ABSORPTION OF DIAZEPAM IN MAN FOLLOWING RECTAL ADMINISTRATION OF A SUPPOSITORY, SOLUTION AND EMULSION

R. Walker, Department of Pharmacy Sunderland Polytechnic/Newcastle General Hospital.
P. Newman, Department of Neurology, Middlesbrough General Hospital.
P. Candlish, Pharmacy Department, Freeman Road Hospital, Newcastle.
C. Hiller, Pharmacy Department, Newcastle General Hospital.
J. Seviour, Institute of Pathology, Newcastle General Hospital.

The efficacy of intravenous diazepam as an anticonvulsant is well documented (Avery 1980). Rectal administration of the parenteral diazepam solution has also been shown to be effective, attaining peak serum levels in adults within 10 to 20 min (Magnussen et al 1979). However, the solvent of this solution has been reported to cause rectal irritation and haemorrhage (Schobben 1979). The aim of the present study was to compare the plasma concentrations of diazepam,and the incidence of irritation,following rectal administration of a parenteral solution (Valium) with a recently marketed suppository (Valium) and parenteral emulsion (Diazemuls).

One 10 mg diazepam suppository, 2 ml diazepam parenteral solution (5mg/ml) or 2 ml diazepam parenteral emulsion (5mg/ml) were administered per rectum to five adult volunteers at 14 day intervals. The solution or emulsion was injected via an Argyle tube inserted 6 cm into the rectum. 5 ml blood samples were taken for up to 24 h after drug administration. All plasma samples were assayed by HPLC using a modification of the method described by Tjaden et al (1980). Eight randomly selected plasma samples were also assayed by GLC according to the method of Dhar and Kutt (1979).

The assay results obtained by HPLC and GLC showed a good linear correlation (correlation coefficient = 0.97: $p < 0.01$). Rectal administration of the solution resulted in a peak diazepam plasma concentration of 216 $\pm$ 10 ng/ml which was significantly greater than that observed after the suppository 156 $\pm$ 25 ng/ml ($p < 0.05$) or emulsion 143 $\pm$ 15 ng/ml ($p < 0.01$). Similarly, the mean time to reach peak diazepam plasma concentration after administration of the solution was 10 $\pm$ 2 min which was significantly quicker than that observed after the suppository 48 $\pm$ 5 min ($p < 0.1$) or emulsion 44 $\pm$ 7 min ($p < 0.05$). However, there was no significant difference in the area under the diazepam plasma concentration time curve between any of the formulations tested. Rectal irritation was reported by each subject only after administration of the suppository.

The results obtained demonstrate that a rectally administered diazepam solution is rapidly absorbed and attains high plasma levels. This is consistent with the findings of other workers who have also studied adult subjects (Magnussen et al 1979). However, the solution caused no rectal irritation or discomfort as previously reported by others (Schobben 1979). In addition the results have also demonstrated that the rate of diazepam absorption from a suppository or emulsion is much slower than that observed with the solution, although the extent of absorption from all three preparations is similar. The implication of these results to clinical practice, particularly when the rectal route is used to maintain anticonvulsant levels following intravenous diazepam, needs to be studied further.

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