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The Sorption of Isosorbide Dinitrate to Intravenous Delivery Systems

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Abstract—The sorption of isosorbide dinitrate from 0·9% sodium chloride and 10% glucose solutions, by intravenous delivery systems has been investigated under simulated infusion conditions. Isosorbide dinitrate was stable in both 0·9% sodium chloride and 10% glucose solutions. Intravenous fluid containers, burettes, a syringe, infusion sets and end-line filters were evaluated. Glass containers, methacrylate butadiene styrene burettes and polybutadiene giving sets did not sorb isosorbide dinitrate. Neither did polypropylene syringes when a 10% glucose solution was used. The sorption of isosorbide dinitrate to end-line filters was unimportant but there was a significant loss to the PVC tubing used to connect the filter housing to the catheter.

Numerous patients, infused with isosorbide dinitrate (ISDN) require higher doses than expected to obtain the desired haemodynamic effects. This may suggest that ISDN is lost by sorption to the plastic material of the infusion system. Although there is some literature available on this subject (Cossum & Roberts 1981; Lee & Fenton-May 1981; Morrison et al 1982; Remon & Bogaert 1983), some questions still remain unanswered.

In the present study the availability of ISDN from 0·9% NaCl and 10% glucose solutions has been investigated in order to evaluate the influence of the composition and the type of polymer of the infusion systems on drug sorption.

Materials and Methods

Materials

Cedocard IV ampuls (Cedona, Haarlem, Holland) containing an aqueous solution of 10 mg/10 mL ISDN were used in all experiments. Drug dilutions were obtained using 10% glucose or 0·9% sodium chloride solutions. We examined four infusion bags, three burettes, a syringe, five infusion tubings, three complete infusion sets (burette + infusion tubing) and four end-line filters. The main specifications of the materials are given in Table 1.

Analysis

Solutions of ISDN were assayed by HPLC (Gelber & Papas 1983). The system consisted of a HPLC pump (Waters Model 5000 A, Milford, MA, USA), a reversed phase column (5 μm particles Rosil C18 HL; 150 mm × 4·6 mm, Alltech RSL, Eke, Belgium), a variable wavelength UV-detector (Pye Unicam, LC 3, Cambridge, UK) set at 215 nm and a septumless syringe loaded injector loop of 50 μL (Valco Instr. Corp., Houston, USA). The mobile phase was methanol water (40:60, v/v). The flow rate was 1·0 mL min^{-1}.

Calibration curves (peak height versus concentration) for ISDN concentrations between 75 and 300 μg mL^{-1} showed excellent correlation ($y = 3{\cdot}929x + 0{\cdot}154$ with $r^2 = 0{\cdot}9982$). The standard deviation, calculated on the slope of the calibration curve, is 3·97% (n = 4). In all experiments the samples were taken using a glass syringe and 50 μL were directly injected onto the column.

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Storage in infusion bags, burettes and syringes (static experiment)

To the 500 mL infusion bags containing 0·9% NaCl or 10% glucose solutions the ISDN solution was added, to obtain a final concentration of 100 μg mL^{-1}. The glass containers were stored upright eliminating the influence of stoppers or silicon rubber parts. The burettes (100 mL) and the syringes (50 mL) were filled with a 0·9% NaCl or 10% glucose solution to obtain 250 μg mL^{-1} ISDN. The change in concentration of ISDN in the solution was monitored by sampling the solution at specified times.

Simulated infusion (dynamic experiments)

The infusion of ISDN to patients was simulated under laboratory conditions. Equal sized infusion tubing (180 cm) was connected to a modified borosilicate beaker fitted with a glass outlet. The influence of end-line filters was studied by using a polybutadiene infusion set connected to a beaker modified as described above. In all experiments an initial concentration of 250 μg mL^{-1} and a delivery rate of 20 mL h^{-1} was used. The delivery rate was adjusted by a peristaltic infusion pump (Terufusion, infusion pump, model STC-503, Terumo Corporation, Tokyo, Japan). The error on the volume delivered was about 10%. The effluent from the infusion tubing, the sets and the end-line filters were sampled at specified times and analysed.

All experiments were performed three times.

Results and Discussion

The percentage ISDN bound to the different intravenous devices at the end of the static experiments are shown in Table 2. ISDN is not sorbed by glass bottles. HDPE sorbs ISDN to a larger extent when diluted in 0·9% NaCl, while

Table 1. Specifications of containers, infusion sets and end-line filters examined for ISDN sorption.

Code	Device	Material	Manufacturer
A	500 mL container	Glass	NPBI Emmer Compascum, Holland
B	500 mL container	High dens. polyeth.	Braun, Melsungen, W. Germany (Plasco)
C	500 mL bag	PVC	Baxter, Travenol, Lessen, Belgium (Viaflex)
D	500 mL bag	Polyamide (as an inner wall)	Braun, Melsungen, W. Germany (Soluflex)
E	Burette	Methacrylate butadiene styrene (MBS)	Avon, Redditch, U.K. (Sureset A 2001)
F	Burette	Cellulose propionate (CP)	Abbott, Donegal, Ireland (Venisystem)
G	Burette	Butadiene styrene (BS)	Braun, Melsungen, W. Germany (Dosifix)
H	Syringe	Polypropylene	Terumo Corp., Tokyo, Japan.
I	Infusion tubing	Polybutadiene (PBD)	Avon, Redditch, U.K. (Sureset A 261)
J	Infusion tubing	(HDPE)	Rehau, Erlangen, W. Germany
K	Infusion tubing	Double polymer (PVC/PE)	Abbott, Donegal, Ireland (Venisystem Nitroglycerin set)
L	Infusion tubing	PVC	Braun, Melsungen, W. Germany (Dosifix)
M	Infusion tubing	PVC	Abbott, Donegal, Ireland (Venisystem, IV pump set)
N	Infusion set (burette + infusion tubing)	MBS + PBD	Avon, Redditch, U.K. (Sureset A 2001)
O	Infusion set (burette + infusion tubing)	CP + PVC	Abbott, Donegal, Ireland (Venisystem)
P	Infusion set (burette + infusion tubing)	BS + PVC	Braun, Melsungen, W. Germany (Dosifix)
Q	End-line filter	Cellulose ester	Braun, Melsungen, W. Germany (Sterifix inf. filter)
R	End-line filter	Cellulose ester	Millipore, 67 Molsheim, France (IVEX-HP filter)
S	End-line filter	Polyamide (Nylon 66)	Pall, FAE 020 LYL, Fajardo, USA
T	End-line filter	Polyamide (Nylon 66) (positively charged)	Pall, ELD 96 LL, Fajardo, USA

Table 2. Percentage ISDN sorbed by infusion bags after 7 h and to burettes and syringes after 5 h (n = 3).

Material code	0·9% NaCl solution	10% glucose solution
A	0·90% (±0·36)	1·01% (±0·79)
B	7·23% (±1·39)	2·25% (±1·03)
C	24·60% (±2·82)	20·22% (±2·80)
D	25·74% (±2·19)	22·83% (±2·11)
E	1·85% (±0·41)	1·71% (±0·61)
F	13·24% (±2·30)	15·39% (±2·98)
G	22·92% (±4·73)	25·91% (±4·78)
H	12·17% (±2·43)	2·24% (±1·36)

ISDN losses are less pronounced when diluted in 10% glucose solution. An influence of the vehiculum was also observed with PVC bags and plastic containers having a PA inner wall. However, the quantity of drug sorbed is higher for PA and PVC in comparison to HDPE bags (Fig. 1). To explain the influence of the vehiculum on the amount of drug sorbed, the partition coefficient hexane—0·9% NaCl and 10% glucose solutions was determined (Serota et al 1972). The value of the partition coefficient is 11·3 and 5·8 for 0·9% NaCl and 10% glucose solution, respectively. An explanation for the difference in partition behaviour could be that ions may salt out ISDN in the same way electrolytes decrease the aqueous solubility of non-polar solutes (Pikal et al 1977).

The sorption of ISDN to burettes on the contrary, seems, to be independent of the nature of the infusion fluid used. The difference in ISDN loss observed between the butadiene styrene and the cellulose propionate burettes is only due to a less pronounced initial adsorption to cellulose proprionate (Fig. 2). However, when the copolymer methacrylate butadienestyrene is used the sorption is reduced to a minimum.

As an alternative for the administration of drugs by intravenous sets, syringe pumps fitted with a polypropylene syringe are often used. As with the HDPE, PVC and PA bags, the sorption is strongly dependent on the composition of the diluents used.

The plots of ISDN sorption to PVC and PA bags show a biexponential loss of ISDN with time. The parameters of the

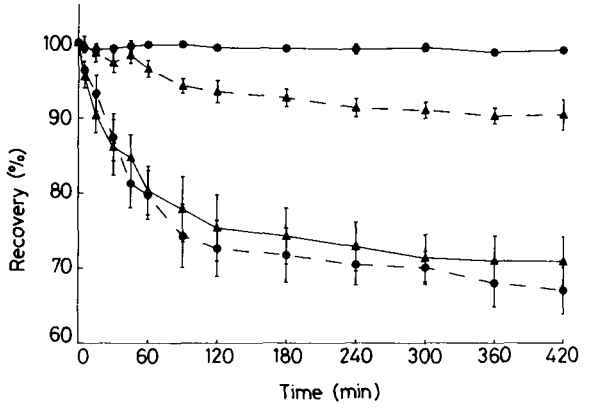

FIG. 1. Loss of ISDN in 0·9% NaCl solutions to LVP containers stored upright (initial concentration 100 μg mL^{-1}) bars: standard error of the mean (n = 3). ● A; -▲- B; ▲ C; -●- D.

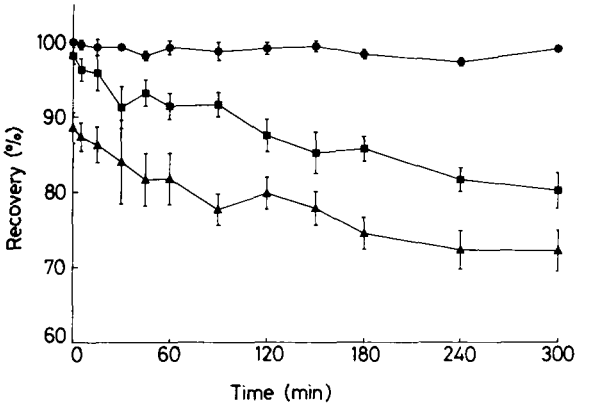

FIG. 2. Percentage of original ISDN concentration (250 μg mL^{-1}) remaining in 0·9% NaCl solutions after storage in burettes. ● E; ■ F; ▲ G.

biexponential equation are calculated using the method described by Malick et al (1981) and the ESTRIP model described by Brown & Manno (1978). The different parameters of the equation $A = \alpha e^{k1t} + \beta e^{k2t}$ are given in Table 3.

The experimental data show an excellent fit with the theoretical plots ($r^2 = 0.9882$) indicating that the loss of ISDN is probably due to an adsorption to the surface and an absorption into the matrix.

The percentages of ISDN sorbed by the different tubings, infusion sets and end-line filters are shown in Table 4. Fig. 3 visualizes the sorption pattern of ISDN by the different infusion sets. When PBD tubings are used a minimal sorption is seen with the glucose solution. HDPE sorbs the ISDN in an amount comparable with that of the double polymer PVC/PE. In the first hour of administration the PVC/PE sorbs more ISDN than the HDPE. After a 20 min initial absorption of ISDN to PVC tubing, a constant absorption into the matrix is seen (Fig. 3). The difference in sorption profiles observed for the two PVC tubing sets is probably due to a different concentration in plasticizer and a different manufacturing process. With a PVC/PE tubing more than 15% is lost after 5 h when 0·9% sodium chloride is used as infusion fluid while only 7% is lost when 10% glucose is used. Even so, a larger amount is sorbed by PVC tubing when the electrolyte is used. The difference in sorption profiles and the amount sorbed is probably due to the great difference in permeability of the different polymers (Pikal et al 1977). As was observed during the static experiments the nature of the solvent influences the amount sorbed. Fig. 4 shows the adsorption pattern when a dilution of ISDN-

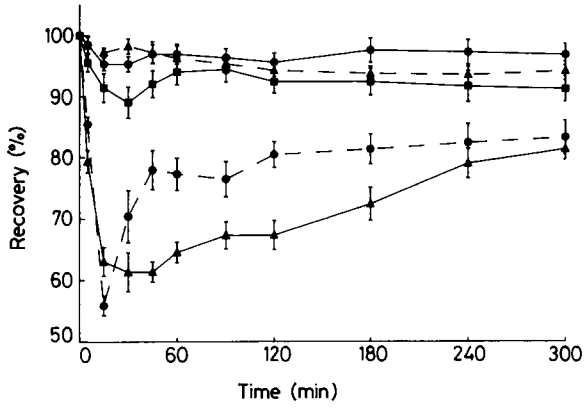

FIG. 3. Sorption pattern of ISDN in 10% glucose solution by different infusion sets (initial concentration 250 $\mu g\ mL^{-1}$ delivery rate 20 $mL\ h^{-1}$). ● I; -▲- J; ■ K; -●- L; ▲ M.

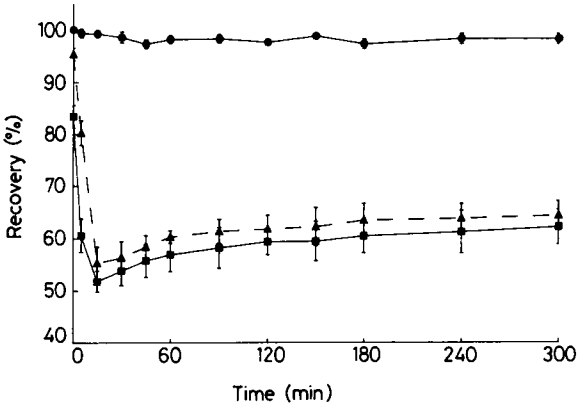

FIG. 4. Loss of ISDN to administration sets (burette+infusion tubing) after dilution of ISDN in 0·9% NaCl (initial concentration 250 $\mu g\ mL^{-1}$; delivery rate 20 $mL\ h^{-1}$) ● N; ▲ O; ■ P.

Table 3. The parameters and correlation coefficients of the biexponential functions describing the sorption of ISDN to PVC and PA infusion bags from 0·9% NaCl and 10% glucose solutions.

	0·9% NaCl	10% glucose
PVC (C)	$\alpha = 75.458$	$\alpha = 78.97$
	$k1 = 1.63\ 10^{-4}$	$k1 = 9.13\ 10^{-5}$
	$\beta = 21.73$	$\beta = 22.90$
	$k2 = 0.0212$	$k2 = 0.024$
	$R^2 = 0.9942$	$R^2 = 0.9875$
PA (D)	$\alpha = 73.18$	$\alpha = 75.63$
	$k1 = 1.94\ 10^{-4}$	$k1 = 1.004\ 10^{-5}$
	$\beta = 27.11$	$\beta = 24.69$
	$k2 = 2.30\ 10^{-2}$	$k2 = 1.90\ 10^{-2}$
	$r^2 = 0.9928$	$r^2 = 0.9786$

Table 4. Percentage ISDN sorbed to infusion tubing, sets and end-line filters after 5 h (n = 3).

Material Code	0·9% NaCl solution	10% glucose solution
I	2·14% (±1·03)	3·70% (±1·76)
J	15·92% (±1·63)	6·29% (±1·53)
K	15·99% (±3·33)	7·92% (±2·10)
L	35·45% (±3·02)	22·79% (±4·78)
M	36·56% (±4·20)	32·58% (±3·73)
N	2·27% (±0·99)	1·91% (±0·93)
O	38·13% (±2·77)	32·80% (±3·39)
P	42·60% (±3·27)	34·40% (±4·39)
Q	22·25% (±1·75)	15·55% (±1·92)
R	26·01% (±2·30)	23·84% (±2·30)
S	13·05% (±3·25)	9·87% (±2·11)
T	11·07% (±1·41)	9·08% (±1·76)

sodium chloride, prepared in the burette, is administered through infusion tubing. In all cases investigated, with the exception for the MBS burette in connection with a PBD tubing, drug sorption during the first 20 min is observed, due to adsorption in both the burette and the tubing. A continuous penetration of the drug in both the burette and the tubing explains the plateau observed after the initial adsorption (Fig. 4).

Nowadays end-line filters are frequently connected to infusion sets. The major reasons for their use are the removal of particulate matter and microorganisms, the prevention of phlebitis and air-embolism. The filter consists of a filterhousing and a PVC tubing connecting the housing to the catheter. The filtration system is composed of a 0·22 μm hydrophilic filter to eliminate particles and microorganisms and a hydrophobic filter to remove the air from the liquid. We investigated the sorption of ISDN on four filters with an equal hydrophilic surface (±10 cm^2). There is a major decrease in ISDN concentration after the first 5 min (Fig. 5). When the infusion is started ISDN is bound to the hydrophilic filter. Once all binding sites seem saturated the sorption profile is similar to the ones observed with the PVC infusion tubing. Due to differences in internal diameter, length and flexibility of the tubings, different amounts of ISDN are

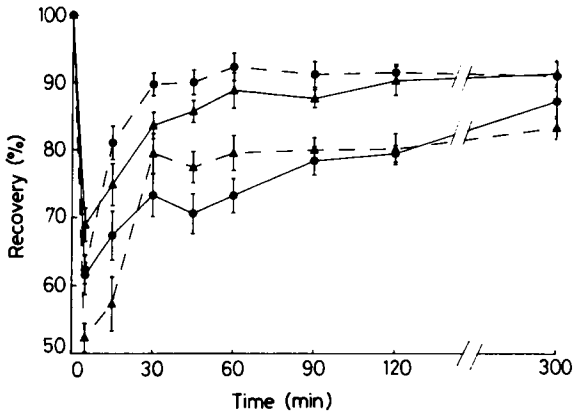

FIG. 5. Recovery (%) ISDN in 0·9% NaCl after administration through 4 types of end-line filters (initial concentration 250 μg mL^{-1}; delivery rate 20 mL h^{-1}). ● Q; -▲- R; ▲ S; -●- T.

sorbed. As mentioned previously the sorption from a 0·9% NaCl solution is more important than from a 10% glucose solution (Table 4).

DeLuca (1979) recommended as a guideline that drugs administered in concentrations below 5 μg mL^{-1}, or when the total amount of drug is lower than 5 mg over a 24 h period, a filter should be avoided unless a binding study has been performed.

Conclusion

With the exception of glass bottles and the MBS burette—PBD tubing combination (N), all other intravenous devices investigated showed sorption of ISDN. This could result in an unpredictable clinical response. To minimize the loss of ISDN to infusion systems it is advisable to use glass bottles as intravenous fluid containers, 10% glucose as infusion fluid, MBS (E) burettes, polypropylene syringes (H), PBD (I) administration sets and Nylon 66 end-line filters (S,T).

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