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Original Article

The effect of temperature on di(2-ethylhexyl) phthalate leaching from PVC infusion sets exposed to lipid emulsions

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Summary

Poly vinyl chloride (PVC) infusion equipment contains substantial amounts of the plasticiser di(2-ethylhexyl) phthalate (DEHP). We determined the amount of DEHP leached from Mediplus Dual TIVA® Infusion sets, into lipid and non-lipid infusates. Two propofol admixtures (Diprivan® 1%, Propoven® 1%), Intralipid® 10% and 0.9% saline were evaluated as infusates. Solutions were infused through TIVA sets at 12 $ml.h^{-1}$ for 6 h at 24, 32 and 37 °C. In addition, TIVA sets were filled with 2 ml infusates, sealed and incubated at 24 and 37 °C for 6 h. Di(2-ethylhexyl) phthalate was detected in all lipid infusates after dynamic infusion and static contact, and in 0.9% saline after dynamic infusion at 37 °C. At 32 and 37 °C, the quantity of di(2-ethylhexyl) phthalate leaching into the lipid infusates may exceed the recommended maximum exposure amount set by the European Union for DEHP of 20–48 $\mu g.kg^{-1}.day^{-1}$ if lipid based infusates are used for sedation or intravenous feeding of infants or neonates.

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Di(2-ethylhexyl) phthalate (DEHP) is a commonly used plasticiser in polyvinyl chloride (PVC) manufacture, imparting flexibility to a wide variety of applications. Di(2-ethylhexyl) phthalate is ubiquitous in the environment and it is estimated that approximately 70–100% of a given human population will have a detectable concentration of DEHP and/or its metabolites in their blood or urine at any time [1–5]. In animal studies, DEHP is a liver carcinogen and causes reproductive abnormalities in offspring exposed to the chemical during gestation and through to puberty; males are particularly affected [6–9]. However, the variability of effects between species means that, at present, the validity of extrapolating animal data to man remains unresolved.

The use of DEHP as a plasticiser results from its non-covalent binding to PVC molecules, allowing the latter to slide over each other [10]. However, the non-covalent binding also results in DEHP's leaching from PVC into the surrounding environment [11]. Di(2-ethylhexyl) phthalate is a highly lipophilic molecule, so immersion in a lipid-containing environment will increase leaching [12]. In 2005, following concerns

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about the possible adverse effects of DEHP on human health, the European Union (EU) banned the use of phthalate plasticisers in children's toys, particularly those that are likely to be put into the mouth, such as teething rings [13]. In 2007, European Council Directive 2007/47/EC [14] mandated specific labelling for phthalate-containing medical devices, as an amendment to European Council Directive 93/42/EEC [15], which had previously regulated phthalate labelling and restrictions on the use of phthalate-containing devices in children and pregnant or nursing women.

Infant exposure to DEHP is of particular concern, because detoxification pathways are immature in children compared with adults [16–18]. Therefore, quantifying DEHP exposure associated with medical interventions in neonates and infants is important. Animal studies suggest that there may be a causal link between hepatobiliary dysfunction in babies who have received long-term total parental nutrition and toxins leached from plastic medical devices [19, 20].

Previous research has suggested that release of DEHP from PVC may be temperature dependent [21–24]. This study was designed to quantify the effect of temperature on the leaching of DEHP from PVC infusion lines containing propofol (Propoven 1% and Diprivan 1%), Intralipid 10% and 0.9% saline. We hypothesised that increasing temperature from a typical room temperature of 24 °C, to a maximum of 37 °C, with 32 °C as an intermediate temperature, would increase leaching.

Methods

Experiments were performed in triplicate in an incubator (MIR-153; Sanyo, Leicester, UK) at 24, 32 and 37 °C for the dynamic study (continuous flow) and at 24 and 37 °C for the static study (no flow).

To determine leaching of DEHP under dynamic conditions, syringe drivers (Harvard Apparatus 22; Harvard Apparatus Ltd, Kent, UK) pumped Diprivan 1% (AstraZeneca, Cheshire, UK), Propoven 1%, Intralipid 10% (both supplied by Fresenius Kabi, Cheshire, UK) or 0.9% saline (Maco Pharma Ltd, Middlesex, UK) (control) from Plastipak 50-ml polyethylene syringes (Beckton Dickinson, Oxford, UK) at 12 $ml.h^{-1}$ for 6 h through Mediplus Dual TIVA infusion sets (Mediplus, Bucks, UK). This infusion set is manufactured from DEHP-plasticised PVC with a length of 2 m, as used in our local hospital. The infusates were collected into glass beakers for DEHP assay.

To determine the extent of DEHP leaching under static conditions, Mediplus Dual TIVA sets were filled with drug solution, sealed with PVC-free Luer ends and incubated for 6 h. After incubation, the infusates were expelled into glass beakers for subsequent DEHP assay. Each device (infusion line) was used only once, three devices were used per infusate and sampling from each line was performed in triplicate. The aim was to simulate medical use of the device and therefore each device was used from new, allowing for accurate comparison of DEHP leaching across infusates.

Chromatographic analysis was performed using a Jasco PU-2085 Plus Semi Micro HPLC Pump, equipped with a Jasco AS-950 Intelligent Autosampler and a Jasco UV-2075 Plus UV detector operating at a wavelength of 225 nm. Chromatographic separation was achieved using a 3-μ Phenomenex Luna C18 column (150 × 2 mm ID) (Phenomenex, Cheshire, UK) at 45 °C. Di(2-ethylhexyl) phthalate was eluted isocratically using a mobile phase consisting of (75:25 v/v) Far UV acetonitrile:acetic acid (0.05% v/v) (both obtained from Fisher Scientific, Leicestershire, UK) at a flow rate of 200 $\mu l.min^{-1}$. All reagents used were HPLC grade unless otherwise stated. The autosampler injection syringe was cleaned between samples by four rinses in 100% acetonitrile. The method was validated using our standard laboratory method validation protocol, based on the ICH harmonised tripartite guideline for the validation of analytical procedures [25]. This included validation of robustness with temperature, flow rate and mobile phase composition, stability indication (forced degradation studies), precision of injection and intra-day precision. The concentration of DEHP in infusates was determined by external calibration curve constructed using an analytical standard of DEHP (0.986 $g.ml^{-1}$, 99.7% purity; Wako Chemicals, Neuss, Germany). During sample analysis, two calibration curves were used: a high concentration plot for the static study which was linear over the range 500–900 $\mu g.ml^{-1}$ ($r = 0.9660$, $n = 5$); and a low concentration plot for the dynamic study which was linear over the range 10–90 $\mu g.ml^{-1}$ ($r = 0.9995$, $n = 5$) (limit of detection 0.05 $\mu g.ml^{-1}$). Before assay, samples and

standard solutions were diluted in 100% acetonitrile (1:20 for the dynamic study; 1:50 for the static study). Aliquots of 20 μl were analysed using HPLC.

Only polypropylene tubes (non-PVC containing) and/or glass containers were used throughout the study. All drug and control solutions were assayed for DEHP content before infusion line filling to establish baseline DEHP concentrations that may have resulted from prior environmental contamination. The same procedures and equipment were used to prepare controls and experimental samples. All solutions were infused from 50-ml polypropylene syringes to standardise the experiments. Experimental samples were prepared (diluted as above) and assayed immediately after collection to reduce the potential for additional DEHP contamination occurring during storage. The use of PVC-containing products in the laboratory was minimised as far as possible, for example, the use of nitrile gloves rather than PVC.

Data were analysed using Microsoft Excel 2007 and SPSS (PASW Statistics 19; IBM; Armonk, New York, US). The dynamic data were rank transformed and one-way ANOVA was performed using Tukey-Kramer for post hoc analysis between pairs of groups. The Mann–Whitney U-test was used for analysis of the static data that consisted of two groups. Confidence intervals were set at 95%. We considered differences statistically significant when the two-sided p value was less than 0.05.

To calculate the exposure value of a neonate or infant to DEHP from the PVC lines, a previously described equation [26] was followed:

$$Y(\mu g.kg^{-1}.day^{-1}) = \frac{X(ng.ml^{-1}) \times \text{volume infused}\,(ml.day^{-1})}{\text{Weight}\,(kg) \times 1000}$$

where Y equals the exposure value and X is the concentration of DEHP leached.

Results

Propoven was supplied in glass bottles, Diprivan in glass syringes and Intralipid in polypropylene bags. Only saline was supplied in a PVC bag. Di(2-ethylhexyl) phthalate was not detected in any of the baseline samples for each solution, therefore environmental contamination was either not present or was present at a concentration below the HPLC assay limit of detection of 0.05 $\mu g.ml^{-1}$.

After exposure to the TIVA sets, DEHP was detected in all lipid infusates, and in the control (saline) infusate after dynamic incubation at 37 °C (mean (SD) 425 (144) μg). In both the dynamic and static studies (Figs. 1 and 2, respectively), increasing incubation temperature was associated with significantly increased DEHP levels in all lipid infusates.

Assuming a linear rate of leaching into Diprivan infused at a rate of 4 $mg.kg^{-1}.h^{-1}$ (7.2 ml) for 6 h at 32 °C, the hypothetical mean (SD) exposure to DEHP for a 3-kg neonate was calculated to be 24.9 (2.5) $\mu g.kg^{-1}$. Higher exposures would occur for Propoven and Intralipid, or if the infusate were at 37 °C.

Discussion

Di(2-ethylhexyl) phthalate (DEHP) leaches from PVC into lipid solutions more readily at higher temperatures, and will also leach into a 0.9% saline solution under dynamic flow when environmental temperatures exceed 32 °C. This is important clinically, because warming of infusate to 37 °C has been recommended both to maintain patient temperature and to reduce injection pain [27]. Where PVC infusion equipment is used, and especially when lipid-containing infusates are required, significant quantities of DEHP may be transferred to the patient as a result, the potentially detrimental effects of which may outweigh the benefit of reduced injection pain.

Di(2-ethylhexyl) phthalate has limited solubility in aqueous solutions (approximately 3 $ng.ml^{-1}$ in distilled water at 20 °C [28]), but is non-covalently bound to PVC, so will leach into an aqueous solution at higher temperatures [29] and during the mechanical stress associated with dynamic flow [30]. The lipophilicity of DEHP explains the greater rate of leaching into lipid-containing solutions [12], and may also be affected by other factors, including the length and volume of the infusion line, infusate pH, infusion duration, plasticity and agitation of the PVC equipment [31].

Previous studies have reported similar amounts of leaching of DEHP from medical devices. In 2003, Kambia found that PVC administration sets could leach 0.8–2 $mg.kg^{-1}.day^{-1}$ of DEHP into a lipid-based total

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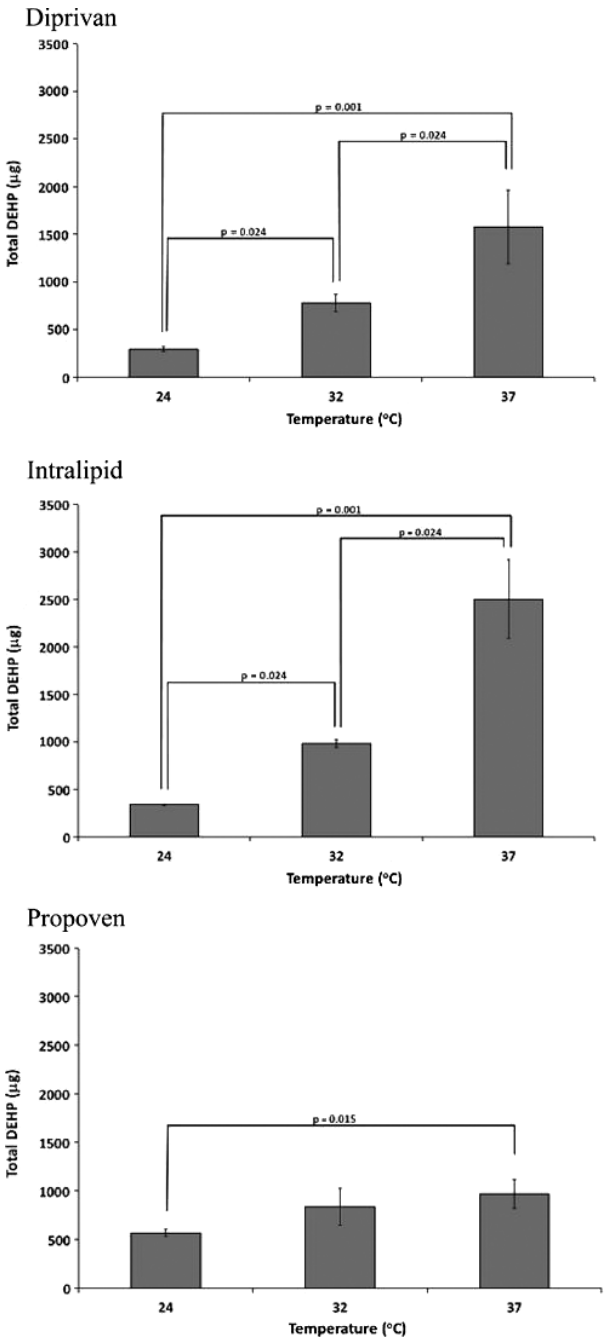

Figure 1 Dynamic experiment. Cumulative di(2-ethylhexyl) phthalate (DEHP) leaching from infusion line tubing during 12 ml.h^{-1} flow over 6 h (72 ml total) at different temperatures. Data presented as mean (SD) (n = 3 for each infusate at each temperature).

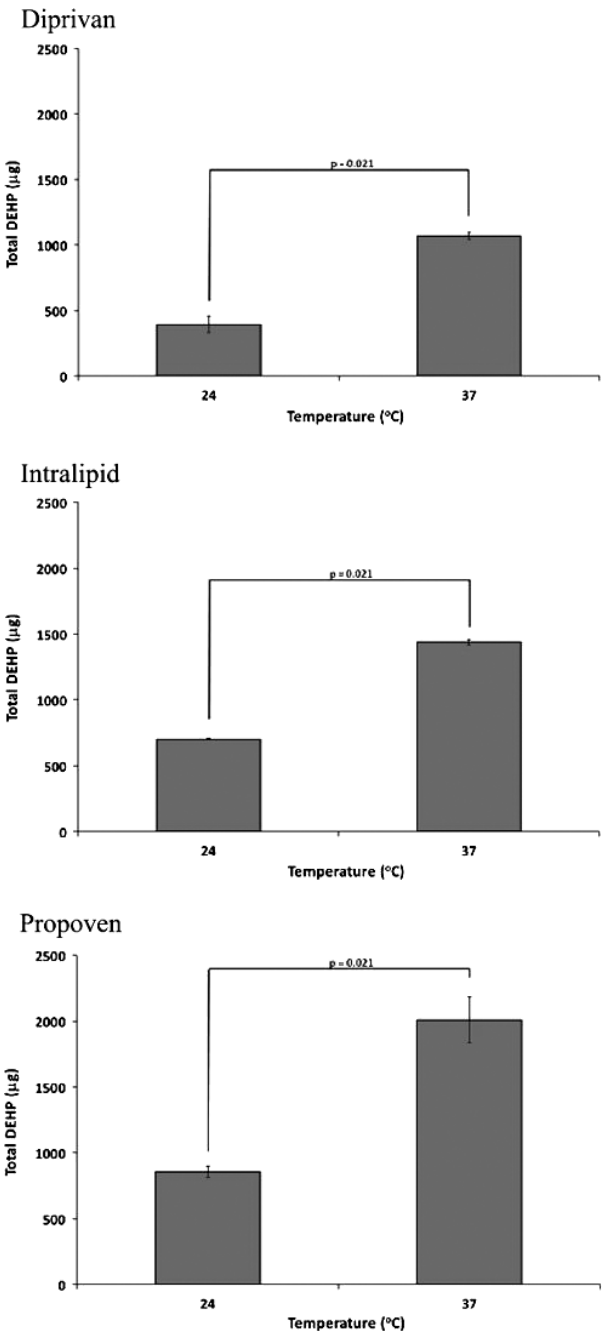

Figure 2 Static experiment. Cumulative di(2-ethylhexyl) phthalate (DEHP) leaching from infusion line tubing during static incubation over 6 h (2 ml total) at two different temperatures. Data are mean (SD), n = 3 for each infusate at each temperature. Phthalate in saline was not detectable at either temperature.

parenteral nutrition (TPN) solution at room temperature [32]. These TPN formulations had lower lipid concentrations (1–3.85% lipid) than the infusates in our study (10% lipid), but were infused at higher flow rates (46–215 ml.h^{-1} over 10–11 h). The authors reported that leaching of DEHP is dependent on both the lipid content of the infusate and the flow rate.

Loff et al. [33] reported an increase in DEHP leaching from a 2.25-m PVC line into a 20% lipid emulsion at a flow rate of 1 $ml.h^{-1}$ from 10 $mg.day^{-1}$ at 27 °C, to 13 $mg.day^{-1}$ at 33 °C. These results are similar to those of our present study, in which 2.5 mg DEHP leached from a 2-m PVC infusion line into a 10% Intralipid solution over 6 h at 24 °C. Importantly, Loff et al. noted that the leaching rate was non-linear, with DEHP extraction rates increasing after 20 h of dynamic flow. Similarly, Takatori et al. [26] reported DEHP leaching of approximately 10 $mg.day^{-1}$ at 25 °C from a 142.5-cm enteral nutrition system into a 7.2% lipid-containing solution infused at 210 $ml.h^{-1}$, but suggested that it was the presence of emulsifiers rather than the lipid content per se that affected leachability.

In 2008, the EU Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) published a report on the specific risks of neonatal exposure to DEHP-plasticised medical devices [34]. Their review concluded that the potential for high DEHP exposure during medical interventions was a cause for concern, particularly for prematurely born male neonates in whom DEHP doses could feasibly reach those observed to induce reproductive toxicity in animal studies. The EU suggests that a daily intake exceeding 20–48 $\mu g.kg^{-1}.day^{-1}$ DEHP may be harmful to neonates, based on the tolerable daily intake (TDI) values derived from such animal toxicity studies [35–37]. Our data suggest that a neonate, receiving lipid-based infusates at 32 or 37 °C through a PVC infusion line, might receive a DEHP dose exceeding the lower limit within 6 h and potentially much more if leaching persists beyond the sixth hour of infusion. Such a dose would certainly contribute to the high daily exposures among neonatal intensive care patients inferred by measurement of urinary DEHP metabolites [38]. However, it has been suggested that reference to a TDI may not be appropriate for patients considered to be highly vulnerable to the potential effects of high DEHP exposure [34].

To date, single doses of DEHP have not been associated with any specific medical conditions, although a causal link between DEHP and systemic inflammatory response syndrome has recently been proposed [39]. Systemic inflammatory response syndrome is a serious condition related to systemic inflammation, organ dysfunction and organ failure [40]. Di(2-ethylhexyl) phthalate is a known xenobiotic peroxisome proliferator-activated alpha receptor (PPARα) agonist, upregulating nuclear transcription, and so triggering an intrinsic, pro-inflammatory reaction [41–44] as implicated in such conditions as chorioamnionitis and inflammation mediated preterm delivery. Di(2-ethylhexyl) phthalate has been implicated in the induction of hepatobiliary dysfunction in neonates who have received long-term TPN [20].

In view of the current EU advice [15], pricing, availability of alternative products and the increasing concerns regarding DEHP toxicity, evaluation of current DEHP exposure levels in UK clinical settings would seem prudent, particularly in vulnerable patient groups. Our study supports the assertion that PVC infusion lines should be replaced in favour of non-DEHP containing alternatives wherever possible, particularly when infusing lipids to neonates and children, and unnecessary warming of infusion systems should be avoided. If a priming solution is required to prepare an infusion line, then 0.9% saline is preferable to a lipid-containing primer [45] and should only be infused immediately before use.

Competing interests

This study was supported, in part, by Veeda Clinical Research, Plymouth, UK, who are not involved in the manufacture of either medical devices or medicinal products. No competing interests declared.

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