Placental transfer of fentanyl in early human pregnancy

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To investigate the transfer of fentanyl across the early human placenta, we have collected samples of maternal blood and fetal fluids and/or blood, simultaneously, between 5 and 22 min following an intravenous bolus of fentanyl (1.5 µg/kg) to the mother. The pregnancies were between 6 and 16 weeks of gestation and scheduled for elective termination of pregnancy under general anaesthesia. Total fentanyl concentration was determined by radioimmunoassay in 11 pairs of first trimester maternal serum and fetal coelomic fluid samples, 14 pairs of maternal serum and amniotic fluid samples, seven series of first trimester maternal serum and coelomic and amniotic fluid samples, and 10 series of early second trimester maternal and fetal sera and amniotic fluid samples. Fentanyl was not detected in coelomic fluid samples at any gestational age and in amniotic fluid samples collected after 12 weeks of gestation. Measurable concentrations of fentanyl were found in maternal serum collected within 15 min after the initial bolus and in fetal serum collected between 10 and 12 min later. These findings indicate that fentanyl is transferred across the early placenta into the amniotic cavity and fetal blood circulation but not into the exocoelomic cavity. The distribution of this molecule inside the early gestational sac is probably influenced by the increased binding by maternal and fetal sera, its short half-life of distribution and the specific biology of the fetal fluid formation and composition.

Key words: amniotic fluid/coelomic fluid/fentanyl/fetus/placenta

Introduction

Fentanyl, a synthetic opioid analgesic without active metabolites has been widely used in obstetric practice to provide analgesia in labour and during Caesarean section (Hull, 1985; Reynolds and Knott, 1989). It provides rapid onset, cardiovascular stability and has a short half-life. When administered to pregnant women at term, fentanyl has little effect on neonatal outcome (Justins et al., 1982; Paech et al., 1990; Desprats et al., 1991; Roseag et al., 1992). It is also used in women undergoing surgery during the first half of pregnancy. The fetal–maternal pharmacokinetics and placental passage of anaesthetic drugs has been studied at term but not early in human pregnancy.

During the first trimester of human pregnancy, fetal blood cannot be obtained in sufficient quantities to allow biochemical investigation. At this stage, the fetus is surrounded by two fluid cavities: the amniotic cavity which occupies the space between the fetal skin and the amniotic membrane; and the exocoelomic or chorionic cavity which lies between the amniotic membrane and the fetal plate of the placenta. Fluid from these cavities can be selectively aspirated and we have shown that inulin diffuses in both cavities whereas diazepam is preferentially transferred to the amniotic cavity (Jauniaux et al., 1996, 1997). From 12 weeks of gestation, pure fetal blood can be obtained by intracardiac puncture. In this study, we have studied the capacity of fentanyl to penetrate the early gestational sac cavities and the fetal circulation at 12–16 weeks following a single bolus dose.

Materials and methods

Forty-two healthy women, with apparently normal and uncomplicated pregnancies between 6 and 16 weeks and requesting elective surgical termination under general anaesthesia for psychological reasons, were recruited for this study. Written consent was obtained from each woman after receiving complete information on the procedure. All women consented to sampling of peripheral venous blood and fetal fluids or blood during the surgical procedure. The study was approved by the University College London Hospitals Committee on the Ethics of Human Research.

Gestational age of the pregnancy was determined from the date of the last menstrual period and confirmed by ultrasound measurements of crown–rump length between 6 and 13 weeks and biparietal diameter after 13 weeks. In each case, a detailed transvaginal ultrasound was performed to exclude a fetal anatomical defect. Peripheral maternal venous blood, fluid samples from the exocoelomic and amniotic cavities of first trimester pregnancies and fetal intracardiac blood and amniotic fluid from pregnancies between 12 and 16 weeks were obtained during the surgical procedure. The samples were collected between 5 and 22 min following the i.v. administration of a standardized bolus of 1.5 µg/kg of fentanyl to the mother. Propofol and nitrous oxide were used for induction and maintenance of anaesthesia, respectively.

Coelomic fluid was first aspirated using a 20-gauge needle introduced transvaginally into the exocoelomic cavity under continuous ultrasound guidance. Within 10 s, another needle of the same size was inserted into the amniotic cavity and the corresponding fluid
interassay coefficients of variation were calculated for both assays (Table II). No amniotic fluid was aspirated before 8 weeks and no coelomic fluid could be aspirated after 11 weeks for anatomical reasons. Matched samples of fetal blood and amniotic fluid were also collected in 10 pregnancies between 12 and 16 weeks of gestation.

Fentanyl was detected in 23 of the 42 maternal serum samples and in 15 of the 25 amniotic fluid samples using the Janssen-Biotech assay. Fentanyl concentrations in matched samples of maternal serum and amniotic fluid obtained before 13 weeks are displayed in Table I. No fentanyl was found in 10 coelomic fluid samples using both assays (Table II). Using the Janssen-Biotech assay, fentanyl was detected in four of the 10 fetal serum samples obtained between 12 and 16 weeks of gestation (Table III). Fentanyl was not detectable in fetal serum when the interval between injection and sampling was longer than 12 min, and in amniotic fluid samples collected later than 12 weeks and 6 days of gestation.

Discussion

The present data show that fentanyl is rapidly transferred by the human early placenta and can be detected in the amniotic cavity and fetal blood circulation, but not in the exocoelomic cavity. Fentanyl is a lipid-soluble molecule with a large volume of distribution and an α elimination half-life of 4 min (Hull, 1985; Reynolds and Knott, 1989). It is bound principally (80–90%) with high affinity to α1-acid glycoprotein, which has a lower binding capacity than albumin. At term, in humans, the fetal extraction ratio of fentanyl is about 50% and a large difference between arterial and venous cord blood concentrations suggests that it is rapidly metabolized by the fetal liver and/or that it accumulates in other tissues (Paech et al., 1990; Desprats et al., 1991). Early in pregnancy, the immaturity of the liver function suggests that tissue accumulation, in particular in the placenta, is the main factor limiting the redistribution of protein-bound molecules to other fetal compartments.
We have recently suggested that the study of drug transfer in the first trimester of human pregnancy is feasible using samples obtained from the exocoelomic cavity (Jauniaux et al., 1997). Diazepam is a lipophilic and undissociated molecule with a low molecular weight of about 280 Da, which has 95% binding to albumin and easily crosses biological membranes via water-filled extracellular channels or directly through the cells, as is the case for the trophoblastic barrier (Kanto, 1982).

Our previous data suggested that diazepam enters the first trimester amniotic cavity mainly via the fetal circulation and subsequently through the fetal skin (Jauniaux et al., 1996). The variable presence of diazepam inside the coelomic cavity may reflect chronic accumulation in benzodiazepine users. This hypothesis is supported by the fact that fentanyl, which has similar characteristics, was not detectable in any coelomic fluid samples whereas like diazepam it was detected in about half of the amniotic fluid samples. In contrast, inulin, which is a hydrophilic molecule with no specific transport systems and not metabolized by human tissue, freely diffuses across the placenta to the exocoelomic cavity and subsequently to the amniotic cavity (Jauniaux et al., 1997).

Using a chronic maternal–fetal sheep model, Craft et al. (1983) have demonstrated that fentanyl is detectable in fetal blood after 1 min and peaks at 5 min. After equilibrium, maternal concentrations remain high and both maternal and fetal serum concentrations decline in parallel. Fentanyl concentrations were not measured in amniotic fluid at any gestational age. In the sheep model the gestational age of the fetus was comparatively greater than in our study, which may explain the more rapid decline in fetal fentanyl concentrations in the sheep. Fentanyl was found in detectable concentration in most (18 of 25) maternal serum samples collected between 5 and 15 min after the i.v. bolus but was found in only four fetal serum samples obtained between 10 and 12 min after administration to the mother using the Janssen-Biotech assay, whereas detectable concentrations were measured in the 10 maternal serum samples assayed using the Diagnostic Products Corporation system, which has a lower detection limit in serum. Variations in maximum peak concentration and fetal:maternal ratio at different gestational ages may be affected by changes in uterine blood flow, which increases sharply inside the uteroplacental circulation after 12 weeks (Jauniaux et al., 1995). Furthermore, variation in equilibrium ratio may be due to differences in serum protein concentration and/or pH gradient across the placenta (Hull, 1985; Reynolds and Knott, 1989).

Protein-bound molecules such as fentanyl or diazepam are more likely to accumulate in first trimester fetal circulation and tissues and only subsequently in the amniotic cavity, by diffusion through the fetal skin. Although we found that protein concentrations are higher in coelomic fluid than in amniotic fluid (Jauniaux et al., 1993), the very slow formation and turnover of the coelomic fluid may explain why fentanyl did not accumulate in the corresponding cavity within our maximum sampling time. Other biological characteristics of coelomic fluid may influence the pharmacokinetics of the drug and in particular, the lower pH (7.18) compared with that of maternal peripheral venous blood or fetal blood may influence the distribution of basic drugs such as fentanyl. After 12 weeks of gestation, the amniotic fluid pH drops from 7.45 to 7.23 within a week (Jauniaux et al., 1994; Gulbis et al., 1996). This phenomenon may be offset by a dilution effect due to increased urine production by the metanephros of the definitive kidney and the normal urine acidity (Gulbis et al., 1996). This may explain why fentanyl was not detectable in the amniotic fluid samples collected after 12 weeks using both assays. These findings also suggest that the fetus will not be chronically exposed on swallowing amniotic fluid if propofol is administered during pregnancy.

This study shows that placental transfer of anesthetic drugs can be studied during the first half of pregnancy by sampling the fetal fluid cavities and circulation. We have shown that fentanyl is detectable in amniotic fluid as early as 8 weeks and in fetal blood from 12 weeks of gestation. This indicates that fentanyl enters the early fetus, although the fate of the drug is largely unknown at that gestational age. The pharmacokinetics of fentanyl in the fetus during the first trimester remains unknown, but it does not appear to be freely diffusible, as it is not detected in the coelomic fluid. Further comparison with other human data is difficult as previous studies have investigated maternal and umbilical cord fentanyl concentrations after epidural injection at term. A larger study is needed to establish and compare the pharmacokinetics of commonly administered opiates for maternal procedures at early gestational age using this model.

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