Non-Narcotic Analgesics
Use in Pregnancy and Fetal and Perinatal Effects

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Summary

Aspirin and related non-narcotic analgesics such as paracetamol (acetaminophen) are present in almost every 'Western' household and are so commonly used that the public often does not think of them as drugs. Although the toxic effects of overdoses are well recognised by the medical and related professions, the potential adverse effects of repetitive dosing, within the commonly recommended therapeutic range, are not. This is particularly true during pregnancy, where the relative overall general safety of the agents is overshadowed by the possible subtle but potentially pervasive effects on the fetus. Marketing publicity, particularly about recently introduced related agents, has at times failed to take into account these less obvious, but nevertheless potentially lethal, side effects. It is now likely that aspirin and/or paracetamol are used during pregnancy by most women and that the earlier figures are underestimates.

Although animal studies have shown significant effects of non-steroidal anti-inflammatory agents (NSAIDs) on the fetal circulation, particularly on the developing pulmonary circulation, the data on human pregnancy are less convincing. Nevertheless, the possible association of these drugs with prolonged gestation, and an increased incidence of the syndrome of persistent pulmonary hypertension of the newborn and of intracranial haemorrhage, demand that prudence be exercised when using these drugs during pregnancy. At the very least, more conclusive evidence is necessary that fetal and neonatal complications are not increased.

1. Acidic Non-Steroidal Anti-Inflammatory Analgesics (NSAIDs)

1.1 Inhibition of Prostaglandin Biosynthesis

The non-steroidal anti-inflammatory analgesics, such as aspirin, indomethacin, ibuprofen and naproxen, are thought to exert their major pharmacological effects by inhibition of prostaglandin biosynthesis (Flower and Vane, 1974; Vane, 1971). This effect occurs by an action on the cyclo-oxygenase enzyme system responsible for the primary step in the metabolic conversion of the precursor, arachidonic acid, to the unstable cyclic endoperoxides. Although other enzymes in the prostaglandin cascade (e.g. thromboxane synthetase) also can be inhibited, the major effect of the NSAIDs is on cyclo-oxygenase. As a result, administration of these agents can lead to inhibition of the entire prostaglandin cascade and therefore inhibition of the production of the unstable intermediary substances as well as thromboxane and all prostaglandins. Prostaglandins and the synthetic pathways responsible for their production have been identified in virtually all mammalian tissues, including fetal tis-
issues. Their physiological effect depends on continued synthesis, since they are rapidly catabolised and are not stored in tissues. Generalised inhibition of prostaglandin synthesis, therefore, is likely to have far-reaching physiological effects. Since arachidonic acid is not only converted to cyclic endoperoxides by cyclo-oxygenase but is also converted by lipoxygenases into leukotrienes or hydroeicosatetraenoic acids, one must consider that inhibiting the conversion of arachidonic acid to cyclic endoperoxides could lead to overproduction of these other substances, with additional potential pathophysiological effects.

1.2 Placental Transfer and Kinetics

1.2.1 Aspirin

Pharmacokinetic studies in humans (recently reviewed by Levy, 1981) have shown that salicylates ingested by the mother before delivery are present in umbilical cord plasma or the plasma of newborn infants (Garrettson et al., 1975; Levy and Garrettson, 1974; Levy et al., 1975b; Lynd et al., 1976; Perkin et al., 1980). Although free salicylate apparently crosses the placenta rapidly, maternal-fetal equilibration is fairly slow after administration to the mother because of maternal plasma protein binding. However, equilibration does occur within 60 to 90 minutes. Postnatal salicylate elimination is slow because of inefficient glucuronidation as well as reduced urinary excretion associated with the relatively low glomerular filtration rates normally found in the newborn period (Levy and Garrettson, 1974). In animals, after maternal salicylate administration, physiological or haemodynamic effects on the fetus, indicating transplacental passage of active agent, have been demonstrated in rats, rabbits and sheep (Heymann and Rudolph, 1976; Sharpe et al., 1975). In both of these studies ductus arteriosus constriction was observed in the fetus, although drug concentrations in fetal plasma were not measured. Administration of aspirin to pregnant rabbits also inhibited platelet and pulmonary arachidonic acid metabolism in the fetuses (Simberg, 1984).

1.2.2 Other Acidic NSAIDs

Indomethacin has also been shown to cross the placenta, but maternal-fetal equilibration was even slower than for salicylate (Parks et al., 1977). Novy (1978) indicated that after indomethacin administration to pregnant rhesus monkeys, the drug was detected in umbilical cord blood at the time of delivery. In several animal studies, although fetal blood concentrations were not measured, placental transfer was indirectly demonstrated by physiological effects on the fetus after maternal administration. In particular, the effects on the ductus arteriosus have been studied in some detail (Levin et al., 1979a,b; Sharpe et al., 1974, 1975). Other NSAIDs have not been studied to a similar extent. Naproxen does cross the placenta in humans (Wilkinson, 1980) and in sheep and also exerts a constrictor effect on the fetal lamb ductus arteriosus (Rudolph and Heymann, unpublished observations).

Very little is known about the pharmacokinetics of NSAIDs in the perinatal period and nothing about ontogenetic differences. Protein binding and the capacity for biotransformation are, for example, different between young and adult animals. It is likely, therefore, that further developmental changes may occur during advancing gestation and that the immature (preterm) fetus or neonate behaves differently from the fetus or neonate at term. Other factors, such as volumes of drug distribution or clearance rates, may also be different. Because some of these NSAIDs may be specifically indicated therapeutically (for example, to inhibit premature labour) these gestational differences may be crucial when the ability of the fetus to handle the drugs appropriately is considered.

1.3 Administration and Ingestion During Pregnancy

1.3.1 Clinical Therapeutic Use During Pregnancy

NSAIDs have widespread therapeutic use in medical practice. They are used to treat collagen diseases, various forms of arthritis and many other