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A CLINICAL STUDY OF LOW MOLECULAR WEIGHT-HYDROXYETHYL STARCH, A NEW PLASMA EXPANDER

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1 The pharmacokinetics of a new plasma expander, low molecular weight-hydroxyethyl starch (LMW-HES) were examined in six normovolaemic men.

2 One hour post-infusion, 13.5% of the total dose of LMW-HES injected was excreted in the urine, 50.2% was present in the intravascular space, and 36.3% was unaccounted for.

3 Twenty-four hours post-infusion, 65.5% of the total dose of injected LMW-HES had been excreted in the urine, 4.1% remained intravascularly, and 30.4% was unaccounted for.

4 The plasma volume increased rapidly from a mean value of 45.7 ml kg^{-1} to a maximum value of 57.9 ml kg^{-1} immediately post-injection, then gradually returned to normal over 24 h.

5 The infusion of an average of 58.1 g had no effect on ESR, renal and hepatic biochemical indices.

6 LMW-HES appears to be safe and effective, and should be of value clinically when rapid and short-lived augmentation of the plasma volume is required.

Introduction

Based on its similarity to normal body glycogen, starch should be theoretically acceptable as a colloidal agent in plasma volume expansion. However, ordinary starch solutions are physically unstable; moreover, they are rapidly degraded in the bloodstream. If on the other hand, physically stable branched polymers of starch, such as amylopectin, are reacted with ethylene oxide, hydroxyethyl groups are attached by ether linkages to the hydroxyl groups of the starch molecule, producing a polymer partially resistant to enzymatic catabolism.

Initial clinical trials of such a hydroxyethylated polymer, called hydroxyethyl starch (HES), appeared in 1968 (Solanke) and it was shown to augment effectively the plasma volume without untoward effects. Subsequent studies (Metcalf, Papadopoulos, Tufaro & Barth, 1970) reported that the intravascular behaviour of HES ($M_{\bar{w}}$ 450,000 *d*, $M_{\bar{n}}$ 71,000 *d*, 60–70 hydroxyethyl groups/100 glucose units) paralleled that of Dextran 70 ($M_{\bar{w}}$ 70,000 *d*) during the first 24 h post-injection. However, the time for the plasma concentration to fall to half its peak value (26 to 31 h) (Metcalf *et al.*, 1970; Mishler, Borberg, Emerson & Gross, 1977) appeared to be unsuitable for clinical situations requiring rapid and short-lived plasma expansion. Preliminary studies in animals (Bogan, Gale & Walton, 1969; Thompson, Britton & Walton, 1962) and in man (Mishler, Parry & Petrie, 1978), have reported that the disappearance of HES from the intravescular space is influenced by both the weight average molecular weight ($M_{\bar{w}}$) and the degree to which hydroxyethyl group substitution had taken place on the glucose units of starch.

A plasma expander with reduced persistence characteristics, would have theoretical advantages in the short-term management of patients undergoing cardiopulmonary by-pass surgery or when awaiting cross-matched blood. The need for such an agent prompted us to investigate the pharmacokinetics of a new low molecular weight-HES (LMW-HES, $M_{\bar{w}}$ 264,000 *d*, $M_{\bar{n}}$ 63,000 *d*, 43 hydroxyethyl groups/100 glucose units) species. The present experiment was designed to study the effects of infusion of LMW-HES on normovolaemic man.

Methods

Six normovolaemic men (ages 21 to 45 years) comprised the study group. Their weights varied from 68.1 to 100.8 kg (mean 83.2 kg) which corresponded to measured plasma volumes ranging from 3,226 to 5,132 ml (mean 3,799 ml). The experiment was thoroughly explained to each subject and their consent was obtained.

A standard dose (0.7 g kg^{-1}) of a 14% LMW-HES solution in 0.9% isotonic saline, was infused through a 19-gauge cannula inserted in a forearm vein, over a 13

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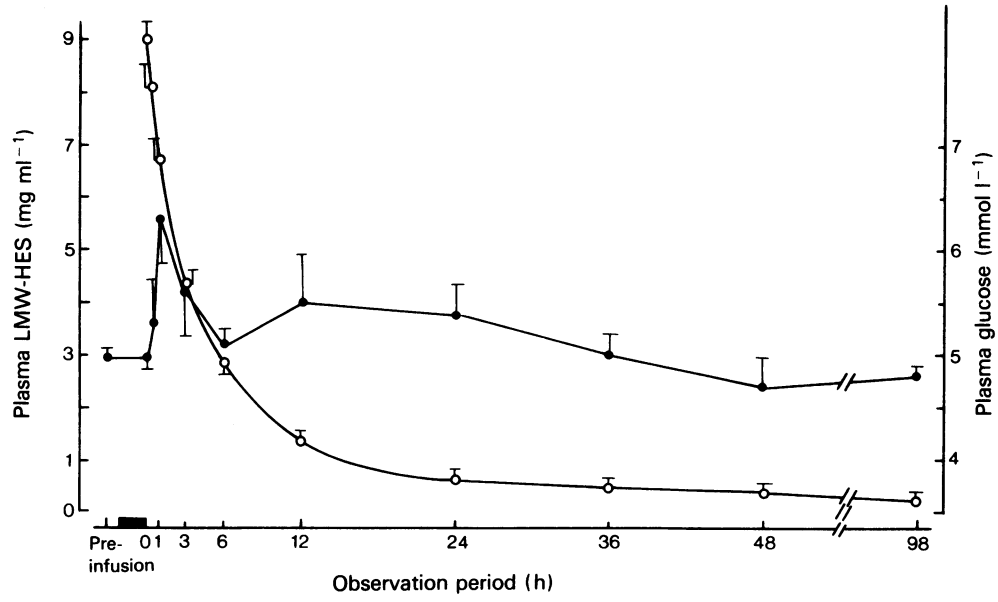

Figure 1 Plasma concentrations of LMW-HES (O) and glucose (●) in six normal men given a standardized dose (■) of a 14% solution in 0.9% isotonic saline. Data points represent mean values ± 1 s.e. mean. Glucose conversion factor: mmol $l^{-1} \times 18 = mg\ ml^{-1}$.

to 21 min period (mean injection rate: 0.28 ml kg^{-1} min^{-1}). Plasma concentrations of LMW-HES and glucose were measured immediately and at 0.5, 1, 3, 6, 12, 24, 36, 48, and 96 h post-infusion. Urinary LMW-HES concentrations were determined from aliquots of the total volumes of urine spontaneously voided from each subject during the periods 0–1, 1–3, 3–6, 6–12, 12–24, 24–36, 36–48, 48–72, and 72–96 h post-infusion. Haemoglobin, haematocrit, ESR, renal and hepatic biochemical parameters were determined at regular intervals.

The difference between total plasma carbohydrate, measured in triplicate by a simplified anthrone method (Brake, 1966) on trichloroacetic acid filtrates, and plasma glucose determined by glucose oxidase, constituted the LMW-HES concentration. Urinary LMW-HES concentrations were measured in triplicate by the same anthrone method, utilizing urine samples boiled in 30% KOH for one hour to destroy monosaccarides. The ESR was determined by the Westergren method, and haemoglobin and haematocrit by the Coulter Counter Model S. Plasma biochemical indices were measured on the Abbott AB-100 analyser. Plasma volumes were measured before the LMW-HES infusion by ^{131}I-human serum albumin (Veall & Vetter, 1958). Two plasma samples drawn 10 and 20 min following isotope injection were counted after precipitation of plasma proteins and removal of the supernatant. Serial plasma volumes at time t after the LMW-HES infusion, were calculated from the original (time o), and subsequent values of haemoglobin and haematocrit at time t, and similarly from the serum protein values with corrections for the sampling.

$$PV_t = PV_o - S) \times \frac{Hgb_o}{Hgb_t} \times \frac{1 - Hct_t}{1 - Hct_o}$$

$$PV_t = (PV_o - S) \times \frac{Protein_o}{Protein_t}$$

The mean of the two values was taken as the actual plasma volume at time t.

Results

The intravenous infusion of LMW-HES was well tolerated by all subjects without serious untoward effects.

The plasma concentration of LMW-HES fell to half its peak value in 124 to 186 min (mean 164 min) following the injection (Figure 1), whilst the blood glucose level rose to its maximum value 60 min post-infusion, and thereafter gradually subsided. The plasma volume increased rapidly from a mean value of 45.7 ml kg^{-1} to a maximum value of 57.9 ml kg^{-1}, immediately post-injection, then gradually decreased toward the control level over a 24 h period (Figure 2). On average, the plasma volume was increased by

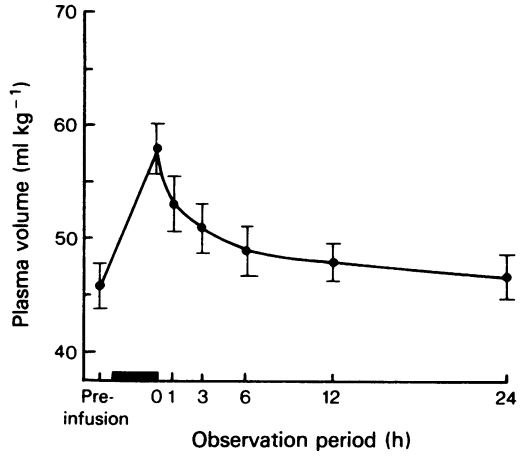

Figure 2 Changes in the plasma volume as determined by [^{131}I]-human serum albumin in six normal men administered 0.7 g kg^{-1} LMW-HES (■). Data points represent mean values ± 1 s.e. mean.

1,024 ml; this following the infusion of approximately 420 ml of 14% LMW-HES. One hour post-infusion, 13.5% of the total dose of LMW-HES injected was excreted in the urine (Figure 3). During this same period, 50.2% of the total injected LMW-HES was present in the intravascular space, whilst 36.3% was unaccounted for. Twenty-four hours post-infusion, 65.5% of the total dose of injected LMW-HES had been excreted in the urine, 4.1% remained intravascularly, and 30.4% was unaccounted for. The infusion of an average of 58.1 g of LMW-HES per subject, had no effect on the ESR. Biochemical analysis performed on plasma and urine samples, were within normal limits during the 96 h observation period following the infusion of LMW-HES. Plasma and urinary creatinine levels as was the creatinine clearance, were within normal limits throughout the entire study period.

Discussion

The ability to significantly change the intravascular persistence characteristics of HES by adjusting the weight average molecular weight and/or the degree of hydroxyethylation, makes this material quite unique, in as much as it can be tailored to meet the need for either short- or long-term plasma expansion management (Mishler, 1979). This concept has been previously demonstrated in man, where on the one hand, if the degree of hydroxyethylation (60–70% substitution of the glucose units) is constantly maintained in two different HES species, the intravascular half-life can be reduced from 26.4 to 9.6 h, by simply lowering the weight average molecular weight from 450,000 *d* (Metcalf *et al.*, 1970) to 150,000 *d.* (Mishler *et al.*, 1978). The present study has shown that an intravascular half-life of 2.7 h can be achieved, with an HES species possessing a weight average molecular weight of 264,000 *d*, combined with a 43% hydroxyethyl group substitution on the parent starch molecule.

The effect of LMW-HES on the intravascular volume, was quite pronounced immediately following the infusion. In addition to the rapid increase in

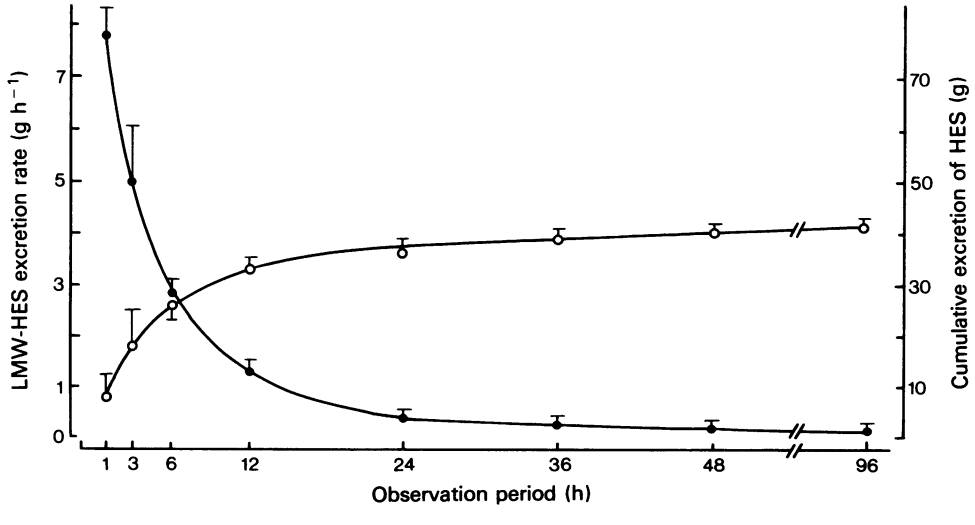

Figure 3 The rate (●) and cumultative (○) renal excretion of LMW-HES in six normal men. Data points represent mean values ± 1 s.e. mean.

colloidal osmotic activity, the plasma volume was expanded by a factor of 2.4 over the quantity of colloid injected. The expanded plasma volume was adequately maintained during the subsequent 3 h, even though 46% of the intravascular mass of LMW-HES had been eliminated. These pharmacokinetics suggest that large molecules of LMW-HES were hydrolysed to smaller molecules, and that the large number of osmotically active small molecules maintained constant osmotic pressure concomitant with plasma volume, while the major portion of the injected dose was cleared from the bloodstream. The modest increment in plasma glucose was most likely explained by rapid catabolism of the LMW-HES, and this was substantiated by the increased glomerular filtration of this material as demonstrated by the fact that 44% of the injected dose, was excreted in the urine within 6 h following the injection.

The present study has shown that LMW-HES is safe and effective, and should warrent additional investigation into the support of patients with plasma volume deficiencies.

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