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Oxytocin Dosing and Maternal-Fetal Effects Using a Pharmacokinetic Model

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Abstract

Objective- Although oxytocin is widely used in labor and childbirth, questions remain regarding the pharmacokinetics (PK), pharmacodynamics (PD) and dose of oxytocin in pregnant people as well as the potential effects on the fetus and newborn. The objective of the current study was to use published studies to investigate the PK/PD and dose of oxytocin in pregnancy, examine the placental transfer of oxytocin through the development of a physiologically-based PK (PBPK) model, and postulate whether the model predicts the effect(s) of oxytocin on fetuses and newborn infants. Methods- A literature review of articles related to oxytocin in the areas of PK/PD, placental transfer and its influence on newborns were reviewed and summarized. A PBPK model for oxytocin was developed to predict maternal-fetal transfer. Results- Previous studies have demonstrated a positive relationship between the plasma oxytocin concentration and uterine contractions during labor. An ex vivo study demonstrated maternal to fetal and fetal to maternal oxytocin transfer, but a clinical study investigating oxytocin concentrations in umbilical blood could not confirm these results. Previous studies have suggested that a high concentration of oxytocin is related to fetal bradycardia and possibly autism in the child. Conclusion- The current study developed a PBPK model to measure the placental transfer of oxytocin and its potential for adverse effects on the fetus and developing child. Further research is needed to determine oxytocin's efficacy and safety in the maternal population and in their fetuses and developing children, and modeling techniques such as PBPK will contribute to that understanding.

Keywords: Oxytocin, Placenta transfer, Physiologically-based pharmacokinetics, Maternal-fetal, Autism.

INTRODUCTION

Drug safety in pregnancy and for the fetus is a major concern both during drug development and in the clinical use of medications during this period. The increasing use of modeling techniques for drugs administered to pregnant people and children is one option for closing this gap in knowledge about drug safety.

Oxytocin is a polypeptide hormone which is used extensively in childbirth to induce and stimulate labor and to control postpartum uterine hemorrhage. Oxytocin is produced and secreted from the hypothalamus into the posterior pituitary where it activates the oxytocin receptor and circulates to the uterus where it promotes uterine contractions. Oxytocin and oxytocin receptors increase exponentially during pregnancy until close to term. In addition, oxytocin is secreted by the fetus which can be renally excreted into the amniotic fluid. Although oxytocin is widely used in pregnant women, there is no consensus regarding the optimal standard dose of oxytocin to induce labor. Oxytocin is used in a wide range of dosages from 1 to 6 mU/min with a maximum dose 20 mU/min.[1] However, the dosage may be much higher in some clinical practices settings. This dosage range may relate to the amount of oxytocin receptors or to their sensitivity, both of which increase during pregnancy.

Oxytocin administered to the mother has potential effects on the fetus. Hyperstimulation of uterine contractions by oxytocin without adequate uterine relaxation can reduce uterine blood and delivery of oxygen to the fetus. This effect could lead to fetal hypoxia, which should obviously be avoided during oxytocin administration. Therefore, oxytocin usage during pregnancy has risks. Additionally, a recent study demonstrated an association between oxytocin administration prior to birth and autism in the child.[2] In summary, although oxytocin is primarily used during labor and immediately after delivery, questions about the safety of exposure to oxytocin for the fetus and newborn remain unresolved.

It remains uncertain whether oxytocin that crosses the placenta has a direct negative effect on the fetus and newborn. The objective of this study was to address the potential for modeling to add to our information about oxytocin use and placental transfer.

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METHODS

A PubMed literature search was conducted for oxytocin pharmacokinetics (PK), pharmacodynamics (PD), oxytocin placenta transfer, and any negative effects of oxytocin on the fetus and newborn. The previously published information on oxytocin concentrations were incorporated into a physiologically-based pharmacokinetic (PBPK) model. The modeling techniques using physiologically-based PK (PBPK) in pregnancy and for the fetus are described in detail in previous works by the author.[3, 4]

RESULTS

Pharmacokinetics-pharmacodynamics of oxytocin

Pharmacokinetics: Oxytocin is a 9 amino acid, peptide hormone with molecular weight 1007.2 Da, most commonly used by intravascular infusion and intramuscular injection in pregnancy. The metabolism of oxytocin is via oxytocinase in plasma with a circulating half-life of oxytocin of 1-6 minutes.[5] A small amount of oxytocin is eliminated via the kidney.[5] Oxytocin distributes throughout extracellular fluid, and only a small amount oxytocin is distributed to the fetus.[6] In the Leake et al study, the oxytocin metabolic clearance rate was 25.4 ml/kg/min in pregnant women, which was similar in men, non-pregnant women and the fetus.[7, 8]

Pharmacodynamics: Since oxytocin promotes uterine contraction, the most direct PD measure of oxytocin effect during pregnancy is uterine contraction frequency and force. Perales et al[9] studied the relationship between oxytocin dose and uterine activity in both a continuous infusion group and in an intermittent infusion group with one minute infusions every five minutes. The dose was doubled every 20 minutes to a maximum of 32 mU/min. The study included 140 pregnant women who were consecutively allocated to the study groups who were treated with oxytocin dosages from 1 mU/min to 32 mU/min. A satisfactory response to oxytocin represented three effective contractions in 10 minutes. The percentage of patients showing a favorable response increased with increasing dosages of oxytocin. The mean doses to achieve a satisfactory response were 7.16 mU/min and 17.65 mU /pulse for continuous infusion group and pulsed infusion group, respectively. The effective dose for 50% (ED50) to achieve a satisfactory response were 5.86 and 2.24 mU/min for continuous and pulsed dose groups respectively. The continuous infusion group achieved a good response in less time, and the pulse group required less oxytocin to achieve a satisfactory response. In contrast, Otsuki et al found no significant relationship between plasma oxytocin concentration and uterine contraction during normal spontaneous labor.[10] The concentration of oxytocin during uterine contraction periods was 12.1 µU/ml vs. 11.5 µU/ml during uterine relaxation periods in the Otsuki study.[10]

Placental transfer of oxytocin

Two publications reported results regarding oxytocin placental transfer. Malek et al. conducted an ex vivo human placental perfusion experiment in which oxytocin was added into a closed perfusion system.[6] The investigators studied both maternal to fetal and fetal to maternal directions of drug transfer. They used the following equation to describe the placenta transfer permeability:

$$P * S = \frac{[FR]_{120} - [FR]_{60}}{[MR]_{60}} * \frac{maternal\ perfusate\ vol}{60\ min * cotyledon\ wet\ weight}$$

In the equation, $[FR]_{120}$ and $[FR]_{60}$ represent the concentration in the fetal reservoir at 120 and 60 minutes, and $[MR]_{60}$ represents the concentration in the maternal reservoir at 60 minutes.

The results demonstrated that oxytocin was transferred in both maternal to fetal and fetal to maternal directions. The transfer from the maternal to fetal reservoirs occurred primarily in the first 15-20 minutes and then declined with a linear decrease of concentrations until 75 minutes. Since the ex vivo placenta transfer study may have risk of deterioration of placental tissue with edema that can reduce membrane passage of drugs, the model stability in this period is very important. The fetal concentration of oxytocin was about 13% of the maternal concentration at the end of the experiment. The fetal to maternal transfer of oxytocin was observed in the first 20 minutes. The rate of oxytocin transfer from the fetus to the maternal side was less than the rate of maternal to fetus transfer. About 10% of the maternal concentration of oxytocin was transported to the fetus. The investigators concluded that oxytocin crosses the placenta from both the maternal to the fetal compartment and from the fetal to maternal direction by simple diffusion even though oxytocin is a large molecule.

In contrast to the ex vivo study, clinical studies have suggested the opposite results. Patient et al. studied maternal and fetal plasma concentrations of oxytocin during labor by measuring umbilical vein and artery separately.[11] The results showed that a maternal oxytocin infusion did not influence the oxytocin concentration in the umbilical artery, the umbilical venous concentration, and the artery-vein ratio of oxytocin. The concentrations of oxytocin in the umbilical artery were 14.8 pmol/L for the group receiving oxytocin infusions vs 17.7 pmol/L for the groups receiving no oxytocin infusion. The difference was not statistically significant. The concentrations of oxytocin in the umbilical vein were 7.8 pmol/L vs 7.3 pmol/L for the no oxytocin infusion group and the group with an oxytocin infusion, respectively, which was also not statistically significant. However, the study showed an important phenomenon in that the fetus was making more oxytocin than it was receiving from the mother.

Ex vivo model of oxytocin placenta transfer

Since oxytocin clinical data are limited, modeling is possibly a better way to investigate the oxytocin exposure in the mother and fetus. An ex vivo PBPK model was built in MoBi® for oxytocin placenta transfer to quantify the oxytocin transfer for physiological maternal level at multiple therapeutic levels. The model of placental ex vivo transfers demonstrated that the placenta transfers oxytocin. The ex vivo PBPK model was used first to determine the permeability of oxytocin for placental transfer. This study demonstrated that the placenta transfer of oxytocin can be successfully described in high dose range (Figure 1). Multiple therapeutic oxytocin levels were then applied to the model. Fetal oxytocin levels associated with different maternal levels are listed in Table 1. Placental oxytocin transfer increases with increasing maternal oxytocin concentrations within the range studied. In fact, the oxytocin transfer is more likely a transporter mediated transfer, which is not saturated at those concentration.

As mentioned above, placenta transfer of oxytocin can potentially cause negative effects on the child. According to the study by Gottlieb et al,[12] the oxytocin concentration which reaches fetal circulation can cause the oxytocin receptor to be desensitized as described by the following equation:

$$\frac{D}{C(override)} = T$$

Where D is the desensitization constant of 1.8E6 (pg/min)/ml; C(override) is the oxytocin override concentration; T is the time to reach desensitization. The maternal oxytocin level and fetal oxytocin receptor desensitization can then be combined by the results of the placenta transfer model and desensitization process (Table 1).

DISCUSSION

Oxytocin is an important drug for use in pregnancy. While oxytocin has a long history of clinical use, some unresolved issues need to be investigated. One of these issues is the maternal/fetal placental transfer of oxytocin and its effects on the health and safety of the fetus. The current study combined the placental ex vivo model and

oxytocin receptor desensitization to investigate the placental transfer of oxytocin and the potential negative effects on the fetus. Our results suggested that high dose oxytocin can be transferred through the placenta to the fetus while a low dose or physiological level cannot be transferred. Oxytocinase plays an important role in oxytocin placental transfer. The enzyme, which is found in the placenta, can rapidly metabolize oxytocin. As shown in prior clinical studies, oxytocin did not demonstrate placental transfer during delivery without infusion of oxytocin even at low doses of oxytocin. However, high dose oxytocin can saturate the metabolizing enzyme and lead to the placental transfer of oxytocin. Thus, an ex vivo model was built for high dose oxytocin placental transfer. Since a high dose is frequently used in the clinical setting, it is important to quantify the placental transfer of oxytocin and evaluate its potential negative effect on the fetus.

Table 1: Maternal oxytocin level, fetal oxytocin level and fetal oxytocin receptor desensitization

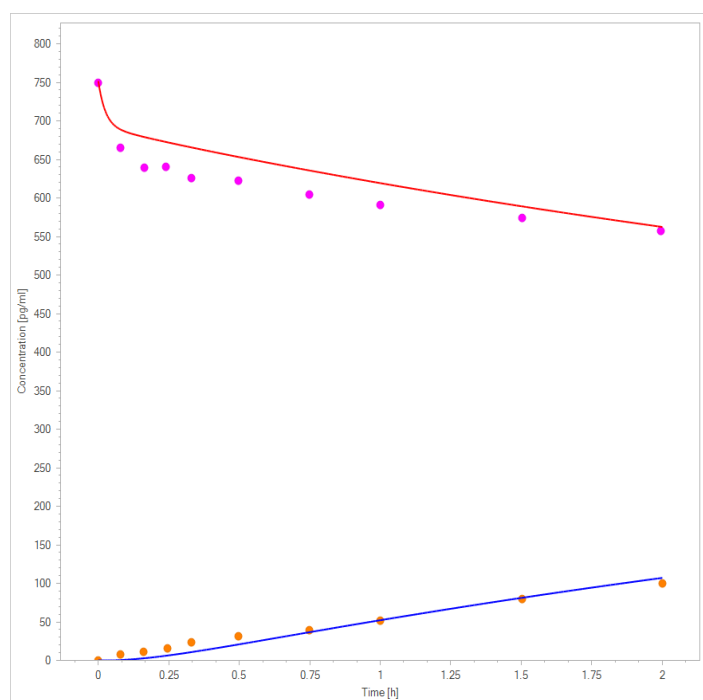| Maternal oxytocin dose (mU/min)	Maternal oxytocin level (pg/ml)	Fetal oxytocin level (pg/ml)	Fetal oxytocin receptor desensitization (days)
0	40	73	17
10	105.4	100.3	12
20	170.8	117.3	10
30	236.3	134.3	9
40	301.7	151.2	8

Figure 1: Placenta transfer of oxytocin in *ex vivo* model (from Malek data[6]).

These results demonstrated that the oxytocin receptor desensitization time was shorter when the fetal oxytocin level is higher and within the time range that occurs in the clinical setting. Although the oxytocin recommended maximum dose is 20 mU/min, the reported maximum doses in clinical practice were much higher than this range. When the higher maternal oxytocin concentration saturates oxytocinase, the fetal oxytocin level starts to rise. Although the increased fetal oxytocin level is not dramatically high, the influence on newborns is significant since newborns do not have oxytocinase until after about 2 weeks of age. Thus, the maternal oxytocin dosage commonly used, maternal oxytocin level, fetal oxytocin level and oxytocin receptor desensitization time were calculated in Table 1. The results

demonstrated that a high dose of oxytocin shortens the time of oxytocin receptor desensitization to less than 2 weeks, when the oxytonase is not fully developed by newborns. This may cause desensitization of the oxytocin receptor in newborns and furthermore could cause developmental changes that lead to autism. Thus, clinical monitoring of oxytocin levels during high dose administration or for prolonged infusion could be important to avoid oxytocin receptor desensitization, maternal fetal transfer of oxytocin and any potential risk of adverse effects in the fetus and developing child. Since Gregory et al demonstrated that there was a correlation between the development of autism in children and oxytocin receptor desensitization, the current model supports the potential for the adverse effect.[2]

The long-term effects of oxytocin on the association with autism in children remains controversial. Fein et al. studied over 600 preschool children with autism, including both high-functioning and low-functioning autistic children, and their results did not support an association between oxytocin administration during delivery and autism.[13] However, a more recent study by Gregory et al.[2] of more than 5,500 children with autism found that oxytocin use during delivery was associated with an increased odds of the child developing autism. This study concluded that oxytocin use increased the chance of the child having autism by 23%.

Oxytocin-induced uterine contraction can be too intense or sustained to allow fetal blood flow and oxygen delivery to the fetus between contractions and is termed, hypercontraction. If sustained, this can cause fetal hypoxemia and an abnormal fetal heart rate which have been demonstrated in several studies. Liston et al.[14] studied 658 deliveries and their results demonstrated that patients receiving an oxytocin infusion had more fetal distress, low Apgar scores at five minutes and more special nursery admissions. However, two other studies demonstrated that oxytocin did not affect the Apgar scores of newborns.[15, 16]

There are limitations with the oxytocin model, and the current model did not include the oxytocin endogenization process. Oxytocin is a biologically generated substance, which requires systemic modeling to be built in to incorporate the endogenic process in the model of the oxytocin infusion to the mother, which increases the complexity of the model. Future PBPK models can incorporate these physiological aspects of oxytocin disposition.

CONCLUSION

Oxytocin is a commonly used drug during delivery. The study of the PK/PD of this hormone is important to help dosing decisions for maternal and fetal health. The lack of clear information regarding dosing and fetal oxytocin concentrations is due to the complexity of the drug and physiological situation during the pregnancy. PBPK modeling is a powerful tool to study drug PK and PD in the human body. The current study used PBPK modeling to identify the placental transfer of oxytocin and its subsequent potential for adverse effects on the fetus and developing child. The American College of Obstetricians and Gynecologists clearly states that the benefits of labor induction must be weighed against the potential maternal and fetal risks associated with this procedure.[17] These observations emphasize the importance of the clinical monitoring of oxytocin use, and the need for additional quantitative information for oxytocin clinical use and its effects on fetal safety. Modeling and simulation, such as the use of PBPK, should have a positive impact on our knowledge of drug safety in pregnant people and fetuses in the future.

Disclosures

The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Ethical Approval and Informed Consent

The author asserts that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. Given the nature of this study, informed consent was not required.

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