ELSEVIER

International Journal of Pharmaceutics 110 (1994) 197–201

international journal of pharmaceutics

Sorptive loss of diazepam, nitroglycerin and warfarin sodium to polypropylene-lined infusion bags (Softbags)

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Received 8 March 1994; modified version received 20 April 1994; accepted 25 April 1994

Abstract

The sorption of diazepam, nitroglycerin, and warfarin sodium to a new polypropylene-lined infusion bag (Softbag) was studied. For comparison, the loss of the same drugs was measured in two other types of containers. Clinical amounts of the drugs were added to 100 ml of 0.9% sodium chloride infusion solution in glass bottles, polyvinyl chloride (PVC) bags, and Softbag containers composed of inner and outer layers of polypropylene and a middle layer of a polypropylene-based elastomeric alloy. The containers were stored at room temperature (21 ± 2°C) without protection from light for 24 h (diazepam) and 120 h (nitroglycerin and warfarin sodium). Samples were taken at various intervals and assayed for drug concentration by UV spectrophotometry and/or high-performance liquid chromatography (HPLC). UV spectrophotometry was the primary method for diazepam and warfarin sodium whereas nitroglycerin was assayed only by HPLC. There were no appreciable changes in pH after 24 or 120 h and all the admixtures remained clear and colorless. Diazepam, nitroglycerin, and warfarin sodium did not show any sorption to glass bottles or Softbag containers. In PVC bags, however, up to 70% of diazepam was lost after 24 h, and 75% of nitroglycerin and 70% of warfarin sodium were sorbed after 120 h when the pH of the solution was 4.9. The sorption of warfarin sodium was only 30% when the pH of the solution was 5.6. There was no sign of extra peaks of degradation products in the chromatograms of the compounds and the purity of the chromatographic peaks was evident when studied by HPLC with a diode array detector.

Key words: Diazepam; HPLC; Infusion bag; Nitroglycerin; Softbag; Sorption; Spectrophotometry; Warfarin sodium

1. Introduction

The sorption of drugs in aqueous solution to polyvinyl chloride (PVC) infusion bags results in reduced drug delivery to the patient (D'Arcy, 1983). To overcome this problem, considerable effort has gone into developing plastic materials that do not interact with drugs. Studies on various plastics have shown that the degree of sorption to polyethylene- or polypropylene-lined infusion bags is substantially less than sorption to PVC (Kowaluk et al., 1981; Illum and Bundgaard, 1982; DeRudder et al., 1987; Martens et al., 1990). Polyethylene and polypropylene are now widely used materials. A new polypropylene-lined

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SSDI 0378-5173(94)00126-P

plastic infusion container, Softbag, designed to prevent or reduce sorptive loss of drugs, was recently introduced (Orion Corporation Farmos, Oulu, Finland). Softbag is made from three-layer plastic film. The inner and outer layers are polypropylene and between these layers is a polypropylene-based elastomeric alloy. The three layers are kept together solely by forces of strong adhesion, without any additives (Lambert, 1991).

The drugs diazepam, nitroglycerin, and warfarin sodium readily sorb to PVC administration sets (Kowaluk et al., 1981; Illum and Bundgaard, 1982; DeRudder et al., 1987; Martens et al., 1990). All of these drugs are used as injections or slow continuous infusions. Diazepam is administered especially in prolonged epileptic seizure, in premedication, and as an inducing agent in anesthesiology. Nitroglycerin infusion is administered to relieve severe and prolonged pain in the chest associated with heart infarct or unstable angina. Warfarin sodium is administered orally but also parenterally in the prophylaxis and treatment of thromboembolic conditions.

The purpose of our study was to compare the sorptive profiles of diazepam, nitroglycerin, and warfarin sodium in glass, PVC, and the new polypropylene-lined Softbag containers. The primary assay used for diazepam and warfarin sodium was UV spectrophotometry because it is a rapid and easy method to measure a great number of samples especially when there is no possibility of using an autosampler. However, degradation products of the compounds cannot be detected by spectrophotometry. This is one reason why an HPLC assay was also used for diazepam and warfarin sodium. The other reason for using two independent methods was to check the reliability of the results obtained by UV spectrophotometric assay. Nitroglycerin was assayed only by HPLC.

2. Materials and methods

2.1. Preparation of admixtures and samples

2 ml of fluid was withdrawn from each of six 100 ml glass bottles (Orion Corp., Farmos, Oulu, Finland, lot SIL 45 AA), PVC bags (Baxter, Healthcare S.A., Castlebar, Ireland, lots 91L18G-50 and 92I29G50), and Softbag containers (Orion Corp., Farmos) containing 0.9% sodium chloride infusion. Admixtures of the three drugs were tested using concentrations within the ranges commonly used or recommended by the respective manufacturer. The content of one diazepam ampul (Diapam 5 mg/ml, 2 ml/ampul, Orion Corp., Orion Pharmaceutica, Espoo, Finland, lot RH 1-2) was added to each container, producing a nominal concentration of 100 μg/ml. Nitroglycerin admixtures were prepared as described for diazepam but using nitroglycerin ampuls containing 2 ml of solution (Nitro 5 mg/ml, Orion Corp., Orion Pharmaceutica, lot QK 18-2). In the case of warfarin sodium, 0.5 ml of fluid was withdrawn from each container and 0.5 ml of Marevan solution 5 mg/ml (Marevan 25 mg + aq. ad inject. 5 ml, Orion Corp., Orion Pharmaceutica, lot RD 1-1) was added to each, resulting in a nominal concentration of 25 μg/ml. After mixing by gentle agitation, solutions were stored at room temperature (21 $\pm$ 2°C) without protection from light. During the study, the glass containers were kept upright to minimize contact between drugs and the rubber stoppers. The plastic containers were hung from their support ring.

At 0, 1, 2, 4, 6, and 24 h, the admixtures of diazepam, and at 0, 1, 3, 6, 24, 48, 72, 96, and 120 h those of nitroglycerin and warfarin sodium were visually inspected for clarity and color change; accurately measured samples of 2.0 ml (diazepam and nitroglycerin) and 3.0 ml (warfarin sodium) were then transferred from the infusion bottles and bags. The size of the sample was 5.0 ml when the pH of the solution (diazepam at 0 and 24 h and nitroglycerin and warfarin sodium at 0 and 120 h) was measured (PHM 83 Autocal pH meter, Radiometer, Copenhagen, Denmark). The contents of diazepam and warfarin sodium were determined by UV spectrophotometry and, for comparison, also by a previously described high-performance liquid chromatographic (HPLC) method with UV detection (Hancock and Black, 1985; Moore and Lau-Cam, 1986). Nitroglycerin concentrations were measured only by HPLC (Martens et al., 1990).

2.2. Assay of diazepam

For UV spectrophotometric quantitation (spectrophotometer Philips PU 8740, Cambridge, U.K.), the diazepam sample was accurately diluted with water to 5 μg/ml. The measurements were carried out at 230 nm with a cell width of 1 cm. A calibration graph was prepared for the range of 1–6 μg/ml of diazepam.

A 25 cm × 4 mm C_{18} Lichrosorb column (Merck, Darmstadt, Germany) was used in the HPLC assay. The pump (model 2150, LKB, Bromma, Sweden) delivered the mobile phase, consisting of HPLC-grade methanol in water (75:25, v/v) at a rate of 1 ml/min. A UV detector (model 2151 variable-wavelength monitor, LKB) monitored column eluents at a wavelength of 230 nm. Peak areas were integrated after each injection by an integrator (model D-2000, Hitachi Ltd, Tokyo, Japan). Nitrazepam 4 μg/ml (Orion Pharmaceutica, Orion Corp.) was used as an internal standard. Under these conditions, nitrazepam and diazepam standard (University Pharmacy, Helsinki, Finland) eluted from the column at 5.4 and 8.5 min, respectively. For the HPLC measurement, the diazepam sample was diluted with eluent to 5 μg/ml. The injection was carried out with a 20 μl loop injector.

A five-point calibration graph (representing concentrations ranging from 1.0 to 6.0 μg/ml) of diazepam concentration against the ratio of integrated peak areas for diazepam and nitrazepam was constructed.

2.3. Assay of nitroglycerin

Nitroglycerin sample 100 μg/ml was assayed without dilution by the HPLC method (Martens et al., 1990), using a 20 cm × 4.6 mm C_8 column (Hewlett-Packard 79915 MO-174). A methanol-water mixture (65:35, v/v) was used as eluent, the flow rate being 1 ml/min. Nitroglycerin was detected at a wavelength of 218 nm. The HPLC equipment was as described above for diazepam. A calibration graph was prepared for the range 20–120 μg/ml of nitroglycerin (10% ethanolic solution, Orion Corp., Orion Pharmaceutica) and under these conditions nitroglycerin eluted from the column at 4.7 min.

2.4. Assay of warfarin sodium

Warfarin sodium sample 25 μg/ml was assayed as such by spectrophotometric and HPLC methods; the equipment was the same as described for diazepam. The spectrophotometric measurements were carried out at a maximum wavelength of 308 nm. A 15 cm × 3.9 mm C_{18} Nova-Pak column (Waters Assoc., Milford, MA, U.S.A.) was used in the HPLC method. The eluent was a mixture of tetrahydrofuran, methanol, water, and acetic acid (35:10:65:0.1, v/v) and the flow rate was 1 ml/min. The drug was detected at a wavelength of 308 nm and its retention time was 5.7 min. In both methods the concentration range of the calibration graphs was 5–30 μg/ml of warfarin sodium (Orion Corp., Orion Pharmaceutica).

2.5. Evaluation of the assays

The possible interference of the excipients used in injections of the compounds studied was measured by UV spectrophotometry and HPLC using blank solutions containing the same inactive components in the same concentrations as the dosage forms.

The purity of the chromatographic peaks of the compounds was checked for each compound under the conditions described above. An HPLC system with two Waters 501 pumps and a Waters 991 Photodiode Array (PDA) system with a Waters 5200 printer/plotter were employed. The PDA system consisted of a Waters 991 diode-array detector, an NEC PowerMate 386/25 computer, and PDA software (all from Waters Assoc., Milford, MA, U.S.A.). The spectra of the drugs were registered at three different points of each peak and displayed together.

The calibration graphs in each case showed correlation coefficients within the range $r = 0.9985–0.9999$. The calibration graphs were checked each day during the experiments. Intra-day and inter-day coefficients of variation were $< 3.6\%$.

3. Results and discussion

There was no decrease in the concentration of diazepam, nitroglycerin, or warfarin sodium in 0.9% sodium chloride infusion when stored in glass or Softbag containers for 24 or 120 h, however, the concentration of the compounds declined rapidly in the PVC containers (Fig. 1–3).

The concentration of diazepam decreased by about 70% at 24 h in PVC bags (Fig. 1). This value is consistent with literature reports (Cloyd et al., 1980; Illum and Bundgaard, 1982; Martens et al., 1990) of 60–80% losses of diazepam to plastic containers in 24 h. The reliability of our results was confirmed in two independent assays. Student's t-test did not reveal significant ($p = 0.05$) differences between the analytical data obtained by UV spectrophotometry and by HPLC.

The sorption of nitroglycerin was studied for 120 h and after this period only 25% of the initial concentration remained when stored in the PVC containers (Fig. 2). In most earlier studies, the sorption of nitroglycerin to infusion containers was followed for only 24 h and during this period the decrease in concentration was about 40–50% (Baaske et al., 1980; Martens et al., 1990). Our result of a decrease of 45% after 24 h in PVC containers is in good agreement with this.

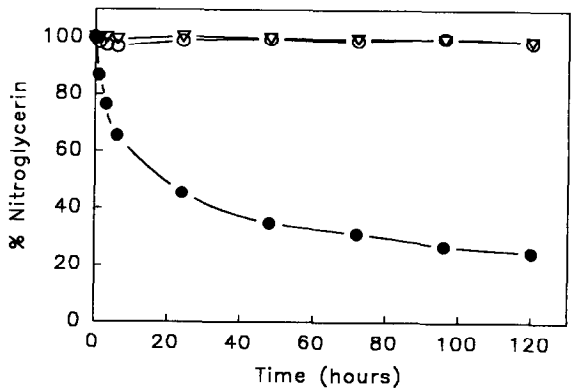

Fig. 2. Concentration of nitroglycerin (measured by HPLC) as a function of time. Values expressed as means of six determinations. ±C.V. values varied between 0.71 and 2.21%. Symbols as in Fig. 1.

We used two different batches of infusion solutions in our study of the sorption of warfarin sodium to PVC bags. After the addition of warfarin sodium injection, the pH of the infusion solutions was 4.9 in four bags and 5.6 in two bags. Since warfarin is a weak acid with a pK_a of 5.1, the extent of drug loss was expected to decrease at pH 5.6 where the ionization of warfarin is greater. In our study, the concentration of warfarin sodium decreased during 24 h by about 51% at pH 4.9 but only by about 17% at pH 5.6 (Fig.

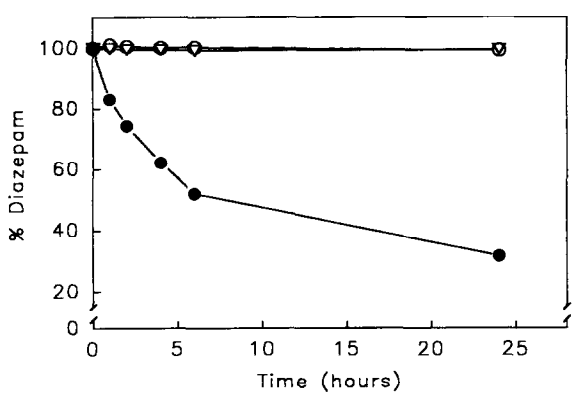

Fig. 1. Concentration of diazepam (measured by UV spectrophotometry) as a function of time in glass bottles (○) and in PVC (●) and Softbag (▽) infusion bags. Values expressed as means of six determinations. ±C.V. values varied between 0.50 and 3.26%.

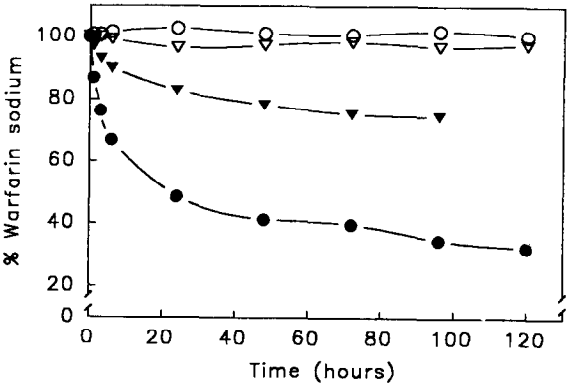

Fig. 3. Concentration of warfarin sodium (measured by UV spectrophotometry) as a function of time in glass bottles (○) and in PVC pH 4.9 (●), PVC pH 5.6 (▼) and Softbag (▽) infusion. Values expressed as means of two (pH 5.6) or four (pH 4.9) determinations. ±C.V. values of the latter varied between 0.38 and 3.09%.

Table 1
pH values for drug admixtures in 0.9% sodium chloride injection

Drug		pH values in different containers (±C.V.% [a])		
		Glass	PVC	Softbag
Diazepam	$t = 0$	6.0 ± 0.1	4.9 ± 0.3	6.0 ± 0.3
	$t = 24$ h	5.6 ± 0.1	5.0 ± 0.2	5.7 ± 0.1
Nitroglycerin	$t = 0$	6.0 ± 0.3	5.0 ± 0.2	5.5 ± 0.2
	$t = 120$ h	5.8 ± 0.3	4.7 ± 0.3	5.3 ± 0.4
Warfarin sodium	$t = 0$	5.9 ± 0.3	4.9 ± 0.1/5.6 ± 0.1	5.9 ± 0.1
	$t = 120$ h	6.1 ± 0.2	5.1 ± 0.1/5.8 ± 0.1	5.8 ± 0.4

[a] $n = 6$, except warfarin sodium in PVC bags pH 4.9, $n = 4$ and pH 5.6, $n = 2$.

3). Earlier studies (Kowaluk et al., 1981; Illum and Bundgaard, 1982; Martens et al. 1990) support these results. We followed the sorption for 120 h, at which time the loss of warfarin sodium was about 70 and 30% at pH 4.9 and 5.6, respectively. Warfarin sodium was also quantified in two independent assays, with no significant difference in the results ($p = 0.05$).

At no time was there appreciable change in pH (Table 1) or notable discoloration or visual precipitation of sample solutions. The excipients of the injections interfered with neither the UV spectrophotometric nor the HPLC assay of diazepam or warfarin sodium. Even when some of the admixtures were stored for 10 (diazepam) or 40 (nitroglycerin and warfarin sodium) days there was no sign of extra peaks in the chromatograms, thus confirming the stability of the compounds studied. In addition, no interference was observed when the purity of the chromatographic peaks of the compounds was checked by registering spectra at three different points of each peak. When the three spectra of the peak were displayed together and found to be identical, the peak could be assigned to a single component.

4. Conclusions

The results show that the new polypropylene-lined containers (Softbags) can safely be used clinically for the administration of diazepam, nitroglycerin, and warfarin sodium in 0.9% sodium chloride by intravenous infusion. Admixtures did not lose potency when stored at room temperature without protection from light for 24 h (diazepam) or 120 h (nitroglycerin and warfarin sodium).

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