Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers

Dileep N. Lobo, DM, FRCS; Zeno Stanga, MD; Mark M. Aloysius, MRCS; Catherine Wicks, BMedSci, BM, BS; Quentin M. Nunes, MRCS; Katharine L. Ingram, FRCA; Lorenz Risch, MD, MPH; Simon P. Allison, MD, FRCP

Objective: **To study the changes in blood volume and hormones controlling sodium and water homeostasis after infusions of 0.9% saline, Gelofusine (4% succinylated gelatin in 0.7% saline, weight-average molecular weight 30 kD), and Voluven (6% hydroxyethyl starch in 0.9% saline, weight-average molecular weight 130 kD) in healthy volunteers.**

Design: **Randomized, three-way crossover study.**

Setting: **University teaching hospital.**

Subjects: **Ten healthy adult male volunteers.**

Interventions: **Volunteers received 1-L infusions of 0.9% saline, Gelofusine, and Voluven over 1 hr on three occasions. Body weight, hematocrit, serum biochemistry, and plasma concentrations of vasopressin, aldosterone, brain natriuretic peptide, and total renin were measured before infusion and hourly thereafter for 6 hrs. Changes in body water, blood volume, and extravascular fluid volume were calculated.**

Measurements and Main Results: **Although changes in body weight (total body water) after the infusions were similar, blood volume expansion by the two colloids was significantly greater than that produced by 0.9% saline ($p < .01$). At the end of infusions, 68%, 21%, and 16% of the infused volumes of 0.9% saline, Gelofusine, and Voluven, respectively, had escaped from the intravascular space to the extravascular space. Over the 6 hrs, the magnitude and duration of blood volume expansion by the two colloids were similar ($p = .70$). There were no significant differences in urinary volume, osmolality, and sodium content after the three infusions. Hormonal changes were similar after the three infusions, with the increase in natriuretic peptide being transient. The reduction in aldosterone and total renin concentrations was more sustained.**

Conclusions: **The effects of Gelofusine and Voluven were similar despite the 100 kD difference in weight-average molecular weight. Excretion of an acute fluid load containing sodium and chloride may be dependent on a sustained suppression of the renin-angiotensin-aldosterone system rather than on natriuretic peptides. (Crit Care Med 2010; 38:464–470)**

KEY WORDS: renin angiotensin aldosterone system; volume loading; sodium chloride; hydroxyethyl starch; succinylated gelatin; crystalloid; colloid; intravenous; aldosterone; natriuretic peptide; arginine vasopressin; randomized study

In previous studies, we compared the physiologic responses with intravenous infusions of 0.9% saline, 5% dextrose (1), and Hartmann's solution (Ringer's lactate) (2) in normal subjects showing that, even in health, the excretion of sodium is slow and can be further impaired by hyperchloremia (3, 4). In the present study, we used a similar protocol (1, 2) to compare the responses of normal subjects with 0.9% saline and two colloid preparations.

The main objectives were:

- To compare the blood volume-expanding capacity of an infusion over 1 hr of 1 L of a 30-kD (MWw) colloid (4% succinylated gelatin in 0.7% saline [Gelofusine, B Braun, Chapeltown, UK]) and a 130-kD (MWw) colloid (6% hydroxyethyl starch 130/0.4 in 0.9% saline [Voluven 6%, Fresenius Kabi, Runcorn, UK]) with 0.9% saline (Baxter Healthcare, Thetford, UK);
- To compare serum sodium, chloride, and bicarbonate concentrations in the 6 hrs post infusion;
- To measure sodium and water excretion over the same period; and
- To study the effects of these infusions on the plasma concentrations of hormones controlling water and sodium excretion.

From the Division of Gastrointestinal Surgery (DNL, MMA, CW, QMN, SPA), Nottingham Digestive Diseases Centre NIHR Biomedical Research Unit, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK; Divison of Endocrinology (ZS), Diabetes and Clinical Nutrition and Department of Internal Medicine, Inselspital, Berne, Switzerland; Department of Anaesthesia (KLI), Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK; and IRL Medical Laboratories (LR), Schaan, Liechtenstein.

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For information regarding this article, E-mail: Dileep.Lobo@nottingham.ac.uk

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METHODS

Study Design and Setting

This randomized, three-way crossover volunteer study was set in a university teaching hospital. Although the infusions were not masked, laboratory, data, and statistical analyses were performed in a blinded manner.

Subjects and Ethics

Ten healthy young adult male volunteers with a body weight of 65 kg to 80 kg and a body mass index of 20 kg/m^2 to 25 kg/m^2 were recruited after obtaining their informed written consent. Those with chronic medical conditions or acute illness in the preceding 6 wks, on regular medication, or with a history of substance abuse were excluded.

The University of Nottingham Medical School Ethics Committee granted approval for the study, which was performed in accordance with the Declaration of Helsinki of the World Medical Association.

Baseline Assessment, Blood and Urine Samplings

Subjects reported at 9 AM after a fast from midnight and having abstained from alcohol, nicotine, tea, and coffee from 6 PM. After voiding of the bladder, height was recorded to the nearest 0.01 m and weight was measured to the nearest 0.1 kg, using Avery 3306ABV scales (Avery Berkel, Royston, UK). Subjects were not allowed to eat or drink for the duration of the study and remained supine most of the time. They stood up to void urine and be weighed, but blood samples were taken after lying supine for at least 20 mins.

A 19G venous cannula was inserted into each antecubital fossa. The cannula on the left side was used solely for blood sampling and that on the right for infusion. An initial 30-mL blood sample was drawn from the indwelling venous cannula 20 mins after insertion for analysis of full blood count, serum electrolytes, urea, creatinine, albumin, osmolality, plasma renin, aldosterone, arginine vasopressin (AVP), and brain natriuretic peptide (BNP). The urine collected was analyzed for osmolality and concentrations of urea, sodium, and potassium. A urine sample was collected for 24 hrs before each study and creatinine clearance was calculated (5).

Infusion and Sampling Protocol

One liter of 0.9% saline, Gelofusine or Voluven 6% (Table 1) (6–8) was infused over 60 mins in random order on separate occasions, each at least 10 days apart, with subjects supine, using an infusion pump (IVAC Corporation, San Diego, CA), starting at time 0.

Table 1. Characteristics of the three infusions (6–8)

	0.9% Saline	Gelofusine	Voluven
Sodium, mmol/L	154	154	154
Chloride, mmol/L	154	120	154
Sodium supplied as	NaCl 9 g/L	NaCl 7.01 g/L + NaOH 1.36 g/L	NaCl 9 g/L
Colloid	—	Succinylated gelatin	Hydroxyethyl starch
Weight-average molecular weight of colloid, MWw	—	30,000	130,000
Number-average molecular weight of colloid, MWn	—	23,200	60,000–65,000
Polydispersity ratio, MWw/MWn	—	1.29:1	2.0–2.17:1
Molar substitution	—	—	0.4
Weight of colloid/L	—	40 g (4%)	60 g (6%)
pH	5.4	7.1–7.7	4.5–5.5
Theoretical osmolarity, mOsm/L	308	274	308
Na^+/Cl^- ratio	1:1	1.28:1	1:1
Colloid osmotic pressure at 37°C, mm Hg	—	33.3	36
Hydrodynamic particle radius (Rh_w), nm[a]	—	4.1	6.1
Price per 500-mL bag	£0.40	£4.70	£12.5

[a]Measured by B Braun Medical SA, Crissier, Switzerland.

Body weight measurements and blood samples were repeated hourly for 6 hrs. Subjects passed urine as needed and, in all cases, at the end of 6 hrs. The time of each micturition was noted and urine volume was measured. Pooled urine was analyzed for osmolality and concentrations of urea, creatinine, sodium, and potassium.

Hematologic, Biochemical, and Hormonal Analyses

Hematologic and biochemical parameters were measured by methods we have used previously, with coefficients of variance of 0.6% to 4% (1, 2). Plasma aldosterone was measured by radioimmunoassay, using an aldosterone assay kit (ALDOCTK-2, DiaSorin, Saluggia, Italy). Plasma AVP concentrations were measured by radioimmunoassay (Vasopressin Direct RIA, Bühlmann Laboratories, Allschwil, Switzerland). Plasma BNP concentrations were measured by a microparticle enzyme immunoassay test (Architect BNP Assay, Abbott Laboratories, Abbott Park, IL). Plasma total renin was measured by chemiluminescent assay of immunoreactive renin in plasma (LIAISON Direct Renin, DiaSorin, Saluggia, Italy). The interassay imprecisions, expressed as coefficients of variance, of the assays were 6.6% to 17.2% for aldosterone, 6.8% to 13% for AVP, 1.7% to 6.7% for BNP, and 4.4% to 14.5% for renin.

Change in Blood Volume, Total Body Water, and Extravascular Fluid Volume

Blood volume at time 0 was estimated using Nadler's formula (9):

$$BV_0(L) = 0.0329 \times BW_0 + 0.3669 \times Ht^3 + 0.6041,$$

where BV_0 (L) is the blood volume in liters at time 0, BW_0 is the body weight in kg at time 0, and Ht is the height in m.

$$\Delta Hct_t(\%) = \frac{Hct_0 - Hct_t}{Hct_0} \times 100,$$

where Δhematocrit $(Hct)_t$ (%) is the percentage change in hematocrit at time t, Hct_0 is the hematocrit at time 0, and Hct_t is the hematocrit at time t.

$$\Delta BV_t(\%) = \left[\frac{100}{100 - \Delta Hct_t(\%)} \times 100\right] - 100,$$

where $\Delta BV_t(\%)$ is the percentage change in blood volume at time t.

$$BV_t(L) = \frac{BV_0 \times [100 + \Delta BV_t(\%)]}{100},$$

where BV_t (L) is the blood volume in liters at time t.

$$\Delta BV_t(L) = BV_t - BV_0,$$

where ΔBV_t (L) is the change in blood volume in liters at time t from baseline (time 0).

$$\Delta TBW_t(L) = BW_t - BW_0,$$

where ΔTBW_t (L) is the change in total body water in liters at time t, BW_t is the body weight in kg at time t, and BW_0 is the body weight in kg at time 0.

$$\Delta EFV_t(L) = \Delta TBW_t - \Delta BV_t,$$

where ΔEFV_t (L) is the change in extravascular fluid volume in liters at time t, ΔTBW_t is the change in total body water in liters at time t from baseline (time 0), and ΔBV_t is the change in blood volume in liters at time t from baseline (time 0).

Statistical Analysis

Data were expressed as mean (SE). Statistical analysis was performed with SPSS for Windows v 16.1 software (SPSS, Chicago, IL). Differences

between groups were considered significant at $p < .05$, using the Student t paired test. Between-subjects effects (saline vs. Gelofusine, saline vs. Voluven, and Gelofusine vs. Voluven) were tested, using the general linear model repeated-measures procedure.

RESULTS

Baseline parameters before each infusion were similar (Table 2). All subjects completed the three arms of the study and none experienced side effects.

Weight changes were proportional to the volume infused and urine excreted (Fig. 1, Table 3). Although these changes were similar after the three infusions, blood volume expansion was significantly greater after colloids than after saline, suggesting that >68% (SE = 6%) of the saline infused had escaped into the extravascular fluid compartment at 1 hr (Fig. 1). Despite the 100-kD difference in weight-average molecular weight (MWw) between the colloids, the degree and duration of blood volume expansion were identical. However, 21% (SE = 7%) and 16% (SE = 12%) ($p = .76$, Student t paired test) of the infused volumes of Gelofusine and Voluven, respectively, had leaked from the intravascular compartment.

Changes in serum osmolality, sodium, potassium, chloride and bicarbonate, and strong ion difference after the infusions were not significantly different (Fig. 2). Hyperchloremia and strong ion difference tended to be less after Gelofusine than after Voluven or 0.9% saline, reflecting the lower chloride concentration in Gelofusine. Correspondingly, venous bicarbonate decreased after Voluven and 0.9% saline but increased after Gelofusine, showing that, unlike the other solutions, Gelofusine in the volume used produced no hyperchloremic acidosis. There were no significant differences between the percentage changes from baseline in plasma aldosterone, AVP, BNP, and renin after the infusions (Fig. 3) and urinary responses were similar (Table 3).

Table 2. Baseline parameters before infusions

	Before Saline	Before Gelofusine	Before Voluven
Weight, kg	72.1 (1.9)	72.4 (2.0)	72.3 (1.9)
Height, m	1.75 (0.01)	1.75 (0.01)	1.75 (0.01)
Body mass index, kg/m^2	23.5 (0.5)	23.6 (0.6)	23.6 (0.6)
Hemoglobin, g/dL	14.9 (0.3)	14.9 (0.3)	14.7 (0.4)
Hematocrit, %	44.9 (0.6)	44.8 (0.7)	44.1 (0.6)
Serum albumin, g/L	42.9 (1.2)	43.2 (0.8)	43.1 (0.9)
Serum osmolality, mOsm/kg	298 (1.6)	299 (1.0)	297 (1.7)
Serum urea, mmol/L	5.1 (0.4)	4.8 (0.3)	5.2 (0.3)
Serum creatinine, μmol/L	80 (1.9)	81 (1.9)	82 (0.9)
Creatinine clearance, mL/min	118 (11)	123 (9)	120 (10)
Calculated blood volume, L	4.9 (0.1)	5.0 (0.1)	4.9 (0.1)

n = 10, all values mean (standard error). Differences were not significant for all parameters (Student t paired test).

DISCUSSION

In these normovolemic healthy volunteers, as expected, colloids were more ef-

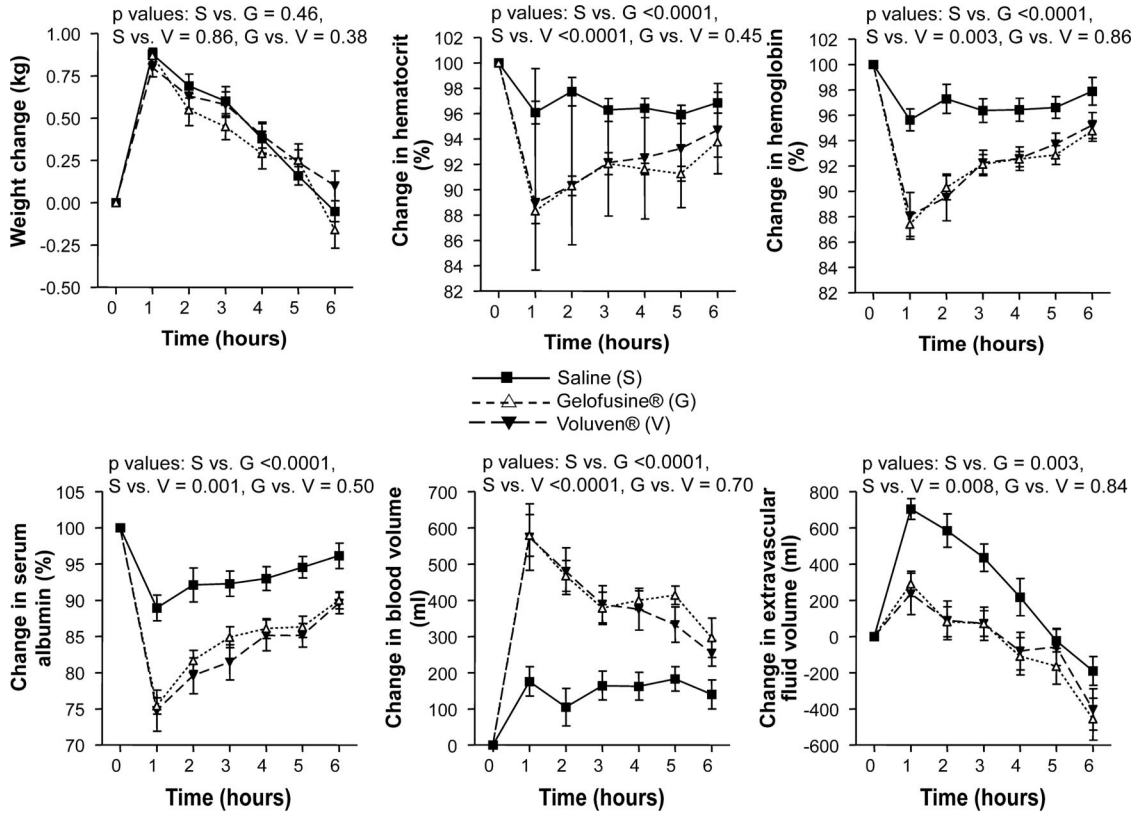

Figure 1. Changes in body weight, percentage changes in hematocrit, hemoglobin and serum albumin concentration, and changes in blood volume, and extravascular fluid volume after infusion of 1 L of 0.9% saline (*S*), Gelofusine (*G*), and Voluven (*V*) over 1 hr. All values are mean (SE). The p values are for tests of between-subjects effects (*S vs. G, S vs. V, and G vs. V*), using the general linear model repeated-measures procedure.

fective blood volume expanders than a crystalloid. Unexpectedly, however, there was no difference between the effects of a colloid with an MWw of 30 kD and one with an MWw of 130 kD. At the end of the 1-hr infusion, 68%, 21%, and 16% of the infused volumes of 0.9% saline, Gelofusine, and Voluven, respectively, had escaped from the intravascular to the extravascular space. It has traditionally been thought that low MWw colloids would escape faster through the capillary pores and, hence, be less effective volume expanders than those with high MWw (10). However, studies in animal models of trauma suggested that the plasma volume-expanding properties of gelatins and hydroxyethyl starch, which have similar oncotic pressures (Table 1), may be similar (11–13). Furthermore, according to the two-pore theory for transport of macromolecules across the microvasculature (14), small solutes pass through pores in the capillary membrane along the entire microvascular bed, whereas larger molecules pass only through the considerably fewer large pores on the venous side of the capillary network and in venules. As the oncotic pressure on both sides of the large pores is in equilibrium, flow of fluid across these pores is governed solely by hydrostatic pressure. The loss of macromolecules across the pores is along the direction of fluid flux and occurs mainly by convection (14–17). Hence, even in health, an increase in capillary hydrostatic pressure caused by volume expansion can result in leakage of larger molecules from the intravascular compartment to the extravascular space. Hypervolemia may disrupt endothelial integrity, which is maintained by the endothelial glycocalyx which binds to large anionic molecules

Table 3. Urinary changes

	0.9% Saline (S)	Gelofusine (G)	Voluven (V)	*p* (S vs. G)	*p* (S vs. V)	*p* (G vs. V)
Time to first micturition, min	167 (24)	152 (20)	151 (27)	.46	.43	.60
No. of micturition episodes	2.4 (0.2)	2.6 (0.3)	2.1 (0.4)	.51	.31	.21
Postinfusion urinary volume, mL	663 (49)	697 (91)	535 (42)	.73	.12	.09
Preinfusion urinary osmolality, mOsm/kg	828 (99)	725 (99)	814 (68)	.35	.72	.23
Postinfusion urinary osmolality, mOsm/kg	615 (46)	582 (52)	652 (56)	.18	.25	.15
Total postinfusion urinary sodium, mmol	70 (10)	89 (11)	62 (6)	.58	.74	.38
Total postinfusion urinary potassium, mmol	39 (3)	38 (3)	32 (4)	.79	.22	.81
Total postinfusion urinary urea, mmol	129 (18)	99 (9)	128 (14)	.10	.96	.22
Total postinfusion urinary creatinine, mmol	4.6 (0.4)	4.2 (0.2)	5.1 (0.3)	.41	.42	.30

All values are mean (standard error). Statistical significance was calculated using the Student *t* paired test.

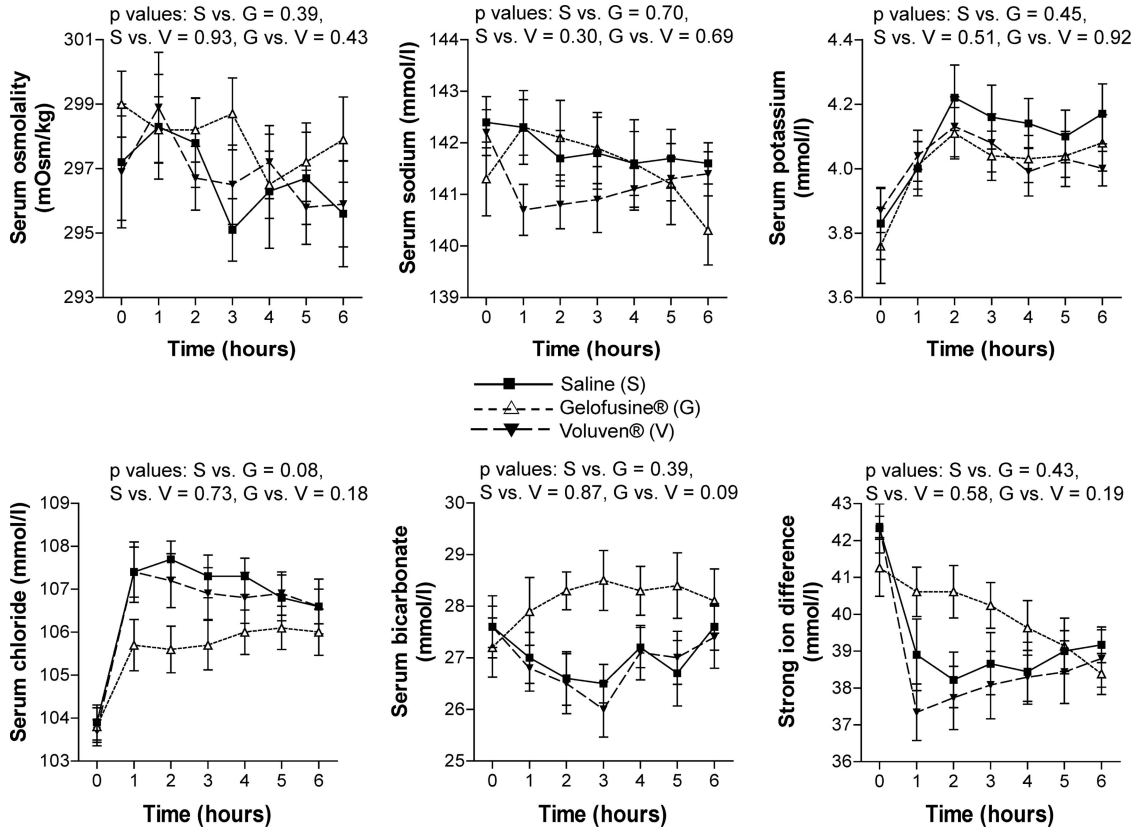

Figure 2. Changes in serum osmolality, sodium, potassium, chloride, bicarbonate, and strong ion difference ($[Na^+] + [K^+] - [Cl^-]$) after infusion of 1 L of 0.9% saline (*S*), Gelofusine (*G*), and Voluven (*V*) over 1 hr. All values are mean (SE). The *p* values are for tests of between-subjects effects (*S vs. G, S vs. V, and G vs. V*), using the general linear model repeated-measures procedure.

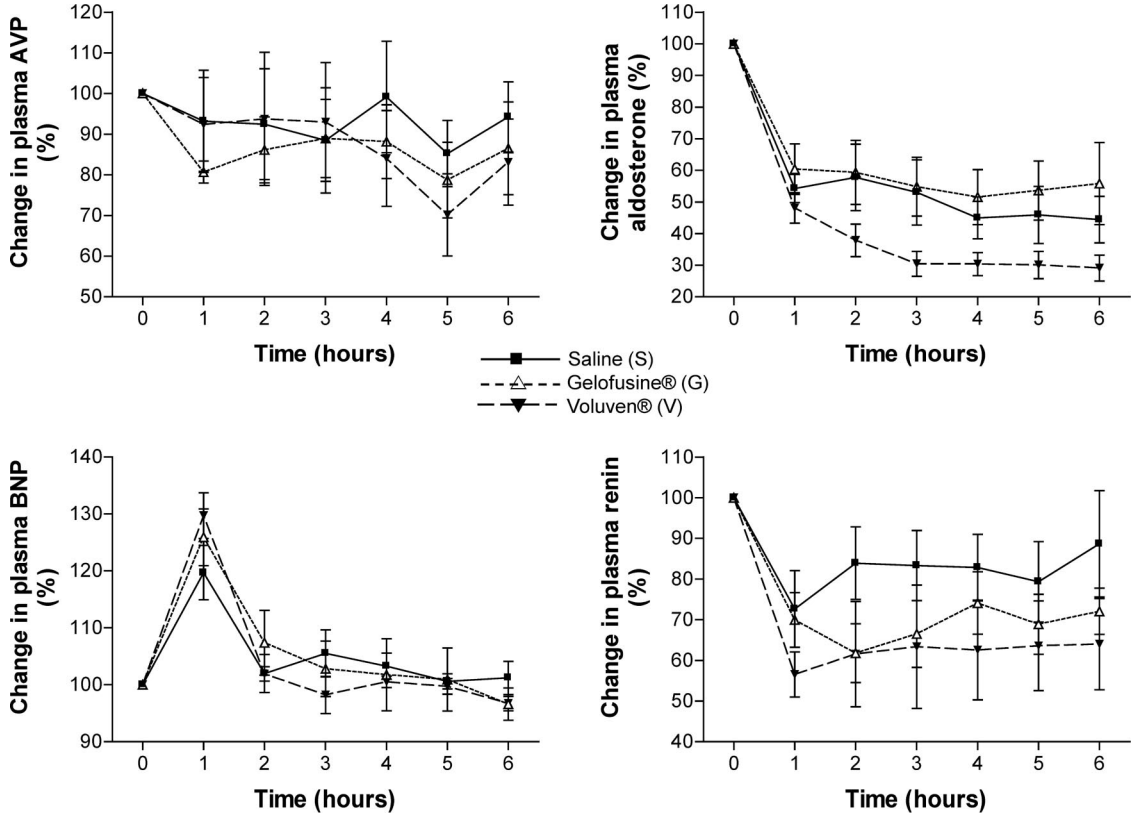

Figure 3. Percentage changes from baseline (100%) in plasma concentrations of arginine vasopressin (*AVP*), aldosterone, brain natriuretic peptide (*BNP*), and total renin after infusion of 1 L of 0.9% saline (*S*), Gelofusine (*G*), and Voluven (*V*) over 1 hr. All values are mean (SE). The *p* values for tests of between-subjects effects (*S vs. G, S vs. V, and G vs. V*), using the general linear model repeated-measures procedure, were not significant ($p > .05$ in all cases).

and prevents their extravasation (18). This may be another mechanism for escape of colloids from the intravascular compartment (19), and, to some extent, may explain the similar effects of Gelofusine and Voluven in the present study. In addition, the escape of a molecule across the pores is more dependent on the diameter of the molecule than the molecular weight (20). The measured hydrodynamic radii (Rh_w) of succinylated gelatin and hydroxyethyl starch (Table 1) are greater than the Rh_w of human serum albumin (2.6–3.3 nm) (21), but larger than the small capillary pore radius of 2.5 nm to 3 nm, and smaller than the large capillary pore radius of 10 nm to 11 nm in subcutaneous tissue and skeletal muscle where the large/small pores ratio is 1:3000 to 1:3600 (22). This may also be one of the reasons for the lack of difference in the plasma-expanding properties of the two colloids.

The similar duration of action of Gelofusine and Voluven may also be due to the fact that hydroxyethyl starch is eliminated by the cleavage action of amylase. A fourfold increase in serum amylase concentrations has been observed after the infusion of hydroxyethyl starch in healthy volunteers (23), not due to pancreatic damage but because starch-amylase complexes are detected by assay in addition to amylase itself.

The changes in serum albumin concentration, hemoglobin, and hematocrit in response to the three infusions were in keeping with the degree of blood volume expansion that we (1, 2) and others (24) have found. The percentage decrease in hematocrit at 1 hr was 3.9% after 0.9% saline, 11.7% after Gelofusine, and 11.1% after Voluven; the corresponding decreases in serum albumin concentration were 11.1%, 24.6%, and 25.2%, possibly reflecting the differential distribution of albumin and red blood cells within the intravascular space. Plasma volume expansion is equal to blood volume expansion in absolute terms (mL), but the relative expansion and dilution (%) are greater in the smaller plasma and albumin space. For example, a decrease in hematocrit by 3.9% (after 0.9% saline) is the result of expansion of the blood volume by 4.1% $\left(\frac{100 \times 100}{100 - 3.9} - 100\right)$. With a preinfusion hematocrit of 45% (and plasma volume of 55%), this expansion in total blood volume would result in a 7.5% increase in plasma volume $\left(\frac{(55 + 4.1) \times 100}{55} - 100\right)$ (1). The changes in serum albumin concentration after the infusions are more than can be explained by dilution alone, suggesting a change in albumin distribution also, according to the convection hypothesis (1, 14–16, 25).

In an experiment on acute normovolemic hemodilution during anesthesia for major gynecologic surgery, Rehm et al (26) showed a lower increase in plasma volume (using fluorescein-labeled red blood cells) post colloidal infusion than in our study. On the other hand, in a study on starch infusions after acute hypovolemia in healthy volunteers, James et al (27), using ^{51}Cr-labeled red blood cells, showed that the volume expansion produced at the end of the loading period was greater than the administered volume. We used theoretical calculations based on changes in hematocrit to determine changes in blood volume in normovolemic volunteers, and these may be different from actual changes in blood

volume measured, using labeled techniques. Nevertheless, there were no differences between the blood volume-expanding effects of the two colloids that we used.

After modest infusions, all subjects developed hyperchloremia persisting for at least 6 hrs (Fig. 2). Hyperchloremia was more marked after 0.9% saline and Voluven than Gelofusine, reflecting the lower concentration of chloride in the latter. The use of newer preparations of colloids in balanced solutions results in less derangement in acid base status and seems to be a promising strategy to overcome metabolic acidosis associated with colloids suspended in 0.9% saline (28).

Despite the different compartmental distribution of the crystalloid compared with the two colloids, urinary excretion of water and electrolytes after the three infusions was similar. However, Figure 1 shows that the equal volumes of urine excreted after the three infusions may, to some extent, be due to the fact that the colloids drew fluid from the extravascular space into the intravascular space, resulting in a negative extravascular space fluid balance.

The suppression of the renin-angiotensin-aldosterone system (RAAS) is one important mechanism for both the immediate and long-term regulation of sodium excretion post sodium loading (29–33). However, little is known regarding the impact of serum chloride concentration on the RAAS. Studies in rodents have demonstrated that chloride depletion is a potent stimulus for the release of renin (34, 35). Chronic chloride depletion can produce a significant increase in plasma renin activity and up-regulation of angiotensin receptors in the adrenal gland, renal glomeruli and medulla (36), and anterior pituitary gland (37). Hyperchloremia has also been shown to induce renal vasoconstriction and a decrease in glomerular filtration rate in anesthetized dogs (3) and suppress renin activity in humans (35, 38).

Volume expansion after infusion of the three solutions seemed to have similar effects on the concentration of plasma renin (Fig. 3), although this tended to return to baseline more rapidly after 0.9% saline than after the two colloids. The volume effect may be attributed to the baroreflex response (39), whereby the rate of renin release varies in response to changes in stretch detected by receptors present in the juxaglomerular apparatus. Thus, increased stretch causes inhibition of further renin secretion, as observed.

For all three infusions, the initial decline in renin concentrations coincided with a decrease in aldosterone (Fig. 3), as renin via angiotensin II has the ability to regulate aldosterone secretion (40, 41). Plasma concentrations of BNP increased 1 hr after the start of all three infusions in response to the increase in right atrial filling (42, 43). Thereafter, the BNP concentrations declined almost in unison (Fig. 3), in agreement with previous work, (31, 44, 45), suggesting that the role of BNP and atrial natriuretic peptide in sodium excretion may only be to protect against intravascular hypervolemia and that it is not responsive to excess sodium loading *per se*. Singer et al (45) suggested that atrial natriuretic peptide may play a role in determining the immediate increase in sodium excretion but that other mechanisms, such as suppression of the RAAS, may be of equal or greater importance in the longer term.

An initial decrease in AVP concentrations immediately after all three infusions was observed. The nature of the AVP and renin response showed similar patterns of decrease. Usberti and colleagues (46) have shown during angiotensin II infusions a concomitant increase in plasma AVP concentrations in normal volunteers, thus supporting the findings of the present study. Although Gelofusine is hyposmolar, with a theoretical osmolarity of 274 mOsm/L, this did not reflect changes in serum osmolality.

Limitations of this study include the fact that it was performed on healthy normovolemic adult male volunteers in whom the transcapillary rate of albumin was normal. Changes in blood volume were theoretical, as these calculations were based on the dilution of hematocrit. However, more complex techniques, such as isotope or dye labeling, may have provided a better estimate of changes in blood volume.

In conclusion, despite the 100-kD difference in MWw, Gelofusine and Voluven possess comparable blood volume-expanding capacities in healthy volunteers. However, further investigations are required to determine whether this similarity is maintained in patients in whom the transcapillary rate of albumin may be increased. In addition, excretion of an acute fluid load containing sodium and chloride may be dependent on a sustained suppression of the RAAS rather than on natriuretic peptides.

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