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Population Pharmacokinetic Analysis of Vaginally and Intravenously Administered Oxytocin in Postmenopausal Women

The Journal of Clinical Pharmacology
2017, 00(0) 1–9

DOI: 10.1002/jcph.961

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Abstract

Oxytocin is a neuropeptide hormone used clinically for more than 50 years due to its ability to induce uterine contractions and milk ejection. Vagitocin is a vaginal oxytocin gel developed as a potential treatment of vaginal atrophy in postmenopausal women. The aim of this study was to characterize the oxytocin pharmacokinetics following vaginal and intravenous administration in postmenopausal women. Data from 33 participants enrolled in 2 clinical studies were used in the analysis, with a total of 651 observed oxytocin plasma concentrations, of which 78 were baseline observations, 178 observations following intravenous administration (10 IU), and 395 observations following vaginal administration (100 or 400 IU). The population pharmacokinetics of oxytocin was described using a 2-compartment disposition model with a flexible parallel absorption model accounting for double-peak profiles following vaginal administration. The clearance, volume of distribution at steady state, distribution half-life, and terminal half-life were estimated to be 27 L/h, 15 L, 5.5 minutes, and 1.2 hours, respectively. The bioavailability following vaginal administration was estimated to be 2.5% for the typical patient, but with considerable variability both between individuals (interindividual variability of 374%) and between occasions (interoccasion variability of 79%). The data and the developed model add new and important information as to the clinical pharmacokinetics of oxytocin.

Keywords

oxytocin, population pharmacokinetics, postmenopausal women, vaginal gel, bioavailability

Oxytocin is a 9-amino-acid neuropeptide hormone that is produced in neurons within the paraventricular nuclei and supraoptic nuclei of the hypothalamus. Some of the neurons project to the posterior pituitary, from where oxytocin is released into the circulation to exert its well-known contractile effects on uterine muscles during labor and of myoepithelial cells during breastfeeding. Oxytocinergic nerves originating in the paraventricular nuclei also project to a multitude of regulatory areas within the brain and modulate a multitude of behavioral and physiological functions.[1,2] Recently it has also been found that oxytocin and its receptor are produced in several peripheral organs such as the cardiovascular system, the gastrointestinal tract, and in epithelial cells in the skin. Oxytocin produced in peripheral tissues or cells most often exerts local effects and is involved in the control of growth and repair.[3,4]

Oxytocin has been used clinically for more than 50 years in order to initiate or augment uterine contractions during labor, to contract the uterus postpartum, and to facilitate milk let-down during breastfeeding. During labor, oxytocin is administered as an intravenous infusion with gradually increasing infusion rates titrated to desired contraction strength and frequency (maximum 1.2-2.4 IU/h),[5] and immediately after birth, an intramuscular or intravenous bolus injection (5-10 IU) may be administered. During breastfeeding oxytocin is usually administered as a nasal spray (4-8 IU).

In recent years oxytocin has also gained an increasing research interest, and several new therapeutic applications are currently under investigation.[6–10] One such product is Vagitocin®, an oxytocin-containing gel that is to be applied locally as an estrogen-free alternative for treatment of vaginal atrophy. Vaginal atrophy develops in about 50% of all women after menopause and is characterized by a dysfunction of the vaginal epithelium and feelings of vaginal dryness and irritation and pain during intercourse.[11] Vaginal oxytocin administration has been evaluated in 3 placebo-controlled

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Submitted for publication 7 April 2017; accepted 15 May 2017.

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clinical efficacy studies with doses of oxytocin ranging from 100 to 600 IU.[12–14] In these studies vaginal application of oxytocin has been shown to rejuvenate the vaginal mucosa and to relieve symptoms such as dyspareunia. The contribution of locally and systemically available oxytocin concentrations to the overall effect and possible side effects is currently not known.

The pharmacokinetic (PK) characteristics of oxytocin are still to a large extent unknown. Early studies performed in healthy male subjects reported a very rapid oxytocin elimination following intravenous oxytocin administration, with a half-life as quick as a couple of minutes.[15] However, in later studies, using alternative study designs and improved analytical methods, data suggest the elimination half-life to be substantially longer, generally >30 minutes.[16,17] In patients, most PK studies have been related to its use in obstetrics and gynecology. The main focus of these studies has been to assess steady-state oxytocin levels obtained following intravenous infusions, with limited ability to provide a detailed description of the oxytocin disposition.[18,19]

The aim of the present study was to characterize the oxytocin PK following vaginal and intravenous administration in postmenopausal women. A clinical PK study was performed in which oxytocin concentrations were assessed using rich sampling following vaginal (400 IU once daily for 15 days) and intravenous (10 IU Syntocinon®, single dose) administration. The data were combined with sparse oxytocin concentration data available from 1 of the clinical efficacy studies.[12] A population nonlinear mixed-effects analysis was performed to adequately handle and describe the endogenous baseline of oxytocin[20] and the different random effects, including variability between subjects, between occasions, and residual variability.

Methods

Ethics

The data used in this analysis were compiled from 2 clinical trials (studies A and B) with study protocols approved by the Regional Ethical Review Board in Stockholm, Sweden (2013/1233-31/2 and 2011/1978-31/2) and by the Swedish Medical Product Agency (LVFS 2011:19; 2013-07-24 and 2012-02-01). Before any trial-related activity took place, the participants were provided a written and oral explanation of the trial, and all participants provided written informed consent prior to participation. The studies were carried out in accordance with the principles of the Declaration of Helsinki and The Guidelines of Good Clinical Practice (CPMP/ICH/135/95). Further, both trials were registered at ClinicalTrials.gov (study A NCT01975129, and study B NCT01987804).

Subjects

The studies were performed at Karolinska University Hospital, Huddinge, Sweden, between September and December 2013 (study A) and between February and June 2012 (study B). Healthy postmenopausal women over 40 years with vaginal atrophy and body mass index <30 (study A) or ≤32 and ≥19 kg/m^2 (study B) were included. Patients were excluded if they were hospitalized or showed symptoms of acute illness. Patients were also excluded if they had used any sex steroids within 3 months prior to screening and if they had a known history of significant allergies, sensitivity to oxytocin or related derivatives, known or suspected drug or alcohol abuse, or if they had uncontrolled hypertension and/or hypercholesterolemia and/or follicle-stimulating hormone levels <40 IU/L.

Study Product

Oxytocin was provided by Grindex (Riga, Latvia), and the vaginal gel (Vagitocin®) in strength of 100 IU and 400 IU and the placebo gels were prepared as 1-mL single-dose glass syringes by Recipharm AB (Stockholm, Sweden). The pH of the gel was adjusted to 3.75, and benzoic acid was used as a preservative. The placebo gel was identical to the active gel except for the absence of oxytocin. Syntocinon® 10 IU/mL solution for injection (Swedish Orphan Biovitrum AB, Stockholm, Sweden) was used for the intravenous administration.

Study Design

The first study (study A) was a single-center, open-label, 2-period PK study performed in 12 patients. Each patient was treated with vaginal gel 400 IU once daily for 15 days (period I). After a 7-day washout period, a single intravenous dose of oxytocin, 10 IU Syntocinon® was administered on day 22 (period II). Serial blood samples were collected on day 1, day 15, and day 22, at the following time points relative to dosing: –1.0, –0.5, 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 hours. In addition, single blood samples were collected in the morning on days 5, 8, 12, 16, and 19 (period I) and on days 23 and 26 (period II). Patients self-administered the vaginal gel in the evening. At days 1 and 15, the vaginal gel was administered at the clinic in the morning, and the patients were instructed to skip their evening dose on these dates.

The second study (study B) was a single-center, double-blind, randomized, placebo-controlled, dose-response study with parallel design.[12] In total, the study comprised 64 patients randomized to treatment once daily for 7 weeks with vaginal gel 100 IU (n = 24), vaginal gel 400 IU (n = 24), or placebo (n = 16). PK sampling was performed in the first 24 randomized patients. In these patients 1 sample was taken at the

baseline visit (predose), and 4 samples (predose and 30, 60, and 120 minutes postdose) at visit 2, after 2 weeks of treatment. The patients self-administered the product in the evenings, except for the days of PK sampling (baseline visit and visit 2), when the doses were administered at the trial site in the morning and the patients were instructed to skip the evening dose. Only patients randomized to active treatment with PK sampling (400 IU n = 11, 100 IU n = 10) were included in the current analysis.

Bioanalytical Assay

Venous blood samples (7.5 mL) were collected in tubes containing EDTA. Immediately after collection each sample was put on ice, and plasma was retrieved within 15 minutes and kept frozen (–20°C) until analysis. Oxytocin levels in plasma were analyzed using a validated radioimmunoassay method. In short, plasma was centrifuged, and after acidification with hydrochloric acid, solid-phase extraction was performed using the standard protocol for Oasis HLB Cartridges (Waters, Milford, Massachusetts). Following evaporation and resolving in assay buffer, the radioimmunoassay was performed in triplicate for calibrators and duplicates for controls and samples. The assay was based on an antiserum raised against oxytocin in rabbit. ^{125}I-Oxytocin was produced by a modified chloramine-T method purified with reverse-phase high performance liquid chromatography (RP-HPLC) using a μ-Bondapack C18 column (Waters). The lower limit of quantification was 5 pmol/L, and the intra-assay coefficient of variation was 14%, 8%, and 10% at 12, 31, and 60 pmol/L, respectively, with corresponding values for interassay variability of 15%, 12%, and 10%. All bioanalytical assays were performed at the Neurochemistry laboratory, Sahlgrenska University Hospital (Mölndal, Sweden).

Population Pharmacokinetic Analysis

The population PK model was developed in a stepwise fashion. First, a model was established describing the disposition of oxytocin based on PK data following intravenous oxytocin administration (study A). In the second step the model was expanded to also describe the vaginal absorption following administration of vaginal gel. Initially, only data following vaginal administration in study A was used, with the individual disposition model parameters fixed according to final estimates from the previous step. Thereafter, all data from study A (intravenous and vaginal) and PK data obtained in study B (vaginal) were combined, and all model parameters were reevaluated to form the final PK model.

One-, 2-, and 3-compartment models were evaluated for the characterization of oxytocin disposition. The endogenous baseline value of oxytocin was estimated as a parameter in the model with associated interindividual variability (IIV) and interoccasion variability (IOV), with an occasion defined as each dosing associated with PK sampling. In each individual the baseline was assumed constant during 1 occasion. A first-order absorption model was used as the starting point to characterize the absorption following vaginal administration. Other absorption models, including 0-order absorption and sequential first- and 0-order absorption, were also evaluated. Initial plots of observed oxytocin concentrations vs time following vaginal administration of oxytocin showed the absorption profile to be highly variable with, in some cases, the presence of a double peak of significant magnitude. The mechanistic reason for this second peak is currently not known, and therefore, an empirical modeling strategy was applied in which a flexible model, allowing for 2 parallel first-order absorption processes,[21] with or without a time-delay, was evaluated. To account for the observation that only some individuals showed double-peak profiles, a mixture model was used in which the individuals were allocated to 1 of 4 different mixtures: (1) having no double peaks, (2 and 3) having a double peak in the first or second intensive PK sampling period, respectively, (4) having double peaks in both sampling periods. The probability of a sampling period to not have a double peak was estimated as a parameter ($P1$). Further, the probability of having a double peak was assumed to be the same for the 2 sampling periods. Thus, the probability of having no double-peak profiles can be calculated as $P1 \cdot P1$, to have a double peak in 1 of the occasions but not the other as $P1 \cdot (1 - P1)$, and to have double peaks in both occasions as $(1 - P1) \cdot (1 - P1)$.

IIV and IOV were allowed and initially assumed to be log-normally distributed. If needed, other parameter distributions, such as the logit transformation, boxcox transformation, or the heavy tail transformation were tested.[22] One occasion was either defined as each separate dosing occasion associated with PK sampling (used for baseline) or as each separate dosing occasion associated with intensive PK sampling (ie, day 1 and day 15 for study A, used for absorption-related parameters). Additive, proportional, and combined additive and proportional residual error models were tested on untransformed data.

Model development was performed using NONMEM version 7.3.[23] R (version 3.1.2) (www.r-project.org), Xpose (version 4.2.3), and PsN (version 4.0.3)[24] were used for model evaluation. Parameter uncertainty was assessed using the covariance matrix. To also allow asymmetry in the parameter uncertainty, sampling importance resampling was used to assess parameter confidence intervals for the final model.[25] Model fit was evaluated based on goodness-of-fit plots and prediction-corrected visual predictive checks.[26]

Table 1. Demographics of the Total Study Population (Studies A and B)

	n	Mean	Median	Min	Max
Age (y)	33	61.9	63	52	71
Body weight (kg)	33	66.4	67	46	90
Body mass index (kg/m^2)	33	24.5	24.3	18.4	29.3
Body surface area (m^2)	33	1.72	1.72	1.43	2.09
Time following menopause (y)[a]	12	16.8	15.5	5	28
Observed oxytocin baseline (pmol/L)[b]	33	15.8	15.0	9.0	25.0

y = years

[a]Information only available from study A.

[b]Mean oxytocin concentration as observed prior to drug administration.

Selection between nested models was performed using the NONMEM objective function value (OFV) in the likelihood ratio test, where a difference of at least 3.84 in the OFV for 1 degree of freedom corresponds to statistical significance ($P < .05$).

Results

Study Population

The full data set (study A and study B combined) included 33 patients with a total of 651 observed oxytocin plasma concentrations. Study A included 12 patients with 36 baseline (predose) observations, 178 observations following intravenous administration, and 338 observations following vaginal administration (400 IU). Study B included 21 patients with 42 baseline observations, 30 observations following vaginal administration of 100 IU and 27 observations following vaginal administration of 400 IU. For study A, 1 patient withdraw after the first vaginal dose and was excluded from the analysis due to the lack of observations following intravenous administration. For study B, 2 patients withdraw early (contributing 2 samples per patient). The data from these patients were still included in the final estimation. Patient demographics of the study population are shown in Table 1. Observed oxytocin levels vs time after dose for the 12 subjects included in study A (rich sampling) are shown in Figure 1.

Population Pharmacokinetic Analysis

Parameter estimates of the final model obtained with the full dataset are found in Table 2, with the structure of the final model schematically illustrated in Figure 2. The model fit is illustrated as population and individual predictions for patients with rich PK sampling in study A (Figure 1), as observations vs population and individual predictions for the combined dataset (Figure 3) and as a prediction-.corrected visual predictive check for the combined dataset (Figure 4). The prediction correction is performed here in order to enable a combined evaluation across different dose levels and is done by normalizing observed and simulated oxytocin concentrations based on the typical population prediction for the median independent variable in each of the simulated bins.

The disposition of oxytocin following intravenous administration was adequately described using a 2-compartment model with estimation of the structural parameters clearance (CL), intercompartmental clearance, volumes of distribution for the central and peripheral compartments, and the endogenous (predose) oxytocin concentration (baseline). IIV was included in CL, peripheral compartment volume of distribution, intercompartmental clearance, and baseline. Compared to a 1-compartment model, the 2-compartment model produced a statistically significant drop in OFV (71.3 units) and improvements in goodness-of-fit plots. The estimation of a 3-compartment model was not supported by the data.

The absorption following vaginal administration was found to be highly variable, both between and within individuals. The total bioavailability was here estimated to be 2.49%, with a high variability (IIV and IOV of 374% and 79%, respectively). The parameter distribution of the bioavailability deviated from the initially assumed log-normal distribution, and to relax the assumptions, a logit transformation including the estimation of 2 shape parameters was used. This resulted in a significant drop in OFV (19 units) and improved goodness-of-fit plots. However, even after this transformation, there was a trend for the model to overpredict the oxytocin concentration for the upper percentile following vaginal administration and to underpredict the concentration for the lower percentile following intravenous administration (Figure 4).

In a few individuals in study A a clear double-peak profile was observed (Figure 1; ID11 day 1, ID5 day 15, with an incidence of 1/12 per occasion). To allow the model to characterize such double peaks, a flexible absorption model with double absorption compartments was evaluated.[21] In this model structure the intravenous dose is administered directly into the central compartment while the vaginal dose is administered into 2 separate, parallel absorption compartments (Figure 2). In the mixture model, the probability of having no double peak was estimated to be 84% (*P1·P1*),

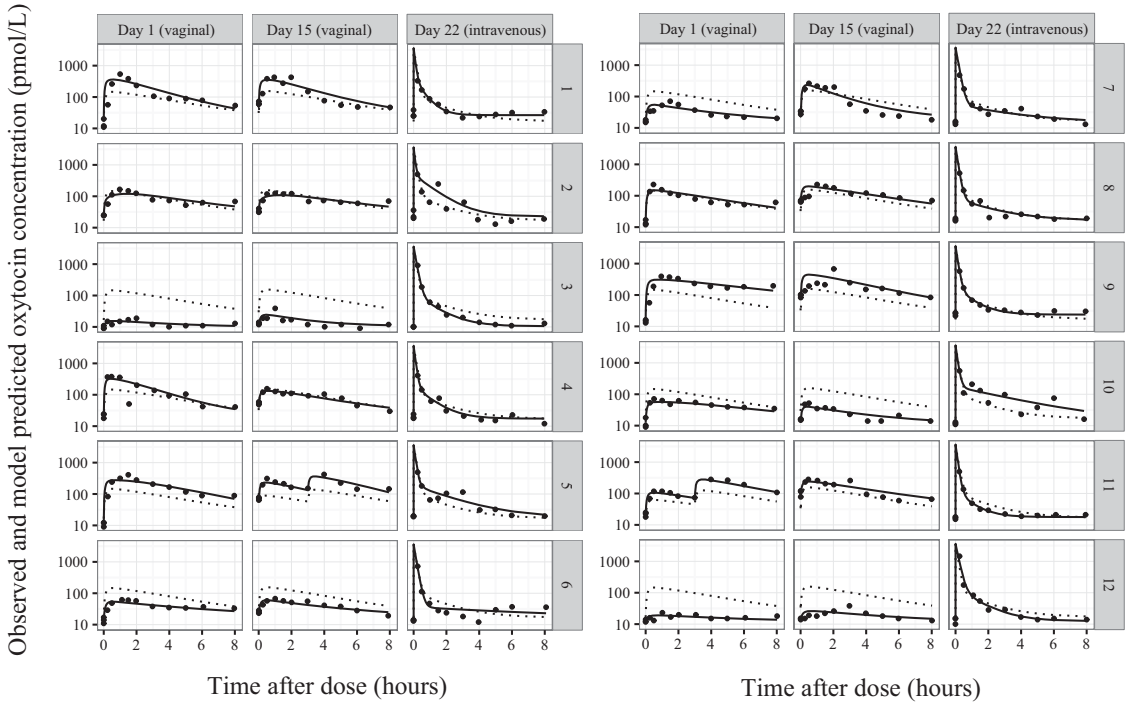

Figure 1. Observed (dots), population model-predicted (dashed lines), and individual model-predicted (solid lines) oxytocin concentration vs time after dose following vaginal administration of 400 IU, day 1 (left) and day 15 (middle) and intravenous administration of 10 IU, day 22 (right), for the 12 subjects included in study A.

and consequently, the probability of having a double peak in 1 of the occasions was estimated as 7.7% ($P1 \cdot [1 - P1]$), and of having double peaks in both occasions as 0.7% ($[1 - P1]^2$). For the individuals having double-peak profiles, 65% of the dose was estimated to be absorbed at the second, slower absorption site. For the second compartment the dose was estimated to be absorbed after a time lag of 3 hours. The absorption rate constant was estimated to be the same for the 2 absorption processes. Of the other absorption models tested, a sequential 0-order and first-order absorption model and a model including a lag parameter also for the first, rapid absorption compartment did not result in significant improvements in OFV and only minor improvements in goodness-of-fit plots.

The final population PK model was used to predict and visually compare the oxytocin concentration-time profile (Figure 5) following different oxytocin doses and routes of administration (100 IU vaginal, 400 IU vaginal, 10 IU intravenous bolus, 10 IU 5-hour intravenous infusion).

Discussion

In this study oxytocin absorption, bioavailability, and disposition were assessed following intravenous and vaginal oxytocin administration in postmenopausal women using a population-modeling approach. Oxytocin has been used clinically for over a half-century and has recently gained an intensified research interest due to its novel indications with over 300 registered clinical trials at ClinicalTrails.gov specifying oxytocin as the intervention during the last decade. Even so, the PK of oxytocin is still to a large extent unknown.

In agreement with previous studies,[16,27] a biphasic decline in the oxytocin concentration was observed following intravenous administration, and a 2-compartment model was found to adequately describe the oxytocin disposition. The oxytocin CL and total volume of distribution were here estimated to 27 L/h and 15 L, respectively, with the half-lives of the 2 phases estimated to 0.09 hours and 1.2 hours, respectively. Initially only the data following the intravenous administration were used to assess the disposition parameters. Only minor differences in the estimates were observed when all data were used in the estimation process (<10% for CL and volume of distribution), indicating a robust parameter assessment. Comparing the results with previous publications is challenging because of differences in study population, study design, and methods used for oxytocin and PK analysis. Overall, although the volume of distribution is similar to those reported earlier, the CL is somewhat lower. De Groot et al reported CL and volume of distribution to be 67 (range 48-83) L/h and 12 (range 8.2-21)

Table 2. Model Parameters Describing Oxytocin Absorption, Bioavailability, and Disposition Following Vaginal and Intravenous Administration in Postmenopausal Women

	Estimate (%RSE)	95%CI
Structural model		
CL (L/h)	27.2 (9.13)	23.3–32.6
Vc (L)	4.67 (13.9)	3.71–6.27
Vp (L)	10.2 (23.1)	7.40–15.0
Q (L/h)	7.61 (10.8)	5.86–10.2
Baseline (pmol/L)	16.6 (4.97)	14.7–18.6
F (–)	0.0249 (15.7)	0.0150–0.0404
FR (–)	0.647 (12.6)	0.486–0.774
tLag (h)	3.00 (0.02)	...
ka (1/h)	0.296 (7.49)	0.270–0.327
P1 (-)	0.916 (6.12)	0.817–0.980
Interindividual variability[a]		
CL (%CV)	23.8 (14.3)	17.4–33.2
Vp (%CV)	91.0 (18.8)	60.8–136
Q (%CV)	77.2 (21.4)	44.9–134
Baseline (%CV)	29.1 (23.4)	20.4–41.1
F (%CV)[b]	374 (38.6)	215–636
FR (%CV)	37.6 (15.9)	20.4–49.7
Interoccasion variability[a]		
Baseline (%CV)	19.3 (21.3)	12.8–25.8
F (%CV)	78.7 (14.1)	59.3–109
ka (%CV)	42.3 (20.2)	26.9–64.4
Residual variability		
Proportional residual error (%)	27.8 (4.95)	26.1–29.7

CL indicates clearance; Vc, central volume of distribution; Vp, peripheral volume of distribution; Q, intercompartmental clearance; Baseline, model-estimated endogenous (predose) oxytocin concentration; F, total bioavailability; FR, fraction of the total dose absorbed at the second, slow absorption site; tLag, absorption lag time for the second slow absorption site; ka, absorption rate constant, *P1*, the probability of a sampling period not showing a double-peak profile; RSE, relative standard error; CI, confidence intervals obtained using sampling importance resampling.

[a]The relative standard errors for omega and sigma are reported on the approximate standard deviation scale (SE/variance estimate)/2.

[b]Logit-transformed with shape parameters estimated as (%RSE) 0.543 (9.08) and 3.98 (8.90).

L in healthy male volunteers[16] following intravenous administration of 1 IU. This may suggest differences in the elimination capacity between the study populations or be a result of the suggested nonlinearity in oxytocin CL[27] with the intravenous doses differing 10-fold between studies (10 vs 1 IU).

The absorption following administration of the vaginal gel was here found to be highly variable both between and within subjects. Also other extravascular routes of oxytocin administration, such as intranasal, buccal, and sublingual administration, have been shown to result in wide intra- and interindividual variability in bioavailability.[16,17,28] In study A a rich sampling protocol was used, and from these data it was evident that double-peak profiles can occur. This phenomenon can create difficulties in the determination and interpretation of the PK, in particular if a sparse sampling protocol is used.[29] Even if the second peak occurred in only some individuals, it was judged to be of such magnitude that it had to be taken into account for an adequate PK characterization. Ideally, a mechanistic modeling approach would have been applied. However, the reason for the double-peak phenomenon for oxytocin is currently not known. Several

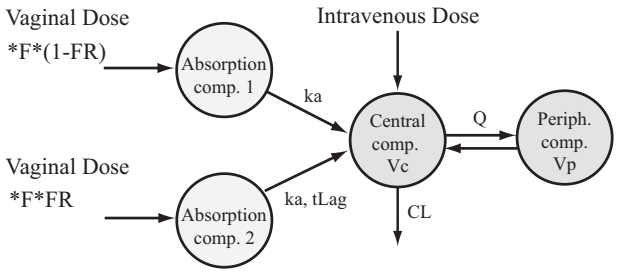

Figure 2. Schematic illustration of the final model used to describe the pharmacokinetics of oxytocin following vaginal and intravenous oxytocin administration. F indicates total bioavailability following vaginal administration; FR, fraction of the dose absorbed at the second, slow absorption site; ka, first-order absorption rate constant; tLag, absorption lag time used for the second, slow absorption site; CL, clearance; Q, intercompartmental clearance; Vc, volume of distribution for central compartment; Vp, volume of distribution for peripheral compartment.

mechanisms could be postulated including fluctuations in the endogenous oxytocin production (eg, due to circadian rhythm or a stimulation of endogenous release), oxytocin storage and subsequent release from a postabsorption depot site, or a discontinuous release and/or absorption from the vaginal gel. The daily pattern of secretion of oxytocin has been studied in

healthy young and elderly male subjects, showing the oxytocin concentrations to have a peak (4.6 pmol/L) at 02:00 and then gradually to decrease to a nadir value (1.9 pmol/L) during late afternoon.[30] Based on these results, the second peak does not seem to reflect daily fluctuation in oxytocin secretion. Instead, an empiric modeling strategy, including 2 parallel absorption compartments with different lag times was applied.[21] In the final model the second peak was identified on 1 occasion in 2 out of 12 individuals in study A. However, fluctuations in the concentration-time profile around the time of the second peak (approximately 4 hours after dosing) were also observed in other sampling occasions, even following the intravenous administration, although to a smaller extent (Figure 1). Even though the empirical modeling strategy applied here describes the concentration-time profile adequately, a better understanding of the underlying mechanism for the double-peak profiles would be beneficial and warrants further investigation.

The endogenous level of oxytocin was in this analysis estimated as a parameter in the model (baseline, 17 pmol/L). At present it is not known whether exogenously administered oxytocin has the potential to affect the synthesis and/or release of endogenous oxytocin. To explore a potential shift in the endogenous oxytocin level, the baseline parameter was allowed to vary between days of oxytocin administration by including IOV. When the individual baseline estimates are plotted vs time, no sign of any systematic change in the endogenous oxytocin level during the course of treatment was evident (data not shown). Further, no signs of drug accumulation were evident during the study period.

In the past, several problems have been associated with the analytical method used to quantify oxytocin concentrations in biological samples. This is evident when we compared results between studies, with the reported endogenous baseline oxytocin concentration varying over 100-fold between studies. This has been nicely highlighted in a recent review,[31] stressing the importance of using validated methods that include appropriate sample preparation processes. In the current study a validated radioimmunoassay method was used with a preanalytical extraction process to eliminate interfering substances and concentrate the sample. A limitation with the current method is that it does not make it possible to separately quantify the exogenously administered oxytocin and oxytocin endogenously synthesized and released. If this were possible it could shed light on the mechanisms involved, eg, related to the double-peak profiles observed here. Further, the small number of study participants in the study with rich PK sampling (study A) is a limitation. The small number of individuals in combination with an extensive variability made it challenging to accurately describe the variability components. Even though the final model adequately describes the mean tendency in the population, there is a trend for the model to underpredict the oxytocin concentration for the upper percentile following vaginal administration and to underpredict the lower percentile following intravenous administration (Figure 4). Further, due to the small study population, no covariate analysis was performed at this stage. When data from a larger study population become available, the model structure developed here may be an aid for investigating the relationship between the variability in parameter estimates, eg, bioavailability, and different patient-related characteristics, such as age, time following menopause, or endometrial thickness, with the overall aim to be able to individualize the treatment.

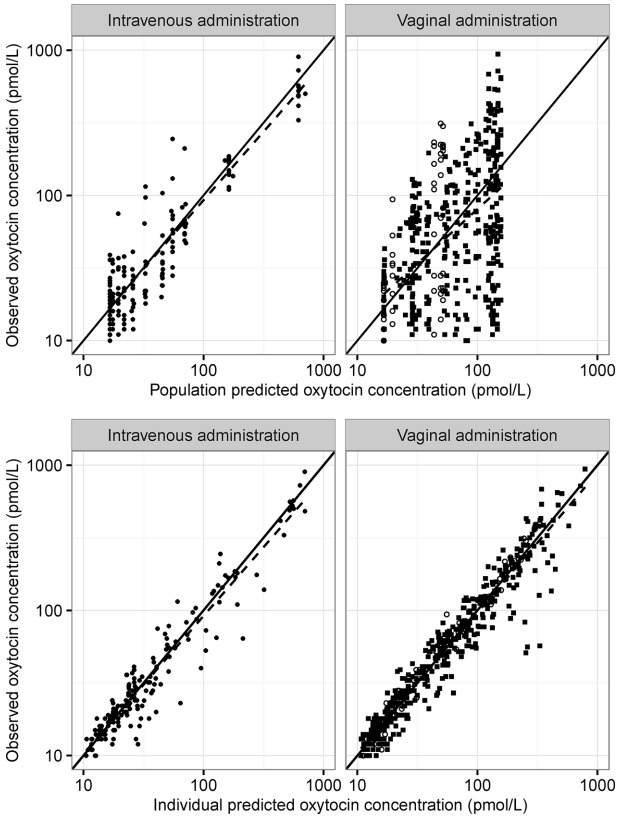

Figure 3. Observed oxytocin concentrations vs population model-predicted concentrations (top) and individual model-predicted concentrations (bottom) following intravenous and vaginal administration. Oxytocin observations following administration of 10 IU Syntocinon®, 100 IU Vagitocin®, and 400 IU Vagitocin® are represented as filled circles, open circles, and filled squares, respectively. Solid lines represent line of identity; dashed lines represent a smoothed fit to observed data.

Conclusions

In conclusion, oxytocin PK was characterized here in postmenopausal women following intravenous

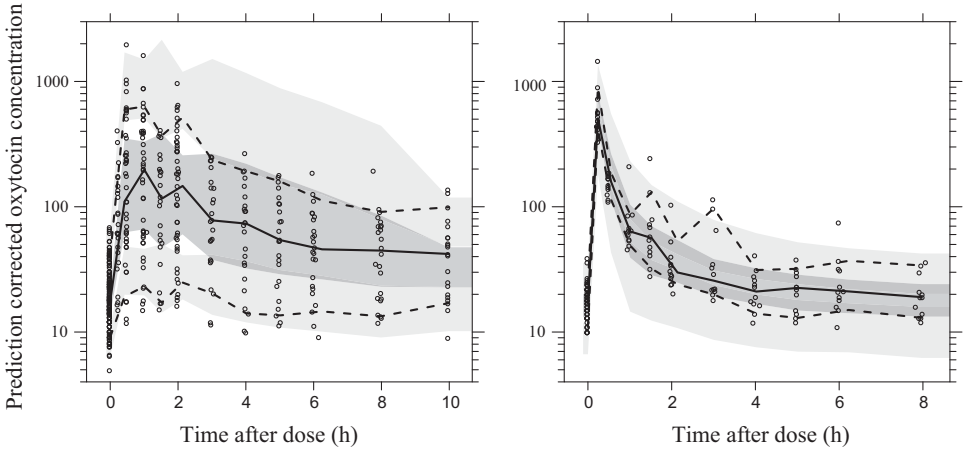

Figure 4. Population prediction-corrected oxytocin plasma concentrations vs time after dose following vaginal administration (left) and intravenous administration (right). Dots show individual observations; dashed and solid black lines are the 10th, 50th, and 90th percentiles of the observed data; shaded areas represent the 95% confidence intervals around the corresponding percentiles of simulated data based on the final model.

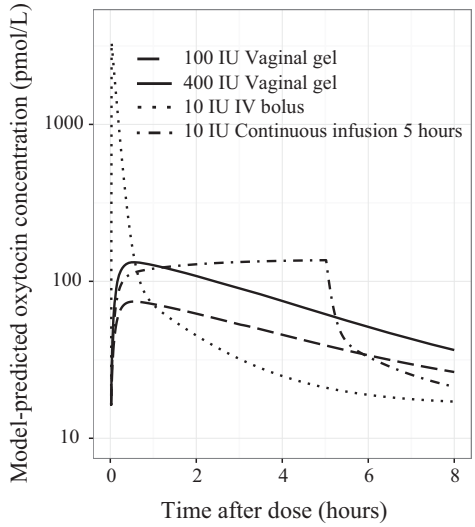

Figure 5. Model-predicted oxytocin concentrations following administration of 100 IU vaginally, 400 IU vaginally, 10 IU as intravenous bolus dose, and 10 IU as intravenous infusion with a duration of 5 hours.

and vaginal administration using a 2-compartment disposition model with a flexible parallel absorption model. Oxytocin CL and volume of distribution were estimated to be 27 L/h and 15 L, respectively. The bioavailability following vaginal administration was estimated to be 2.5%. However, the rate and extent of absorption showed considerable variability both between and within individuals. Given the lack of previous information related to the PK of oxytocin, these data add new and important information with potential implication for its clinical use. The developed model may be used in the future to characterize the link between oxytocin exposure and drug effect/side effects and further increase the understanding of factors contributing to interindividual differences in response.

Acknowledgment

This work was sponsored by Peptonic Medical, Sweden.

Disclosures

This work was sponsored by Peptonic Medical (Bromma, Sweden). E.I.N. reports grants to cover the performance of the analysis from Peptonic Medical paid to Uppsala University. S.H.A. has nothing to disclose. A.F.J. reports grants to cover the study from Peptonic Medical paid to Karolinska Institutet and owns stock at Peptonic Medical. K.U.M. is a board member, consultant, and owns stock in Peptonic Medical.

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