Placental transfer of fentanyl in early human pregnancy and its detection in fetal brain

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We have investigated the transfer of fentanyl across the early human placenta in 38 women (8–14 weeks’ gestation) undergoing termination of pregnancy. After administration of a bolus dose of fentanyl 2 µg kg⁻¹ at induction of anaesthesia, maternal blood (n=38), placenta (n=38), amniotic fluid (n=38) and fetal brain (n=7) samples were collected and assayed for fentanyl by radioimmunoassay. Fentanyl was detected in all placental and fetal brain samples but not in amniotic fluid. There was a rapid decrease in fentanyl concentrations in maternal serum after the bolus but placental concentrations had not started to decline 30 min later. There was no difference in placental drug concentrations at different gestational ages. These data suggest that there is rapid transfer of fentanyl to the fetus in early pregnancy and that the drug remains in fetal tissue for some time after the initial dose is given to the mother.

Fentanyl is used widely in patients undergoing general anaesthesia, including women having a variety of surgical procedures throughout pregnancy. Knowledge of the pharmacokinetics of drug transfer from mother to fetus in early pregnancy is important as this is the time of organogenesis, when most side effects from drugs are likely to occur. It is also relevant in relation to the ability of the fetus to detect nociceptive stimuli.1 Most studies on placental drug transfer are carried out at term using umbilical arterial and venous sampling, mainly at the time of Caesarean section.2 However, these results cannot be extrapolated to early pregnancy because of the anatomical and pharmacological differences in the placenta. Animal models such as sheep can be used, but there are important anatomical differences from the human placenta, in terms of the thickness of the membrane and direction of maternal and fetal blood flow.3 In early pregnancy, measurement of fetal drug concentrations is more difficult, but one method is to study women undergoing termination of pregnancy. We have studied materno-fetal transfer of fentanyl by sampling maternal serum, amniotic fluid, placental tissue and fetal brain in women undergoing surgical termination of pregnancy in the first and early second trimesters.

Methods and results

The study was approved by the UCLH Ethics Committee and participants gave written informed consent. The women were undergoing surgical termination of pregnancy for psychosocial reasons, at 8–14 (median 12.3 ) weeks’ gestation. Gestational age was confirmed by trans-abdominal ultrasonographic measurement of crown–rump length or biparietal diameter.

General anaesthesia was induced with fentanyl 2 µg kg⁻¹ and propofol 2.0–3.5 mg kg⁻¹, and maintained with 0.5–2% isoflurane and 70% nitrous oxide in oxygen, with the subject breathing spontaneously via a laryngeal mask. Subjects were allocated randomly to have an amniotic fluid and maternal blood sample taken at 5, 10, 15 or 20 min after administration of an i.v. bolus dose of fentanyl. One sample of amniotic fluid and one maternal blood sample were obtained from each subject. Amniotic fluid was aspirated trans-abdominally using a 22-gauge needle under ultrasound guidance. Maternal blood (10 ml) was obtained from an antecubital vein simultaneously. After the surgical procedure, which was performed between 10 and 30 min after administration of fentanyl to the mother, fetal brain
and placental samples were separated using the dissecting microscope and stored at –20°C.

Concentrations of fentanyl and its metabolites were measured by solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA). The detection limit of the assay was 0.1 ng ml\(^{-1}\) and intra- and inter-assay coefficients of variation were <7%. Data were analysed using a biomedical processing statistical package (Statgraphics, Manugistics, Rockville, USA).

We studied 38 women. Placental tissue, amniotic fluid and maternal blood were sampled in all subjects. Only seven samples of fetal brain were collected as additional consent from the subject was required, and was not obtained in the other 31 women.

Fentanyl was not detected in any of the amniotic fluid samples (<0.1 ng ml\(^{-1}\)), but was present in all 38 placental and seven brain samples. Median maternal and placental fentanyl concentrations after the i.v. bolus dose of fentanyl to the women (for all gestational ages) are shown in Figure 1. Whereas maternal serum concentrations followed an exponential decline, there was no significant change in placental fentanyl concentration over time (Kruskal–Wallis test, \(P=0.45\)). There was no significant difference in fentanyl concentrations at different gestational ages when samples from women <12 weeks’ gestation were compared with those >12 weeks’ gestation (Kruskal–Wallis test, \(P=0.24\)).

Median fentanyl concentration in fetal brain was 1.5 ng g\(^{-1}\) of tissue compared with 4.5 ng g\(^{-1}\) in the placental tissue samples from the same seven subjects. This difference was not significant (Mann–Whitney rank test, \(P=0.16\)).

**Comment**

The trophoblast acts like a lipid membrane, across which lipid-soluble drugs with a low molecular weight (such as fentanyl) move easily by passive diffusion. We have confirmed that there is rapid transfer of fentanyl to the placenta and to fetal brain. However, there was no difference in the concentration of drug found in the placenta at different gestational ages. This is surprising as there is a sharp increase in uterine blood flow after 12 weeks’ gestation\(^4\) which might increase transplacental passage of the drug, especially as the transfer rate of lipid-soluble substances is flow-dependent, so maternal and fetal placental flow are potentially important determinants of equilibration rate.

There was no significant change in placental fentanyl concentration over time, even 30 min after the maternal bolus dose had been given. This is not unexpected as although a lipid-soluble drug may approach equilibrium across the placental membrane in a single circuit, it takes time to saturate fetal tissues. Although concentrations of pethidine in maternal and umbilical venous plasma may start to decrease within a short time after i.m. injection, Tomson and colleagues\(^5\) showed that pethidine accumulated in the fetus for 3–4 h after administration of an i.m. dose to the mother. Unfortunately, only seven fetal brain samples were available for analysis in this study and therefore it is not possible to determine how fetal brain fentanyl concentrations might change over time. There were also large inter-individual variations in both placental and brain drug concentrations.

The difference in fentanyl concentrations in placenta and fetal brain was not significant, although this may reflect the small number of fetal brain samples: it is also difficult to compare concentrations in different tissues directly. Fetal brain and placental tissue fentanyl concentrations were measured per gram of tissue and so direct comparisons of maternal serum drug concentrations with those in placental tissue and fetal brain were not possible.

Our failure to detect fentanyl in amniotic fluid might be explained by the observation that in the first trimester, protein-bound molecules pass into this cavity by diffusion through fetal skin and so might not be detected for a considerable time.\(^6\)

In summary, we showed that fentanyl rapidly crossed the placenta and entered the fetal brain in the first and early second trimesters. Over the time period studied (10–30 min

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Fig 1 Maternal serum and placental fentanyl concentrations for all gestational ages, sampled at different times after administration of a bolus dose of fentanyl 2 µg kg\(^{-1}\) to the mother (median (interquartile range)).
after administration of fentanyl) there was no decline in placental or fetal brain concentrations of drug, indicating likely accumulation in the fetus. The degree of placental transfer of the drug did not vary with gestational age of the fetus, between 8 and 14 weeks’ gestation.

References