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The persistence of dextran 70 in blood plasma following its infusion, during surgery, for prophylaxis against thromboembolism

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An infusion of dextran (mean molecular weight 70 000) in normal saline (either 1 litre or 500 ml) was given to patients undergoing hysterectomy. The infusion was started at induction of anaesthesia and continued throughout the operation and for up to 6 h thereafter. The rate of elimination of dextran was independent of the dose given. The time to eliminate half the dose was nearly two days and up to 10% was still present in the circulation after one week. The persistence of dextran in the plasma in these amounts and for this length of time may have considerable implications in the prophylaxis of post-operative deep venous thrombosis.

When infused at the time of surgery, dextran has been shown both experimentally and clinically (Kline, Hughes & others, 1975) to reduce the frequency of post operative thrombo-embolic complications (Bygdeman, 1969). The minimum effective dose, the dosing regimen and the plasma concentration required for a sustained anti-thrombotic effect are still matters for conjecture. In experimental studies, dose levels claimed to be effective have ranged from 0·2 g kg^{-1} body weight (Ashwin & Jaques, 1961) to 2 g kg^{-1} (Bonchek & Braunwald, 1967). Its molecular weight has also been shown (Bryant, Bloom & Brewer, 1963, 1964) to be a factor in preventing thrombosis, a mol. wt of 70 000 apparently giving optimum protection. Some workers (for example Johnson, Bygdeman & Eliasson, 1968) have given repeated infusions for up to 12 days following surgery.

The length of time the dextran remains in the circulation has not been assessed. In the trials of Bonnar & Walsh (1972), patients undergoing hysterectomy for benign pelvic disease were given an infusion of 1 litre or 500 ml of Lomodex 70 (6% w/v dextran 70 of mean molecular weight 70 000 in normal saline). The infusion was commenced at the induction of anaesthesia, continued throughout the operation and for up to 6 h thereafter. We have measured dextran in blood samples taken immediately and for up to seven days after the operation.

MATERIALS AND METHODS

Determination of dextran

A chemical method, essentially that of Wallenius (1953) was employed, mainly because of the convenience in handling a large number of samples. In this method, blood glucose is first removed by incubating the plasma with baker's yeast, before estimating the remaining dextran with anthrone reagent. However, we found that

this original method gave inconsistent results after the 1–2 h incubation period recommended and that high blank values in the colorimetric measurement were also obtained. These might be due to variations in the quality of the baker's yeast employed. Therefore, after confirming that it did not affect the dextran or interfere with the anthrone procedure, we decided to use the enzyme glucose oxidase for the removal of the plasma glucose. Also we found that an ethanolic sulphuric acid—anthrone reagent gave more reproducible results.

After experimentation, the optimum conditions and reagents were found to be:

Reagents

(a) Ethanolic sulphuric acid; concentrated H_2SO_4 in ethanol (2:1). (b) Anthrone reagent; 0·2% w/v anthrone in ice-cold ethanolic sulphuric acid. (c) Stock standard glucose solution containing 60 μg ml^{-1}. Dilute working standards were then prepared from this stock solution, containing 0, 12, 24, 36 and 60 μg ml^{-1}. (d) Glucose oxidase (BDH Chemicals). (e) 10% w/v trichloroacetic acid. (f) 3·8% w/v sodium citrate.

Calibration graph

1 ml aliquots of the dilute working standards (0–60 μg ml^{-1} glucose) were pipetted into 20 ml glass stoppered tubes. Anthrone reagent (8 ml) was added from a burette and the solutions mixed and immediately immersed in a boiling water bath for exactly 6 min. The solutions were then cooled and the absorbances read at 620 nm in 10 mm glass cells against a water blank. A graph of absorbance *vs* concentration, after allowing for the blank, was linear and passed through the origin.

Removal of blood glucose

Whole blood, which may contain sodium citrate or heparin anticoagulants was first centrifuged to remove the red cells. The supernatant plasma (1 ml) was diluted to 50 or 100 ml. The diluted plasma solution (20 ml) was pipetted into a vessel containing glucose oxidase (10 mg) and then sodium citrate buffer (1 ml) was added and the mixture allowed to stand for at least 4 h. A blank of distilled water (20 ml), enzyme (10 mg) and buffer (1 ml) was allowed to stand for the same period. When many samples were to be analysed an overnight digestion was preferred.

At the end of the incubation period trichloroacetic acid (1 ml) was added and the mixture heated at 60° for 15 min to precipitate the proteins. The mixture was washed into a 100 ml volumetric flask and diluted to volume, then mixed thoroughly and centrifuged. Duplicate aliquots (1 ml) of the clear supernatant were pipetted into two 20 ml glass stoppered test tubes and treated as in the calibration procedure above.

RESULTS

The mean daily plasma dextran concentrations for patients receiving 1 litre and 500 ml infusions are shown in Table 1. At any one time the dextran remaining in circulation after a 1 litre infusion was about twice that after a 500 ml infusion indicating that the rates of loss of dextran for both dose levels were similar to a first order chemical reaction. Both sets of mean results when plotted are linear and fall about the same line: $t = (2{\cdot}303/K) \times \log(a/a-x)$. Where K = specific reaction rate, t = time following operation, a = initial dextran concentration, (a–x) = dextran concentration after time "t".

Table 1. *Comparison of Group 1 and Group 2 mean plasma dextran concentrations.*

Post-operative days	Mean plasma dextran concentrations mg ml^{-1} Group 1 (1 litre infusion)	Group 2 (500 ml infusion)
	15·8 (15 results)	8·6 (9 results)
1	9·6 (15)	2·8 (1)
2	7·0 (14)	3·5 (7)
3	4·6 (8)	3·5 (1)
4	3·4 (8)	2·2 (4)
5	2·5 (3)	1·2 (3)
6	2·2 (3)	—
7	1·1 (2)	0·9 (7)

The rate of elimination was thus independent of the dose given and the specific reaction rate (or specific elimination rate) was determined as 0·39 day^{-1}. The time to eliminate half of the dose was calculated as 1·8 days and 5–10% of the dose could still be detected in the circulation after 7 days.

DISCUSSION

The persistence of dextran in the circulation for the length of time established may well be of clinical significance as 50–75% of post operative thromboembolic complications start during or in the first few days after an operation. Thus the presence of dextran in the circulation during this time indicates that continued post-operative infusions may be unnecessary.

In a separate study of the effect of dextran 70 infusion on blood volume changes during and after surgery (Bonnar & Smith, personal communication) the plasma volume increase in patients receiving dextran 70 was related to the volume administered. In patients receiving 1 litre of dextran 70 the blood volume did not return to the pre-operative level for 3–5 days, whereas in those receiving 500 ml the pre-operative blood volume was regained 1–2 days after operation. This closely parallels the concentration of dextran in the plasma and suggests that once the concentration is below 4 mg ml^{-1} the dextran 70 may no longer increase the blood volume. These findings suggest that to cover the critical periods of surgery and 3–4 days thereafter 1 litre would be advisable except in patients with renal impairment or cardiovasuclar disease where this amount of blood volume increase would be undesirable.

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