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DOSE RESPONSE EFFECTS OF HYPERTONIC SALINE AND DEXTRAN ON CARDIOVASCULAR RESPONSES AND PLASMA VOLUME EXPANSION IN SHEEP

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ABSTRACT—Despite the established efficacy of 7.5% NaCl/6% dextran-70 in the treatment of hypovolemia, the optimal formulation of a hyperosmotic/hyperoncotic small volume resuscitation solution has yet to be defined. The present study investigates the cardiovascular effects of hypertonic saline ranging from 3.75%-25% NaCl (HS) and dextran-70 (D-70) ranging from 3 to 24%. HS and D-70 were studied alone or in specific combinations at a dose of 4 mL/kg, in euvolemic sheep. Blood samples were collected before, during and up to 60 min after infusion of the test solutions. Dose-dependent effects of HS were immediate increases in cardiac output (CO) of 30–85%, falling to 10–35% over baseline after 60 min. HS concentrations over 3.75% significantly reduced systemic vascular resistance, but HS had no significant effect on mean arterial pressure (MAP). Plasma volume (PV) expansion with HS was an immediate, but transient increase of 12–35%. Infusion of D-70 induced sustained 10–20% increases in CO and 10–30% increases in PV, peaking 10 min post-infusion. D-70 also resulted in small (5–12 mmHg) increases in MAP. Cardiovascular effects of D-70 correlated with a dose-dependent increase in plasma dextran concentrations. All HS solutions significantly increased plasma Na, which peaked at ≥ 200 mEq/L in the 25% group. The effects of D-70 and HS combined were additive on PV expansion and CO. These data indicate that concentrations of HS and D-70 which are higher than those currently used have a greater capability for expanding PV, but use of HS >7.5% may be limited by resulting hypernatremia.

INTRODUCTION

The rationale behind fluid resuscitation of the hypotensive trauma patient is restoration of vascular volume for normalization of venous return to the heart and the subsequent perfusion of vital organs. Optimal fluid resuscitation should be prompt and limit the period of ischemia. Unfortunately, two to four times the bled volume of conventional isotonic solutions is required to restore normal vascular volume and cardiac output. In situations in which prehospital transport times of these patients are short (<30 min), administration of large volumes of isotonic fluids is difficult and not believed to offer much benefit (1).

The limitations of resuscitation with conventional fluids are even more severe in military trauma, where logistical constraints can preclude the field availability of several liters of fluid per casualty. Consequently, the past decade has seen a surge in efforts to assess the potential efficacy of small volume resuscitation with hyperosmotic-hyperoncotic solutions, recognizing their potential benefit not only in the above scenarios, but particularly in civilian or military trauma situations with significant delays transporting the hypotensive patient (2–4).

Since Velasco et al. (5) demonstrated that small volume infusion of 7.5% NaCl rapidly restored arterial pressure and cardiac output and improved survival in dogs subjected to an otherwise lethal hemorrhage, other investigators have explored the potential benefit of adding a hyperoncotic colloid, e.g., dextran or hetastarch to the hypertonic saline (HS) solution (6). The combination of hypertonic saline-dextran solution produced a greater and more sustained improvement in hemodynamics than HS alone (7).

Of these hyperosmotic/hyperoncotic solutions, one containing 7.5% NaCl/6% dextran-70 (HSD) has received the most research. A number of studies have shown HSD, at a dose of 4–6 mL/kg, to be effective in improving hemodynamics and renal function, ameliorating hormonal and metabolic disturbances, and improving survival in animal models of hemorrhagic hypotension (7–12). The optimal formulation for a small volume resuscitation solution, however, has not been established. Recent studies by Halvorsen et al. (13) and

The experimental studies of the authors described in this report were reviewed and approved by the Institutional Review Committee/Animal Care and Use Committee at Letterman Army Institute of Research and by the University of California, Davis Animal Health and Welfare Committee. The manuscript was peer reviewed for compliance prior to submission for publication. In conducting the research described here, the authors adhered to the "Guide for the Care and Use of Laboratory Animals," DHEW Publication (National Institutes of Health) 85-23.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official nor do they reflect the views of the Department of the Army or the Department of Defense (AR 360-5).

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Walsh and Kramer (14) have shown that better resuscitation was achieved with solutions containing 12% or 24% dextran-70, respectively.

The predominant physiologic response to hypertonic saline-dextran solutions is plasma volume expansion. Thus a critical analysis of the plasma volume expansion capabilities of HS alone, dextran alone, and their combination, is needed. The present study was designed to better evaluate the cardiovascular response and plasma volume expansion capabilities of .9% to 25% NaCl and 3% to 24% dextran-70 solutions infused either alone or in specific combinations at a dose of 4 mL/kg in euvolemic sheep. Although these solutions are primarily intended for use in the treatment of hypovolemia, the present study employed euvolemic animals. This allowed for the evaluation of the pure hemodynamic effects of these solutions without the compounding effects of hypotension or shock. The use of euvolemic animals also precluded justifying the validity of employing one hemorrhage model versus another, or having our results valid for only the hemorrhage model investigated.

MATERIALS AND METHODS

Animal preparation

Thirty-five female sheep weighing 40–50 kg were surgically prepared with chronic catheters in the carotid artery, the right atrium, and the pulmonary artery (Swan-Ganz) under halothane general anesthesia using aseptic conditions. Other aspects of animal preparation and husbandry were performed as previously detailed (7, 13, 14).

Study design

On the day of each study, the animal was placed in a quiet room for at least a 1 h baseline period. Sheep were then randomly infused intravenously over 2 min with the various test solutions (Table 1) at a dose of 4 mL/kg. A total of 39 experiments were performed with concentrations of NaCl ranging from .9% to 25% (n = 16), concentrations of dextran-70 (D-70) ranging from 3% to 24% in .9% NaCl (n = 15), and combination solutions (n = 8) of 7.5% NaCl/6% D-70 (HSD) and 25% NaCl/24% D-70 (SSD). Normal saline, .9% NaCl (NS), served as the control solution and the solvent for the D-70. Arterial blood samples were withdrawn prior to (baseline), 1 min into the infusion, immediately after infusion (0), and 1, 3, 5, 15, 30, and 60 min later. Withdrawn blood was replaced with an equal volume of normal saline. During the 1 h baseline period, six determinations of cardiac output (CO) were made. CO was repeated in duplicate at the above sampling times.

Physiological measurements

Hemodynamic variables were recorded every 30 min during the baseline period and continuously during and after infusion of the test solution. These variables included mean arterial pressure (MAP), heart rate, and central venous pressure. Cardiac output (CO) was measured six times during baseline and in duplicate at each time point during the study. Systemic vascular resistance (SVR) was calculated from a standard formula using MAP, central venous pressure, and CO data. Blood hematocrit was determined, and the changes in plasma volume after dextran infusions were calculated from the changes in hematocrit and the baseline measurement of blood volume using Evan's Blue dye (13). Changes in plasma volume after hypertonic saline infusions were calculated from changes in plasma protein (15).

Biochemical measurements

Plasma sodium, potassium, chloride, glucose, and protein were measured using standard laboratory methods (COBAS-FARA System; Roche Analytical Instruments, Belleville, NJ). Total plasma carbohydrate concentrations were determined by the method of Roe (16). Plasma dextran concentrations were calculated by subtracting glucose concentrations from total carbohydrate concentrations as previously described (9). Plasma free hemoglobin concentrations were determined by the method described by Fairbanks and Klee (17).

Statistical analysis

Data were statistically analyzed by analysis of variance adjusted for repeated measures with $p < .05$ accepted as the level of significance. The Newman-Keuls method of multiple comparison was employed to determine significant differences between the means. Comparisons were made among the groups infused with NaCl solutions, among the groups infused with D-70, and between the groups infused with HSD or SSD. Where appropriate, bivariate analysis was used to evaluate correlations among the treatment groups and hemodynamic variables. In addition, comparisons were made among the groups infused with HSD or SSD and their individual components. To evaluate the separate and combined effects of HS and D-70, data for changes in MAP, SVR and CO are presented for .9% and 25% NaCl and 0% and 24% D-70 in a 2 × 2 matrix.

RESULTS

Hemodynamic variables

As expected, infusion of 4 mL/kg .9% saline (NS) in euvolemic sheep had minimal effect on the baseline MAP of 88.8 ± 2.7 mmHg (Fig. 1). Infusion of 3.75% and 7.5% HS solutions did not induce >5 mmHg increase in MAP, whereas infusion of a 15% or 25% HS solution induced statistically significant increases in MAP compared with NS infusion. At 2 min after infusion of the HS solutions, a statistically significant correlation was observed between the change in MAP and the concentration of HS infused ($r = .575$; $p < .05$).

D-70 solutions ranging from 3% to 24% initially induced a nonsignificant 5–15 mmHg change in MAP over the baseline value of 85.9 ± 2.1 mmHg; levels returning to baseline by the end of the experimental period (Fig. 1). In contrast to HS, no significant correlation was observed between change in MAP and the concentration of the dextran solution infused ($r = .198$). In addition, infusion of the HS or D-70 solutions did not show any statistically significant correlations between a change in MAP and a change in heart rate ($r = .39$, $r = .15$, respectively). Infusion of 4 mL/kg HSD resulted in about a 5 mmHg increase in MAP, similar to that seen with 7.5% HS alone. The infusion of SSD produced a similar effect on MAP in comparison with both 24% D-70 and 25% HS (Table 2).

SVR was not significantly affected by NS nor the D-70 solutions in any consistent manner from baseline values of

TABLE 1. **Hypertonic saline-dextran solution infused in euvolemic sheep**

Saline concentration (%)	n	Dextran-70 concentration (%)	n	Combination solutions	n
.9%	3	3%	4	7.5% NaCl/6% Dextran-70 (HSD)	4
3.75%	3	6%	4	25% NaCl/24% Dextran-70 (SSD)	4
7.5%	3	12%	3		
15%	3	24%	4		
25%	4				

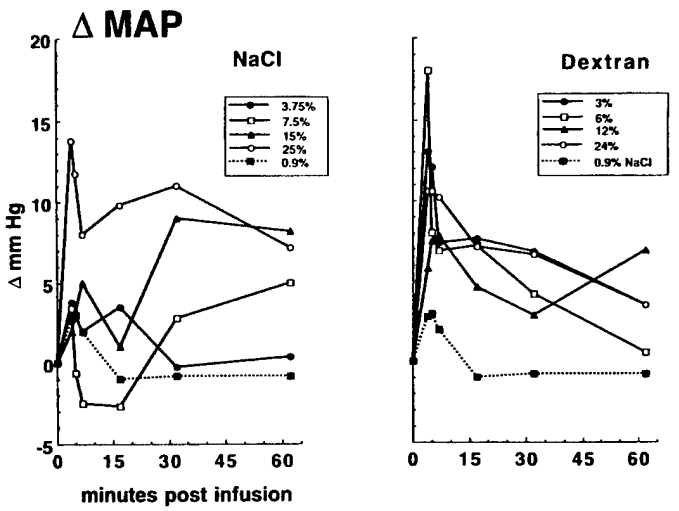

FIG. 1. **Change in mean arterial pressure following 2 min infusion of different NaCl or dextran-70 solutions in sheep.** Baseline MAPs are 88.8 ± 2.7 and 85.9 ± 2.1 mmHg in the NaCl and dextran groups, respectively. Time scale plotted from initiation of infusion. The means for three or four animals/group are plotted. Pooled S.E.M. for NaCl solutions are: .9%, 2.9; 3.75%, 1.8; 7.5%, 2.8; 15%, 2.9; 25%, 3.2. Pooled S.E.M. for D-70 solutions are: 3%, 4.4; 6%, 3.8; 12%, 1.9; 24%, 3.0.

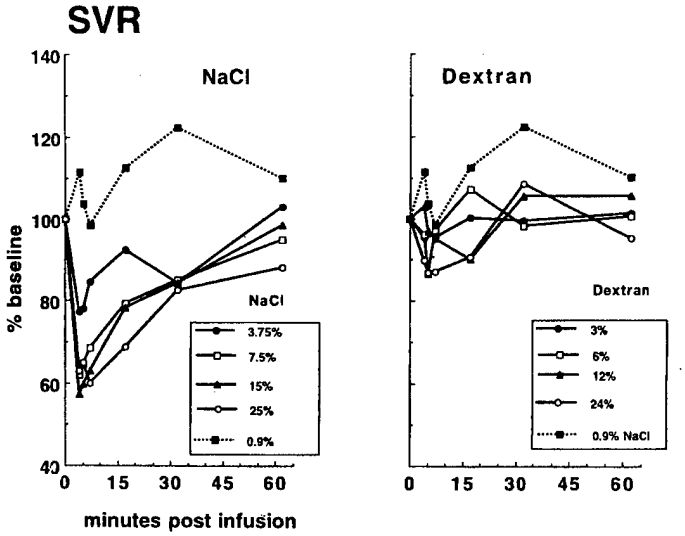

FIG. 2. **Systemic vascular resistance following infusion of NaCl or dextran-70 solutions in sheep.** Baseline SVRs are 1016 ± 88 and 1032 ± 72 dynes-s^{-1}-cm^{-5} in the NaCl and dextran groups, respectively. Time scale plotted from initiation of infusion. The means for three or four animals/group are plotted. Pooled S.E.M. for NaCl solutions are: .9%, 5.9; 3.75%, 5.1; 7.5%, 6.8; 15%, 7.1; 25%, 10.5. Pooled S.E.M. for D-70 solutions are: 3%, 4.1; 6%, 16.5; 12%, 8.8; 24%, 11.7.

TABLE 2. **Changes in cardiovascular variables at 2 min (top entry) and at 60 min (bottom entry) following infusion of NaCl solutions without or with dextran**

	Dextran	
	0%	24%
Mean arterial pressure (% baseline)		
NaCl		
25%	112 ± 2	111 ± 5
	106 ± 3	107 ± 5
.9%	103 ± 2	110 ± 3
	99 ± 3	103 ± 3
Cardiac output (% baseline)		
NaCl		
25%	169 ± 17	196 ± 6
	127 ± 8	135 ± 8
.9%	95 ± 4	121 ± 14
	90 ± 4	110 ± 13
Systemic vascular resistance (% baseline)		
NaCl		
25%	65 ± 16	57 ± 5
	88 ± 8	80 ± 8
.9%	112 ± 6	88 ± 14
	110 ± 7	95 ± 15

Data expressed as Mean ± S.E.M. for three to four animals/group. For cardiac output and systemic vascular resistance data in 25% NaCl and 25% NaCl/24% D-70 (SSD) groups are significantly different ($p < .05$) from the .9% NaCl group.

1016 ± 88 and 1032 ± 72 dynes-s^{-1}-cm^{-5} in the saline and dextran groups, respectively (Fig. 2). On the other hand, all HS solutions greater than 3.75% reduced SVR to 60% of baseline ($p < .05$) by 5 min after infusion. SVR rose to 80% of baseline at 30 min after infusion and returned toward normal by 60 min (Fig. 2).

The combination NaCl/dextran-70 solutions, HSD and SSD, did not induce effects on SVR different from those observed following infusion of 7.5% or 25% NaCl, respectively (Fig. 2, Table 2).

NS did not significantly affect CO from the baseline value of 7.0 ± .6 L/min. The 4 mL/kg dose of HS induced a rapid dose-dependent increase in CO ($r = .463$, $p < .05$ at 2 min after infusion). All HS-induced increases in CO were statistically significant compared with NS infusion. A maximum initial increase of about 80% was observed (Fig. 3), and CO remained elevated at 30% above baseline in the 25% HS group at the end of the 60 min experimental period. In contrast, at 4 mL/kg, all D-70 solutions increased CO only about 15–20% over the baseline value of 6.7 ± .5 L/min (Fig. 3) and no correlation was observed between the change in CO and the concentration of dextran infused ($r = .09$).

Infusion of HSD resulted in an increase in CO comparable to that observed after infusion of 7.5% HS (about 60% over baseline), except that the effect was more sustained. CO after HSD infusion remained above 25% over baseline at the end of the experimental period. Likewise, after infusion of SSD, the increase in CO followed the pattern observed after infusion of 25% HS (Table 2). Generally, HSD and SSD resulted in a similar increase in CO except that the initial increase peaked at a higher level (196% vs. 167% of baseline) in the SSD than HSD group.

Infusion of 4 mL/kg HS solutions induced a rapid dose-dependent expansion of plasma volume (PV), with peak expansion measured at the first post-infusion sample (Fig. 4). At 3 min after infusion of the HS solutions, PV was highly correlated to the NaCl concentration of these solutions ($r = .84$; $p < .05$), and PV expansion induced by HS solutions ≥ 7.5% was significantly greater than PV changes observed in

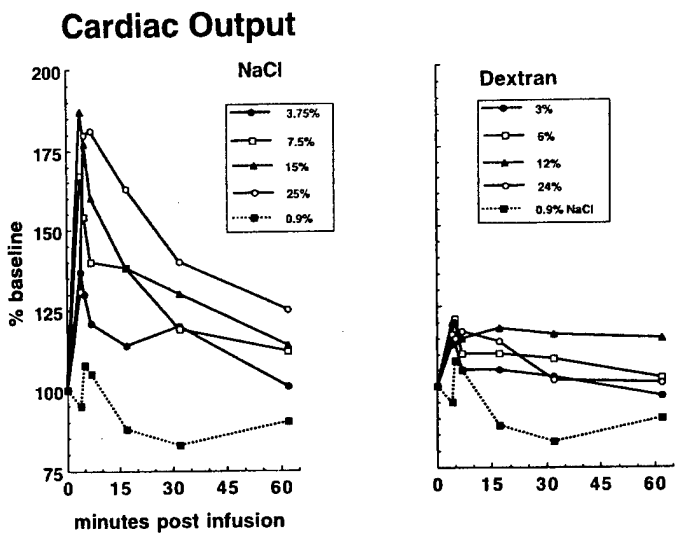

FIG. 3. **Change in cardiac output from baseline following infusion of NaCl or dextran-70 solutions in sheep.** Baseline COs are 7.0 ± .6 and 6.7 ± .5 L/min in the NaCl and dextran groups, respectively. Time scale plotted from initiation of infusion. The means for three or four animals/group are plotted. Pooled S.E.M. for NaCl solutions are: .9%, 4.2; 3.75%, 5.8; 7.5%, 6.8; 15%, 7.1; 25%, 17.2. Pooled S.E.M. for D-70 solutions are: 3%, 5.6; 6%, 16.5; 12%, 10.2; 24%, 11.9.

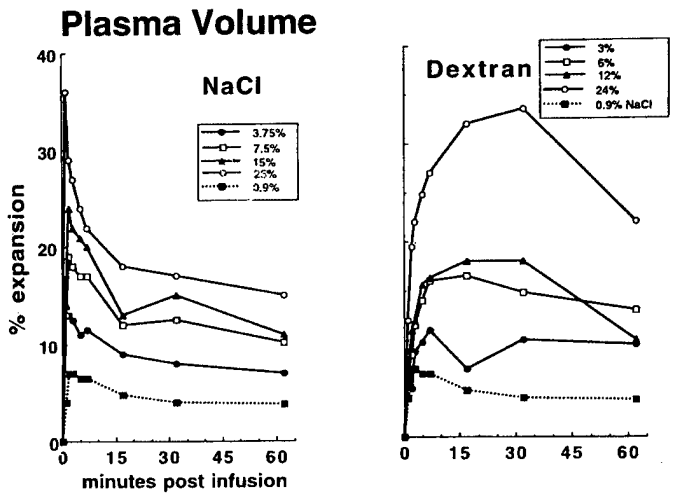

FIG. 4. **Plasma volume expansion following infusion of NaCl or dextran-70 solutions in sheep.** Time scale plotted from initiation of infusion. The means for three or four animals/group are plotted. Pooled S.E.M. for NaCl solutions are: .9%, 1.0; 3.75%, .8; 7.5%, 1.3; 15%, 2.3; 25%, 1.4. Pooled S.E.M. for D-70 solutions are: 3%, 1.7; 6%, 1.4; 12%, 2.6; 24%, 2.3.

the NS group. PV then quickly returned to near baseline levels (Fig. 4).

D-70 solutions also expanded plasma volume in a dose-dependent fashion ($r = .72$; $p < .05$), but peak expansions occurred 10–30 min after infusion, and the effects were sustained longer than observed with HS (Fig. 4). Infusion of D-70 solutions ≥ 6% resulted in significantly greater volume expansion compared with the NS group.

PV expansion was slightly greater in HSD-infused sheep than in animals infused with either 6% D-70 or 7.5% HS, alone. PV in HSD-infused sheep peaked at about 125% of baseline and remained above 120% of baseline throughout the experimental period. PV expansion was about 33 to 40% higher in SSD- than HSD-infused sheep.

Biochemical measurements

A dose-dependent increase in plasma dextran concentrations were observed throughout the experimental period in these animals (Fig. 5*A*). HSD infusion resulted in plasma dextran concentrations similar to that induced by 6% D-70 alone, whereas SSD infusion resulted in significantly lower plasma dextran concentrations than those observed following infusion of 24% D-70 (Fig. 5, *A* and *B*).

Infusion of HS solutions resulted in dose-dependent increases in plasma sodium and chloride, but no change in potassium concentrations (Fig. 6). Plasma sodium was markedly higher after infusion of 25% HS compared with the other HS or NS solutions, with peak sodium concentrations reaching about 200 mEq/L. After infusion of HSD, plasma electrolyte concentrations were similar to those observed after infusion of 7.5% HS (Table 3 and Fig. 6). Infusion of SSD increased plasma sodium and chloride concentrations as much as those seen after 25% HS infusion, but the preinfusion levels of

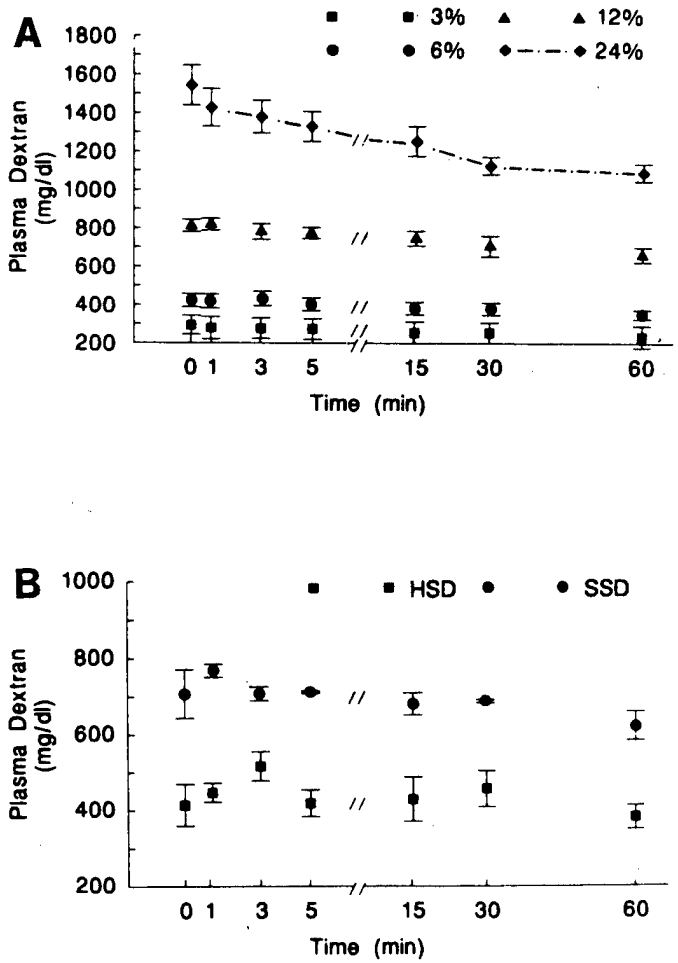

FIG. 5. **Plasma dextran concentrations following infusion of (*A*) dextran-70 solutions or (*B*) HSD or SSD in sheep.** Time scale plotted from the end of infusion. Data expressed as mean ± S.E. for three or four animals/group.

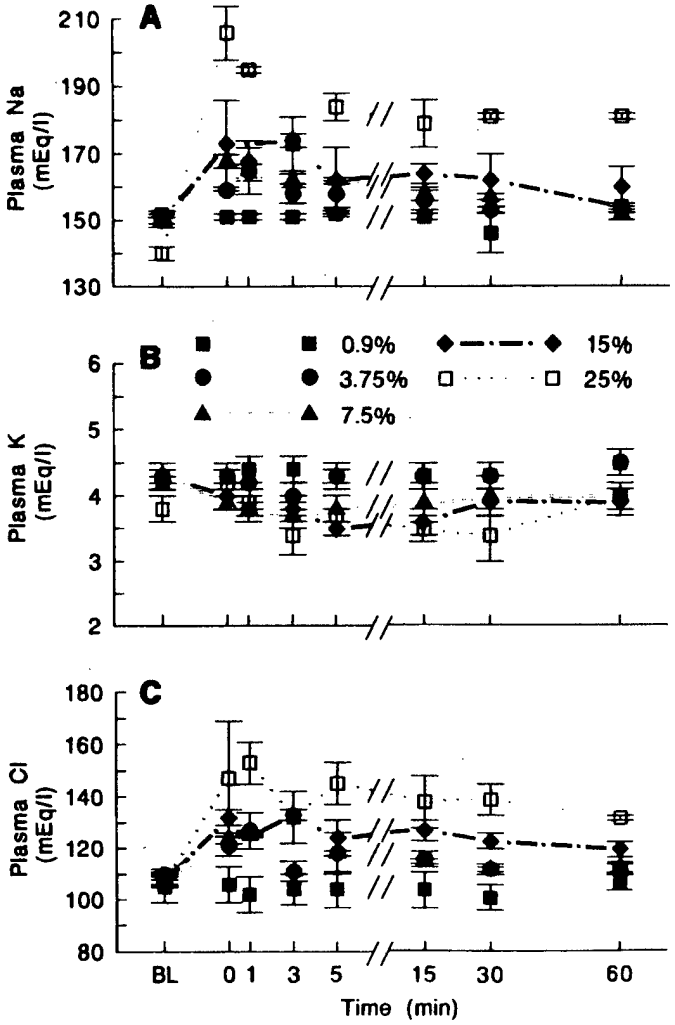

FIG. 6. **Plasma electrolyte concentrations following infusion of different NaCl solutions in sheep.** Time scale plotted from the end of infusion. Data expressed as mean ± S.E. for three or four animals/group.

sodium and chloride were lower in the SSD animals than the other groups (Table 3 and Fig. 6).

Plasma free hemoglobin concentrations were not significantly different between the NS and 3.75, 7.5, and 15% HS groups (Fig. 7*A*). Infusion of 25% HS induced a two- to threefold increase in plasma free hemoglobin concentrations (Fig. 7*A*). Infusion of 4 mL/kg HSD or SSD did not induce significant changes in plasma free hemoglobin concentrations (Fig. 7*B*).

DISCUSSION

Research over the past decade exploring the efficacy of small volume hypertonic resuscitation in both experimental animals and humans has concluded that such solutions are much more effective than isotonic crystalloid solutions on a volume-to-volume basis (1, 18). In addition, data from studies in a number of animal species suggest that a combination hypertonic saline-colloid solution is a more efficacious treatment for hypovolemic shock than either solution alone (6, 7, 19). The HS solutions draws water from the cellular compartment into the circulation, expanding plasma volume, while the colloid primarily holds the water in the vascular space, prolonging the plasma volume expansion (14).

Of the hypertonic saline-hyperoncotic colloid solutions available, the one that has received the most attention in the U.S. is HSD (7.5% NaCl/6% dextran-70) (6, 8–12). It should be recognized, however, that the initial formulation for HSD was arbitrary and the dose of 4 mL/kg was selected as a single dose which induced only modest hypernatremia (14, 19). Few studies have addressed the dose-response effects of HS or D-70 solutions or their possible synergistic combinations to evaluate optimal concentrations of the HS and D-70 components.

The present study clearly indicates an initial dose-dependent effect of HS on MAP, CO, and PV expansion in euvolemic sheep. However, the early (2 min postinfusion) dose-dependent effect of HS on MAP was only maintained with HS solutions of 15% and 25%, possibly due to HS-induced increased cardiac contractility (20). The lack of a sustained increase in MAP after infusion of 3.75% and 7.5% HS, also observed following HSD infusion in euvolemic swine (9), is probably due to the decrease in SVR since hyperosmolality has a direct vasodilatory effect on vascular smooth muscle (21). In hemorrhaged, hypotensive animals, a similar vasodilatory effect of HS and HSD on SVR has been reported (18, 19), although, in these animals, blood pressure increased toward prehemorrhaged levels. It should be stressed, however, that increased CO and PV expansion are more desirable than direct increases in MAP in resuscitation of hypovolemic trauma, because increased MAP may induce increased uncontrolled internal bleeding (22).

The present physiological data indicated that HS and D-70 expanded PV in a dose-dependent manner. Although the magnitude of PV expansion determined in the present study is less than that reported following the administration of D-70 solutions to hemorrhaged animals (6, 7), the data are consistent with previous observations in euvolemic animals (9, 23, 24). D-70 infusion did not induce a consistent increase in MAP, but similar increases in CO were induced and maintained throughout the experimental period with all doses of D-70. Again, this may relate to the present study being performed in euvolemic animals. As opposed to HS, the PV increases with D-70 were slower to peak, with maximum values achieved after 15–30 min. Peak PV after HS infusion was achieved immediately, but PV expansion was sustained better with D-70 than HS. These data show how a combination of 7.5% HS with D-70 could potentially achieve near immediate and sustained PV expansion and augmented CO.

To further address the optimal concentrations of HS and D-70, the present study also examined formulations in which HS and D-70 were combined (HSD and SSD). Both of these solutions have been investigated experimentally as small volume resuscitation solutions for the treatment of hypovolemia. HSD has been studied the most and has been found to effectively improve hemodynamic stability, improve organ perfusion, and correct metabolic abnormalities associated with animal models of hemorrhagic hypotension (11, 12, 25, 26). In the few studies in which SSD has been evaluated, it has been as effective as HSD when administered at lower doses (approxi-

TABLE 3. **Plasma electrolytes in sheep infused with HSD or SSD***

Time (min)	Sodium (mEq/L)		Potassium (mEq/L)		Chloride (mEq/L)	
	HSD	SSD	HSD	SSD	HSD	SSD
Baseline	150 ± 1	138 ± 10	4.3 ± 0.1	3.9 ± 0.4	107 ± 2	105 ± 4
0	168 ± 3‡	188 ± 5‡	4.0 ± 0.1	4.0 ± 0.1	124 ± 2‡	120 ± 5
1	161 ± 2‡	170 ± 3	3.8 ± 0.1	3.7 ± 0.2	112 ± 3	130 ± 2‡
3	158 ± 1‡	167 ± 7	3.8 ± 0.2	3.6 ± 0.2	120 ± 3	128 ± 5
5	158 ± 2	176 ± 16	3.9 ± 0.2	3.7 ± 0.4	119 ± 3	122 ± 1
15	157 ± 2	167 ± 2	4.0 ± 0.2	3.7 ± 0.1	117 ± 4	127 ± 5
30	155 ± 1	164 ± 9	4.1 ± 0.2	3.8 ± 0.2	114 ± 3	124 ± 7
60	155 ± 2	158 ± 7	4.1 ± 0.2	3.8 ± 0.1	113 ± 4	118 ± 6

* Data expressed as mean ± S.E. for three to four animals/group.
‡ $p < .05$ from baseline.

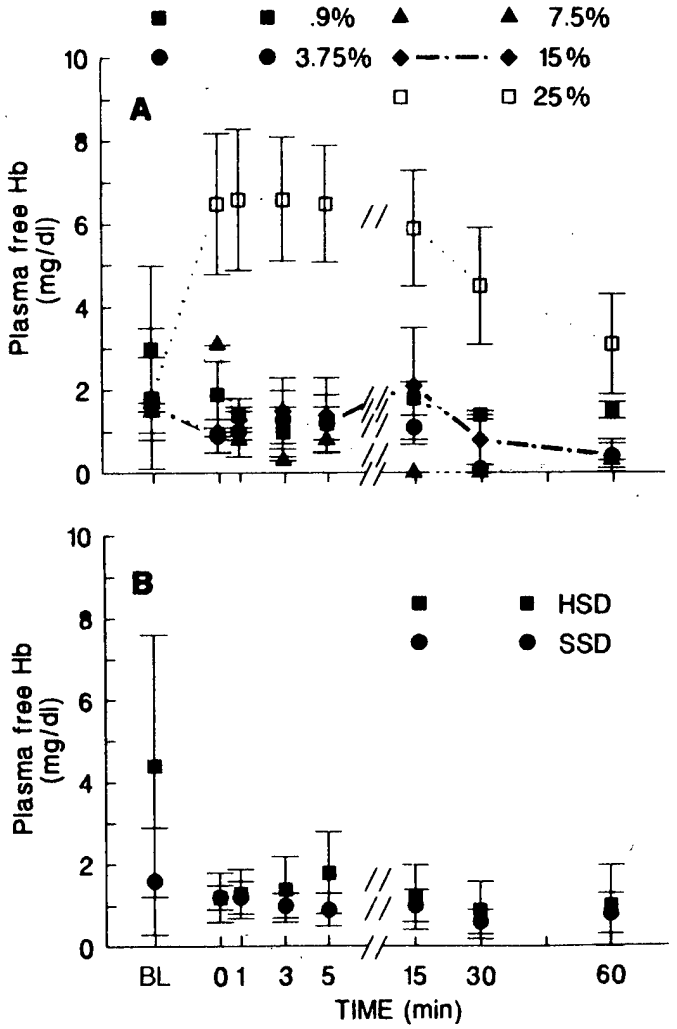

FIG. 7. **Plasma free hemoglobin concentrations following infusion of (*A*) NaCl solutions or (*B*) HSD or SSD in sheep.** Data expressed as mean ± S.E. for three or four animals/group.

mately 1.2 mL/kg) than those currently evaluated with HSD (4–6 mL/kg) (27, 28). In the present study, the effects of HSD and SSD on plasma volume expansion reflected the initial HS-induced expansion with the maintained D-70-induced expansion. It appeared that, for HSD and SSD, the effects on CO reflected the HS component of the solution, with only a small contribution from the D-70 component.

A major factor in selecting the optimal HS/D-70 combination solution addresses concerns regarding the safety of such solutions. In the present study a dose-dependent increase in plasma sodium and chloride was observed following infusion of HS solutions. Although, as expected, the concentration of these electrolytes was significantly higher than that observed following infusion of NS, the plasma concentrations in the 3.75% and 7.5% HS groups were not significantly different from each other. Importantly, these concentrations were consistent with previous studies in experimental animals and have not been associated with any overt behavioral effects or serious metabolic acidosis (29, 30). In general, the increase in plasma sodium and chloride concentrations in the HSD and SSD groups was similar to those observed in the 7.5% and 25% HS groups. Differences in peak sodium and chloride concentrations between the SSD and 25% HS groups reflect lower baseline concentrations in the SSD group.

In addition, the present study also showed a dose-dependent increase in plasma dextran concentrations. Previous studies with HSD did not observe any detrimental effects on blood coagulation or blood typing (23, 31, 32), or serum aminotransferase activity (29). The plasma concentrations of dextran following infusion of 6% D-70 or HSD in the present study, are consistent with previously published plasma concentrations following HSD infusion (9, 24). The plasma concentrations of dextran after infusion of 4 mL/kg 24% D-70 exceed 1200 mg/dL, concentrations previously shown to be associated with *in vitro* disturbances in prothrombin time and platelet aggregation (31) as well as elevated activity of serum aminotransferases and alkaline phosphatase (29). Plasma dextran concentrations following SSD infusion were significantly less than those observed following 24% D-70 infusion. This probably reflects a dilutional effect induced by greater PV expansion in the SSD than the 24% D-70 group.

Previous studies have raised concern over infusion of hypertonic saline solutions with sodium concentrations equal to or exceeding 15%, particularly with respect to the potential for red blood cell hemolysis. Roche e Silva et al. (33) reported marked increases in plasma free hemoglobin after infusion of 15% HS in dogs. However, in recent studies using SSD in pigs (28) or sheep (34), infusion of SSD or HS, alone or in concentrations as high as 25%, caused only small and not clinically significant increases in plasma free hemoglobin. The present study in sheep also reflected a low level of hemolysis, although the plasma concentrations of free hemoglobin were significantly higher in the 25% HS group than in any other

group, including the SSD group. In addition, Moore et al. (32) observed that when HSD was incubated *in vitro* with human blood at a ratio of 1:5, no significant red cell lysis was observed with fresh blood and only minimal lysis was observed with stored blood. Taken together, these studies suggest that therapeutic doses of HS/D-70 solutions will induce minimal hemolysis of human red cells (32).

In addition to HSD, 7.2% NaCl/10% dextran-60 (35), 7.5% NaCl/12% dextran-70 (13), and 7.5% NaCl/24% dextran-70 solutions (14) have been investigated for their efficacy in resuscitation from hypovolemia. These studies suggest that better resuscitative capabilities may be achieved by increasing the colloid concentration of the solution. A higher colloid concentration combined with 7.5% NaCl may allow the effective dose to be lowered, minimizing any potential hypernatremia. It has also been proposed that sustained resuscitation can be achieved by an initial infusion of 4 mL/kg HSD followed by an infusion of 6% D-70 as needed (13).

In conclusion, infusion of combinations of HS and D-70 derives maximum physiological benefit from both components. The predominant effects of both HS and D-70 are dose-related plasma volume expansion and increased cardiac output, with the effects of HS being more rapid and those of dextran more sustained. In general, the effects of HS and D-70 on CO and SVR are at least additive, although synergistic effects are not completely ruled out. The currently advocated dose of 4 mL/kg HSD is effective with relatively modest, and clinically unimportant, increases in plasma electrolyte concentrations. The same volume (4 mL/kg) with concentrations of HS greater than 7.5% (10% or higher (13)), increase plasma sodium to levels which raise clinical concerns. The data suggest similar physiological effects can be achieved with lower doses of HS and higher doses of D-70. As previously shown, however, even a near saturated solution such as SSD can be administered safely when the total dose or volume is adjusted to deliver similar dextran and sodium loads as for HSD (14, 28).

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