

FACTORS AFFECTING DIAZEPAM AVAILABILITY FROM INTRAVENOUS ADMIXTURE SOLUTIONS

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SUMMARY — The authors studied the availability of parenteral solutions of diazepam in glass bottles or polyethylene (PE) containers during infusion through polyvinyl chloride (PVC) administration sets. Diazepam solutions in concentration of 1000mg/500ml in 0.9% sodium chloride (NS) and 5% glucose (G5W) injection were infused at a flow rate of 30ml/h, and samples were taken from the bottle and at the end of the administration set, till 12 hours of infusion. The samples were tested in triplicate using ultraviolet spectrophotometry. The greatest loss of diazepam was observed in all solutions at 30 minutes of infusion (63.5% G5W glass, 60.5% NS glass, 55% G5W PE and 58% NS PE from the original concentration of 200 ug/ml). The diazepam concentrations in the containers did not significantly changed. The loss of diazepam from solutions infused through PVC administration sets should be kept in mind in severe clinical situations as status epilepticus, tetanus and eclampsia.

Fatores que influenciam a infusão endovenosa contínua de diazepam.

RESUMO — Foram estudadas as variações de concentração do diazepam diluído em diferentes solventes e frascos, para emprego endovenoso contínuo. Foram feitas soluções em soro fisiológico (NS) e soro glicosado a 5% (G5W), frascos de vidro ou de polietileno (PE), volume total de 500ml, concentração inicial de diazepam de 200 ug/ml. Cada frasco foi conectado a equipo de polivinilcloroto (PVC) e as soluções foram infundidas a razão de 30 ml/h. Amostras coletadas dos frascos e dos equipos até 12 horas de infusão foram testadas em triplicata, por espectrofotometria ultravioleta. O maior decréscimo da concentração de diazepam ocorreu em todos os frascos aos 30 minutos de infusão, com concentrações 63,5% (G5W vidro), 55% (G5W PE), 60,5% (NS vidro) e 58% (NS PE) da concentração inicial. As concentrações nos frascos de vidro e PE permaneceram constantes. A diminuição das concentrações de diazepam deve-se à adsorção do diazepam aos equipos de PVC e essa perda deve ser levada em conta durante seu emprego em situações clínicas graves como status epilepticus, tétano e eclâmpsia.

Continuous intravenous (i.v.) infusion of diazepam has been used in the treatment of convulsions¹, tetanus³ and eclampsia², for i.v. anesthesia as an adjunct to analgesia during labor, and as a sedative for patients requiring prolonged artificial ventilation¹⁷. Several reports have mentioned the problem of variable drug delivery because of diazepam interaction with the infusion system^{8,9,12,14,16}. The potential hazards of incomplete delivery include not only inadequate therapy because of decreased drug administration but also possible drug overdose if compensatory increases in the infusion rate are continued after the tubing has become saturated with the drug.

The purpose of this study was to compare glass and polyethylene containers with 0.9% sodium chloride and 5% glucose solutions of diazepam and to measure losses of diazepam during a simulated infusion through plastic infusion sets.

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MATERIALS AND METHODS

The experiment was carried out at room temperature under normal room-light conditions. Diazepam (VALIUM, Roche, lot 25690 262) was prepared in concentration of 1000 mg/500ml (200 ug/ml) in 0.9% sodium chloride (NS) injection and 5% glucose (G5W) injection in glass containers and polyethylene containers (B. Braun, lot 8111). The polyethylene bottles were made of semirigid polyethylene (PE), which contains no additives. The infusion-set tubing (INTRAFIX, B. Braun) was made of polyvinyl chloride (PVC). Every administration set has a drip chamber of crystal polystyrene, a latex flash ball and an intermediary end part of high density polyethylene. The length of the PVC tubing was 128 cm. The injections were added to glass bottles through rubber stoppers and to polyethylene bottles through the plastic wall in the upper part of the bottles. Immediately after adding the injection solutions to NS and G5W, the containers were shaken for 20 seconds to ensure through mixing and the administration sets were attached to the bottles. Samples (5ml) were taken initially (time 0) and at each 15 minutes, during the first two hours, and each 2 hours in the subsequent 10 hours using sterile needles and glass syringes. At 0, 2, 6 and 12 hours a sample was taken from the bottle and simultaneously at the end of the administration set. The samples were analysed in triplicate. A flow rate of 30ml/h was maintained during the experiment.

The absorbance of the sample solutions was measured using a ultraviolet spectrophotometer (SPECTRONIC 700, Bausch-Lomb) at a wave length of 312 nm. For statistical purposes the Student t test was employed.

RESULTS

The diazepam concentrations in glass and polyethylene bottles did not differ significantly. At the end of the study (12 h) the concentration was 202 ± 3 ug/ml (G5W glass), 196 ± 1 ug/ml (NS glass), 218 ± 1 ug/ml (G5W PE) and 202 ± 4 ug/ml (NS PE). The extent of diazepam adsorption to the i.v. administration systems is shown in table 1. There is an initial rapid decrease of the concentrations which is maximal at 30 minutes. At this time the concentrations were 127 ± 0 ug/ml (63.5%) (G5W glass), 121 ± 1 ug/ml (60.5%) (NS glass), 110 ± 2 ug/ml (55%) (G5W PE) and 116 ± 1 ug/ml (58%) (NS PE).

After 30 minutes, there is a progressive increase of diazepam concentration at the end of the administration sets in all systems (Fig. 1). At the end of the experiment (12 h) the concentrations of diazepam were respectively 88.5% (G5W glass), 97.5% (G5W PE), 94.0% (NS glass) and 98.5% (NS PE).

Concentrations of diazepam (ug/ml)

Time (h)	G5W (glass)	G5W (PE)	NS (glass)	NS (PE)
00:30	127 ± 0	110 ± 2 ***	121 ± 1	116 ± 1 ***
01:00	165 ± 2	155 ± 4 **	163 ± 1	154 ± 1 ***
02:00	169 ± 1	163 ± 1 ***	175 ± 2	157 ± 2 ***
04:00	168 ± 2	176 ± 3 **	177 ± 3	163 ± 1 ***
06:00	171 ± 1	174 ± 1 **	177 ± 2	176 ± 1 *
08:00	173 ± 2	183 ± 2 ***	181 ± 2	183 ± 2 *
10:00	173 ± 2	188 ± 2 ***	182 ± 1	192 ± 3 ***
12:00	177 ± 3	195 ± 1 ***	188 ± 3	197 ± 2 **

Table 1 — Student t test comparing same solutions (G5W or NS) in glass and PE bottles:

*, non-significant; **, $p < 0,05$; ***, $p < 0,01$.

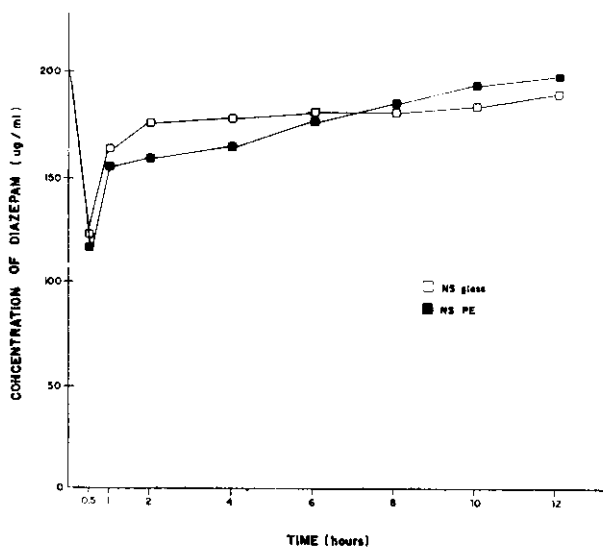
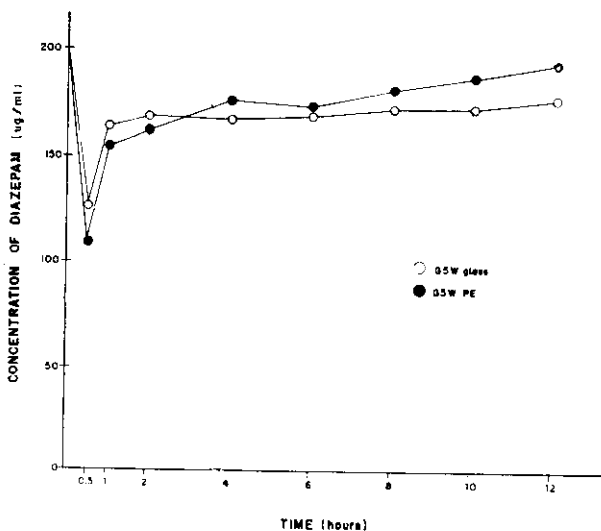


Fig. 1 — A (above) illustrates the initial decrease (30 minutes) and further increase of diazepam concentrations in G5W solutions, in glass and PE bottles. B (below) illustrates the initial decrease (30 minutes) and further increase of diazepam concentrations in NS solutions, in glass and PE bottles.

COMMENTS

The use of plastic components in intravenous delivery systems has gained widespread acceptance in clinical medicine due to its practicality. The interaction between several drugs (e.g., clomethiazole edisylate, chlorpromazine hydrochloride, heparin, insulin, nitroglycerin, promazine hydrochloride, promethazine hydrochloride, thiopental sodium, thioridazine hydrochloride, and trifluoperazine dihydrochloride) and intravenous PVC delivery systems and PVC administration sets has been reported^{7,8}. In fact, the use of PVC containers has been precluded^{4,13} for storage of clomethiazole, thiopental, and diazepam⁷. The use of glass or PE bottles is preferred in these situations¹⁵. To our particular interest are the reports of adsorption of diazepam to polyvinyl chloride tubing sets and PE bottles^{6,11,12,16}. The adsorption of diazepam to PVC tubing was clearly observed and is more important during the first 30 minutes. Thereafter a progressive increasing of diazepam concentrations is observed till an apparent steady state is noted at two hours of infusion. Then we observe a further increase of concen-

trations more marked in the effluent solution from PE bottles (NS or G5W). This increase would be due to the presence of substances leached from the PE bottles, which would increase the absorbance of the solutions stored in these containers⁸. The loss of diazepam in polyethylene bags are less important^{15,16}, as observed in our experiment.

Changes in diazepam concentration appeared to be independent of the i.v. fluids used in this study^{4,6,12,14}. What measures can be taken in order to minimize the loss of diazepam during continuous i.v. administration? Two alternatives seem suitable: the use of PVC set with the shortest possible length^{8,9,12,16}, and the use of the highest possible flow rate that is clinically safe^{12,16}. Polyethylene-lined administration sets⁶, polyolefin tubings⁹ and pluronic surfactants¹⁰ are other alternatives that are not yet available here. The monitoring of diazepam serum levels is suggested in clinical situations where continuous i.v. infusion of diazepam is required for longer time (e.g. tetanus). The use of greater concentrations of diazepam in the infusion solutions to override the adsorption may be dangerous, as the actual amount of drug that is delivered to the patient is unknown.

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