DIAZEPAM AND MIDAZOLAM FOR SEDATION DURING BRONCHOSCOPY

Sir,—It is regretted that the interesting paper by Korttila and Tarkkanen (1985) does not state which preparation of diazepam they used. The early relative potency studies of midazolam and diazepam were undertaken with the organic solvent preparation, Valium. A review (Dundee et al., 1984) of these puts the relative potency of the two drugs at about 1.5:2:1:1. However, if Korttila and Tarkkanen used the emulsion preparation (Diazemuls) this would be expected to be about 20% less potent than Valium and patients would have been given relatively less diazepam (Fee et al., 1984).

While the authors found no difference in duration of action of small doses, with larger doses (midazolam 0.3 mg kg\(^{-1}\) and diazepam 0.5 mg kg\(^{-1}\)) there is a very obvious difference in recovery time between the two benzodiazepines.

Changes in relative bioavailability, depending on the solvent, have been demonstrated for both midazolam and propofol (Cummings et al., 1984). It is thus important that authors should state which preparation of diazepam they used.

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Sir,—The diazepam preparation used in our study (Korttila and Tarkkanen, 1985) was Diapam, Orion, Espoo, and the midazolam preparation Dormicum, Roche, Basle. It is regretted that the trade names were omitted from the printed version of the paper. We have published the composition and clinical effects of Diapam earlier (Korttila, Sothman and Anderson, 1976) and it is as potent as Valium, but is less likely to cause venous complications when compared with Valium (Korttila and Aromaa, 1980). Actually, as mentioned in our summary we were able to compare the two benzodiazepines in "doses of comparable potency", that is amnesic action, patient co-operation, and did not find a faster recovery with midazolam 0.1 mg kg\(^{-1}\) when compared with diazepam 0.2 mg kg\(^{-1}\).

Consequently, we did not give relatively less diazepam, as might have been the case with the same dose of Diazemuls.

The half-life at elimination phase \(T_1^\beta\), which is dependent on both volume of distribution \(V^\beta\) and clearance \(Cl\) of the drug:

\[
T_1^\beta = \frac{V^\beta \times 0.693}{Cl}
\]

is important during continuous treatment with the drug (Duvaldestin, 1981). It has been suggested that a benzodiazepine derivative is "short acting" if its elimination half-life is less than, for example, 10 h and if it does not have a tendency to cumulate during continuous therapy in normal clinical doses.

With acute administration, for example i.v. sedation, recovery is associated with liquid solubility and distribution of the drug instead of elimination half-life (Duvaldestin, 1981). The half-life at distribution phase mirrors the movement of the drug from blood (and brain) to peripheral tissues and is related to the duration of action and recovery after acute drug administration.

The half-lives for the initial distribution phase have been reported to be similar for diazepam (0.30 ± 0.11 h) (Ghoneim et al., 1981) and midazolam (0.31 ± 0.08 h) (Greenblatt et al., 1984) which predicts that recovery after acute administration of both agents would also be similar. Jack and colleagues (1983) used a receptor binding model in rat brain to shed light on the onset and duration of action of diazepam, midazolam and lorazepam. Their studies indicate that both diazepam and midazolam occupied the receptors rapidly and disappeared from receptors faster than lorazepam, parallelling the relative onset and duration of the sedative and amnesic properties of these drugs in man.

Recently, Skelly and co-workers (1984) compared diazepam 26 ± 7 mg (mean ± SD) and midazolam 13 ± 3 mg (mean ± SD) as sedatives in 40 patients undergoing minor oral surgery. Recovery was thoroughly studied by six psychomotor tests repeated over 5 h. More amnesia was reported in the midazolam group and there was no significant evidence of the midazolam group recovering more quickly. The authors point out that significant impairment of delayed memory recall persisted in both groups throughout the investigation period.

Similarly to diazepam, in ambulatory practice each patient receiving i.v. midazolam sedation must have an escort when discharged from hospital and patients should refrain from driving or operating machinery for at least 12–24 h.

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REFERENCES
INFUSION THROMBOPHLEBITIS

Sir,—The recent review article (Lewis and Hecker, 1985) highlighted the problem of the definition of thrombophlebitis in the clinical setting resulting in the inability of comparison of incidence and severity.

We recently conducted a study into the reproducibility of a definition of thrombophlebitis which could be used to assess the effects of different agents and cannulae on post-infusion phlebitis. In this study two groups of 10 patients who had received i.v. infusions, which had resulted in a post-infusion reaction, were examined by 10 medically qualified observers. The observations were all made within a designated 1 h period and recorded.

In the first group the definition of the venous reaction was as defined by Thomas, Evers and Racz (1970) (table I).

The results were analysed by Kendal’s Coefficient of Concordance.

For the second group a series of specific criteria was provided for the observers, who were requested only to indicate the presence or absence of these criteria: thrombosis; swelling; erythema; tender; painful; suppuration.

The results from this group were analysed by Cochran’s Q test. Two separate methods of statistical analysis were used because of the nature of the two sets of data: an ordinal scale in group one and a nominal scale in group two.

Results indicate that there was significant agreement between the observers in each of the two groups. However, the first study resulted in gross discrepancy between individual observers ranging from no reaction (grade 0) to thrombophlebitis (grade 3) in one particular instance. If one also asked the observers to categorize further into mild, moderate and severe phlebitis and thrombophlebitis, further discrepancy occurred. This gross discrepancy did not occur in the second group where complex definitions were not used.

If one accepts that any erythema, pain, tenderness, swelling or thrombosis constitutes a venous reaction to that infusion, it was our impression that the second study, by clearly requesting a simple Yes or No response for each sign and symptom of a venous reaction, gave a more consistent and reproducible result. The use of these complex definitions can then be dispensed with and the severity of the post-infusion reaction related to the simple signs and symptoms producing morbidity in the patient.

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Sir,—We have read with interest the letter of Gemmell, Donaldson and Smith on the definition of infusion phlebitis. We, as have many others, have had considerable difficulty in adopting a suitable definition and agree that a convenient simple classification of signs is needed. A simple check list that cannot create confusion between different observers such as the one presented in the letter is preferable to a more complex system which is not so clearly delineated in some patients.

Some points may be pertinent to their list of criteria:

(1) Pathological studies of infusion phlebitis are notable by their absence and it cannot be said with certainty that all palpable thickening is the result of presence of a thrombus. We suggest that "Palpable vein thickening" ("cording") is a more honest description than "Thrombosis".

(2) Swelling can occur in phlebitis (as a result of general inflammatory oedema), but it also occurs with extravasation of infusate ("tissuing, infiltration") which we believe has similarities with infusion phlebitis (Hecker, Fisk and Lewis, 1984). Indeed, some cases of infusion failure show some phlebitis signs, but also show signs of extravasation. If our suggestion that they usually have a common etiology is proven, then an inclusive definition of Inflammatory Infusion Failure could be useful.