# Pharmacokinetics of Oxycodone in Labouring Women With Preliminary Estimates of Fetal Exposure

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## Objectives

To investigate the pharmacokinetics of oxycodone in labouring women and to preliminary quantify the neonatal exposure to oxycodone following maternal administration.

## Methods

Fifteen women were included in the study. The participants were previously healthy and their pregnancies were normal. The women received an initial intravenous dose of 780 µg of free oxycodone base and the dose was repeated as necessary in five minute intervals (up to a maximum of 3.9 mg). Venous blood samples were taken 5 minutes after each oxycodone administration, at 10, 30, 60 minutes after the last oxycodone dose, and after that at every 60 minutes until birth. The umbilical cord was clamped at delivery, and venous and arterial blood samples were drawn. The samples were analyzed with a highly sensitive LC-MS/MS method [2].

A total of 171 venous plasma samples from mothers, 15 arterial and 14 venous umbilical cord samples were above limit of quantitation. The pharmacokinetics of oxycodone in mother was characterized by a two-compartment model. In addition, umbilical vena, the fetus, and umbilical artery were implemented as separate compartments (Figure 1). The volumes of distribution in Vena and Artery compartments were set to 0.1 L, and the volume of distribution in Fetus compartment was set to $V_{ss,mother}$*3.5/$WT_{mother}$. Otherwise the parameters were estimated.

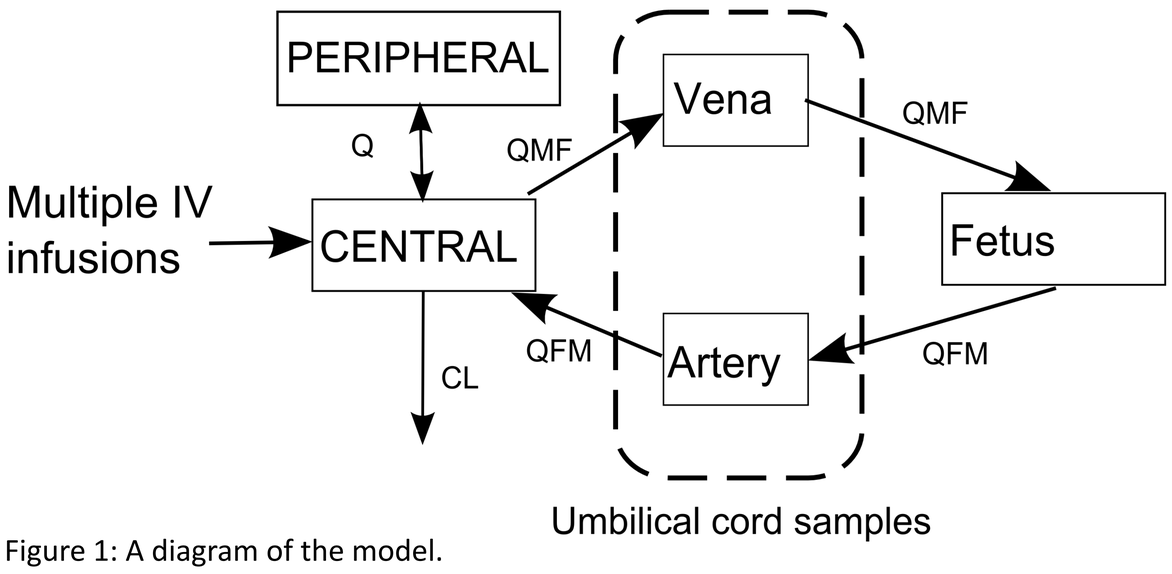


Figure 1: A diagram of the model.

**Table 1: Final parameter estimates of the model**

| Parameter | Estimate (relative standard error) | Nonparametric confidence interval (bootstrap) |
|---|---|---|
| Clearance (L/min) | 0.84 (8.0 %) | 0.68-0.97 |
| BSV(Clearance) | 27 % (72 %) | 12-49 % |
| Central Vd (L) | 79 (9.6 %) | 64-99 |
| BSV(central Vd) | 28 % (37 %) | 14-37 % |
| Peripheral Vd (L) | 88 (6.1 %) | 75-98 |
| Inter-compartmental clearance (L/min) | 2.9 (20 %) | 1.7-4.3 |
| Residual error (mother) | 12 % (7.7 %) | 9.9-15 % |
| QMF (L/h) | 0.051 (14% ) | 0.033-0.10 |
| QFM (L/h) | 0.053 (12 %) | 0.042-0.11 |
| Residual error (umbilical cord) | 32 % (13 %) | 16-38 % |

The inter-compartmental clearances from mother to fetus (QMF) and from fetus to mother (QFM) were similar to each other. This means that the model would predict similar steadystate-concentrations for mother and fetus if continuous infusion was used. The figures below present some preliminary predictions about the relationship between maternal and fetal oxycodone consentrations.

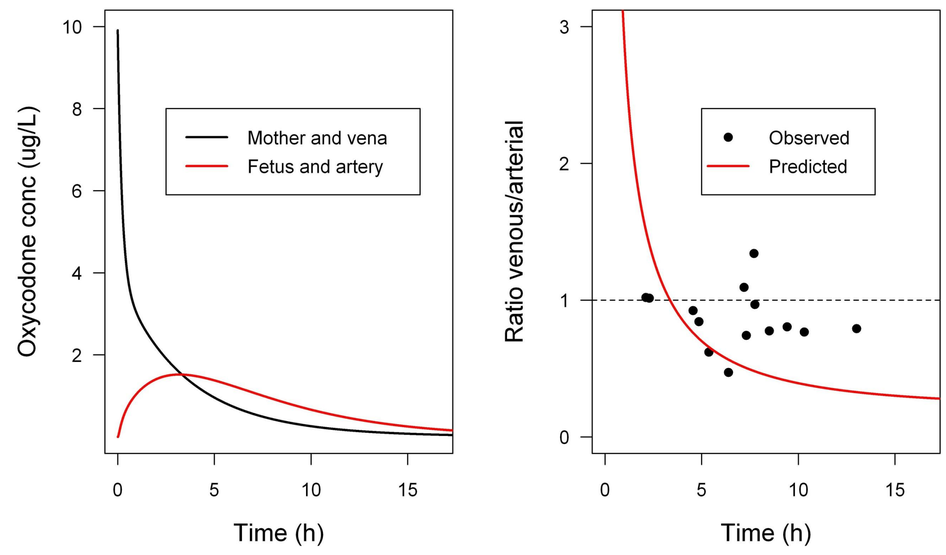


Figure 2: Left: Simulated umbilical cord artery and vena concentrations.
Right: The observed and predicted umbilical cord venous-to-arterial concentration ratios.

## Results

The venous umbilical cord concentrations were very similar to maternal plasma concentrations of oxycodone. The clearance of oxycodone was 0.84 L/min/$(70kg)^{0.75}$. The central and peripheral volumes of distribution were 79 and 88 L/70kg, respectively. The inter-compartmental clearance was 2.9 L/min /$(70kg)^{0.75}$. Further results are presented in Table 1.

## Conclusions

The pharmacokinetics of oxycodone in labouring women was similar to that in healthy volunteers [3]. Oxycodone permeates the placenta and distributes into the neonate. Since the number of subjects in this study was small, these results should be considered preliminary.

## References

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# Appendix: Rationale for the current model of umbilical cord pharmacokinetics

**Examples of previous models of umbilical cord pharmacokinetics**

A model of amoxicillin PK [4] has combined the venous and arterial umbilical cord concentrations into a single compartment. The study also included PK samples from the neonate.

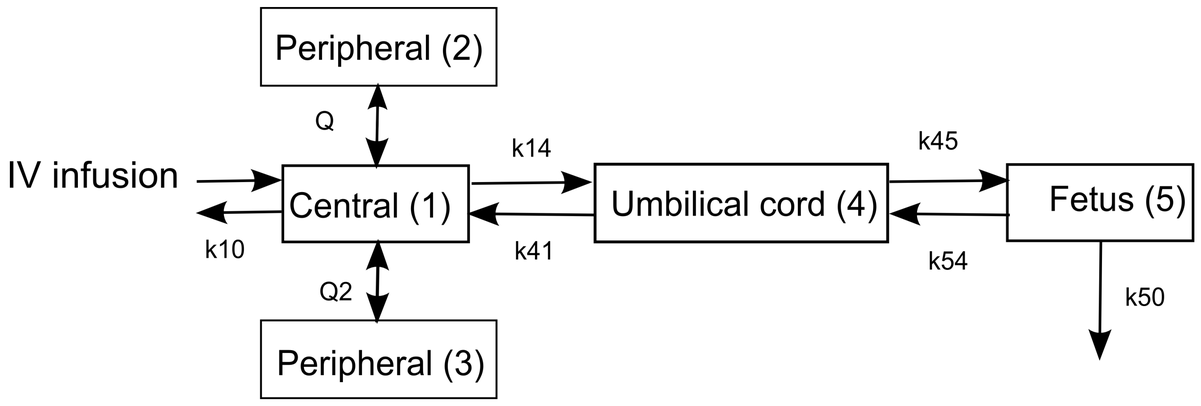


Figure 3: A diagram of the model of amoxicillin pharmacokinetics

A different modeling approach has been used to describe the maternal and umbilical cord concentrations of various HIV treatment drugs [5,6,7,8]. The umbilical cord samples in these studies did not differentiate between venous and arterial blood. The umbilical cord concentrations were included as an effect compartment, i.e. a compartment which is dependent on the maternal drug concentrations but does not affect these concentrations.

**Anatomy and physiology of fetal circulation**

The maternal and fetal blood are not mixed during pregnancy. Oxygen, nutrients and waste products are carried from from fetus to mother and from mother to fetus across placenta by both diffusion and active transport. Figure 4 presents a diagram of placental blood diffusion.

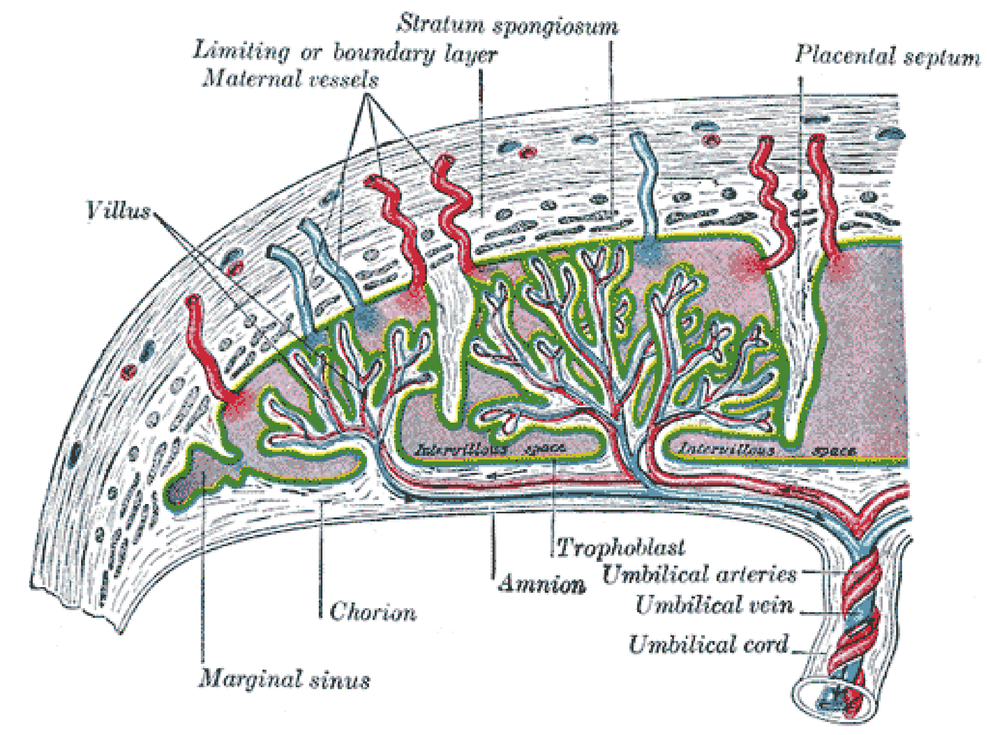


Figure 4: A scheme of placental circulation. From Gray's Anatomy of the Human Body, 20th edition (1918). Taken from Wikimedia Commons in 16th May, 2011. URL: http://commons.wikimedia.org/wiki/File:Gray39.png

With that knowledge, a mechanistic model of maternal, umbilical cord and fetal pharmacokinetics might be constructed in the manner of Figure 5.

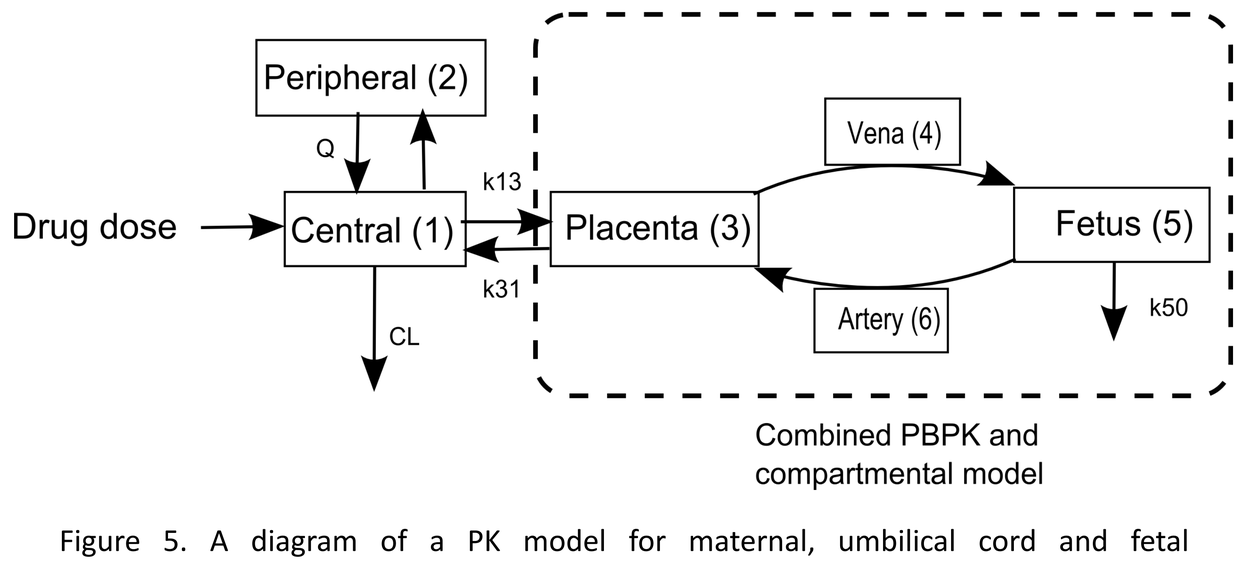


Figure 5. A diagram of a PK model for maternal, umbilical cord and fetal pharmacokinetics in ideal settings.

When using this approach, the blood flow rate in umbilical cord might be incorporated as prior knowledge.

**Assumptions in the current maternal and umbilical cord PK model**

The model assumes a rapid diffusion of oxycodone from mother to venous umbilical cord. Similarly, arterial umbilical cord concentrations of oxycodone are assumed to be almost identical to fetal concentrations. The reason for this is that inter-compartmental clearances from mother to fetus and vice versa are used, and the volume of distribution of venous and arterial compartments was set to 0.1 L. In the raw data, maternal concentrations and venous umbilical cord concentrations correlated very well. Thus, the assumption seems to hold for these data.

This model also did not estimate fetal elimination rate for oxycodone. The rationale for this was that no post-partum PK samples were taken from the child. Because the ratio of venous versus arterial umbilical cord concentrations was close to one, the fetal elimination was likely not a major influence in time-concentration profiles.

Under these assumptions, it seems that the parameterization used in this model was adequate for these data. However, the same model could be inappropriate for some other drug.


**References:**

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