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EFFECT OF AMANTADINE ON DRUG-INDUCED PARKISONISM: RELATIONSHIP BETWEEN PLASMA LEVELS AND EFFECT

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1 Amantadine, administered at a dose of 200 mg/day, antagonized the extapyramidal symptomatology induced by neuroleptic drugs in fifteen psychiatric patients.

2 Steady-state levels were reached within 4-7 days of treatment. Individual plasma levels ranged from 200-900 ng/ml.

3 Apparent plasma half-lives varied from 10-28.5 h with an apparent V_D of 200-400 litres.

4 A significant relationship was found between the plasma levels of amantadine and the effects on the extrapyramidal symptomatology.

5 The data suggest a direct effect of amantadine on dopaminergic receptors.

Introduction

The antiparkinson activity of amantadine, firstly described by Schwab, England, Poskanzer & Young (1969) has been subsequently confirmed by several authors in controlled trials where the drug was administered either alone (Fieschi, Nardini, Casacchia, Tedone & Robotti, 1970a; Parkes, Zilkha, Marsden, Baxter & Knill-Jones, 1970; Hunter, Stern, Laurence & Armitage, 1970a; Bauer & McHenry, 1974; Mann, Pearce & Waterbury, 1971) or in association with levodopa (Fieschi, Nardini, Casacchia, Tedone, Reitano & Robotti, 1970b; Hunter, Stern, Laurence & Armitage, 1970b; Mawdsley, Williams, Pullar, Davidson & Kinloch, 1972; Fünfgeld, 1972; Schwab, Poskanzer, England & Young, 1972). Amantadine has also been found to be variably active in the extrapyramidal syndrome induced by chronic administration of neuroleptic drugs (Fanali, Nardini & Sorgona, 1970; Nardini, Fanali, Sorgona, Vergnano & Fieschi, 1971; Kelly & Abuzzahab, 1971). The considerable intersubject variability in the amantadine effects in these patients and on the other hand, its utility in those cases in which a classic anticholinergic therapy is not satisfactory prompted us to evaluate the possible relationships between amantadine plasma levels and effects. No data are in fact available on amantadine pharmacokinetics in the course of chronic treatment.

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Methods

Observations were carried out on fifteen female patients admitted to the psychiatric unit with various psychiatric syndromes and behavioural changes. Their ages ranged from 31-62 years and all were on constant treatment with neuroleptics and anticholinergic drugs. The motivation for their inclusion in the study was the poor control of the extrapyramidal syndrome by classical anticholinergic drugs.

Observations were carried out according to a double-blind crossover design; the neurologists who performed the clinical evaluations were not aware of the experimental design. Upon admission to the observation period, the anticholinergic medication was substituted by a placebo, while neuroleptics (butyrophenones and/or phenothiazines) were continued at the usual dose. After 7 days, amantadine was administered for 15 days at a dose of 200 mg, and then the amantadine

treatment was again switched to placebo for 4 days. Amandatine and placebo matching capsules were used. No variations in the neuroleptic dose were introduced, and no other drugs were administered concomitantly throughout the entire observation period.

Clinical assessment

Clinical evaluations were performed before initiating amantadine treatment on days 1, 4, 7 at 09.00 h and on days 8, 11, 14, 17, 20, 21, 22, 23, 24, and 25. The severity of the extrapyramidal syndrome was assessed according to Fieschi *et al.* (1970a) and to Fieschi, Nardini, Casacchia, Reitano, Tedone, Ferrari & Robotti (1970c) by a 22 items rating scale evaluating akinesia, rigidity, tremor, postural impairment, vegetative symptoms, etc.

Each item was scored from absent (score 0) to very marked (score 3). In addition, three timed performance tests (walking 2 x 3 m; putting finger to nose ten times with each arm; and opening and closing each hand ten times) were carried out on each occasion.

Occurrence of possible side effects was also evaluated by means of routine physical and laboratory controls.

Blood sampling and chemical analysis

Blood sampling was performed before and 6 h after the daily intake of amantadine or placebo on days 8, 11, 14, 17, 20, 21 and 22. Serial blood samples were also collected after the last amantadine dose. The blood collected from the antecubital vein into heparinized test tubes was immediately centrifuged and the plasma so obtained kept at -20° C until analysis. Amantadine plasma levels were measured by means of a g.l.c. procedure involving extraction in toluene and derivatization with trichloracetylchloride (Biandrate, Tognoni, Belvedere, Frigerio, Rizzo & Morselli, 1972).

Calculations

Amantadine plasma elimination rates were evaluated by plotting log-concentration versus time curves and the terminal slope calculated by the method of least-squares to yield the apparent elimination rate constant (K_{el}) and the apparent plasma half-life

$$T_{½} = \frac{0.693}{K_{el}}$$

The area under the curve (AUC) following the last dose was calculated by the trapezoidal rule with extrapolation to infinity after correction for the initial amount, and the apparent volume of distribution was calculated according to the equation

$$V_D = \frac{D \times F}{AUC \times K_{el}}$$

(where D is the dose and F is the fraction absorbed) assuming complete (F = 100) bioavailability.

Statistical analysis of the clinical data and performance tests was carried out by trend analysis, while eventual relationships between plasma levels and clinical data were evaluated by means of univariate and multivariate regression and correlataion analysis.

Results

Clinical effects

The amantadine administration led in most of the patients to a rapid and marked improvement of the extrapyramidal symptomatology with a noticeable decrease in rating within 4-6 days for all the items considered. Statistical analysis of the data showed highly significant ($P < 0.001$) differences in the scores on day 7 (end of placebo period) and day 22 (end of amantadine period).

Rigidity and tremor were favorably affected as well as hypokinesia and vegetative disturbances, but to a lesser extent.

As shown in Figure 1, however, remarkable differences were present within individual patients and the positive effect did not appear to be related in any way to the severity of the extrapyramidal symptomatology. No evident or noticeable side effects were present. With the discontinuation of amantadine administration, a clear reemergence of extrapyramidal symptoms was observed within 48-72 h.

Amantadine plasma levels

Plasma levels of amantadine were measured before the morning dose and 6 h after drug administration. The latter can be considered as 'during the course of absorptive phase' since in volunteers we observed that the absorption peak of amantadine may occur between 2 and 8 h, with a mean value of 6 ± 2 h (Morselli, Nardini, Pacifici, Sorgona, Latini, Ferrari & Fieschi, 1974). Daily administration of amantadine (200 mg), by the oral route at 08.00 h, leads within 4-7 days to plasma levels fluctuating between 400 and 900 ng/ml (Table 1).

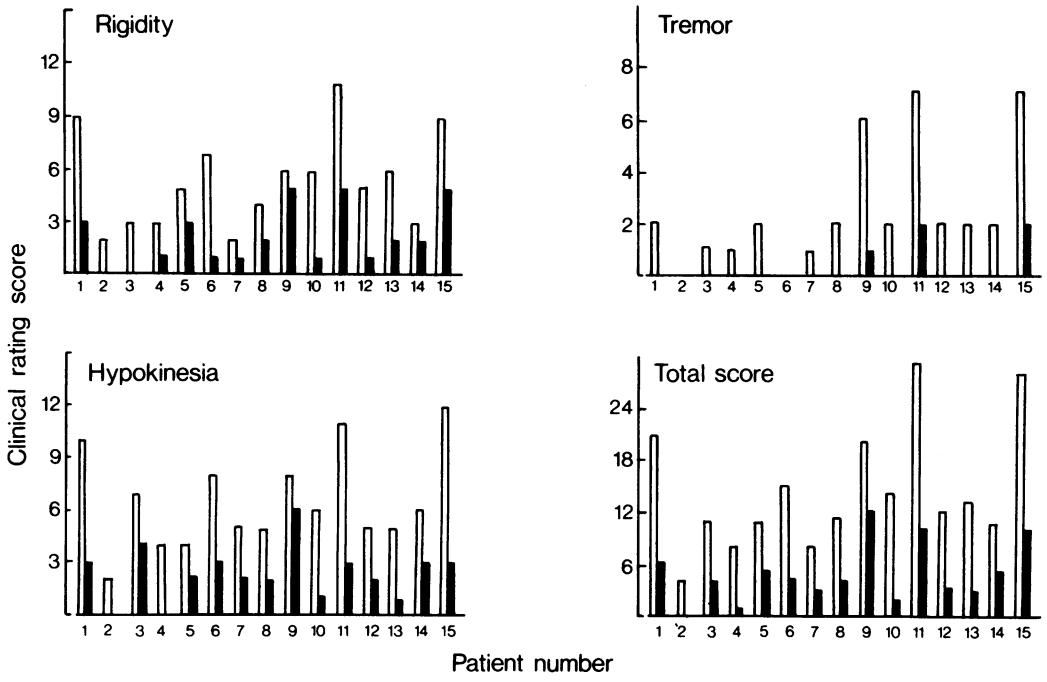

Figure 1 Effect of amantadine (200 mg/day) on clinical rating score before (open columns) and after (closed columns) 15 days of treatment.

The mean basal morning values (08.00 h) appeared to be relatively constant after 7 days of treatment, while absorptive phase values were more irregular with day to day fluctuation of ± 30%.

A remarkable interindividual variability was however present considering both the 08.00 h and 14.00 h values as shown in Figure 2 where the individual plasma concentrations relative to day 17 are reported. Discontinuation of amantadine administration resulted in all cases in a fall of plasma levels and in complete disappearance of the drug within 72 h in five of the subjects; while in seven significant amounts were still measurable 96 h after drug discontinuation. The drug plasma levels appeared to decay monoexponentially according to a first order kinetics. Analysis of the apparent plasma decay curves after amantadine discontinuation led to the values reported in Table 2. It can be seen that a noticeable

Table 1 Mean (+ s.e. mean) plasma levels (μg/ml) of amantadine during the course of administration of amantadine (200 mg/day) orally at 08.00 h to fifteen psychiatric patients

Sampling time (h)	*Study days*									
	7	11	14	17	20	21	22	23	24	25
08.00	0	331 ± 38	404 ± 47	429 ± 59	450 ± 65	461 ± 60	453 ± 57	222 ± 42	118 ± 24	61 ± 17
14.00	278 ± 18	745 ± 43	841 ± 55	891 ± 64	729 ± 69	974 ± 64	n.d.	n.d.	n.d.	
18.00						743 ± 72				

Drug was started on day 7 and discontinued on day 22. (Last administration at 08.00 h on day 21)
n.d. = not determined

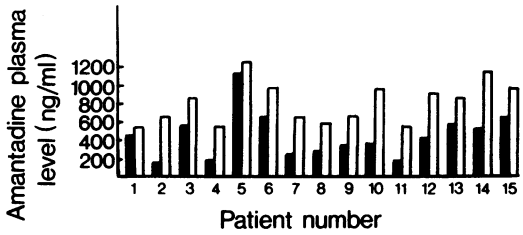

Figure 2 Individual plasma levels of amantadine on day 17. ■ 08.00h; □ 14.00 h values.

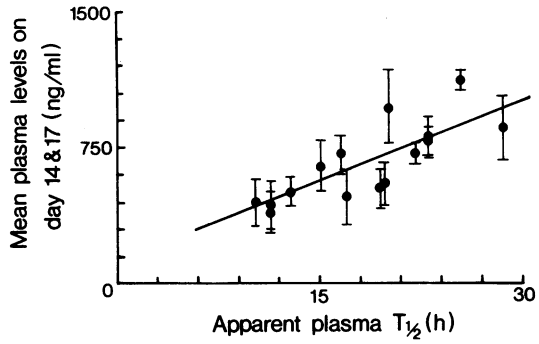

Figure 3 Relationships between apparent plasma half-lives and mean (± s.e. mean) plasma levels on days 14 and 17. Means are calculated on 08.00 h and 14.00 h plasma values. Correlation coefficient (r) = 0.790 ($P < 0.01$).

interindividual variability was present also for plasma half-lives values which ranged from 10-28.5 hours.

A trend towards a longer half-life in older subjects was present but did not reach significance. The mean plasma levels on day 14 and 17 correlated nicely ($P < 0.01$) with the apparent half-life values (Figure 3), while no relationships were evident between absorptive values (14.00 h on day 17 and 21) and plasma half-lives, suggesting no dose dependent kinetics. The apparent V_D calculated assuming complete bioavailability (F = 100) was of the same order as that observed in volunteers and ranged between 206-453 litres (mean value 304 ± 20 litres), suggesting an extensive tissue distribution of the drug. The apparent plasma clearance ranged from 115-363 ml/min, and is of the same order of clearance values observed in volunteers.

Relationships between plasma levels and effects

No direct relationships could be observed between clinical rating scores and amantadine plasma levels considering the subjects individually. However an

Table 2 Pharmacokinetic parameters of amantadine in psychiatric patients

Patient number	*Age (years)*	*AUC* (ng ml^{-1} h)	K_{el} (h^{-1})	*Plasma* $T_{½}$ (h)	V_D (l)	*Plasma clearance (ml/min)*
1	38	12953	0.0535	12.9	288	257
2	42	13656	0.0675	10.3	217	244
3	47	20667	0.0313	22.1	309	161
4	44	12779	0.0605	11.4	258	260
5	44	28750	0.0272	25.4	255	116
6	49	18710	0.0303	23.0	356	180
7	45	09174	0.0609	11.4	358	363
8	62	17403	0.0350	19.8	328	191
9	51	13972	0.0355	19.5	402	238
10	40	20327	0.0460	15.1	214	164
11	41	10810	0.0408	17.0	453	308
12	30	20539	0.0418	16.6	232	162
13	51	16345	0.0300	23.0	407	203
14	59	26841	0.0243	28.5	285	115
15	33	28118	0.0344	20.1	206	118
Mean ± s.e.mean		18070 ±1598	0.0413 ±0.0035	18.4 ±1.4	304 ±20	209 ±19

Evaluation of kinetic parameters was performed on decay plasma curve after discontinuation of 15 days treatment with amantadine (200 mg/day).

AUC = area under the plasma concentration-time curve extrapolated to infinity

K_{el} = Rate constant of elimination;

Plasma $T_{½}$ = Apparent plasma half-life;

V_D = Apparent volume of distribution

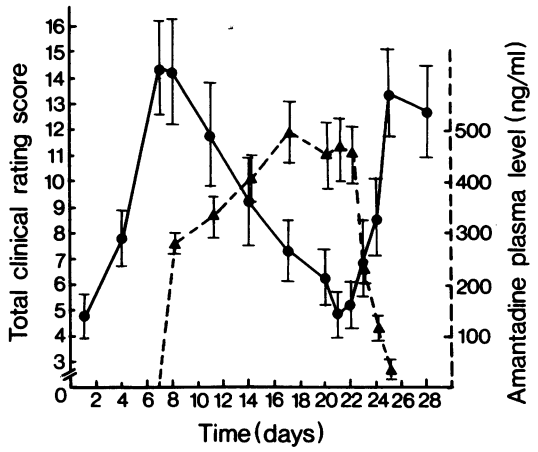

Figure 4 Relationship between the mean (± s.e. mean) total clinical rating score and the mean (± s.e. mean) amantadine plasma levels, over the observation period. ----- plasma levels; ——— = rating score.

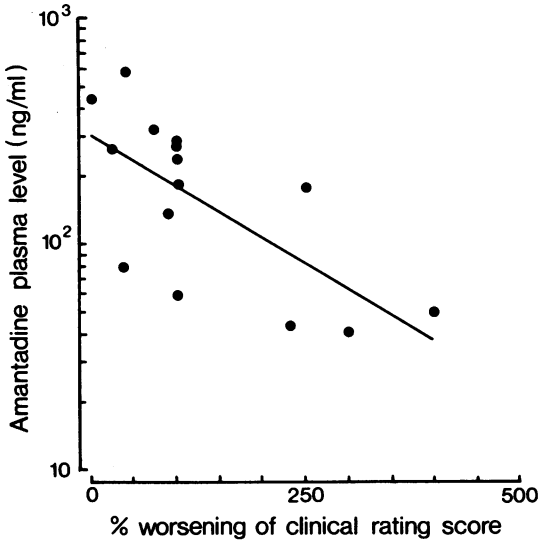

Figure 5 Relationship between the percentage worsening of clinical rating scores 48 h after the last administration of amantadine and log plasma levels at the same time. Correlation coefficient (r) = 0.686 ($P<0.02$).

evident relationship could be observed by plotting the mean of the rating scores and the mean of 08.00 h plasma levels over the observation time (Figure 4). It can in fact be seen that a gradual increase of amantadine plasma levels mirrors the concomitant decrease in the mean rating score, and that the inverse holds true after amantadine discontinuation. Moreover, a significant relationship ($P < 0.02$) was observed between the plasma levels 48 h after drug discontinuation and the percentage worsening of the symptomatology in each individual patient (Figure 5). In other words, where the disappearance rate of amantadine was faster, there was a more evident and severe reappearance of extrapyramidal symptomatology.

Discussion

Administration of amantadine to fifteen psychiatric patients suffering from extrapyramidal symptoms due to neuroleptic drugs induced, in most cases, a remarkable control and reduction of the symptomatology. This effect was observed with plasma levels ranging from 200-900 ng/ml. Steady state plasma levels were achieved within 4-7 days of treatment, in good agreement with preliminary observations run on four depressed patients (Rizzo, Biandrate, Tognoni & Morselli, 1973) and with the kinetic profile of the drug indicating an apparent plasma half-life of 10-28 hours.

After drug discontinuation plasma concentrations decayed monoexponentially according to first order kinetics.

A significant relationship was present between apparent plasma half-life and mean steady-state plasma levels, and there was no evidence of dose dependent kinetics.

The observed interindividual four-fold variation in plasma levels is probably due to differences in absorption (Figure 2) and excretion rate. Amantadine is virtually entirely excreted as such, and in volunteers, showing an apparent plasma half-life of 13-19 h, 98-99% of the dose can be recovered in urine within 80-120 h (Morselli *et al.*, 1974). In studies on volunteers we demonstrated that even small variations in urinary pH may have a definite impact on amantadine plasma half-life (Latini, unpublished results). Unfortunately, in the present observations, due to poor patient cooperation, this important variable could not be adequately controlled. The computed apparent volume of distribution during chronic treatment was of the same order of that observed in volunteers after a single dose (200-400 litres or 4-6 l/kg) (Morselli *et al.*, 1974). The large apparent V_d suggests that amantadine distributes not only to all the body fluids but also accumulates in certain tissues. Due to pH differences between plasma and extra and intracellular fluids, the out-flow from tissues could

also be another important variable determining individual differences in the drug decay. In agreement with previous reports of Nardini *et al.* (1971), Kelly & Abuzzahab (1971), and Merrick & Schmitt (1973), amantadine antagonized efficiently the extrapyramidal syndrome induced by neuroleptic medication. The exact chemical nature of the mechanism by which amantadine counteracts the extrapyramidal syndrome is still unclear and various hypotheses have been advanced so far (Strömberg, Svensson & Waldeck, 1970; Scatton, Cheramy, Besson & Glowinsky, 1970; Farnebo, Fuxe, Goldstein, Hamberger & Ungerstedt, 1971; Maj, Sowinska & Baran, 1972; Papeschi, 1974; Brown & Redfern, 1974). However, in analogy with the data obtained by Maj *et al.* (1972) the observations of Papeschi (1974) in the experimental animals and of Rizzo *et al.* (1973) in depressed patients, tend to suggest a direct activation of dopaminergic receptors. Supportive evidence for such a mechanism has also been recently given by Stone & Bailey (1975). The lack of correlation between plasma levels and effects in a steady condition is not surprising since either suprathreshold concentrations could have been present, or, accepting the hypothesis of a direct effect on dopaminergic receptors, this effect could well have been differently antagonized by different concentrations of neuroleptics, which unfortunately we could not determine. However, the fact that a significant relationship was observed between the worsening of the clinical picture and the actual plasma levels present 48 h after discontinuation of amantadine appears to us to be a further suggestion for a competitive antagonism at the receptor level.

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