DRUG TRANSFER IN THE FETALLY-PERFUSED GUINEA-PIG PLACENTA; USE OF AN INDICATOR DILUTION METHOD

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The in-situ fetally-perfused placenta of the guinea-pig has been used to study placental transfer of both substrates such as amino acids (Hill & Young 1973) and xenobiotics such as cadmium (Kelman & Walter 1980). We describe the use of this preparation with an indicator dilution technique to study placental transfer of drugs used in late pregnancy.

The placenta of the guinea-pig, like that of man, is haemochorial. It is however more efficient because of counterflow of fetal and maternal blood in the trophoblastic labyrinth, while the human placenta has pool flow. The dam at full term was anaesthetised with IV pentobarbitone, a foetus delivered by section and later removed, the umbilical vessels cannulated and the placenta perfused with modified tissue culture medium containing albumin and buffered with HCO_3^- and CO_2 to pH 7.40. The physiological state of the mother was continually monitored on a Grass chart recorder; the parameters measured were carotid blood pressure, respiration rate, heart rate and body temperature. Also recorded simultaneously were the perfusion pressure and perfusate pH. A double indicator dilution method was used to measure loss of ^{14}C-drug from the perfused fetal circuit, relative to ^{3}H-sucrose which was used as an extracellular reference and leakage indicator (Yudilevich 1975). The single-pass extraction was estimated from a series of samples of the outflow following injection of a bolus containing the two indicators (extraction = $(1-(^{14}C/^{3}H_{out})/(^{14}C/^{3}H_{in}))$). The change in indicator ratio from the injectate to the outflow due to exit of the drug across the trophoblastic plasma membrane, together with the measured perfusate flow and the inflowing concentration, allowed the flux of drug across the fetal boundary of the trophoblast to be estimated with high reliability.

The reference indicator was recovered to the extent of 90 - 100% in each run indicating that the perfused placenta did not normally leak. The use of a reference material allowed an accurate measure of the bolus recovery in the outflow; it was therefore possible to correct for a slightly leaky placenta. The relation of drug flux to concentration over a 10 - 100 fold concentration range can be studied in repeated runs to search for evidence of mediation. Similar experiments involving possible competitor substances are possible. Interventions affecting the ionic and binding equilibria during a run can be used to establish the role of these properties in determining transport. The method offers the prospects both of describing drug transfer quantitatively and of establishing fundamentals of the transfer process from fetal circulation to trophoblast during a single transit of the fetal exchange surface.

Using this technique, we have examined the first-pass extraction of chlorthalidone in the fetal circulation of the guinea-pig fetally-perfused placenta. At a concentration of 10^{-5} mol.dm^{-3}, the extraction of chlorthalidone was 0.180 $\pm$0.027 (mean $\pm$s.d.). The technique has also been used to examine the placental transport of a series of beta-adrenoceptor antagonists (Day et al 1982).

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