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Variations in the clearance of isosorbide dinitrate and its two active metabolites according to the nature of the membrane in simulated dialysis

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Abstract

Many dialysis patients with chronic terminal renal failure also suffer from cardiovascular conditions such as angina pectoris, for which they are treated with isosorbide dinitrate (ISDN). It is now accepted that nitrates can interact with many plastics and other biomaterials, but no work has been published on dialysis membranes. Accordingly, we studied the influence of dialysis, and in particular the influence of the nature of the membrane on the plasma concentration and the elimination of ISDN and its two active metabolites, isosorbide 2- and 5-mononitrates (2- and 5-ISMN). We simulated dialysis in vitro, to study the influence of seven different membranes on the levels of these nitrates. The concentrations of the three nitrates were measured upstream and downstream of the membrane (A and B, respectively), and in the ultrafiltrate (C), at times 5, 15, 30, 45 and 60′. Significant differences in concentration were found for ISDN in the three sample solutions A, B and C against time with the polysulfone, polyacrylonitrile, cellulose acetate and cellulose triacetate. These differences are apparently due to an interaction of ISDN with these membranes. In addition, significant differences in ISDN concentrations were observed between the polysulfone membrane and the polyacrylonitrile, hemophan and cuprophan membranes. However, these differences diminished with time and were no longer significant after 1 h. There was no significant difference in 2- and 5-ISMN concentrations in time between any of the sample solutions that could be attributed to metabolite-membrane interactions, or between different membranes. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Isosorbide dinitrate; Active metabolites; Ultrafiltration; Membranes; Interactions; Biomaterials

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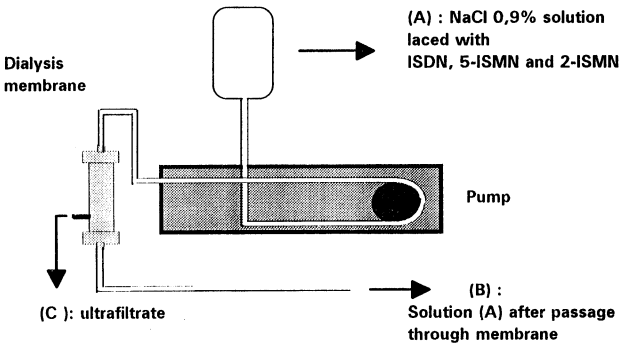

Fig. 1. Opened-circuit simulated dialysis set-up.

1. Introduction

Three main mechanisms are discernable in the process of purification of blood through a dialysis membrane; diffusion, convection (or ultrafiltration) and adsorption. Adsorption is due to chemical interactions that can bind certain molecules to certain membranes. This property depends on differences in the physico-chemical structure of the membranes (homogeneity, symmetry, hydrophilicity, etc). The adsorption of proteins on dialysis membranes, especially inflammatory proteins has been studied (Kandus et al., 1989; Guttierez et al., 1990; Brown and Metha, 1991; Barrera et al., 1992; Pascual and Schifferli, 1993). Many patients with terminal chronic renal failure being regularly hemodialysed also suffer from cardiovascular diseases, and isosorbide dinitrate (ISDN) or isosorbide 5-mononitrate (5-ISMN), one of its active metabolites along with isosorbide 2-mononitrate (2-ISMN), are commonly used to treat angina pectoris in such patients (Schorderet, 1989). However, little work has been done to evaluate the effects of hemodialysis on the plasma levels and elimination of ISDN, 5- and 2-ISMN (Bauer et al., 1986; Evers et al., 1987). Similarly, the effects of the nature of the dialysis membrane has never been studied, though is now well known that nitrates can interact with many medical plastics and other biomaterials (Roberts et al., 1983; Postaire, 1991; Sautou et al., 1994). The purpose of this work was similarly to study the influence of the nature of the dialysis membrane on levels of ISDN, 5- and 2-ISMN in a simulated dialysis.

In previous work (Gremeau et al., 1997), we developed an open-circuit apparatus with which we studied the influence of five dialysis membranes (three cellulose-based; cellulose acetate (CA-110G, Baxter), cuprophan (Alpha 500 Lundia, Gambro), hemophan (Alwall GFS PLUS 16, Gambro) and two made of synthetic polymers; polyacrylonitrile (Filtral 10, Hospal) and polysulfone (Hemoflow, Fresenius)) on the behavior of ISDN and 5-ISMN (Fig. 1). Samples were taken upstream and downstream of the membrane (A and B, respectively), and in the ultrafiltrate (C) at the end of the simulation, which lasted 10 min. This preliminary study on ISDN and 5-ISMN, thus, revealed a difference in dialysability according to the nature of the membrane used (Tables 1 and 2), due to adsorption: the differences, found with some membranes, between the quantities present in A and the sum of those present in B and C showed that the loss of ISDN and 5-ISMN between A and B was not recovered in the ultrafiltrate, but could be due to binding to the membrane. However, we compared nitrate concentrations in B and C with those in A at time $t = 10$ min, whereas, a dialysis takes several hours. The concentrations we measured might not be constant over this time span. Accordingly, we conducted a further study, described here, that monitors the nitrate concentrations in the different compartments for 60 min. In addition, we included 2-ISMN and two further membranes (cellulose triacetate and polyamide).

Table 1
Concentration (%) of ISDN before and after passage through membranes during an opened-circuit simulated ultrafiltration lasting 60 min

	Concentration* (ng/ml)		Statistical analysis
	Solution (A) before passage through membrane	(B): Solution (A) after passage through membrane	
Polysulfone	101 ± 8	14 ± 3	$p < 0.001$
Cellulose acetate	102 ± 5	30 ± 3	$p < 0.001$
Cuprophan	95 ± 8	83 ± 7	$p > 0.05$
Hemophan	101 ± 8	96 ± 8	$p > 0.05$
Polyacrylonitrile	100 ± 7	58 ± 3	$p < 0.001$

Concentrations: mean $\pm$ S.D.; $n = 3$.
* p is set-up at 0.05.

2. Materials and methods

2.1. Materials

2.1.1. Dialysis

This comprised a set of arteriovenous blood lines for dialysis (Gambro), an AK 10 pump (Gambro) and the seven dialysis membranes studied:

1. Four cellulose membranes:
   Cuprophan (Alpha 500 Lundia, Gambro).
   Hemophan (Alwall GFS PLUS 16, Gambro).
   Cellulose acetate (CA-110G, Baxter).
   Cellulose triacetate (CT-110G, Baxter).
2. Three synthetic polymer membranes:
   Polyacrylonitrile (Filtral 10, Hospal).
   Polysulfone (Hemoflow, Fresenius)
   Polyamide (FH 66D, Gambro).

Consumables used for the dialysis simulation were 0.9% NaCl (Biosedra) and water for hemodialysis obtained from the supply of the Clermont-Ferrand Teaching Hospital, France.

2.1.2. Chromatography

ISDN, 5- and 2-ISMN were assayed by gas phase chromatography after solid-phase extraction (Gremeau et al., 1995).

The solid-phase extraction was performed with a Vac-Elut apparatus (Analytichem), and Envil 8 500 mg cartridges (Supelco, St-Germain-en-Laye, France). The compounds were then separated on a 25 m $\times$ 0.32 mm ID fused silica capillary column with a film thickness of 0.5 μm (Perkin Elmer, Norwalk, CA) and detected by electron capture.

The compounds studied were ISDN (Theraplix, Paris, France) and its metabolites 2- and 5-ISMN (Ethypharm, Houdan, France). The internal standard was trinitrine (Merck, Darmstadt, Germany). The reagents used for the extraction and assay were methanol for analysis (Carlo Erba, Milan, Italy) and sterile water (Bruneau, Boulogne-Billancourt, France).

2.2. Methods

2.2.1. Dialysis

The purpose of the study was to compare different dialysis membranes. Before doing this in a real situation in patients, we simulated a dialysis in vitro, studying each membrane under identical controlled conditions defined beforehand. To do this we set up the apparatus depicted in Fig. 2 with the membrane to be studied, a set of lines and a pump. The patients blood was simulated with 5 l of an isotonic solution of NaCl laced with ISDN (100 ng/ml), 5-ISDN (200 mg/ml) and 2-ISMN (100 ng/ml). The set-up was a closed circuit and no dialysate passed through the membrane.

The membrane was first rinsed with 2 l of water for hemodialysis, and the solution simulating the blood compartment was then 'dialysed' with a flow rate of 250 ml/min and a pressure of 150

Table 2
Concentration (%) of 5-ISMN before and after passage through membranes during an opened-circuit simulated ultrafiltration lasting 60 min

	Concentration* (ng/ml)		Statistical analysis
	Solution (A) before passage through membrane	(B): Solution (A) after passage through membrane	
Polysulfone	233 ± 41	175 ± 39	$p > 0.05$
Cellulose acetate	207 ± 2	182 ± 2	$p < 0.001$
Cuprophan	198 ± 6	171 ± 6	$p > 0.05$
Hemophan	236 ± 33	228 ± 32	$p > 0.05$
Polyacrylonitrile	213 ± 17	195 ± 18	$p > 0.05$

Concentrations: mean $\pm$ S.D.; $n = 3$.
* p is set-up at 0.05.

mmHg for 60 min. At times 5, 15, 30, 45 and 60′, 3 ml of the solution was sampled at three different points; before passing through the membrane (A), after passing through the membrane (B) and in the ultrafiltrate (C). Equally a blank set-up was performed without membrane to check if the nitrates interact with the set of line. For each type of membrane, the procedure was carried out in triplicate with three new membranes.

2.2.2. Chromatography

ISDN and its two metabolites were extracted from 1 ml of A, B and C and assayed by gas phase chromatography. With each sample we carried out three extractions and three assays. Both the extraction and the analysis were performed using validated procedures [13].

There is a good precision of the method for the simultaneous determination of ISDN and its two metabolites. The intra-day and inter-days coefficients of variation are less than 10%, except the inter-day coefficient of variation for the assay of 5-ISMN which is less than 15%. The accuracy of the method is satisfactory ($< 10\%$) for all the compounds tested.

2.2.3. Statistical analysis

For each nitrate (ISDN, 5- and 2-ISMN) we first averaged the three triplicate concentrations obtained for each sample with each membrane. This was done for each membrane type at all the different times and for A, B and C.

Since the data was normally distributed we used a parametric test; a two-way analysis of variance. The first axis was time, the second was either the membrane type or the sample solution A, B or C. Whenever a significant difference was observed in the two-way variance analysis (where the different samples were considered globally over time), the samples responsible for this difference were systematically sought using comparison in pairs (Newman-Keuls or Dunian tests); p was set at 0.05.

3. Results and discussion

3.1. Results

The set-up without membrane (blank set-up) reveals no adsorption of the nitrates on the set of lines whatever the sample time ($p > 0.05$).

3.1.1. Comparative study of the influence of membrane type on nitrate concentrations at the different sampling points

First, we studied the influence of each of the seven dialysis membranes of the behavior of ISDN, 5- and 2-ISMN in (A), (B) and (C) during the simulated dialysis. We were, therefore, studying the time course of a set of three items. This was repeated independently for each membrane. The data for statistical analysis were the concentrations in ng/ml of the active substances in the

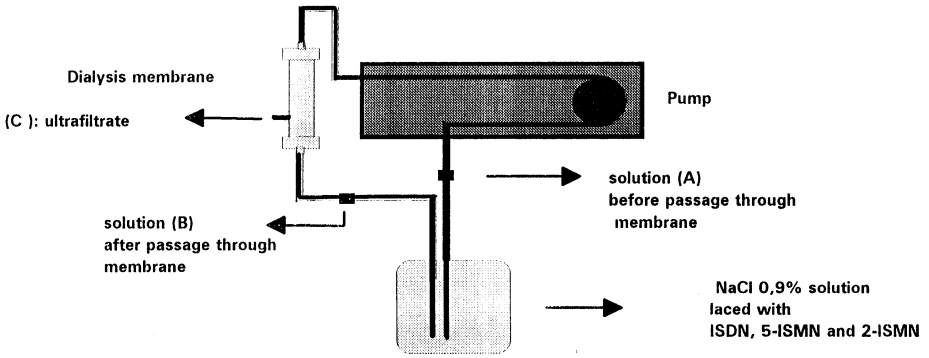

Fig. 2. Closed-circuit simulated dialysis set-up.

Table 3
Concentration (ng/ml) of ISDN before and after passage through a polysulfone membrane during a closed-circuit simulated ultrafiltration lasting 60 min

Concentration (ng/ml)	Time (min)				
	5′	15′	30′	45′	60′
Before passage through the membrane	93.0 ± 23.4	54 ± 20	47.0 ± 10.8	38.7 ± 10.0	33.0 ± 16.0
After passage through the membrane	9.2 ± 2.0	17.7 ± 7.6	24.7 ± 11.6	33.7 ± 12.9	29.3 ± 15.0
Ultrafiltrate	3.6 ± 0.6	11.7 ± 3.8	20.7 ± 5.0	25.0 ± 11.1	25.0 ± 12.5

Concentration: mean ± S.D.; $n = 3$.

three sample solutions A, B and C. The results are presented in Tables 3–6.

3.1.1.1. ISDN. The polysulfone membrane produced a significant overall difference ($p = 0.017$) in the concentrations of ISDN in A, B and C in the course of the simulated dialysis (Table 3). Although the polyacrylonitrile and cellulose acetate membranes produced no significant differences ($p > 0.05$) among A, B and C at any time, both membranes produced significant differences in ISDN concentration on the time axis ($p < 0.001$). In other words the times course of the concentrations of ISDN in A, B and C was the same with these two membranes. The cellulose triacetate membrane produced a significant overall difference in the concentration of ISDN among A, B and C ($p = 0.02$) and in time ($p < 0.0001$) (Table 4). However, for all these four membranes, i.e. polysulfone, polyacrylonitrile, cellulose acetate and cellulose triacetate, the differences in concentration of ISDN among A, B and C diminished with time, and by $t = 60$ min they were no longer significant ($p > 0.05$).

In contrast, there was no significant difference in ISDN concentration ($p > 0.05$) among A, B and C in time with the hemophan, cuprophan and polyamide membranes, i.e. the ISDN concentration was stable in time with these three membranes.

3.1.1.2. Metabolites 5- and 2-ISMN. The concentrations of these two nitrates did not vary significantly ($p > 0.05$) in A, B and C at any time with any of the membranes studied (Tables 5 and 6). The concentrations were stable in time.

3.1.2. Comparison of the influence on nitrate concentrations of type of membrane for each sample solution

Secondly, we compared the influence in time of all the membranes on the three nitrate concentrations separately for each sample solution. We were, therefore, studying the time course of a set

Table 4
Concentration (ng/ml) of ISDN before and after passage through a cellulose triacetate membrane during a closed-circuit simulated ultrafiltration lasting 60 min

Concentration (ng/ml)	Time (min)				
	5′	15′	30′	45′	60′
Before passage through the membrane	98.0 ± 4.0	76.7 ± 9.5	58.7 ± 6.5	66.0 ± 1.0	59.7 ± 7.6
After passage through the membrane	15.7 ± 2.5	44.7 ± 2.5	80.7 ± 6.5	71.0 ± 10.0	71.0 ± 11.0
Ultrafiltrate	10.0 ± 1.0	59.3 ± 6.4	76.7 ± 6.5	74.7 ± 4.6	57.0 ± 6.0

Concentration: mean ± S.D.; $n = 3$.

Table 5
Concentration (ng/ml) of 5-ISMN after passage through a polysulfone membrane during a closed-circuit simulated ultrafiltration lasting 60 min

Concentration (ng/ml)	Time (min)				
	5′	15′	30′	45′	60′
Before passage through the membrane	189.7 ± 35.4	209.7 ± 24.5	177.3 ± 34.6	224.07 ± 23.8	199.3 ± 24.7
After passage through the membrane	191.3 ± 57.9	176.3 ± 34.4	195.3 ± 15.6	209.7 ± 8.4	226.7 ± 12.6
Ultrafiltrate	229.7 ± 98.6	183.3 ± 22.2	202.3 ± 51.0	211.3 ± 17.0	179.0 ± 10.1

Concentration: mean ± S.D.; $n = 3$.

of seven items (polysulfone, polyamide, polyacrylonitrile, cellulose acetate, cellulose triacetate, hemophan and cuprophan) for A, B and C separately for each of the three nitrates. The statistical analysis was carried out on concentrations in B and C expressed as percentages of concentrations in A. The results are shown in Tables 7 and 8.

3.1.2.1. ISDN in B. There was a significant overall difference in concentrations in B compared to A ($p < 0.0001$). This difference was observed between the polysulfone membrane and the polyacrylonitrile, hemophan and cuprophan membranes in time (Table 7). This means that the time course of the concentration of ISDN is not the same for these membranes. However, as in the sample solutions, this difference diminished with time.

3.1.2.2. ISDN in C. In the ultrafiltrate C there was a significant overall difference ($p < 0.0001$). This was found between the polysulfone membrane and the polyacrylonitrile and hemophan membranes in time. These membranes, thus, produce a different time course of ISDN concentration, the effects of which diminish with time.

3.1.2.3. Metabolites 5- and 2-ISMN in B and C. There was no significant difference ($p > 0.05$) in the concentrations of either of the two active metabolites with any of the membranes at any time (Table 8).

4. Discussion

The results of the comparative study of the influence of membrane type on nitrate concentrations at the different sampling points are of interest on several counts.

4.1. ISDN

The results support and extend those of our preliminary study, i.e. certain membranes are not inert toward ISDN, in particular polysulfone, polyacrylonitrile, cellulose acetate and cellulose triacetate. The dialysability of ISDN thus varies

Table 6
Concentration (ng/ml) of 2-ISMN after passage through a polysulfone membrane during a closed-circuit simulated ultrafiltration lasting 60 min

Concentration (ng/ml)	Time (min)				
	5′	15′	30′	45′	60′
Before passage through the membrane	113.0 ± 28.6	103.0 ± 18.5	107.3 ± 23.1	115.0 ± 21.0	90.1 ± 42.1
After passage through the membrane	119.7 ± 22.8	84.3 ± 16.0	85.0 ± 35.4	99.2 ± 11.1	100.0 ± 32.1
Ultrafiltrate	97.0 ± 33.0	82.0 ± 12.2	101.0 ± 19.7	111.1 ± 20.3	82.3 ± 20.4

Concentration: mean ± S.D.; $n = 3$.

according to the nature of the membrane. However, the measurements show that the resulting differences in concentration diminish in time with these four membranes and that by $t = 60$ min they become non-significant ($p > 0.05$). This may be due to binding of ISDN to certain membrane sites causing a fall in ISDN concentrations in B and C, compared to A. Once these sites are saturated, binding ceases and the concentrations on either side of the membrane balance. In contrast, with the hemophan, cuprophan and polyamide membranes the ISDN concentrations in the three sample solutions do not change ($p > 0.05$). This confirms the results of our previous open-circuit study, extending it to a greater time span.

4.2. Metabolites 5- and 2-ISMN

There was no significant difference in the concentration of the two active metabolites at any time with any of the membranes tested. Unlike our previous study this work showed no interaction of 5-ISMN with the cellulose acetate membrane. The high standard deviations found in the earlier study may account for this discrepancy.

These results are consistent with work conducted to date on the interactions between nitrates and biomaterials. Several studies have revealed interactions between nitrates and plastics in perfusion sets (Schorderet, 1989; Guttierez et al., 1990; Brown and Metha, 1991). They have shown that 5-ISMN does not interact with plastics (Brown and Metha, 1991), unlike ISDN, which interacts with many synthetic polymers including PVC, polyurethanes and silicones (Schorderet, 1989). Roberts et al. (1983) explain this difference by the chemical structures of the molecules. ISDN, with two nitrite groups against one nitrite and one hydroxyl for 5- and 2-ISMN, is less hydrophilic and so has less affinity for the saline solution and more for the polymer material than its two metabolites.

The results of the comparison of the influence on nitrate concentrations of type of membrane for each sample solution show that the polysulfone membrane produces a different ISDN concentration in time from that obtained with the polyacrylonitrile, hemophan and cuprophan membranes in B, and with the polyacrylonitrile and hemophan membranes in C. However, this difference diminishes with time. There was no such difference with the two metabolites for either B or C with any of the membranes at any time.

Bauer et al. (1986) studied the influence of hemodialysis on the pharmacokinetics of ISDN. They found a clearance rate by dialysis of 100 ml/min (loss < 0.5%), when the total clearance of ISDN was 4.1 l/min. They showed in this way that dialysis made only a small contribution to ISDN clearance, and they explain the 4.1 l/min by the intense metabolisation of ISDN to active metabolites in the body. They conclude that ISDN pharmacokinetics are not affected by dialysis in general. Bauer and colleagues used a cuprophan membrane in their work. We also show that this membrane is inert, but our results with other membranes suggests that their results might have been different if they had used another membrane, at least during the first hour of dialysis (e.g. a polysulfone membrane).

Similarly, the impact of hemodialysis on the pharmacokinetics of 5-ISMN was studied by Ev-

Table 7
Concentration of ISDN in (B) accordingto the membrane

Concentrations (%)	Time (min)				
	5′	15′	30′	45′	60′
Polysulfone	14 ± 8	38 ± 11	69 ± 4	87 ± 19	88 ± 5
Polyamide	79 ± 3	81 ± 11	87 ± 10	87 ± 12	95 ± 5
Polyacrylonitrile	69 ± 9	100 ± 7	101 ± 4	99 ± 10	102 ± 16
Cellulose acetate	41 ± 8	84 ± 5	100 ± 23	96 ± 12	99 ± 4
Cellulose triacetate	19 ± 3	64 ± 9	89 ± 11	105 ± 9	110 ± 14
Hemophan	108 ± 16	88 ± 7	102 ± 9	101 ± 9	94 ± 3
Cuprophan	89 ± 10	98 ± 6	99 ± 9	93 ± 4	95 ± 6

Concentrations: mean ± S.D.; $n = 3$.

Table 8
Concentration of 2-ISMN in (B) according to the membrane

Concentrations (%)	Time (min)				
	5′	15′	30′	45′	60′
Polysulfone	100 ± 7	102 ± 18	104 ± 26	104 ± 8	109 ± 10
Polyamide	75 ± 11	91 ± 4	91 ± 22	110 ± 7	109 ± 13
Polyacrylonitrile	109 ± 4	101 ± 10	111 ± 7	98 ± 21	96 ± 10
Cellulose acetate	110 ± 15	102 ± 8	92 ± 13	96 ± 6	99 ± 4
Cellulose triacetate	97 ± 5	90 ± 10	95 ± 10	94 ± 4	95 ± 17
Hemophan	107 ± 14	104 ± 20	104 ± 14	105 ± 13	96 ± 4
Cuprophan	100 ± 8	106 ± 4	99 ± 16	92 ± 15	97 ± 7

Concentrations: mean ± S.D.; $n = 3$.

ers et al. (1987), who observed a fall of 20% in C_{max} ($p < 0.001$) and an increase in plasma clearance. They conclude that doses of 5-ISMN need to be adjusted if the plasma clearance of the dialysis exceeds 30% of the total clearance. However, they do not state the nature of the membrane they used.

5. Conclusion

Choosing a dialysis membrane depends on criteria of performance (hydraulic permeability and screening), biocompatibility and cost. Additionally, compatibility with any drugs the patient is taking on a long term basis is also relevant. This study shows that certain membranes interact with ISDN. This drug apparently binds to polysulfone, polyacrylonitrile, cellulose actetate and cellulose triacetate membranes. However, the effect is short-lasting and disappears after 1 h. The behavior of the active metabolites was not affected by any of the membranes studied. This study was done in vitro, as a preliminary to validation in real dialysis sessions. Many hemodialysis patients are polymedicated. It would, therefore, be interesting to study the influence of the nature of the membrane on the behavior of drugs with narrow therapeutic dose ranges, to define what dosage adjustments would be necessary to maintain efficient drug concentrations during dialysis and in the hours that follow.

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