HYDROXYETHYL STARCH. AN AGENT FOR HYPOVOLAEMIC SHOCK TREATMENT II. URINARY EXCRETION IN NORMAL VOLUNTEERS FOLLOWING THREE CONSECUTIVE DAILY INFUSIONS

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1 Urinary hydroxyethyl starch (HES) concentrations were determined by the anthrone method, in four healthy normal male volunteers following three consecutive daily 500 ml infusions (total 1500 ml), in order to ascertain excretion rates under normal controlled conditions.

2 The HES was excreted at a rate of 2.57, 2.46, and 2.44 g/h during the first hour postinjection, on days 1, 2, and 3, respectively.

3 The rate during the interval 12–24 h postinjection, averaged 0.14, 0.21, and 0.10 g/h, on days 1, 2, and 3, respectively.

4 In the intervals 24–72, 72–120, and 120–168 h after the third and final injection, the excretion rate was 0.07, 0.04, and 0.02 g/h, respectively.

5 Renal function, as assessed by serum creatinine and uric acid concentrations and 24 h void volumes, was normal during the entire period of observation.

6 The results indicate that HES is excreted at a similar rate following three consecutive daily infusions without evidence of renal injury.

Introduction

In animal models producing moderate to severe haemorrhagic shock, hydroxyethyl starch (HES) has compared favorably with dextran in therapeutic efficacy (Ballinger, Solanke & Thompson, 1966; Brown, Evangelista, Green & Guilt, 1968; Dillon, Lynch, Myers, Butcher & Moyer, 1966; Evangelista, Green & Guilt, 1969; Gollub, Vanichanan, Schaefer & Schechter, 1969; Murray, Solanke, Thompson & Ballinger, 1965; Takaori, Safar & Galla, 1968). In patients receiving single infusions to augment plasma volume deficiency, HES was well tolerated and without untoward effects (Gollub, Schechter, Hirose & Bailey, 1969; Lee, Cooper, Weidner & Murner, 1968; Metcalf, Papadopoulos, Tufaro & Barth, 1970; Solanke, 1968).

Renal function indices are normal in animals (Murphy, Demaree & Gagnon, 1965; Murphy, 1965; Silk, 1966; Thompson, Walton & Lee-Benner, 1964) and humans (Ballinger, Murray & Morse, 1966; Lee *et al.*, 1968; Metcalf *et al.*, 1970; Solanke, 1968) given single HES infusions. In dogs administered HES over a 3 to 5 day period, renal function parameters were normal (Thompson & Walton, 1963). In humans, the question of renal excretion and function following repeated daily infusions, however, remains to be answered.

Our purpose, therefore, was to determine renal excretion rates and function in normal volunteers following consecutive HES infusions, in order to ascertain the kinetics of HES removal under these conditions.

Methods

Four normal healthy male (ages 20–29 years) volunteers comprised the study group. The range of body surface area varied from 1.86–2.01 m², which corresponded to approximate blood volumes of 4660 to 5035 ml. Full written consent was obtained from each volunteer, and the experiment thoroughly explained to them.

Five hundred millilitres of a 6% HES solution (450,000 weight average molecular weight, 70,000 number average molecular weight, 6–7 hydroxyethyl groups/10 glucose units, McGaw Laboratories, Irvine, California, U.S.A., Lot N° A5N177A) in 0.9% saline, was infused through a 19 gauge butterfly needle inserted in a forearm vein, on each of three consecutive days (total 1500 ml). The infusion period ranged from 24–47 min (mean injection rate was 15.0 ml/min) on these 12 occasions. Urinary HES

Figure 1 Urinary HES excretion (▲) following a single 500 ml infusion, given over a mean period of 33 min (■). The % change from pre-infusion concentrations were plotted for serum creatinine (●) and uric acid (○) during this time period. Each point represents the mean of four determinations.

Figure 2 Following a second 500 ml HES infusion administered over a mean period of 35 min (■), urinary excretion (▲) and the % change from pre-infusion concentrations of serum creatinine (●) and uric acid (○), were plotted versus time. Each point represents the mean of four determinations.

Figure 3 HES excretion rate (▲) following the third and final 500 ml infusion given over a mean period of 36 min (■). The % change from pre-infusion concentrations of serum creatinine (●) and uric acid (○) were plotted versus time. The mean of four and three determinations were plotted in the intervals 0–24 and 24–480 h, respectively.

concentrations were determined from pooled samples starting from the termination of the infusion period, in intervals of 0–1, 1–3, 3–6, 6–12, and 12–24 h following each injection, on study days 1, 2, and 3. In three volunteers, pooled samples were obtained in the intervals 24–72, 72–120, and 120–168 h following the third and final infusion. Serum creatinine and uric acid concentrations were measured at 10 min, 1, 3, 6, 12, and 24 h after each injection on study days 1, 2, and 3, and in three volunteers 72, 120, 168, 312, and 480 h following the third and final infusion.

Urinary HES concentrations were measured in triplicate by a simplified anthrone technique (Brake, 1966) utilizing urine samples boiled in 30% KOH to destroy monosaccharides. The recovery of this method for determining serum HES concentrations was approximately 69–73% (Mishler, Borberg, Emerson & Gross, 1977). Standard laboratory methods were used in determining serum creatinine and uric acid concentrations.

Results

Following the initial 500 ml infusion, the excretion rate was 2.57 (range 2.05–2.97), 0.80 (0.67–0.94), 0.50 (0.49–0.51), 0.30 (0.23–0.42), and 0.14 (0.11–0.14) g/h, during the postinjection intervals 0–1, 1–3, 3–6, 6–12, and 12–24 h, respectively (Figure 1). Serum creatinine and uric acid concentrations were relatively unchanged from pre-infusion values, during this period. From a mean pre-infusion serum concentration of 1.0 mg% (0.8–1.1), the creatinine values were 1.0 (1.0–1.1), 0.9 (0.8–1.0), 1.0 (0.8–1.1), 1.0 (0.8–1.2), 1.0 (0.7–1.1), and 0.9 mg% (0.7–1.0); 0.17, 1, 3, 6, 12, and 24 h postinjection, respectively. Serum uric acid concentrations were as follows: 31 (29–34), 31 (28–36), 29 (25–32), 30 (25–34), 28 (22–30), 29 (26–33), and 23 mg% (20–27); pre-infusion, 0.17, 1, 3, 6, 12, and 24 h postinjection, respectively. The void volume during this 24 h period ranged from 751–2990 ml (mean: 1830 ml).

Similar rates of HES excretion were measured following the second infusion in as many days (Figure 2). A total of 2.46 (1.74–2.76), 0.89 (0.87–1.07), 0.63 (0.47–0.69), 0.26 (0.14–0.30), and 0.21 (0.10–0.50) g/h were eliminated in the intervals 0–1, 1–3, 3–6, 6–12, and 12–24 h postinfusion, respectively. Serum creatinine concentrations during the periods 0.17, 1, 3, 6, 12, and 24 h postinjection, were 0.9 (0.8–0.9), 0.9 (0.7–1.0), 0.9 (0.8–1.0), 1.0 (0.8–1.0), 1.0 (0.9–1.1), and 1.0 mg % (0.8–1.1), respectively. Serum uric acid concentrations were 23 (18–28), 24 (19–28), 24 (24–25), 26 (20–32), 26 (19–33), and 26 mg% (15–32), during the postinjection periods of 0.17, 1, 3, 6, 12, and 24 h, respectively. The total quality of urine voided during this second 24 h period, ranged from 935–2627 ml (mean: 1617 ml).

The excretion rate following the third and final infusion, mimicked those previously measured. During the postinjection intervals of 0–1, 1–3, 3–6, 6–12, and 12–24 h, the rate was 2.44 (1.97–2.94), 0.72 (0.55–0.98), 0.47 (0.43–0.54), 0.27 (0.15–0.57), and 0.10 (0.06–1.18) g/h, respectively (Figure 3). Serum creatinine concentrations were 0.8 (0.7–0.9), 0.8 (0.6–1.0), 0.9 (0.7–1.0), 0.9 (0.7–1.2), 1.0 (0.8–1.1), and 1.0 mg% (0.8–1.0) for the periods 0.17, 1, 3, 6, 12, and 24 h postinjection respectively. Serum uric acid concentrations during the periods 0.17, 1, 3, 6, 12, and 24 h postinjection, were 23 (16–26), 26 (18–36), 24 (20–28), 25 (14–31), 26 (13–38), and 25 mg% (15–32), respectively. A range of 796 to 3165 ml (mean: 1925 ml) of urine was voided during this 24 h period.

During the intervals 24–72, 72–120, and 120–168 h after the third and final injection, the rate of HES excretion was 0.07 (0.04–0.12), 0.04 (0.02–0.05), and 0.02 (0.018–0.03) g/h, respectively (Figure 3). Serum creatinine concentrations during the periods 72, 120, 168, 312, and 480 h after the third and final infusion were 1.0 (0.9–1.0), 1.0 (0.8–1.1), 0.9 (0.8–1.0), 0.9 (0.8–1.1), and 0.9 mg% (0.8–1.0), respectively. Uric acid concentrations were 22 (15–28), 25 (24–27), 23 (19–29), 24 (20–28), and 31 mg% (18–42) during the periods 72, 120, 168, 312, and 480 h, respectively. The mean quantity of urine voided in the intervals 24–72, 72–120, and 120–168 h following the third injection, was 3730 (1950–4750), 3297 (1580–4470), and 2733 ml (1400–4750), respectively.

Discussion

The safety of HES utilization during multiple use situations, is of paramount importance, especially in hypovolaemic patients requiring repeated plasma volume rather than erythrocyte mass augmentation. Prior to addressing this question directly, it was thought prudent to examine renal kinetics and function, in normal volunteers given repeated HES injections, in efforts to determine if a potential for injury could occur.

In clinical investigations (Ballinger, Murray *et al.*, 1966; Lee *et al.*, 1968; Metcalf *et al.*, 1970; Solanke, 1968) monitoring renal function indices, the single injection of HES was not associated with abnormal effects.

A decrease in urine flow following HES and dextran infusions in dogs has been reported, but the decrease associated with dextran was significant (Murphy, 1965). Additional animal (Silk, 1966) and human (Lee *et al.*, 1968) studies have observed a characteristic increase in creatinine clearance following HES injections. In dogs, intravenous infusion of 170–250 ml HES/kg over a 3–5 day period, produced no significant changes in creatinine clear-

ance, T_m glucose or T_m PAH, but produced marked increments in PAH clearance (Thompson & Walton, 1963). During brief tissue storage of HES in the liver and renal proximal tubular epithelium, these cells appear vacuolated when tissue sections are exposed to water, and the renal cells appear swollen (Thompson, Britton & Walton, 1962; Thompson, 1963). Despite these morphological changes, renal function is not impaired as measured by creatinine clearance, glucose reabsorption and PAH excretion (Thompson, 1963). In addition, renal blood flow is increased in dogs after 130–250 ml HES/kg in 2–5 days (Thompson, 1963). In the present series, renal function, as assessed by serum creatinine and uric acid concentrations and 24 h void volumes, was normal during the entire period of observation, thus substantiating previous studies monitoring renal parameters. It thus appears that following consecutive daily infusions of HES, renal function is not compromised.

Hydroxyethyl starch disappearance from the circulation following a *single* injection (1000 ml) is compound in nature and has been resolved into three exponential components; fractions with slow ($T_{\frac{1}{2}}$ 67 h), intermediate ($T_{\frac{1}{2}}$ 6.1 h), and rapid ($T_{\frac{1}{2}}$ 0.86 h) clearance rates (Metcalf *et al.*, 1970). The compound nature of this disappearance curve is due in part to the heterogenous distribution of varying molecular weight populations contained in the injected solution. The smaller molecules (70,000 mol. wt or below) are rapidly sieved through the glomerular and systemic capillary beds (Metcalf *et al.*, 1970; Thompson *et al.*, 1962), accounting for the elevated rate of excretion observed during the first postinjection hour. Hydroxyethyl starch is also metabolized to smaller molecules (Farrow, Hall & Ricketts, 1970); this being reflected in the intermediate and slow rates of serum clearance, concomitant with gradually declining urinary excretion rates (Metcalf *et al.*, 1970). Large HES molecules are eliminated from the circulation by the RES and can be detected histochemically in liver cells, renal proximal tubular epithelium, and phagocytes in all organs for brief periods (Thompson, 1963). The excretion rate curves (Figures 1, 2, and 3) generated in the present series, would tend to confirm this compound nature of HES serum clearance; as shown by the rapid elimination rate during the first hour postinjection, and the subsequent decline in excretion over the next 23 hours.

Based on an approximate calculation of total plasma volume from changes in PCV, haemoglobin, and serum protein prior to and 10 min following the *initial* 500 ml infusion (Mishler *et al.*, 1977) and the % HES recovery by the anthrone method, it was

estimated that 40–45% of the infused colloid, was excreted in the urine by 24 h postinjection. Similar rates have been reported after a *single* 1000 ml injection of HES (Metcalf *et al.*, 1970). Absolute analysis of excretion rates on days two and three, and the postinjection period, is hindered by the residual serum HES concentration and subsequent clearance kinetics following the *initial* 500ml infusion on day one. In man, single HES injections (500–1000 ml) are associated with a 53–70% retention of the infused amount, 24 h postinfusion (Ballinger, Murray *et al.*, 1966; Metcalf *et al.*, 1970; Mishler, 1977; Mishler *et al.*, 1977; Solanke, 1968). Based on the studies of Metcalf *et al.* (1970), the HES species remaining 24 h following a single infusion, should consist of the slow, large molecular weight fraction possessing a $T_{\frac{1}{2}}$ of 67 h. The uniformity of excretion rates on all three infusion days, would thus primarily seem to reflect the elimination of HES molecular weight species possessing rapid ($T_{\frac{1}{2}}$ 0.86 h) and intermediate ($T_{\frac{1}{2}}$ 6.1 h) serum clearance rates. This observation is supported by the number average molecular weight of HES, which is approximately 70,000; indicating that 50% of the injected molecules have a molecular weight less than or equal to this number, and thus would be expected to be efficiently eliminated through the kidneys. On day 2, excretion rates during the intervals 1–3, 3–6, and 12–24 h postinjection, were higher than on day one; this added elimination of HES presumably coming from the metabolism of the residual slow fraction contributed on days 1 and 2. Excretion rates on day 3 were not higher than on day 2, possibly reflecting the increased voiding of a more dilute urine or saturation of enzymatic (amylase) activity.

The cumulative excretion rate, up to and including 168 h following the third and final injection, was approximately 41–46% of the total quantity of HES infused (calculated from total plasma volumes and % HES recovery by the anthrone method). The present study indicates that rapid and intermediate serum clearance fractions are eliminated in a similar fashion after consecutive daily HES infusions, while the slow serum component is excreted in a non-uniform manner during these periods.

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