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Sorption of parenteral nitrates during administration with a syringe pump and extension set

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Summary

The sorption of glycerol trinitrate to PVC bags and administration sets during intravenous infusion has been widely reported. Nitrate interactions during continuous administration using a pre-filled plastic syringe and syringe pump, connected to the injection site using a plastic extension set, are reported in this study. Losses from sorption to PVC, nylon and polyethylene tubing were compared. Factors influencing sorption were also assessed. Results showed that sorption to polypropylene syringes and polyethylene tubing were negligible, while PVC and nylon tubing sorbed GTN and ISDN. Sorption to PVC approached 90% in some instances. Losses were greatest with GTN. The concentration of ethanol influenced sorption while propylene glycol had no detectable effect. Other factors examined were drug concentration, flow rate and tube length. It is recommended that PVC or nylon extension sets should be avoided for intravenous nitrate administration using a syringe pump.

Introduction

The use of intravenous nitrates for the treatment of myocardial ischaemia and other acute aspects of coronary care is now common practice. The agents used are glyceryl trinitrate (GTN) or isosorbide dinitrate (ISDN). The drugs are administered, after dilution, by slow intravenous infusion, achieved by a volumetric pump and administration set or syringe pump, the syringe connected to the venous access point by a short plastic tube. Patients may often be infused through an indwelling i.v. catheter.

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GTN and ISDN are poorly soluble in water. The concentrated injection requires a solubiliser to maintain a stable formulation. For this purpose, various solvents are employed, especially propylene glycol and ethanol. In addition the formulations may be buffered.

The loss of GTN onto plastic materials used to administer intravenous infusions has been widely reported. Sorption occurs to PVC film and tubing (Roberts et al., 1980; Lee, 1986), the process being described recently as diffusion. In contrast, losses to glass bottles, polyethylene or polybutadiene is negligible (Lee, 1986; Kowaluk et al., 1983). In contrast to the extensive work associated with GTN, ISDN sorption has been examined only recently. However, ISDN clearly is bound to PVC although the extent of migration from solutions

compared to that of GTN is unknown (Lee, 1986; Lee and Fenton-May, 1981). Almost all reports refer to sorption in relation to intravenous infusion of nitrates. Binding to plastic or glass syringes and extension sets used to connect the syringe to the injection site has received very little attention. Cossum et al. (1978) reported that GTN losses were considerably reduced using glass syringes and polyethylene tubing compared to traditional methods of infusion. A later study (Roberts et al., 1981) showed that losses to one type of plastic syringe were also negligible. It was therefore the principal aim of this study to examine the losses of ISDN and GTN to plastic syringes and extension lines (connecting syringe to injection point) commonly used for drug administration using a syringe pump.

Materials and Methods

ISDN B.P. (diluted in lactose 25% w/w) was obtained from Graesser Laboratories Ltd., Sandycroft, U.K. ISDN injection (Cedocard IV, 1 mg/ml in 10-ml ampoules) was obtained from Tillotts Laboratories Ltd., Henlow, U.K. and GTN injection (Tridil Injection, 5 mg/ml in 10-ml ampoules) from American Hospital Supplies Ltd., Didcot, U.K. Propylene glycol B.P. was obtained from Evans Medical Ltd., Speke, Liverpool, U.K. and Tween 80 from B.D.H. Ltd., Poole, U.K.

Solutions of ISDN were prepared from the powder by dissolving in 20 ml absolute ethanol (James Burrough Ltd., London, U.K.) then diluting to 100 ml with freshly distilled water. The injections were diluted using freshly distilled water as required.

60-ml syringes (Plastipak) were obtained from Becton-Dickinson Ltd., Wembley, U.K.; polyvinyl chloride (PVC) extension sets (Manometer K Lines) from Kimel Scientific Products Ltd., Uxbridge, U.K.; polyethylene extension sets (Lectrocath) from Vygon Ltd., Cirencester, U.K. and nylon extension sets (Portex Manometer Lines) from Portex Ltd., Hythe, U.K.

Analysis of ISDN and GTN was by liquid chromatography (Lee and Fenton-May, 1981) using a reverse-phase O.D.S. column (Radial-Pak μ-Bondapak C18 (Water Associates Ltd., Watford, U.K.)). The solvent was methanol : water (50 : 50) flow rate 1.5 ml/minute, detection at 216 nm using a sensitivity setting of 0.08–0.16 AUFS. Injection was by fixed volume loop (20 μl) using a Rheodyne injector model 7125. Quantification was by electronic integration. This method was stability indicating (Baaske et al., 1979). Accuracy and precision of the assay were satisfactory, over the range 80–400 μg/ml ISDN ($r = 0.9994$; S.E.M. of repeated injections ($n = 6$) = 1.29%). For analysis of samples each solution was injected in triplicate, together with standards, using a bracketing technique.

To assess sorption of nitrates to different plastics, two types of test were devised. The main method comprised a simulated in-use test:

The solution was diluted in water and a syringe primed with a suitable volume of this dilution. The extension set was connected to the nozzle of the syringe and the syringe clamped into the Syringe Pump (Model 800, Imed Ltd., Abingdon, U.K.) The pump was operated with two syringes in place. The pump was then set at the maximum rate and activated to prime the line. When the line was completely primed, the pump was immediately switched off, the desired flow rate set and "injection" commenced.

Samples were collected into amber glass vials via a disposable needle (19 gauge). All samples were collected over 1-h periods and the flow rate was 0.75 ml/h/syringe (Pump setting = 1.5 ml/h) unless otherwise indicated. Samples were also collected from each syringe at the completion of each study period (normally 24 h). Controls comprised a sample of the diluted solution stored in an amber glass volumetric flask for 24 h.

A static test was also used in some experiments. Solutions were diluted in water. Each extension set was primed using a syringe which was then left attached to one end. The other end of the line was closed using a blind-hub Luer lock. Each line was then stored for the designated period at ambient temperature (unless otherwise stated), the syringe removed and the whole contents withdrawn into a glass vessel. Control solutions were stored in glass volumetric flasks. All test materials were protected from exposure to daylight.

Results

Isosorbide dinitrate sorption

Losses of ISDN to extension sets were examined during simulated in-use conditions. Cedocard Injection was diluted to a concentration of 400 μg/ml and administered at a rate of 0.75 ml/h. Three different sets were tested and the results described in Fig. 1. Sorption to polyethylene (Lectro-Cath) was relatively slight. Losses by sorption to nylon (Portex) were significant, especially over the first 4–6 h period, after which saturation of the plastic material became evident and the concentration of ISDN in the injection rose. After 24 h continuous administration, sorption losses had become insignificant. In contrast, losses of ISDN by sorption to a PVC line were extensive and the length of the extension line alone markedly influenced the process. In the extreme case, losses were so great that less than 20% of the drug was eluted over many hours after commencing the injection. Saturation conditions were not achieved after 24 h continuous injection through that line.

The effect of different concentrations of ISDN on the proportions sorbed to PVC lines during administration was examined. The results are shown in Fig. 2. It can be seen that sorption losses are not markedly influenced by the concentration of ISDN over the range examined (100–1000 μg/ml). Losses by sorption are proportional to the drug concentration. Losses of ISDN (400 μg/ml) diluted in water for injection, 5% dextrose or 0.9% saline were compared during simulated administration. There was no significant difference in the results obtained indicating that the aqueous diluent did not influence sorption (Student's t-test: $P = 0.05$).

The effect of varying the flow rate of administration on the sorption of ISDN to PVC lines was examined. The results are shown in Fig. 3. The data suggest that the rate of delivery of the injection does not markedly effect the dose of drug administered, at least at the relatively low concentrations studied.

The degree of inter-experimental variation is

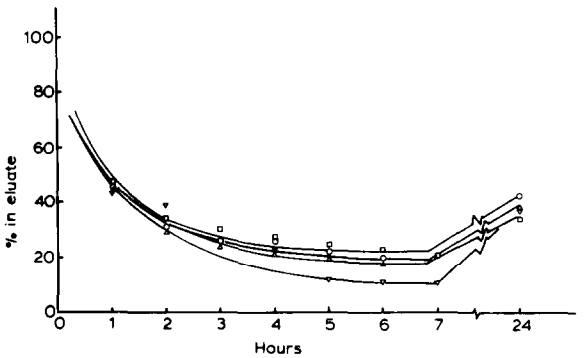

Fig. 2. Effect of concentration on the sorption of ISDN (Cedocard) to PVC extension sets. Conditions: Kimel manometer line, 200 cm; Flow rate, 0.75 ml/h. ○, 100 μg/ml; △, 200 μg/ml; ▽, 400 μg/ml; □, 1-mg/ml.

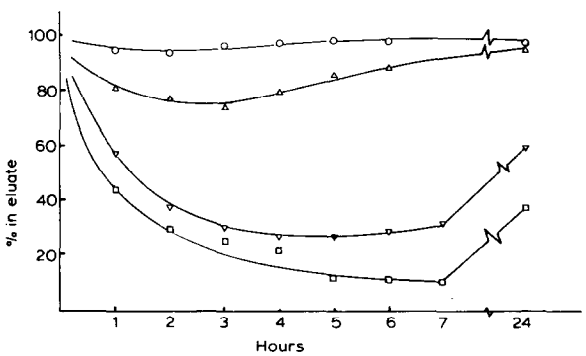

Fig. 1. Sorption of ISDN (Cedocard) to different extension sets during administration. Conditions: concentration of ISDN, 400 μg/ml; flow rate, 0.75 ml/h. ○, lectrocath 100 cm; △, Portex 150 cm; ▽, Kimel 100 cm; □, Kimel 200 cm.

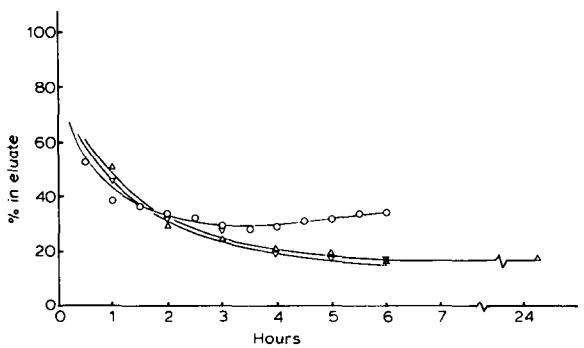

Fig. 3. Effect of flow rate on the sorption of ISDN (Cedocard) to PVC extensions sets. Conditions: Kimel Manometer line 200 cm; concentration, 100 μg/ml): △ 0.5 ml/hour; ▽ 1 ml/hour; ○ 1.5 ml/hour.

illustrated in Fig. 4, using PVC lines and standard solutions and conditions. In these experiments, ISDN solutions were prepared in the laboratory from the drug powder in 20% ethanol. Sorption losses were similar to those reported for Cedocard Injection. The results of combining data from 4 experiments indicate that the variation between experiments was relatively small although some scatter was noted at the start and completion of each experiment. The former could be influenced by difficulties in reproducing exactly the priming techniques in different experiments.

Because ISDN is poorly soluble in water, additional solvents are required in the injection to stabilise the preparation. Solubility is enhanced by the use of ethanol, propylene glycol, Tween 80 or a combination of these. The influence of these co-solvents on the sorption process was therefore examined.

In the first experiment, solutions of ISDN were prepared in vehicles containing different proportions of ethanol. PVC lines were then primed by filling with the solution of ISDN, closed and stored at room temperature. After 24 h storage, the contents were removed for analysis. In a second set of lines, Tween 80 was also included. The results are summarised in Fig. 5. It is clear that the concentration of ethanol has a substantial influence on the sorption of ISDN. When the concentration of ethanol is increased, the sorption of ISDN is reduced. This is especially evident above 30–40% ethanol. In contrast the addition of

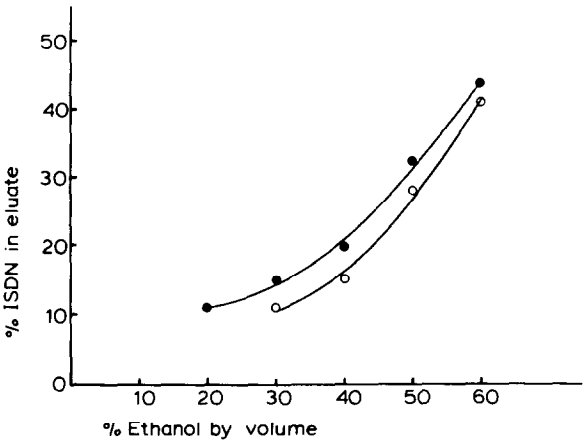

Fig. 5. Effect of ethanol and Tween 80 on losses of ISDN to PVC line after storage for 24h. Conditions: Kimel Manometer line 200 cm; concentration, 400 μg/ml; ●, with Tween (1% by volume); ○, without Tween.

Tween 80 had only a minor effect on sorption, the response being to increase sorption by ca. 5%.

The effect of increasing the concentration of propylene glycol over the range 5–30% on sorption of ISDN was examined using the same experimental method. The results indicate that propylene glycol has no significant effect on ISDN sorption.

The effect of ethanol concentration on sorption of ISDN during simulated administration was examined.

The results are shown in Fig. 6. The effect of

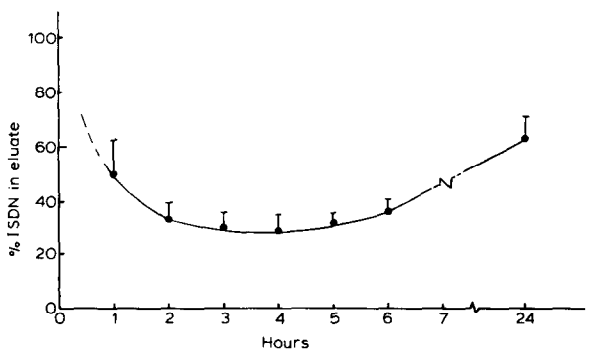

Fig. 4. Reproducibility of sorption curve for ISDN to PVC lines. Conditions: Kimel Manometer lines 100 cm; concentration, 400 μg/ml. Each point represents mean of 4 experiments; bar lines = S.D.

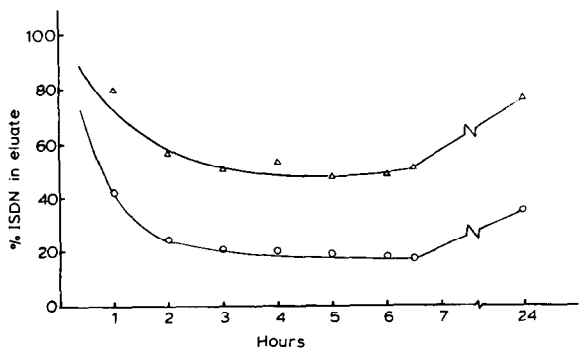

Fig. 6. Effect of ethanol concentration on sorption of ISDN to PVC extension sets. Conditions: Kimel manometer line, 200 cm; flow rate 0.75 ml/min. ISDN, 400 μg/ml, △, 50% ethanol; ○, 20% ethanol.

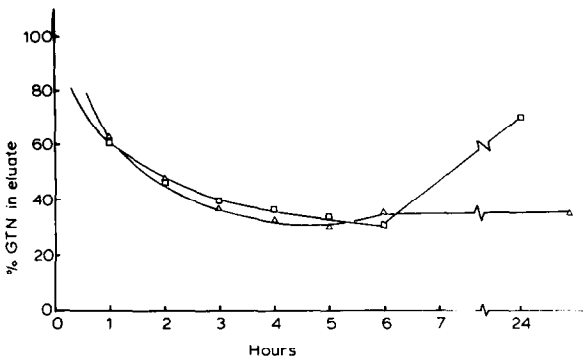

Fig. 7. Sorption of GTN to nylon extension set (Portex). Conditions: length of sets 200 cm; flow rate, 0.75 ml/h. □, 400 μg/ml GTN; △, 2.5 mg/ml GTN.

50% ethanol is to reduce sorption by 30–40% throughout the study period.

Glyceryl trinitrate

Sorption of GTN to extension sets during simulated administration was studied.

The results of this study are summarised in Fig. 7. Repeated examination of the syringe contents confirmed that no sorption had occurred. Similarly sorption to polyethylene extension sets was negligible. In contrast, sorption losses to PVC and nylon lines were extensive. In both systems, the extent of sorption was nearly unaffected by concentrations between 0.4 and 2.5 mg/ml GTN (commonly used in clinical practice). This suggests that an equilibrium is rapidly established and saturation conditions are not achieved within the conditions of the experiment. It is also clear that sorption of GTN is more extensive than loss of ISDN. In the case of a PVC line, losses are so great as to imply that the dose actually delivered is negligible.

Discussion

The sorption of parenteral nitrates to plastic containers and administration sets is well documented (Roberts et al., 1980; Baaske et al., 1980; St Peter and Cochran, 1982; Lee and Fenton-May, 1981; Lee, 1986). Uptake by PVC film and tubing is substantial, while losses to polyethylene (Cossum et al., 1978), polyolefin (Kowaluk et al., 1983), polypropylene (Lee and Fenton-May, 1981), polybutadiene (Lee, 1986) or glass (Baaske et al., 1980) are negligible. Losses of up to 80% have been shown to occur if PVC containers and administration sets were employed to deliver GTN. If syringe pumps are used to administer drugs continuously, more concentrated solutions can be used. The pre-filled syringe must be connected to the injection site by means of an extension set, consisting of a length of tubing 100-200 cm in length with a relatively narrow internal diameter. This substantially reduces contact surface area for drug sorption, and may then theoretically reduce the rate and extent of nitrate sorption. Cossum et al. (1978) reported, in fact, that losses of GTN were negligible if the drug was administered from a glass syringe through a polyethylene extension set by slow continuous infusion. No other reports have appeared examining this method of administration. In the present study, the effect of various clinically related factors on drug delivery have been examined, especially with ISDN. This choice was governed by the wide use of this drug and its availability in dry powder form. Losses by sorption to polypropylene syringes were found to be negligible, indicating the suitability of plastic syringes. It also confirms that all the losses reported during the study occurred during passage of drug solution through the extension set.

Results confirmed that sorption to polyethylene was of no significance. In contrast, uptake by PVC tubing was very substantial. For a typical experiment up to 80% of ISDN was sorbed into the plastic matrix. The process of uptake continued at almost constant levels for long periods of time indicating that the plastic was not rapidly saturated by the compound. This is in marked contrast to plastic interactions with, for example, insulin (Whalen et al., 1979) or diazepam (Mason et al., 1981).

The equilibrium between solute and plastic was substantially in favour of the plastic and was relatively independent of concentration. The mechanism of this interaction, at least between GTN and PVC, has been described by various authors as absorption by a first order process (McNiff et al., 1979; Sokolski, 1980). Malick et al.

(1981) proposed that surface adsorption was followed by dissolution of GTN into the plastic, whilst Cossum et al. (1978) suggested that GTN loss was due to diffusion into and through the plastic matrix. This view was later reinforced (Roberts et al., 1980). The present study would appear to equate most closely with this latter view. Sorption losses clearly occur almost continuously for long periods of time and saturation conditions are not attained. This is true irrespective of concentration or flow rate (contact time). It was also observed that the equilibrium was influenced by the solvent since ethanol changed the rate of sorption and equilibrium between plastic and solution. This will have practical significance because the various manufacturers employ different vehicles for the formulation of nitrate infusions. The current study also confirms the observation by Lee and Fenton-May (1981) that GTN is even more strongly sorbed than ISDN.

Finally, it is important to note that, while the greatest losses were observed with PVC, significant losses of nitrates were also observed in contact with nylon tubing.

The practical issues raised by this study are that losses of nitrates to PVC tubing are so extensive, even when using the syringe pump method of delivery, that PVC materials must be avoided. Nylon tubing performs rather more satisfactorily but nevertheless clinical control remains uncertain. In contrast, if a polyethylene extension set is connected to a polypropylene syringe, losses of nitrates are negligible. This offers the most economical and controlled method of nitrate administration to critically ill patients.

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