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# Pharmacokinetics of Methylergometrine (Methylergonovine) in the Rabbit and Man

By

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*Abstract:* Methylergometrine concentrations in human and rabbit plasma were determined by a new radioimmunoassay after a single intravenous injection (0.2 mg in man and 0.05, 0.1 and 0.2 mg/kg in rabbits). Both in man and in the rabbit methylergometrine disappeared quickly from the plasma with a mean $T_{1/2\alpha}$ of 1.8 and 1.2–1.7 min. respectively. Similarly, the $T_{1/2\beta}$-values were 32.1 and 27.3–93.2 min. The mean maximal response in the rabbit uterus *in situ* after 0.05, 0.1 and 0.2 mg/kg intravenously dose was found at 40 sec., 26 sec., and 26 sec. after the drug administration, respectively, and the dose response curve was quite steep. A significant correlation was found between the dose and response.

*Key-words:* Methylergometrine – radioimmunoassay – pharmacokinetics – rabbit – man.

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Ergometrine and its congener, methylergometrine (methylergonovine), are the oxytocic drugs widely used clinically. STOLL & HOFFMANN synthesized methylergometrine from d-lysergic acid in 1943 and since that time its effectiveness as an oxytocic agent has been proved in hundreds of reports (GROEBER & BISHOP 1960). However, knowledge about the pharmacokinetics of methylergometrine is scanty because of the lack of a rapid and sensitive method for measuring the drug in nanogram amounts in the plasma after its usual, single, 0.125–0.2 mg dose. In our laboratory radioimmunoassay for ergot alkaloids was developed making it possible to perform the present pharmacokinetic study on methylergometrine in the rabbit and in man. The primary purpose was to investigate the pharmacokinetics of two different methylergometrine preparations methergin® and myomergin®.

## Materials and Methods

Methylergometrine (methylergonovine) concentrations in the plasma were determined by radioimmunoassay in 10 abortion patients at 0 time and then at 1, 3, 5, 10, 15, 30 and 60 minutes after a single 0,2 mg intravenous injection. Five patients received 0.2 mg of myomergin® (methylergometr. maleas, Leiras, human Group I), and five patients received 0.2 mg methergin® (methylergometr. maleas, Sandoz, human Group II). Their average ages, weights, and heights were 26.6 ± 6.8 (S. D.) years, 66.0 ± 9.2 kg and 165.5 ± 2.9 cm in the human Group I and 33.6 ± 7.3 years, 64.2 ± 9.3 kg, and 162.4 ± 8.2 cm in the human Group II. According to the medical history and physical examination, as well as urinanalysis, complete blood cell count, serum creatinine and chest X-ray examination, the patients were normal.

The patients were undergoing legal abortion which was performed by abdominal hysterotomy. All of them received the same premedication: atropine + pethidine (meperidine) + promethazine. Anaesthesia was induced with thiomebumal (thiopentone) and maintained with 70 % nitrous oxide in oxygen. A semi-open system with a respirator was used. Muscle relaxation was achieved with suxamethonium followed by an infusion of suxamethonium in 5 % glucose. During the operation pethidine was given if required. After hysterotomy 0.2 mg of methylergometrine (methylergonovine) was given intravenously.

In the animal part of this study non-gravid post-partum (1.5–2 months) rabbits weighing 2.2–3.5 kg were used. There was no knowledge about the stage of the ovarian cycle in the animals. They were anaesthetized with urethane 1.5 g/kg subcutaneously. The effects of methylergometrine were tested on the rabbit uterus *in situ* (Rothlin 1946/1947; Fregnan & Glässer 1964). The ovarian end of a uterine horn was attached to an isotonic myograph and connected to a physigraph (E & M Physiograph "six"). The uterine horn was stretched with a force of 20 g. Three animal groups were tested. In the animal Group I 0.05 mg/kg of methylergometrine was injected intravenously via an ear vein of 4 rabbits, in the animal Group II 0.1 mg/kg and in the animal Group III 0.2 mg/kg via an ear vein of 8 rabbits in each group. Half of the rabbits in each group received myomergin® (Leiras) and the other half methergin® (Sandoz). The samples (2 ml blood) were taken from the carotid artery at 0 time and then at 1, 3, 5, 15, 30, and 60 minutes after the injection. The same volume (2 ml) of normal saline in 5 % glucose was injected into the carotid artery after taking each sample.

Antiserum for a radioimmunoassay for ergot alkaloids was prepared by immunizing sheep with lysergic acid-human serum albumin conjugate (Koskinen & Kleimola 1976). It was purified by using affinity chromatography. Tritiated tracers were used in the assay. The antibodies reacted with all the tested lysergic acid derivatives but no cross reactivity with simpler indole structures was found. The method is sensitive enough for determining ergotamine, dihydroergotamine, dihydroergotoxine, ergometrine, and methylergometrine concentrations in the human plasma or urine after a normal therapeutic dose. Since we have no knowledge about the possible metabolism of methylergometrine, the cross-reactivity with its metabolites cannot be given. The assay can detect as little as 0.85 ng/ml of methylergometrine in the plasma and the standard deviation at this level is 10 per cent. The reproducibility of the assay was kept constant by obtaining the standard curve from a single solution which was kept frozen.

Pharmacokinetic calculations for the single intravenous dose of methylergometrine were based on the equation for a 2-compartment open model (Ritschel 1973).

$$C_p = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \quad [ng/ml]$$

where B = intercept of back-extrapolated monoexponential declining with the ordinate,

$$\beta = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} [\text{min.}^{-1}]$$ = slope of monoexponential declining line (hybrid constant)

$$\alpha = \frac{\ln C_{1\ \text{diff.}} - \ln C_{2\ \text{diff.}}}{t_2 - t_1} [\text{min.}^{-1}]$$ = slope of monoexponential distribution line (hybrid constant)

A = intercept of monoexponential line with ordinate [ng/ml]

$k_{12} = \alpha + \beta - k_{21} - k_{el}$ [min.$^{-1}$] = distribution rate constant for transfer of drug from central to peripheral compartment

$$k_{21} = \frac{A \cdot \beta + B \cdot \alpha}{A + B} [\text{min.}^{-1}]$$ = distribution rate constant for transfer of drug from peripheral to central compartment

$$k_{el} = \frac{\alpha \cdot \beta}{k_{21}} [\text{min.}^{-1}]$$ = elimination rate constant of drug

$t_{1/2\alpha}$ = αphase half-life [min.]

$t_{1/2\beta}$ = βphase half-life [min.]

$V_{dc}$ = volume of distribution at central pool [L/kg]

$Cl_p$ = total plasma clearance [ml/min.]

$V_{dss}$ = volume of distribution at steady state [L/kg]

$V_{d\beta}$ = volume of distribution at βphase [L/kg]

AUC = area under plasma level curve [(ng/ml) · min.]

The AUC was calculated by means of the trapezoid rule.

The drug response in the animal part of this study was calculated as the area under the drug response curve recorded by the physiograph [mm²].

The statistical analyses of the results have been performed by Student's t-test and by regression analysis (partial correlation coefficient).

## Results

Following the injection of methergin®, significantly higher methylergometrine concentrations in the patients' plasma were observed at 15 min. ($P < 0.01$) and at 30 min. ($P < 0.02$) than after the injection of myomergin®. No other significant differences were found between the two brands of methylergometrine in the plasma drug concentrations in man and rabbit or in the drug response in the rabbit. Hence therefore the combined results of the two groups of compounds were presented.

In fig. 1 the plasma concentrations of methylergometrine in the abortion patients after a single 0.2 mg intravenous injection and in the rabbits after a single 0.05, 0.1 and 0.2 mg/kg intravenous dose were observed. The human

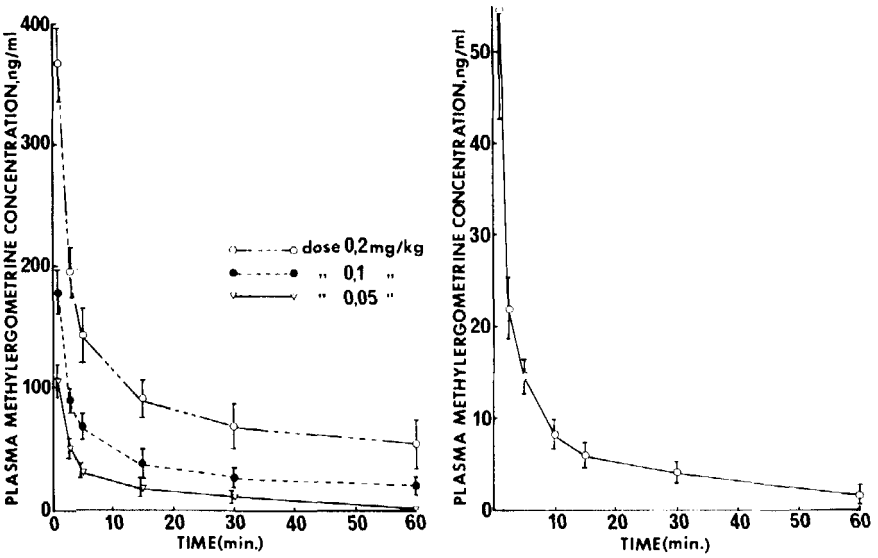


Fig. 1. Plasma concentrations of methylergometrine (methylergonovine, means ± S. E. M.) in abortion patients (0.2 mg intravenously) and in rabbits (0.05, 0.1, and 0.2 mg/kg intravenously).

pharmacokinetic parameters of methylergometrine are presented in table 1, and the same results in the rabbits in table 2. The drug responses in the rabbits are shown in table 3. The mean maximal response (± S. E. M.) in the rabbit uterus *in situ* after a single 0.05, 0.1, and 0.2 mg/kg intravenous dose of methylergometrine was found at 40 ± 4 sec., 26 ± 3 sec., and 26 ± 4 sec., after the drug administration, and the responses lasted 1.5 ± 0.3 min., 1.9 ± 0.3 min., and 6.5 ± 3.4 min., respectively. The dose response curve was quite steep (fig. 2). In the rabbits a significant correlation was found between the dose, AUC, and the response. (y = response, x = AUC, z = dose, $r_{yx/z} = 0.46$, $P < 0.05$, $r_{yz/x} = 0.69$, $P < 0.001$; $r_{xz/y} = 0.76$, $P < 0.001$).

## Discussion

Strips of the horns of the rabbit uterus or isolated seminal vesicles of the guinea pig were used in earlier studies for the standardization of ergot preparations (BROOM & CLARK 1923; BRÜGGER 1945). Later spectophotometric or fluorescence measurements in combination with thin-layer chromatography were performed, but the most promising methods for standardization of ergot preparations seem to be high speed liquid chromato-

*Table 1.*

Pharmacokinetic parameters in abortion patients derived from a single 0.2 mg intravenous dose of methylergometrine (methylergonovine).

| | $\alpha$ [min.$^{-1}$] | $t_{1/2\,\alpha}$ [min.] | $\beta$ [min.$^{-1}$] | $t_{1/2\,\beta}$ [min.] | AUC [(ng/ml)·min.] | $k_{12}$ [min.$^{-1}$] | $k_{el}$ [min.$^{-1}$] | $k_{21}$ [min.$^{-1}$] | $Vd_c$ [L/kg] | $Vd_{ss}$ [L/kg] | $Vd_\beta$ [L/kg] | $Cl_{tot}$ [ml/min./kg] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 0.501 | 1.8 | 0.037 | 32.1 | 582.82 | 0.262 | 0.205 | 0.105 | 0.06 | 0.17 | 0.24 | 2.08 |
| S. E. M. | 0.07 | 0.4 | 0.01 | 9.6 | 132.91 | 0.03 | 0.06 | 0.02 | 0.01 | 0.03 | 0.04 | 0.85 |

*Table 2.*

Mean (± S. E. M.) pharmacokinetic parameters in rabbits derived from a single 0.05, 0.1, and 0.2 mg/kg intravenous dose of methylergometrine (methylergonovine).

| Dose mg/kg | $\alpha$ [min.$^{-1}$] | $t_{1/2\,\alpha}$ [min.] | $\beta$ [min.$^{-1}$] | $t_{1/2\,\beta}$ [min.] | AUC [(ng/ml)·min.] | $k_{12}$ [min.$^{-1}$] | $k_{el}$ [min.$^{-1}$] | $k_{21}$ [min.$^{-1}$] | $Vd_c$ [L/kg] | $Vd_\beta$ [L/kg] | $Cl_{tot}$ [ml/min./kg] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.05 | 0.611 ±0.10 | 1.2 ±0.2 | 0.046 ±0.02 | 27.3 ± 8.9 | 1479.52 ± 406.97 | 0.347 ±0.10 | 0.159 ±0.05 | 0.150 ±0.03 | 0.30 ±0.03 | 1.28 ±0.26 | 16.65 ±10.59 |
| 0.1 | 0.502 ±0.09 | 1.7 ±0.2 | 0.024 ±0.01 | 58.6 ±18.3 | 4523.41 ±1204.75 | 0.269 ±0.03 | 0.094 ±0.02 | 0.129 ±0.04 | 0.43 ±0.04 | 2.00 ±0.38 | 9.51 ± 2.47 |
| 0.2 | 0.535 ±0.10 | 1.6 ±0.2 | 0.017 ±0 | 93.20 ±40.13 | 10961.13 ±3670.80 | 0.350 ±0.08 | 0.088 ±0.02 | 0.113 ±0.01 | 0.40 ±0.05 | 2.47 ±0.71 | 9.47 ± 2.64 |

*Table 3.*

Mean (± S. E. M.) values of AUC and response after a single 0.05, 0.1, and 0.2 mg intravenous dose of methylergometrine (methylergonovine) in rabbits.

| Dose mg/kg | AUC [(ng/ml)·min.] | Response [mm²] |
|---|---|---|
| 0.05 | 1479.52 | 1692 |
| | ± 406.97 | ± 874 |
| 0.1 | 4523.41 | 2274 |
| | ±1204.75 | ± 696 |
| 0.2 | 10996.13 | 7206 |
| | ±3670,80 | ±1897 |

graphy (HEACOCK *et al.* 1973) and gas chromatography (SONDACK 1974). In this work we used a new radioimmunoassay developed for ergot alkaloids (ergotamine, dihydroergotamine, dihydroergotoxine, ergometrine and methylergometrine). At zero time no cross-reaction with the other drugs used in the clinical part of this study was found. With this method however it is possible to determine methylergometrine (methylergonovine) in nanogram amounts in the plasma after the usual clinical doses.

In the abortion patients methylergometrine disappeared quickly from the plasma after a single 0.2 mg intravenous injection with a mean $T_{1/2\alpha}$ of 1.8 minutes. This is in agreement with its rapid clinical response appearing a few minutes after a 0.2 mg intravenous injection (ROTH-BRANDEL *et al.* 1970). According to the distribution rate constants $k_{12}$ and $k_{21}$ methylergometrine is transferred rapidly from the central to the peripheral compart-

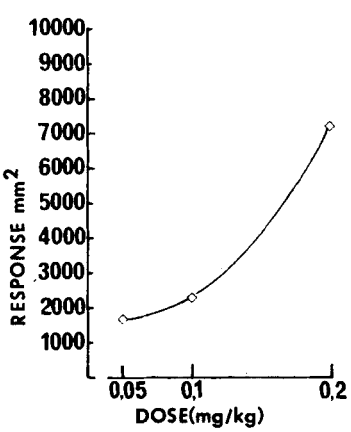


Fig. 2. Dose response curve of methylergometrine (methylergonovine) in rabbit uterus *in situ*.

ment, but the return of the drug back to the central compartment occurres more slowly. The $V_d$-value (0.24 ± 0.04 L/kg, S. E. M.) calculated in the β-phase indicates that methylergometrine is mainly distributed in the plasma water (= 3 L, 3 L/70 kg = 0.04 L/kg) and extracellular water (= 12 L, 12 L/70 kg = 0.17 L/kg).

After a single 0.2 mg intravenous injection the $T_{1/2}$ was 32.1 min. in man. However, after the same intravenous dose the clinical response of methylergometrine has been shown to continue for several hours (ROTH-BRANDEL *et al.* 1970). Thus, apparently there is no correlation between the plasma level and clinical effect of methylergometrine after a single dose. The time of collection is insufficient to draw accurate conclusions about $T_{1/2\beta}$-value, as plasma levels should be determined for at least 3 half-lives during the β-phase to obtain an accurate estimate of the $T_{1/2\beta}$. With our method, however, we were able to measure the plasma levels of methylergometrine only up to one hour after a single 0.2 mg intravenous dose.

The total plasma clearance value (2.08 ± 0.85 ml/min./kg, S. E. M.) of methylergometrine in a subject weighing 70 kg (= 146 ml/min.) is nearly the same as for inulin (about 130 ml/min.) and clearly lower than the usual estimate of hepatic blood flow (1500 ml/min.). According to this value, methylergometrine seems to be excreted mainly by renal glomerular filtration. However, we have no knowledge about the plasma protein binding of methylergometrine.

In the animal studies with rabbits methylergometrine also disappeared quickly from the plasma with about the same $T_{1/2\alpha}$- and $T_{1/2\beta}$-values as in man. The intravenous dose, however, was much higher per kg of body weight than in man, but his was compensated by higher $V_{d\beta}$- and $Cl_{tot}$-values.

Methylergometrine rapidly stimulated the rabbit uterus *in situ,* and the response was proportional to the dose. A similar rapid response of the rabbit uterus *in situ* caused by intravenous ergometrine has been reported by ROTHLIN (1946/1947) and FREGNAN & GLÄSSER (1964).

In this study a significant correlation between the intravenous dose of methylergometrine and the drug response was calculated. Thus, the effect of methylergometrine on the contractions of the rabbit uterus seems to be dose dependent with a steep dose-response curve. Similarly, into the treatment of uterine atony in women by increasing the dose of methylergometrine a dramatic rise in tone can be the consequence, depending on the sensitivity of the uterus (GOODMAN & GILMAN 1971).

In the rabbit uterus *in situ* the mean $T_{1/2\beta}$-value was 27.3–93.2 min., but the mean drug response lasted from 1.5 to 6.5 minutes only. The uterine horn was stretched with a force of 20 g and therefore these results were performed under non-physiological conditions.

In conclusion, both in the rabbit and in man methylergometrine disap-

peared quickly from the plasma to peripheral tissues indicating its rapid action both in animals and man. The proper intravenous dose of methylergometrine should be carefully considered because of the quite steep dose-response curve of this oxutocic. However, the rabbit experiments were performed in non-physiological conditions and hence they do not necessarily relate to a correlation between dose and response in intact animals. The plasma disappearance pattern with more than two exponential phases, consistent with a polycompartmental pharmacokinetic model, can also be obtained following a more prolonged sampling period than was possible in our study

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