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Leaching of diethylhexyl phthalate from PVC bags into intravenous teniposide solution

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Abstract

The stability of teniposide in various diluents and polyvinyl chloride bags was determined, and the extent of leaching of di(2-ethylhexyl) phthalate (DEHP) from PVC bags caused by the teniposide formulation was measured. No significant drug loss was observed during simulated infusions ($n = 4$) for 1 h using PVC infusion bags and administration sets. No significant difference was found between infusion solutions (5% glucose or 0.9% NaCl). To minimize patient exposure to DEHP, teniposide solutions may be stored in a glass or polyolefin container and delivered through polyethylene-lined i.v. administration sets. If PVC bags are used for preparing teniposide solutions, the injections must be used immediately after preparation or stored 4–5 h at +4°C.

Key words: Compatibility; Teniposide; Di(2-ethylhexyl) phthalate; PVC bag; HPLC

Teniposide is a semi-synthetic derivative of podophyllotoxin used mainly in hematological indications or in some solid tumors (Rozencweig et al., 1977). Because of teniposide's poor solubility in water, the current clinical formulation consists of a 10 mg/ml solution of teniposide in a non-ionic surfactant, polyoxyethylated castor oil (Cremophor® EL). For infusion, this formulation is diluted in either 0.9% sodium chloride injection or 5% glucose injection.

Therefore, with the increasing use of continuous i.v. infusion and intermittent small-volume i.v. infusion modes of administration, it is imperative that the stability and the compatibility of teniposide in administration vehicules and PVC containers be investigated. Consequently, when drugs are administered by continuous i.v. infusion with PVC material, knowledge of the rate of drug delivery to the patient is essential (D'Arcy, 1983), as well as the innocuousness of the infusion solution.

The objectives of this study were to observe the physical appearance of the teniposide formulation diluted to concentrations that may be used

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clinically in 0.9% sodium chloride injection or 5% glucose injection and stored in PVC bags and glass containers, and to determine whether the stability of teniposide is compromised during storage and infusion (Hamon et al., 1987). In addition, since more haze is observed in teniposide solutions stored in polyvinyl chloride (PVC) infusion bags and because of the known leaching of the plasticizer di(2-ethylhexyl) phthalate (DEHP) from PVC bags by surfactants such as Cremophor EL (Moorhatch and Chiou, 1974; Venkataramanan et al., 1986), the extent of DEHP leaching was also determined. Since DEHP has been reported to be somewhat hepatotoxic (Ganning et al., 1984) and since teniposide is most likely to be administered to patients whose general health is compromised, the extent of possible exposure of patients to DEHP should be ascertained and methods to minimize such exposure developed.

We have used an HPLC technique to investigate the compatibility of the teniposide with PVC containers and PVC infusion sets and the leaching of DEHP from PVC infusion bags and sets during simulated infusions, and during storage at room temperature in PVC bags and at +4°C without protection from light.

Analyses were performed on a 5 μm C_{18} Interchim column (100 × 4.6 mm i.d. for teniposide and 150 × 4.6 mm i.d. for DEHP) (Interchim, Montluçon) operating at room temperature. Teniposide was eluted isocratically with a mobile phase consisting of methanol and water (65:35, v/v) at a flow rate of 1.5 ml/min. DEHP was eluted isocratically with a mobile phase consisting of acetonitrile and buffer (triethylamine 0.2% adjusted to pH 2.5 with 85% phosphoric acid) mixture (90:10, v/v) at a flow rate of the 2 ml/min. The absorbance was monitored at 230 nm for teniposide and 222 nm for DEHP. For quantification of DEHP, an internal standard, di(*n*-nonyl) phthalate (DNNP) was employed.

Insofar as it was possible, we employed conditions in conformity with the drug concentrations normally used in hospital pharmacy departments for the storage of drugs in infusion bags. To infusion bags containing 250 ml of 5% glucose or 0.9% sodium chloride solution, a known amount of teniposide was added to achieve the following concentrations which are most often used in hospitals: 400 μg/ml in the bags.

For simulated infusion, solution of drug was prepared in PVC bags immediately before the infusion. The bag containing drug was then attached to an administration set connected to the infusion pump that allowed the solution to flow through at a constant rate. At specified times of infusion, samples (1 ml) were withdrawn at regular intervals into the PVC bags, and at the same time, an aliquot of effluent (1 ml) was collected from the administration set and immediately analysed by HPLC. All simulated infusions were carried out at least in duplicate (two infusions in 0.9% NaCl and two infusions in 5% glucose) at

Table 1
Validation data of HPLC assay procedure (n = 5)

Sample substance	Concentrations (μg/ml)	Average concentration found (±SD) (μg/ml)	C.V. Intra-assay (%)	C.V. Inter-assay (%)	Accuracy (%)	Linear regression equation ($y = ax + b$)	Correlation coefficient (r)
Teniposide	20	19.56 ± 0.20	0.85	1.02	97.80		
	40	40.22 ± 0.19	0.35	0.47	100.55	$y = 5.071x + 1.105$	0.999
DEHP	1.25	1.17 ± 0.05	2.49	4.27	93.60		
	2.5	2.46 ± 0.05	0.44	2.03	98.40		
	5	5.10 ± 0.20	0.87	3.92	102.00	$y = 0.047x + 0.141$	0.999
	10	9.64 ± 0.05	1.29	0.51	96.40		
	20	20.55 ± 1.09	1.60	5.30	102.75		
	40	39.93 ± 0.88	1.19	2.20	99.82		

SD, standard deviation; C.V., coefficient of variation.

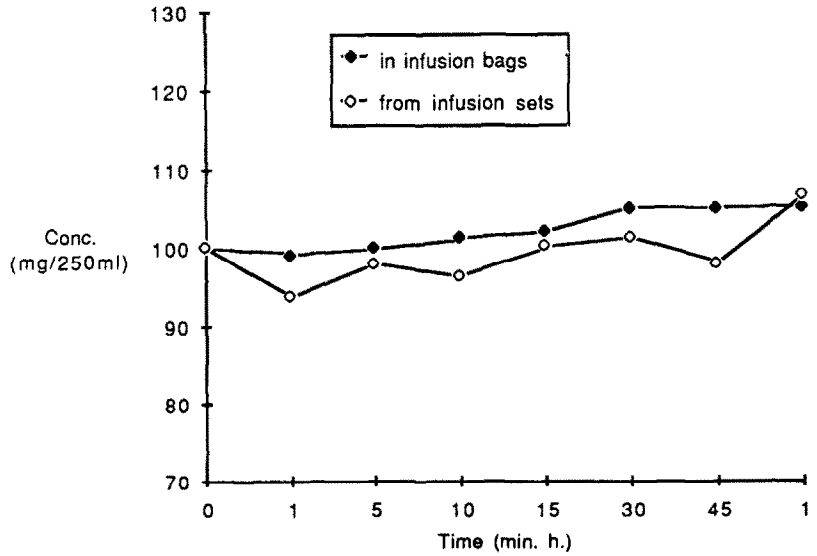

Fig. 1. Concentration kinetics of teniposide during simulated infusion ($n = 4$) using plastic infusion bags and sets.

room temperature (20–24°C) and without protection from light.

For storage studies, after mixing the drug in the bag by rapid shaking, samples (1 ml) were withdrawn at regular intervals in glass tubes. Infusion bags containing the drug were stored at room temperature and at + 4°C for a period of 48 h without protection from light. Drug storage in these bags was carried out in 5% glucose.

Table 1 summarises the validation data of the assay procedure for teniposide and DEHP. We observed good linearity between peak area and concentrations. To assess reproducibility, the same concentration was analysed five times for each point of the calibration curves. The results demonstrate that this analytical method had acceptable accuracy and precision in every case. The analysis of teniposide and DEHP were per-

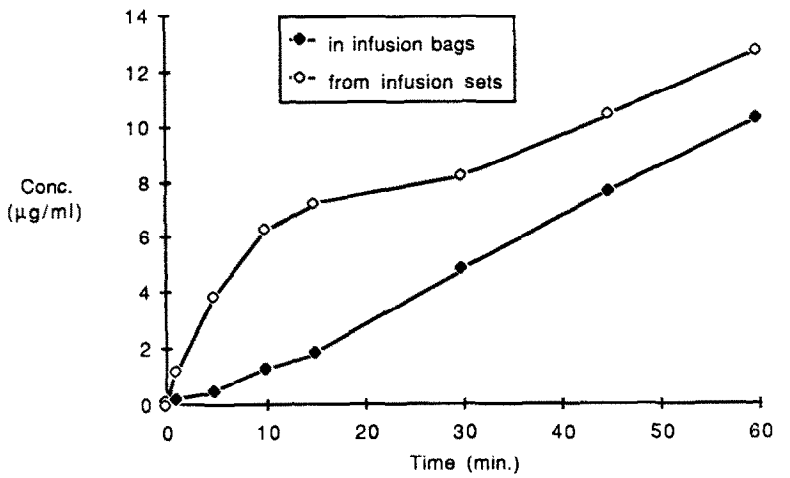

Fig. 2. Concentration over time of di(2-ethyl hexyl) phthalate (DEHP) leached from 250 ml polyvinyl chloride (PVC) during simulated infusions ($n = 4$) using plastic infusion bags and sets.

formed by HPLC after suitable dilution in methanol in order to fit the calibration curves.

Fig. 1 depicts the concentration kinetics of teniposide during simulated infusion ($n = 4$), using PVC infusion bags and sets. When solutions of teniposide were infused through infusion sets from PVC infusion bags over a period of 1 h, the variation in drug concentration in both the PVC bags and effluent in no case exeeded 10%. There was no substantial difference between teniposide concentrations at time zero and at any subsequent time points. This demonstrates that teniposide was not sorbed by the PVC infusion bags and sets during infusion at room temperature. No significant difference was observed with respect to drug stability during simulated infusions using 5% glucose or 0.9% NaCl.

The analysis of DEHP was performed by HPLC after suitable dilution with DNNP (I.S.). Fig. 2 presents the amount of DEHP leaching from PVC bags and sets during simulated infusion ($n = 4$). The amount of DEHP leached into the solutions increased progressivly during the 1 h infusion period. Fig. 2 shows that the concentration of DEHP was dependent on the duration of the infusion period. On the other hand, the amount of plasticizer was greater in effluent from PVC administration sets than in solution PVC bags. Moreover, there was no substantial difference in the amount of DEHP leached from the PVC bags containing 0.9% sodium chloride injection and the bags containing 5% glucose injection. However, these amounts did not appear to be substantial enough to increase the toxic risk in patients.

The concentration kinetics of DEHP present in solution after various periods of storage in PVC infusion bags containing 250 ml of 5% glucose solution at room temperature and at + 4°C without protection from light are presented in Fig. 3. The study of DEHP leached from the PVC bags was carried out in 5% glucose injection only, since beforehand, there was no substantial difference between 0.9% NaCl and 5% glucose during simulated infusion.

DEHP was not detected in diluted teniposide formulation stored in glass bottles or polyolefin containers. However, the solutions stored in PVC infusion bags did contain DEHP. Teniposide itself did not appear to contribute to the leaching of DEHP. Venkataramanan et al. (1986) reported a simular observation when they compared the extent of DEHP extraction by the vehicule in the presence and absence of cyclosporin. The agent

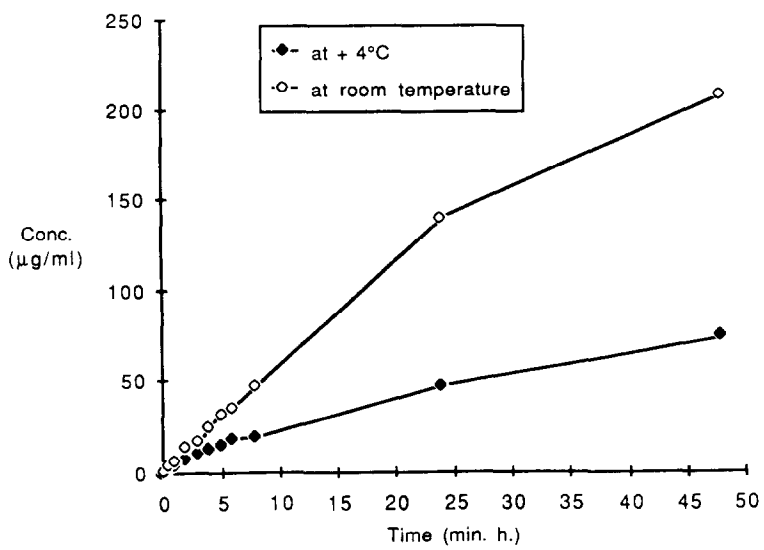

Fig. 3. Concentration over time of di(2-ethyl hexyl) phthalate (DEHP leached from 250 ml polyvinyl chloride (PVC) infusion bags containing 100 mg of teniposide in 5% glucose injection.

responsible for the leaching of DEHP observed during this study was probably the nonionic surfactant Cremophor EL. The storage temperature of infusion PVC bags after teniposide dilution thus contributed to the extent of DEHP leaching. Indeed, higher concentrations of DEHP in infusion solution were observed after 48 h in PVC bags stored at ambient temperature (20–23°C) than in PVC bags stored at + 4°C.

Therefore, the actual amount of DEHP infused into a patient depends on the concentration of Cremophor EL in the solution, the storage temperature of the solution in the PVC bags and the duration of storage or infusion period of the solution in the bag.

Very little or no DEHP is detectable in water, 0.9% sodium chloride or 5% glucose stored in plastic bags for more than 1 year (Dine et al., 1991). However, concentrations of ethanol or castor oil control the amount of DEHP extracted from plastic bags. Hence, in our study, substantial quantities of DEHP (52 mg at room temperature and 19 mg at + 4°C) were leached into intravenous solutions over 48 h, when teniposide formulation was diluted in PVC bags.

The clinical consequences of using PVC bags and infusing large quantities of DEHP into patients are not completely known at this time. However, the occurrence of hepatotoxicity after the use of PVC tubing for patients undergoing renal dialysis has been attributed to the release of DEHP from the tubing. It has been estimated that these patients receive about 100–200 mg of DEHP during each dialysis treatment (Kevy and Jacobson, 1983). Consequently, since DEHP is hepatotoxic, it is essential to minimize patient exposure to this compound (Ganning et al., 1984).

In conclusion, the HPLC procedure described in this paper is rapid and reproducible for the determination of teniposide and DEHP in parenteral solutions. The present study has examined the kinetics of teniposide and DEHP concentration during simulated infusion using PVC bags and administration sets. The results demonstrate satisfactory compatibility of teniposide with PVC infusion material over the 1 h infusion period. However, large amounts of DEHP were extracted from PVC infusion bags and administration sets by solutions containing the teniposide formulation. Therefore, in order to minimize the risk of exposure of the patient to the toxicity of DEHP, it is recommended that the intravenous teniposide administration in the PVC bags should be used immediately after preparation or stored for a maximum of 4–5 h at + 4°C or diluted teniposide formulation be prepared and stored in a glass or polyolefin container and delivered through a polyethylene-lined i.v. administration set.

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