

Bioavailability and Pharmacokinetics of Sublingual Oxytocin in Male Volunteers

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Abstract

The aim of this investigation was to assess the bioavailability and pharmacokinetics of oxytocin in six male subjects after a sublingual dose of 400 int. units (684 µg) and after an intravenous dose of 1 int. unit (1.71 µg).

After intravenous administration, the pharmacokinetic profile could be described with a two-compartment model. The distribution half-life was 0.049 ± 0.016 h, the elimination half-life was 0.33 ± 0.23 h, the total body clearance was 67.1 ± 13.4 L h⁻¹ and the volume of distribution was 33.2 ± 28.1 L. After sublingual administration, a poor bioavailability with a 10-fold variation between 0.007 and 0.07% was observed. The pharmacokinetic profile could be described with a one-compartment model. The lag time was subject-dependent and ranged between 0.12 and 0.30 h (40% CV). The absorption half-life was 0.45 ± 0.29 h, and the apparent elimination half-life 0.69 ± 0.26 h.

This study showed a very poor and interindividual variability in bioavailability. The sublingual route of administration with its 'long' lag time and 'long' absorption half-life would not seem a reliable route for accurate high dosing for immediate prevention of post-partum haemorrhage.

Postpartum haemorrhage (PPH) is still one of the most common causes of maternal death (Royston & 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. Oxytocin belongs to the group of oxytocic drugs enhancing uterine motility. Prophylactic use of these drugs in the third stage of labour reduces the risk of 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 1988a, b; Royston & Armstrong 1989; WHO 1990).

Drugs in tropical climates must fulfil extra requirements. They need to be stable (Walker et al 1988; Hogerzeil et al 1991, 1992) and the route of administration should be simple. Also untrained people should be able to administer the drug safely. Compared with other oxytocics, oxytocin is the preferred drug in the prevention and management of blood loss after childbirth because it is more stable under (simulated) tropical conditions and gives less side-effects (McDonald et al 1993; Hogerzeil et al 1994). In general, oxytocin is administered intramuscularly. Besides oxytocin ampoules, preparations for intranasal and buccal or sublingual administration exist.

Pharmacokinetic studies on sublingual oxytocin are scarce and show an unfavourable latent period of the oxytocic effect after drug administration of 26–53 min (Obolensky & Kupferschmied 1969; Tobias 1975; Dawood et al 1980). Sublingual demoxytocin tablets are not widely used as greater control is accorded by intravenous or intramuscular administration and because sublingual absorption is more unpredictable (Noriega-Guerra et al 1966). Despite unfavourable absorption data we thought it useful to examine whether sublingual oxytocin would be an acceptable non-parenteral prophylactic oxytocic. Published pharmacokinetic studies used small numbers of patients and were not fully convincing on the limitations of sublingual oxytocin as an alternative non-parenteral oxytocic for active management of the third stage of labour.

To assess the pharmacokinetics of sublingual oxytocin, male volunteers were used. Experiments in female volunteers introduce possible difficulties because of (higher) circadian levels of endogenous oxytocin levels as shown in pregnancy (Honnebier 1993). A constant low (< 3 pg mL⁻¹) endogenous level of oxytocin was measured in male volunteers. Plasma elevation after sublingual administration of 200 int. units (one dose) was too low (de Groot et al unpublished results); therefore a dose of two tablets (400 int. units = 684 µg) was chosen. RIA analysis was developed to enable the pharmacokinetic analysis of oxytocin.

Materials and Methods

Subjects

Six male volunteers were screened for possible contra-indications (cardiovascular disease and chronic obstructive

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Table 1. Demographic data of six male volunteers.

	Subject					
	1	2	3	4	5	6
Age (years)	53	18	34	26	42	26
Weight (kg)	79	71	78	74	85	61
Height (cm)	179	190	182	179	175	178
Blood pressure	120/70	110/70	120/65	120/78	120/80	115/80
Basal oxytocin concn (pg mL ⁻¹) ^a						
Sublingual	1.70 ± 0.40	1.10 ± 0.10	1.30 ± 0.26	1.15 ± 0.23	1.26 ± 0.21	0.87 ± 0.29
Intravenous	0.90 ± 0.17	1.33 ± 0.35	1.57 ± 0.23	1.43 ± 0.25	1.50 ± 0.26	1.30 ± 0.10

^a n = 3.

lung disease). Body-weight/height, blood pressure, haemoglobin level, liver and renal functions were recorded (Table 1). All subjects 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, Nijmegen, The Netherlands.

Drugs

Pure oxytocin (O-6379) was obtained from Sigma (St Louis, MO, USA). Oxytocin for intravenous administration (Syntocinon) was obtained from Sandoz Pharma AG, (Basel, Switzerland). Oxytocin for sublingual administration (Pitocin) was obtained from Parke-Davis GmbH, Gödecke AG, (Berlin, Germany). The pure oxytocin material fulfilled the requirements of a content uniformity test according to standard quality control criteria. Intravenous and sublingual preparations conformed with the NIBSC standard.

Dosage

The dosages were administered in a cross-over design. A single sublingual dose of oxytocin (400 int. units = 684 µg) was taken after a standard breakfast containing two sandwiches, no cheese and unrestricted amounts of coffee or tea. Two weeks later 1 int. unit (1.71 µg) oxytocin was injected intravenously to the same volunteer after a similar standard breakfast.

Sampling

Sublingual administration. Five-millilitre blood samples were collected through an intravenous canula (Venflon 1.0 mm o.d.) in tubes containing 0.5 mg EDTA at times: -10, -5, 0, 10, 20, 30, 40, 50, 60, 90, 180, 240, 270, 300 min after oxytocin administration.

Intravenous administration. Intravenous injection took place over 1 min in the opposite arm where the Venflon was located. In addition to the sampling times as described for sublingual administration, two extra samples were taken 3 and 5 min after the start of the injection.

Drug assay

Oxytocin in plasma was measured by RIA as described by Dogterom et al (1977), with some modifications as follows.

Standard. The oxytocin standard (O-6379; Sigma) was calibrated against the WHO standard 76/575 (National Institute for Biological Standard and Control, South Mimms, Hertfordshire, UK).

Labelling. Oxytocin was iodinated with Na¹²⁵I using the lactoperoxidase method with Enzymobead, followed by purification using Sep-pack C18 cartridges.

Antiserum. Polyclonal rabbit anti-oxytocin was kindly donated by Dr T. Higuchi (Kochi, Japan) (Higuchi et al 1985), and used in a final dilution of 1:600 000. Cross-reactivities for arginine-vasopressin, lysine-vasopressin, arginine-vasotocin, deamino-D-arginine-vasopressin were < 0.01% and for isotocin 0.9% (on mass bases).

Sample preparation. Oxytocin was extracted from 2.0 mL EDTA plasma using Sep-Pak C18 cartridges.

Assay. Oxytocin was measured by non-equilibrium radioimmunoassay. Rabbit oxytocin antiserum (50 µL) (final dilution 1:600 000 and diluted in oxytocin RIA-buffer (0.02 M phosphate buffer (pH 7.4) containing 13 mM EDTA, 0.02% sodium azide, 0.25% BSA, 0.1% Triton X-100 and 250 000 int. units aprotonin (Trasylol) mL⁻¹)) was added to 50 µL sample or standard. The mixture was preincubated for three days at 4°C, then, tracer (approx. 6000 disintegration min⁻¹/50 µL) was added and incubation was continued for another day. Bound and free oxytocin were separated by a second antibody by addition of 100 µL 10% sheep antirabbit IgG and 0.01% rabbit IgG and 1.0 mL 7.5% polyethylene glycol 6000 solution. The standard curve for the oxytocin assay was run in triplicate with a range of 0.25–32 pg per assay tube.

Assay performance. The sensitivity of the assay system was 0.32 pg mL⁻¹ (extraction of 2 mL plasma). There was 50% displacement for 1.25 pg. Within-assay and between-assay coefficients of variation of the extraction and RIA procedure were < 8%. Recovery of oxytocin added to plasma was about 80%. Oxytocin values of 15 normal male volunteers was < 3 pg mL⁻¹.

Pharmacokinetic analysis

Net plasma concentrations were used (total oxytocin in the sample minus mean baseline value) (n = 3, at t = -10 min,

-5 min, and 0 h of each subject). Curve-fitting was carried out ($r^2 > 0.97$) and pharmacokinetic parameters were calculated using the two-compartment model after intravenous administration and the one-compartment model with extravascular administration and lag time of the MW/Pharm computer program (Mediware, Groningen, The Netherlands) (Proost & Meyer 1992). C_{max} is the maximum plasma concentration read from the fitted plasma concentration-time curve, 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_{2abs}^1 and $t_{1/2}^1$ were obtained by line feathering and linear regression analysis. $AUC_{0-\infty}$ 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/β with C_t being the last measured concentration. Total body clearance $CL = Dose/AUC_{0-\infty}$. The bioavailability (F) is $AUC_{oral} \cdot Dose_{i.v.}/AUC_{i.v.} \cdot Dose_{oral}$. Vd_{ss} is the volume of distribution at steady state ($Vd_{ss} = Dose \times AUMC_{0-\infty}/AUC_{0-\infty}^2$). Mean absorption time after sublingual administration (MAT_s) was defined as $[MRT_s - t_{lag}] - [MRT_{i.v.}]$.

Average values are expressed as means \pm s.d. The statistical significance was determined by analysis of variance. A value of $P < 0.05$ was considered significant.

Results

Fig. 1 shows the oxytocin plasma concentration-time curves after sublingual administration of 400 int. units (684 μ g) oxytocin and after intravenous administration of 1 int. unit (1.71 μ g) in one male volunteer (subject 1). After sublingual administration the compound is rapidly absorbed after a lag time of 0.28 h. A maximum plasma concentration of 7.9 $pg\ mL^{-1}$ was reached after 0.59 h. The apparent half-life of oxytocin was 0.62 h in this volunteer. After the intravenous administration the half-life was 0.28 h. The relative bioavailability (F) in this subject was calculated to be 0.072%. The mean absorption half-life was 0.52 h.

Table 2 summarizes the pharmacokinetic parameters of intravenous oxytocin in six male volunteers. The pharmacokinetic profile can be described by a two-compartment model. The distribution half-life ($t_{1/2\alpha}^1$) shows a relatively small variation among the volunteers (CV = 32.6%). The elimination half-life ($t_{1/2\beta}^1$) was 0.33 ± 0.23 h, (range 0.11-0.74 h, CV = 69.4%). The total body clearance (CL) was $67.1 \pm 13.4\ L\ h^{-1}$ (range 47.7-83.0, CV = 20.0%) and the

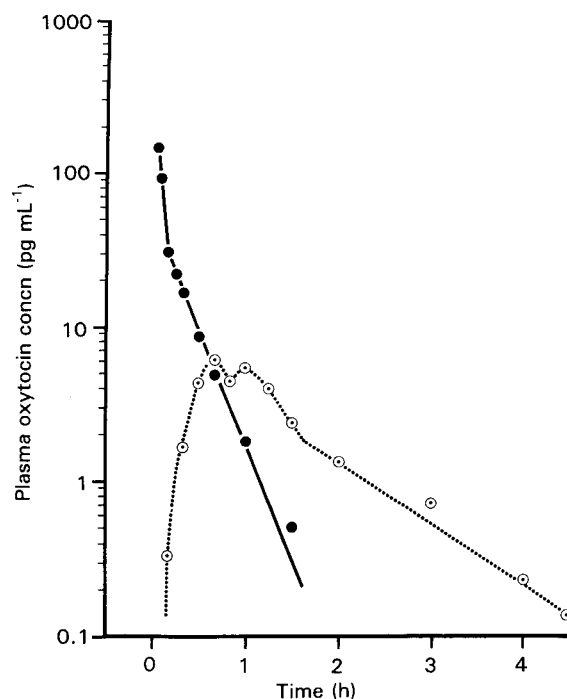


FIG. 1. Oxytocin plasma concentration-time curves after administration of an intravenous dose of 1 int. unit (1.71 μ g) oxytocin (-●-, $t_{1/2}^1 = 0.28$ h) and after sublingual administration of 400 int. units (684 μ g) oxytocin (-○-, $t_{1/2}^1 = 0.62$ h) to subject 1.

steady state volume of distribution (Vd_{ss}) was $12.2 \pm 5.6\ L$ (range 5.8-20.7 L, CV = 45.9%).

Table 3 summarizes the pharmacokinetic parameters of sublingual oxytocin in the same six volunteers. After sublingual administration, the pharmacokinetic profile can be described by a one-compartment model. The bioavailability (F) is poor, subject-dependent and ranges between 0.007 and 0.07% (CV = 50.0%) with the assumption that the total body clearance is similar after intravenous and sublingual administration. The lag time (t_{lag}) was 0.20 ± 0.08 h (range 0.12-0.30 h, CV = 40%), the absorption half-life (t_{2abs}^1) was 0.45 ± 0.29 h, (range 0.12-0.80 h, CV = 65.3%) and the apparent elimination half-life ($t_{1/2\beta}^1$) 0.69 ± 0.26 h, (range 0.43-1.13, CV = 37.8%).

Two volunteers experienced flushes immediately after injection of 1 int. unit oxytocin (subjects 1 and 5). After sublingual administration no side-effects were noted.

Table 2. Pharmacokinetic parameters of intravenous oxytocin (1 int. unit).

Parameter	Subjects						Mean \pm s.d.
	1	2	3	4	5	6	
$t_{1/2\alpha}^1$ (h)	0.075	0.042	0.063	0.032	0.037	0.045	0.049 \pm 0.016
$t_{1/2\beta}^1$ (h)	0.31	0.39	0.74	0.11	0.13	0.28	0.33 \pm 0.23
MRT (h)	0.26	0.15	0.25	0.99	0.12	0.21	0.33 \pm 0.33
AUC (ng L ⁻¹)	27.4	27.0	20.8	20.6	35.8	26.8	26.4 \pm 5.6
CL (L h ⁻¹)	62.5	63.3	82.1	83.0	47.7	63.7	67.1 \pm 13.4
Vd ₁ (L)	28.2	35.5	87.0	13.6	8.78	25.8	33.2 \pm 28.1
Vd _{ss} (L)	16.2	9.17	20.7	8.24	5.80	13.3	12.2 \pm 5.6

Table 3. Pharmacokinetic parameters of sublingual oxytocin (400 int. units).

Parameter	Subjects						Mean \pm s.d.	P
	1	2	3	4	5	6		
F (%)	0.072	0.100	0.112	0.106	0.0072	0.073	0.078 \pm 0.039	< 0.00001
t _{lag} (h)	0.29	0.12	0.15	0.30	0.16	0.15	0.20 \pm 0.08	
t _{max} (h)	0.59	1.08	1.03	1.34	0.48	0.77	0.88 \pm 0.33	
C _{max} (ng mL ⁻¹)	7.86	4.12	3.89	3.09	6.32	4.41	4.95 \pm 1.78	
t _{1/2abs} (h)	0.12	0.80	0.60	0.72	0.16	0.31	0.45 \pm 0.29	
t _{1/2α} (h)					0.23		0.23	
t _{1/2β} (h)	0.43	0.56	0.62	0.73	2.91	1.13	1.06 \pm 0.94	0.091
MRT _s (h)	1.07	2.08	1.91	2.39	2.91*		0.69 \pm 0.26**	
MAT (h)	0.52	1.82	1.51	1.10	3.63	1.48	2.09 \pm 0.88	0.0010
AUC (h ng L ⁻¹)	7.88	10.83	9.32	8.75	3.34	1.13	1.57 \pm 0.97	
CL _s (Lh ⁻¹)	62.5	62.6	82.1	83.0	10.29	7.84	9.15 \pm 1.24	< 0.0001
Vd _{ss} (L)	38.6	50.6	73.5	86.9	34.9	63.7	64.8 \pm 17.5	> 0.8
					38.2	56.6	57.2 \pm 19.7	0.12

* Outlier, ** without outlier.

Discussion

Oxytocin is a posterior pituitary hormone which is not regulated by hypothalamic releasing hormones. It is synthesized in the hypothalamus and then transported intracellularly to the posterior pituitary, from which it is released into the circulation. Oxytocin has an important role in contractions during labour. The sensitivity of the uterus to oxytocin depends strongly on the amount of oxytocin-receptors, increasing with increasing gestational age. Honnebier (1993) suggested that the demonstrated circadian rhythm of oxytocin at term plays a role in the onset of labour, influencing the shift from contractures to contractions. In therapeutic doses, oxytocin stimulates the contractions of uterine smooth muscle (Brazeau 1970). Its primary use is for induction of labour at term, when a large oxytocin receptor population is present in the uterus. It is also given intramuscularly postpartum to control uterine bleeding. Oxytocin may be prepared by a process of extraction from the glands of oxen or other mammals or by synthesis. Oxytocin was isolated in 1928 from the posterior lobe of the pituitary gland and showed vasoactive, antidiuretic and uterotonic properties (Kamm et al 1928). In 1953, the synthesis of the polypeptide oxytocin was performed and it was marketed in 1963 (Du Vigneaud et al 1953a, b).

According to the Pharmacological Basis of Therapeutics (Brazeau 1970; Rall 1990), and Martindale (Reynolds 1988) sublingual oxytocin is absorbed rapidly. Others have reported that sublingual absorption is unpredictable (Noriega-Guerra et al 1966). We conclude from our studies that oxytocin absorption by male volunteers (65% CV) after the lag time, cannot be reliably assessed. Sublingual absorption is prolonged and causes a long mean absorption half-life of 2 h and consequently a longer apparent t_{1/2} and MRT. The mean pharmacokinetic lag time of 0.20 h in males corresponds to the latent periods of 13–96 min reported by Tobias (1975), and 31 min reported by Obolensky & Kupferschmid (1969) in non-pregnant women.

The total body clearance of 60 L h⁻¹ corresponds with the reported metabolic clearance rate (MCR) of 1 L min⁻¹ reported by Amico et al (1984, 1987), Dawood et al (1980), Leake et al (1980) and Thornton et al (1990).

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