Placental Transfer of Drugs Administered to the Mother

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Summary

Drugs administered to mothers have the potential to cross the placenta and reach the fetus. Under particular circumstances, the comparison of the drug concentration in the maternal and fetal plasma may give an idea of the exposure of the fetus to the maternally administered drugs. In this review drugs are classified according to their type of transfer across the placenta.
Several drugs rapidly cross the placenta and pharmacologically significant concentrations equilibrate in maternal and fetal plasma. Their transfer is termed 'complete'. Other drugs cross the placenta incompletely, and their concentrations are lower in the fetal than in maternal plasma. The majority of drugs fit into 1 of these 2 groups. A limited number of drugs reach greater concentrations in fetal than maternal plasma. It is said that these drugs have an 'exceeding' transfer. The impression prevails that suxamethonium chloride (succinylcholine chloride) and doxorubicin do not cross the placenta. However, a careful analysis of the literature suggests that this impression is wrong and that all drugs cross the placenta, although the extent transfer varies considerably.

The following parameters were considered as possible factors determining the extent of placental transfer: (i) the molecular weight of the drug; (ii) the pKa (pH at which the drug is 50% ionised); and (iii) the extent of drug binding to the plasma protein. Drugs with molecular weights greater than 5000D have an incomplete transfer across the human placenta. Strongly dissociated acid drug molecules should have an incomplete transfer, but this does not seem to be an absolute rule. For example, ampicillin and methicillin transfer completely and they are strongly dissociated at physiological pH. The extent of drug binding to plasma protein does not influence the type of drug transfer across the human placenta.

In order to present large amounts of information in a clear and concise format the description of placental transfer of each group of drugs is followed by a table summarising the following data: the molecular weight of the drug, pKa (the pH at which the drug is 50% ionised), protein binding and type of transfer. The molecular weights given are those of the free base. The molecular weight, pKa and protein binding of drugs were obtained from various standard reference sources.\(^1\)\(^-\)\(^7\)

Among all membrane systems in the body, the placenta is unique. It separates the blood of 2 distinct individuals, the mother and the fetus, and provides for delivery of oxygen and nutrients to the latter. As drugs cross the placenta in the same manner as nutrients, it is inevitable that drugs administered to the mother reach the fetus. A way to avoid the problem of treating the mother and subsequently exposing the fetus to the drug is to use drugs that produce the desired therapeutic effect and cross the placenta poorly. On the other hand, when drugs are administered for the pharmacological benefit of the fetus it is necessary that these drugs reach therapeutic concentrations in the fetus.

The huge pharmacological armamentarium of today provides drugs with different molecular structures, but with overlapping pharmacological properties. For example, ampicillin\(^8\) and methicillin\(^9\) achieve similar concentrations in both the fetal and maternal plasma, whereas several cephalosporins are poorly transferred to the fetus. The aim of this review is to classify drugs according to their type of transfer across the placenta.

From a 'physical' point of view, almost all drugs equilibrate in the fetal and maternal compartments, but in some cases the equilibrium is achieved at insignificant therapeutic concentrations of the drug. In writing this article, we had to bear in mind the proposed benefit of drug treatment. Equilibrium is defined as the simultaneous achievement of therapeutically significant concentrations in the fetal and maternal compartments.

Waddell and Marlowe\(^10\) have postulated the existence of at least 3 types of transfer pharmacokinetics across the placenta. The drugs that equilibrate rapidly in the fetal and maternal compartments fit in the so-called 'type I' class. It is likely that these drugs have a complete transfer profile (see table I). 'Type II' drugs have higher fetal than maternal plasma concentrations, and thus exhibit exceeding transfer. The mechanisms at the basis of this type of transfer are not fully understood. Cer-