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Self-Inhibiting Action of Nortriptylin's Antidepressive Effect at High Plasma Levels

A Randomized, Double-Blind Study Controlled by Plasma Concentrations in Patients with Endogenous Depression

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Abstract. Below the toxic plasma level of nortriptyline (NT) an upper therapeutic limit has been postulated in patients with endogenous depression. If so the clinical significance is obvious and a double-blind, randomized study was performed in order to solve this problem. Two groups of patients were controlled at different plasma levels (< 150 ng/ml and > 180 ng/ml). The degree of depression was rated weekly. Only about one third ($n = 24$) of the patients originally included, were carried through the full protocol, the most prominent reason for drop out beeing spontaneous remission during an initial placebo period. After 4 weeks of NT treatment the majority in the high level group was still depressed, but the difference barely significant ($P = 5.5\%$). However, a randomized reduction of the plasma level among the patients at the high level resulted in a significant correlation to remission. Evaluation of the total material after 6 weeks of NT treatment demonstrated a strong correlation of high plasma level to poor antidepressive effect of NT. No correlation could be obtained between side-effects, which were few, and plasma level. The non-proteinbound fraction in plasma was found to 7% (SD 1.83) by simultaneous determinations of NT in plasma and CSF in 13 patients. The variation in the proteinbinding was not likely to invalidate the over all results based on total NT determination. A therapeutic plasma range of 50–150 ng/ml is recommended.

Key words: Endogenous depression – Tricyclic antidepressants – Plasma concentrations – Self-inhibition.

About one third of the patients treated with tricyclic antidepressants (TA) for endogenous depressions do not respond satisfactorily (Bennet, 1967). One approach to solve at least a part of this problem is to control the plasma levels of these drugs, as the applied standard dosages often result in ineffective or in toxic plasma concentrations (Sjöqvist, 1971). This implies elaborated analytical methods as well as a detailed knowledge of the plasma level/effect relation for these drugs.

Recently, this relationship has been investigated in a number of studies (Walthers, 1971; Åsberg *et al.*, 1971; Braithwaite *et al.*, 1972; Burrows *et al.*, 1972; Kragh-Sørensen *et al.*, 1973; Modestin, 1973). General conclusions can, however, not be derived as *e.g.* the diagnostic criteria, the analytical techniques, the design and the drugs used vary greatly between the studies, and so do the results. In two investigations concerned with nortriptyline (NT) (Åsberg *et al.*, 1971; Kragh-Sørensen *et al.*, 1973) the antidepressive effect was found to decrease at high, but non-toxic plasma levels. This unexpected observation seems to find some experimental support (Haefely *et al.*, 1964; Pletcher, 1965; Møller-Nielsen, 1970), although it is not confirmed by some clinical studies (Braithwaite *et al.*, 1972; Burrows *et al.*, 1972). The therapeutic consequences of such a self-inhibiting effect are obviously important, in particular for drugs with a wide individual variation in the plasma level/dose ratio. The purpose of the present study was therefore to investigate, under strictly controlled conditions, whether or not an upper therapeutic limit for the plasma level of NT could be demonstrated.

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Hypotheses

The investigation was designed to test the following hypotheses concerned with NT treatment:

1. After 4 weeks of treatment patients with a plasma level below 150 ng/ml have recovered, whereas

patients beyond a limit of 180 ng/ml remain depressed.

2. Patients that remain depressed after 4 weeks on a high plasma level (> 180 ng/ml) will recover after further 2 weeks of NT treatment, provided that the NT plasma concentration is adjusted to a level below 150 ng/ml.

3. After 6 weeks of treatment patients above 180 ng/ml will still be depressed and patients below 150 ng/ml have recovered.

Materials and Methods

General Design

The study was based on a double blind design with the therapeutic control and the assessment of clinical respons completely separated. This design has also be referred to as "triple blind".

Adult patients admitted to Glostrup Mental Hospital with a primary diagnosis of depression requiering antidepressants were consecutively considered for the study. If they fullfilled certain inclusion criteria they went through a diagnostic inventory (Gurney, 1971; Gurney *et al.*, 1972). Provided this resulted in the diagnosis "endogenous depression", the patients were tested quantitatively by a rating scale (Cronholm and Ottosson, 1960; Cronholm *et al.*, 1973), on which more than 8 scores met the final inclusion criteria. The included patients were assigned at random to one of two groups. Group A was aimed at a steady state plasma level of NT at <150 ng/ml, group B was aimed at a level of >180 ng/ml. The NT treatment was started after 1 week on placebo. At the end of the placebo period the degree of depression was reassessed, and patients less than 8 scores were excluded from the study, as they were considered in possible spontaneous remission.

The groups were treated with individualized doses of NT in order to obtain the desired steady state plasma level within 3 weeks based on bi-weekly plasma determinations. The degree of depression was assessed once a week. After 4 weeks on NT treatment, half of the patients in the high level group were assigned at random into two subgroups: One continuing at the same level (group C), the other one being adjusted to the low level (group D). After totally 6 weeks of NT treatment the investigational period was brought to an end.

The entire investigation was scheduled to terminate either after about 18 months or when about 40 patients had completed the study. However, after 22 months only 24 patients had completed a full protocol and it was decided to break the code.

Details of the Design

Criteria of Inclusion. No signs or symptoms of schizophrenia, organic brain damage, or a history of drug or alcohol abuse. No signs or symptoms of hepatic, renal or hematological disorders as judged by physical examination and standard biochemical tests.

Criteria for Exclusion during the Study. Refuse to take medicine, severe detoriation of psychical state (especially danger of suicide) and decision of switching to NCE treatment. (Such decisions were always taken by the house staff not involved in the study.) Development of mania or an intercurrent somatic disease. Development of signs or symptoms that could be considered severe side-effects of the NT treatment, in particular changes in the ECG. Loss of blindness at any stage. Measurable amounts of NT in plasma after the placebo period.

The qualitative diagnostic evaluation was carried out according to a diagnostic inventory (Gurney, 1971; Gurney *et al.*, 1972) by two of the investigators (P.K.S. and C.E.H.). This inventory differentiates between endogenous and non-endogenous depression. The interrater reliability was found to 0.92 ($P < 0.001$).

For the quantitative evaluation of the degree of depression, a modified Cronholm-Ottosson rating scale was used (Cronholm and Ottosson, 1960; Åsberg *et al.*, 1973; Cronholm *et al.*, 1973). The ratings were carried out before and after the placebo period and then once a week, performed only by P.K.S. and C.E.H. and always between 8 and 10 a.m. The interrater reliability was found to 0.91 ($P < 0.001$). Before the study was started a score of 3 or below was defined as "recovered" (Kragh-Sørensen *et al.*, 1973).

Side-effects were recorded by means of a 4-grade scale that included the eleven most common side-effects (Åsberg *et al.*, 1970). ECG was taken once a week, but only seen by the investigators controlling the plasma level.

Randomization Procedure. The patients were allocated at random to the two groups according to a prearranged envelope code system (Geigy tables of random numbers). The number of patients in group B (> 180 ng/ml) was arranged to exceed that of patients in group A (< 150 ng/ml) by 30%. The pre-made, numbered envelopes for group B contained also a randomized, sealed order whether or not the patient after the fourth week of NT treatment should continue on the high level (group C) or have the dose reduced in order to obtain a plasma level below 150 ng/ml (group D).

Blind Principles. The patients as well as the house staff were unaware of the dose schedules used in the individual patient, but were informed that the NT treatment would be controlled on a certain plasma level. The investigators were devided into two groups. P.K.S. & C.E.H. performed the ratings and P.C.B. & E.F.H. controlled the treatment on the basis of plasma concentrations of NT, but did never see the patients. The two groups of investigators were unawere of the results from the other group. The day to day clinical-psychiatric problems were taken care of by the house-officers. No other medication was allowed.

Each patient received 4 identically looking tablets 3 times daily (6 a.m., 2 p.m. and 10 p.m.) during the whole study. These tablets could be either placebo or contain 25 mg NT. The first week all tablets were placebo, but after that time the individual daily dosage could vary between 0 and 300 mg.

Blood Sampling and Analytical Procedure. Blood was drawn at 1 p.m. twice a week during the entire investigational period. After separation the plasma was stored at $-25°C$ until NT was analyzed by gas chromatography (Kragh-Sørensen *et al.*, 1974). The sensitivity of the method is about 1 ng/ml plasma with an accuracy of $\pm 5\%$ at the lower limit. The results were usually available for the plasma level controlling team within 2 or 3 days.

Steady state conditions were defined as established, if two consecutive plasma concentrations on seperate days within the same week did not exceed $\pm 10\%$ of the mean of the two determinations. In fact, for most of the patients the steady-state levels are based on three or four determinations during a 10 days period before the end of week 4 and 6, respectively. Only in three patients (*cf.* Table 1) it was not possible to obtain a steady-state level on these conditions

Table 1. Patients excluded from the study during the investigational period

Reason for exclusion	Placebo period (*n*)	First 3 weeks of NT-treatment (*n*)	Total (*n*)
Depression scores too low (< 8) at the end of placebo period	18		18
More than 5 ng/ml NT in plasma at the end of placebo period	2	–	2
Left hospital	1	–	1
Clinical condition got worse, ECT-treatment initiated	7	4	11
Diagnostic failures	2	2	4
Developed mania	2	2	4
Steady state plasma level impossible to obtain	–	3	3
Interfering disease	–	1	1
Not completed	–	1	1
Excluded during placebo period	32		45
Excluded during the first 3 weeks of NT-treatment		13	
Excluded because of ECG-changes in 5th week			1
Total number of patients excluded			46

and they were withdrawn from the study. In a few patients the steady-state levels were not identical in week 4 and 6, respectively, although the patient remained in the same group. This is due to dose adjustments in week 5 as the level was considered too high or, in one case, too near the lower limit.

Cerebro-Spinal Fluid Determinations. In order to estimate the size of the possible error of the conclusions based on the total NT-concentration, spinal fluid was examined in a number of cases as an in vivo protein binding examination. Totally 13 patients in controlled NT treatment agreed to participate, 6 of whom originating from the present study. The spinal puncture was performed in the third week of treatment in fasting state at 8 a.m. and a blood sample was taken simultaneously. None of the CSF samples were contaminated with blood and all showed a normal cell-count and protein content. The analytical procedure was the same as for plasma (Kragh-Sørensen *et al.*, 1974).

Statistical Methods. The Wilcox-Mann-Whitney test was used to estimate if the initial rating values were distributed evenly in groups A and B. In testing the three hypotheses a unilateral hyper-geometric test was utilized (Bradley, 1968). A significance level of 5% (for type 1 error) was fixed in advance. In testing the possible correlation between side-effects scores and the NT plasma concentration a Spearman rank correlation test was performed.

Ethical Considerations. The principles of the Helsinki Declaration were the guideline of the investigation. However, for an investigation of this kind it was not found advisable to explain to the patients the details of the therapeutic trial or to obtain their consent. This decision was found to be fully in line with the respect for the patients interests, as neither of the treatments (high or low concentrations) differ from the therapeutic practice generally applied to endogenously depressed patients in Danish psychiatric institutions. Furthermore, the patients were constantly supervised by the house staff who were not involved in the trial and who allowed to ask for breaking the code at any time. Thus, none of the patients were exposed to an inferior therapeutic or clinical situation compared with an admittance to any other mental hospital.

The cerebro-spinal fluid examinations were primarily carried out in order to investigate the monoamine metabolism in the central nervous system during depression. The NT determinations were made on a part of the obtained sample, and before the lumbar puncture each patient was thoroughly informed of the procedure, the reasons for it and its potential risks. It was also made clear that this procedure was not a part of their ordinary treatment. Several patients refused, which of course had no influence on their subsequent treatment. Only 13 patients agreed to participate.

Results

Ninety-seven patients were primarily referred to the study and 69 of these fullfilled the inclusion criteria. However, 45 patients were excluded during the placebo period or within the first 4 weeks of treatment. The reason for exclusions are tabulated in Table 1. A major reason for drop-out was possibility of spontaneous remission during the placebo period. Furthermore, in eleven patients ECT treatment was initiated. The reason for this was in the majority of the cases refusal to take the medicine. Thus, totally 24 patients, or only one third of the patients originally included, were available for testing of hypotheses 1 and 2 and totally 23 patients for testing hypothesis 3.

The total amount of data obtained from the study is given in Table 2. Ten patints were allocated to group A (< 150 ng/ml) and fourteen to group B (> 180 ng/ml). Five of the patients did not meet the criteria for a correct NT plasma level during week 4, as their plasma concentrations fell in between the two groups. These patients (no. 7, 27, 46, 51 and 62) are therefore not used for the calculation for the testing of the two first hypotheses.

Group A and B are comparable with respect to the rating scores for depression measured at the end of the placebo period (P = ca. 50%). This means that the final result should not be correlated to the initial severity of depression.

Table 2

Sex	Age Yr.	Code		Depression score, baseline	Dose[a] NT (mg/day)	Outcome					
		no	groups			After 4th week		Depression score	After 6th week		Depression score
						NT plasma level			NT plasma level		
						intended	obtained		intended	obtained	
F	47	1	A	13.0	175	150	114	2.5	150	112	1.5
F	25	3	B + C	14.0	175	180	296	8.0	180	210	5.0
F	36	5	B	9.0	300	180	200	8.5	Excluded: ECG changes 5th week		
F	60	7	B + C	13.5	125	180	170	0	180	240	0
F	40	9	B + D	10.5	225	180	189	0	150	145	0
F	32	10	A	10.0	125	150	95	0	150	93	0
F	45	12	A	11.5	175	150	123	7.5	150	116	0
F	45	14	B + D	10.5	225	180	235	4.5	150	92	1.0
M	46	18	B + D	8.5	200	180	214	0	150	108	0
F	28	24	B + C	13.5	200	180	255	9.0	180	189	11.0
F	49	26	A	14.5	75	150	138	10.0	150	121	2.5
F	57	27	A	21.5	100	150	168	9.5	150	95	0
M	24	32	B + D	9.0	250	180	192	8.0	150	125	2.0
M	58	34	B + C	16.0	225	180	217	9.0	180	233	5.5
F	42	36	A	9.5	50	150	94	3.0	150	82	3.0
F	39	42	A	12.5	100	150	119	2.0	150	130	0.5
F	36	46	B + D	12.0	250	180	177	5.5	150	104	0.5
F	56	47	B + C	15.0	300	180	252	7.0	180	191	4.0
M	58	49	B + C	13.0	150	180	189	10.5	180	263	9.5
F	69	51	A	14.0	100	150	171	1.0	150	129	0
F	51	57	B + C	10.5	100	180	193	1.5	180	216	4.5
M	57	60	A	9.5	150	150	127	0	150	126	0
F	56	62	B + D	15.5	125	180	172	10.5	150	126	0
F	25	66	A	13.5	75	150	82	2.5	150	133	1.0

[a] Dose at the time where the first steady-state level was obtained (or tried obtained).

Table 3. Collected results after 4th week

NT plasma level	Total (*n*)	Recovered (*n*)	Not recovered (*n*)	*P*
< 150 ng/ml	8	6	2	5.5%
> 180 ng/ml	11	3	8	
150–180 ng/ml	5	2	3	

Table 4. The correlation between reduction of plasma level and recovery from depression during 5th and 6th week

NT plasma level	Total (*n*)	Recovered (*n*)	Not recovered (*n*)	*P*
Continued > 180 ng/ml	5	0	5	4.9%
Reduced to < 150 ng/ml	2	2	0	
Reduced from 168–178 ng/ml to < 150 ng/ml	3	3	0	
Recovered 4th week but relapsed on continued > 180 ng/ml	1	–	1	

From a statistical point of view hypotheses 1 and 2 are identical apart from the fact that they are based on differently collected data. It might therefore be misleading to test the two hypotheses separately (see below).

The results after the fourth week of NT-treatment are given in Table 3. More recovered patients are found in the group with low plasma level than in the high level group. The difference is not quite significant ($P = 5.5\%$), but must be seen in connection with the testing of hypothesis 2 as stated above.

Only seven patients were available for the testing of hypothesis 2. Table 4 demonstrates that the two patients, in whom the plasma concentration was reduced, recovered, while 5 patients remaining at the high level did not recover. In spite of the very few patients this difference is just significant ($P = 4.9\%$). However, some additional support for the hypothesis can be derived from Table 4. Three patients not responding after the fourth week at an intermediate

Table 5. Collected results after 6th week

	NT plasma level ng/ml	Total (*n*)	Recovered (*n*)	Not recovered (*n*)	Recovered (%)	95% confidence limits (%)
I[a]	< 150	16	16	0	100	79–100
	> 180	7	1	6	14	1– 58
II[b]	< 150	14	14	0	100	77–100
	> 180	9	3	6	33	8– 70

[a] The results presented as they actually were recorded at the end of 6th week.
[b] The results presented as they would have been, if two patients who recovered before the 4th on a NT concentration > 180 ng/ml, had continued on this level and still have been recovered after the 6th week.

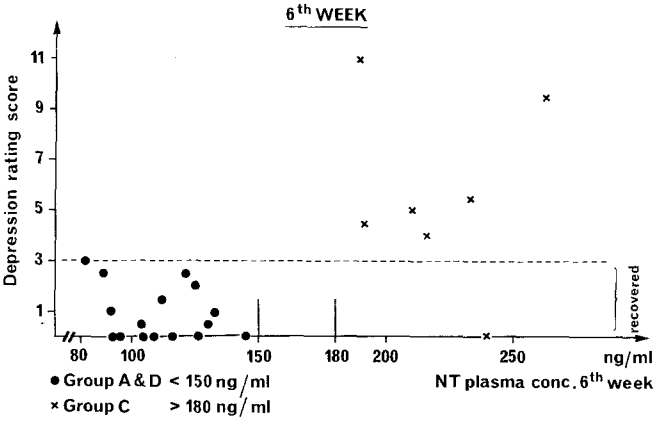

Fig. 1. The correlation between therapeutic effect (Depression rating scores, final scores) and plasma level of NT after 6 weeks of treatment with nortriptyline. Depression score 3 denotes recovered patients (dotted line). Two of the patients recovered before the 4th week on high NT levels. For calculations confer Table 5

plasma level (all about 175 ng/ml) recovered after a reduction to below 150 ng/ml. Furthermore, one patient who recovered after the fourth week, relapsed after continuing at the high plasma level. If statistics are applied to the data including both hypotheses, the result demonstrates that high plasma levels of NT is tantamount to poor therapeutic effect ($P = 1.0\%$).

After 6 weeks of NT-treatment the patients showed to be correctly adjusted and the data from all patients were analyzed in order to test hypothesis 3. Table 5 and Fig. 1 demonstrate the significant correlation between non-recovery and high plasma concentration. However, it could be argued that the final low level group it is not correct to include two patients, who recovered on a high concentration before the fourth week, but later had their plasma level reduced. If these two patients are switched to the opposite group (*cf.* Table 5, part 2) the correlation is still significant.

Rating for side-effects revealed that these in general were few. Neither in week 4 nor in week 6 any correlation was found between the plasma concentrations and the scores of the rating for side-effects ($r = 0.33$ and $r = 0.23$, respectively). Only one patient was excluded because of ECG changes (right bundle branch block at a concentration of 200 ng/ml).

The results of the CSF examinations are given in Table 6. The ratio between NT in CSF and plasma (reflecting the plasma protein binding) is found to an average of 7% independant of the actual plasma concentration. The interindividual variation is maximally two-fold and the standard deviation amounts to 26% in this limited number of patients.

Discussion

The all over result of the present controlled investigation is the demonstration of a significantly less chance to recover from endogenous depression within 6 weeks of NT-treatment with a plasma level above 180 ng/ml. However, the validity of the result depends entirely on the control measures of design and performance.

It has not been possible to detect any leak in the blindness by a retrospective analysis. For instance, the occurrence of characteristic side-effects is crucial, but no loss of blindness was caused this way, mainly because side-effects were not a dominating problem. No contact between the two groups of investigators about the included patients was made at any time. An other important control measure is the randomization procedure. This was carried out regardless of the

Table 6. The plasma protein binding of NT measured as the CSF/plasma ratio in 13 patients (see text)

Sex	Age yr.	CSF protein g/l	NT concentration		NT CSF/plasma ratio %
			Plasma ng/ml	CSF ng/ml	
F	60	0.20	100	7.0	7.0
F	28	0.16	118	7.5	6.4
F	40	0.10	118	7.5	6.4
F	46	0.23	119	9.0	7.6
F	46	0.25	129	6.0	4.7
F	65	0.17	130	15.0	11.5
F	69	0.33	130	12.0	9.2
F	72	0.42	132	10.0	7.6
F	63	0.34	146	10.0	6.8
F	62	0.25	160	10.0	6.3
F	37	0.30	178	12.5	7.0
F	23	0.30	204	18.0	9.0
F	25	0.16	297	15.5	5.2
$n = 13$	Mean:	0.25	–	–	7.0
	Range:	0.10–0.42	100–297	7.0–18.0	4.7–11.5 SD: 1.83
Sjöqvist *et al.*, 1969 $n = 15$, CSF protein about 0.4 g/l					Mean: 6.5% Range: 4–10

individual rate of metabolism of NT. Thus, patients with rapid or slow metabolism of the drug, respectively, were by chance allocated to the two treatment groups. This is a distinct difference to previous studies, in which the actual plasma level, obtained on a fixed dosage, determined whether the patient was included in the high level or in the low level group. A third important problem in the performance of the study was to establish the desirable steady-state plasma level within 3 weeks of NT-treatment. In the majority of patients an acceptably stable plasma level was obtained (*cf.* Table 2). The difficulties in achieving the correct average plasma level in five patients during week 4 are not surprising as the adjustment to at least the high level in several cases was imposed on the patient against his natural rate of metabolism. In usual clinical practice this will not be the case as fast metabolizers automatically will remain in the lower end of the spectrum.

For technical reasons only the total plasma concentration, protein-bound plus free, is measured in all studies of this kind, although only the free fraction is considered pharmacologically active. The magnitude of individual differences in the plasma protein binding may, however, be of great importance. The significance of this problem has recently been emphasized (Glassman *et al.*, 1973; Glassman and Perel, 1974) and is therefore necessary to examine. NT is protein-bound in plasma by 93–95% (Alexanderson and Borgå, 1972; Glassman *et al.*, 1973) and variations in this rather high binding may invalidate conclusions based on measurements of the total concentrations. The plasma protein binding of imipramine was found to vary considerably judged from *in vitro* studies (Glassman *et al.*, 1973). Thus, a range from 5.4–23% in different individuals, *i.e.* a fourfold variation, was demonstrated. In contrast NT does not seem to have an interindividual variation of that magnitude in the protein-binding (Borgå *et al.*, 1969; Alexanderson and Borgå, 1972). From Table 6 it is seen that a two fold variability is the extreme for NT, which is in complete agreement with results of Sjöqvist *et al.* (1968), examined by a different analytical method. From the cited studies it is also evident that the ratio of NT in CFS/plasma in the same as results of protein-binding found by usual *in vitro* methods. Fig. 1 demonstrates a clear destinction in the therapeutic results correlated to the two levels of NT in plasma. An invalidation of this result is not likely in the light of the demonstrated average variation in the protein-binding.

A very important problem in the execution of the present investigation is the great drop-out ratio, a consequence of the strict criteria of exclusion. The number of patients withdrawn from the study was, however, similar in the two groups of treatment and took mostly place during the placebo period. This means that the final result is not influenced by a great number of "recovered", who possibly would have done so anyway. An other source of error could be that the four patients, who were excluded within the

first 3 weeks of treatment (switched to NCE-treatment), in particular if they all belonged to group A. This was, however, not the case as they were evenly distributed.

A crucial problem is the defining and selection of depressive patients (Roth *et al.*, 1974). It must be emphazised that it is difficult to outline a homogenous population of depressive patients because of the variability of the diganostic criteria in use (Åsberg, 1973). Only patients suffering from endogenous depression, as defined by the quantitative rating were considered for the present study. Furthermore, only moderately to severely depressed patients were investigated in accordance with the quantitative rating scale employed. The results of the present study should therefore be considered in the light of this selection, which results in a highly homogenous group of patients.

The main problem concerning the most correct quantitative description of improvement from depression, has in the present study been tried solved by using the final scores for calculations, although this problem is still under debate (*cf.* Hamilton, 1975). Amelioration scores, final scores or percentage improvement scores have been widely used, but in our opinion the final scores are the most appropriate way to describe alterations in depression for several reasons. Thus the scale is not supposed to be linear and, if amelioration scores are used, two patients improving *e.g.* 10 scores from baseline 20 and 10, respectively, will be calculated equally improved, which they of course not are. However, in order to be able to estimate also the relative degree of improvement, Table 2 includes the baseline depression scores. The arbitrary limit of 3 scores for being considered fully recovered is choosen because it is in excellent agreement with the clinical impression of being non-depressed.

The mechanism for the postulated inhibiting effect of NT at high plasma levels is not well understood. One explanation could be an excess of anticholinergic effects, producing a mild toxic psychosis which masks the depressive symptoms (Lader, 1974). However, this hypothesis is neither in accordance with our data for the quantitative rating for depression nor with the results of our rating for side-effects. More attention should be paid to some animal studies (Haefely *et al.*, 1964; Møller-Nielsen, 1970) in which the action of biogenic amines was blocked by high dosages of TA. Thus it is possible that the inhibition of antidepressive effect at high NT concentrations could be due to a blockade of the monoamine receptors in the brain (Åsberg *et al.*, 1971).

Freyhuss *et al.* (1970) found a high correlation between the height of the NT plasma level and the blockade of i.v. tyramine effects in man. Their observations indicate a fairly constant responsiveness of the receptor organs between individuals. The relevance of a closer examination of the relationship between plasma concentration and response of these drug is therefore evident.

Significant pharmacological differences among the various TA make it problematic to compare the results of studies carried out with different drugs. The results of the present investigation should therefore not be extended to other TA, until further research has been done in this field. However, the present and the previous studies of NT strongly suggest a therapeutic plasma concentration range from about 50 to not much above 150 ng/ml.

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References

Alexanderson, B., Borgå, O.: Interindividual differences in plasma protein binding of nortriptyline in man—A twin study. Europ. J. clin. Pharmacol. **4**, 196—200 (1972)

Bennet, J. F.: Is there a superior antidepressant? In: Antidepressant drugs, S. Garattini and M. N. G. Dukes, eds. Excerpta Medica International Congress Series No. 122, pp. 375—393. Amsterdam 1967

Borgå, O., Azarnoff, D. L., Forshell, G. P., Sjöqvist, F.: Plasma protein binding of tricyclic antidepressant in man. Biochem. Pharmacol. **18**, 2135—2143 (1969)

Bradley, J. V.: Distribution-free statistical tests. Englewood Cliffs: Prentice Hall 1968

Braithwaite, R. A., Goulding, R., Theano, G., Naily, J., Coppen, A.: Plasma concentration of amitriptyline and clinical response. Lancet **1972 I**, 1297—1300

Burrows, G. D., Davies, B., Scoggins, B. A.: Plasma concentration of nortriptyline and clinical response in depressive illness. Lancet **1972 II**, 619—623

Cronholm, B., Ottosson, J. O.-O.: Experimental studies of the therapeutic action of electroconvulsiv therapy in endogenous depression. The role of the electrical stimulation and of the seizure studied by variation of stimulus and modification by lidocaine of seizure discharge. In: Experimental studies of the mode of action of electroconvulsiv treatment, N.-O. Ottosson, ed. Acta psychiat. scand. **35**, Suppl. 145, 69—97 (1960)

Cronholm, B., Schalling, D., Åsberg, M.: Development of a rating scale for depressive illness. In: Psychological measurement. Modern problems in pharmacopsychiatry, P. Pichot, ed. Basel: Karger 1973

Freyhuss, U., Sjöqvist, F., Tuck, D.: Tyramine pressor effects in man before and during treatment with nortriptyline or ECT: Correlation between plasma level and effect of nortriptyline. Pharmacol. Clin. **2**, 72—78 (1970)

Glassman, A. H., Hurwic, M. J., Perel, J. M.: Plasma binding of imipramine and clinical outcome. Amer. J. Psychiat. **130**, 1367—1369 (1973)

Glassman, A. H., Perel, J. M.: Plasma levels and tricyclic antidepressants. Clin. Pharmacol. Ther. **16**, 198–200 (1974)
Gurney, C.: Diagnostic scales for affective disorders. Proceedings of the Fifth World Conference of Psychiatry, Mexico City, p. 330 (1971)
Gurney, C., Roth, M., Garside, R. F., Kerr, T. A., Schapira, A.: Studies in the classification of affective disorders. The relationship between anxiety state and depressive illness. Brit. J. Psychiat. **121**, 162–166 (1972)
Hamilton, M.: In classification and prediction of outcome of depression. In: Symposia Medica Hoechst 8, J. Angst, ed., p. 195. Stuttgart-New York: Schattauer 1975
Haefely, W., Hürkmann, A., Thoenen, H.: Scheinbare paradoxe Beeinflussung von peripherer Noradrenalwirkungen durch einige Thymoleptica. Helv. physiol. pharmacol. Acta **22**, 15–33 (1964)
Kragh-Sørensen, P., Hansen, C. E., Åsberg, M.: Plasma-nortriptyline levels in endogenous depression. Lancet **1973I**, 113–115
Kragh-Sørensen, P., Hansen, C. E., Larsen, N.-E., Næstoft, J., Hvidberg, E. F.: Long-term treatment of endogenous depression with nortriptyline with control of plasma levels. Psychol. Med. **4**, 174–180 (1974)
Lader, M.: Plasma concentrations of tricyclic antidepressive drugs. Brit. J. clin. Pharmacol. **1**, 281–283 (1974)
Modestin, J.: Über die Abhängigkeit der klinischen Wirksamkeit des Dibenzepine (Noveril®) von seiner Plasmakonzentration. Pharmako-Psychiat. **6**, 29–33 (1973)
Møller-Nielsen, J.: Does a true qualitative difference exist in the mode of action of neuroleptica on catecholamine neuron system? In: The neuroleptics modern problems of pharmacopsychiatry, Vol. 5, D. P. Bobon, P. A. J. Janssen, J. Bobon, eds., pp. 68–70. Basel: Karger 1970
Pletcher, A.: Akute Intoxikation mit Antidepressiva: Pharmakologische Grundlagen. Therapeut. Umsch. **2**, 158–165 (1965)
Roth, M., Garside, R., Gurney, C.: Classification of depressive disorders. In: Classification and prediction of outcome of depression, pp. 3–26 (1974)
Sjöqvist, F.: A pharmacokinetic approach to the treatment of depression. Intern. Pharmacopsychiat. **6**, 147–169 (1971)
Sjöqvist, F., Hammer, W., Borgå, O., Azarnoff, D. L.: Pharmacological significance of the plasma level of monomethylated tricyclic antidepressants. Excerpta Med. International Congress Series, No. 180. The present status of psychotropic drugs. Proceedings of the VI. International Congress of the C.I.N.P. (1968)
Walther, C. J. S.: Clinical significance of plasma imipramine levels. Proc. roy. Soc. Med. **64**, 282–285 (1971)
Åsberg, M.: Nortriptyline in the treatment of depression: Relationship between plasma levels and effects. Thesis, Karolinska Institute, Stockholm 1973
Åsberg, M., Cronholm, B., Sjöqvist, F., Tuck, D.: Correlation of subjective side-effects with plasma concentrations of nortriptyline. Brit. med. J. **1970IV**, 18–21
Åsberg, M., Cronholm, B., Sjöqvist, F., Tuck, D.: Relationship between plasma level and therapeutic effect of nortriptyline. Brit. med. J. **1971III**, 331–334
Åsberg, M., Kragh-Sørensen, P., Mindham, R. H. S., Tuck, J. R.: International reliability and communicability of a rating scale for depression. Psychol. Med. **3**, 458–465 (1973)

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