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Comparison of the bioavailability and pharmacokinetics of oral methylergometrine in men and women

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Abstract. *Objective:* To assess and compare the pharmacokinetics and bioavailability of methylergometrine (ME) in men and non-pregnant women. *Design:* A cross-over design was used for an oral dose of 0.125 mg and an intravenous dose of 0.200 mg of ME in 6 men and 6 non-pregnant women (parallel-design in gender). *Results:* After intravenous administration, the pharmacokinetic profile of ME was described with a 2-compartment model. The distribution half-life ($t_{1/2\alpha}$) in men was 0.19 ± 0.27 h, in women 0.10 ± 0.04 h, the elimination half-life ($t_{1/2\beta}$) 1.85 ± 0.28 h, respectively, 1.94 ± 0.34 h and the total body clearance (CL) 33.2 ± 11.8 l.h⁻¹, and, respectively, 22.18 ± 3.10 l.h⁻¹. For these intrinsic pharmacokinetic parameters differences between men and women were not statistically significant. After oral administration, the pharmacokinetic profile was described with a 1-compartment model. The lag time was subject dependent and was significantly longer in men 0.33 ± 0.09 h than in women 0.09 ± 0.07 h. $T_{1/2\beta}$ in men was 2.08 ± 0.43 h and was longer than in women 1.42 ± 0.31 h ($p = 0.012$). In both men and women a large variation of bioavailability was shown ranging between 22% and 138%. *Conclusion:* This study with oral methylergometrine showed a comparable large interindividual variability in bioavailability in both men and women.

Key words: post partum hemorrhage (PPH) – methylergometrine maleate – HPLC analysis – pharmacokinetics – bioavailability

Introduction

Methylergometrine belongs to the group of oxytocic drugs enhancing uterine motility. Prophylactic use in the third stage of labor of these drugs, such as ergometrine, methylergometrine and oxytocin, reduces the risk of post partum hemorrhage (PPH) and the need for further oxytocic therapy in the puerperium [Van Dongen et al. 1991]. The use of oxytocics in the post partum period is advocated for the prevention and the management of PPH [Prendiville et al. 1988].

PPH is still one of the most common causes of maternal death [Royston and Armstrong 1989]. In such cases death invariably occurs within a few hours after childbirth. Prevention and management of this condition should take place at all levels of obstetric care as emergency referral is

often difficult to arrange, especially in circumstances prevailing in many third world countries. Drugs in tropical climates have to fulfill extra requirements. They have to be stable [Hogerzeil et al 1991, 1992, Walker et al. 1988], the route of administration has to be simple. Also untrained people should be able to administer the drug safely. From the group of oxytocics, only the ergot alkaloids (ergometrine maleate and methylergometrine maleate) can be given by mouth.

Because pharmacokinetic data of ergometrine in men showed such a great variation in bioavailability, a comparable study was performed for methylergometrine in both men and (non-pregnant) women to investigate and compare the results with the data obtained before [De Groot et al. 1994]. A sensitive and selective high performance liquid chromatographic (HPLC) system with fluorescence detection developed for ergometrine was modified for the analysis of methylergometrine to enable its pharmacokinetic analysis and bioavailability [De Groot et al. 1993a]. The aim of this study was to investigate pharmacokinetics and bioavailability of methylergometrine in men and women.

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Subjects, material and methods

For the assessment of the bioavailability of methylergometrine a randomized cross-over design was used for the intravenous and oral administration of methylergometrine. The interval between administration of both was at least 2 weeks.

A single oral dose of methylergometrine maleate 0.125 mg (= 0.095 mg base) was taken after a standard breakfast containing 2 sandwiches, no cheese and unrestricted amounts of coffee or tea by all subjects. 0.200 mg methylergometrine maleate (= 0.152 mg base) was injected intravenously in the same volunteer after a similar standard breakfast.

Subjects

Six men and 6 women volunteered for the pharmacokinetic study of both oral and intravenous administration of methylergometrine. The subjects were screened for possible contra-indications (cardiovascular disease and chronic obstructive lung disease). Bodyweight/height, blood pressure, hemoglobin level, liver and renal functions were recorded. In Table 1 the mean \pm SD of the demographic data of the volunteers are shown. They all had normal liver and renal functions. During the experiments blood pressure was monitored. This study was approved by the Committee Experimental Research Involving Human Subjects (CEOM) of the Academic Hospital Nijmegen Sint Radboud, the Netherlands.

Drugs

Pure methylergometrine (reference substance 108) was obtained from Sandoz Pharma AG (Basel, Switzerland). Methylergometrine maleate 0.125 mg tablet Methergin (equivalent to 0.095 mg free base) was obtained from Sandoz Germany (Nürnberg, Germany, batch No 3001).

Methylergometrine maleate 0.20 mg ml⁻¹ (injectable solution) was obtained from Sandoz (Uden, The Netherlands, batch No 475 MFD 920812). These methylergometrine batches fulfilled the requirements of a content uniformity test according to standard quality control criteria.

The injectable solution contained $93.3 \pm 6.5\%$ of the claimed content ($n = 20$).

Sampling

Oral administration of methylergometrine: Five ml blood samples were collected through an intravenous (IV) canula (Venflon 1.0 mm OD) in tubes containing 0.5 mg Li heparin at times: 0, 10, 20, 30, 60, 90, 180, 270, 360, 450 and 540 minutes after administration.

Table 1 Pharmacokinetic parameters (mean \pm SD) of methylergometrine (0.152 mg i.v.) in females and males ($n = 6$)

Parameter		Females	Males	p
$t_{1/2\alpha}$	(h)	0.10 ± 0.04	0.19 ± 0.27	0.46
$t_{1/2\beta}$	(h)	1.94 ± 0.34	1.85 ± 0.28	0.64
MRT _{i.v.}	(h)	2.31 ± 0.31	2.25 ± 0.44	> 0.8
AUC _{0-∞}	($\mu\text{g}\cdot\text{h}\cdot\text{l}^{-1}$)	6.02 ± 0.63	4.59 ± 1.82	0.10
CL	($\text{l}\cdot\text{h}^{-1}$)	22.2 ± 3.10	32.2 ± 11.8	0.073
V _{ss}	(l)	50.8 ± 8.23	71.5 ± 25.9	0.091
V _{ss} kg ⁻¹	($\text{l}\cdot\text{kg}^{-1}$)	0.84 ± 0.12	0.96 ± 0.36	0.43

Intravenous administration: Intravenous injection took place over 1 minute in the opposite arm where the Venflon was located. In addition to the sampling times as described under oral administration, 2 extra samples were taken at 3 and 5 minutes after the start of the injection.

After centrifugation of the blood samples at 11,000 g for 5 min, plasma samples from both the oral and intravenous groups were stored at -20°C pending analysis.

Care was taken that the whole intravenous dose was administered by cleaning the i.v. dosage line with 1 ml 0.9% saline.

Drug analysis

Methylergometrine in plasma was measured using the modified HPLC assay with fluorescence detection of de Groot et al [1993a]. In short the HPLC analysis is as follows:

Column: 25 cm \times 4.6 mm ID packed with Spherisorb 5-ODS (particle size 5 μm , Chrompack, Middelburg, the Netherlands) with a guard column (75 mm \times 2.1 mm ID) packed with 10 μm pellicular reversed phase (Chrompack, catalogue No 028653). An injection loop of 100 μl was used.

The mobile phase consisted of a mixture of 0.067 M potassium dihydrogenphosphate and 0.5 ml of diethylamine in water (1 : 1, v/v) as solvent A, and acetonitrile as solvent B. The mixture consisted of 60% A and 40% B (v/v). All reagents were of analytical grade (Merck, Darmstadt, Germany). The flow rate was 1.2 ml.min⁻¹. Fluorescence detection was achieved at 315 nm excitation and 430 nm emission. The retention time was 8.61 min, capacity factor was 3.76 and the analysis was carried out at room temperature. The quantitation limit of methylergometrine in water was 120 $\mu\text{g}\cdot\text{ml}^{-1}$ and that in plasma 150 $\mu\text{g}\cdot\text{ml}^{-1}$, both at a signal-to-noise ratio of 3. The intra-day variation was 3% and inter-day variation 5%.

Sample treatment

Plasma samples of 300 μl were deproteinated by acetonitrile 300 μl , and centrifuged at 11,000 g for 5 minutes. Of the clear supernatant 100 μl were injected onto the column.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated using a 2-compartment model after intravenous administration and after oral administration a 1-compartment model with lag-time of the MW/Pharm computer program (Mediware, Groningen, the Netherlands) [Proost and Meyer 1992]. C_{max} is the maximum plasma concentration read from the fitted plasma concentration-time curve ($r^2 > 0.98$), and t_{max} the time at which C_{max} occurs. The $t_{1/2\beta}$ values were calculated from $\ln(2)/\beta$, where β is calculated by log-linear regression analysis of the terminal log-linear phase. The $t_{1/2\text{absorption}}$ and $t_{1/2\alpha}$ were obtained by line feathering and linear regression analysis.

Mean absorption time (MAT) was used as a measure of the rate of absorption and calculated as the difference between (MRT_{po}-t_{lag}) and MRT_{i.v.}.

AUC_{0-∞} is the area under the plasma concentration-time curve and was calculated using the linear trapezoidal rule with extrapolation of $t = \infty$, using C_t/β with C_t being the last measured concentration.

The bioavailability (F) is $\text{AUC}_{\text{oral}} \cdot \text{dose}_{\text{i.v.}} / \text{AUC}_{\text{i.v.}} \cdot \text{dose}_{\text{oral}}$. Total body clearance $\text{CL} = \text{F} \cdot \text{dose} / \text{AUC}_{0-\infty}$. V_{ss} is the volume of distribution in steady state ($V_{\text{ss}} = \text{F} \cdot \text{dose} \cdot \text{AUMC}_{0-\infty} / \text{AUC}_{0-\infty}^2$).

Analysis of variance was conducted according to standard procedures. The level of significance was defined at $p = 0.05$.

Results

Mean age (years) was 35.7 ± 13 in men and 41.2 ± 5 in women. The mean weight (kg) was 75 ± 4 in men and 61 ± 7 in women. The mean height (cm) was 181 ± 8 in men and 167 ± 7 in women. The mean blood pressure was systolic (mmHg) 119 ± 4.9 and, respectively, 114 ± 10 ; diastolic pressure (mmHg) 78 ± 7.1 and, respectively, 71 ± 7 . Only weight and height were statistically different in men and women.

Figure 1 (left panel) shows the methylergometrine plasma concentrations (ng ml^{-1}) versus time curves after oral administration of 0.125 mg methylergometrine maleate (= 0.095 mg free base) and after intravenous administration of 0.200 mg methylergometrine maleate (= 0.152 mg free base) in 1 representative male subject (# 6) and in 1 female subject (# 3, right panel).

In the male the compound was fairly rapidly absorbed after oral administration; the lag time is 30 minutes. The half-lives after oral and intravenous administration were comparable. The relative bioavailability (F) in this subject of the oral administration was calculated to be 1.36 (136%).

In the female a maximum plasma concentration of 1.28 ng.ml^{-1} was reached after 38 minutes and a lagtime of 7 minutes. The relative bioavailability (F) in this subject of the oral administration was calculated to be 0.73 (73%).

Table 1 summarizes the pharmacokinetic parameters of 0.152 mg methylergometrine (base) after intravenous administration in the 6 men and 6 women. The pharmacokinetic profile can be described with a 2-compartment model. No statistically significant difference between men and women was observed in intrinsic pharmacokinetic parameters $t_{1/2\alpha}$, $t_{1/2\beta}$, total body clearance (CL) and the volume of distribution (V_{ss}).

Table 2 summarizes the pharmacokinetic parameters of 1 dose of oral methylergometrine (base) in the same men (6) and women (6). The pharmacokinetic profile can be described with a 1-compartment model. In men and women, the bioavailability (F) is subject-dependent and ranges between 22.2% and 138.0%, with the assumption that the total body clearance is similar after intravenous and oral administration. No statistical differences between men and women were observed in $t_{1/2\text{abs}}$, mean absorption time (MAT), CL and $V_{ss} \text{ kg}^{-1}$.

Side effects: Three men experienced a "weird" sensation after intravenous administration. These and other side effects were not noted by the other men. Three women became dizzy after the methylergometrine injection, after oral dosing none of them experienced side effects.

Discussion

The prophylactic use of oxytocic drugs as (methyl)ergometrine is generally advocated to prevent maternal deaths from post partum hemorrhage (PPH) [WHO 1990]. On a world-wide basis, logistic problems are encountered when these prophylactic drugs should be administered intravenously. Moreover, methylergometrine administered i.v. may cause severe hypertensive and cardiovascular accidents [De Groot et al. 1993b]. The aim of this study was to examine whether oral methylergometrine could be a possible alternative to injectable oxytocics used in the third stage of labor.

We showed unexpected large variations in bioavailability and pharmacokinetics of oral ergometrine in men [De Groot et al. 1994]. In this study we show an identical variation in bioavailability of methylergometrine in men

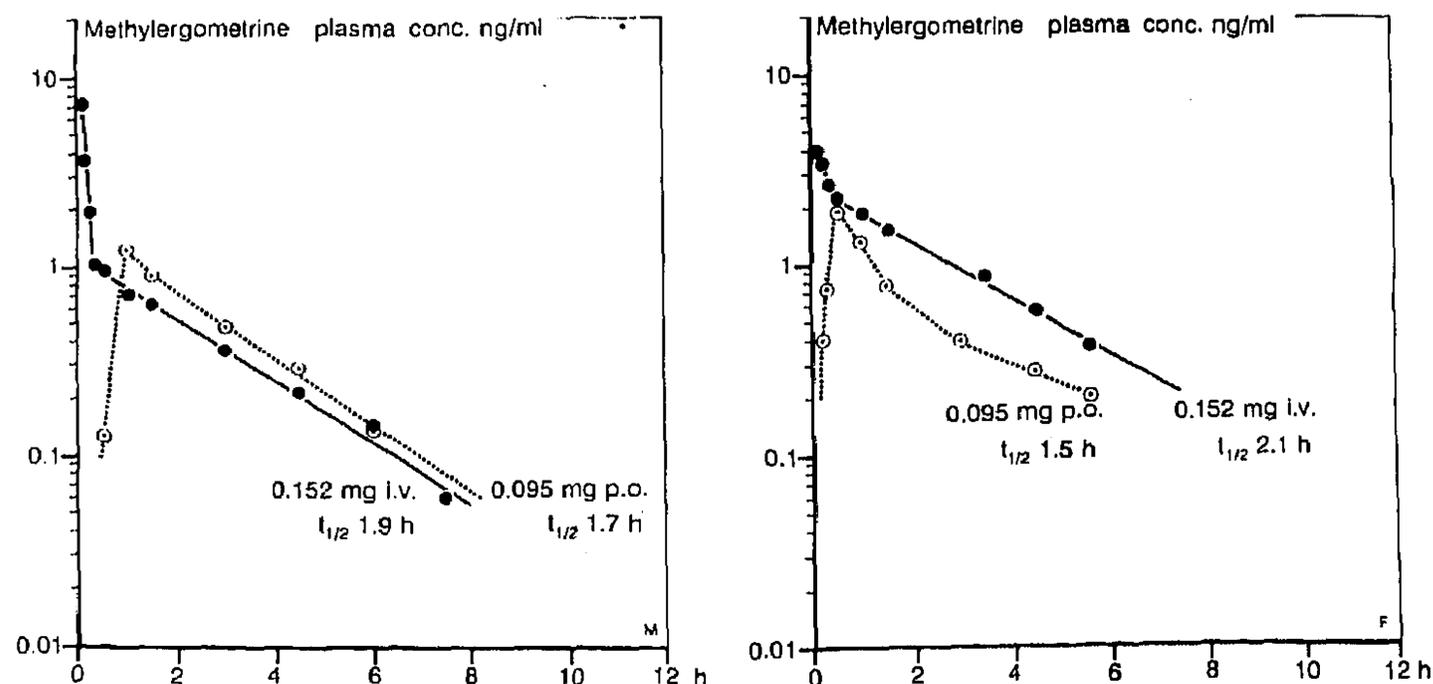


Fig. 1 Left panel (M): Methylergometrine plasma concentration curves versus time curves after administration of an intravenous (i.v.) dose of 0.152 mg methylergometrine base and after oral administration (p.o.) of 0.095 mg methylergometrine base to 1 representative male.

Fig. 1 Right panel (F): Methylergometrine plasma concentration curves versus time after administration of an intravenous (i.v.) dose of 0.152 mg methylergometrine base and after oral administration (p.o.) of 0.095 mg methylergometrine base to 1 representative female.

and non-pregnant women. After oral administration of the drug, absorption is subject dependent.

The half-life of absorption ($t_{1/2abs}$) is the result of absorption and distribution processes. Because it was not possible to calculate the "distribution phase" after oral administration the 1-compartment model was used for the data. Calculated by a 1-compartment model ($t_{1/2abs}$) data are underestimated as this model neglects the distinct distribution phase. Therefore we calculated the mean absorption time (MAT). MAT is an alternative method to measure the rate of absorption and is model-independent. MAT can be calculated from $(MRT_{po-tlag}) - MRT_{i.v.}$. For men and women the MAT did not differ significantly. The intrinsic pharmacokinetic parameters such as $t_{1/2\beta}$, CL and V_{ss} in men and women depend on the drug and not on the route of administration (Table 1). The drugs used in the experiments fulfilled the content uniformity test's requirements. Therefore, instability of the used tablets was ruled out as a possible explanation of the large interindividual variations of bioavailability and lag time, after oral administration.

The intravenous dose was stable and care was taken that all of the dose was administered by cleaning the syringe with 2 ml of 0.9% saline. The pharmacokinetic

parameters of methylergometrine after intravenous administration did not show any difference between men and women except for the V_{ss} , which was bigger in men ($p = 0.091$). This effect was more pronounced after oral administration of the drug ($p = 0.001$).

Oral administration showed more differences between the pharmacokinetic parameters in men and women. Men showed a longer lagtime ($p = 0.0004$), a greater volume of distribution ($p = 0.001$), and a longer $t_{1/2\beta}$ ($p = 0.0123$). The mean bodyweight of the men was significantly larger than that of the women ($p = 0.0010$). Corrected for the bodyweight, the V_{ss} did not differ for men and women after intravenous administration of 0.2 mg methylergometrine, respectively, $0.83 \pm 0.12 \text{ l.kg}^{-1}$ for men and $0.96 \pm 0.36 \text{ l.kg}^{-1}$ for women ($p = 0.4$). The $V_{ss} \text{ kg}^{-1}$ remained larger in men $1.27 \pm 0.50 \text{ l.kg}^{-1}$ than in women $0.77 \pm 0.05 \text{ l.kg}^{-1}$, $p = 0.0393$, after oral administration of 0.125 mg methylergometrine.

The vast variability of pharmacokinetic parameters reported for ergometrine [De Groot et al. 1994] was not reported in literature for methylergometrine [Anonymous 1989, Rall and Schleifer 1985]. It was reported that methylergometrine had a fast gastrointestinal absorption,

Table 2 Pharmacokinetic parameters (mean \pm SD) of methylergometrine (0.95 mg oral) in females and males (n = 6)

Parameter		Females	Males	p
F	(%)	96.4 \pm 27.5	84.9 \pm 37.2	0.56
t_{lag}	(h)	0.09 \pm 0.07	0.33 \pm 0.09	0.0004
t_{max}	(h)	0.97 \pm 0.74	0.68 \pm 0.22	0.39
C_{max}	($\mu\text{g.l}^{-1}$)	1.21 \pm 0.40	0.77 \pm 0.34	0.064
$t_{1/2abs}^*$	(h)	0.50 \pm 0.55	0.08 \pm 0.08	0.10
$t_{1/2\alpha}$	(h)	-	-	-
$t_{1/2\beta}$	(h)	1.42 \pm 0.31	2.08 \pm 0.43	0.0123
MRT_{po}	(h)	2.87 \pm 0.56	3.45 \pm 0.56	0.10
MAT^{**}	(h)	0.57 \pm 0.35	0.87 \pm 0.72	0.38
$AUC_{0-\infty}$	($\mu\text{g.h.l}^{-1}$)	3.49 \pm 0.70	2.17 \pm 0.80	-
CL	(l.h^{-1})	23.6 \pm 4.01	31.1 \pm 10.3	0.13
V_{ss}	(l)	47.0 \pm 6.05	94.4 \pm 38.9	0.01
$V_{ss} \text{ kg}^{-1}$	(l.kg^{-1})	0.78 \pm 0.05	1.26 \pm 0.50	0.039

- = not detected, * = 1-compartment model, ** = model independent

Bioavailability	(F)	$AUC_{oral.dose_{i.v.}}/AUC_{i.v.dose_{oral}}$
t_{lag}	(h)	lag time
t_{max}	(h)	the time at which C_{max} occurs
C_{max}	($\mu\text{g.l}^{-1}$)	the maximum plasma concentration read from the plasma-concentration-time curve
$t_{1/2abs}$	(h)	the half-life of absorption, calculated by least-square linear regression analysis
$t_{1/2\alpha}$	(h)	the half-life of distribution, calculated by least-square linear regression analysis
$t_{1/2\beta}$	(h)	the half-life of elimination, calculated by least-square linear regression analysis
MRT_{po}	(h)	the mean residence time $AUMC/AUC$ after oral administration
$MRT_{i.v.}$	(h)	the mean residence time $AUMC/AUC$ after intravenous administration
MAT	(h)	the mean absorption time ($MRT_{po-tlag}$) and $MRT_{i.v.}$
$AUC_{0-\infty}$	($\mu\text{g.h.l}^{-1}$)	the area under the plasma-concentration-time curve extrapolated to infinite time
CL	(l.h^{-1})	total body clearance = $dose/AUC_{0-\infty}$
V_{ss}	(l)	the volume of distribution in steady state ($V_{ss} = dose \times AUMC_{0-\infty}/AUC_{0-\infty}^2$)

The pharmacokinetic parameters were calculated using the Mediware computer programme (12).

and that about 60% of the orally administered dose reaches the systemic circulation [Mäntylä and Kanto 1981, Mäntylä et al. 1978]. This information was based on only 2 subjects; more subjects may probably have revealed more variation in absorption and other kinetic parameters. We found a large variation in bioavailability in methylergometrine for both men and women. In the present study the overall bioavailability in males was $84.9 \pm 37.2\%$, but the variation was 50% (CV), in females these data were, respectively, $96.4 \pm 27.5\%$ (28.5% CV).

However, the purpose of administration of oral (methyl)ergometrine is to reduce post partum blood loss. Therefore, a randomized trial has been set up to show whether a clinical effect despite possible varying pharmacokinetics can be demonstrated. For the time being, further pharmacokinetic research in post partum women is out of question, former investigations showed a delayed absorption compared to absorption in men of oral methylergometrine [Allonen et al. 1978].

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