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Pharmacokinetic parameters of mescaline in rabbits

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SUMMARY

By means of a highly specific and sensitive mass fragmentographic method mescaline was measured in rabbit plasma samples, taken at various points after an i.v. injection. The pharmacokinetic behaviour conformed to the two-compartment open model. Half-life times of alpha and beta phases, velocity constants and steady-state distribution volumes of four subjects are reported.

INTRODUCTION

Mescaline (3,4,5-trimethoxyphenethylamine) is an alkaloid, that was isolated in 1896 from the peyote cactus *Lophophora williamsii.* Pharmacologically it causes unusual psychic effects and visual hallucinations.

In the United States it is not considered as a narcotic drug. In Belgium, as in most other countries, it is on the list of illicit drugs. An excellent review of its chemistry, biogenesis, and biological effects was published in 1970 (1).

Very few methods have been elaborated for the specific quantitative determination of mescaline. A radioimmunological technique with ^{125}I-iodinated N-(3,4,5-trimethoxyphenethyl)-4-hydroxyphenylacetamide as the labelled derivative has been described (2). The development of a GLC-mass spectral analytical procedure for plasma samples, using a ^{2}H-labelled homologue of natural mescaline as the internal standard, was the basis of the present work (3). Due to the previous lack of an appropriate analytical method, little is known of the pharmacokinetic profile of mescaline in man and animals. According to Charalampous et al. (4), the compound is excreted primarily via the urine in humans. Subjects given 500 mg of mescaline orally, excreted 87% of the dose in 24hrs. The unchanged molecule accounted for 60% and 3,4,5-trimethoxyphenylacetic acid for another 30% of the ingested dose.

The aim of this work was to establish some pharmacokinetic parameters in the blood compartment. A highly specific and sensitive technique for quantitative analysis of plasma samples was essential for this purpose.

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METHODS AND MATERIALS

Animals

Four rabbits (± 2 kg) were given a rapid intravenous (ear vein) injection of 1 ml of an aqueous solution of mescaline sulphate at a dose of 10 mg/kg of bodyht (calculated as mescaline base). Blood was withdrawn from the other ear and collected in heparinized tubes. No food was available, but water was given *ad libitum.*

Reagents

Mescaline sulphate (99% pure) was obtained from Koch and Light Laboratories, England.

The internal standard for mass fragmentographic analysis was synthesized from 3,4,5-trimethoxyben-

zaldehyde by condensation with nitromethane and subsequent reduction with lithium aluminium deuteride.

Analytical procedure

The analytical procedure has been detailed in a previous paper (3).

Pharmacokinetic analysis

The plasma concentrations were plotted on semilogarithmic paper as a function of time. The parameters were calculated from the slope of the terminal phase by the method of the residuals. Each slope was fitted by the method of the least squares.

RESULTS AND DISCUSSION

An example of a mass fragmentogram of a plasma extract is shown in Fig. 1. Due to the elevated specificity of the detection no interfering peaks were detected. No co-eluting substances were found when blank plasma samples were analyzed. This made the method very suitable for pharmacokinetic work. The precision of the technique, expressed as coëfficient of variation, was in the order of 5%. For the GLC-mass spectral detection it was shown to be 1.7% (6 repetitive injections of the same extract). Although the apparent extraction efficiency with a labelled internal standard added before the extraction was 100%, the actual efficiency was checked and shown to be about 95% for spiked serum samples.

The pharmacokinetic behaviour of mescaline conformed to the two-compartment open model represented by the following equation:

$$C_{p(t)} = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

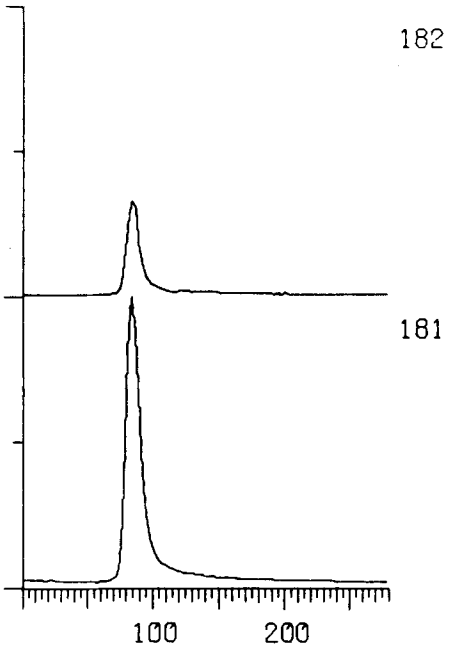

Fig. 1 : Typical mass fragmentogram of a plasma extract.

where A and B are constants and α and β hybrid rate constants, which depend on the velocity constants $k_{1,2}$, $k_{2,1}$ and k_c. The latter permit the calculation of the plasma half-lives of the alpha and beta phase by means of the following equations:

$$T_{1/2(\alpha)} = \frac{0.693}{\alpha} \qquad \text{(Eq. 2)}$$

$$T_{1/2(\beta)} = \frac{0.693}{\beta} \qquad \text{(Eq. 3)}$$

β reflects the terminal and linear part of the curve and was determined by linear regression, while α was calculated by the method of the residuals and subsequent linear regression by the method of least squares.

Table 1 : Pharmacokinetics of mescaline in rabbits after a single intravenous injection of 10 mg/kg of body weight

SUBJECT	α (min.$^{-1}$)	$T_{1/2(\alpha)}$ (min)	β (min.$^{-1}$)	$T_{1/2(\beta)}$ (hrs)	$k_{2,1}$ (min.$^{-1}$)	$k_{1,2}$ (min.$^{-1}$)	k_e (min.$^{-1}$)	$V_{d_{ss}}$ (liter)
A	0.0290	10	0.598×10^{-3}	8.38	0.0099	0.0180	0.0017	285
B	0.0226	13	0.759×10^{-3}	6.60	0.0102	0.0115	0.0017	328
C	0.0242	12	0.526×10^{-3}	9.53	0.0115	0.0115	0.0011	152
D	0.0248	12	0.621×10^{-3}	8.07	0.0094	0.0144	0.0016	271

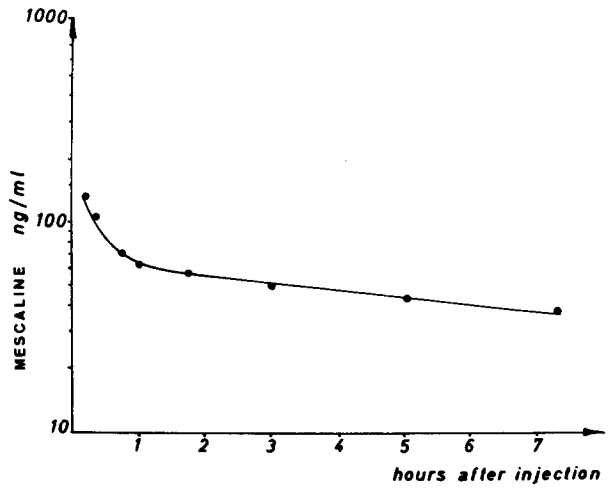

Fig. 2 : Pharmacokinetic profile of subject D of Table I.

The steady state distribution volume $V_{d_{ss}}$ is given by the equation:

$$V_{d_{ss}} = \frac{k_{1,2} + k_{2,1}}{k_{2,1}} \qquad \text{(Eq. 4)}$$

All the data obtained from the present study are compiled in Table I. The pharmacokinetic profile of subject D is given as an example in Fig. 2.

The rather long half-life of mescaline in plasma conforms very well with its prolonged period of activity when administered as a single dose. Its effects are known to last for 12 hours (5).

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