily dose, diluted to 250 ml of normal saline, was administered at 0900 hours over an infusion period of two hours. Oral replacement doses were given three times daily, at 0900, 1200 and 2200 hours. The full intravenous dose of 125 mg started on day 9 of treatment and the full oral dose of 125 mg was given from day 19 onwards. Within the following two weeks patients were discharged, when they were maintained on lower doses with weekly clinical assessment as out-patients.

(ii) Oral treatment of WSH patients

Following the 'wash-out' period the WSH patients were immediately started on a fixed dose of clomipramine hydrochloride (Anafranil), administered orally in a dose of 50 mg at 0700, 1400, and 2200 hours. This dosage schedule continued unchanged for the next twenty-one days.

Clinical assessment

In all patients the severity of their depressive state was quantified by means of the Hamilton rating scale (Hamilton, 1960). As assessment was made again on day 0, 6, 10, 18 and 32 of treatment and on day 3, 7 and 21 of treatment for the UF patients and the WSH patients respectively. These assessments were carried out at approximately the same time of day on each occasion in order to minimize the effect of diurnal variation of symptoms. The change in the severity of depression was expressed as the percentage reduction between the Hamilton score on various days and initial scores. Full interrater reliability studies were not feasible but psychiatrists from both centres met and clarified the entry criteria in detail. There was no difference between the means of Hamilton scores at inclusion in the study between the two

groups thus emphasizing the close similarity in illness severity. At the end of the trial an independent clinical assessment was made, using all available information about individual patients concerning response, favourable or unfavourable, over as long a follow-up period as possible.

Plasma estimations

Plasma concentrations of CI and DMCI were measured at various times during CI treatment. The UF patients had blood samples taken 1 hour and 22 hours after the intravenous infusion of the preceding dose was terminated. During full oral treatment blood samples of UF patients and WSH patients were taken two hours after administration of the morning dose. The blood (10 ml) was collected into heparinized tubes or into tubes containing sodium citrate. Plasma levels of CI and DMCI were measured by gas liquid chromatography using a nitrogen detector. The method has been described previously (Broadhurst *et al*, 1977). The chromatographic peaks found for CI and DMCI where shown to be related to the authentic substances by mass spectrometry.

Benzodiazepines were shown not to interfere with the analysis and moreover it has been shown that these drugs do not modify the pharmacokinetics of tricyclic antidepressant drugs in man (Silverman and Braithwaite, 1973; Gram *et al*, 1974).

Statistical methods

Statistical analyses including numerical values of the Hamilton scale were carried out with the use of non-parametric techniques (χ^2, Mann-Whitney U test and Spearman rank order correlation coefficient).

Results

Fig 1 shows the concentrations of CI and DMCI in plasma against time, during treatment of the 20 UF patients. When plasma concentrations were measured 1 hour after the intravenous infusion, CI levels increased almost linearly up to a maximum of about 300 ng/ml, following the highest intravenous dose of 125 mg, then a decrease followed the gradual substitution with the oral dose. When CI concentrations were measured 22 hours after the previous dose much lower values were found as compared to 1 hour post-infusion levels. However no significant difference was observed when approaching full oral dosage. In the case of i.v. CI it is interesting to observe that CI levels at 22 hours were decreased by 50 per cent from 1 hour values. This chance finding suggests that the mean half-life of CI could be approximately 22 hours under these conditions.

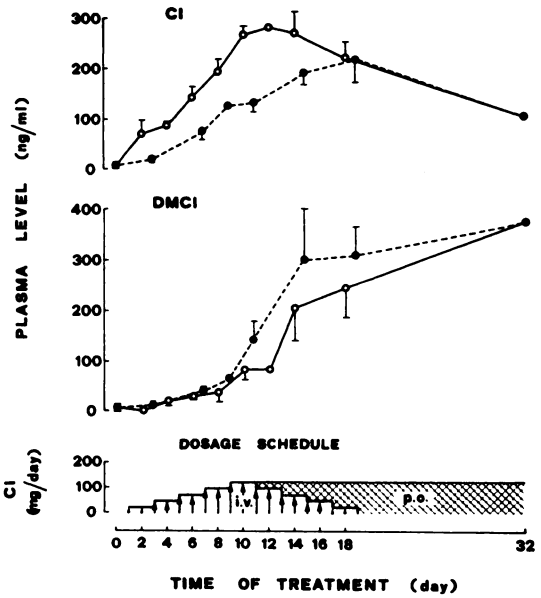

FIG 1.—Tricyclic plasma levels for the 20 UF patients. (○——○, 1 hour after i.v. infusion; ●——●, 22 hours after i.v. infusion). Each point represents the mean value of 5–12 patients ± S.E.

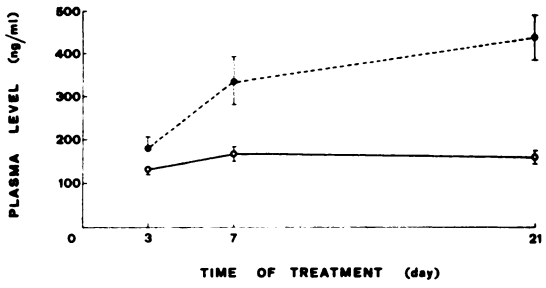

FIG 2.—Relationship between tricyclic levels and duration of oral CI treatment in the 30 WSH patients. (○——○, plasma CI mean ± S.E.; ●——●, plasma DMCI mean ± S.E.).

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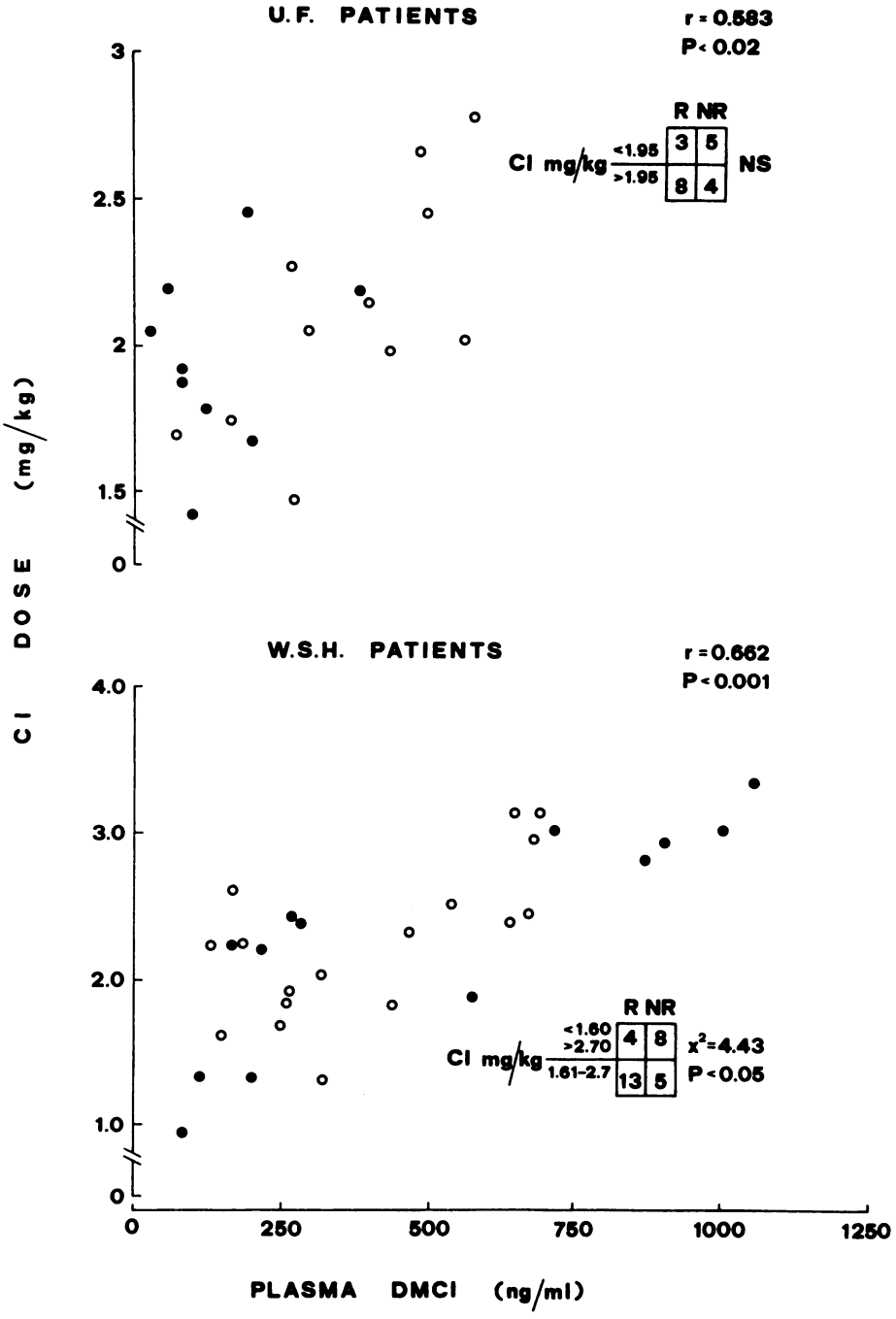

FIG 3.—Relationship between plasma DMCI and dose of CI (mg/kg body weight). UF patients from day 10 onwards, and WSH patients at day 21 of treatment. ○ = responders. ● = non-responders.

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Plots of DMCI levels against time gave sigmoidal curves, both at 1 hour and 22 hours after the preceding dose. Although values at 22 hours were higher, the variability was such that they were not significantly different from those obtained at 1 hour. The first phase of the sigmoidal curves was represented by a very slow increase during the whole period of intravenous infusion. DMCI was less than 100 ng/ml following the maximum intravenous dose, then a dramatic increase was observed when oral treatment started. Levels of about 400 ng/ml were reached two weeks after total substitution with oral treatment.

A different pattern of CI and DMCI plasma levels was obtained during treatment of the 30 WSH patients (Fig 2). Plasma levels of CI were found not significantly changed between the third and the twenty-first day of treatment. However, DMCI plasma levels were found to increase with time, doubling their concentrations between the third and the twenty-first day of treatment. When the results obtained from the two groups of patients are compared, it is interesting to observe that while higher levels of CI were reached following intravenous treatment, the oral treatment was characterized by higher levels of the metabolite DMCI. Another interesting finding is that the inter-patient variation of plasma levels was marked, DMCI showing a much higher variation than CI, in spite of the fact that all patients were receiving the same dose of CI.

Considerable variations in the body weight of the patients could have been responsible, at least in part, for the inter-patient variation seen in plasma levels. There was found to be a significant relationship between the dose of CI, expressed in mg/Kg body weight, and the plasma level of DMCI. This relationship was significant, for the UF patients starting from day 10 of treatment, after full intravenous dosage had been reached and on day 21 of treatment for the WSH patients (Fig 3). In both groups no correlation was found to exist between dose per unit body weight and plasma CI concentrations.

As to clinical improvement not all patients responded adequately to treatment. The therapeutic effect was monitored by using the

TABLE

CI dosage, plasma concentration of CI and DMCI and clinical response in 50 depressed patients. Figures represent means, standard errors and ranges

Group of patients	Day of treatment	Dose (mg/Kg)	Plasma concentration (ng/ml)			Hamilton score improvement (percentage)	DMCI / CI
			CI	DMCI	CI+DMCI		
UF							
Responders (n = 11)	18*	2.11±0.12 (1.47–2.78)	217±30 (85–384)	361±49 (70–570)	579±57 (174–819)	64±5 (42–77)	1.96±0.34 (0.45–3.83)
Non-responders (n = 9)	16*	1.95±0.10 (1.42–2.45)	144±26 (55–281)	136±36 (26–378)	280±53 (100–659)	25±6 (0–56)	1.11±0.32 (0.33–3.42)
	N.S.	N.S.	N.S.	P <0.01	P <0.01	P <0.01	P <0.05
WSH							
Responders (n = 17)	21	2.18±0.15 (1.30–3.13)	173±20 (79–338)	396±50 (127–684)	568±50 (222–913)	75±4 (52–95)	2.61±0.39 (0.72–5.86)
Non-responders (n = 13)	21	2.29±0.20 (0.94–3.33)	144±13 (40–198)	492±99 (83–1053)	637±105 (183–1237)	19±6 (0–50)	3.67±0.75 (0.46–9.17)
	—	N.S.	N.S.	N.S.	N.S.	P <0.001	N.S.

* Median day of treatment from data obtained at different times from day 10 onwards (see text).

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Hamilton rating scale together with final assessment as described earlier. The Hamilton scores for the two treatment groups are shown in Fig 4. Maximum agreement between clinical assessment and reduction in the Hamilton score was found when a reduction in the Hamilton scores higher than 50 per cent was taken as an index of reasonably satisfactory improvement. Patients who, at the end of treatment, achieved a reduction in the Hamilton scores higher than 50 per cent were classified as responders. Responders showed a significantly lower Hamilton score from day 10 onwards in the UF group and on day 21 in the WSH group. These findings were reliably confirmed by clinical assessment of response.

The possibility that a difference of CI and/or DMCI plasma levels could be responsible for a difference in clinical improvement was examined separately for responders and non responders. Plasma levels of CI, DMCI and CI plus DMCI, measured at 22 hours after the preceding dose, in responders were characterized by a regression line significantly higher than non-responders. They showed plasma levels of both CI and DMCI significantly higher from day 10 onwards during the whole period of treatment. However no significant difference could be found between responders and non-responders when plasma levels measured at 1 hour were analysed.

In the WSH group CI and DMCI plasma levels in responders at no time were significantly different from non-responders. However the DMCI plasma levels of the non-responders showed a coefficient of variation twice that of responders.

The finding that a significant clinical improvement was accompanied with higher levels of CI and DMCI only in the UF patients, prompted us to study in more detail the relationship between these variables in both groups. For WSH patients only data obtained at 21 days were considered. For the UF patients only data obtained from 10 onwards, after full intravenous dosage had been reached, were examined; this data was obtained on the latest day of treatment when both plasma levels and Hamilton scores were available. Data are summarized in the Table.

When the relationship between clinical improvement and plasma levels was studied no correlation was found between CI levels and Hamilton score improvement in either group. However the correlation between DMCI and Hamilton score improvement was significant in the UF group (Fig 4). Most responders showed DMCI plasma levels higher than 240 ng/ml, while most non-responders had DMCI levels below 240 ng/ml. Included in this instance were two patients for whom Hamilton scores were not available; one classified as a non-responder on the grounds of clinical assessment (plasma DMCI 378 ng/ml) and another classified clinically as a responder (plasma DMCI, 293 ng/ml).

When data obtained from WSH patients were examined (Fig 4) a clear curvilinear pattern was evident. Most responders showed DMCI concentration between 240 and 700 ng/ml, while most non-responders had DMCI levels either below 240 ng/ml or higher than 700 ng/ml.

The finding of a therapeutic range for DMCI plasma levels together with the observation of a significant correlation between CI dosage in mg/Kg body weight and DMCI plasma levels would suggest that non-responders received a dose of the drug which was either too low or too high. This is true, at least in part, as shown in Fig 3. Most responders of the UF group were characterized by a CI dose higher than 1.95 mg/Kg, non-responders however were almost equally distributed among those who received a dose over or below 1.95 mg/Kg. In the WSH group a range of CI dosage in mg/Kg of 1.6–2.7 was found to include most responders while 8 out of 13 non-responders had received a CI dosage outside this range.

The ratio of DMCI/CI plasma levels, which might be considered as an indicator of demethylation capacity, was also studied. There was a 10 fold variation and a 20 fold variation in this ratio in the UF group and the WSH group respectively, with a significant difference between responders and non-responders only in UF patients. In both groups of treatment the ratio DMCI/CI was significantly correlated to DMCI plasma levels (Fig 5). Most UF non-responders, having a ratio below 1.5, and most of WSH non-responders having either a ratio

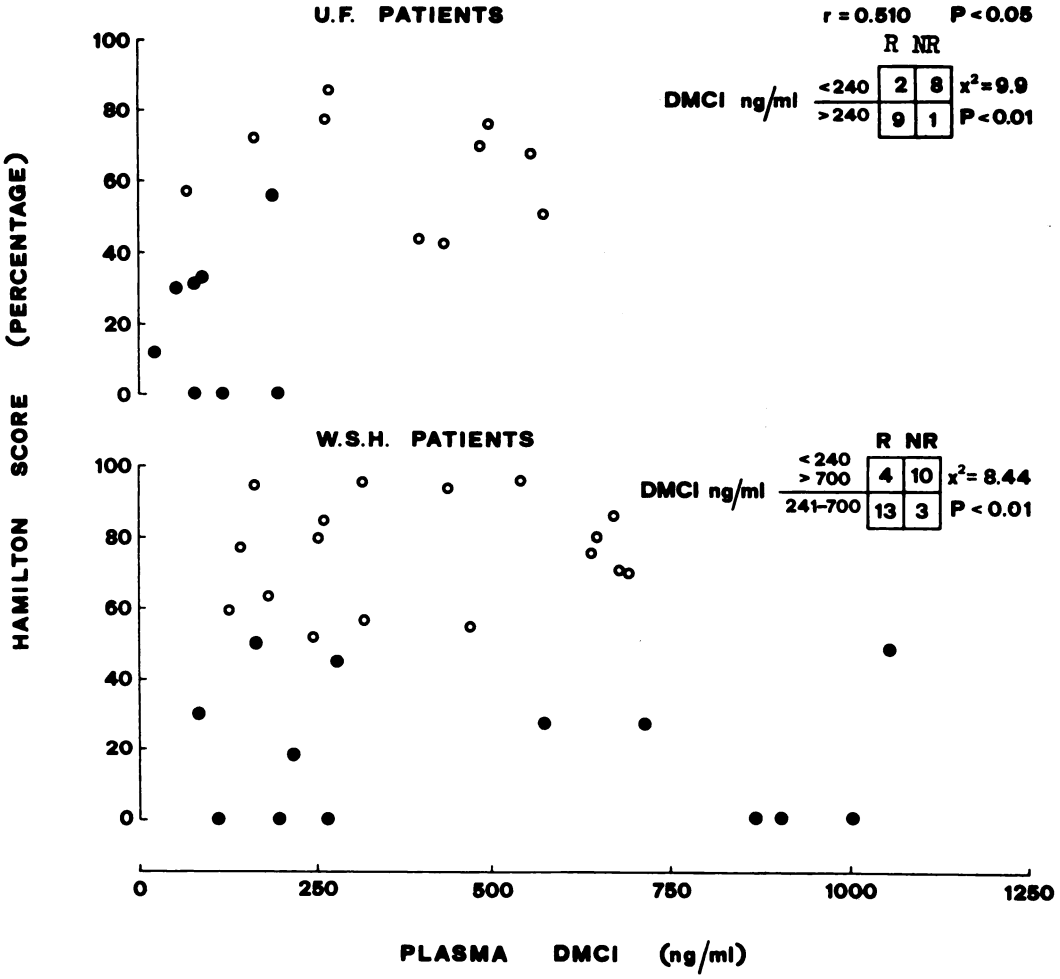

FIG 4.—Relationship between per cent reduction in Hamilton score rating and plasma DMCI level. ○ = responders. ● = non-responders.

below 1.8 or higher than 5, showed either a too low or too high demethylation capacity. Responders of both groups however were almost equally distributed among low, intermediate and high values of this ratio.

Finally, side-effects throughout were insignificant and on no occasion did they necessitate alteration of the prescribed dosage regimens.

Discussion

The different dosage-regimens adopted in the two groups resulted in different patterns of CI and DMCI plasma levels with time. This is in agreement with previous studies (Nagy and Johansson, 1977), which also showed that oral and parenteral administration produced different relative concentrations of CI and DMCI. Whereas, after oral administration of CI the plasma curve of CI was below that resulting from intravenous infusion, the reverse was true for DMCI. This relationship was found both in the UF patients, before replacement with oral doses started, and in the orally treated WSH patients. Furthermore at the end of treatment of the UF patients, after full oral dosage had been reached, CI and DMCI plasma levels showed a clear tendency towards levels obtained

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in WSH patients treated only orally. These higher degrees of demethylation after oral administration have been claimed to be a consequence of drug metabolism in the liver before it reaches systemic circulation (first pass effect) (Dencker *et al*, 1976). Nagy and Johansson (1977) indeed observed how demethylation of imipramine and CI can be reduced by switching from oral to parenteral administration.

Measurement of plasma levels at one hour

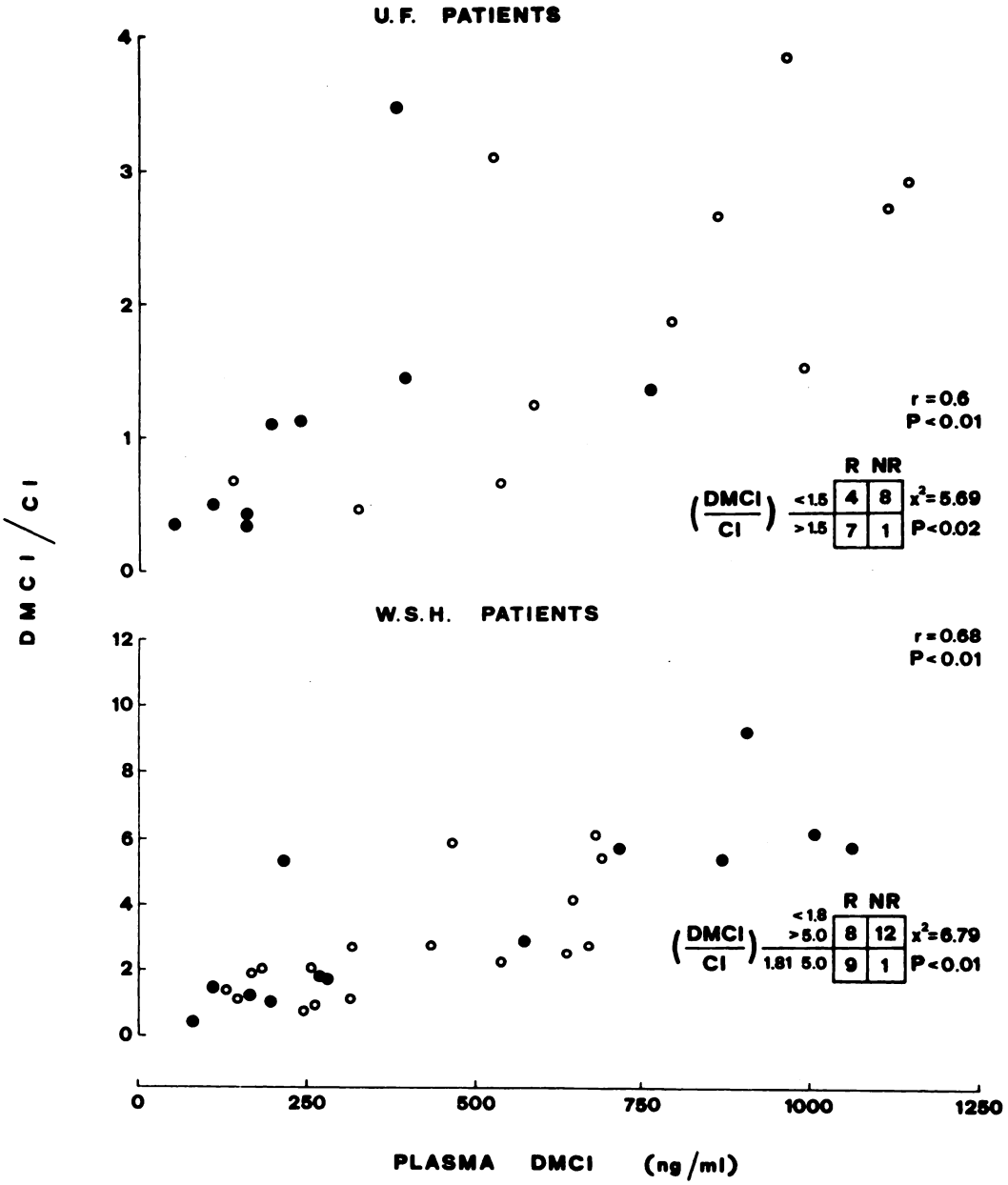

FIG 5.—Relationship between plasma DMCI/CI ratio and plasma DMCI concentration. ○ = responders. ● = non-responders.

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and 22 hours following the morning dose, during treatment of UF patients, gave an indication of a half-life of about 22 hours for CI. This is in good agreement with values of 20.8 and 24.7 found by Nagy and Johansson (1977).

During treatment of UF patients plasma levels of clinical significance were obtained from sampling at 22 hours but not at 1 hour after drug administration, while in WSH patients plasma levels positively correlated to clinical response were found by blood sampling at two hours after the morning dose. It should be noted that the difference between plasma levels obtained by one hour and 22 hour sampling tends to disappear when approaching full oral dosage in UF patients and values become close to those obtained from 22 hour sampling of WSH patients.

The different profile of CI and DMCI plasma levels did not seem to affect the overall clinical response. At the end of the study both groups of patients responded similarly to CI treatment, a satisfactory improvement being achieved by 55 per cent and 57 per cent of the UF and WSH patients respectively. This percentage of response is in agreement with the large number of non-responders, 35–40 per cent, found in most clinical trials with CI as well as other tricyclic antidepressants (Benett, 1967). As to rate of improvement there did not seem to be a difference between UF and WSH patients.

The clinical response of both groups of depressed patients treated with CI was found to be significantly correlated to DMCI plasma levels. No association between CI plasma level and clinical response could be found even in the UF patients where higher levels of CI were reached. This finding suggests a more important antidepressant effect for DMCI. Not excluding an activity for both drugs it is possible that the action of CI may be actually over-shadowed by the higher levels of the desmethyl metabolite. Of relevance to this point it is interesting to observe that in the UF group, where higher levels of CI were reached, although at the end of treatment CI plasma levels were not correlated to clinical improvement, the regression line of CI plasma levels against time was significantly higher in responders that in non-responders.

There was found to be a lower threshold of the DMCI therapeutic range of about 240 ng/ml in both groups of patients. The high levels obtained in WSH patients were found to be associated with unfavourable therapeutic effects and a higher threshold of about 700 ng/ml was found which seemed to demonstrate the presence of a 'therapeutic window'. The higher limit of the therapeutic range was not tested in the UF patients where DMCI plasma levels remained below 700 ng/ml during the whole period of treatment. The concept of a 'therapeutic window' was first introduced by Åsberg *et al* (1971) for nortriptyline and confirmed later by Kragh-Sørensen *et al* (1973) and Ziegler *et al* (1977) while Burrows *et al* (1972, 1974) found no relationship between plasma levels and clinical response. Indications of a therapeutic range for protriptyline came from separate studies where the upper and lower limit of the range had been examined (Whyte *et al*, 1976; Biggs and Ziegler, 1977), while studies on imipramine and amitriptyline suggest a more linear relationship between plasma levels and clinical response for tertiary amine tricyclics. With regard to CI therapy, the presence of a curvilinear relationship between DMCI plasma levels and therapeutic response found in our preliminary study (Della Corte *et al*, 1976; Broadhurst *et al*, 1977) for WSH patients has now been confirmed. Furthermore Miller *et al* (1977) had reported a tendency for poor responders to have higher than average plasma levels during CI treatment. The fall-off in clinical response at plasma levels beyond the optimal range is difficult to explain, Åsberg *et al* (1971) suggested receptor blockade as a possible cause. However more extensive studies are needed to confirm a curvilinear relationship for some or all tricyclic antidepressants. It would appear desirable that the whole range of plasma concentrations in relation to clinical response be studied for each tricyclic amine using standardized procedures of analysis. The presence of a therapeutic range for DMCI together with the finding of a significant correlation between plasma DMCI concentration and CI dosage strongly suggests that CI could be adjusted to keep the patient within the therapeutic range of DMCI plasma levels. This could help those non-responders for

whom a too low or a too high plasma level is explainable in terms of too much or too little of the administered drug. However the role played by individual demethylation capacity in response failure should also be considered, thus switching from oral to parenteral administration or vice versa could be useful for a further control of DMCI plasma levels. We are not aware of any investigation which has been designed specifically to assess the clinical value of such an approach in the management of patients who are considered to be poor responders to this treatment. The therapeutic strategy outlined by Sjöqvist (1975) while relying on plasma level monitoring for nortriptyline unfortunately appears not to do so for CI. Such investigations are of the utmost importance if the relationship between pharmacokinetic variability and clinical response is to be defined more precisely. Also a clinical trial with DMCI would seem appropriate in view of the present findings.

The relationship between plasma levels and clinical response and the finding that DMCI seems to give a major contribution to the antidepressive effect adds credence to the theory that central noradrenergic systems are involved in depressive illness. Recent studies on the effect of tricyclic antidepressants on postsynaptic sites (Sulser *et al*, 1978) continue to stress the role of noradrenergic receptors in the pathogenesis of affective disorders.

In conclusion at the present time the relatively low response rate to tricyclic antidepressant drugs has not been overcome. It is very frustrating for those who work with depressed patients to have to accept that 35–45 per cent of patients fail to respond to tricyclic therapy. The reproducibility of the method and the conclusions drawn from this study suggest strongly that treatment, success or failure depends on pharmacokinetic factors. The relation of dosage to plasma levels of DMCI and hence to clinical responses offers great hope for precision in treating these patients. We hope that others also will be encouraged to give this method a wider application.

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