Original Article

Time-course of Transplacental Passage of Diazepam: Influence of Injection-delivery Interval on Neonatal Drug Concentrations

Olav M. Bakke and Kjell Haram

Clinical Pharmacology Unit, Laboratory of Clinical Biochemistry, and Department of Obstetrics and Gynaecology, Haukeland Sykehus, University of Bergen, Bergen

Summary

Neonatal drug concentrations and neonate/mother concentration ratios are reported in 73 cases of elective Caesarean section and forceps deliveries where diazepam was used as an intravenous sleep-inducing agent. The various parameters were plotted against the injection-delivery interval and the correlation was tested using a non-parametric ranking method.

The concentration of diazepam in mixed arteriovenous umbilical cord blood was negatively correlated with the injection-delivery interval in the range of 55 to 810 seconds. Statistically significant positive correlations (p < 0.001) were found between the injection-delivery interval and the neonatal concentrations at 2 and 24 hours. The corresponding neonate/mother concentration ratios varied considerably, and were not so strongly correlated to the duration of antenatal drug transfer.

The results suggest that with a slowly eliminated agent like diazepam, the drug concentration in capillary blood obtained from the newborn a few hours after delivery gives a reasonably good indication of the fetal drug exposure. The transplacental passage of diazepam is rapid, with distribution equilibrium between mother and fetus being approached within 5 to 10 minutes after intravenous injection of the drug.

It is an important aim of obstetric anaesthesia to minimise fetal drug exposure and neonatal depression. Due to interspecies variation in placental morphology and function, animal experiments are of limited value for the assessment of drug transfer to the human fetus (Kauffman et al., 1975; Krauer et al., 1980; Nishimura, 1973). It is seldom possible to obtain blood samples from the fetus in utero, and drug concentrations in arteriovenous or venous cord blood are unfortunately not representative of the amount of drug in the fetal unit as a whole (Haram et al., 1978; Sereni, 1973).
Ideally, in order to study the time-course of drug equilibration between mother and child, the concentration should be measured in a number of blood samples collected before and at delivery, and at various times thereafter. This is usually not feasible for ethical and practical reasons, and there are few published studies yielding good quantitative data on which to base general pharmacokinetic theory (Goldstein et al., 1974; Krauer and Krauer, 1977; Levy and Hayton, 1973). Since human data can only be obtained when the drugs are clinically indicated, there is a need for simple and meaningful sampling protocols which are compatible with the routine activities in the delivery room.

In our hospital blood levels of diazepam were studied in 122 mothers and their newborn babies after a single intravenous injection of the drug for induction of sleep prior to delivery (Bakke et al., 1981; Haram and Bakke, 1980; Haram et al., 1978, 1979). The main purpose was to study the effect of uterine contractions, the type of presentation, and the method of delivery on fetal drug exposure and the neonatal condition. However, since we deliberately varied the sampling protocol in order to gain experience about the relevance and usefulness of neonatal drug concentrations and neonate/mother concentration ratios at different times after delivery, a separate study of these pharmacokinetic aspects is presented.

Materials and Methods

Patients

73 patients were selected from a total of 122 cases of previously published investigations (Bakke et al., 1982. Haram and Bakke, 1980; Haram et al., 1978, 1979) Since uterine contractions and possibly also breech delivery are associated with reduced drug transfer to the fetus (Haram et al., 1978, 1979), only cases with cephalic presentation given diazepam in the relaxation phase prior to vaginal delivery and patients undergoing elective Caesarean section were included in the present study of the rate of drug transfer to the fetus. Twin pregnancies and cases with severe pre-eclampsia, Rh-immunisation and diabetes mellitus where the exchange between mother and fetus could be disturbed, were excluded (Finster and Pedersen, 1979).

The mean age of the selected patients was 28.0 years (range 17 to 44 years) and the bodyweight 73.5kg (range 55 to 94kg). The mean gestational age was 39.6 weeks (range 36 to 41 weeks) and the mean neonatal bodyweight was 3510g (range 2560 to 4540g).

None of the patients had received diazepam during the last 2 weeks of pregnancy.

Drug Administration

15 of the patients received a fixed dose of 30mg of diazepam (Valium, Roche) administered intravenously in the relaxation phase immediately before forceps delivery (Haram et al., 1978). The remaining 58 cases were given 0.3mg/kg or a fixed dose of 20mg of the drug as a sleep-inducing agent for elective Caesarean section (Bakke et al., 1981; Haram and Bakke, 1980). The injection time was 15 seconds in all patients. Further details on the anaesthesia, obstetric procedures and neonatal condition are given in the above-mentioned reports.

Sampling Protocols

A stop-watch recorded the time lag between completed injection of the drug to the mother and clamping of the umbilical cord after delivery. This period is referred to as the injection-delivery (I-D) interval which is the time available for drug transfer in utero. At delivery whole blood samples were obtained from the mothers (venous blood) and the newborn babies either from the proximal end of the umbilical cord (mixed arteriovenous blood) or by heel prick (capillary blood). Alternatively, the samples were taken simultaneously from mother and child at 5 minutes. A 2-hour sample from mother and child was included