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Binding of human insulin to burette administration sets

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Summary

The binding of human insulin (20 iu/500 ml dextrose 5% w/v) to three types of burette administration sets (A200, A2000 and A2001; Avon Medicals, U.K.) has been examined. Binding to the burette chambers and administration tubing was examined separately since they were manufactured from different plastic materials. The A2001 sets which are prepared from the novel plastics, methacrylate butadiene styrene (burette) and polybutadiene (tubing), and which have been shown to be resistant to binding of other drugs, bound insulin more extensively than the A200 and A2000 sets (cellulose propionate burettes with polyvinyl chloride tubing). Binding was studied over a contact period of 6 h. Maximum binding in the burettes sets was 30% while up to 96% of the insulin placed in the administration tubings was lost due to binding to the tubing surface.

Introduction

The non-specific surface binding of insulin from dilute solutions was first reported by Ferrebee et al. (1951). In this first report the binding surface was laboratory glassware but since then it has been confirmed that binding takes place with both siliconised and borosilicate glassware (Hill, 1959). These latter two types of glassware are usually more resistant to drug adsorption than normal sodaglass. Although binding to glassware is an obvious problem in the laboratory and in the industrial setting during insulin extraction and purification a further binding problem presents itself in the clinical situation during the administration of insulin to patients. There is undoubtably binding to syringes during subcutaneous or intramuscular administration of insulin, however, since the concentration of insulin for injection is high and the surface area for binding is low, the percentage loss of insulin is clinically insignificant. These parameters are reversed when insulin is used by intravenous infusion, i.e., low insulin concentration and high surface area available for binding. It is not surprising therefore that there have been many reports of significant loss of insulin to infusion containers and administration apparatus. Depending on the experimental conditions used for simulated insulin infusion, loss of the drug to the infusion apparatus has ranged from 3 to 100% (Schildt et al., 1978; Whalen et al., 1979). Conventional types of apparatus all appear to bind insulin, i.e. those prepared from glass, polyethylene and polyvinylchloride (Petty and Cunningham, 1974). Sorption of insulin is also problematic during intraperitoneal administration

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of insulin to patients being treated with continuous ambulatory peritoneal dialysis. In one study, for example, it was shown that as much as 65% of insulin added to two litres of dialysis solution was retained by sorption to the material of the plastic container (Wideroe et al., 1983). It is clear therefore that methods of preventing insulin container interactions are required. Although changes in vehicle, composition and the use of additives, for example, human serum albumin and hydrolysed gelatin (polygeline) are effective in decreasing insulin binding (Kraegen et al., 1975) the adoption of these approaches is not always clinically practical. Addition of urea as well as reducing insulin self-association also reduces surface adsorption (Sato et al., 1983).

A further possible approach would be the use of novel materials which are resistant to drug binding. Such a novel combination of plastics has recently been developed and manufactured into burette administration sets for use with drugs with which sorption is a practical problem. The aim of the present study was to examine insulin binding to this new administration set (Sureset) and to compare its binding with that to sets made from more conventional plastics materials.

Materials and Methods

Three types of burette administration set (manufactured by Avon Medicals, Redditch, U.K.) were examined, namely the A200 Standard Sets, the A2000 Amberset and A2001 Sureset. Five of each type of set were prepared for experimentation by removing the top of each burette chamber at the 100 ml mark; the drip chamber administration tubing were also removed from each set (Fig. 1). The outlet needles from the burettes were sealed by bending and the burettes and administration tubings were clamped in position to allow filling with insulin infusion solution. The experimental set up allowed examination of binding to be carried out in burettes and tubing separately. This was considered important since the two parts of the administration sets are made from differing plastics materials (Table 1).

The test infusion solution of insulin was prepared using Humulin S (100 iu/ml; Eli Lily) to give a final concentration of 20 iu/500 ml in 5% Dextrose Injection B.P. (This vehicle is always used in the local hospital to administer insulin to diabetic patients during surgery.) The glassware used in preparing the insulin solution and for

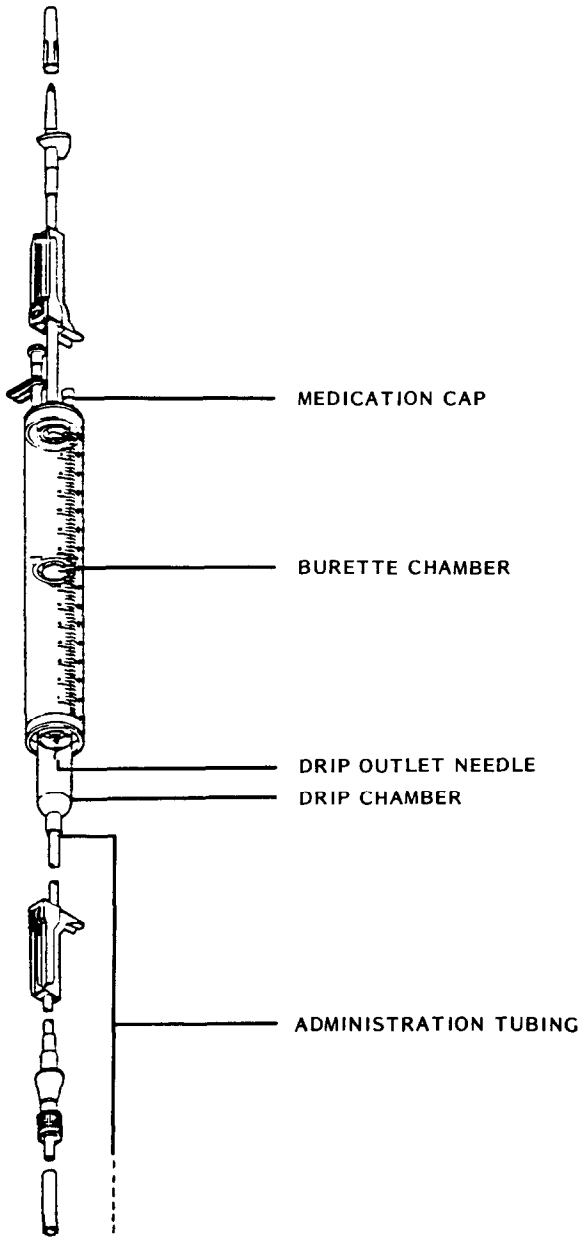

Fig. 1. A typical Avon Medicals Burette Set.

TABLE 1

Types of burette administration sets used in insulin binding studies

Plastic materials		
Brand name	Burette	Tubing
A200 Standard set	cellulose propionate	polyvinyl chloride
A2000 Amberset	cellulose propionate (sleeved with shrink PVC containing amber pigments)	polyvinyl chloride co-extruded (outer layer containing amber pigments)
A2001 Sureset	methacrylate butadiene styrene	polybutadiene

sampling was presoaked with the same concentration of insulin overnight, rinsed once with distilled water and dried. Just prior to addition of the insulin solution to the infusion apparatus iodinated human insulin (50 μCi; I^{125}-labelled at tyrosine-B26, 2110 Ci/mmol, 78 TBq/mmol, Amersham International, Amersham U.K., lot no. 22) was mixed thoroughly with 1.2 litres of the 20 iu/500 ml stock solution. After taking duplicate samples at time zero the administration tubings of all sets were completely filled with the insulin solution while 50 ml aliquots were placed in each of the burette chambers. Duplicate samples were taken from each of the 15 tubings (1 ml) and burettes (3 ml) after 5 min, 0.5, 1, 2, 4 and 6 h. All sample volumes were measured using borosilicate glass bulb pipettes. The samples were analysed for insulin content by counting for 1 min in a gamma counter (LKB Wallac 8000). At the end of the sampling period measured sections of the burettes and tubings were removed and also counted to obtain an estimate of the amount of insulin bound to the plastic. During all experiments the infusion apparatus was protected from light using aluminum foil. This was done to avoid possible photodegradation of the human insulin which could not be detected using the presently employed assay procedure.

Results and Discussion

Sureset burette administration sets have been shown to be resistant to binding of a number of drugs including glyceryltrinitrate, isosorbide dinitrate and diazepam (Lee, 1986). The results, however, of the present investigation indicate that this resistance to binding does not extend to the binding of insulin (Figs. 2 and 3). It can be seen clearly that insulin concentration dropped steadily over the 6 h experimental time period when in contact with the burettes. As expected, since both burette types are constructed from PVC (Table 1), loss from the A200 and the A2000 sets was almost identical (minimum insulin concentration ($\pm$S.D.) = 17.25 ± 0.3 iu/500 ml). Surprisingly, however, loss was greatest from the A2001 sets (minimum insulin concentration ($\pm$S.D.) = 14.02 ± 0.45 iu/500 ml) which are constructed from the novel plastic methacrylate butadiene styrene. Similar data were obtained for the administration tubing, i.e. the novel plastic material, polybutadiene sorbed insulin to a greater extent than the polyvinyl chloride tubing of the A200 and A2000 sets. Loss of insulin to the administration tubing was much more extensive than loss to the burettes. The minimum insulin concentrations recorded ($\pm$S.D.) in the three types of tubing were 2.84 ± 0.39; 2.26 ± 0.63 and 0.80 ± 0.08 iu per 500 ml, respectively, for A200, A2000 and A2001 tubing. This greater overall loss was obviously due to the much larger surface area:volume ratio available for insulin binding in the case of the tubing. Also an

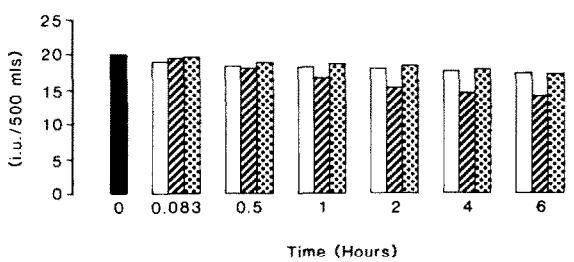

Fig. 2. Concentration versus time profile for human insulin when stored in burette chambers of A200 (□), A2000 (▨) and A2001 (▨) burette administration sets. ■, represents mean control data at zero time. (Maximum coefficient of variation within replicate data points was 3.2%.)

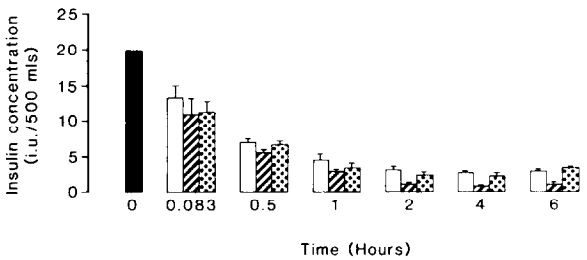

Fig. 3. Concentration (±S.D.) versus time profile for human insulin when stored in administration tubing from A200 (□), A2000 (▨), and A2001 (▨) burette administration sets. ■, represents mean control data at zero time.

equilibrium binding state was reached much sooner (i.e. after 2 h) in the case of the tubing. The preferential binding to Sureset components was confirmed by examination of the segments removed from the burettes and tubing after the 6 h exposure time (see Table 2).

Statistical analysis, using a two-factor analysis of variance with repeated measures of one factor, indicated that there was a significant difference in the concentration versus time profiles between burette sets ($P < 0.05$); however, no such difference was apparent in the profiles for insulin binding to tubing ($P > 0.05$). One factor analysis of variance followed by a Newman-Keuls multiple range test for the 6 h data for both burettes and tubing indicated a significant difference ($P < 0.05$) in data for A2001 versus A200 and for A2001 versus A2000 sets; however, when the data for A2000 and A200 sets were compared no statistically significant difference was found ($P > 0.05$).

It is clear therefore that although the novel plastic materials are resistant to binding of certain drugs (Lee, 1986) this resistance is not applicable to insulin. Based on the present results and the findings that insulins bind to siliconised glass, borosilicate glass, paper, polyethylene and PVC (Newerly and Berson, 1957; Hill, 1959; Petty and Cunningham, 1974) it appears that this non-specific physical adsorption (Twardowski et al., 1983) of insulin could best be approached by altering the method of infusion together with some changes in vehicle composition. Although often not practical to add polygeline or human serum albumin to insulin infusions, it is interesting to note that sorption is less from saline than from dextrose 5% w/v (Hirsch et al., 1977) and the presence of electrolytes can also reduce the extent of the insulin binding (D'Arcy, 1983). Sefton and Antonacci (1984) have also found that hydrophobic materials (Teflon, silastic) adsorbed more insulin than hydrophilic materials (e.g. polyacrylamide, glass).

Alternative and possibly more practical methods of reducing insulin loss is to administer the insulin in a small volume via a syringe pump. The syringe may sorb an appreciable amount of insulin but the surface area for sorption is much reduced compared with the total amount of insulin present; losses to the administration set are largely eliminated by using a short cannula (Allwood, 1983).

In conclusion, insulin bound extensively to all plastics tested including the novel plastics materials present in A2001 Sureset burette administration sets. The binding to methacrylate butadiene styrene and polybutadiene followed a

TABLE 2

Estimated concentration [a] (mean ± S.D.) of insulin sorbed on to samples [b] of burette chambers and their corresponding administration tubing after being in contact with 20 iu/500 ml human insulin for 6 h

	Standard set (A200)	Amberset (A2000)	Sureset (A2001)
Measured concentration of burette/chamber samples (iu/500 ml)	2.48 ± 0.49	2.61 ± 0.23	9.25 ± 0.18
Measured concentration of tubing/samples (iu/500 ml)	14.93 ± 1.28	12.46 ± 2.15	17.38 ± 1.05

[a] Samples of plastic submitted to same assay as liquid samples and measured on same calibration curve. Since no standard curve could be prepared of insulin bound to the plastics the results should be regarded as qualitative in nature.

[b] Surface area of tubing used in counting vial = 15.40 cm^2; surface area of burette chamber used in counting vial = 24.45 cm^2. (Concentration measured on control burette chamber and tubing sample was zero.)

similar pattern to the binding to cellulose propionate and PVC in burette chambers and administration tubing, respectively. The Sureset, although offering advantage for other sorbable drugs, e.g. glyceryl trinitrate, isosorbide dinitrate and diazepam (Lee, 1986), does not offer any advantage in the case of insulin as there was in fact increased insulin binding by Suresets. This is likely due to the much more non-specific nature of insulin binding when compared with the other named drugs.

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