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COMMUNICATIONS

The sorption of isosorbide-5-mononitrate to intravenous delivery systems

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Abstract—The sorption of isosorbide-5-mononitrate, diluted in 0·9% NaCl or 10% glucose solutions, to intravenous delivery systems was investigated. Infusion bags, burettes, a syringe, infusion tubings and end-line filters were tested in static and in dynamic experiments. No clinically significant sorption was detected during those experiments. The use of PVC tubings of different hardness did not influence the results.

The anti-anginal compound isosorbide dinitrate is lost to intravenous delivery systems by ad- and absorption (Remon & Bogaert 1983; De Muynck et al 1988). Due to this unfavourable characteristic the flow rate of the intravenous infusion often has to be adjusted to obtain the required cardiovascular effects.

The metabolites of isosorbide dinitrate, isosorbide-5-mononitrate (IS-5-MN) and isosorbide-2-mononitrate have proven to be effective drugs for anti-anginal therapy when given intravenously (Bogaert & Rosseel 1972; Wendt 1972; Stauch et al 1975; Michel 1976).

In this study we investigated the sorption of IS-5-MN from 0·9% NaCl and 10% glucose solutions to the different parts of an intravenous delivery system.

Materials and methods

Materials. IS-5-MN was adsorbed on NaCl (1:8·85; w/w) (Schwarz Pharma AG 4019 Monheim, West Germany). Drug dilutions were obtained using 10% glucose or 0·9% NaCl solutions. Two infusion bags, two burettes, one syringe, five infusion tubings and four end-line filters were examined. The main specifications of the materials are given in Table 1.

The hardness of all PVC materials was determined according to the Shore A hardness testing procedure (DIN 53505-ISO R 868), using a hardness meter Härteprüfer HP-AR (Bareiss, 7938 Oberdischingen, West Germany).

Analysis. Solutions of IS-5-MN were assayed by the HPLC method of Gelber & Papas (1983). The system consisted of an HPLC pump (Waters Model 5000 A, Milford, MA, USA), a reversed phase column (Lichrospher RP-18, 5 μm particles, 125 mm × 4 mm, E. Merck, Darmstadt, West Germany), a variable wavelength UV-detector (Pye Unicam, LC3, 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 IS-5-MN concentrations between 50 and 300 μg mL^{-1} were linear ($y = 1{\cdot}33x + 0{\cdot}018$, $r^2 = 0{\cdot}999$). The standard deviation, calculated on the slope of the calibration curve, was 3·12% (n = 4). In all assays the samples were directly injected onto the column.

Storage in infusion bags, burettes and syringes (static experiments). IS-5-MN, adsorbed on NaCl, was dissolved in the appropriate infusion solution and added to the infusion bags to obtain a final concentration of 100 μg mL^{-1}. The IS-5-MN concentration in the burettes (100 mL) and in the syringes (50 mL) was 250 μg mL^{-1}. The change in IS-5-MN concentration in the solutions was monitored by sampling the solution at specified times over 48 h. The infusion bags were not protected from daylight and were stored at room temperature (21 ± 1 °C). All experiments were performed in triplicate.

Simulated infusion (dynamic experiments). Intravenous infusion was simulated under laboratory conditions. All infusion tubings were equally sized to 180 cm and were connected to a PVC infusion bag containing 250 μg mL^{-1} IS-5-MN in either 0·9% NaCl or 10% glucose. In all experiments delivery rate was 20 mL h^{-1} using a peristaltic infusion pump (Terufusion infusion pump, model STC-503, Terumo Corporation, Tokyo, Japan). The effluent from the infusion tubing, the sets and the end-line filters were sampled at specified times over 5 h. All experiments were performed in triplicate.

Results and discussion

The percentage IS-5-MN lost during the static experiments is shown in Table 1. No more than 4% of the initial amount of IS-5-MN was lost during those experiments to the materials tested over 48 h. This means that the addition of IS-5-MN could be included in a reconstitution program of a hospital pharmacy. This is in contrast with isosorbide dinitrate where, under the same experimental conditions losses up to ±25% after 5 h were observed (De Muynck et al 1988).

The amount of IS-5-MN sorbed to the different infusion tubings and end-line filters is also shown in Table 1. As reported for the static experiments, a negligible amount of IS-5-MN was lost to the different tubing materials and end-line filters. These results are consistent with the data of Roberts et al (1983) who reported IS-5-MN not to be sorbed by PVC and cellulose propionate strips. In their study the partition coefficient chloroform–water showed good agreement with the PVC–water partition coefficient. The partition coefficient of IS-5-MN (0·7) being much lower than that for isosorbide dinitrate (20·6) may explain the difference in amount of drug sorbed to the PVC tubings.

In this study, the influence of the amount of plasticizer in the PVC infusion tubing was determined by the Shore A hardness index for elastomers (Table 1.). None of the tubings showed any affinity for IS-5-MN. Even for the most flexible tubing (hardness index = 65) the sorption is negligible. As the exact composition of the different tubings is unknown it was not possible to

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Table 1. Percentage sorption of IS-5-MN to intravenous delivery systems.

		% Sorption from 0·9% NaCl	% Sorption from 10% Glucose
Static experiments (48 h)			
Infusion fluid containers			
High density polyethylene (HDPE)	Braun Melsungen West Germany (Plasco)	3±0·7	3·7±1·2
PVC (Shore A hardness: 80)	Baxter, Travenol Lab. Lessen, Belgium (Viaflex)	0	0
Burettes			
Cellulose propionate (CP)	Abbott N.V., Ottignies, Belgium (Venisystems Vented pump set)	1·9±0·7	2·0±0·9
Methacrylate butadiene styrene (MBS)	Avon, Redditch, UK, (Sureset A 2001)	0	0
Syringe			
Polypropylene (PP)	Terumo Corp., Tokyo, Japan	2·2±0·9	1·6±0·5
Dynamic experiments (5 h)			
Administration sets			
PVC (Shore A hardness: 78)	Abbott N.V., Ottignies, Belgium (Venisystems Vented pump set)	2·0±0·9	2·9±1·3
PVC (Shore A hardness: 80)	Travenol Laboratories, Lessen, Belgium	1·6±0·9	2·0±1·5
PVC (Shore A hardness: 65)	REHAU, Erlangen, West Germany	2·5±0·4	3·7±0·7
Polybutadiene (PBD)	Avon Medicals UK (Sureset A 261)	0·2±0·1	2·3±1·1
High density polyethylene (HDPE)	REHAU, Erlangen, West Germany	0	0
End-line filter			
Cellulose ester	Braun Melsungen (West Germany) (Sterifix)	1·2±0·2	0·9±0·6
Cellulose ester	Millipore 67 Molsheim France (Ivex HP)	0·8±0·3	0·7±0·4
Polyamide (Nylon 66)	Pall, Fajardo, USA (FAE-020 LL)	0·2±0·1	0·2±0·1
Polyamide (Nylon 66) positively charged	Pall, Fajardo, USA (ELD-96 LL)	0·3±0·1	0·2±0·1

determine whether the nature of the plasticizer could have an influence on the amount of drug sorbed to the PVC tubings.

The maximal loss of IS-5-MN when administered in 0·9% NaCl or 10% glucose from a system consisting of a syringe, an infusion fluid container or a burette through an infusion tubing with end-line filter is estimated to be 10%.

When compared with the results obtained with nitroglycerin (De Rudder et al 1987) and isosorbide dinitrate (De Muynck et al 1988), IS-5-MN shows definite advantages when used in continuous intravenous infusion.

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