EFFECTS OF THE RECTAL ADMINISTRATION OF DIAZEPAM

Diazepam Concentrations in Children Undergoing General Anaesthesia

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Pharmacokinetic studies have compared parenteral and various rectal preparations of diazepam in adults (Moolenaar et al., 1980; Magnusson et al., 1979) and children (Meberg et al., 1978) and indicated that systemic concentrations increase rapidly and are well maintained after rectal administration. Such a profile is of interest to the anaesthetist as it will provide a rapid increase to sedative concentrations for premedication and an effect which will last into the period after operation. We have studied serum concentrations of diazepam for 24 h after its rectal administration, in solution or by suppository, to children undergoing general anaesthesia.

**PATIENTS AND METHODS**

Following consent from the parents and the approval of the local Ethics Committee, 14 children (aged 1.5–8 yr) weighing 11–22.5 kg (mean 16.9 kg) were given diazepam before minor surgery (mainly squint operations). Seven were given a solution (solvent: propyleneglycol) through a rectal tube (Stesolid, AS Dumex) and seven received suppositories (Stesolid supp., AS Dumex). No special precautions were taken to keep the drug in the rectum. A dose of 1 mg/kg body weight, adjusted to the nearest 5 mg, was used. This resulted in a mean dose of 0.99 mg kg⁻¹ (range 0.8–1.2) of the rectal solution and 0.96 mg kg⁻¹ (range 0.8–1.1) of the suppositories.

Venous blood was withdrawn before administration and at the following intervals for measurement of serum diazepam concentration: for rectal solution—5, 10, 15, 20, 30, 40 min, 1, 1.5, 2, 4, 8, 24 h; for suppositories—10, 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 8 and 24 h. Slight deviations in sampling times occurred and all times are given with the range within which blood sampling was performed. Samples could not be obtained at all intervals in all children. Serum was deep frozen for later analysis of the concentration of diazepam using the gas-chromatographic method described by Arnold (1975). Drugs used during anaesthesia and the period after operation included halothane, thiopentone, pancuronium, trimethazine, ketamine, paracetamol and salicylic acid. The possibility that any or all of these drugs may have affected the determination of the diazepam concentration was assessed.

**Statistical methods**

Each serum concentration was standardized to a given dose of 1 mg kg⁻¹, whereafter serum concentrations at corresponding intervals were tested with the Wilcoxon rank sum test (Colton, 1974) at the 95% confidence level with the zero hypothesis that...
there was no difference between the two methods of administration.

RESULTS

The interference measurements did not suggest that the diazepam peaks included any of the other drugs given to the patients.

After the rectal solution the serum concentration of diazepam increased rapidly, whereas suppositories caused a slower increase, but to a higher serum concentration (fig. 1). The suggested sedative value of 150 ng ml⁻¹ (Mattila et al., 1981) was exceeded in five of the seven children given the rectal solution at 5 min and in all of them at 10 min. Diazepam concentrations were not measured at 5 min after suppositories, but at 10 min only three of the seven children had serum concentrations greater than 150 ng ml⁻¹ and at 40 min one was still below this value.

The rectal solution group had its peak median value of 619 ng ml⁻¹ (range 315–945) at 30 min, whereas in the children receiving suppositories, the peak median value of 848 ng ml⁻¹ (range 560–1141) was obtained at 2 h ± 15 min. At 10 and 20 min the diazepam concentration after rectal solution was significantly greater than after suppositories, the reverse being the case at 2 h ± 15 min. At all other intervals there were no statistically significant differences between the two methods of administration. The median values after suppositories were, however, higher at all intervals after 1.5 h.

DISCUSSION

Diazepam administered by the rectal route, either as solution or as suppository, produced high but variable serum concentrations, a finding similar to that in other studies (Knudsen, 1977; Dulac et al., 1978; Moolenaar et al., 1980; Mattila et al., 1981). Practical difficulty in administration has been proposed as a possible explanation for this variability, with solution remaining in the rectal tube or being lost from the rectum (Dulac et al., 1978; Magnusson et al., 1979). This may be the case, but in our study variability was great even in the suppository group, where drug loss should be minimal.

The initial serum concentrations found in our study after the administration of the rectal solution are in agreement with the reports of Meberg and colleagues (1978) and Mattila and co-workers (1981), but lower than those obtained by Dulac and associates (1978) who used half our dose. The explanation for the latter result is probably that their patients weighed less than ours. The significantly earlier peak with rectal solution compared with suppositories is also in agreement with previous work (Knudsen, 1977). With regard to the maintenance of the serum concentrations, over a 24 h period our measurements confirm the results from the three children receiving rectal solution in the report by Meberg and colleagues (1978).

In two of five measurements in the children receiving rectal solution and in three of seven children in the suppository group, the concentration at 8 h was higher than at 4 h. In both groups, the values at 8 h did not differ from those at 4 h, indicating a second peak at 6–12 h as reported by Meberg and co-workers (1978) and attributed to reabsorption from the intestinal mucosa after the postoperative ingestion of food (Kortilla, Mattila and Linnoila, 1976). In the adult patients in that study the serum concentrations of diazepam only increased after ingestion of fatty food and not plain water. As our patients only received water in the relevant period, the higher serum concentrations at 8 h were probably the result of stochastic variation. Diazepam in suppository resulted in a peak in serum concentration at 2 h after administration. This is in accordance with the study by Moolenaar and colleagues (1980) in young adults, although the doses given in that study were less than those used here.

If a diazepam suppository is given 30 min before anaesthesia in order to achieve the proposed sedative concentration of 150 ng ml⁻¹, the peak in serum concentration will coincide with the end of the
anaesthetic or the early postoperative period, since many surgical procedures in children are rather short. A smaller dose given earlier will decrease this peak, but will make the degree of sedation less predictable. In our opinion the rapid increase and well maintained serum concentrations associated with the use of a rectal solution of diazepam is to be preferred. It also allows a wide variation in administration time and a smooth recovery after minor paediatric surgery.

REFERENCES


