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Adsorption of vincristine, vinblastine, doxorubicin and mitozantrone to in-line intravenous filters

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Summary

The adsorption of four cytotoxic drugs, vinblastine, vincristine, doxorubicin and mitozantrone, to in-line intravenous filters and giving lines has been investigated using the slow administration rates used in clinical practice. Adsorptive losses to polyethylene lines were negligible. The maximal loss to a polyvinylchloride line was 9% for vincristine during the first hour of administration. Doxorubicin, vinblastine and vincristine were adsorbed to Pall ELD 96 h filters; up to 35% of the potency was lost during the initial hour of delivery. No adsorption could be detected for mitozantrone to the Pall ELD 96 h filter nor for all drugs to filters composed of polysulphone or cellulose acetate. The extent of adsorption for vinblastine, vincristine and doxorubicin to the Pall ELD 96 h filter increased as the pH of their solutions was increased from 4.5 to 7.8.

Introduction

The use of in-line filtration for intravenous (i.v.) infusions is now common practice in many critical care areas. Filters are able to retain particulates, air bubbles, and bacteria which can contaminate the infusion solution, and their use has been shown to reduce the incidence of phlebitis (Falchuk et al., 1985) and infection (Baumgartner et al., 1986). Prolonged use of i.v. filters has, in the past, led to complications because bacteria retained by the filter can break down to form pyrogens which will freely pass through the filter medium (Holmes et al., 1980). However, the development of a filter which retains both bacteria and pyrogens has overcome these problems. The Pall ELD 96 h intravenous filter (ELD 96) has a positively charged nylon membrane as its filter medium which, together with the 0.2 μm nominal pore size of the membrane, results in a filter capable of retaining both bacteria and pyrogens. Pyrogens are retained by the filter as a result of the interaction between the pyrogen molecule and the positive charge of the filter. It is possible, therefore, that drugs which are also weak bases could interact similarly with the filter membrane.

Intravenous filters are commonly used with patients undergoing cytotoxic drug therapy where

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the need to reduce the risk of infection in such immuno-compromised patients is paramount. Their advantages have already been discussed but one of their disadvantages is that the properties of the filters which increase their filtration efficiency can also result in drug adsorption to the filter and a consequent reduction in potency. A previous study using doxorubicin, daunarubicin, methotrexate and mitozantrone has shown negligible adsorption to ELD 96 filters when drug solutions were infused through the filters at a flow rate of 100 ml per h (Stevens and Wilkins, 1989). The rate and extent of drug losses to i.v. administration systems is, however, affected by a number of factors including drug concentration, flow rate and the pH of the solution (Lee, 1985). Therefore, since it was intended to use the ELD 96 during administration of four cytotoxic drugs, vincristine, vinblastine, mitozantrone and doxorubacin as slow i.v. infusions using a syringe pump driver operating at low flow rates, it became necessary to investigate the extent of any adsorption of these four drugs onto filters at the concentrations and flow rates used in clinical practice. Vincristine has previously been shown to adsorb onto cellulose ester filters and nylon filters. After filtration through a 0.22 μm cellulose ester filter, 6.5% of a 1 mg in 50 ml solution in 5% w/v glucose and 12% of a 1 mg in 50 ml solution in 0.9% w/v sodium chloride was bound to the filter (Butler et al., 1980). Vincristine sulphate, 1.5 mg in 3 ml, when injected as a bolus through a 0.2 μm nylon filter and, after flushing the filter with 10 ml normal saline showed losses of 10% of the vincristine to the filter (Ennis and Merritt, 1983). There was, however, no adsorption to cellulose ester filters when vinblastine sulphate solution 10 mg in 50 ml in 5% w/v glucose or 0.9% w/v sodium chloride was filtered through a 0.2 μm cellulose ester membrane filter (Butler et al., 1980). There are no published reports of the adsorption of either mitozantrone or doxorubicin to in-line filters.

The aim of this study was to investigate the extent of adsorption of the four drugs to a range of filters including the ELD 96 and to different administration lines at the drug concentrations and flow rates used in clinical practice. The effect of varying the pH of the solution on the extent of adsorption to the ELD 96 was also evaluated.

Materials and Methods

Materials

All filters and administration lines used in this study are commercially available in the U.K. The materials of construction and surface areas of five filters tested are described in Table 1. Two administration lines were studied, a polyvinylchloride (PVC) line (C0056, Baxters, Thetford, U.K.) with a priming volume of 1.8 ml and a polyethylene (PE) line (1155.55 Vygon, U.K.) with a priming volume of 1.7 ml. Polypropylene syringes (Plastipak, Becton Dickenson) were used throughout the study.

Sample Preparation

The four drugs tested were doxorubicin hydrochloride (Farmitalia), mitozantrone (Lederle), vinblastine sulphate (Lederle) and vincristine sulphate (David Bull Laboratories). Studies were carried out using either unbuffered solutions of drugs in 0.9% w/v sodium chloride or with solutions in 0.9% w/v sodium chloride buffered to four points between pH 4.3 and 7.9.

Mitozantrone was supplied ready to use at a concentration of 1 mg ml^{-1} in 0.9% w/v sodium chloride. The other drugs were reconstituted in 0.9% w/v sodium chloride to give final concentrations of doxorubicin 1 mg ml^{-1}, vinblastine 250 μg ml^{-1}, and vincristine, 25 μg ml^{-1}. The manufacturer's recommended diluent for vincristine was not used, since it contained benzyl alcohol which interfered with the assay. Immediately following preparation or reconstitution, all solutions were assayed after which a 10 ml sample was filled into a 10 ml syringe. When studying the effects of pH on adsorption to the ELD 96, solutions, prepared as detailed above, were buffered to pH 4.3, 5.9, 7.1 and 7.9 using phosphate buffer solution. The pH values of the solutions were measured and the drug content analysed spectrophotometrically. Then a 10 ml sample of the solution was filled into a 10 ml syringe.

Adsorption studies

Filters and administration lines were tested independently. The syringe containing the drug solution connected to either the administration line or filter, was mounted onto a Graseby MS16A syringe pump driver and the system primed. Solution was pumped from the syringe at a plunger speed of 5 mm h^{-1} (equivalent to 0.875 ml h^{-1}) for unbuffered solutions, or 16 mm h^{-1} (2.8 ml h^{-1}) for the buffered solutions. Samples were collected into glass vials over intervals of 15 min (doxorubicin; mitozantrone) or 30 min (vinblastine; vincristine) at the lower flow rate and over intervals of 15 min at the faster flow rate. When each experiment was completed, a final sample was taken from the syringe reservoir for analysis. Experiments were carried out at ambient temperature in duplicate.

All samples were assayed by UV spectrophotometry (Perkin-Elmer UV-Vis 522) using a 3 cm pathlength at wavelengths of 256 nm for vincristine, 268 nm for vinblastine, 487 nm for doxorubicin and 608 nm for mitozantrone. Samples were diluted with 0.9% w/v sodium chloride prior to analysis. Vinblastine and vincristine were diluted 1 in 10 and mitozantrone or doxorubicin were diluted 1 in 100. Drug contents were expressed as the percentage of their zero time concentrations.

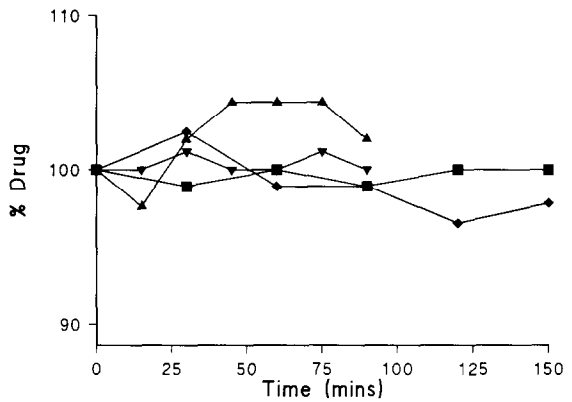

Fig. 1. The adsorption of doxorubicin, mitozantrone, vinblastine and vincristine to the Vygon polyethylene giving line. (▲) Doxorubicin; (▼) mitozantrone; (■) vinblastine; (◆) vincristine.

Results and Discussion

Administration lines

Adsorptive losses to the PE extension line were negligible for all four drugs studied (Fig. 1). Adsorption to the PVC line was only detectable for vincristine and even then the maximum loss of potency was only 9% during the first h (Fig. 2). Significant absorption of vinblastine to PVC tubing has been reported in static systems (McElney et al., 1988) but no losses were found during this study.

Filters

Mitozantrone was not adsorbed by the ELD 96 but adsorption of doxorubicin, vincristine and vinblastine occurred onto this filter (Fig. 3). A loss of potency of between 25 and 35% was observed within the first hour of sampling for these three drugs. Losses over a 24 h treatment period may not be significant in empirical terms since they occurred only during the initial stages of therapy and within 3 h the drug concentrations returned to their initial values. The importance of the losses relates to the slow rates for delivery when drugs are administered using these techniques and flow rates of less than 1.0 ml h^{-1} are not uncommon. In these circumstances, the clinical efficacy may be compromised depending upon

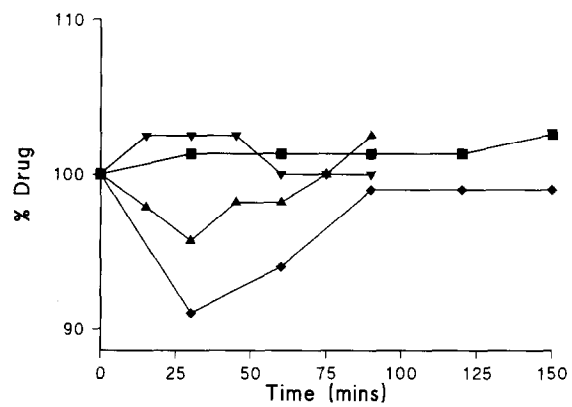

Fig. 2. The adsorption of doxorubicin, mitozantrone, vinblastine and vincristine to the Travenol polyvinylchloride giving line. (▲) Doxorubicin; (▼) mitozantrone; (■) vinblastine; (◆) vincristine.

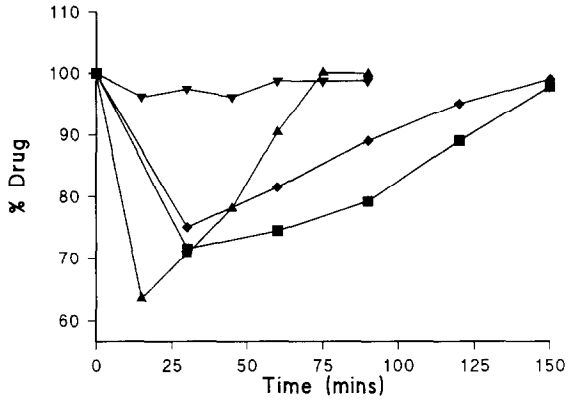

Fig. 3. The adsorption of doxorubicin, mitozantrone, vinblastine and vincristine to the Pall ELD 96 filter. (▲) Doxorubicin; (▼) mitozantrone; (■) vinblastine; (◆) vincristine.

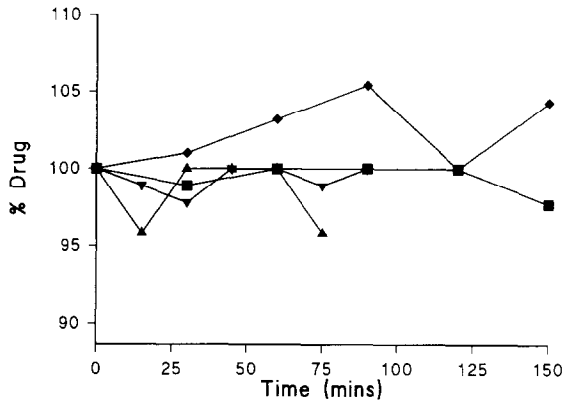

Fig. 4. The adsorption of doxorubicin, mitozantrone, vinblastine and vincristine to the Sartorius cellulose acetate filter. (▲) Doxorubicin; (▼) mitozantrone; (■) vinblastine; (◆) vincristine.

the plasma/tumour levels reached and the half-life of the drug. Adequate plasma levels may not be reached during a significant portion of therapy due to adsorptive losses and there may be a delay in the time taken to reach steady-state pharmacokinetics for drugs with very short half-lives. The results differ from those reported earlier (Stevens and Wilkins, 1989) when administration rates of 100 ml h^{-1} were used, but the data demonstrate the significance of flow rate when evaluating interactions between drugs and administration systems.

No adsorption could be detected onto the cellulose acetate (Fig. 4) or the polysulphone (Fig. 5) filters. The adsorptive losses to the ELD 96 filters may be due to the larger surface area of the ELD 96 compared to those of the cellulose acetate or polysulphone filters (Table 1) or, alternatively, due to the positively charged surface treatment of the ELD 96. For comparison, therefore the Nylaflo and Utipore filters were examined. These are nylon filters with the same surface areas as the ELD 96 but do not have the positively charged surface. Smaller losses were seen for vincristine, vinblastine and doxorubicin to the Nylaflo (Fig. 6) and Utipore (Fig. 7) filters. Mitozantrone, because it was not adsorbed to the ELD 96, was not examined.

Surface treatment of the filter medium affects the quantity of drug adsorbed. Interestingly, Nylaflo and Utipor, which are both nylon filters

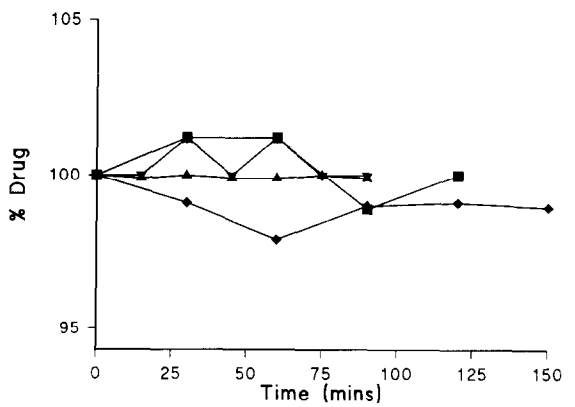

Fig. 5. The adsorption of doxorubicin, mitozantrone, vinblastine and vincristine to the Gelman polysulphone filter. (▲) Doxorubicin; (▼) mitozantrone; (■) vinblastine; (◆) vincristine.

TABLE 1

Filters used in this study

Manufacturer	Filter	Material	Surface Area (cm^2)
Gelman	Acrodisc 45	polysulphone	2.77
Sartorius	Minisart 45	cellulose acetate	5.33
Pall	Posidyne ELD96	posidyne nylon	10.0
Gelman	Nylaflo	nylon	10.0
Pall	Utipore	nylon	10.0

Data obtained from Manufacturer's information sheets.

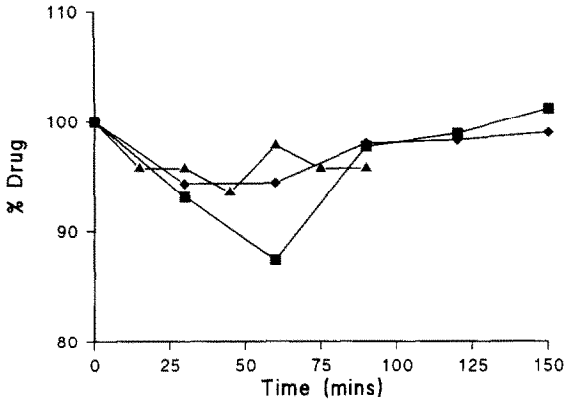

Fig. 6. The adsorption of doxorubicin, vinblastine and vincristine to the Nylaflo nylon filter. (▲) Doxorubicin; (■) vinblastine; (♦) vincristine.

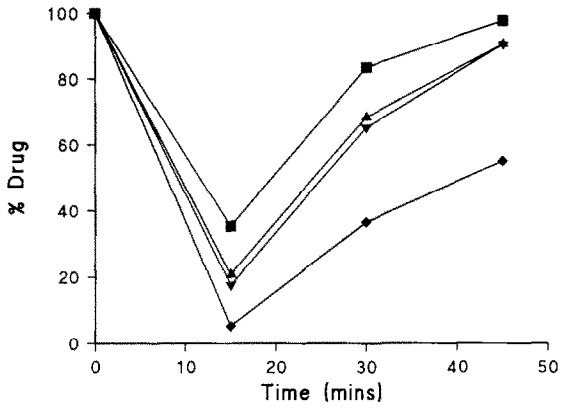

Fig. 8. The effect of pH on the adsorption of doxorubicin to the ELD 96 filter. (■) pH 4.82; (▲) pH 6.05; (▼) pH 7.11; (♦) pH 7.98.

without the surface treatment of the ELD 96, show different adsorption levels. This may have been related to treatment of the materials during the manufacturing process. Similar variations have been found when assessing the adsorption of antimicrobial preservatives to different nylon filters (Guilfoyle et al., 1990).

Effect of pH on adsorption

Adsorption of vinblastine, vincristine and doxorubicin to the ELD 96 increased as the pH increased (Figs. 8–10). Above pH 7 the potency of drug solution dropped to less than 40% of the initial concentration of vincristine and to below 20% of the initial value for vinblastine and doxorubicin. For the latter drug, the observed losses will be partially due to precipitation of doxorubicin from solution since, at pH 7.9, a red granular precipitate was visible on the filter at the end of the experiment.

The ELD 96 was developed as an inactive i.v. filter capable of retaining bacteria and pyrogens. The latter are actively adsorbed by the filter membrane by a positively charged nylon surface. A similar effect may be expected with other weakly basic molecules. The drugs used in this study have pK_a values of 5 and 7.4 (vincristine), 5.4 and 7.5 (vinblastine), and 8.3 (doxorubicin).

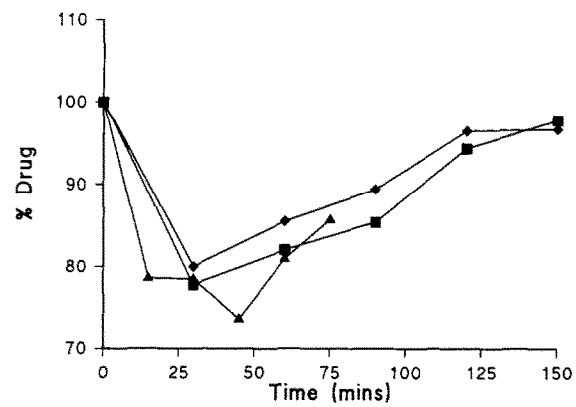

Fig. 7. The adsorption of doxorubicin, vinblastine and vincristine to the Utipore nylon filter. (▲) Doxorubicin; (■) vinblastine; (♦) vincristine.

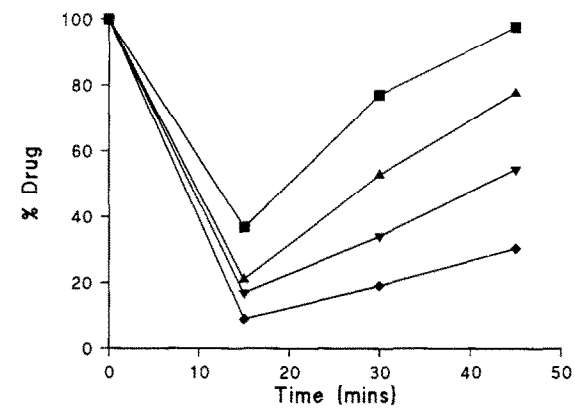

Fig. 9. The effect of pH on the adsorption of vinblastine to the ELD 96 filter. (■) pH 4.23; (▲) pH 5.80; (▼) pH 7.10; (♦) pH 7.81.

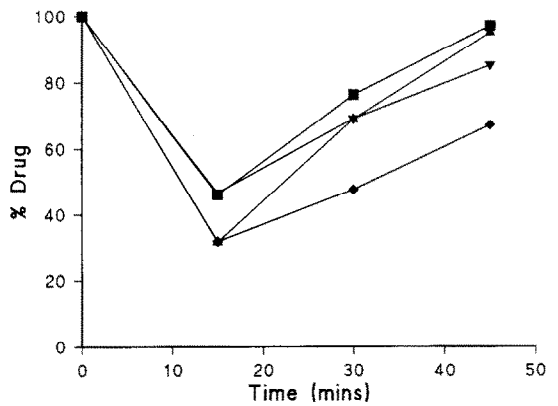

Fig. 10. The effect of pH on the adsorption of vincristine to the ELD 96 filter. (■) pH 4.45; (▲) pH 6.12; (▼) pH 7.10; (◆) pH 7.80.

For the vinca alkaloids increasing the pH of the solution would increase the proportion of the unionised drug. This increase in the basic form of the drug results in a greater adsorption at the higher pH values. A similar effect is observed with doxorubicin but, since it is an amphoteric drug, increasing the pH of the solution would increase the proportion of the negatively charged species which would more easily interact with the filter membrane. The effect of pH on doxorubicin is further complicated because of decreased solubility of the drug above pH 7. Hence at pH 7.9, precipitated drug particles were retained by the filter. When studying the effect of pH, mitozantrone was not included because no adsorption was found with the unbuffered solutions. To facilitate the generation of data the speed of the syringe driver was faster than that used for the earlier experiments. However, the data demonstrate clearly the effect of pH and, at the slower rates used in clinical practice, the effect is likely to be worse.

In practice, such high pH values (above 7) would only be found in compound sodium lactate infusion or sodium bicarbonate infusion, and i.v. additions would not normally be made to these solutions. However, multiple i.v. additions, which can produce a higher pH in unbuffered solutions, may sometimes be used. Alternatively, several drugs may be administered via one central line, where the pH of the ultimate mixture is unknown. In these circumstances any increase in pH will lead to increased adsorption of weakly basic drugs.

Conclusions

Measurable losses of vinblastine, vincristine and doxorubicin are found due to adsorption onto filter membranes when solutions are pumped at low flow rates through nylon i.v. filters. Surface treatment of the membrane to produce a positively charged surface increases the adsorptive losses and adsorption to the latter membrane is increased further when the drug solution is buffered to higher pH values. The adsorptive losses are more apparent at the low flow rates used and would be clinically significant when trying to achieve steady-state kinetics for drugs with short half-lives (< 30 min.)

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