

Correlation of Subjective Side Effects with Plasma Concentrations of Nortriptyline

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British Medical Journal, 1970, 4, 18-21

Summary: Plasma levels of tricyclic antidepressant drugs vary considerably between individuals receiving the same amount of drug. The bearing of this variation on the occurrence of subjective side effects was investigated in 40 psychiatric inpatients with depressive disorders. Plasma levels were determined before and during four weeks of treatment with nortriptyline 50 mg. three times a day and patients were rated for subjective side effects, the assessors being unaware of the plasma levels of the drug.

Plasma levels varied widely between individual patients, but in any given patient the plasma level tended to be constant over a period of time. The side effects of nortriptyline diminished significantly with time and were in most cases absent during the fourth week of treatment. There was a significant positive correlation between plasma level of nortriptyline and subjective side effects.

The steady-state plasma level of a drug which is metabolized is usually a more important determinant for its effect than dosage, since it reflects the amount of drug available for biological action. Very high plasma levels of nortriptyline should presumably be avoided, since there is no evidence that they are needed for therapeutic effect and they are potentially harmful.

Introduction

During continuous treatment with tricyclic antidepressant drugs the drug concentration in plasma increases successively until a plateau is reached. This plateau level varies considerably between individuals (Hammer *et al.*, 1967). For nortriptyline a range from 8 to 78 ng./ml. was observed in healthy volunteers after eight days' administration of 0.2 mg./kg. body weight three times daily (Alexanderson *et al.*, 1969). The bearing of this variation on the clinical effects of the drug has not previously been investigated, but preliminary observations (Sjöqvist *et al.*, 1968) indicated that a high plasma level might be of importance for the occurrence of side effects.

The aim of the present investigation was to study the occurrence of subjective side effects of nortriptyline, a monomethylated tricyclic antidepressant, in relation to the plasma level of the drug. Nortriptyline was used because of its known pharmacokinetic properties—that is, steady-state kinetics (Hammer *et al.*, 1967) and little interindividual variation in plasma protein binding (Borgå *et al.*, 1969). Nortriptyline is active per se, and there is no indication that its main metabolites in man, 10-OH-nortriptyline and desmethyl-nortriptyline (this laboratory, unpublished), contribute to the therapeutic action (Sjöqvist *et al.*, 1969; Borgå *et al.*, 1970).

Side effects of tricyclic antidepressant drugs are often reported in connexion with evaluations of their therapeutic efficacy—for example, Rose *et al.* (1965) and Stewart and Mitchell (1968). Some of the side effects attributed to the drug, such as dryness of mouth, constipation, and fatigue, are, however, also well-recognized symptoms of depression. Others, such as tremor and increased perspiration, are somatic manifestations of anxiety (Hamilton, 1959) as well. Symp-

toms similar to side effects may exist before treatment, as was shown by Green (1964), who found a variety of "side effect symptoms" present in non-treated "well" subjects as well as in medical patients not under drug treatment. These symptoms tended to be accentuated by placebo treatment.

Quantitative ratings of side effects are thus likely to include symptoms of non-pharmacological origin. The importance of relating "side effect symptoms" during drug treatment to the incidence of symptoms during a control period when no drug has been given, or preferably when no drug has been found in the body fluids with sensitive analytical methods, is further shown by the investigations of Berry and Turner (1968). In a cross-over trial they found that patients excreted significant amounts of psychotropic drugs during a period when these drugs were not administered by the physician.

Patients and Methods

Forty-two depressed inpatients were studied. The material was classified into "neurotic" (8 men and 9 women, age range 25-63, mean age 41.5 years) and "endogenous" (8 men and 17 women, age range 25-72, mean age 53.6 years) depressions. The classification was made after a clinical evaluation. Endogenous depression was operationally defined as a disease characterized by the following features: (1) lowering of mood, usually without adequate psychological cause, (2) retardation, (3) diurnal variation of symptoms with amelioration in the afternoon, and (4) early awakening, in accordance with the description of Cronholm and Ottosson (1960). The "neurotic" group included patients with various types of depression not exhibiting these features. The severity of depression was such as to warrant admission to hospital.

Drug Regimen.—Nortriptyline 50 mg. was given by mouth thrice daily for four weeks after a period of four to seven days of placebo administration. The placebo tablets consisted of lactose. The tablets were given at 06.00, 14.00, and 22.00 hours, and the patients were routinely observed to ingest the drug. With the exception of hypnotics (pentobarbitone or glutethimide) and occasional doses of sedatives (diazepam, meprobamate), which do not interfere in the method used to assay nortriptyline, no additional drugs were allowed. Blood and urine analyses for barbiturates, phenothiazines, and meprobamate performed during the placebo period and every other week during nortriptyline therapy showed no discrepancies to the prescribed treatment.

Determination of Plasma Level of Nortriptyline.—Plasma levels of nortriptyline were determined during the placebo period and twice weekly during treatment with nortriptyline according to the principles of Hammer and Brodie (1967) as further described by Sjöqvist *et al.* (1969). Blood samples were drawn at 13.00 hours, collected in heparinized tubes, stored at 4°C. and centrifuged within one hour at 600 g. Plasma duplicates, 2 ml. each, were acidified with 0.5 ml. of 0.1 N HCl and stored frozen at -20°C. until analysed.

Ratings.—The patients were rated for side effects once weekly, starting during the placebo period, on a rating scale, designed for the purpose (Table I), consisting of 11 items graded from 0 to 3 in increasing severity. The summed scores on these 11 items are called "raw side effect scores." The rating was made by two psychiatrists in a joint interview. At the interview no attempt was made to discriminate between pharmacologically-induced side effects and symptoms of other

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TABLE I—Rating Scale for Side Effects

1. Physical tiredness	0
None	0
Slightly tired, but needs no extra rest	1
Has to lie down and rest at times	2
Lies all day	3
2. Sleep disturbance	0
Normal sleep without hypnotics	0
Normal sleep with hypnotics	1
3-6 hour's sleep with hypnotics	2
Less than 3 hours' sleep with hypnotics	3
3. Headache	0
None	0
Occasional, no analgesics needed	1
Constant moderate, or occasional severe, headache. Salicylates effective	2
Constant severe headache. Salicylates ineffective	3
4. Vertigo	0
None	0
Occasional slight dizziness	1
Constantly slightly dizzy, or occasional severe dizziness	2
Constant severe dizziness. Has to lie down	3
5. "Orthostatic" symptoms	0
None	0
Feels slightly like fainting on sudden rising	1
Has to rise slowly to avoid feeling like fainting	2
Fainting	3
6. Palpitations	0
None	0
Slight palpitations	1
Occasional disturbing palpitations	2
Constant disturbing palpitations	3
7. Tremor	0
None	0
Slight tremor, movements not affected	1
Obvious tremor, small movements impaired	2
Severe tremor	3
8. Perspiration	0
Normal	0
Slightly increased	1
Obviously increased	2
Profuse	3
9. Dryness of mouth	0
None	0
Some, but not subjectively disturbing	1
Obvious, but not severe or painful	2
Severe, makes speaking difficult	3
10. Constipation	0
None	0
Slight constipation, purgatives not needed	1
Obvious constipation. Purgatives taken	2
No bowel movements in spite of purgatives	3
11. Micturition disturbances	0
None	0
Slight difficulties in passing water	1
Difficulties in emptying bladder. Treatment needed	2
Urinary retention	3

TABLE II—Percentage Subjective Side Effects of Placebo and Nortriptyline

	Placebo	Nortriptyline			
		Week 1	Week 2	Week 3	Week 4
1. Physical tiredness	68	76	62	50	54
2. Sleep disturbance	100	92	90	89	89
3. Headache	30	29	26	17	14
4. Vertigo	30	37	33	31	25
5. Orthostatic symptoms	18	24	28	39	46
6. Palpitations	35	45	28	11	14
7. Tremor	35	53	49	50	46
8. Increased perspiration	35	45	41	36	29
9. Dryness of mouth	58	89	95	72	64
10. Constipation	43	61	51	44	29
11. Micturition disturbance	5	5	5	8	7

origin. Patients with endogenous depression were also rated for severity of depression according to a rating scale designed by Cronholm and Ottosson (1960). Those making the rating were kept unaware of the plasma levels of nortriptyline until the study was finished.

Results

General Outcome.—A few patients recovered during the placebo period and were immediately withdrawn from the study. Of the remaining 42 patients, two (one neurotic woman and one man with an endogenous depression) were found to have significant (more than 20 ng./ml.) amounts of nortriptyline in plasma during the placebo period. These patients were excluded. Thirty-one patients received nortriptyline continuously for four weeks. During the last week two patients thought themselves too well to remain in hospital and one was referred to another clinic because of an intercurrent somatic disease (nasopharyngeal carcinoma). In five patients worsening of depressive symptoms occurred or amelioration

TABLE III—Side Effect Scores, Mean and Standard Deviation

	Placebo	Week 1	Week 2	Week 3	Week 4
A. Raw Side Effect Scores					
Mean	6.23	7.68	7.38	6.06	5.25
S.D.	2.93	2.89	3.38	3.23	2.76
Number of patients	40	38	39	36	28
B. Corrected Side Effect Scores					
Mean	1.58	1.21	0.03	-1.04	-1.04
S.D.	3.10	3.14	3.75	2.96	2.96
Number of patients	38	39	36	28	28

S.D. = Standard deviation.

TABLE IV

Week No.	n	\bar{d}	t	Level of Significance
A. Differences Between Raw Side Effect Scores on Nortriptyline and Placebo				
1-2	38	1.58	3.1414	P < 0.005
2-3	39	1.21	2.3977	P < 0.025
3-4	36	0.03	0.0442	N.S.
4-1	28	-1.04	-1.8501	P < 0.10
B. Differences Between Corrected Side Effect Scores Weeks 2, 3, 4, and Week 1				
2-1	37	0.38	1.4189	N.S.
3-1	34	-1.59	-3.7413	P < 0.001
4-1	26	-2.23	-4.1633	P < 0.001

\bar{d} = Mean of differences.
N.S. = Not significant.

was so slight that it was considered unethical to withhold alternative treatment. In one case side effects were severe enough to necessitate a reduction of dosage after three weeks. These patients are included in the study up to that time.

Plasma Levels of Nortriptyline.—As in earlier studies, there was a large interindividual variation in plasma levels of nortriptyline. The distribution of mean plasma levels of individual patients was slightly skewed (mean 96.1, S.D. 51.6, median 83, range 31-283 ng./ml.). One patient differed considerably from the remainder, with an exceptionally high plasma level. The mean plasma levels of the patients with endogenous depression were lower than those of the neurotic depressions during all four weeks (Fig. 1). This difference is, however, not significant in a three-way analysis of variance (Winer, 1962) ($F=1.039$), nor is there any significant variation within weeks ($F=2.370$).

Side Effects

The percentages of patients who have any of the 11 rated "side effects" are shown in Table II. If no account is taken of symptoms occurring during placebo therapy and the severity of symptoms, conclusions regarding the incidence of side effects may be misleading.

In most cases the side effects of nortriptyline were rather moderate. In two cases out of 40 there were, however, more alarming side effects. In one of these cases, a 44-year-old woman, the dosage had to be reduced because the patient

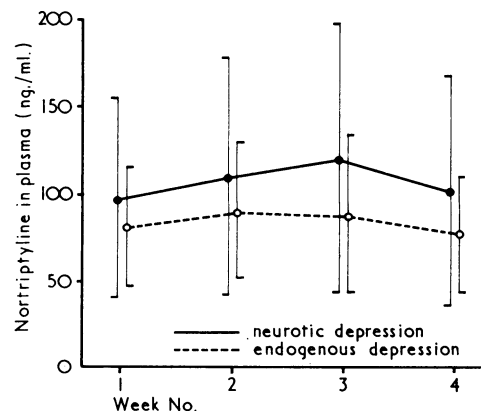


FIG. 1.—Plasma levels of nortriptyline in endogenous and neurotic depressions. Means and standard deviations.

TABLE V—Relationship of Side Effects to Severity of Depression

Week No.	n	r	t	Level of Significance
<i>A. Correlation of Raw Side Effect Scores to Severity of Depression</i>				
0	24	0.61	3.6504	P < 0.005
1	22	0.51	2.6578	P < 0.02
2	23	0.74	4.9952	P < 0.001
3	20	0.62	3.3825	P < 0.005
4	16	0.54	2.4169	P < 0.05
<i>B. Correlation of Corrected Side Effect Scores to Severity of Depression</i>				
1	22	0.32	1.5273	N.S.
2	23	0.33	1.6106	N.S.
3	20	0.25	1.0851	N.S.
4	16	0.07	0.2651	N.S.

n = Number of patients—that is, pairs of observations.

r = Correlation coefficient.

N.S. = Not significant.

TABLE VI

Week No.	n	b	r	t	Level of Significance
<i>A. Regression of Corrected Side Effect Scores (y) on Plasma Level of Nortriptyline (x)</i>					
1	35	0.04	0.50	3.3558	P < 0.005
2	39	0.03	0.46	3.1407	P < 0.005
3	36	0.03	0.42	2.7339	P < 0.01
4	26	0.01	0.12	0.5899	N.S.
<i>B. Regression of Corrected Side Effect Scores (y) on Dosage of Nortriptyline in mg./kg. Body Weight (x)</i>					
1	38	0.99	0.14	0.8576	N.S.
2	39	0.89	0.12	0.7507	N.S.
3	36	0.05	-0.01	-0.0349	N.S.
4	28	1.40	0.18	0.9158	N.S.

n = Number of patients—that is, pairs of observations.

b = Regression coefficient.

r = Correlation coefficient.

N.S. = Not significant.

fainted. Another patient, a 51-year-old man, developed during an E.C.G. exercise test a right bundle-branch block which disappeared after withdrawal of nortriptyline (cf. Freyschuss *et al.*, 1970a). There was no difference in placebo side effect scores between endogenous and neurotic depressions (neurotic mean 6.13, S.D. 3.07; endogenous mean 6.29, S.D. 2.90). Therefore the material was treated as a whole.

The raw side effect scores on placebo and active therapy appear in Table III A. This shows a slight but significant increase in side effects during the first and second weeks of active therapy as compared with placebo. During the third and fourth weeks the side effect scores diminished and were lower than on placebo, though not significantly so (Table IV A).

Throughout the study there was a significant correlation between raw side effect scores and severity of depression in the endogenous depressions (Table V A). This may be due to the fact that this score measures depressive symptoms as well as side effects. Therefore an estimate of pharmacologically induced side effects was obtained by subtracting each patient's placebo score from his scores on nortriptyline. The resulting corrected side effect score is not correlated to the severity of the depression (Table V B).

The distribution of corrected side effect scores is about normal. The corrected side effect scores diminish mono-

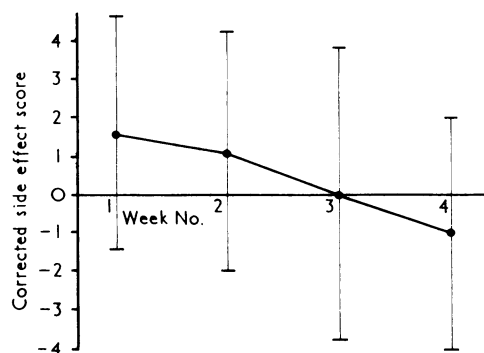


FIG. 2.—Corrected side effect scores. Means and standard deviations.

tonically with time (Fig. 2, Table III B). The scores of weeks 3 and 4 are significantly lower than those of week 1; in fact the mean side effect score for the fourth week is negative (Tables III B, and IV B).

Relationship of Side Effects to Plasma Level of Nortriptyline.—The two above-mentioned patients with severe side effects had the highest plasma levels in the material (maximum values 340 and 235 ng./ml. in the woman and man respectively). There was a significant correlation between corrected side effect scores and plasma level of nortriptyline during the first three weeks of treatment (Table VI A). Though all patients received the same amount of nortriptyline, there is still a variation in dosage due to differences in body weight (range 1.69-3.06 mg./kg.). There is, however, no correlation between dosage in mg./kg. body weight and corrected side effect scores (Table VI B).

Discussion

The plateau plasma levels of nortriptyline are under genetic control and presumably determined by the rate of metabolism of the drug (Alexanderson *et al.*, 1969). The finding that occasional patients develop extremely high plasma levels of nortriptyline on a conventional dosage suggests that there may be genetic polymorphisms forming a polygenic system controlling the metabolism of the drug, a hypothesis which is at present being evaluated.

The tendency of side effects to diminish with time accords with clinical experience. It might be due to the development of receptor tolerance to the peripheral effects of the drug, since there is no corresponding trend in the plasma levels. Psychological factors, such as decreased awareness of side effects with amelioration of the depression, may also contribute. This would be in keeping with the finding that after successful electric convulsion treatment depressed patients tend to judge their memory as improved, independently of objective change (Cronholm and Ottosson, 1963).

The inhibitory effect of tricyclic antidepressants on the neuronal uptake of various monoamines within the central nervous system is thought to be closely related to the antidepressant effect (Carlsson, 1965; Schildkraut and Kety, 1967). Controlled studies are in progress on the relationship between plasma level and therapeutic efficacy of the drug. So far, however, there is no evidence that very high plasma levels (over, say, 100 ng./ml.) are necessary for a therapeutic effect, and it therefore becomes important to reduce dosage in patients who develop high plasma levels and so avoid a potentially harmful accumulation of the drug. This is particularly desirable in elderly patients in whom cardiotoxicity could reasonably be expected to have more serious consequences. In view of the many factors that contribute to the occurrence of subjective side effects in the individual patient, it is, however, questionable whether the side effects could be used as criteria to determine optimal dosage.

Detailed analysis of the rating protocols revealed no straightforward correlation between any particular side effect and the plasma level of nortriptyline. Such side effects as dryness of mouth and constipation may be due both to an anticholinergic effect and to a central adrenergic inhibition of parasympathetic activity. In this connexion blockade of tyramine pressor effects by nortriptyline in man is strongly correlated to the plasma level of the drug but not to the dose (Freyschuss *et al.*, 1970b).

The steady-state plasma level is an estimate of the amount of biologically available drug, and when drug effects are compared in different individuals is more relevant than dosage. Since it is difficult to determine optimal dosage of tricyclic antidepressants by clinical methods, a pharmacokinetic approach—that is, monitoring the plasma levels of the drug—might be rewarding in terms of improved patient care.

This study was supported by grants from Carl-Bertel Nathhorst Foundation, the Swedish Medical Research Council B70-21x-1021-05, the National Institutes of Health, Bethesda, U.S.A. (GM 13978-05), the Association of the Swedish Pharmaceutical Industry, and by funds from Karolinska Institutet.

The polynomial analysis of variance was performed by Mr. Jan Lindell.

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Comparative Trial of Nutrizym in Chronic Pancreatic Insufficiency

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British Medical Journal, 1970, **4**, 21-24

Summary: A cross-over trial of pancreatic replacement therapy was carried out in 12 adults with chronic pancreatic insufficiency. The standard enteric-coated preparation, Pancrex V forte, was compared with Nutrizym, which has an enteric-coated core of pancreatic extract and a shell of bromelains—a mixture of proteolytic enzymes derived from the stem of the pineapple.

Nutrizym was significantly more effective than Pancrex V forte in improving fat absorption, and reduced faecal weight. Protein digestion was assessed by measuring the urinary excretion of hydroxyproline after a gelatin meal. Nutrizym produced an earlier and significantly higher peak in hydroxyproline excretion than Pancrex V forte, but the cumulative effect was similar. The value of bromelains was investigated by including a period on the Nutrizym core alone. This was similar to Pancrex V forte in improving fat absorption but had less effect on protein digestion, suggesting that the beneficial effect of Nutrizym compared with Pancrex V forte was due to the added bromelains, and not to differences in enzyme content or enteric coating.

Introduction

Several reports have shown that pancreatic extracts can increase body weight, fat, and nitrogen absorption (Buckle, 1965; Harris *et al.*, 1955) and can improve absorption curves (Mullinger, 1968). The response is often incomplete, however, even if large doses are given throughout the day (Jordan and Grossman, 1959), and even if sodium bicarbonate is added (Glaessner and Sigel, 1904; Veeger *et al.*, 1962; Haro and Faloon, 1964). Plant and bacterial enzymes have been incorporated in some pancreatic preparations to improve their effectiveness (Goebell and Bode, 1969). A mixture of brome-

lains and pancreatin is available in two preparations (Nusser and Donath, 1968; Schultis and Wagner, 1968), one of which is Nutrizym (Merck). Bromelains is a mixture of proteolytic enzymes found in the stem of the pineapple (*Ananas comosus*); it has maximal proteolytic activity between pH 3 and 8, and is stable at pH 2.0 for a short period. Studies in vitro have shown that its effect in the digestion of casein at pH 3.3 is similar to that of pepsin and at pH 6.0 is similar to that of trypsin (Hennrich *et al.*, 1965). Nutrizym has an enteric-coated core containing concentrated pancreatic extract, surrounded by a layer of bromelains and a sugar coating.

We describe here a cross-over trial comparing Nutrizym with Pancrex V forte (pancreatin, *B.P.*), which is the most widely used of the pancreatic replacement preparations available in the British Isles. The effect of the added bromelains was also investigated by including in the trial a period on Nutrizym core, which was identical in appearance to Nutrizym but contained enteric-coated pancreatin alone.

Design of Trial

Fourteen outpatients (3 female and 11 male) were admitted to the trial: two middle-aged patients with chronic pancreatitis and 12 (aged 15-29) with cystic fibrosis. The latter were chosen because they had considerable steatorrhoea even while taking Pancrex V forte (10 patients) or pancreatin granules (two patients). Other treatment was unaltered during the trial. Each patient was in the trial for three months and received Pancrex, Nutrizym, and Nutrizym core, each for one month in random order. A tablet of Nutrizym contained 50 mg. of bromelains. The amount of pancreatin in a tablet of Nutrizym was greater than in Pancrex V forte, and the doses given with each of the three main meals in a day were either three tablets of Pancrex V forte or two tablets of the Nutrizym preparations. At the end of the trial the three preparations were assayed in vitro. Each tablet of Nutrizym and Nutrizym core was found to contain: trypsin 2,500 units, lipase 8,100 units, and amylase 18,000 units; the corresponding figures for Pancrex V forte were 1,230, 4,000, and 9,600 units respectively.

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