A PROSPECTIVE RANDOMISED CONTROLLED TRIAL OF DIAZEPAM (VALIUM) VS EMULSIFIED DIAZEPAM (DIAZEMULS) AS A PREMEDICATION FOR UPPER GASTRO-INTESTINAL ENDOSCOPY

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Two hundred and forty four patients were randomised to receive either diazepam or emulsified diazepam (diazemuls) intravenously prior to routine upper gastrointestinal endoscopy. The groups were comparable with regard to age, sex, medical condition, vein size, and amount of drug administered. A quantitative assessment of symptoms at the injection site during the ensuing week was made by analysing questionnaires on pain and tenderness, which the patients graded each day, on a scale 0-3. Twenty-one out of 82 patients who received diazepam (25.6%) and 22 out of 84 who received diazemuls (26.2%) had local symptoms. Although the mean symptom scores over 7 days for the two groups were not different (5.95 ± 5.19 and 7.27 ± 6.30 respectively), more patients who received diazepam reported induration ($P = 0.033$).

In 112 patients, signs of thrombosis in the injected veins were looked for 3-7 weeks later without knowledge of the preparation given. Thrombosis was present in 13 (25%) patients who had received diazepam and two (3.6%) who had received diazemuls ($P < 0.002$). Only eight (53%) patients with thrombosed veins had symptoms.

Thrombosis after intravenous injection of diazepam or diazemuls may be symptomless, and is significantly less likely following diazemuls.

Keywords diazepam diazemuls premedication endoscopy

Introduction

Intravenous diazepam is commonly used as a premedication for upper gastrointestinal endoscopy. Because the drug is poorly soluble in water, it is made up in propylene glycol and ethyl alcohol, and buffered with sodium benzoate and benzoic acid. Intravenous injection has been associated with a high incidence of thrombophlebitis (Siebke *et al.*, 1976; Hegarty & Dundee, 1977), and pain on injection may occur in up to 78% of patients (Olesen & Huttel, 1980).

Recently, diazemuls (Kabi-Vitrum), a preparation of diazepam dissolved in soya bean oil and emulsified in water with monoglycerides and egg yolk phosphatides has become available. Olesen & Huttel (1980) compared intravenous diazepam with diazemuls, and reported a lower incidence of pain during injection and subsequent thrombophlebitis with the latter. However, follow up was limited to observation over a few days and a questionnaire at 2 weeks. The actual incidence of thrombophlebitis may have been markedly underestimated as it may not be manifest for up to 4 weeks following injection (Siebke *et al.*, 1976) and may also be asymptomatic. We have, there-

fore, compared intravenous diazepam with diazemuls over a period of 1 to 7 weeks in patients undergoing gastrointestinal endoscopy.

Methods

Two hundred and forty-four outpatients undergoing upper gastrointestinal endoscopy were studied. They were randomised by tossing a coin to receive either diazepam or diazemuls intravenously as premedication. Where possible, the largest left arm antecubital vein was selected, but in 32 the right had to be used. The sedative was administered slowly (10 mg/min) via an 18 gauge needle until the patient developed ptosis or dysarthria. The presence and severity of pain was ascertained, and the vein size was graded on a scale of 1-3, depending on whether they were small, medium or large. Patients were excluded if extravasation was seen, or if the endoscopic findings necessitated hospital admission and further venepunctures or endoscopies.

Table 1 Details of patients and symptom analysis over 6 days following injection

	<i>Diazepam</i>		<i>Diazemuls</i>	
Total number of patients	82	(44 M)	84	
Mean age (years) and range	54.5	(19–83)	50.6	
Mean amount of drug given (mg)	19.27 ± 4.9		20.75 ± 3.1	
Number with vein grading of (1)	7		6	
Pain or tenderness occurring	21	(25.6)	22	(26.2%)
Mean symptom score	5.9 ± 5.19		7.27 ± 6.30	[N.S.]
Number with induration	11	(13.4%)	4	(4.8%)*

* $P = 0.033$ Fisher's exact test

Patients were asked to complete a form on which they recorded pain, induration and tenderness at the injection site over the ensuing 6 days. Each symptom was graded daily on a scale of 0–3, and a total symptom score was calculated for the 6 day period. Completed forms were returned at the outpatient clinic usually 4 weeks later (range 3–7), where an assessment by one of the authors (D.G.) of the injected vein was made without reference to the preparation given, and patients were asked about any pain or tenderness noted since completing the form. When outpatient attendance was not feasible, they were asked to return the completed forms by post.

Results

The drugs were administered satisfactorily in 234 patients. Mild discomfort was common during injection of both agents, but moderate or severe pain occurred in only eight patients, all of whom received diazepam. Sixty-eight failed to attend follow up or to return their forms, 38 of whom had received diazepam, and 30 diazemuls. The remaining 166 patients form the basis of the results.

The two groups were comparable with regard to age, sex, mean vein grading, number of small veins (grade 1) and amount of drug given (Table 1). There was no significant difference between the two groups with regard to frequency or severity of pain, tenderness or induration in the 6 days following injection (Wilcoxon sums of ranks of cumulative scores $P > 0.1$) (Table 1).

Further assessment at 3–7 weeks was possible in 112 patients, who were required to attend outpatients for follow up (Table 2). None experienced pain or tenderness after 6 days. There was a significantly greater incidence of thrombosis in the patients who received diazepam (Fisher's exact test $P < 0.002$). Mean follow up time of the patients with thrombosis was not significantly different from those without. Of the 15 patients with thrombosis, when assessed at 3–7 weeks (mean 4.7), all were asymptomatic and only eight had experienced pain or tenderness in the 6 days following injection.

Mean vein size grading of those with thrombosis (2.60 ± 0.625) and those with symptoms (2.53 ± 0.60) in the first 6 days did not differ statistically from that of the unaffected patients (2.56 ± 0.87). In particular, those with small veins (grade 1) were not more prone to complications.

Discussion

Emulsified diazepam, whilst of comparable therapeutic efficacy (Thom-Alquist, 1977), is more expensive than the standard preparation. Does it have advantages to justify its use? In contrast to others (Olesen & Huttel 1980; Graham *et al.*, 1978; Kavar & Dundee, 1982) we found the incidence of pain during diazepam injection to be low (6.6%), probably because we disregarded mild discomfort, which we feel is a non-specific accompaniment of any intravenous injection and because we used the larger ante-

Table 2 Objective assessment at 3–7 weeks

	<i>Diazepam</i>		<i>Diazemuls</i>	
Total number of patients	56		56	
Mean follow up time (weeks)	4.7 ± 1.0		4.4 ± 0.9	
Number of patients with objective thrombosis	13	(25%)	2	(3.6%)*

* $P = 0.0018$ Fisher's exact test

cubital veins rather than small veins on the back of the hand (Kawar & Dundee, 1982).

It is difficult to compare reports of local reactions to diazepam because of differing methods of assessment. We considered that pain and tenderness determined by the patient were the clinically important criteria of an early local reaction. We found, like Hegarty & Dundee (1977), that they were always manifest within the first week. Their equal incidence and severity in the two groups is in apparent contradiction to the results of Kawar & Dundee (1982) and Olesen & Huttel (1980), who found diazemuls much less likely to cause thrombophlebitis. However, the latter authors used a Teflon cannula for injection, and a

different method of assessment. Their 45% incidence of local tenderness 1–2 weeks following diazepam was much higher than the 11 to 22% of other series (Hegarty & Dundee, 1977; Siebke *et al.*, 1976; Dutt & Thompson, 1982).

We have considered thrombosis separately because it occurred later, was never symptomatic when seen at 3–7 weeks, and was often not preceded by discomfort. While there was no significant difference in the incidence of induration over the first 6 days, objectively assessed thrombosis at 3–7 weeks was significantly greater in patients receiving diazepam. We therefore suggest that diazemuls is to be preferred, especially if repeated endoscopies are envisaged.

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