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Plasma and Tissue Concentrations of Methylergometrine (Methylergonovine) in the Rabbit

By

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Abstract: The concentrations of methylergometrine (M) (methylergonovine) in the plasma, uterus, liver, and kidneys of the rabbit were determined by a radioimmunoassay after a single 0.2 mg/kg intravenous injection and the drug responce was studied in the uterus *in situ.* M disappeared quickly from the plasma with a mean distribution phase half-life of 0.91 min. According to the fast uterine tissue uptake of M the drug response in this effector organ began quickly. The simulated concentrations in the peripheral compartment of the two-compartment open model can be useful in the understanding of the rapid drug effect, but they do not describe the real situation in any particular tissue.

Key-words: Methylergometrine (methylergonovine)- pharmacokinetics – rabbit.

After developing a new radioimmunoassay (Kleimola 1978) we have been able to study the pharmacokinetics of methylergometrine (methylergonovine) in animal (Mäntylä *et al.* 1977a & b) and human (Mäntylä *et al.* 1977a & 1978a; Allonen *et al.* 1978; Erkkola *et al.* 1978; Kanto *et al.* 1978) studies. Both in the rabbit and man methylergometrine disappeared quickly from the plasma with a mean distribution phase half-life of about 1 to 2 min. which was in agreement with the rapid clinical response of this ergot alkaloid appearing a few minutes after a single 0.2 mg intravenous injection (Roth-Brandel *et al.* 1970). Similarly, the mean maximal responce in the rabbit uterus *in situ* after a single 0.05, 0.1, and 0.2 mg/kg intravenous dose was found at 26 to 40 sec. after the drug administration, and the dose response curve was steep (Mäntylä *et al.* 1977a). In this study we have measured the concentrations of methylergometrine in order to find the rate of the tissue uptake in relation to the drug response in the rabbit uterus *in situ.* The levels in two other important tissues liver and kidneys, were determined as well.

Materials and Methods

Methylergometrine concentrations in the rabbit plasma were determined by radioimmunoassay (Kleimola 1978) at 0-time and then as seen in fig. 1. after a single 0.2 mg/kg intravenous injection (methylergometrine maleas, Myomergin^{R}, Leiras, Turku, Finland). The seven non-gravid *post partum* (1.0 – 1.5 months) rabbits weighed 2.1 – 2.8 kg. They were anaesthetized with urethane 1.5 g/kg subcutaneously. The blood samples (2 ml) were taken from the carotid artery and the same volume (2 ml) of normal saline in 5% glucose was injected into the carotid artery after taking each sample. The assay can detect 0.85 ng/ml of methylergometrine in the plasma and the standard deviation at this level is 10 per cent. The concentrations in the uterus, liver, and kidneys were determined as follows. The tissue sample of about 0.4 – 0.6 g was homogenized with borate buffer (pH 9,1:5) and 1.0 ml of the homogenate was extracted twice with benzene-isoamyl alcohol. Then the extract was evaporated to dryness under nitrogen. The recovery percentage

(mean±S.D.) of methylergometrine in the uterus, liver, and kidneys was 92.2±10.2, 89.2±12.2, and 102.5±9.6, respectively (n=8–10). The concentrations in the uterus, liver, and kidney, are given in ng/g of wet weight.

We had no knowledge about the stage of the ovarian cycle in the animals. The pharmacodynamic effects of methylergometrine were tested on the rabbit uterus *in situ* (Rothlin 1946/1947; Fregnan & Glässer 1964; Mäntylä *et al.* 1977a). The ovarian end of a uterine horn was attached to an isotonic myograph and connected to a physiograph (E & M Physiograph "six"). It was stretched with a force of 20 g. The first two uterine samples (about 400–600 mg) at 3 and 15 min. were taken from the free uterine horn not attached to the myograph and the third one at 30 min. from the other uterine horn after recording the drug effect until 30 min. (table 1). The drug response was calculated as the area under the drug response curve recorded by the physiograph (mm^2). In addition, one sample from the liver and kidney was taken at 30 min. (table 1).

The pharmacokinetic model for each experiment was selected by using the AUTOAN decision making computer programme (Sedman & Wagner 1974). This programme also computed the pharmacokinetic parameters with the aid of NONLIN (Metzler 1969), a least-squares non-linear fitting computer program (weighting $1/Y^2$). In each experiment the best fit was obtained when a two-compartment open model was used as described in our earlier studies with methylergometrine (Mäntylä *et al.* 1977a & 1978a; Kanto *et al.* 1978). The concentrations in the peripheral compartment were simulated from the plasma concentrations by the equation

$$\frac{A\beta + B\alpha}{\alpha - \beta}\,(e^{-\beta t} - e^{-\alpha t})$$

Results

The concentrations of methylergometrine in the plasma, liver, and kidneys of the rabbit after a single 0.2 mg/kg intravenous injection can be seen in fig. 1 and table 1. The simulated concentrations in the peripheral compartment do not satisfactorily describe the real situation in the effector organ, the uterus (fig. 1). According to the plasma levels

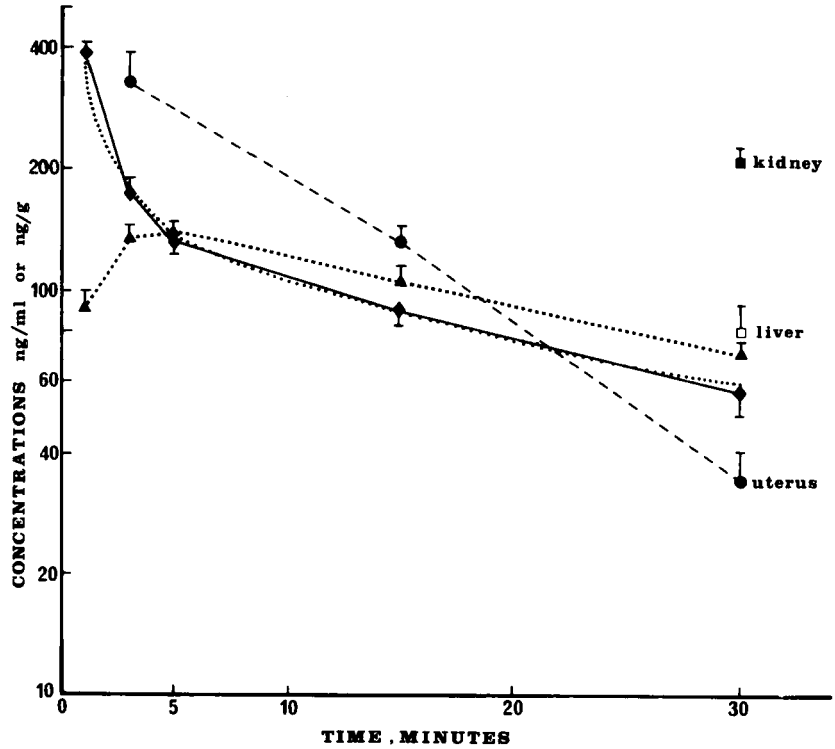

Fig. 1. The concentrations of methylergometrine in the plasma (continuous line) (fitting curve=dotted line) and the simulated levels in the peripheral compartment (dotted line) after a single 0.2 mg/kg intravenous injection. The concentrations in the uterus were determined at 3,15, and 30 min. and those in the kidney and liver at 30 min. The simulated concentrations in the peripheral compartment correlated with the measured concentrations in the uterus ($r=0.84$, $P<0.05$).

Table 1.

The concentrations of methylergometrine (ng/g) in the uterus, liver and kidney of the rabbit after a single 0.2 mg/kg intravenous injection.

Rabbit no.	Uterus 3 min.	Uterus 15 min.	Uterus 30 min.	Liver 30 min.	Kidney 30 min.
1	515	129	37	nm	503
2	244	121	23	65	166
3	213	162	24	nm	165
4	283	186	30	80	148
5	390	138	25	133	nm
6	153	98	70	53	152
7	499	92	30	68	84
mean	328	132	34	80	203
S.D.	142	34	17	32	150

nm=not measured

methylergometrine disappeared quickly from the plasma, and at the same time a fast and quantitatively prominent uptake occured in the uterus. The mean uterine concentrations at 30 min. were below those of the kidneys and liver. The drug response (mm^2) in the rabbit uterus *in situ* began quickly (t_{max} 0.5±0.1 (S.D.) min.), according to the fast uterine tissue uptake of methylergometrine, but disappeared faster than the levels in this effector organ (after 3.8±1.1 min.). A positive correlation was calculated between the area under the plasma level curve and the area under the response curve recorded by the physiograph ($r=0.94$, $P<0.01$). Similarly, the simulated concentrations in the peripheral compartment correlated with the measured levels in the uterus ($r=0.84$, $P<0.05$). Some pharmacokinetic parameters calculated from the plasma concentrations are shown in table 2.

Discussion

In our earlier study methylergometrine rapidly stimulated the rabbit uterus *in situ* and the response was proportional to the dose (Mäntylä *et al.* 1977a). The maximal response after 0.05, 0.1, and 0.2 mg/kg intravenous doses was found as early as at 40 to 26 sec. This fast pharmacodynamic effect was supported by our pharmacokinetic data in animal (Mäntylä *et al.* 1977a & b) and human studies (Mäntylä *et al.* 1977a & 1978a; Kanto *et al.* 1978).

Table 2.

Pharmacokinetidc parameters calculated from the plasma concentrations of methylergometrine in the rabbit after a single 0.2 mg/kg intravenous injection. $T_{1/2\alpha}$=distribution phase half-life, $T_{1/2\beta}$=elimination phase half-life, V_{dc}=volume of the central compartment, V_{dss}=volume at steady state, $V_{d\beta}$=volume during the terminal phase AUC_{tot}=total area under the plasma level-time curve, Cl_{tot}=total plasma clearance, C_o=concentration at zero time, k_{12}=distribution rate constant for transfer of drug from central to peripheral compartment, k_{21}=distribution rate constant for transfer of drug from peripheral to central compartment, k_{el}=elimination rate constant of drug.

	C_O ng/ml	k_{12} min.$^{-1}$	K_{21} min.$^{-1}$	k_{el} min.$^{-}$			
mean	755.3	0.577	0.180	0.140			
S.D.	215.8	0.098	0.036	0.069			
	$T_{1/2\alpha}$ min.	$T_{1/2\beta}$ min.	V_{dc} l/kg	V_{dss} l/kg	$V_{d\beta}$ l/kg	AUC_{tot} [ng/ml)·min.]	Cl_{tot} ml/min.
mean	0.91	26.34	0.29	1.13	1.44	6060.88	83.74
S.D.	0.35	9.48	0.09	0.30	0.55	2005.30	17.86

The distribution half-life of only 1 to 2 min. explains the fast tissue uptake and response of methylergometrine observed in this study. The good tissue availability is reflected by the fast uterine response both in the rabbit (Mäntylä *et al.* 1977a) and man (Roth-Brandel *et al.* 1970). This is a beneficial property of this oxytocic drug when used in the treatment of uterine atony.

In the rabbit our simulated concentrations of methylergometrine in the peripheral compartment increased similarly to those of dihydroergotamine in the beagle (Mäntylä *et al.*, unpublished results, 1978) after a single intravenous dose explaining the fast pharmacodynamic effect of these ergot alkaloids (Mäntylä *et al.* 1977a & 1978b; Hilke *et al.* 1978). However, these simulated levels of methylergometrine are hypothetical mean values of the real situation in different tissues: initially high concentrations were determined in the uterus, but at 30 min. they were below those in the liver and kidneys. Possibly, the levels in the liver and kidneys were initially low increasing until 30 min. In addition, a positive correlation was found between the simulated concentrations in the peripheral compartment and the measured concentrations in the effector organ, the uterus. Thus, the pharmacokinetic calculations in the two-compartment open model can be useful in the understanding of drug effects, but the different compartments and their drug levels do not correspond with exact anatomical tissues. The fast tissue uptake of methylergometrine needs further studies in order to find the subcellular distribution of this oxytoxic drug.

The pharmacokinetic parameters calculated from the plasma concentrations of methylergometrine in this study were similar to those of our earlier results (Mäntylä *et al.* 1977a). In addition, a positive correlation between the area under the plasma level curve of methylergometrine and the response of the uterus was found. Similarly, in our previous work the effect of methylergometrine on the contractions of the rabbit uterus *in situ* was dose dependent with a steep dose-response curve (Mäntylä *et al.* 1977a). Clinically, however, there is no apparent correlation between the plasma level and effect, because the half-life of methylergometrine varies between 0.5 to 2 hours (Mäntylä *et al.* 1977a & 1978a; Kanto *et al.* 1978) but the response has been shown to continue for several hours after a single 0.2 mg intravenous injection (Roth-Brandel *et al.* 1970).

Although a positive correlation was found between the simulated concentrations in the peripheral compartment and the measured concentrations in the uterus the concentration-time course was highly different in the terminal linear parts of the curves. Hence, the uterine uptake and disappearance of methylergometrine in the rabbit seems to occur rapidly. No definite conclusions, however, can be made because of the few samples we were able to take from one animal. The low uterine level at 30 min. could have been caused by circulatory changes after the two previous samples.

Our method was developed to measure many ergot alkaloids, and, therefore, we might have determined some of the possible metabolites of methylergometrine. However, today we have no knowledge about the possible metabolism of this agent.

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