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# Oral administration of methylergometrine shows a late and unpredictable effect on the non-pregnant human menstruating uterus

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## Abstract

**Objective:** To study the pharmacodynamic and pharmacokinetic properties of oral and intravenous methylergometrine upon uterine motility during menstruation. **Study-design:** Intra-uterine pressure was measured in six volunteers with a fluid-filled sponge-tipped catheter during menstruation. Methylergometrine was given orally (0.5 mg) or intravenously (0.2 mg) in a cross-over design. **Results:** After intravenous administration, a fast increase of the frequency of uterine contractions and basal tone occurred with a decrease of amplitude, lasting at least 30 min. Oral administration had a late and less marked effect on uterine motility. An intravenous dose administered 24 h after an oral dose had no effect on uterine motility. Pharmacokinetic data, such as the maximum plasma concentration ( $C_{max}$ ), the time at which  $C_{max}$  is reached ( $t_{max}$ ) and the half-life of absorption ( $t_{1/2abs}$ ) also demonstrated large individual variations after oral administration. **Conclusion:** Oral administration of methylergometrine had an unpredictable and late effect on uterine motility on the menstruating uterus, probably due to an unpredictable bioavailability, in contrast with the fast and predictable effect after intravenous administration.

**Keywords:** Methylergometrine; Oral administration; Intravenous administration; Pharmacokinetic properties; Uterine Motility

## 1. Introduction

Uterine activity can be stimulated during menorrhagia or the postpartum period. Secale alkaloids were one of the earliest stimulants in obstetrics, applied as treatment or prevention of postpartum haemorrhage first noticed by Caspar Schwenkfeldt in 1600 [1]. In contrast to oxytocin and prostaglandins, secale alkaloids can be given orally, which has the advantage of easy drug administration. Pharmacokinetic and pharmacodynamic data on oral secale alkaloids are, however, sparse.

Postpartum haemorrhage is responsible for 150 000 deaths worldwide a year [2], ~ 98% of which occur in developing countries [3]. In these countries, active management of the third stage of labour with oxytocics is particularly advocated [4]. Intramuscular oxytocin, the

standard care in the third stage, is not available to all women. Oral use of methylergometrine, although not recommended by the manufacturer, may be considered as an easy alternative. Before starting worldwide distribution of these tablets, extensive studies on the stability, pharmacokinetic and pharmacodynamic parameters and clinical effects had to be performed.

This study simultaneously assessed pharmacodynamic and pharmacokinetic parameters of oral and intravenous methylergometrine on uterine muscle in six non-pregnant women at the second day of the menstrual cycle (CD 2), because at CD 2 the menstruating uterus resembles the uterus in the postpartum period [5].

## 2. Materials and methods

### 2.1. Subjects

Six non-pregnant women with regular menstrual cycles volunteered for the pharmacokinetic and phar-

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macodynamic studies with methylergometrine. They were screened for possible contra-indications such as cardio-vascular disease, chronic obstructive lung disease, fibroids or uterine surgery, and should have had a tubal ligation to prevent any negative interaction with fertility. This study was approved by the Committee for Experimental Research Involving Human Subjects (CEOM) of the University Hospital Nijmegen Sint Radboud, Nijmegen, the Netherlands.

### 2.2. Intra-uterine pressure (IUP) recordings

Intra-uterine pressure was recorded using a fluid-filled sponge-tipped catheter [5,6]. The portio vaginalis was cleansed and disinfected with iodine. The open-tip sponged catheter was inserted over a guiding tube. The uterus was manipulated as less as possible in order not to cause any interference with the uterine contractility pattern. A gauze was left in the vagina while the catheter was fixed on the upper leg to prevent expulsion. The catheter was connected to a pressure transducer, which was connected to a computer. The woman was in the supine position during the registration. The pressure transducer was fixed on the mattress, being the level of the surface supporting the supine volunteer. Zero pressure was set at atmospheric pressure at this 'mattress' level [7]. The location of the catheter was controlled by asking the volunteer to cough. Proper intra-uterine position then showed a pressure elevation (about 10 mmHg).

Because the presence of any foreign body in utero causes an increase of basal pressure level for at least 20 min [8], we waited 30 min to allow the 'cyclic-specific' pattern to develop and then started the study. After recording uterine activity at least 60 min after the insertion of the sponge-tipped catheter, methylergometrine was administered either intravenously or orally. The registration ended when the catheter was expelled. If the catheter remained in its position, it was removed after 5 h. A trans-urethral catheter was inserted to provide continuous bladder drainage because filling of the bladder was reported to effect IUP [8].

### 2.3. Digitalization of the signal (IUP)

The intra-uterine pressure signal was filtered by a 0.65 Hz filter. Total noise with shortened impulse was measured over 15 min (mean  $\pm$  S.D. =  $0.442 \pm 0.084$ ), which did not disturb the general activity pattern.

To obtain an accurate signal, the range of the mercury scale had been set to 0–150 mmHg. Measurements were made using the DTX/plus pressure transducer (Viggo-spectramed, Oxnard, California, USA) and a specially developed amplifier before the signal was fed to a personal computer (DASH-8, Metrabyte). Special care had been taken for patient safety using a safety chart. The software had been developed with Borland C++ (Scotts Valley, California, USA). Events were marked by special keys. Recordings were stored in files which were

Microsoft Excel compatible. The resolution of the whole system was about 0.5 mmHg. The system was calibrated electronically and mechanically (mmHg).

### 2.4. Pharmacodynamics

Mechanical uterine activity was measured by IUP recordings. Contractions were expressed in IUP cycles. An IUP cycle was defined as a transitory rise above the basal tone. To describe uterine activity, IUP cycle-specific parameters were distinguished: frequency ( $F$ ), basal tone ( $BT$ ), intensity ( $I$ ) and amplitude ( $A = I - BT$ ). The number of IUP cycles in a 5 min period were recorded and the mean value of  $F$ ,  $BT$  and  $A$  of the IUP cycles in each 5 min period were calculated.

The mean values of these parameters ( $F$ ,  $BT$  and  $A$ ) during the 30 min registration of the 'cyclic-specific' pattern were regarded as baseline values and set at 100%. For each parameter the relative increase in a 5 min period was expressed as a percentage of baseline value and plotted against time. For each IUP recording, the area under the curve ( $AUC$ ) was calculated in time intervals of 30 min from the time of drug administration until 90 min after administration.

### 2.5. IUP recordings

Registration took place at the 2nd day of the cycle (CD 2) of two subsequent menstrual cycles to rule out a possible refractory period, i.e. uterine insensitivity to methylergometrine. In addition four women were also examined when 0.2 mg methylergometrine was injected on the third day of menstruation of the second cycle (CD 3), i.e. 24 h after the oral test.

### 2.6. 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; batch number 3001. Methylergometrine maleate (0.20 mg/ml injectable solution; equivalent to 0.152 mg free base) was obtained from Sandoz, Uden, The Netherlands; batch number 475 MFD 920812. These methylergometrine batches fulfilled the requirements of standard quality control criteria.

### 2.7. Dosage

*Dosage A.* For the assessment of the bioavailability of methylergometrine, a cross-over design was used for the intravenous and oral administrations. The interval between both administrations was one menstrual cycle. An intravenous dose of 0.2 mg methylergometrine maleate was injected at CD 2 after a standard breakfast containing two sandwiches, no cheese and unrestricted amounts of coffee or tea by all subjects. The drug was ad-

ministered at least 1 h after insertion of the IUP catheter. Care was taken that all of the intravenous dose was administered by cleaning the intravenous dosage line with 2 ml 0.9% saline. An oral dose of 0.5 mg methylergometrine maleate was given after a standard breakfast on the second day of the next menstrual cycle.

**Dosage B.** An additional intravenous administration was administered in four women on CD 3, 24 h after oral administration at CD 2.

### 2.8. Sampling

**Oral administration.** Blood samples of 5 ml were collected through an intravenous (IV) internal catheter (Venflon® 1.0 mm OD) in tubes containing 0.5 mg Li heparin at 0, 10, 20, 30, 60, 90, 180 and 240 min.

**Intravenous administration.** Intravenous administration of methylergometrine took place for 1 min in the opposite arm to where the Venflon was located. In addition to the sampling times as described under oral administration, two extra samples were taken at 3 and 5 min 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  $-20^{\circ}\text{C}$  pending analysis.

### 2.9. Drug analysis

Drug analysis was performed by High Pressure Liquid Chromatography (HPLC) according to de Groot et al. [9].

### 2.10. Pharmacokinetic analysis

The pharmacokinetic parameters were calculated from a two-compartment model after intravenous administration, and from a one-compartment model with lag-time fitted to oral data (MW/Pharm computer program, Mediware®, Groningen, the Netherlands) [10].  $C_{max}$  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  $\beta$  is calculated by log-linear regression analysis of the terminal log-linear phase. The  $t_{1/2absorption}$  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  $MRT_{iv}$ .

$AUC_{0-\infty}$  is the area under the plasma concentration-time curve and was calculated using the linear trapezoidal rule with extrapolation of  $t = \infty$ , using  $C_t/\beta$  with  $C_t$  being the last measured concentration. The bioavailability ( $F$ ) is  $AUC_{oral} \cdot Dose_{iv} / AUC_{iv} \cdot Dose_{oral}$ . Total body clearance,  $CL = F \cdot Dose / AUC_{0-\infty}$ .  $V_{ss}$  is the volume of distribution in steady state ( $V_{ss} = F \cdot Dose \cdot AUMC_{0-\infty} / AUC_{0-\infty}^2$ ). Analyses of variance

were conducted according to standard procedures. The level of significance was defined as  $P = 0.05$ .

## 3. Results

### 3.1. Subjects

Six women entered the study. Their mean age was  $38 \pm 5$  years, mean weight  $59 \pm 5$  kg and mean length  $167 \pm 6$  cm (mean  $\pm$  S.D.). The blood pressure ranged between normal values; mean systolic pressure  $113 \pm 11$  mmHg, mean diastolic pressure  $73 \pm 8$  mmHg. They all had a uterus in an anteversion-anteflexion position.

### 3.2. Pharmacokinetic results

Table 1 summarizes the mean pharmacokinetic parameters of 0.2 mg methylergometrine after intravenous administration and of 0.5 mg after oral administration in the six women at CD 2. After intravenous administration, the distribution half-life ( $t_{1/2\alpha}$ ) was  $0.09 \pm 0.04$  h. The elimination half-life ( $t_{1/2\beta}$ ) was  $2.0 \pm 0.3$  h. The total body clearance ( $CL$ ) amounted to  $22.0 \pm 2.7$  l/h

Table 1

Pharmacokinetic parameters (mean  $\pm$  S.D.) of methylergometrine after intravenous 0.2 mg (0.152 mg base) and oral 0.5 mg (0.380 mg base) administration in six female volunteers

	Intravenous	Oral	Significance (P)
Dose (mg)	0.152	0.380	
F (%)		$74.2 \pm 18.5$	
$t_{lag}$ (h)		$0.30 \pm 0.08$	
$t_{max}$ (h)		$0.75 \pm 0.40$	
$C_{max}$ ( $\mu\text{g/l}$ )		$3.88 \pm 2.19$	
$t_{1/2abs}$ (h)		$0.14 \pm 0.12$	
$t_{1/2\alpha}$ <sup>a</sup> (h)	$0.09 \pm 0.04$	—	
$t_{1/2\beta}$ (h)	$2.0 \pm 0.3$	$1.6 \pm 0.3$	0.0855
$MRT$ (h)	$2.3 \pm 0.4$	$2.8 \pm 0.4$	0.0855
$MAT$ <sup>b</sup> (h)		$0.40 \pm 0.35$	
$AUC_{0-\infty}$ ( $\mu\text{g} \cdot \text{h/l}$ )	$6.2 \pm 0.57$	$9.6 \pm 4.8$	
$CL$ (l/h)	$22.0 \pm 2.7$	$30.0 \pm 8.8$	0.0607
$V_{ss}$ (l)	$50.5 \pm 5.8$	$68.6 \pm 24.0$	0.1048

<sup>a</sup>One-compartment; <sup>b</sup>model independent; —, not detected.

Bioavailability ( $F$ ),  $AUC_{oral} \cdot Dose_{iv} / AUC_{iv} \cdot Dose_{oral}$ ;  $t_{lag}$  (h), lag time;  $t_{max}$  (h), the time at which  $C_{max}$  occurs;  $C_{max}$  ( $\mu\text{g/l}$ ), 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;  $MRT_{iv}$  (h), the mean residence time  $AUMC/AUC$  after intravenous administration;  $MAT$  (h), the mean absorption time, difference between ( $MRT_{po} - t_{lag}$ ) and  $MRT_{iv}$ ;  $AUC_{0-\infty}$  ( $\mu\text{g} \cdot \text{h/l}$ ), the area under the plasma-concentration-time curve extrapolated to infinite time;  $CL$  (l/h), total body clearance,  $Dose/AUC_{0-\infty}$ ;  $V_{ss}$  (l), the volume of distribution in steady state ( $V_{ss} = Dose \cdot AUMC_{0-\infty} / AUC_{0-\infty}^2$ ).

Table 2  
Pharmacokinetic parameters (mean  $\pm$  S.D.) in four females

	A	B	Significance (P)
$t_{1/2\alpha}$ (h)	0.09 $\pm$ 0.04	0.05 $\pm$ 0.02	0.14
$t_{1/2\beta}$ (h)	2.0 $\pm$ 0.3	1.9 $\pm$ 0.5	0.78
$MRT_{iv}$ (h)	2.3 $\pm$ 0.4	2.2 $\pm$ 0.6	0.65
$AUC_{0-\infty}$ ( $\mu\text{g} \cdot \text{h/l}$ )	6.2 $\pm$ 0.6	7.0 $\pm$ 3.1	0.55
$CL$ (l/h)	22.0 $\pm$ 2.7	24.0 $\pm$ 9.3	0.63
$V_{ss}$ (l)	50.5 $\pm$ 5.8	49.8 $\pm$ 15.9	>0.8

A, intravenous methylergometrine (ME) (0.2 mg) without preceding oral ME; B, intravenous ME (0.2 mg) with preceding oral ME (0.5 mg).

Abbreviations: see Table 1.

and the steady state volume of distribution ( $V_{ss}$ ) was  $50.5 \pm 5.8$  l/h. After oral administration of methylergometrine, the lag time was  $0.30 \pm 0.08$  h, the absorption half-life ( $t_{1/2abs}$ ) was  $0.14 \pm 0.12$  h, the mean absorption time ( $MAT$ ) was  $0.40 \pm 0.35$  h and the elimination half-life ( $t_{1/2\beta}$ ) was  $1.59 \pm 0.32$  h. Total body clearance was  $30.0 \pm 8.8$  l/h and the volume of distribution was  $68.6 \pm 24$  l. The bioavailability ( $F$ ) was subject dependent and ranged between 47.7% and 94.6%, with the assumption that the total body clearance is similar after intravenous and oral administration. Large inter-individual differences in  $C_{max}$  (53% C.V.),  $t_{max}$  (56% C.V.) and  $t_{1/2abs}$  (85% C.V.) after oral

administration were recorded. Two volunteers showed prolonged absorption and were left out in the calculation of the means.

Table 2 summarizes the pharmacokinetic parameters after additional intravenous administration of 0.2 mg methylergometrine in four women when it was injected on CD 3 of the second cycle, i.e. 24 h after the oral administration. There is no difference in pharmacokinetic parameters after the intravenous dosage at CD 2 of the first menstrual cycle and at CD 3 of the second cycle ( $P > 0.05$ ).

### 3.3. Pharmacodynamic results — effect of methylergometrine on IUP

When 0.2 mg methylergometrine was injected intravenously on CD 2 of the first menstrual cycle, the frequency of uterine contractions and basal tone increased in all six women, while the amplitude of the uterine contractions decreased. This effect lasted at least 90 min with a maximum at 30 min. Within one woman the effect of 0.5 mg oral methylergometrine on uterine activity on CD 2 of the second menstrual cycle was much less marked than after the intravenous administration.

Fig. 1 shows the effect of methylergometrine on IUP in volunteer 1. At the top of the figure the IUP recordings after intravenous (left panel) and oral (right panel) administrations are given. At the bottom the mean values of  $F$ ,  $BT$  and  $A$  of the IUP cycles over 5 min periods are shown.

The left panel shows the fast increase in frequency,

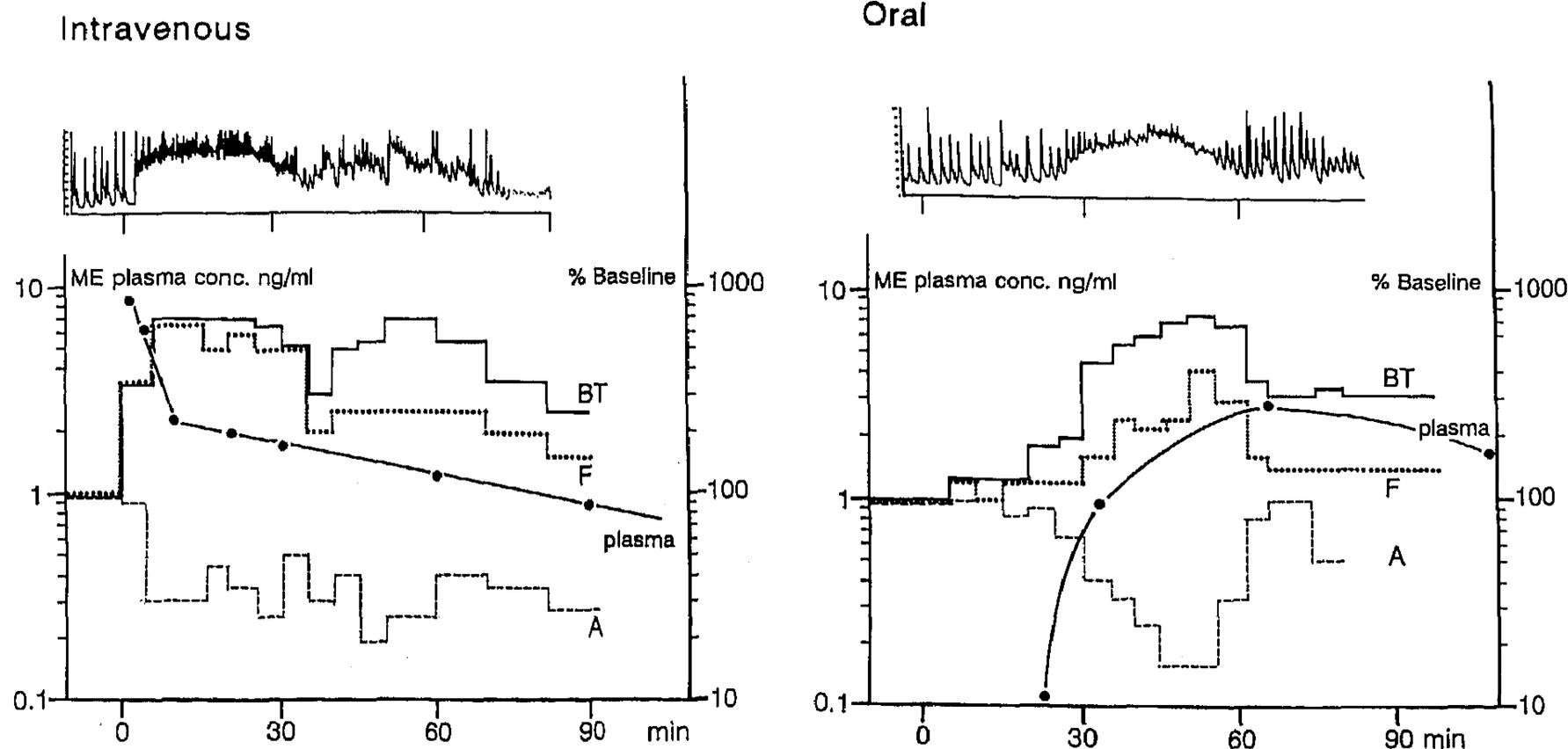


Fig. 1. Effect of methylergometrine (ME) after intravenous (0.2 mg) (left) and oral (0.5 mg) (right) administration in one representative volunteer. At  $t = 0$ , ME was administered. Top-tracing: Effect on intra-uterine pressure. Bottom-tracing: Effect on frequency ( $F$ ), basal tone ( $BT$ ) and amplitude ( $A$ ). The mean values of  $F$ ,  $BT$  and  $A$  during 30 min before drug administration were regarded as baseline values and set at 100%, the increase in a 5 min period was expressed as a percentage of baseline value and plotted vs. time after intravenous (0.2 mg) ME and oral (0.5 mg) ME administrations.

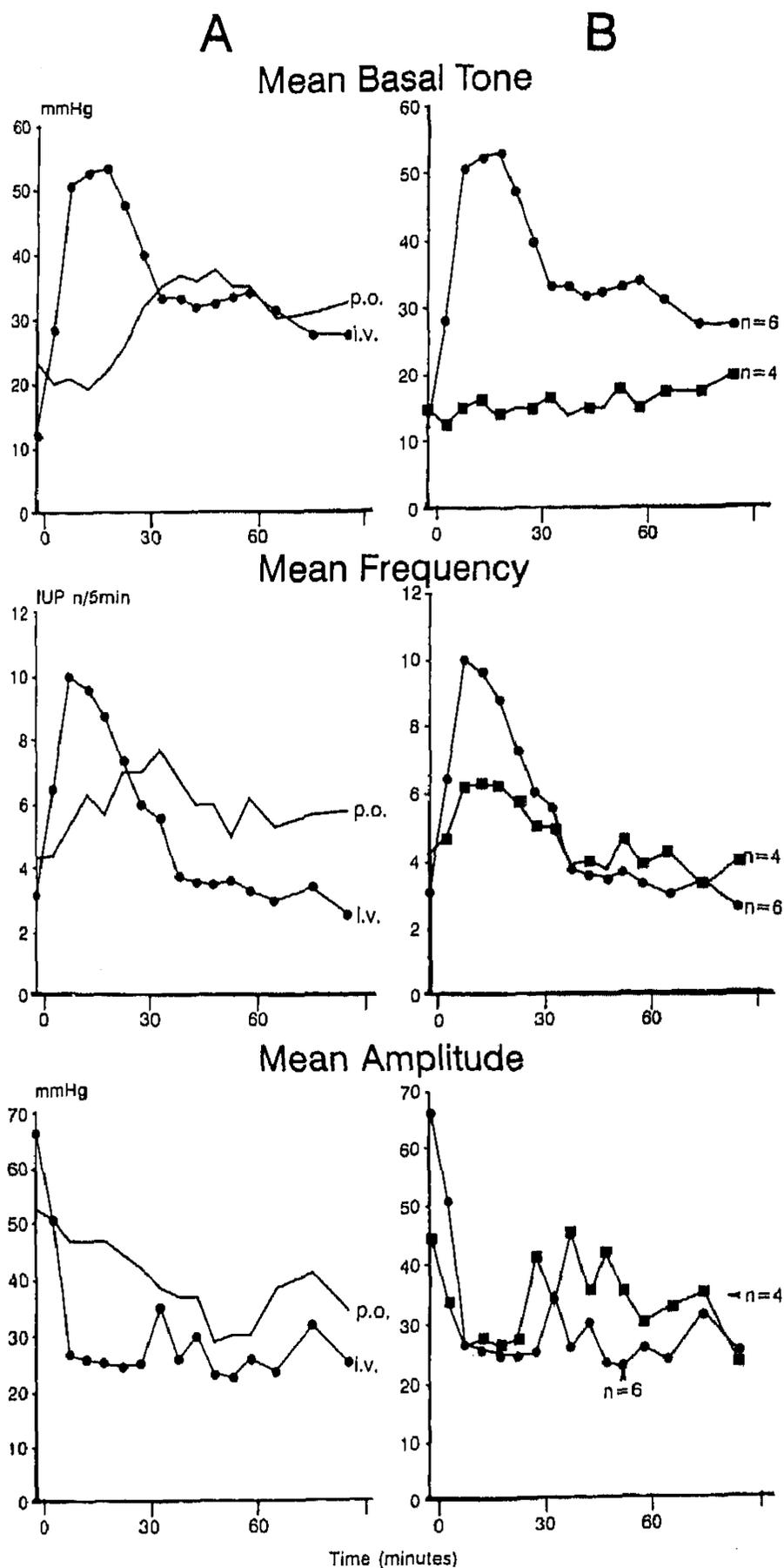


Fig. 2. Mean basal tone (*BT*), mean frequency (*F*) and mean amplitude (*A*) of intra-uterine pressure (IUP) cycles in a 5 min period vs. time. At  $t = 0$ , methylergometrine (ME) was administered. A, left panel: The effect of intravenous (0.2 mg) and oral (0.5 mg) administrations of ME on mean *BT* (mmHg), mean *F* (number of IUP/5 min period = IUP  $n/5$  min) and *A* (mmHg) of IUP cycle in a 5 min period, in menstruating women ( $n = 6$ ). B, right panel: The effects of 0.2 mg ME on the same parameters are shown without ( $n = 6$ ) and with ( $n = 4$ ) 0.5 mg ME given orally 24 h before the intravenous administration.

basal tone and decrease in amplitude of uterine contractions after intravenous administration of 0.2 mg methylergometrine. Within 3 min after the injection, the frequency of contractions increased by 350% to a maximum of 650% as a percentage of the baseline frequency value. After 35 min the increase of frequency was

reduced to 200% of the baseline value. The basal tone showed a fairly identical pattern with a maximum increase of 700% within 10 min after drug administration. Basal tone remained increased to 550% of its baseline value until 70 min after drug administration. The amplitude decreased to 30% of its baseline value within 10 min and remained reduced during further recording.

The right panel shows the late and less marked effect after oral administration of 0.5 mg methylergometrine. An increase in frequency of 240% occurred 35 min after drug administration. A maximum increase of 320% of the baseline value was reached after 50 min. An increase in basal tone was seen after 30 min with maximum values of 700% after 50 min. The basal tone remained elevated compared to the baseline values. The amplitude decreased to 17% after 55 min, but returned to its baseline value 80 min after drug administration.

Fig. 2 illustrates the mean frequency, mean basal tone and mean amplitude in 5 min periods after oral and intravenous administrations (A, left panel) and after intravenous administration at CD 2 and the day after an oral test CD 3 (B, right panel). The values used in the figure are the mean values of the 6 volunteers.

The figure clearly illustrates the different patterns in *F*, *BT* and *A* after intravenous or oral administrations (left panel). It also shows that there is hardly any uterine response to a 0.2 mg intravenous dose if this is preceded by 0.5 mg methylergometrine 24 h before (right panel).

Table 3 shows the *AUC* of the individual IUP recordings. When *AUC* 30 min before drug administration ( $AUC_{-30-0}$ ) is compared to *AUC* 30 min after drug administration ( $AUC_{0-30}$ ), a marked increase in *AUC* is seen after intravenous administration and hardly any after oral administration. After oral administration, a (slight) change in *AUC* is seen in the period between 30 and 60 min after the intake of 0.5 mg methylergometrine.

When 0.2 mg methylergometrine was injected 24 h after the oral test, hardly any changes in *BT*, *F* and *A* of intra-uterine pressure were recorded (Fig. 2B). The *AUC* was less increased than after the injection of 0.2 mg methylergometrine at CD 2 of the first menstrual cycle and even less than after the oral administration of 0.5 mg methylergometrine (Table 3).

### 3.4. Side effects

Three women experienced dizziness after intravenous injection, while all experienced abdominal cramps within 5 min after intravenous administration. After an oral dose, three out of six experienced abdominal cramps approximately 1 h after drug administration.

## 4. Discussion

This study demonstrates the feasibility of assessing the effect of uterine stimulation during human menstru-

Table 3

Area under the curve during several time periods in relation to administration of methylergometrine (ME) intravenously (0.2 mg) and orally (0.5 mg)

	Volunteer					
	1	2	3	4	5	6
<i>A (without preceding oral ME)</i>						
Intravenous						
<i>AUC</i> <sub>-30-0</sub>	726	843	1456	1320	339	682
<i>AUC</i> <sub>0-30</sub>	2163	1329	2042	2384	580	943
<i>AUC</i> <sub>30-60</sub>	1829	1352	1119	1479	651	914
<i>AUC</i> <sub>60-90</sub>	1725	1311	857	1764	236	650
<i>AUC</i> <sub>0-90</sub>	5717	3992	3018	5627	1467	2507
Oral						
<i>AUC</i> <sub>-30-0</sub>	640	1209	1077	1420	1062	1453
<i>AUC</i> <sub>0-30</sub>	857	1240	1018	1320	953	998
<i>AUC</i> <sub>30-60</sub>	1857	1307	1205	1851	1249	736
<i>AUC</i> <sub>60-90</sub>	1358	1330	1216	1944	1244	1627
<i>AUC</i> <sub>0-90</sub>	4072	3883	3439	5115	3446	3361
<i>B (with preceding oral ME<sup>a</sup>)</i>						
Intravenous						
<i>AUC</i> <sub>-30-0</sub>	365	474	872	971	—	—
<i>AUC</i> <sub>0-30</sub>	777	384	805	782	—	—
<i>AUC</i> <sub>30-60</sub>	719	460	731	984	—	—
<i>AUC</i> <sub>60-90</sub>	541	426	719	1294	—	—
<i>AUC</i> <sub>0-90</sub>	2037	1270	2255	3060	—	—

*AUC*, area under the curve, calculated by  $\Sigma IUP/\text{sample points} \times \text{time (min)}$ .

*AUC*<sub>0-30</sub>, *AUC* over a time period from 0–30 min after drug administration.

<sup>a</sup>Oral ME 24 h before intravenous administration.

ation with pharmacokinetic data. Although uterine stimulation is not frequently used to treat menorrhagia, this model may provide indirect evidence for the more important issue of postpartum haemorrhage. It is likely that the human uterus functions similarly during menstruation and labour, i.e. in providing an expelling force. This can be demonstrated by the intra-uterine pressure patterns, which are similar in both situations [5,11,12]. The same holds true for coagulating and fibrinolytic properties within the uterine cavity [13,14].

It is also our experience that the method used in this study, i.e. the sponge-tipped fluid-filled catheter, is more reliable in the non-pregnant uterus than in the postpartum uterus because of the increased degree of expulsion in the latter. In the postpartum uterus, only trans-abdominally placed open-tip catheters are thought to provide the most reliable quantitative information on uterine contractility. This procedure, however, encounters medical and ethical contra-indications when used just for research purposes. Micro-transducers at the catheter tip were not used because of possible artifacts [15] and the impossibility of calibration during the recording [16].

The most striking observation was the wide variation of bioavailability of oral methylergometrine, which corresponds with the recently published data found in male volunteers [9]; former data on methylergometrine [17]

described only a fast absorption of methylergometrine tablets.

Uterine motility was reflected in *BT*, *F*, *A* and *AUC* of the IUP cycle. The values of two *AUC*<sub>-30-0</sub> in the same volunteers in different tests were not similar which makes it irrational to compare *AUC*<sub>0-90</sub> after intravenous and oral administrations within the same volunteer (e.g. volunteer 5). In one volunteer (volunteer 5), *F*, *BT* and *A* showed quantitative variations at CD 2 of two subsequent menstrual cycles before administration of methylergometrine. This explains why differences in *AUC*<sub>-30-0</sub> existed in the subsequent menstrual cycles in one volunteer. Volunteers 3, 5 and 6 (Table 3) had a higher *BT* before oral administration than before the injection of methylergometrine. This explains why *AUC*<sub>0-90</sub> is larger after oral than intravenous administration. The changes in *BT*, *F*, *A* and *AUC* after oral administration of methylergometrine show a rather late and unpredictable stimulating effect on uterine motility. They reflect the same wide variation as observed in the pharmacokinetic data after oral administration.

The observation of the strongly diminished effect of intravenously-administered methylergometrine 24 h after oral administration suggests a long-lasting receptor blockade. It seemed as if the uterus was insensitive to the methylergometrine dose. The first dose may affect and change the uterine receptors for methylergometrine.

This could explain the insensitivity to the second dose of 0.2 mg methylergometrine in postpartum uteri lasting 3 h, measured by external tocography as reported in 1959 [18] and observed in our experiments even 24 h after oral administration of 0.5 mg methylergometrine. Methylergometrine probably blocks  $\alpha$ -receptors in the inner layer, specifically affecting the basal tone of this layer [19–21].

## 5. Conclusion

Oral administration of methylergometrine shows a late and unpredictable effect on the menstruating uterus in contrast to the fast and predictable effect of an intravenous dose. A relation between plasma concentration and pharmacodynamic effect could not be demonstrated after oral administration. Therefore, oral secal alkaloids cannot be advocated for either the treatment of menorrhagia or for postpartum haemorrhage.

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