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Exposure of hemodialysis patients to di-2-ethylhexyl phthalate

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Abstract

The migration of di-2-ethylhexyl phthalate (DEHP) from dialyzers was studied in 21 patients with chronic renal failure undergoing maintenance hemodialysis. The circulating concentrations of DEHP were measured by high performance liquid chromatography in blood of patients obtained from the inlet and the outlet of the dialyzer during a 4-h dialysis session. During treatment of renal failure using plasticized tubing, the plasma level of DEHP increased. On average, an estimated 75.2 mg of DEHP was extracted from the dialyzer during a single dialysis session, with a range of 44.3–197.1 mg. On the other hand, the total amount of DEHP retained by the patient during the dialysis session was evaluated by the difference between the AUC_{out} and the AUC_{in} and ranged from 3.6 to 59.6 mg. The rate of extraction of DEHP from the dialyzer was correlated ($r = 0.705$, $P < 0.05$) with serum lipid content (cholesterol and triglyceride).

So, we confirmed that patients on hemodialysis are always regularly exposed to considerable amounts of DEHP. However, several metabolic effects have been reported in various animal species following treatment with DEHP, such as changes in lipid metabolism and in hepatic microsomal drug-metabolizing enzyme activities. DEHP is now a well-known hepatic peroxisomal proliferator in rodents and an inducer of many peroxisomal and non-peroxisomal enzymes. So, lipid metabolism modifications and hepatic changes observed in hemodialysis patients could be explained from chronic exposition to DEHP. In the coming years, it seems necessary to reconsider the use of DEHP as a plasticizer in medical devices. Highly unacceptable amounts of DEHP leached during the dialysis session could be easily avoided by careful selection of hemodialysis tubing. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Hemodialysis; Di-2-ethylhexyl phthalate; Polyvinyl chloride tubing

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1. Introduction

Di-2-ethylhexyl phthalate (DEHP) is a compound used in large quantities in polyvinyl chloride (PVC) processing industries to make PVC plastics more flexible. Studies (Dirven et al., 1993a,b) showed that workers in PVC factories were occupationally exposed to DEHP by inhalation and that DEHP metabolites may be measured in urine.

DEHP is the major plasticizer of most PVC biomedical materials, like hemodialysis tubing or PVC containers. However, like other lipid-soluble PVC plasticizers, DEHP comprises 30–40% of the final polymer weight, and is not covalently bound within the PVC matrix. So, it is now known that the phthalate DEHP leaches from PVC into blood products (Dine et al., 1991; Racz and Baroti, 1995; Turner et al., 1995) and into intravenous solutions (Ventakataramanan et al., 1986; Waugh et al., 1991; Faouzi et al., 1995) stored in PVC bags (Allwood, 1986; Arbin et al., 1986). On the other hand, exposure to DEHP has been studied in patients undergoing cardiopulmonary bypass surgery (Barry et al., 1989), in infants receiving an exchange transfusion (Sjöberg et al., 1985; Plonait et al., 1993) and in patients undergoing regular continuous ambulatory peritoneal dialysis (Mettang et al., 1996a). Finally, several studies have reported the leaching of DEHP into patients undergoing hemodialysis treatment using PVC tubing (Flaminio et al., 1988; Christensson et al., 1991; Mettang et al., 1996b). With regard to hemodialysis patients, the estimated values for DEHP exposure in the literature range widely. Nässberger et al. (1987) estimated the DEHP leaching to be between 0.8 and 4.2 μg/ml serum in hemodialysis patients, when Pollack et al. (1985) estimated that DEHP was extracted from the dialyzer during a single dialysis session with a range of 23.8–360 mg.

Toxicity associated with acute administration of DEHP or its major metabolites (mono-2-ethylhexyl phthalate (MEHP), 2-ethylhexanol and phthalic acid) to experimental animals appears not to be very important, but chronic studies suggest adverse effects on several major organ systems. So, when DEHP is administered intravenously, accumulation is seen primarily in the liver, and in smaller quantities in the lungs, brain, spleen and gastrointestinal tract. A study completed by the National Institutes of Health found DEHP to be carcinogenic when rats and mice were fed large oral doses for 103 weeks (Kluwe et al., 1982). Prolonged administration of phthalate esters, in doses comparable with those occuring in human exposures, has been shown to have a toxic effect on the liver. Finally, the teratogenic effects were established through studies using pregnant animals (Tomita et al., 1982). Toxicity studies in animals have demonstrated an association between exposure to DEHP and changes in hepatocellular structure and liver function, as well as the development of hepatocellular carcinoma (Conway et al., 1989a). However, the exact mechanism of hepatocarcinogenesis and site of action of DEHP remain undefined. It has been postulated that DEHP and several structurally dissimilar compounds (hypolipidemic drugs like fibrates and halogenated hydrocarbons) induce hepatic peroxisome proliferation leading to excess H_2O_2 generated in the peroxisome and causing oxidative damage to nuclear macromolecules (Reddy, 1990; Bojes and Thurman, 1994; Winberg and Badr, 1995).

So, although DEHP effects have been clearly demonstrated in animal models and the initial investigations about DEHP leaching from PVC materials date back several years, phthalate plasticizers are always used in medical PVC devices. Patients undergoing maintenance hemodialysis therapy would seem particularly at risk of potential toxicity from DEHP, due to regular exposure to the plasticizer over prolonged periods of time.

The aim of this study was to quantitate DEHP in the blood of hemodialyzed patients from several years and to prove that at the present time, these patients are still especially prone to be exposed to high concentrations of plasticizer.

2. Material and methods

2.1. Subjects

The following study was approved by the local

Ethics Committee and informed consent was obtained from all subjects. Twenty-one patients, 12 men and nine women aged 36–68 years, with chronic renal failure, undergoing maintenance renal hemodialysis in the Dialysis Unit, Lille General Hospital, participated in the study. Patients with congestive heart failure, pulmonary oedema, hepatic dysfunction and acute renal failure or hematocrit values below 21% were excluded from the study. The duration of dialysis treatments ranged from 10 months to 12 years. Each patient underwent dialysis for a 4-h period three times weekly, with a double needle access in arterio-venous fistulas using a membrane dialyzer (NT 1508 Sorin or Crystal 3400 Hospal) and a single-pass dialysate delivery system with a constant dialysate flow rate of 500 ml/min. The blood flow rate entering the hemodialysis circuit was set at approximately 300 ml/min and was measured by pump revolutions and bubble transit time. The mean plasma flow rate was obtained using the hematocrit of each patient.

2.2. Chemicals

DEHP and di-*n*-nonyl phthalate (DNNP), used as internal standard, were obtained from commercial sources purchased from Sigma–Aldrich (Saint-Quentin-Fallavier, France) and were used as analytical standards without further purification.

Phosphoric acid and triethylamine were analytical grade and obtained from Prolabo (Paris, France). All organic solvents were high performance liquid chromatography (HPLC) grade or of the highest purity available and were obtained from Alchym (Marchiennes, France). The water used to prepare buffers and dilutions was de-ionized and purified by distillation (Milli-Q, Millipore, Saint-Quentin Yvelines, France).

2.3. Chromatographic equipment

HPLC analyses were performed using a Hewlett-Packard (HP) 1090M system equipped with a variable-volume injector, an automatic sampling system and a HP 79994 linear photodiode array UV detector operating at suitable wavelength. The output from the detector was connected to a HP 9000 model 300 integrator to control data acquisition and integration. Retention times and peak areas were determined by computer, recorded on a HP Thinkjet terminal printer.

Chromatographic analyses were performed on a 5-μm C_{18} HYPERSIL BDS column (150×4.6 mm^2, i.d.) (Phase Separator, Waters Division, Saint-Quentin en Yvelines, France) operating at room temperature. DEHP and DNNP were eluted isocratically using a mobile phase consisting of acetonitrile buffer (triethylamine 0.2% adjusted to pH 2.5 with phosphoric acid) mixture (90:10, v/v) and delivered at 1.5 ml/min. Ultraviolet absorbance of the effluent was monitored at 222 nm.

2.4. Blood sampling

Samples were collected directly on the hemodialysis line by sample site into heparinized glass tubes. Venous blood samples (5 ml) were drawn immediately prior to dialysis, and then arterial and venous blood samples entering and leaving the dialyzer were obtained simultaneously from the inflow and outflow tubing of the dialyzer at 0.5, 1, 2, 3 and 4 h during the regular dialysis session.

The hematocrit of each blood sample was measured immediately. Blood samples were then centrifuged to obtain plasma. Each plasma aliquot was placed in acid-washed glass tubes and frozen (−20°C) immediately to avoid spontaneous hydrolysis of DEHP to MEHP, until HPLC analysis.

2.5. Chemical assays

Since DEHP is a persistent environmental pollutant, rigorous precautions were taken to avoid contamination during sample handling and analysis. All the samples were prepared and diluted in glass tubes washed previously in first with tetrahydrofuran–methanol mixture then rinsed with an acid solution.

After defrosting, each plasma sample (1 ml aliquot) was spiked with 100 μl of DNNP (10 μg) as an internal standard. The sample was then mixed with 2 ml acetonitrile and 1 ml sodium hydroxide (1 N). The mixture was shaken for 10 min using an alternating agitator and centrifuged at 3000 × *g* for 10 min. The clear supernatant (50 μl) was then injected into the chromatograph.

2.6. Quantitative determination

For DEHP quantification, the peak area ratio (DEHP/DNNP) (y) was calculated for each sample and the amount of DEHP (x) was determined using the calibration curve ranged from 0.15 to 10 μg/ml and obtained during the validation of method. The linear regression equation was $y = 0.093x - 0.006$ with a correlation coefficient of 0.999. The validation of the analytical method for DEHP determination has been previously described by Dine et al. (1991). DEHP and DNNP were well separated, identified and quantified by this HPLC procedure and no interferent peak was detected in blank plasma. The retention times were 13.95 and 15.92 min. for DEHP and DNNP, respectively (Fig. 1). The results show that this method had acceptable accuracy and precision with intra-assay and inter-assay coefficients of variation all below 6.5%, and the recoveries for DEHP were all better than 95%. The method showed a sensitivity of 0.1 μg/ml.

2.7. Data analysis

The amount of DEHP extracted from the plasticized hemodialysis tubes over a 4-h dialysis session can be estimated from the increase in DEHP concentration following transit of blood through the dialyzer.

The amount of DEHP contaminating the patient during the dialysis session, dQ, was obtained by calculating the AUC_{out} (area under the output dialyzer) concentration–time curve (venous line) and multiplied by the plasma flow rate (D_p).

$$dQ = D_p \times AUC_{out}$$

The quantity of DEHP retained by the patient during dialysis session dQ' can be estimated by calculating the difference between AUC_{out} and AUC_{in} for the area under the input dialyzer concentration–time curve (arterial line) and multiplied by the plasma flow rate (D_p).

$$dQ' = D_p(AUC_{out} - AUC_{in})$$

The area under the plasma concentration time curve (AUC) was calculated by the trapezoidal rule.

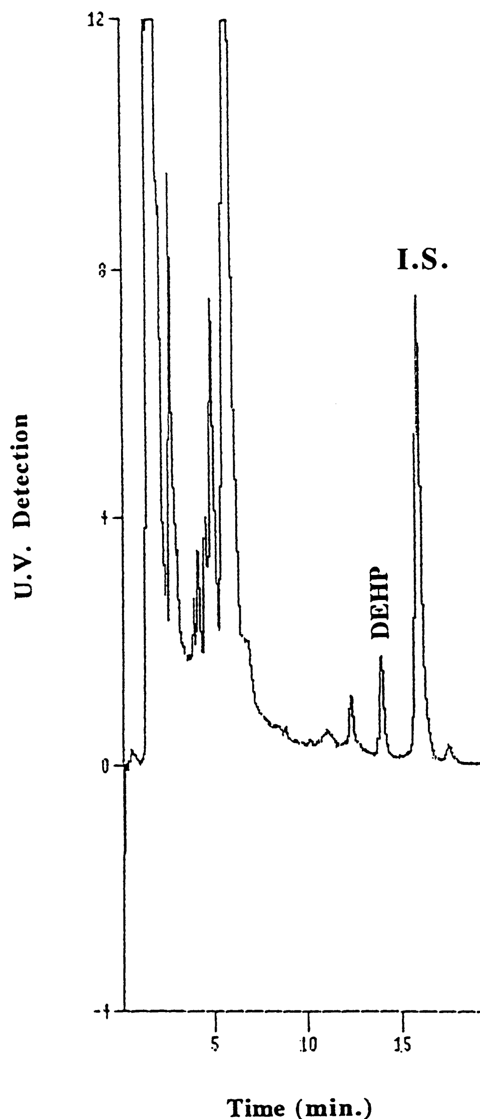

Fig. 1. HPLC chromatogram of plasma extract from a hemodialysis patient obtained at mid-dialysis of a 4-h session. DEHP concentration was estimated at 1.55 μg/ml.

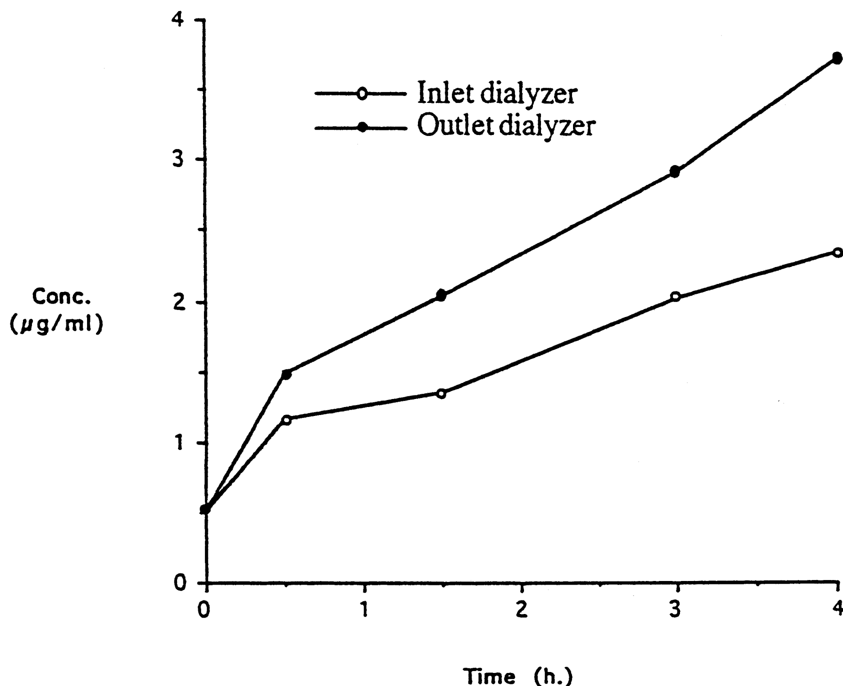

Fig. 2. Time-course of DEHP plasma concentrations at the inlet and outlet of the dialyzer during dialysis for one patient.

3. Results and discussion

Fig. 1 shows a chromatogram obtained after extraction of DEHP from the blood of a hemodialysis patient during a dialysis session. DEHP and DNNP are satisfactory resolved with retention times of 13.95 and 15.92 min, respectively. Fig. 2 shows the DEHP concentration time-course obtained from a hemodialysis patient at the inlet and the outlet of the dialyzer during a 4-h dialysis session. The mean plasma concentration with standard error for DEHP in five normal healthy volunteers was 0.62 ± 0.12 μg/ml when the mean concentration of DEHP present in the predialysis plasma samples obtained from the hemodialysis patients was 0.43 ± 0.19 μg/ml. This observation is consistent with previous reports of the ubiquitous presence of this plasticizer in the environment (Dirven et al., 1993b). DEHP has a short elimination half-life (about 12 h) and is rapidly metabolized and excreted. The difference observed between volunteers and patients could be explained from enzymatic inducer properties of DEHP and/or MEHP, its main metabolite (Grolier and Elcombe, 1993), particularly by auto-induction of its metabolism (Dirven et al., 1992). On the other hand, this plasticizer and its metabolites might accumulate in patients with renal failure and contribute to any long-term toxic effects.

The present study provides quantitative data on concentrations of DEHP in the arterial and venous blood tubes of 21 patients. Fig. 2 shows that the plasma concentration of DEHP measured in a patient during a single dialysis session at the entering point into the dialyzer at the arterial point showed a linear increase. This finding is consistent with earlier reports that significant amounts of DEHP are introduced into the systemic circulation of patients during dialysis (Pollack et al., 1985). However, the estimated values for DEHP exposure in the literature range widely. For instance, Kevy and Jacobson (1983) estimated that patients receive 32–90 mg at each dialysis session. Gibson et al. (1976) found a larger range, 9–150 mg per dialysis. Finally,

Table 1
Total DEHP exposure, DEHP retained by the patient and plasma concentrations of cholesterol plus triglycerides in 21 dialyzed patients[a]

Patient number	DEHP exposure (mg)	DEHP retained by patient (mg)	Plasma cholesterol + triglycerides (g/l)
1	61.5	17.98	3.39
2	94.7	17.33	7.11
3	44.32	19.32	3.29
4	46.19	8.53	2.51
5	80.16	25.14	4.32
6	64.55	16.18	6.65
7	61.52	13.7	1.98
8	101.26	23.5	6.06
9	62.41	9.41	2.29
10	55.41	17.92	3.8
11	69.68	11.7	1.98
12	102.66	18	6.1
13	63.92	10.7	ND
14	76.45	10	ND
15	56.56	10.1	ND
16	59.49	3.6	ND
17	85.87	14.2	ND
18	197.18	59.6	ND
19	59.97	17.4	2.05
20	91.46	16.9	6.2
21	44.75	8.3	2.89

[a] ND, not determined.

Lewis et al. (1978) calculated a 250-mg yearly dose in the case of the patient dialyzed twice a week. The reason for the discrepancy between these studies is not known, but it may be due to variations in the DEHP content of the dialyzer tubing or to differences in the dialysis protocol. Other factors such as lipid plasma content can influence the DEHP extraction and explain these differences, due to lipophilic characteristics of plasticizer. So, cholesterol and triglycerides were measured in 15 patients (Table 1) and a positive relationship was observed between the extraction of DEHP and the sum of the plasma cholesterol and triglycerides concentrations. The coefficient of correlation was estimated to be $r = 0.705$ (Fig. 3).

In the present study, the mean concentration of DEHP extracted during a single dialysis for the 21 patients was 75.26 mg. Results obtained after HPLC data analysis are summarized in Table 1. Assuming a three times per week treatment schedule, the average patient would be expected to receive approximately 11.74 g of DEHP over the course of a year, with a range of 6.91–30.76 g. On the other hand, the DEHP retained by a hemodialysis patient during a single dialysis session was evaluated. Table 1 shows a high degree of interpatient variability in DEHP retained with a range of 3.6–59.6 mg. DEHP retained by the patient is certainly responsible for biological effects. The distribution of DEHP into tissues is likely to be extensive. High concentrations of the plasticizer have been found in several tissues, especially the liver and the kidneys of animals exposed to the phthalate.

The findings of the present study indicate that patients undergoing dialysis are always exposed to DEHP, and the toxicity of DEHP has been shown in rodents (Kluwe et al., 1982; Tomita et al., 1982). Particularly, phthalic esters as DEHP and its main metabolite monoethylhexyl phthalate, but also clofibrate and nafenopin, are more commonly recognized as hepatic peroxisome proliferators (Elcombe and Mitchell, 1986) and, therefore,

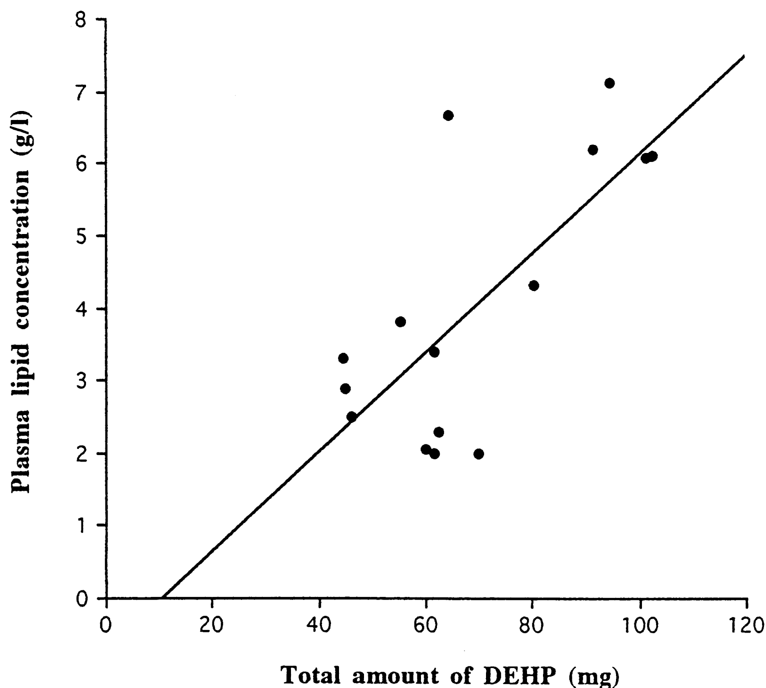

Fig. 3. Correlation between the total amount of DEHP extracted from the dialyzer and the plasma lipid concentration (cholesterol plus triglycerides) ($n = 15$), $r = 0.705$.

may be hepatocarcinogenic in rodents (Conway et al., 1989b). Hayashi et al. (1995) suggest that a high susceptibility caused by peroxisome proliferators to DNA damage would amplify minor DNA damage, and such spontaneous damage could increase the risk of the initiation process of hepatocarcinogenesis. In addition, these various foreign compounds may preferentially induce specific forms of hepatic microsomal P450 and the synthesis of a number of peroxisomal enzymes (Bojes and Thurman, 1994; Roberts and Knights, 1995) associated with β-oxidation of fatty acids such as cytochrome P-452, the latter specifically catalyzing the hydroxylation of fatty acids (Dirven et al., 1992). Disturbances in lipid metabolism are due to ω-hydroxylation of the fatty acid by cytochrome P450 IVA1 (Sharma et al., 1988; Okita and Okita, 1992). This peroxysomal response to xenobiotics has been suggested to be mediated via a peroxisome proliferator-activated receptor (Roberts and Knights, 1995).

On the other hand, DEHP seems to affect the kidneys and the testes. Presently, data in humans are sparse and the biological consequences of increased long-term exposure to phthalic esters are currently unknown. It should be kept in mind, however, that metabolism and toxicity of these compounds show a considerable interspecies variability. Accordingly, results obtained in animal models cannot simply be transferred to humans.

However, disturbances in lipid metabolism and hepatic function observed in chronic hemodialysis patients could be explained by inducer effects of DEHP on peroxysomal proliferation and β-oxidation of fatty acids (Bell et al., 1978).

So, in conclusion, in view of these data, intensive research for the study of a new plasticizer or a new type of flexible plastic for use in hemodialysis tubing is recommended to avoid the long-term exposure of patients with chronic renal failure. Although DEHP is not an acutely toxic compound and although in humans, prolonged exposure to DEHP leached into blood patients was not associated with specific toxicities, its

knowing use in hemodialysis tubing when in animals, hepatocellular effects occurred with DEHP chronic exposure and when it could be avoided through careful selection of material, is both unprofessional and undesirable.

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