Migration of Plasticiser from Haemodialysis Blood Tubing

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Summary

Di-2-ethylhexyl phthalate (DEHP) was found to migrate from polyvinyl chloride (PVC) blood tubing into human blood during both in vivo and in vitro haemodialysis. DEHP blood level increased during in vivo dialysis but decreased again toward the end of a six hour dialysis period. During in vitro haemodialysis of outdated human blood DEHP accumulated up to 5580 ppb.

Although toxic effects have not yet been observed, we believe plastic tubing that does not contain extractable materials should be developed.

Introduction

The use of plastic for the fabrication of disposable medical devices has increased in recent years. The development of such devices has unquestionably contributed to many recent advances in medicine. Haemodialysis depends on such materials. The introduction of plastics such as polyvinyl chloride (PVC) teflon and silastic (Quinton et al, 1960) have contributed enormously to this field.

These medical devices are approved by quality-control tests to assure sterility and lack of pyrogenicity (Brewer & Bryant, 1960; The Pharmacopeia of United States of America, 1965). However, with the recent demonstration of migration of phthalic acid ester (PAE) plasticisers from PVC plastic biomedical devices (Guess et al, 1967; Jaeger & Rubin, 1970, a, b; 1972; Marcel & Noel, 1970; DeHaan, 1971), more extensive testing will in future be necessary to demonstrate general toxic or local reactions (Guess & Haberman, 1968).

In view of the prolonged exposure of haemodialysis patients to plastic materials, this study was undertaken to quantitate the amount of di-2-ethylhexyl phthalate (DEHP), which is the main plasticiser of PVC migrating during in vivo and in vitro haemodialysis.
MATERIALS AND METHODS

In Vivo Haemodialysis

Twenty patients were maintained on a haemodialysis schedule of two to three treatments weekly, each dialysis lasting six hours. Ultra-Flo II coils were used for all patients in a Travenol RSP Canister Module. Using a glass syringe, samples of blood (10 ml) were drawn directly from an arm vein at intervals during haemodialysis. The blood samples were stored in glass tubes and frozen by storage in dry ice. The sample was then analysed according to the scheme outlined in Figure 1. The hexane extract was determined on a Shimazu GC 4A gas chromatograph. The gas chromatographic parameters were as follows: Column 2 m X 4 mm all glass, column packing 2% OV-225 on Chromosorb G (AW-HMDS) column temperature 200°C flow rate nitrogen 2.5 kg/cm².

As a control, samples of venous blood from seven healthy doctors and nurses were analysed. In addition, samples of dialysate were also assayed.

![Analytical scheme for determination of blood DEHP level.](image)

In Vitro Haemodialysis

The rate of extraction of DEHP into human blood during in vitro haemodialysis was determined. Units of outdated blood (1,000 ml) were pooled in a glass bottle and circulated in the Ultra-Flo II coil units with different lot numbers for up to six hours. During haemodialysis, a saline solution was infused to minimise haemo-
concentration. Samples of blood were drawn from the glass bottle and analysed according to the method described previously. The results obtained were corrected for differences in haemoglobin content for the circulating blood.

**Determination of Total Phthalic Acid**

In order to quantitate the total amount of phthalic acid, which is the common structure of DEHP and its metabolites in blood, an alkaline solution was added to aliquots of blood samples and both DEHP and its metabolites were thus converted to phthalic acid. The phthalic acid was then re-esterified to dipropyl phthalate (DPP) by adding propyl alcohol, and the DPP was assayed by gas chromatography. In this procedure, the total amount of phthalic acid in the blood was calculated. Prior to the experiments, all instruments and apparatus were carefully cleaned and found to be free of significant amounts of plasticisers.

**RESULTS**

The results of DEHP migration in human blood during in vivo haemodialysis are summarised in Figure 2. DEHP was not detected in predialysis blood samples of the twenty patients with the exception of one female with secondary amyloidosis. The blood level of DEHP increased during haemodialysis up to 460 ppb. However, the level of blood DEHP decreased again toward the end of the six hour dialysis period. Blood drawn from healthy controls did not contain detectable amounts of DEHP with the exception of one sample which was found to have 41 ppb.

![Figure 2. Blood level of DEHP during in vivo haemodialysis of twenty patients.](image-url)
Figure 3. Blood level of DEHP during in vitro haemodialysis using two blood tubings with different lot numbers. Tube 2 was made of softer polyvinyl chloride.

<table>
<thead>
<tr>
<th>TABLE I. Blood DEHP Content during In Vivo and In Vitro Haemodialysis</th>
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<tr>
<td>Haemodialysis</td>
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<tr>
<td><strong>In vivo</strong> (Patient S M 41-year old, woman)</td>
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<tr>
<td>Predialysis</td>
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<tr>
<td>1.5 hr</td>
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<td>3.0 hr</td>
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<tr>
<td><strong>In vitro</strong> (Outdated human blood, 1,000 ml)</td>
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<tr>
<td>Predialysis</td>
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<tr>
<td>0.5 hr</td>
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<tr>
<td>1.5 hr</td>
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<tr>
<td>3.0 hr</td>
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<td>5.0 hr</td>
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* Not detectable
During in vitro haemodialysis of human blood, DEHP accumulated in the blood as shown in Figure 3. The DEHP level of blood circulating in the tube 2, which was made of much softer polyvinyl chloride, increased up to 5580 ppb at the end of the six hour dialysis period.

Compared to the DEHP level, there was a significant accumulation of phthalic acid in the blood during both in vivo and in vitro haemodialysis. In particular, the total amount of phthalic acid in the blood increased up to 1010 ppb at the end of five hours of in vitro haemodialysis (Table I).

**DISCUSSION**

The compound DEHP is an aromatic diacid ester that meets the physical criteria needed to soften and plasticise the rigid polymer polyvinyl chloride (PVC). DEHP is added to PVC as a plasticiser, and represents between 20 to 40% of the finished weight of the plastic. The plasticiser does not bind firmly to the plastic and may be extracted by a variety of organic solvents. In addition, DEHP is soluble to some extent in biologic solutions such as blood and plasma. Reports of migration of phthalic acid ester plasticiser from plastic medical devices have appeared in recent articles (Guess et al, 1967; Jaeger & Rubin, 1970a,b; 1972; Marcel & Boel, 1970; DeHaan, 1971; Neergaard et al, 1971). However, we could find no study quantitating the migration of DEHP during haemodialysis.

Our study has shown that the blood level of DEHP definitely increased during both in vivo and in vitro haemodialysis. Large amounts of DEHP accumulated in the blood when a soft PVC blood tubing was tried. An interesting observation was the decrease in the level of blood DEHP toward the end of the in vivo haemodialysis. However, the amount of total phthalic acid in the blood accumulated steadily during both in vivo and in vitro haemodialysis. These results indicate that migrated DEHP from PVC blood tubing during haemodialysis is metabolised or taken up by a variety of tissues and removed by the next haemodialysis.

Although the fate of parenterally given DEHP is not thoroughly understood, the data of Jaeger & Rubin suggested that the liver is the site of the metabolism of the original DEHP to water-soluble form and this metabolite is primarily excreted in the urine and feces (Jaeger & Rubin, 1970 b). There is no information currently available which details exactly what toxicologic hazards may result from intravenous exposure to DEHP and its metabolites (Calley et al, 1966). The amount of migrated DEHP might be negligibly small in each individual haemodialysis, but a patient who is maintained on haemodialysis has impaired urinary excretion and permanently requires at least 100 to 150 treatments a year unless he receives a kidney transplant. Such patients receive an extremely large amount of migrated DEHP during the entire course of treatment; consequently, DEHP and its metabolites may accumulate in the body.

Although toxic effects from DEHP have not yet been reported in patients on
haemodialysis, these may occur in the future. In view of our findings, we believe that plastic materials which do not contain additives that will migrate during dialysis should be available.

References

Brewer, J H and Bryant, H H (1960) *Journal of the American Pharmaceutical Association*, 49, 652
DeHaan, R L (1971) *Nature*, 231, 85
Guess, W L, Jacob, J, and Autian, J (1967) *Drugs Intelligence and Clinical Pharmacy*, 1, 120
The Pharmacopeia of the United States of America, (1965) Seventeenth revision, 902

Open Discussion

NIELSEN (Copenhagen) What is your spread of measurements of DEHP, and how exact are they? It is difficult to measure this compound in blood.

ONO The measurement of DEHP was done by Dr Totskauwa who is a chemist; I am not sure about the method.