LOCAL REACTIONS TO I.V. DIAZEPAM IN THREE DIFFERENT FORMULATIONS

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SUMMARY
Local venous reactions during and after i.v. injections of three different formulations of diazepam were studied in 200 patients undergoing gastroscopy. Of the patients receiving diazepam in propylene glycol (Stesolid) 78% experienced pain on injection and 48% subsequently developed clinical evidence of thrombophlebitis. The figures for Stesolid MR (diazepam in Cremophor EL) were 38% and 9% respectively. A significant decrease was achieved (pain on injection 1%; clinical thrombophlebitis 4%) when using Diazemuls, a new formulation in which diazepam is dissolved in oil and emulsified in water. Since no difference in the therapeutic effect of the different formulations was observed, Diazemuls represents a clear advantage to Stesolid and Stesolid MR.

Diazepam dissolved in propylene glycol (Stesolid), causes a high frequency of pain (Siebke, Ellertsen and Lind, 1976) and venous thrombosis (Hegarty and Dundee, 1977) when injected i.v. Assuming that the solvent system may be responsible for these complications, attempts have been made to use macrogol ricinoleas (Cremophor EL) as an alternative solvent (Stesolid MR). However, although the frequency of venous complications was decreased, the change to this preparation led to the appearance of severe adverse reactions (Schou Olesen and Hüttel, 1978).

Since diazepam is lipid-soluble, it is possible to dissolve the drug in oil, which can then be emulsified in water (Jeppsson and Ljungberg, 1975) without influencing the clinical effect of the drug (Thorn-Alquist, 1977).

On the basis of this principle Kabi-Vitrum, Sweden have produced a new formulation (Diazemuls —under registration in the U.K.) in which diazepam is dissolved in soybean oil and emulsified in water by means of acetylated monoglycerides and egg-yolk phosphatides. The same technique has been employed for Intralipid, the fat emulsion used for i.v. nutrition.

The aim of this investigation was to compare local venous reactions during and after the i.v. injection of these three preparations (diazepam in propylene glycol, diazepam in Cremophor EL and diazepam in oil) all of which have a diazepam concentration of 5 mg ml⁻¹.

PATIENTS AND METHODS
Two hundred consecutive adult patients admitted to the hospital for gastroscopy were studied. They were allocated randomly to the three groups. It was not possible to perform a true double-blind study because of the different appearances of the preparations, but as the authors did not administer the drug they were unaware of the formulation given.

A disposable Teflon cannula (Venflon no. 1.2 Viggo, Sweden) was used in all patients, placed in the left cephalic vein. Using an injection rate of 5 mg min⁻¹, sufficient medication was given to sedate the patient or until a maximum dose of 30 mg was reached. No other drug was given through this cannula. After completion of the injection the cannula was withdrawn. If leakage outside the vein or haematoma occurred, if, by mistake, the vein was used subsequently for venepuncture, or if an i.v. infusion was given later in that arm, the patient was excluded from the study.

Symptoms of discomfort or pain arising from the injection, mentioned either spontaneously or on questioning, were recorded by the nurse in charge when the immediate local reactions were noted.

Each patient was seen by one of us no later than the following day and again daily until discharged. Mean observation time was 4 days (range 1-14 days). The site of injection was examined and the presence or absence of tenderness on palpation of the vein, venous thickening and local erythema were recorded. Two weeks after the injection patients received a questionnaire referring to the same points. Whenever the written answers left any doubt the patient was seen by one of us.
Thrombophlebitis was diagnosed when at least two out of three symptoms were recorded.

For statistical evaluation Fisher's Exact Probability test was used.

RESULTS

Only three patients did not answer the questionnaire, bringing the numbers taking part to 197. The results are shown in Table I.

<table>
<thead>
<tr>
<th>Symptoms or signs</th>
<th>Diazemuls (n = 67)</th>
<th>Stesolid MR (n = 66)</th>
<th>Stesolid (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elicited spontaneously</td>
<td>0 (0)</td>
<td>9 (14)</td>
<td>28 (44)</td>
</tr>
<tr>
<td>After questioning</td>
<td>1 (1)</td>
<td>25 (38)</td>
<td>50 (78)</td>
</tr>
<tr>
<td>Local reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>4 (6)</td>
<td>3 (5)</td>
<td>20 (31)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>4 (6)</td>
<td>6 (9)</td>
<td>29 (45)</td>
</tr>
<tr>
<td>Induration</td>
<td>2 (3)</td>
<td>5 (8)</td>
<td>24 (38)</td>
</tr>
<tr>
<td>All three symptoms</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>4 (6)</td>
<td>6 (9)</td>
<td>31 (48)</td>
</tr>
<tr>
<td>Without pain or local</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reactions</td>
<td>64 (96)</td>
<td>37 (49)</td>
<td>9 (14)</td>
</tr>
</tbody>
</table>

The groups were comparable with regard to age, sex and mean dose of diazepam, which in all groups was 21 mg (range 7–30 mg).

There were no apparent differences between the three formulations with respect to onset, duration or magnitude of the therapeutic effect.

DISCUSSION

In support of previous studies by Graham, Pagano and Conner (1978), who found a high frequency of painful injections with diazepam dissolved in an aqueous vehicle composed of organic solvents consisting mainly of propylene glycol, ethyl alcohol and sodium benzoate in benzoic acid (Valium), we found that 78% of patients receiving an undiluted aqueous diazepam preparation containing propylene glycol experienced pain on injection, regardless of dosage. This was decreased significantly when the other two preparations were used, and it was noteworthy that only one patient complained when Diazemuls was given (Table I).

The frequency of thrombophlebitis was 48% when the aqueous solution of diazepam (Stesolid) was used. A follow-up of only 2–3 days will underestimate the frequency of venous sequelae, since thrombophlebitis may not appear until 10–14 days after the administration (Hegarty and Dundee, 1977). The present study was designed to counter this problem, and the intense follow-up may be the reason for the relatively high frequency of local reactions observed.

All differences were statistically significant ($P<0.001$) except that comparing Diazemuls and Stesolid MR for thrombophlebitis. Diazemuls is, nevertheless, superior when combining pain on injection and thrombophlebitis.

The introduction of Stesolid MR with Cremophor EL as solvent caused a significant decrease in thrombophlebitis (Siebke, Ellertsen and Lind, 1976) but this led to severe anaphylactic reactions (Schou Olesen and Hüttel, 1978). We have found recently (Hüttel, Schou Olesen and Stoffersen, 1980) that some of these reactions may be a result of complement activation via the alternative pathway. Since the same phenomenon has been shown by Watkins and colleagues (1976) with Althesin, which also has Cremophor EL as solvent, it is probable that the solvent itself is responsible for the reactions.

Von Dardel, Mebius and Mossberg (1976) studying diazepam in an emulsion, found a significant decrease in the frequency of adverse local vascular reactions similar to that observed in the present investigation. Since then von Dardel and colleagues have used Diazemuls safely in more than 10,000 patients without anaphylactic reaction (O. von Dardel, personal communication).

We conclude that a significant decrease in the frequency of local vascular side-effects can be achieved by using diazepam in the lipid emulsion form with no alteration in the therapeutic effect.

ACKNOWLEDGEMENTS

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REFERENCES


LOCAL REACTIONS TO I.V. DIAZEPAM


REACTIONS LOCALES A L’INJECTION INTRAVENUEUSE DE DIAZEPAM PREPARE SUIVANT TROIS DIFFERENTES FORMULES

RESUME ON a etudié sur 200 malades subissant une gastroscopie, les réactions veineuses locales pendant et après l’injection intraveineuse de trois différentes préparations de diazépam. Parmi les malades auxquels on a administré le diazépam dans du propylène glycol (Stesolid), 78% ont ressenti une douleur lors de l’injection, et 48%, ont par la suite développé des signes cliniques de thrombophlébite. Les chiffres correspondants pour le Stesolid MR (diazépam dans cremophor EL) ont été respectivement de 38% et de 9%. On a obtenu une diminution importante de la douleur au moment de l’injection (1%) et des signes cliniques de thrombophlébite (4%), lorsqu’on a utilisé du Diazémuls, qui est une nouvelle formule dans laquelle le diazépam est dissout dans l’huile et éмуsifié dans l’eau. Du fait que l’on n’a observé aucune différence dans les effets thérapeutiques des diverses préparations, le Diazémuls présente un net avantage par rapport au Stesolid et au Stesolid MR.

LOKALE REAKTIONEN AUF INTRAVENÖSE EINSPRITZUNG VON DIAZEPAM IN 3 VERSCHIEDENEN FORMULIERUNGEN

ZUSAMMENFASSUNG Lokale venöse Reaktionen während und nach intravenöser Einspritzung von 3 verschiedenen Formulierungen von Diazepam wurden bei 200 Gastroskopie-Patienten studiert. Von den Patienten, die Diazepam in Form von Stesolid erhielten, erfuhr 78% Schmerzen bei der Einspritzung, und bei 48% zeigte sich später ein klinischer Befund von Thrombophlebitis. Die entsprechenden Zahlen für Stesolid MR waren 38% und 9%. Eine bedeutende Reduzierung (Schmerzen bei der Einspritzung bei 1%, klinischer Befund von Thrombophlebitis bei 4%) wurde mit Diazemuls erreicht, eine neue Formulierung, in der Diazepam in Öl gelöst und in Wasser emulgiert wird. Da in Bezug auf die therapeutische Wirkung kein Unterschied zwischen den verschiedenen Formulierungen festgestellt werden konnte, bietet Diazemuls klare Vorteile gegenüber Stesolid und Stesolid MR.

REACCIONES LOCALES AL DIAZEPAM I.V. EN TRES FORMULAS DISTINTAS

SUMARIO Se estudiaron las reacciones venosas locales durante y después de inyecciones i.v. de tres fórmulas distintas de diazepam en 200 pacientes sometidos a gastroscopia. De los pacientes que recibieron diazepam en glicol de propileno (Stesolid), un 78% padeció de dolores al momento de la inyección y un 48%, demostró consiguientemente prueba clínica de tromboflebitis. Las cifras relativas al MR Stesolid (diazepam en cremofor EL) fueron de 38% y 9%, respectivamente. Se obtuvo una disminución significativa (dolor al momento de la inyección 1%; tromboflebitis clínica 4%) al usar el Diazemuls, una nueva fórmula en la cual se disuelve al diazepam en aceite y se emulsiona en agua. Puesto que no se observó ninguna diferencia en los efectos terapéuticos de las distintas fórmulas, el Diazemuls brinda una clara ventaja sobre Stesolid y Stesolid MR.