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Research paper

Leaching of plasticizers from polyvinylchloride perfusion lines by different lipid emulsions for premature infants under clinical conditions

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ABSTRACT

Plasticizers migrate from polyvinylchloride (PVC) infusion systems into lipid emulsions. The aim of this study was to investigate the leaching of different plasticizers from PVC perfusion lines by a selection of lipid emulsions under clinical conditions. Seven PVC perfusion lines with an equal length of 150 cm and three internal diameters were perfused with three lipid emulsions: Intralipid® 20%, ClinOleic® 20% and SMOFlipid® 20%, mimicking clinical conditions. The concentrations of the plasticizers were measured directly in the emulsions by gas chromatography – mass spectrometry. Of the four plasticizers examined in this study, di (2-ethylhexyl) phthalate (DEHP) leached the most and was found, on average, at 46.5 μg/ml in the emulsions – around one order of magnitude higher than the other plasticizers. This study demonstrates that the leaching of DEHP by lipid emulsions in conditions of total parenteral nutrition is many times higher than should be accepted and higher when compared to the other plasticizers. There was no significant difference in leaching of plasticizers in relation to the type of lipid emulsion. The influence of tube diameter on the leaching rate of plasticizers should be taken into account especially in particular exposed patients.

1. Introduction

For parenteral nutrition and infusion therapy polyvinylchloride (PVC)-perfusion lines are still commonly used, despite the known environmental and health hazards related to the production and disposal of PVC (Van Vliet et al., 2011). Plasticizers are added to the PVC matrix in order to improve the flexibility and elasticity of the stiff polyvinylchloride polymer (Bagel et al., 2011). In the past, in PVC medical devices, di (2-ethylhexyl) phthalate (DEHP) has been used predominantly to impart flexibility, temperature tolerance, optical clarity, strength and resistance to kinking for many years (Loff et al., 2000, 2002, 2004, 2008; Hauser et al., 2005). It is well known that plasticizers are not chemically bound to PVC and that they migrate into infusion solutions, such as parenteral nutrition, depending on the temperature (Loff et al., 2002; Rose et al., 2012), time of incubation (Bagel et al., 2011), and the lipophilicity of the solution (Bagel et al., 2011; Bagel-Boithias et al., 2005). There is no data published yet, concerning the influence of tube diameter on plasticizer migration.

Over the past few years, concerns have been raised about the toxicological impact of DEHP (Bernard et al., 2015). The European Union (EU) classified DEHP as a reprotoxic substance (CMR substance Category 1B) and strongly recommended to replace DEHP in medical devices (European Union, Regulation (EC) No. 1272/2008, 2008). In December 2012, France passed a law, that prohibited the incorporation of DEHP in medical devices for neonatology, paediatric and maternity wards in hospitals from July 2015 (LOI no 2012-1442, 2012). As a consequence of this debate manufacturers were forced to avoid DEHP. Two potential alternative methods to replace DEHP in medical devices are available: substitution of PVC through another polymer, for example polypropylene or silicone that does not require additional plasticizers, or substitution of plasticizers (Van Vliet et al., 2011; Health Care Without Harm, 2008). Alternative plasticizers like diisononylcyclohexan-1,3-dicarboxylate (DINCH), tris(2-ethylhexyl)-trimellitate (TOTM), di(2-ethylhexyl)-terephthalate (DEHT) and others were considered in the manufacturing of perfusion

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lines (Van Vliet et al., 2011). Available physiochemical data on these plasticizers suggest lower migration from PVC compared to that of DEHP (Wilkes et al., 2005). But, there is only little data available on the migration of these plasticizers from PVC in medical devices (Bernard et al., 2015). Toxicological data on alternative plasticizers suggest less adverse effects to humans than DEHP (Scientific Committee on Toxicity, 2004). However, the majority of toxicity data on plasticizers are based on oral intake, where, in contrast to intravenous exposure, bioavailability plays a relevant role (SCENIHR, 2016).

The migration of DEHP from medical devices, on the other hand, is well studied. Especially lipophilic liquids lead to a high migration rate (Rose et al., 2012; Loff et al., 2000, 2004). A study, in which DEHP containing PVC-infusion lines were filled with lipid emulsions and stored for 1 and 24 h showed different leaching rates depending on the type of lipid emulsion. The highest leaching was observed with ClinOleic® 20% (65.8 μg/ml), with Intralipid® 20% it was 2/3 lower (27.8 μg/ml) (Bagel et al., 2011). Parenteral lipid administration is one risk factor for a severe life threatening complication of parenteral nutrition, the intestinal failiure associated liver disease (IFALD) (Lacaille et al., 2015). It has been published that the use of SMOFlipid®, a lipid emulsion composed of soybean oil, medium chain trigylcerides, olive oil and fish oil, improves liver function and avoids development of IFALD in children with long term parenteral nutrition (Pichler et al., 2014). This lipid emulsion was not tested in the study from Bagel et al. (2011).

The question raised by the authors was, whether SMOFlipid® may lead to lower DEHP migration than the other lipid emulsions. If this had been the case, this may explain the improvement of liver function in long term parenteral nutrition.

The aim of this study was to obtain information on the level of plasticizer leaching from PVC perfusion lines by different lipid emulsions commonly used for children, including SMOFlipid® and under clinical conditions. The influence of the internal tube diameter on plasticizer leaching was also examined.

2. Materials and methods

2.1. Lipid emulsions

Three different lipid emulsions were used:

Intralipid® 20% (Fresenius Kabi Austria GmbH, Graz), a soybean oil based lipid emulsion containing individual long-chain triglycerides (LCT).

ClinOleic® 20% (Baxter Switzerland AG, Volketswil), a combination of olive and soybean LCT.

SMOFlipid® 20% (Fresenius Kabi Switzerland AG, Oberdorf), a soybean, olive and fish oil-based lipid emulsion which is a balanced mixture of LCT and additional medium-chain triglycerides (MCT).

The composition of these lipid emulsions is shown in Table 1.

2.2. Samples

Seven PVC perfusion lines from four known international companies (Fresenius Kabi, BBraun, CAIR LGL and Dispomed), which are commonly used in intensive and neonatology care units, were examined. They contain the plasticizers DEHP, di(2-ethylhexyl)-terephthalate (DEHT), tris(2-ethylhexyl)-trimellitate (TOTM) and diisononylcyclohexan-1,3-dicarboxylate (DINCH). The tubes had three different internal diameters (1.5 mm, 2.5 mm and 3.0 mm), whereof two pairs of tubes with 1.5 mm and 3 mm were from the same company (Fresenius Kabi and BBraun) and were plasticized with the same substances. One perfusion line was coated with polyethylene (PE), the other lines were uncoated. The plasticizers in the PVC perfusion lines were analysed as described in (Biedermann-Brem et al., 2008). The method is based on gas chromatographic flame ionization detection (GC-FID) analysis. The samples were dissolved in tetrahydrofuran and the PVC was precipitated by adding ethanol. The high molecular weight plasticizers such as ESBO were analysed after transesterification i.e. all ester groups of the plasticizers are converted to ethyl esters. The transesterification step also enabled a verification of the plasticizers quantified in the direct injection. The characteristics of the perfusion lines are shown in Table 2.

2.3. Migration tests

2.3.1. First assay

In the first assay five PVC perfusion lines with equal length of 150 cm and two different internal diameters (1.5 and 2.5 mm) were perfused by Intralipid® 20%, ClinOleic® 20% and SMOFlipid® to determine the leaching of different plasticizers in similar perfusion lines. The length of 150 cm was chosen to compare the data with literature (Bagel et al., 2011; Loff et al., 2002, 2004). To compare our results with previous studies (Loff et al., 2002, 2004), each run was conducted in vitro in a closed environment reflecting circumstances of a newborn on an intensive care unit.

2.3.2. Second assay

In the second assay two perfusion lines with an internal diameter of 3 mm were perfused with SMOFlipid®. These two perfusions lines were from two companies, where we also examined perfusion lines with 1.5 mm diameter. The perfusion lines from the same producers were plasticized with the same substances (Fresenius Kabi – DEHP; BBraun – DEHT). The aim of this assay was, to get information about the influence of the diameter of perfusion lines on plasticizer leaching. Except for the perfusion lines and the lipid emulsion, the conditions were identical in the first and second assay.

2.3.3. Experimental procedure

Each perfusion line was examined on the type and amount of plasticizer before the perfusion experiments were started. Each lipid emulsion was analysed for the plasticizers found in the corresponding tubes (DEHP, DEHT, DINCH or TOTM) before and after perfusion. PVC free syringes for the use in infusion pumps were filled with 25–35 ml (depending on the internal diameter of the perfusion line) of the pure lipid emulsion and connected to the perfusion line. The perfusion lines were emptied of the containing air by filling with the lipid emulsion. The infusions were conducted

Table 1
Composition of the lipid emulsions.

Composition	ClinOleic® 20% [g/1000 ml]	Intralipid® 20% [g/1000 ml]	SMOFlipid® 20% [g/1000 ml]
Long-chain-triglycerides (LCT)	200	200	140
-Soy bean oil	160	200	60
-Olive oil	40	0	50
-Fish oil	0	0	30
Medium-chain triglycerides (MCT)	0	0	60