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Elimination and Pharmacological Effects Following Single Oral Doses of 50 and 75 mg of Amitriptyline in Man

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Summary. In a companion paper we described the disposition of a 75 mg single dose of amitriptyline in normal volunteers who were phenotyped as extensive or poor metabolizers of debrisoquine and bufuralol, and had a fourfold range in the oral clearance of the antidepressant, 50 mg of amitriptyline was also administered to the same volunteers. This paper compares the results after both doses and suggests that the disposition of amitriptyline is linear even in subjects with a low oral clearance. There was no relation between the pharmacokinetic data and the intensity of sedation or of psychomotor impairment.

Key words: Amitriptyline – Nortriptyline – Hydroxylated metabolites – Linear disposition – Interindividual differences – Pharmacological effects – Psychomotor tests

Introduction

We have reported that normal subjects who were deficient for the hydroxylation of debrisoquine or bufuralol (Dayer et al. 1982) may have a low apparent oral clearance (Clo) of amitriptyline (AT) (Balant-Gorgia et al. 1982). A fourfold range for the values of AT Clo in seven normal healthy subjects was observed after a single oral dose of 75 mg of AT. It was therefore of interest to describe whether the elimination of AT might be nonlinear and whether there was a clinically relevant relation between the AT Clo and the intensity of some of the pharmacological effects which are measurable after a single dose of this sedative antidepressant.

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Table 1. Elimination of AT from whole blood after a 75 and a 50 mg oral dose

Volunteer	AT Clo $(l \cdot h^{-1})$[a]		Demethylation rate[b]		Normalized 75 mg AUC/ normalized 50 mg AUC[c]			
	75 mg	50 mg	75 mg	50 mg	AT	HO-AT	NT	HO-NT
A	272	284	2.27	2.00	1.00	1.00	1.05	0.53
W	260	147	1.96	1.10	0.64	1.50	1.14	1.80
C	83	83	0.35	0.39	1.07	0.66	0.97	–
Ch	88	86	1.08	1.03	0.87	0.94	0.90	[d]
T	86	114	0.60	0.92	1.26	–	0.88	–
K	61	73	1.01	1.08	1.13	–	1.04	–
G	90	96	1.08	0.85	1.05	–	1.23	–

[a] Calculated on the basis of AUC_0^∞
[b] NT AUC_0^{48}/AT AUC_0^{48}
[c] Calculated on the basis of AUC_0^{48} for AT, NT and HO-NT (10-hydroxynortriptyline) and AUC_0^{11} for HO-AT (10-hydroxyamitriptyline)
[d] This subject had HO-NT only after the 75 mg dose

Methods

The volunteers, the blood and urine sampling, the analytical procedures and the pharmacokinetic calculations were presented in our companion paper describing the administration of 75 mg of AT (Balant-Gorgia et al. 1982). To illustrate a possible nonlinearity in disposition, the area under the concentration versus time curve (AUC) were normalized for a 1 mg dose of AT when comparing the results after the 75 and the 50 mg doses. The small dose range used was imposed by clinical and laboratory considerations. Indeed, single doses of AT greater than 75 mg are not well tolerated clinically and doses less than 50 mg would necessitate the availability of a very sensitive assay. The degree of association between variables was expressed using the Pearson correlation coefficient.

Pharmacological Effects

Changes in alertness and in psychomotor performances were tested simultaneously to the blood sampling during the hours ensuing drug administration, at 0, 0.5, 1, 2, 3, 4, 6, 8 and 10 h. A modified version of the Stanford Sleepiness Scale (SSS) consisting of a 10 points scale was used to measure sedation, and psychomotor performances were evaluated using a modified pencil and paper cancellation test (Schulz et al., in press): the time necessary to locate and cross out 3 different geometric symbols presented among 200 similar symbols was measured in triplicate. An overall evaluation of the intensity for the two pharmacological effects was defined by measuring the area under the changes in effects (over baseline) versus time during the 10 h after AT.

Results

Blood Concentrations

From Table 1 it appears that the elimination of AT was linear in all except one subject (W) who had a paradoxically higher AT Clo after the dose of 75 mg. Since this subject presented many kinetic peculiarities, his case will be summarized individually. The demethylation rate of amitriptyline to nortriptyline (NT)

Table 2. Urinary excretion of AT and its metabolites (in % of dose) 48 h after a 75 and a 50 mg oral dose

Volunteer	AT		HO-AT		NT		HO-NT	
	75 mg	50 mg	75 mg	50 mg	75 mg	50 mg	75 mg	50 mg
A	2.4	2.5	19.5	14.4	0.7	Traces	57.2	63.5
W	2.3	2.3	8.2	9.8	1.4	Traces	46.3	53.7
C	3.0	3.1	9.9	14.5	1.1	0.6	47.8	32.2
Ch	1.9	2.5	8.1	10.3	1.8	2.9	50.8	25.7
T	5.4	3.6	5.3	4.0	0.6	0.7	12.1	13.9
K	2.6	3.4	2.6	2.5	1.5	0.5	14.2	7.7
G	2.7	3.0	2.1	2.8	1.0	0.4	6.6	7.8

(NT AUC^{48}/AT AUC^{48}) was constant at both doses ($r=0.85$ for all subjects and 0.95 excluding subject W). A relation between the AT Clo and the demethylation rate was noted after the 75 and the 50 mg doses ($r=0.91$ and 0.87 respectively). The pattern of metabolism of AT into its main metabolites, as reflected by the blood concentrations, did not vary much since the ratios of the normalized AUC for the metabolites after the two doses were comparable. In a few subjects however, the ratios for the normalized AUC of AT and its metabolites were quite different from 1. (Table 1). (The AUC for the hydroxylated metabolite of AT (HO-AT) could only be compared during the first 11 h, because the blood concentrations of this metabolite, when present, were generally low.) Hydroxynortriptyline (HO-NT) was undetectable after the 50 mg dose in subject Ch who had produced measurable amounts of this metabolite after 75 mg of AT. However, the AT Clo remained constant for this subject. We excluded a technical artifact since, after the 75 mg dose, the blood concentrations of this metabolite were much higher than the lower limit of our assay. After the 50 mg dose subject W had a 40% decrease in the AT Clo and in the demethylation rate. These changes were accompanied by a higher normalized AUC for HO-NT and HO-AT after the 75 than after the 50 mg dose. Therefore, the normalized AUC for the parent compound was higher after the 50 mg dose whereas the normalized AUC for all metabolites had decreased.

Urinary Elimination

Table 2 shows the urinary excretion of AT and its metabolites 48 h after the oral administration of the 75 or 50 mg dose. Results are presented only for the total (conjugated plus unconjugated) excretion of each compound, since the percentage unconjugated or the metabolic ratio were comparable after the 50 versus the 75 mg doses (see Table 2 in Balant-Gorgia et al. 1982). Within the time span of 48 h, 12.4% to 80% of the dose was eliminated in the urine (as the sum of AT plus its metabolites) of the seven subjects. These percentages were constant within individuals ($r=0.92$), and weakly related to the AT Clo ($r=0.64$ after 75 mg and 0.77 after 50 mg).

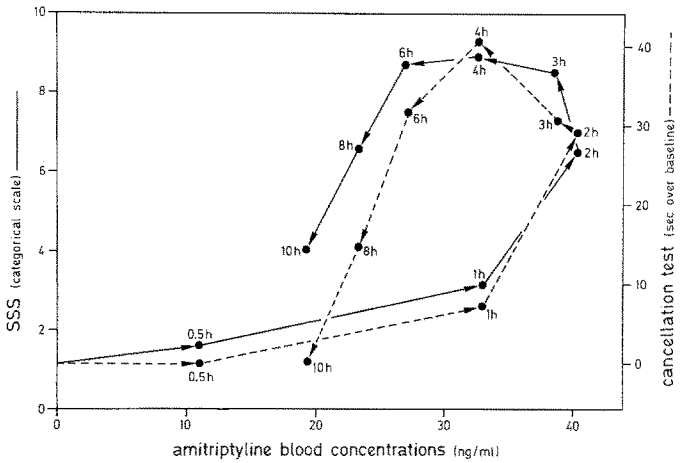

Fig. 1. Sedation and psychomotor impairment in relation to the blood concentration after 75 mg of AT. Sedation was measured with the SSS and psychomotor performances with a paper and pencil cancellation test. The mean blood concentration of AT and the mean values for the intensity of the pharmacological effects are shown for the 7 subjects at each time point during the 10 h after drug administration. A hysteresis curve was also apparent when the sum of the concentrations of AT and its metabolites was used

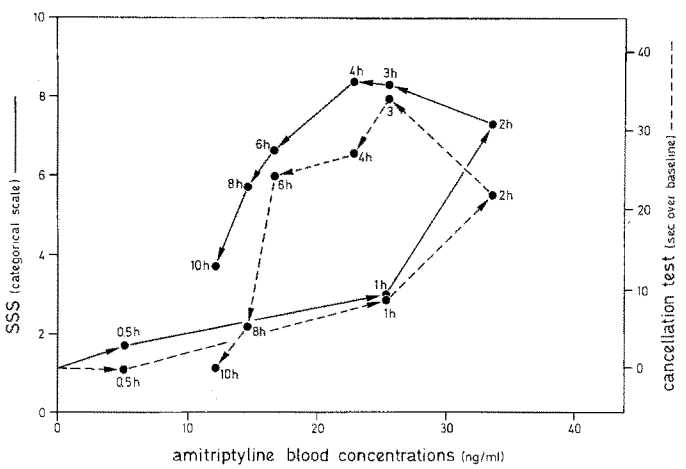

Fig. 2. Sedation and psychomotor impairment in relation to the blood concentration after 50 mg of AT. See text under Fig. 1

Pharmacological Effects

Before the drug administration, all subjects declared no significant sedation (level 1 or 2 on the SSS). They fell asleep (SSS greater than 7) during a few hours after the two doses of AT. The mean of the 14 baseline values for the cancellation test was 115 s (range 77 to 146) and the mean at the time of maximal impairment after AT was 160 s (range 91 to 258). The maximum levels in sedation or in impaired psychomotor performances were observed later than the time of the peak in blood concentrations of AT or that of its metabolites and consequently

Table 3. Pharmacological effects after a 75 and a 50 mg dose of AT

Volunteer	Sedation[a]		Cancellation test[a]	
	75 mg	50 mg	75 mg	50 mg
A	78	65	152	45
W	51	64	403	293
C	67	35	514	190
Ch	73	79	291	499
T	59	56	326	199
K	71	49	33	38
G	65	70	88	30

[a] Measured by the AUC over baseline from time 0 to 10 h

the relation in the intensity of these two pharmacological effects to the drug concentrations in blood exhibited a hysteresis curve (Figs. 1 and 2). Overall, the chronological changes in sedation and in psychomotor performance correlated with each other. However, the individual slopes of the changes in SSS versus those in the cancellation test differed from one subject to the other. In particular, two subjects (K and G) showed minimal impairment in the cancellation test whereas they were very sedated after both doses of AT. There was no correlation between the intensity of the sedation and the individual capabilities to clear AT. This was the case whether the AT AUC, the NT AUC or the AUC for the sum of AT plus all its metabolites were considered. Moreover, the intensity of the sedation was greater after the 50 mg dose in three of the seven subjects. This phenomenon was independent of the order of administration of the two doses, which excludes in part a first dose effect (doses were given more than 10 days apart). For the cancellation test, the drug induced impairment, measured by the AUC for the seconds over the baseline values, was proportional to the individual baseline values of the test ($r=0.85$ after 75 mg and 0.61 after 50 mg) and not to the AT Clo or to other kinetic variables. Table 3 summarized the changes in sedation and in psychomotor performances.

Discussion

Pharmacokinetic Considerations

We studied the linearity of the elimination of AT after doses of 50 and 75 mg. In six of seven subjects, the AT Clo was a constant at both doses. The normalized AUC of the metabolites were also analogous. However, two subjects showed some differences on the elimination of the antidepressant. Subject Ch did not have measurable concentrations of HO-NT after the 50 mg dose. This probable change in the pattern of metabolism was also apparent from the analysis of the urine, since only 25.7% of the dose was eliminated as HO-NT within 48 h (50.8% after 75 mg of AT). After the 50 mg dose, the percentage eliminated as HO-AT did

not change and the AT Clo remained constant. However, the urinary elimination of AT plus the sum of its metabolites decreased from 62.6% to 38.5% of the dose. Thus subject Ch illustrates a situation where blood and urinary data indicate discordant conclusions concerning the overall capability to clear a drug from the organism. The reverse was noted with subject W: the results for urinary elimination were alike after both doses (Table 2), whereas the AT Clo when calculated from the blood concentration was considerably decreased after the lower dose of AT (Table 1). These contradictions seem difficult to explain, but could in part be due to the short duration (48 h) of the urinary collection.

Given the above restrictions, we conclude that the elimination of AT was linear within the dose range studied. In particular, subjects with a low AT Clo, secondary to a lesser demethylation of AT or hydroxylation of AT or NT, did not show indirect evidence that their enzymatic systems were saturated. Had this been the case, we would have expected to measure significant modifications in the normalized AUC for the metabolites (Table 1) and in the pattern of urinary excretion (Table 2). Time related changes in AT Clo appeared to be unimportant in physically healthy subjects. The above results are concordant with the rare studies in which a good prediction of the steady state plasma concentrations of AT has been found from the single dose pharmacokinetics of the drug (Madakasira et al. 1982).

Pharmacodynamic Considerations

Another aim of our study was to compare the intensity of easily measured pharmacological effects of AT to the disposition of the antidepressant. The sedative effect of single doses of AT was impressive, in concordance with the clinical impression that normal volunteers show more drug-induced sedation than do many patients. There was no relation between the degree of sedation and any of the pharmacokinetic variables, and this could indicate that when sedation is the measured effect, 50 or 75 mg doses of AT are already in the supramaximal range on a dose/response curve. Results with the cancellation test showed a clearer dose/response since most subjects had less impairment after the lower dose. However, as observed with sedation, the impairment after the cancellation test bore no relation to the individual capabilities to clear AT. The presence of a hysteresis curve in the relation between the blood concentration of AT and the intensity of the pharmacological effects is of theoretical interest. It might be that a deep brain compartment exists, which has to be filled before any pharmacological effects become noticeable. Alternatively, metabolic or hormonal changes could be induced by the antidepressant and these changes could follow their own independent time course. Clinical observations using short acting sedative drugs indicate that the first hypothesis appears more plausible. A second issue on which we can only speculate is the relative importance of the dynamic effects of the metabolites. HO-AT and HO-NT share some of the actions of AT or NT on the reuptake of neurotransmitters, and all metabolites have less anticholinergic activity than AT (Hyttel et al. 1980). However, sedation is probably best explained by the antihistaminic or α-adrenolytic effects of AT, and the potency of HO-NT or HO-AT for the above actions is still unknown. It appears unlikely that weighting

the AUC of the metabolites by the use of adequate in vitro potency data would show a clearer relation between the kinetics and dynamics of AT. Indeed, the intensity of sedation had minimal interindividual variation, and the impairment in the cancellation test was related to the baseline aptitudes.

Clinical Consequences

We suggest that the adaptation of the daily dose in routine drug monitoring can probably be done according to a linear model even for those patients who have a low AT Clo. The intensity of sedative and psychomotor effects after a single AT dose are not predictive of the disposition of the drug in individual subjects.

The observation that the drug induced impairment is closely related to the level of baseline aptitudes is relevant to the everyday prescription of psychoactive compounds. Although our observation was made with normal young subjects, who all had complex professional activities, the same phenomenon might potentially be present in older patients. We suggest that patients with cognitive impairment should receive low doses of sedative drugs, since the side effects might be more important in these subjects, independently of their capabilities to clear the drug. Our observation may also explain in part the negative findings of other studies aimed at describing a range in the concentrations of psychoactive agents where adverse psychomotor effects are frequent.

Conclusions

From the present results we confirm that the capacity to clear AT varies little with time in individuals, and that at the single doses studied, this antidepressant has a linear disposition even in subjects with a low AT Clo. The absence of any relation between the pharmacokinetic and pharmacodynamic parameters underlines the relevance of taking into account the baseline values in psychomotor tests when studying simultaneously the kinetics and dynamics of psychoactive drugs.

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