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The extraction of diethylhexylphthalate (DEHP) from polyvinyl chloride components of intravenous infusion containers and administration sets by paclitaxel injection[1]

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Abstract

Paclitaxel injection (Taxol™) contains cremophor and ethanol in equal proportions, two agents known to leach diethylhexylphthalate (DEHP) from polyvinyl chloride (PVC) infusion bags and administration sets. The manufacturers of paclitaxel therefore recommend the use of glass, polypropylene or polyolefin containers for storage. This recommendation poses a number of practical problems since the availability of these other types of containers is severely limited and as such staff may be unfamiliar in their handling. The aim of this study was to investigate the extent of DEHP extraction by paclitaxel injection contained in PVC infusion bags and administered by either PVC or non-PVC sets in a bid to verify the manufacturers' recommendations to avoid using PVC containers. The results indicated that during a 3 h infusion period, increasing amounts of DEHP were leached into the paclitaxel vehicle from both the PVC infusion bags and the standard PVC sets. The amounts of DEHP extracted depended on the concentration of the paclitaxel vehicle, the length of contact between the injection vehicle and the container and the type of administration set used. DEHP concentration was at its lowest when a non-PVC set was used to administer the infusate. The addition of 300 and 600 mg paclitaxel to the infusate, administered by non-PVC sets, led to no significant increase in DEHP extraction. Comparative total amounts of DEHP extracted for each dose were 10.0 and 30.3 mg for the paclitaxel vehicle infusion through non-PVC sets and 13 and 30.5 mg respectively for the formulated drug plus vehicle. These amounts of DEHP are substantially less than those delivered during a blood transfusion. Furthermore, the possibility of chronic exposure to DEHP from paclitaxel administered under these conditions is negligible in patients receiving the drug on four to six occasions. The study concludes that there is only minimal risk of DEHP exposure from paclitaxel infusion contained in PVC bags and administered through non-PVC administration sets.

Keywords: Paclitaxel; Polyvinyl chloride; Diethylhexylphthalate; Intravenous infusion; Administration

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1. Introduction

Polyvinyl chloride (PVC) is the material most widely used in the UK and Europe in the manufacture of intravenous infusion containers and administration set tubing. In order to ensure that the PVC is sufficiently flexible for these applications, the polymer is formulated to contain relatively large amounts of plasticiser. The plasticiser currently used for this purpose is diethylhexylphthalate (DEHP). Water insoluble, this phthalate salt is not normally extracted into aqueous infusions prepared in PVC bags. However, when solubilisers such as cremophor or solvents, such as ethanol, are added to those aqueous infusions to increase the solubility of a particular drug, DEHP extraction will occur (Moorhatch and Chio, 1974; Allwood, 1986; Venkataramanan et al., 1986). DEHP is also extracted into whole blood stored in PVC bags (Allwood, 1986). For instance, it has been estimated that a patient infused with 2-3 l stored blood will receive up to 200 mg DEHP (Baker, 1978).

The risks of patient exposure to DEHP salts in infused products has yet to be fully evaluated. Kaul et al., 1982 in their review of the evidence for toxicity of phthalates in intravenous infusions, concluded that whilst the risks of acute toxicity remain relatively low, prolonged, even low level exposure to phthalates, may be harmful. Nevertheless, with one possible exception, there is currently no firm evidence of adverse or toxic effects in recipients. The exception in point, observed by Hillman et al., 1975, refers to levels of DEHP found in neonatal tissues after the administration of regular infusions through administration sets and PVC extension lines.

It is likely that patients receiving regular parenteral infusions or those receiving blood or blood products, are exposed to phthalate salts. This exposure may be to small amounts long-term or large amounts short-term. In none of these instances is there a proven link between DEHP exposure and toxicity. While this should not be regarded as a cause for complacency, experience to date suggests that occasional patient exposure to small amounts of phthalate salts is not particularly hazardous (Harris, 1981). Nevertheless, clinicians may wish to balance the levels of DEHP exposure likely in a particular clinical situation against those levels which patients will have already received and may continue to receive as a result of a variety of therapies.

Paclitaxel injection (Taxol™) vehicle contains equal parts of cremophor and ethanol. It has been reported that paclitaxel injection diluted in aqueous fluids caused extraction of DEHP during storage (Waugh et al., 1992) at a rate which was dependent on the dilution factor. The researchers used their results to calculate the approximate quantities of DEHP likely to have leached into paclitaxel infusions after storage. These data suggest that a 500 ml infusion containing 240 mg paclitaxel (equivalent to the normal median starting dose) will extract some 50 mg DEHP when stored at ambient temperature for a 3 h period and double that amount when stored for 6 h. When the concentration of paclitaxel is reduced there would be a corresponding reduction in the amount of DEHP extracted.

More recently, Pearson and Trissel (1993) observed that relatively large amounts of DEHP were extracted from PVC after 24 h storage. The amounts present in solution after 4 h storage however, were found to be relatively small. Both reports support the hypothesis that DEHP extraction is determined by two principal factors: paclitaxel concentration and length of time stored in PVC infusion bags. A reduction in both factors could possibly lead to a corresponding and substantial reduction in the total amount of DEHP extracted. The same investigators (Pearson and Trissel, 1993) using PVC administration sets during simulated delivery of a similar paclitaxel infusion, reported that these sets will contribute a further 9 mg DEHP. Although the use of non-PVC sets will reduce the risk of exposure to DEHP, Trissel et al., 1994 found that DEHP was released from administration sets labelled as 'non-PVC containing'.

The manufacturers of paclitaxel advise against the use of standard PVC sets to deliver paclitaxel infusions recommending instead that the infusion be stored in non-PVC containers made of glass, polypropylene or polyolefin and administered using sets made of or lined with polyethylene

(Anon, 1993). Since in most countries intravenous infusions and standard administration sets are almost universally constructed using DEHP-plasticised PVC, a recommendation to avoid such equipment, particularly the infusion bags, poses a number of practical problems. Availability of infusions in other types of container is now severely limited, since most countries have long ceased to use glass as an infusion container and polyethylene-packed infusions are available in only limited supply. Furthermore, staff may be neither familiar nor competent in the particular handling or installation techniques required to set up an infusion using non-PVC containers and administration sets.

The aim of this study was to supplement existing data by examining the amount of DEHP extraction by paclitaxel injection vehicle with and without the presence of the formulated drug, stored in PVC bags and administered by PVC and non-PVC sets. The study also set out to verify the manufacturer's recommendation to avoid PVC containers.

2. Materials and methods

2.1. Materials

Polyoxyethylene castor oil (Cremophor EL), as used in the formulation of paclitaxel injection, was supplied by Bristol Myers Squibb Ltd. Absolute alcohol was obtained from BDH chemicals Ltd, Poole, Dorset, UK. Paclitaxel vehicle was prepared to contain in 1 ml Cremophor 527 mg plus absolute alcohol 396 mg (equivalent to 50% by volume of each component). Di(2-ethylhexyl) phthalate (DEHP) 99% was obtained from Aldrich Chemical Co. Ltd., Dorset, UK. Glucose 5% infusions, 500 ml nominal volume, Viaflex, were obtained from Baxter Healthcare Ltd, Thetford, UK. Administration sets used were Solution Administration Sets and Flo-Gard Low Adsorption Sets, obtained from Baxter Healthcare Ltd. Infusion pumps used were the Flo-Gard model 6200 (Baxter Healthcare Ltd).

2.2. Methods

Analysis of DEHP in infusates was performed by high-performance liquid chromatography (HPLC) using a Techsphere 5 μm ODS packed 10 cm column. The solvent was methanol/1% acetic acid/water (in the ratio 90:3:7) at a flow rate of 1 ml/min for 7 min, followed by 3 ml/min for 8 min, returning to 1 ml/min for 5 min. A run-time of 20 min was required for each assay. Detection was at 254 nm. Sample injections volumes of 20 μl were performed by fixed volume loop (Rheodyne Model 7125). Quantification was by computerised electronic integration (PC Integration Pack, Kontron Ltd., Watford, UK). DEHP standards containing 100 μg/ml were prepared in paclitaxel vehicle: 5% glucose (in the ratio of 10:90).

Representative chromatograms (as shown in Fig. 1), indicated that the retention time for DEHP was approximately 7 min. This method was validated by spiking solutions of 5% glucose plus paclitaxel vehicle (90:10) with DEHP in methanol in the concentration range 22-110 μg/ml (5 points, duplicate injections). The linearity of response with concentration was confirmed (r = 0.9997). The precision of repeated injections in glucose/paclitaxel vehicle (100 μg/ml) was determined and confirmed as acceptable between consecutive injections (coefficient of variance = 1.15%; n = 4) and between experiments (coefficient of variance = 0.98%; n = 5).

2.2.1. DEHP extraction using paclitaxel vehicle only

Two paclitaxel-equivalent concentrations were tested: 0.6 and 1.2 mg/ml paclitaxel (50 and 100 ml equivalent volumes of vehicle in a total volume of 500 ml respectively). Six infusion bags were prepared at zero time for each test. The equivalent volume of vehicle was removed from the bags before adding the appropriate volume of paclitaxel vehicle (i.e. 50 or 100 ml) using 50 ml plastic syringes (Plastipak, Becton Dickinson Ltd., UK). The contents of each bag were thoroughly mixed by repeated inversion and infusion commenced immediately for the Zero Time bags. The administration set was attached and administration commenced once the set had been attached to the

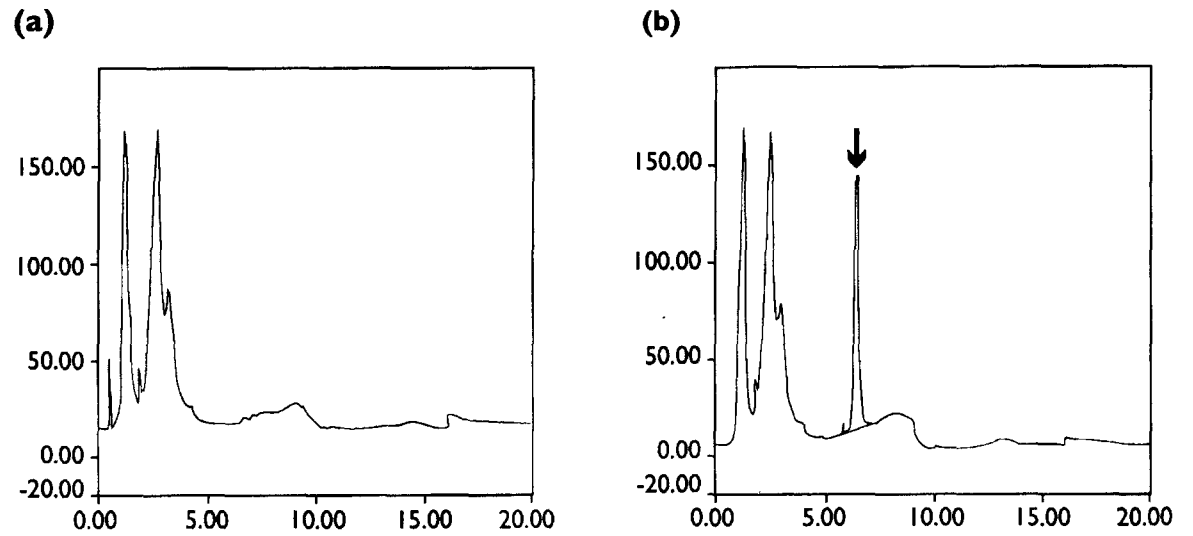

Fig. 1. Representative chromatograms of paclitaxel vehicle 10% by volume (1 part diluted in 9 parts 5% glucose) infusion (a) alone and (b) spiked with DEHP 100 μg/ml. The DEHP peak is labelled 'peak 1'.

infusion pump. Two parallel infusions were performed, one using a standard administration set, the other a non-PVC set. Infusion rates were set to deliver 500 ml in 3 h, with a second pair of bags being attached at the end of this period. The 24 h bags were stored at ambient temperature overnight before commencing simulated administration through the designated administration set. The infusates were collected into glass bottles from the distal end of each administration set. In addition, in order to determine the difference in DEHP extraction between bag and set, small (1–2 ml) samples were also collected into glass vials from the distal end of each administration set every 30 min. Plastic syringes were used to remove additional samples from the additive port of the infusion bags at the same time intervals.

2.2.2. DEHP extraction using paclitaxel injection (drug and vehicle)

Paclitaxel injection was added to 5% glucose infusion as previously described, at doses of 300 and 600 mg paclitaxel per bag. Infusion commenced within 15 min of preparation, using non-PVC administration sets.

2.3. Design of assay

DEHP standards were prepared on each test occasion by dissolving 100 mg DEHP in 100 ml methanol. One milliliter, accurately measured, was diluted to 10 ml with the appropriate paclitaxel vehicle to give a solution containing 100 μg/ml DEHP. Samples were injected from test solutions in the order collected, a standard being included after every 4 test injections. The standards were averaged before calculating the concentrations of DEHP in each test solution.

3. Results

3.1. Paclitaxel vehicle only

Fig. 2 shows the patterns of DEHP release into glucose 5% infusions containing different proportions of paclitaxel vehicle (5% or 10% by volume paclitaxel vehicle, equivalent to 300 or 600 mg paclitaxel dose) and the effect of using either a PVC containing or the non-PVC containing administration set for the infusion. The results are from two experiments.

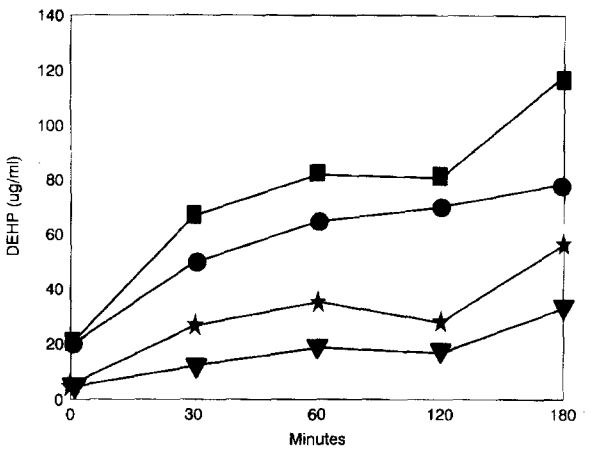

Fig. 2. Release of DEHP from Viaflex containers and infusion sets during simulated infusion of paclitaxel vehicle in 5% glucose PVC bags delivering 500 ml in 3 h. ★ = 5%, PVC: paclitaxel vehicle 5% by volume (corresponding to paclitaxel injection 0.6 mg/ml) using PVC admnistration sets. ▼ = 5%, non-PVC: paclitaxel vehicle 5% by volume (corresponding to paclitaxel injection 0.6 mg/ml) using 'non-PVC' admnistration sets. ■ = 10%, PVC: paclitaxel vehicle 10% by volume (corresponding to paclitaxel injection 1.2 mg/ml) using PVC administration sets. ● = 10%, non-PVC: paclitaxel vehicle 10% by volume (corresponding to paclitaxel injection 1.2 mg/ml) using 'non-PVC' administration sets.

The findings indicate that total DEHP extraction depended on (i) contact time between the paclitaxel vehicle contained and the PVC components, (ii) paclitaxel vehicle concentration and (iii) the type of administration set used to deliver the infusion. It can be seen that the highest readings were obtained with the higher concentrations of vehicle, the longer contact times and the use of PVC administration sets.

Table 1 indicates the respective effects of using PVC and non-PVC sets and minimising length of storage on the total quantities of DEHP delivered to the patient during paclitaxel vehicle infusion. The data show that when storage time is effectively zero because administration begins immediately after preparation of the infusion, and the administration set is made of non-PVC, the minimum quantity of DEHP received by a patient treated with a 300 mg (5% by volume paclitaxel vehicle) or 600 mg (10% by volume paclitaxel vehicle) dose of paclitaxel administered over a 3 h period, will be approximately 10 and 30 mg respectively. When the infusion is stored for 3 h after preparation, the patient will receive approximately 22 and 53 mg DEHP, respectively, from non-PVC administration sets over a 3 h infusion period.

The use of a PVC administration set contributes another 5 to 20 mg DEHP depending on the concentration of paclitaxel vehicle in 5% glucose infusion (Table 1).

The rate of release of DEHP from the PVC bags within the 3 h storage period was also examined. The results are shown in Table 2. The levels of DEHP monitored show that extraction rises rapidly during storage, more than doubling every hour and that the concentration of paclitaxel vehicle is a contributory factor. Storing the equivalent of 300 or 600 mg paclitaxel for 1 h after preparation would contribute approximately 50% more DEHP.

3.2. Paclitaxel vehicle plus drug

The total amounts of DEHP extracted during infusions of two different concentrations of paclitaxel in glucose 5% solution, was approximately 13 and 30.5 mg for the 300 and 600 mg doses of paclitaxel respectively. These results are compat-

Table 1
The release of DEHP into paclitaxel infusions during simulated infusion from PVC bags stored for up to 3 h infused through PVC and 'non-PVC' administration sets

% volume paclitaxel vehicle	Total amounts of DEHP released (mg)[a]			
	Infusion commenced immediately		Bag stored for 3 h before commencing infusion	
	PVC set	'Non-PVC'	PVC set	'Non-PVC' set
5%	15.45 (0.35)	9.95 (0.15)	27.40 (0.20)	22.35 (0.05)
10%	44.30 (2.20)	30.35 (2.25)	70.00 (2.70)	53.00 (3.10)

[a]Mean (S.D.; $n = 2$); infusion contained 5% glucose plus paclitaxel vehicle, total volume approximately 500 ml; infusion time 3 h.

ible with the data obtained from the first part of the study where paclitaxel vehicle alone was used and show that the presence of the active drug does not influence the amount of DEHP extraction.

4. Discussion

The results confirm previous findings (Waugh et al., 1992; Pearson and Trissel, 1993; Trissel et al., 1994) and show that paclitaxel vehicle is associated with DEHP extraction from PVC infusion containers, to a greater or lesser degree depending on length of storage time, the PVC content of the administration set used to deliver the infusion, and the concentration of paclitaxel vehicle. The data also confirm previous findings (Pearson and Trissel, 1993) and show that the extraction of DEHP from PVC bags during paclitaxel administration is not influenced by the presence of the drug and is entirely due to the vehicle. The study was only performed on duplicate runs owing to the costs of the materials involved.

Table 2
The release of DEHP into glucose-paclitaxel vehicle during storage in PVC bags ($n = 2$) at ambient temperature

Time of storage	DEHP concentration after storage	
	% by volume paclitaxel vehicle in 5% glucose	
	5 %	10 %
1 h	6.6 μg/ml	29.4 μg/ml
2 h	18.5 μg/ml	56.6 μg/ml

Research to-date, indicates that DEHP possesses a relatively low magnitude of acute toxicity (Kaul et al., 1982) and is not associated with specific toxicity in patients who have had prolong exposure to DEHP leached into blood products (Harris, 1981). There are currently however, no established limits on the quantities of DEHP which are or are not acceptable for delivery to patients (Trissel et al., 1994). Therefore, when attempting to assess the relative risks of administering paclitaxel infusions from PVC rather than from other types of storage containers, it is necessary to compare the rate of DEHP extraction by paclitaxel vehicle with DEHP extraction by other infusions known to have a similar effect. Jaeger and Rubin, 1972 and Baker, 1978 studied the quantities of DEHP extracted into blood and blood products during storage. These investigators estimated that stored blood contains up to 50 mg DEHP/litre (Baker, 1978), and that patients are likely to receive up to 128 mg per transfusion (Jaeger and Rubin, 1972). By comparison, the present study found that approximately 10 mg DEHP would be received by patients during a 3 h infusion of 300 mg paclitaxel injection using non-PVC administration sets. When the dose of paclitaxel was increased to 600 mg, DEHP exposure rose to 30 mg. Even if infusion was delayed for 1 h following preparation, the levels of DEHP received in a 300 and 600 mg dose of Taxol were 13 and 45 mg respectively, still markedly less than during a blood transfusion. Furthermore, this

comparison must also take into account the respective frequency of each procedure. The likelihood of chronic exposure to DEHP is negligible in patients receiving paclitaxel on four to six occasions.

This study confirms that the risks of DEHP exposure from paclitaxel infusions stored in PVC containers is substantially less than in patients receiving stored blood. Furthermore, the quantities of DEHP extracted and administered during infusion can be reduced still further by commencing infusion immediately after, or within 1 h, of preparation, administering the infusion at the maximum rate allowed (500 ml in 3 h) and using a non-PVC administration set (such as Solution Administration sets, or Flo-Gard Low Adsorption Sets). This study would therefore recommend use of all three measures to minimise DEHP extraction. It is the opinion of this study that the practical problems encountered when switching to alternative containers considerably outweigh the currently recognised risks of DEHP levels when using PVC from which to infuse paclitaxel infusion.

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