FAT EMULSION AS A VEHICLE FOR DIAZEPAM. A STUDY OF 9492 PATIENTS

O. VON DARDEL, C. MEBIUS, T. MOSSBERG AND B. SVENSSON

SUMMARY

Conventional preparations of diazepam for i.v. use contain solvents which cause pain on injection and thrombophlebitis in a high percentage of cases. However, diazepam can be dissolved with advantage in the oleaginous phase of an oil-in-water emulsion (Diazemuls). Diazemuls has been given to 9492 patients without serious side-effects. Following i.v. injection, 2435 patients were studied with respect to pain and clinical effect. Only 0.4% experienced pain. The intended clinical effect was recorded in 99% of the patients. I.m. injection of Diazemuls resulted in a significantly smaller frequency of pain in connection with the injection than did the injection of Valium (7% and 43% respectively). Pharmacokinetic studies have been made after i.v. and i.m. injection of Diazemuls and Valium. The distribution and elimination phases after i.v. injection were the same with both forms. Thus the drug probably quickly separates from the oil particles of the emulsion after injection. After i.m. administration, the plasma concentration shows a wide spread with both preparations. A brief survey of other substances tested in emulsion form is presented.

Many drugs used in anaesthesia dissolve poorly in water but are fat-soluble. In order to manufacture forms suitable for parenteral administration solvent must be added. In many instances the solvents are toxic and can produce local side-effects such as pain on injection and thrombophlebitis. They can also produce anaphylactoid reactions.

One of the drugs in this group is diazepam. Conventional dosage forms of diazepam contain solvents such as propylene glycol, phenylcarbinol and ethanol. These substances are tissue irritants and are associated with a high frequency of pain and thrombophlebitis upon i.v. injection (Langdon, 1973; von Dardel, Mebius and Mossberg, 1976; Schou Olesen and Hüttel, 1980). I.m. injections are also very frequently accompanied by pain (Assaf, Dundee and Gamble, 1975; Korttilla, Sothman and Andersson, 1976). Attempts have been made to reduce these side-effects by administering heparin and steroids and by diluting the drug, but with little success. Diazepam dissolved in macroglol ricinoleate (Stesolid MR) has been reported to produce fewer side-effects (Mattila et al., 1979; Schou Olesen and Hüttel, 1980), but a number of anaphylactoid reactions have been reported with this form (Schou Olesen and Hüttel, 1978; Hüttel, Schou Olesen and Stoffersen, 1980).

The experience with Intralipid, the fat emulsion for parenteral nutrition, has been utilized by KabiVitrum, Sweden, to develop a new dosage form for fat-soluble substances. Diazepam is now available in an emulsion formulation in which the drug is dissolved in the oleaginous phase. The low toxicity of this diazepam emulsion has been documented by Jeppsson and Ljungberg (1975). This drug emulsion is marketed under the name of Diazemuls.

In 1976 von Dardel, Mebius and Mossberg showed that the frequency of pain and thrombophlebitis after i.v. injections of diazepam in conventional formulation was substantially reduced when Diazemuls was administered i.v. Thorn-Alquist (1977) found no differences in respect of clinical effect and pharmacokinetics between the two formulations. In 1980 Schou Olesen and Hüttel reported a significantly decreased frequency of pain and thrombophlebitis after i.v. injections of Diazemuls compared with both Valium and Stesolid MR.

The aim of the present investigation was to study the suitability of the diazepam emulsion for clinical use in a large number of patients, by studying the immediate local and systemic side-effects. Subsequent side-effects such as phlebitis or thrombosis were not within the scope of this study. Our aim was also to ascertain whether the emulsion formulation affects the bioavailability of the drug as compared with the earlier dosage forms. More detailed pharmacokinetic studies have therefore been made after
both i.v. and i.m. administration. In addition it has been our intention to illustrate the suitability of the drug for clinical use over a fairly long period of time and to ascertain whether the frequency of pain can be reduced also after i.m. injection compared with Valium.

PATIENTS AND METHODS

The compositions of Diazemuls and Valium (Hoffmann-La Roche), which was used as the aqueous solution, are shown in Table I. Both preparations have a concentration of 5 mg ml⁻¹.

Diazemuls was administered to a total of 9492 patients in the period 1975–80. The clinical effect, pain in connection with the injection and acute complications of a local and systemic nature were studied in 2435 patients. The age range was 16–96 yr, and the average dose was 7.12 mg (range 2.5–30 mg). Diazemuls was given as an i.v. sedative before anaesthesia and in connection with endoscopy and procedures under local anaesthesia. A single dose was given in association with general anaesthesia, whereas repeated doses were given for endoscopy and procedures under local anaesthesia, which explains the wide variation in the total dose. The injections were given via a Venflon cannula (o.d. 1.20–1.40 mm), most frequently on the back of the hand or in the forearm. The clinical effect was rated as satisfactory or unsatisfactory by an experienced anaesthetist. “Unsatisfactory” signified that the preparation did not bring about the desired sedation. If the patient said that he experienced pain when the injection was being made, this was noted. If the patient did not volunteer such information, he was asked if he experienced any pain. Other immediate complications of a local or systemic nature upon injection were also noted on the trial proforma.

Over a period of 5 years Diazemuls was administered routinely to a further 7009 patients when i.v. diazepam was considered to be indicated. Any complications in connection with the injection were noted in these patients too.

Five healthy volunteers aged 27–49 yr were given i.v. injections of Diazemuls 7.5 mg and Valium 7.5 mg to the cubital vein. The trial was in the form of a cross-over study (time interval 4 weeks). The injection time was 60 s. The blood used to determine the plasma concentration of diazepam was drawn from a Venflon cannula in the cubital vein of the other arm. A sample was taken immediately before the injection and additional specimens were collected up to 50 h after the injection at previously determined time intervals.

Sixty patients were injected with diazepam i.m. for sedation before surgery, 30 receiving Diazemuls and 30 Valium. The patients were selected at random. The average ages were 53.7 yr (range 15–85) for the Diazemuls group and 57.8 yr (range 17–78) for the Valium group. The injection was given in the lateral vastus (injection needle 0.7 x 50 mm). The dose was 0.2 mg/kg body weight. The injection time was 45 s. The patient’s sensation of pain in connection with the injection was recorded using the scale: no discomfort, slight discomfort, pain. The double-blind technique was used in the study. Since Diazemuls is milky white and Valium is yellow, the investigator was given a masked syringe prepared by another medically responsible staff member. Thus the investigator had no way of knowing which solution he injected.

Pharmacokinetic studies were made in 36 patients after i.m. injections. Eighteen patients received Valium and 18 Diazemuls. The patients were randomly selected. The average age for Diazemuls was 43 yr (range 15–81) and for Valium 48 yr (range 15–78). The injection was given to the vastus lateralis for sedation before anaesthesia in patients lying in bed. The needle dimensions were 0.7 x 50 mm, and the injection time was 45 s. The dose was 0.2 mg/kg body weight. Blood for the assay of plasma diazepam was drawn from a Venflon cannula in the cubital vein immediately before the injection and up

<table>
<thead>
<tr>
<th>Table I. Formulation of Diazemuls and Valium injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diazemuls</strong></td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Soybean oil</td>
</tr>
<tr>
<td>Acetyl monoglyc.</td>
</tr>
<tr>
<td>Phospholipids</td>
</tr>
<tr>
<td>Glycerol</td>
</tr>
<tr>
<td>Water for injection to</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
to 48 h after the injection at previously determined time intervals. All blood samples for the determination of plasma concentration level were frozen and analysed by the gas chromatography method described by Berlin and others (1972).

RESULTS

Of 2435 patients studied with regard to painful reactions in connection with i.v. injection of Diazemuls, nine experienced such pain (0.4%). The clinical effect was judged to be satisfactory in 2409 patients (99%) and unsatisfactory in 26 (1%). Neither reddening of the skin nor tenderness along the vein in connection with the injection was noted in any patient. One patient had transient, spotty erythema on the upper part of the body, but no other complications. No other hypersensitive reactions were observed.

Among the remaining 7009 patients receiving Diazemuls there was one instance of general urticaria in a patient in the intensive care ward. He had been given a total of Diazemuls 120 mg divided into doses of 5–10 mg over a period of 5 days. He was being treated concurrently with trimethoprim-sulphonamide. No other complication was noted in more than 9000 patients.

Mean plasma concentrations of diazepam in five patients after i.v. injection of Diazemuls and Valium are shown in figure 1. Pharmacokinetic evaluations were made using an open two-compartment model. Some pharmacokinetic parameters are summarized in table II.

**TABLE II. Pharmacokinetic parameters (mean) of diazepam after i.v. injection of 7.5 mg to five patients, given as Diazemuls and Valium in a cross-over study**

<table>
<thead>
<tr>
<th>Pharmacokinetic index</th>
<th>Diazemuls</th>
<th>Valium</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ng ml⁻¹)</td>
<td>301.9</td>
<td>273.5</td>
</tr>
<tr>
<td>α (min⁻¹)</td>
<td>0.0322</td>
<td>0.0371</td>
</tr>
<tr>
<td>B (ng ml⁻¹)</td>
<td>59.3</td>
<td>92.7</td>
</tr>
<tr>
<td>β (min⁻¹)</td>
<td>0.00047</td>
<td>0.00049</td>
</tr>
<tr>
<td>T₁/² (min)</td>
<td>21.5</td>
<td>18.7</td>
</tr>
<tr>
<td>T₁/³ (h)</td>
<td>24.6</td>
<td>23.6</td>
</tr>
<tr>
<td>AUC (ng min⁻¹ ml⁻¹)</td>
<td>136397</td>
<td>194845</td>
</tr>
<tr>
<td>Cl (ml min⁻¹)</td>
<td>55.0</td>
<td>38.5</td>
</tr>
<tr>
<td>Vₚ (litre)</td>
<td>117.0</td>
<td>78.6</td>
</tr>
<tr>
<td>Vₚ (litre)</td>
<td>20.8</td>
<td>20.5</td>
</tr>
<tr>
<td>Corr.</td>
<td>0.998</td>
<td>0.997</td>
</tr>
</tbody>
</table>

**FIG. 1. Plasma concentrations of diazepam following i.v. injection of Diazemuls 5 mg (■) and Valium 5 mg (○) in five subjects in a cross-over study. Mean ± SEM.**
The distribution and elimination phases were the same regardless of the dosage form used. Although SEM at 5 and 7 h do not overlap, Student's t test could not verify that the difference was significant. However, we do not feel it appropriate to analyse two points on a curve separately. No over-all significant difference between the preparations could be found.

The experience of pain on i.m. injection is indicated in Table III. While 43% of the 30 patients injected with Valium experienced pain, only 6.7% of the patients given Diazemuls had painful reactions in connection with the injection. The difference is statistically significant.

The plasma concentration of diazepam following i.m. injection shows a wide spread. Figure 2 shows that the dispersion is slightly smaller after Diazemuls than after Valium. Initially, Valium produced greater plasma concentrations, but after 6 h the concentrations after Diazemuls tend to be somewhat greater. There is a significant difference between the preparations during the first 4 h, verified by means of an analysis of variance.

DISCUSSION
Penetration of the blood–brain barrier is proportional to the oil/water partition coefficient and is facilitated by high lipophilicity. When a drug cannot be dissolved in water another suitable solvent must be found. One of the prerequisites for i.v. use of a solvent is low toxicity. Furthermore, the solvent should not exert any pharmacological effect itself and it must not interfere with those of the dissolved drug.

The low toxicity of a fat emulsion consisting of soybean oil and egg phosphatides has been documented in several different studies (Schubert and Wretlind, 1961; Håkansson, 1968; Shenkin and Wretlind, 1978). Such a fat emulsion has been used since 1962 in complete parenteral nutrition. It has been demonstrated that the oleaginous phase of the emulsion can be used as a carrier of fat-soluble drugs (Ljungberg and Jeppsson, 1970). Some examples of
substances that have been studied in emulsion form in animal experiments are barbiturates (Jeppsson, 1972), diazepam (Jeppsson and Ljungberg, 1975; Jeppsson, 1976), local anaesthetics (Jeppsson, 1975), nitroglycerin and cyclandelate (Jeppsson and Ljungberg, 1973). Jeppsson (1972) showed that the hypnotic effect of some barbiturates lasted significantly longer in the emulsion form than in the corresponding aqueous formulation as a sodium salt solution. Jeppsson and Ljungberg (1975) found that an emulsion formulation of diazepam had no deleterious effect on the pharmacological action of the drug. Jeppsson (1976) compared the pattern of the elimination of diazepam from the plasma both in the emulsion form and in aqueous solution, and found no difference.

The first drug in a fat emulsion consisting of soybean oil and egg phosphatides tested clinically in man was secobarbitone (von Dardel, Mebius and Mossberg, 1975). The frequency of thrombophlebitis was found to be substantially less than with barbiturates in aqueous solution.

Since the commercially available aqueous solutions of diazepam are associated with a high frequency of vascular complications attributable to the solvents, we were prompted to make a clinical evaluation of diazepam in the fat emulsion formulation. The trial was begun at St Göran's Hospital in Stockholm in 1975, and the preparation has been used by us since that time. The preparation is milky white and thus differs conspicuously from conventional injection formulations of the drug, but this has caused no difficulties in practical use. Up to the present time the preparation has been given to about 10 000 patients without serious side-effect.

Clinical effect

Opinion has been divided as to whether the clinical effect is influenced by the emulsion formulation. Can it be reduced or possibly delayed? Giessing and Tomlin (1977) investigated 60 (30 + 30) patients and concluded that a greater dose of diazepam in emulsion form, compared with Valium, was needed to produce a comparable effect, but Thorn-Alquist (1977) found no difference. Jeppsson and Ljungberg compared the same formulations with respect to anticonvulsive activity in mice and found no difference. It is difficult to find reliable indices to assess the effect of anxiolytic preparations and sedatives. There is no clear connection between plasma concentrations of diazepam and clinical response (Mandelli, Tognoni and Garattini, 1978). We chose to give a sufficiently large dose of the drug to produce the desired clinical effect in each patient and found that the doses given closely paralleled the doses of Valium given previously in corresponding clinical situations.

Pharmacokinetics

Thorn-Alquist (1977) made pharmacokinetic studies of Diazemuls up to 4 h after i.v. and i.m. administration and found no differences compared with Valium. In the present study the plasma concentrations were monitored for a long period of time (up to 50 h) after both i.v. and i.m. injection.

After i.v. injection the plasma concentration curves for Diazemuls and Valium show a similar time course. The drug probably separates quickly from the oil particles of the emulsion after injection. The average diameter of the oil particles has been estimated to be 0.2 µm (Jeppsson, Groves and Yalabik, 1976). The total fat surface area in 1 ml of the emulsion will then be about 6 m². Thus the finely distributed oleaginous phase has a very large area of contact with the plasma, which promotes rapid diffusion of the drug from fat to blood. Furthermore, Jeppsson (1976) found in animal experiments that the elimination pattern for diazepam dissolved in the oleaginous phase of an emulsion was not influenced by the rate of the elimination of the fat particles per se. This also confirms the conclusion that the substance quickly separates from the oleaginous phase after injection.

When diazepam in conventional aqueous solutions is injected i.m., absorption varies greatly (Gamble, Dundee and Assaf, 1975; Kanto, 1975; Korttila and Linnoila, 1975). Important factors are the site and depth of the injection, blood flow, amount of adipose tissue and possible precipitation of the drug at the site of injection. Our investigation confirms that absorption is uneven with both Valium and Diazemuls. A slight tendency to a slow-release effect is discernible in the emulsion dosage form. Oleaginous formulations have been given i.m. before in order to prolong the effect of various drugs. The depot effect of this new oil-in-water emulsion is minimal, however, which is probably a result of the fact that the diameter of the particles is so small and thus affords a large area of contact with the plasma, as described above. The initial peak concentration observed in the Valium series is not seen after the injection of Diazemuls; this may be a benefit which can reduce the risk of overdosage and unwanted side-effects.
I.v. administration of diazepam in aqueous solution causes a high frequency of pain and thrombophlebitis. These complications have been attributed to the solvent. Graham, Pagano and Katz (1977) demonstrated in histological studies that the lesions produced in the blood vessels by aqueous solutions of diazepam have the same appearance as those which occur after injection of the solvent used alone. The cause of the pain is not known, and there is no clear correlation between pain and thrombophlebitis (Langdon, Harlan and Bailey, 1973; Siebke, Ellertsen and Lind, 1976).

It has been possible to alter the frequency of both pain and thrombophlebitis by changing the solvent. For example, by using macrogol ricinoleate it has been possible to reduce the number of painful reactions from 78% to 38% (Schou Olesen and Hütte1, 1980). However, side-effects of an anaphylactoid nature involving circulatory collapse have been described with this preparation. In 1976 von Dardel, Mebius and Mossberg reported thrombophlebitis at a frequency of only 1.1% in patients injected i.v. with diazepam in emulsion form. In the same study it was found that only 0.3% of the patients given this emulsion i.v. experienced pain, compared with 35% after Valium. It has now been possible to confirm these good results in a larger number of patients of whom only nine of 2435 (0.4%) experienced pain.

I.m. injection of diazepam in aqueous solution is associated with a very high frequency of pain. However, after i.m. injection of diazepam in the emulsion form we have observed a marked decrease in the frequency of pain immediately following the injection in comparison with Valium. There has been a recent report (J. W. Dundee, personal communication in comparison with Valium. There has been a recent report (J. W. Dundee, personal communication) of pain at the site of injection 12–24 h after i.m. injection of Diazemuls. The cause has not been clarified.

The use of a fat emulsion as a vehicle for lipid soluble drugs can constitute a good alternative for the administration of drugs of this type. Injection of the emulsion form of diazepam (Diazemuls) results in a sharp decrease in the number of local side-effects compared with conventional aqueous solutions of the drug. As stated before, a solvent must have low toxicity, must not exert any pharmacological effect of its own and must not interfere with those of the dissolved drug. These requirements are met by the described fat emulsion consisting of soybean oil and egg phosphatides.

We are grateful to Roland Jeppsson Ph.D. for technical advice. Diazemuls was kindly placed at our disposal by KabiVitrum AB, Sweden.

REFERENCES
FAT EMULSION FOR DIAZEPAM


UNE EMULSION LIPIDIQUE COMME VECTEUR DU DIAZEPAM. ETUDE DE 9492 PATIENTS

RESUME
Les préparations habituelles de diazépam à destinée intraveineuse contiennent des solvants dont l'injection est douloureuse et qui sont facteurs de thrombophlébite dans un nombre important de cas. Cependant, le diazépam peut être dissous avec bénéfice dans la phase huileuse d'une émulsion huile dans l'eau (Diazemuls). Le Diazemuls a été administré à 9492 patients sans effets secondaires sérieux. La douleur et l'effet clinique ont été étudiés chez 2435 patients. Après une injection intraveineuse, seuls 0.4% ont eu mal. L'effet clinique attendu a été obtenu chez 99% des patients. L'injection i.m. de Diazemuls entraînait une douleur lors de l'injection avec une fréquence significa-tivement moindre que le Valium (7% et 43% respectivement). Des études pharmacocinétiques ont été faites après injection i.v. et i.m. de Diazemuls et de Valium. Les phases de distribution et d'élimination après injection i.v. étaient les mêmes avec les deux formes. Ainsi le produit se sépare-t-il probablement rapidement des particules hulueuse de l'émulsion après l'injection. Après administration i.m., la concentration plasmatique varie dans une large gamme avec les deux préparations; un bref survol d'autres substances testées sous forme d'émulsion est présenté.

SUMARIO

UNAS preparaciones de diazepam para uso i.v. contenían solvents que causaron dolores al momento de la inyección y trombophlebitis en un alto porcentaje de casos. Sin embargo, el diazepam puede disolverse con facilidad en la fase oleaginosa de una emulsion de aceite-en-agua (Diazemuls). Se administró Diazemuls a 9492 pacientes sin que hubieran efectos secundarios graves. Se llevó a cabo un estudio de 2435 pacientes respecto de los dolores y de los efectos clínicos, después de una inyección i.v. Sólo, un 0,4% sintió dolor. Se registró el efecto clínico previsto en un 99% de los pacientes. La inyección i.m. de Diazemuls tuvo por resultado una frecuencia mucho menor de los dolores en relación con la inyección en comparación con una inyección de valium (7% y 43%, respectivamente). Se efectuaron estudios farmacocinéticos después de inyectar i.v. e i.m. Diazemuls y Valium. Las fases de distribución y de eliminación después de la inyección i.v. fueron iguales con ambas formas. Entonces, la substancia se separa probablemente pronto de las partículas de aceite de la emulsión después de la inyección. Después de una administración i.m., la concentración en el plasma exhibe una amplia diseminación con ambas preparaciones. Se presenta una breve encuesta sobre las demás substancias de los ensayos, en forma de emulsión.

EMULSION GRASOSA COMO VEHÍCULO DEL DIAZEPAM UN ESTUDIO EN 9492 PACIENTES

ZUSAMMENFASSUNG


EMULSION GRASOSA COMO VEHÍCULO DEL DIAZEPAM UN ESTUDIO EN 9492 PACIENTES

SUSAMMENFASSUNG


SUMARIO

Unas preparaciones de diazepam para uso i.v. contenían solvents que causaron dolores al momento de la inyección y trombophlebitis en un alto porcentaje de casos. Sin embargo, el diazepam puede disolverse con facilidad en la fase oleaginosa de una emulsion de aceite-en-agua (Diazemuls). Se administró Diazemuls a 9492 pacientes sin que hubieran efectos secundarios graves. Se llevó a cabo un estudio de 2435 pacientes respecto de los dolores y de los efectos clínicos, después de una inyección i.v. Sólo, un 0,4% sintió dolor. Se registró el efecto clínico previsto en un 99% de los pacientes. La inyección i.m. de Diazemuls tuvo por resultado una frecuencia mucho menor de los dolores en relación con la inyección en comparación con una inyección de valium (7% y 43%, respectivamente). Se efectuaron estudios farmacocinéticos después de inyectar i.v. e i.m. Diazemuls y Valium. Las fases de distribución y de eliminación después de la inyección i.v. fueron iguales con ambas formas. Entonces, la substancia se separa probablemente pronto de las partículas de aceite de la emulsión después de la inyección. Después de una administración i.m., la concentración en el plasma exhibe una amplia diseminación con ambas preparaciones. Se presenta una breve encuesta sobre las demás substancias de los ensayos, en forma de emulsión.