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The release of phthallate ester plasticizer from intravenous administration sets into fat emulsion

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Summary

The release of the plasticizer DEHP from administration sets into intravenous fat emulsions was examined. Substantial amounts were extracted into Intralipid after storage for 24 h, while far less was extracted into TPN regimens containing Intralipid. During simulated infusion of Intralipid, extraction of DEHP from the administration set was relatively small, and was present in negligible amounts in TPN regimens containing fat emulsions.

Introduction

Polyvinyl chloride is the plastic of choice used to fabricate administration sets. However, a major component of PVC essential to ensure the plastic tubing has the correct strength and pliability is the plasticizer. The usual compound used for this purpose is D-2-ethylhexylphthallate (DEHP). Medical grade PVC contains up to 40% by weight of plasticizer. Phthallate salts are potentially toxic substances (Kaul et al., 1982). A number of studies have shown that DEHP is released from PVC tubing in contact with certain fluids. Jaegar and Rubin (1972) showed that blood stored in PVC bags contains large amounts of DEHP. DEHP is also extracted by plasma during haemodialysis (Baker, 1978; Fayz et al., 1977), by aqueous ethanolic solutions (Corley et al. 1977), aqueous N,N-dimethylacetamide (Vishnuvajjala and Cradock, 1984) and solutions of polysorbate surfactants (Moorhatch and Chiou, 1974). In contrast, DEHP is almost insoluble in water, electrolyte or carbohydrate solutions. It is likely that fat emulsions may also extract DEHP. Consequently, TPN mixtures containing fat emulsion should be stored in ethylvinylacetate bags rather than PVC packs. However, fat emulsions are administered through PVC-containing administration sets and the possibility exists that DEHP extraction could occur. The purpose of this study was to examine DEHP extraction from administration sets used to administer TPN. Both fat emulsion alone and TPN regimens containing fat emulsion were examined.

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Materials and Methods

Intralipid 10 and 20% was a generous gift from Kabi-Vitrum, Uxbridge, Middlesex, together with Solivito and Vitlipid. DEHP was obtained from Aldrich Chemicals. The following administration sets were used: Solution Administration Set, ref. no. C0334 (Travenol Laboratories, Thetford); Blood Administration Set, ref. no. A100 (Avon Medical, Redditch, Worcs); and Accudot 20 Primary Administration Set (Imed, Aylesbury, Bucks).

The TPN regimen contained Synthamin 14 (1 litre); 30% w/v dextrose (1 litre); 20% Intralipid (0.5 litre), or 20% dextrose (0.5 litre). Multibionta was obtained from E. Merck, Alton, Hants.

Analytical method

DEHP concentrations were measured used HPLC. The details of the method were as follows. Solutions of DEHP prepared in methanol

Column: ODS, Sphaerisorb 5 μm, 0.4 × 30 cm
Solvent; Methanol
Flow rate: 1.5 ml/min
Injection: fixed volume loop (20 μl)
Detection: 270 nm

Quantification was by peak area, measured by computing integration. Response was linear with concentration over the working range ($r = > 0.999$; mean C of V = 1.72%).

Measurement of DEHP in Intralipid

In order to assay fat emulsion for DEHP levels the plasticizer was first extracted, as adapted from the general method described by Pollack et al. (1984). Before extraction the emulsion was cracked by adding calcium ions. If this stage in the method was omitted, fat, emulsifier and solvent did not separate adequately during the extraction process.

The method used was as follows. 10 ml aliquots of the fat emulsion were taken, 0.1 ml of calcium chloride solution (1 mol/l) was added and the mixture allowed to stand for 10 min after shaking thoroughly; 5 ml of ethyl acetate was added, the mixture capped and shaken thoroughly for 15–30 s. Each tube was allowed to stand for 18–20 h at room temperature. Samples from the upper ethyl acetate layer were removed for analysis by HPLC, as previously described. Separation of the DEHP peak from interfering substances extracted from Intralipid was sufficient to allow manual measurement by peak height (see Fig. 1) although electronic integration was more variable due to interference and base-line variation. Samples of 10 or 20% Intralipid were spiked with DEHP to give final concentrations over the ranges 5–50 and 100–500 μg/ml. Analysis was performed as described. The method was shown to be reproducible; the C of V of five consecutive spiked samples (100 μg/ml) was 1.42%. Peak height response was found to be linear with concentration over the concentration ranges measured ($r = > 0.998$). The efficiency of extraction varied with the concentration of fat emulsion; it was ca. 67% and 50.0% for 10 and 20% Intralipid, respectively. In each experiment a spiked control was prepared and used to estimate the concentration measured in each sample. Peak identity and purity was confirmed using scanning U.V. multi-diode array detection (Model 4021, Pye-Unicam, Cambridge).

Design of experiments

Each set was primed according to the manufacturer's recommendations. For storage experiments sets were primed and the distal end sealed. They were then stored at 4–6°C or at ambient temperature for 24 h. The total content of each set was then collected and 10 ml aliquots taken for analysis. To measure release of DEHP during adminis-

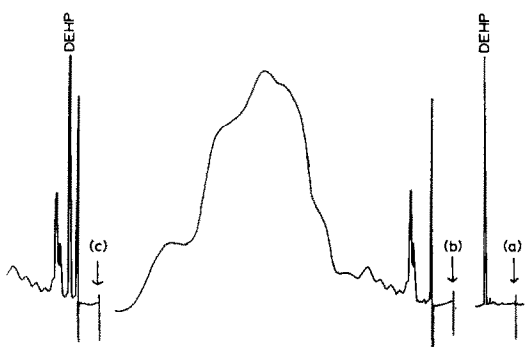

Fig. 1. Chromatograms of: (a) DEHP in Methanol; (b) 20% Intralipid; and (c) 20% Intralipid + 100 μg/ml DEHP, extracted according to the method described in the text. Chromatogram conditions: A.U.F.S. = 0.16; Chart speed = 0.5 cm/min.

tration, each set was attached to the appropriate fluid and primed. The set was attached to a suitable flow-rate controller, set at the required flow rate, and samples (12 ml) collected every hour for analysis.

Results

DEHP extraction during storage of sets containing Intralipid

Intralipid clearly extracts DEHP plasticizer from these sets. The results are summarized in Table 1 and show the quantities to be found in Intralipid after storage for 24 h.

Extraction depends on temperature of storage. refrigeration reduces the rate of DEHP appearance in Intralipid. This difference is significant (Student's t-test, $P = 0.05$). Slightly more DEHP was extracted into 10% compared to 20% Intralipid. However, these differences were not significant (Student's t-test, $P = 0.05$). The rate of extraction of DEHP into a TPN regimen containing Intralipid was substantially lower than into undiluted Intralipid. Quantities released into a TPN regimen without Intralipid were negligible, although in the presence of Multibionta such infusions contained ca. 20 μg/ml DEHP. Solution Administration Sets (Travenol) containing Intralipid were stored for a longer period. After 72 h at ambient temperature, Intralipid contained ca. 600 μg/ml DEHP. At 4–6°C similar emulsions contained ca. 275 μg/ml DEHP. This indicates that extraction continues during storage.

TABLE 1

DEHP CONTENT OF INTRALIPID-CONTAINING INFUSIONS AFTER STORAGE IN SOLUTION ADMINISTRATION SETS (TRAVENOL)

Infusion	DEHP concentration (μg/ml) after 24 h storage at:	
	4–6°C ± S.D.	Ambient ± S.D.
10% v/v Intralipid	70 ± 7.1	160 ± 12.7
20% v/v Intralipid	64 ± 5.7	144 ± 7.3
TPN regimen (2 litre) + 20% Intralipid (0.5 litre)	–	40 ± 0.7
TPN regimen without added Intralipid	–	1.5

TABLE 2

DEHP CONTENT OF INTRALIPID AND TPN REGIMENS AFTER SIMULATED INFUSION

Time of infusion * (h)	DEHP content (μg/ml) in:		
	10% Intralipid	20% Intralipid	TPN regimen containing 20% Intralipid
0	8.5	5.5	1.0
1	5.5	2.8	–
2	3.6	1.5	< 1.0
3	4.2	3.0	–
4	4.2	–	< 1.0
5	5.5	2.0	–
6	–	–	< 1.0

* Solution Administration Set (Travenol).

DEHP contents of 20% Intralipid stored in the other types of sets tested were not substantially different. For example, after storage in the Accudot set (Imed) Intralipid contained ca. 190 μg/ml DEHP, while the content after storage for 24 h in the Blood Set (Avon) was ca. 140 μg/ml DEHP.

DEHP extraction during simulated administration

Intralipid infusion was simulated at a flow rate of 20 drops/min (ca. 60–70 ml/h, equivalent to 0.5 litre in 6–8 h). After priming, the first 12 ml was collected for analysis, followed by 12 ml samples after each hour. Results are summarized in Table 2.

These results show that the DEHP content of fat emulsions infused through these administration sets was far less than was recovered from stored infusions. DEHP concentrations were greater in 10% than 20% Intralipid. The content of an emulsion-containing TPN regimen was extremely small. From these results it is possible to estimate the dose of DEHP received by a patient given Intralipid. A patient being administered 10% Intralipid (500 ml) will receive ca. 2.5–2.75 mg and a patient receiving 20% Intralipid ca. 1.5 mg/day.

Discussion

The release of plasticizer into human blood stored in PVC containers has been widely re-

ported. Baker (1978) has estimated that a patient infused with 2–3 litres stored blood could receive up to 200 mg DEHP. It is further indicated that much higher quantities may be given during dialysis. The possible toxicity of DEHP has recently been reviewed by Kaul et al. (1982). It is concluded that the acute toxicity is relatively low, although the risks of prolonged exposure to even low doses of DEHP are as yet difficult to evaluate. Prolonged exposure of particular 'at-risk' groups, such as expectant mothers or young children, including neonates, should be considered unacceptable. This prolonged exposure is unlikely to occur in patients receiving a blood transfusion, but is going to occur in patients on long-term dialysis or TPN. The present investigation should be considered in this context.

It is clear that Intralipid extracts DEHP from PVC-containing administration sets. This process is time-dependent. If the set is primed with Intralipid and stored for 24 h, the amounts of DEHP extracted are substantial. A blood set requires approximately 15 ml for priming, a solution set rather less. Thus a primed set may contain up to 2 mg DEHP after 24 h storage at room temperature. In practice storage at 4–6°C would be recommended. In this situation a primed set would contain up to ca. 1 mg DEHP after 24 h storage. While no particular clinical risk can be attributed to this relatively small exposure, priming of administration sets should be avoided until immediately before infusion is to commence.

Patients receiving Intralipid infused through a standard (PVC-containing) administration set will receive a small dose of DEHP. This dose will be of the order of 1–3 mg/day. Once again, this appears to be a relatively minor exposure to this compound. However, while it is generally accepted that such degrees of exposure to most patients are relatively safe, and in fact may be no higher than normal background levels found in food and drink, two particular groups may be at greater risk. These are pregnant mothers and very small children (Hillman et al., 1975). It is the latter group which may be of greatest significance in the use of TPN. It has already been suggested that, for these groups, a safer alternative to DEHP-plasticized containers should be sought for blood collection (see review by Kaul et al., 1982). It would appear, in the light of the present study, advisable to use non-phthallate-containing sets or tubing to administer Intralipid to small children, especially neonates.

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