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SINGLE-DOSE PHARMACOKINETICS OF AMINEPTINE AND OF ITS MAIN METABOLITE IN HEALTHY YOUNG ADULTS

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Summary – The pharmacokinetics of the tricyclic antidepressant amineptine (Survector®) and its main metabolite were studied in 12 young healthy adults (6 men, 6 women; mean age 35.8 yr). Plasma samples were taken over 24 h following a single oral dose of 100 mg amineptine chloryhdrate. Plasma levels of both compounds were determined by means of high performance liquid chromatography.

Amineptine was rapidly absorbed. Mean peak plasma concentrations of amineptine and its metabolite occurred 1 h and 1.5 h, respectively, after product administration. The mean apparent volume of distribution was large: 2.4 $l \cdot kg^{-1}$. Elimination was rapid; the mean half-lives of the 2 compounds were short: 0.8 h for amineptine and 2.5 h for the metabolite. The mean apparent plasma clearance of amineptine was high (124.8 $l \cdot h^{-1}$).

When the results were adjusted for body weight and surface area, no significant difference in pharmacokinetic parameters was found between men and women.

Given its pharmacokinetic characteristics there is no risk of amineptine accumulation and thus it is a particularly easy drug to manage.

A standard dosage of amineptine was defined for use in healthy young adults.

amineptine / pharmacokinetics / single dose / healthy adults / high performance liquid chromatography

Introduction

Amineptine (Survector®) is a novel tricyclic antidepressant characterized by a dopaminergic mechanism of action (Poignant, 1979) and a stimulant clinical profile (Kamoun, 1979). Chemically, it is distinguished from classical antidepressants by an amino acid side-chain containing 7 carbon atoms attached to the middle ring.

Amineptine is mainly metabolized by beta-oxidation of the side-chain. Its principal metabolite has the same structure as the parent compound, except that of its side-chain is reduced to 5 carbon atoms. This substance also has antidepressant pharmacological activity (Poignant, 1979).

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An initial study of the pharmacokinetics of amineptine and its principal metabolite was carried out on whole blood by means of mass spectrometry coupled with gas chromatography (Sbarra, 1979). It revealed an extremely rapid elimination half-life, but the study design was open to criticism and lacked easy dosing techniques. The development of a new assay method, high performance liquid chromatography (HPLC), has made it possible to perform assays on a routine basis and thus verify the accuracy of the preliminary pharmacokinetic results. Further, certain reports have suggested that plasma amineptine levels are higher in women than in men, but none has directly compared pharmacokinetics in the 2 sexes allowing for differences in weight and height. In the present study, the plasma kinetics of the product and its principal metabolite were determined by means of HPLC, in young adults free of any history of somatic or psychiatric disease.

Material and Methods

Subjects

The study involved 12 subjects (6 men, 6 women), aged from 23 to 46 yr, and weighing from 42 to 90 kg (Table I). All subjects were in good health, and had not taken any drugs for at least 15 d before the study. Selected electrolytic and hematological parameters were normal in all subjects (creatinine, hepatic enzymes, bilirubin, prothrombin time, protein electrophoresis, hemoglobin, full blood count).

Drug administration; sampling

At 08.00 on the day of the study, fasting subjects were given one 100-mg tablet of amineptine chlorhydrate (Survector®) with half a glass of water and remained fasting for 4 h.

Blood samples (5 ml) were taken from a catheter inserted into an antecubital vein, and collected in heparinized tubes. Samples were taken before amineptine administration, and at the following times after administration (h): 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 24. Within 10 min after sampling, the collected blood was centrifuged and the plasma stored at −20°C.

Table I. Population characteristics, comparison of parameters between sexes (mean ± SD).

Number of subjects	12	6	6
Sex	6 men 6 women	men	women
Age (yr)	35.8 ± 6.6	37.8 ± 5.9	33.7 ± 7.3 (NS)
Weight (kg)	64 ± 14	74.2 ± 10.8	54.1 ± 8.4 **
Height (m)	1.69 ± 0.09	1.75 ± 0.07	1.63 ± 0.04**
Surface area (m^2)	1.73 ± 0.22	1.90 ± 0.16	1.57 ± 0.13**

** $P<0.01$ between men and women.

Assay method

Amineptine and its principal metabolite were assayed in plasma by the HPLC technique of Nicot involving inverse phase polarity and ion-pairing (Nicot *et al.*, 1984). The products were extracted as ion-pairs in a heptane-octanol-tetraheptyl-ammonium bromide mixture (98/2/0.5; vol/vol/wt). The chromatographic system consisted of a column (150 × 4.6 mm ID) filled with a Nucleosil C18 stationary phase (5 μm) and a mobile phase comprising an acetonitrile: distilled water mixture (38/62, vol/vol). The aqueous phase, containing 1.2 g/L of heptane sulfonate, was adjusted to pH 3.0 with phosphoric acid. Detection by UV light at 220 nm enabled concentrations $\geqslant 10\ \mu g \cdot l^{-1}$ to be assayed. The linearity of this method was tested between $10\ \mu g \cdot l^{-1}$ and $1\ mg \cdot l^{-1}$.

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters of amineptine and its principal metabolite were calculated with a PHARM program (Gomeni, 1984) on a Hewlett-Packard HP150 calculator. An open 2-compartment model was employed for 20 parameters out of 24, and a single compartment model for the remaining 4 parameters. Curves of plasma concentration as a function of time were individually adjusted by linear regression.

The following parameters were determined:

- *for amineptine and its metabolite:*
  peak plasma concentration (C_{max}); time to plasma peak (t_{max}); area under the curve from zero to infinity (AUC); terminal elimination half-life ($t_{\frac{1}{2},z}$); mean residence time (MRT);
- *for amineptine only:*
  apparent plasma clearance (Cl/F), where F is the bioavailability, and apparent volume of distribution (V/F), calculated from the AUC.

Normalization of results

The results of administration of a fixed dose of 100 mg of amineptine were normalized for each subject in terms of both body weight (BW; dose expressed as mg/kg) and surface area (dose expressed as mg/m²). Surface area (BSA) was calculated according to the formula of Dubois and Dubois:

$$\underset{cm^2}{\text{surface area}} = \underset{kg}{\text{weight}}^{0.425} \times \underset{cm}{\text{height}}^{0.725} \times 71.84.$$

Statistical interpretation

The kinetic parameters determined in men and women were compared using the nonparametric Mann-Whitney test.

Results

The mean concentration curves of amineptine and its metabolite with respect to time are shown in Fig. 1. The curves may be, on the basis of a 2-compartment model, broken up into 3 phases: an absorption phase, a distribution phase, and an elimination phase ($C = ae^{-ka\ t} + be^{-alpha\ t} + ce^{-beta\ t}$).

Six hours after administration, plasma concentrations of amineptine were generally no greater than $10\ ng \cdot ml^{-1}$. The metabolite also fell to barely detectable levels (at concentrations of about $20\ ng \cdot ml^{-1}$) 8 h after administration of amineptine.

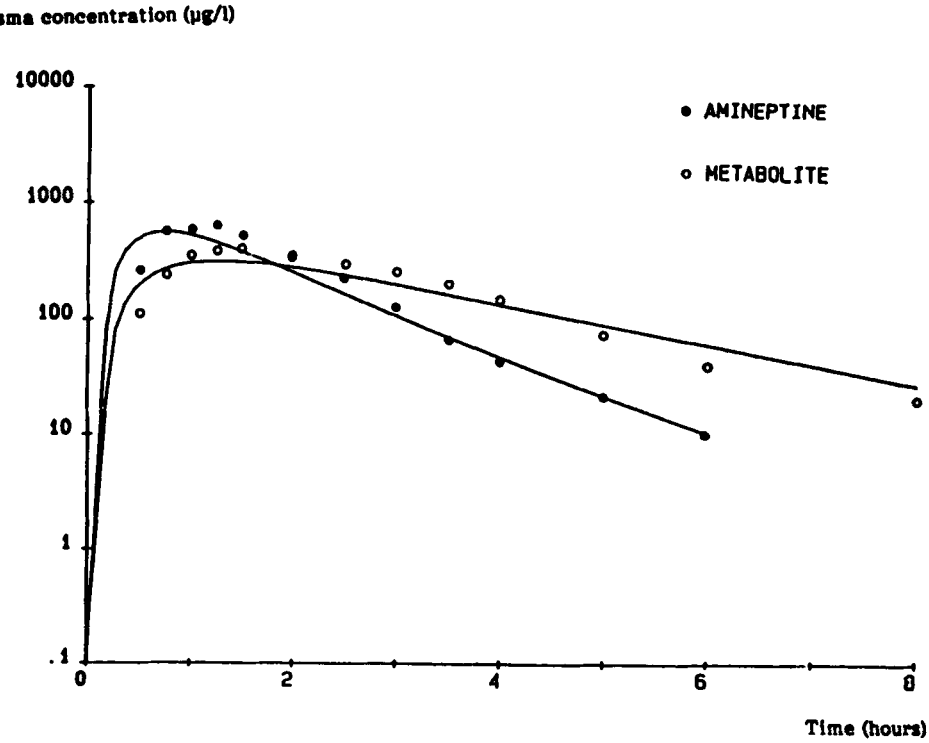

Fig. 1. Pharmacokinetic profile of amineptine and its principal metabolite in young adults following oral administration of a single-100 mg dose.

The pharmacokinetic parameters, both as calculated and following normalization with respect to weight and surface area, are given in Table II, according to the sex of the subjects.

The results of all 12 subjects are summarized in Table III.

Amineptine was absorbed rapidly, with a t_{max} of approximately 1 h (0.92 ± 0.32 h). Seven subjects out of 12 showed a lag time of between 15 and 45 min. The t_{max} tended to occur earlier in women than in men, but the difference was not significant (Table II). In addition, C_{max} was greater in women than in men (1066 ± 776 $\mu g \cdot l^{-1}$ and 477 ± 185 $\mu g \cdot l^{-1}$, respectively), but again, this difference was not significant and was considerably attenuated when the results were normalized (Table II).

The apparent volume of distribution was high (2.44 $l \cdot kg^{-1}$). The normalized apparent volume of distribution was identical in men and women.

The apparent clearance of amineptine was very high (124.8 $l \cdot h^{-1}$). The beta elimination half-life was short: <1 h (0.80 ± 0.24 h). The normalized apparent clearance and half-life were not significantly different between men and women.

For a standard dose of 100 mg, the AUC was considerably greater in women than in men (1 502 and 733 $\mu g \cdot l^{-1} \cdot h$, respectively). There was a high degree of variability, as was true for C_{max}, explaining the lack of statistical significance. However, normalization of dosage with respect to weight and surface area minimized this difference (Table II). The mean residence time was 1.81 h in men and 1.53 h in women (NS).

Table II. Plasma pharmacokinetic parameters of amineptine and its principal metabolite in young adults following oral administration of a single 100-mg dose of amineptine: comparison between sexes.

	Amineptine mean ± SD		Metabolite mean ± SD	
	Men	Women	Men	Women
C_{max} ($\mu g \cdot l^{-1}$)	477 ± 185	1066 ± 776	295 ± 147	647 ± 280*
C_{max} ($\mu g \cdot l^{-1}/mg \cdot kg^{-1}$)	353 ± 152	569 ± 405	225 ± 134	340 ± 135
t_{max} (h)	1.07 ± 0.32	0.77 ± 0.27	1.67 ± 0.47	1.13 ± 0.37
V/F (l)	132 ± 124	181 ± 72	—	—
V/F ($l \cdot kg^{-1}$)	2.44 ± 0.92	2.44 ± 2.25	—	—
V/F ($l \cdot m^{2-1}$)	95.13 ± 36.11	84.20 ± 79.18	—	—
Cl/F ($l \cdot h^{-1}$)	150.5 ± 48.2	99.2 ± 72.5	—	—
Cl/F ($l \cdot h^{-1} \cdot kg^{-1}$)	2.01 ± 0.49	1.83 ± 1.29	—	—
Cl/F ($l \cdot h^{-1} \cdot m^{2-1}$)	78.42 ± 20.19	63.10 ± 45.74	—	—
$t_{\frac{1}{2},z}$ (h)	0.77 ± 0.30	0.82 ± 0.20	2.64 ± 1.23	2.44 ± 1.65
AUC ($\mu g \cdot h \cdot l \cdot^{-1}$)	733 ± 275	1502 ± 941	1069 ± 443	1547 ± 485
AUC ($\mu g \cdot h \cdot l^{-1}/mg \cdot kg^{-1}$)	532 ± 179	791 ± 465	816 ± 431	816 ± 208
AUC ($\mu g \cdot h \cdot l^{-1}/mg \cdot m^{2-1}$)	13.68 ± 4.58	23.33 ± 34.74	20.50 ± 10.02	24.00 ± 6.76
MRT (h)	1.81 ± 0.32	1.53 ± 0.34	3.93 ± 0.68	2.87 ± 0.70

*$P < 0.05$ between men and women.

Table III. Plasma pharmacokinetic parameters of amineptine and its principal metabolite in young adults following oral administration of a single 100-mg dose.

	Amineptine		Metabolite	
	m ± SD*	Range	m ± SD*	Range
C_{max} ($\mu g \cdot l^{-1}$)	772 ± 620	277–2215	471 ± 281	144–1068
t_{max} (h)	0.92 ± 0.32	0.36–1.40	1.40 ± 0.49	0.44–2.32
V/F ($l \cdot kg^{-1}$)	2.44 ± 1.64	0.63–6.61	—	—
Cl/F ($l \cdot h^{-1}$)	124.8 ± 64.4	35–226	—	—
$t_{\frac{1}{2},z}$ (h)	0.80 ± 0.24	0.53–1.35	2.54 ± 1.39	0.97–4.82
AUC ($\mu g \cdot h \cdot l^{-1}$)	1117 ± 773	442–2923	1308 ± 508	720–2271
MRT (h)	1.67 ± 0.35	1.06–2.26	3.39 ± 0.86	2.19–4.77

* Mean ± SD.

The peak concentration of the metabolite was obtained approximately 0.5 h after that of amineptine in both men and women ($t_{max} = 1.40 \pm 0.49$ h).

The value of C_{max} for the metabolite was significantly greater ($P < 0.05$) in women than in men (647 ± 280 $\mu g \cdot l^{-1}$ and 295 ± 147 $\mu g \cdot l^{-1}$, respectively). When C_{max} values were normalized for differences in weight, this difference was no longer significant (Table II).

It was not possible to determine the apparent volume of distribution or the apparent clearance of the metabolite, as the fraction of the product eliminated by metabolism is unknown.

The half-life of the metabolite was identical in men and women. On the average, it was 2.54 h in the 2 populations, and thus greater than that of the unchanged product (1 h).

The area under the curve for the metabolite was greater in women than in men (1547 and 1069 $\mu g \cdot l^{-1} \cdot h$), but the difference was not significant, due to the considerable degree of dispersion of the results. Normalization of the results as a function of BW or BSA (mg/kg or mg/m²) eliminated this difference. The mean AUC for the metabolite was greater than that for the unchanged product. For the metabolite, the mean residence time was 3.93 h in men and 2.87 h in women (NS).

Discussion

These results confirm the very rapid kinetics of amineptine previously reported (Sbarra *et al.*, 1981). Indeed, amineptine has been shown to have a more rapid onset of action than classical tricyclics (Kamoun, 1983). Absorption is more rapid than has been described for other antidepressants (Pribor *et al.*, 1980).

The apparent volume of distribution is large, similar to the volume of distribution of other tricyclic antidepressants (Benet *et al.*, 1984), which indicates a considerable degree of drug diffusion outside the vascular system. A distribution study using labeled drug (Krikorian, 1979; Benard *et al.*, 1986) has shown the brain, liver, and kidney to be the principal sites of drug fixation.

The apparent clearance of amineptine is high, greater than that observed with the majority of tricyclic antidepressants. The rapid elimination half-life of amineptine also differentiates it from other tricyclic antidepressants, which have half-lives 10–20 times greater (Molnar and Gupta, 1980).

The pharmacokinetic parameters of amineptine in men and women are not significantly different. Although the C_{max} and AUC for the metabolite are higher in women than in men, the fact that both parameters are identical after normalization for differences in height and weight suggests that the fraction of the drug that is metabolized is identical in both sexes.

It is not possible to compare the results obtained here with those previously described by Sbarra *et al.* (1979), inasmuch as the latter were obtained with whole blood, and

the distribution of amineptine and its metabolite between plasma and erythrocytes is not equal (two-thirds to one-third).

Furthermore, in the study design used by Sbarra *et al.* (1981), blood levels of amineptine and its metabolite were monitored only over 4 h, which led the authors to postulate a single-compartment model and to underestimate the AUC; it also prevented them from evaluating the terminal elimination half-life. In the present study, the pharmacokinetics of the product were studied at 5, 6, 8, and 24 h.

Finally, the technique employed by Sbarra *et al.* (1979) has a detection limit of 50 $\mu g \cdot l^{-1}$, whereas that of this study is lower (10 $\mu g \cdot l^{-1}$).

Increasing the number of blood samples and improving the detection limit made possible a thorough assessment of the final portion of the elimination curve.

The study of Sbarra *et al.* (1979) may be considered as a preliminary approach to the problem, using the technical resources available at that time. Nevertheless, this study did demonstrate the rapid kinetics of amineptine.

A new parameter, not studied by Sbarra *et al.* (1979), is the mean residence time (MRT), the average time during which a molecule is present in the organism after administration.

This parameter is difficult to interpret when given as an isolated value. However, it may be used as the basis for calculation of the exposure index (Tozer, 1983) which, for a single dose, is equal to the MRT multiplied by the dose. This parameter can be especially useful in evaluating the risk of toxicity or the likely efficacy.

A large difference in MRT between different populations would argue in favor of adjusting the therapy according to the population being treated, which was not the case for men or women.

Therapeutic implications

In a study on acute suicidal overdosage with antidepressants, Conso and Garnier (1981) demonstrated the very high safety margin of amineptine. Thus, no toxic signs were observed following ingestion of single doses of 4000 mg or even higher. Consequently, the differences observed in C_{max} and AUC between men and women using a standard dose do not require dosage modifications relative to sex so far as toxicity is concerned.

Given its pharmacokinetic characteristics, there is no risk of amineptine or its metabolite accumulating in young subjects with repeated administration. Thus, 10 h after administration of the amineptine tablet, neither the drug nor its metabolite was detectable in the plasma of any subject by the technique employed.

These characteristics make amineptine a particularly easy drug to manage. The pharmacokinetic characteristics of a standard treatment regimen (2×100 mg/d at 8 h and 12 h), despite their high variability, obviate the need to monitor plasma concentrations in young adults without somatic disease.

Further pharmacokinetic studies will be performed with the HPLC technique in patients at risk (elderly depressed patients, patients with renal or hepatic insufficiency) in view of the current wide use of amineptine.

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