

Systemic and renal haemodynamic effects of fluid bolus therapy: sodium chloride versus sodium octanoate-balanced solution

Lu Ke, Paolo Calzavacca, Michael Bailey, Clive N May, Wei-qin Li, Joseph Bertolini and Rinaldo Bellomo

Fluid resuscitation is common in critically ill patients. Sodium chloride at 0.9%, or so-called "normal saline" (NS), remains the most commonly prescribed crystalloid solution, despite its non-physiological chloride content.¹⁻³ Its rapid infusion has been associated with adverse effects on renal blood flow (RBF) and function.⁴⁻⁶ In volunteers, magnetic resonance imaging over 30 minutes showed decreased velocity of RBF and decreased renal cortical tissue perfusion with NS compared with Plasma-Lyte 148 (a balanced solution).⁴

Until now, however, no study has measured the effect of a bolus of NS or balanced solution on RBF over several hours. This makes it difficult to estimate the overall magnitude and duration of their effects on renal perfusion. In this experimental study, we compared the systemic haemodynamic, RBF and volume expansion effects of NS with those of a physiological chloride solution containing sodium octanoate as the additional anion. We hypothesised that the chloride-physiological sodium octanoate solution would maintain or increase RBF more than would an equivalent amount of NS.

Methods

Animal preparation

This study was approved by the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health. Experiments were performed on eight conscious adult Merino ewes each housed in an individual metabolic cage.

All sheep underwent two surgical procedures separated by at least 2 weeks.⁷ Anaesthesia was induced by intravenous thiopental sodium (15 mg/kg) and, after intubation, was maintained with 1.5%–2.0% isoflurane in oxygen. In the first surgery, sheep were prepared with a carotid arterial loop to allow subsequent easy arterial cannulation and a 20 mm flow probe (Transonic Systems) was implanted around the pulmonary artery. In the second operation, a 4 mm flow probe was implanted around the left renal artery for measuring RBF. In all operations, animals were treated with intramuscular procaine penicillin (Troy Laboratories). Postsurgical analgesia was maintained with intramuscular injection of flunixin meglumine (1 mg/kg; Troy Laboratories).

ABSTRACT

Background: Solutions with high chloride concentrations, like normal saline (NS), may adversely affect renal blood flow (RBF). We compared the systemic and renal haemodynamic effects of a bolus of NS with those of a novel isotonic solution containing a physiological concentration of chloride and sodium octanoate (SOct) in healthy conscious sheep.

Methods: We performed an experimental double-blind cross-over animal study. After chronic pulmonary and renal artery flow probe insertion, animals were randomly assigned to receive rapid intravenous infusion (1 L over 30 minutes) of either NS or SOct. Haemodynamic parameters were recorded continuously before and after treatment.

Results: NS and SOct had similar dilutional effects on the haematocrit. Both induced a short-lived increase in cardiac output (CO) and total peripheral conductance which dissipated by 60 minutes. However, SOct increased RBF more than NS (peak values, 213.4 ± 34.3 mL/min v 179.3 ± 35.6 mL/min; $P < 0.001$) with a greater RBF/CO ratio (peak values, $12.2\% \pm 3.7\%$ v $10.6\% \pm 3.6\%$; $P < 0.001$).

Conclusions: NS and SOct appear to have similar systemic haemodynamic effects. However, OS significantly increases RBF compared with normal saline.

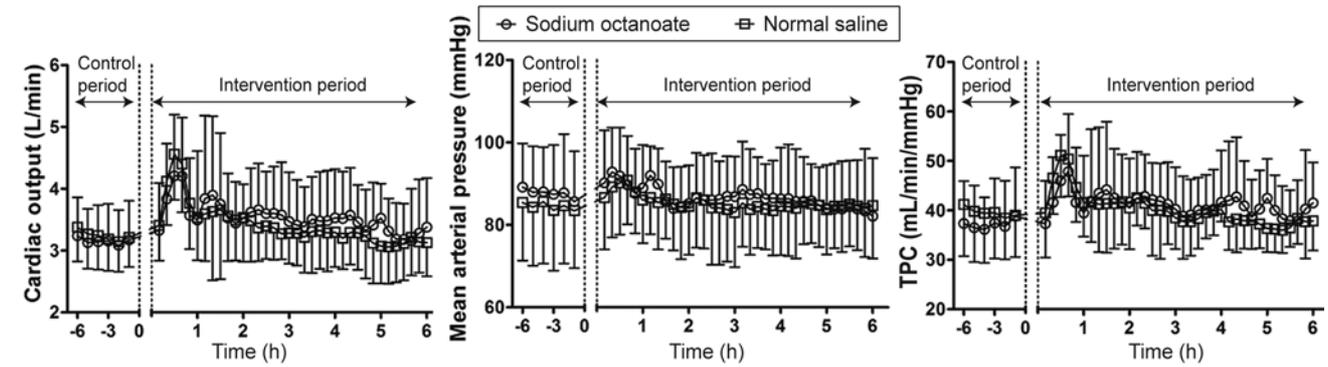
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Experiments were started no sooner than 2 weeks after surgery. On the day before the experiment, an arterial Tygon catheter and two external jugular venous polythene catheters were inserted for blood sampling and fluid infusion, respectively.

Experimental protocol

Animals were randomly assigned to infusion with either sodium octanoate (SOct; 150 mmol sodium, 100 mmol chloride and 50 mmol octanoate) or NS (150 mmol sodium and 150 mmol chloride). The solutions were provided by CSL Behring and blinding was achieved by covering the fluids with an opaque black bag. Assignment was by

Figure 1. Cardiac output, mean arterial pressure and total peripheral conductance with sodium octanoate solution or normal saline fluid boluses during the observation period



TPC = total peripheral conductance.

Baseline data were collected during a 6-hour control period and a 6-hour intervention period in eight conscious sheep. Results are presented as means \pm SDs.

Table 1. Haematocrit levels during fluid therapy with normal saline or sodium octanoate solution*

Time (hours)	Haematocrit level	
	Sodium octanoate	Normal saline
0	30.9% \pm 4.6%	29.3% \pm 5.4%
0.5	27.3% \pm 4.1%	25.6% \pm 4.9%
1	27.0% \pm 4.4%	26.0% \pm 3.8%
2	26.1% \pm 3.1%	26.1% \pm 2.9%
4	26.3% \pm 2.8%	26.6% \pm 3.9%
6	26.3% \pm 2.8%	24.8% \pm 4.2%

* Values expressed as means with standard error. Comparison by analysis of variance.

random allocation and concealed. The following day at the same time, each animal was assigned to the other fluid in a crossover design, with those first assigned to NS receiving SOct the next day and those first assigned to SOct receiving NS the next day.

After baseline measurements, animals received a rapid intravenous infusion of 1000 mL of trial solution over 30 minutes. Data from the flow probes were collected continuously with flow meters (Transonic Systems). Analogue signals of mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), central venous pressure (CVP) and RBF were collected by a computer with a customised data-acquisition system (LabView, National Instruments) as previously described.⁷ Stroke volume (SV; calculated as CO/HR), fraction of CO delivered to the kidney (Fraction; calculated as RBF*2/CO), total peripheral conductance (TPC; calculated as CO/MAP) and renal vascular conductance (RVC;

calculated as RBF/MAP; conductance is the reciprocal value of resistance) were calculated accordingly.

Statistical analysis

To ascertain if the effect on renal parameters of NS was significantly different from that of SOct over the 6-hour period, we performed repeated measures analysis of variance (RM-ANOVA). To determine if treatment effects differed over time, an interaction between treatment and time was fitted using the PROC Mixed procedure in SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA) with each sheep treated as random effects. Eight haemodynamic outcome variables were considered (CO, HR, MAP, TPC, SV, Fraction, RBF and RVC) allowing eight models of response to be constructed. To account for multiple outcomes and to further increase robustness, a two-sided *P* value of <0.01 was used to indicate statistical significance.

Results

The sheep we studied had an average weight of 33.2 kg (range, 26–40 kg). After fluid bolus administration, there was no statistical difference in haematocrit levels over the course of SOct or NS infusion (Table 1).

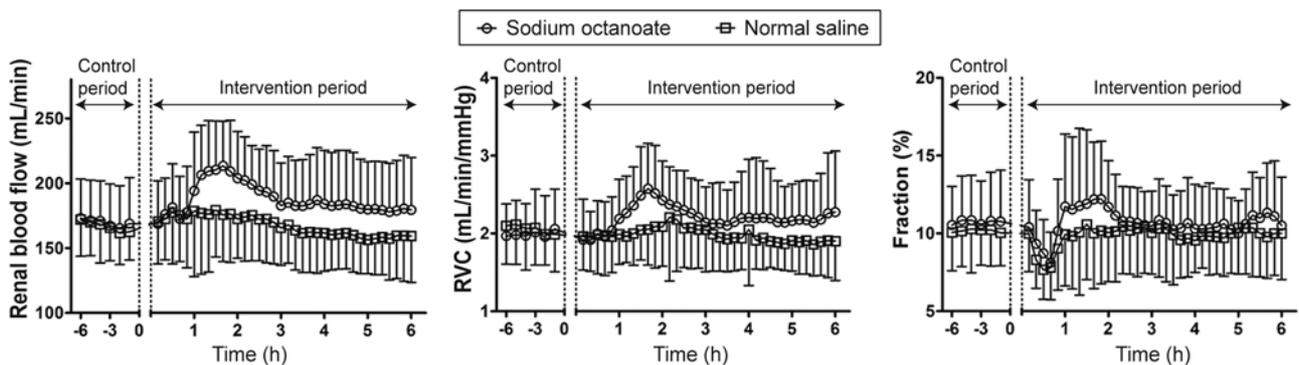
Systemic haemodynamic parameters

Rapid fluid infusion led to similar transient increases in CO in both groups, with peak levels at the end of the infusion (Figure 1, Table 2) and return to baseline values within 60 minutes. Compared with baseline, the CO overall increase in the SOct group persisted for longer and was statistically significant (*P*<0.001) (Figure 1). Stroke volume and HR

Table 2. Differences from baseline (DFB) in systemic haemodynamic profiles with sodium octanoate solution or normal saline fluid boluses

Variable	Sodium octanoate			Normal saline		
	DFB	SE	<i>P</i>	DFB	SE	<i>P</i>
CO (L/min)	0.29	0.77	<0.001	0.08	0.77	0.015
MAP (mmHg)	-1.54	1.67	0.138	-0.61	1.67	0.853
TPC (mL/min/mmHg)	3.37	1.68	<0.001	0.16	1.68	0.074
SV (mL)	2.81	0.13	0.041	1.30	0.13	0.345
HR (beats/min)	3.61	1.62	0.003	-0.87	1.62	0.304
RBF (mL/min)	13.70	10.21	<0.001	-5.28	10.21	0.828
RVC (mL/min/mmHg)	0.18	0.12	<0.001	-0.11	0.12	0.460
Fraction (%)	-0.07	0.03	0.835	-0.34	0.03	0.285

CO = cardiac output. Fraction = $RBF \times 2 / CO$. HR = heart rate. MAP = mean arterial pressure. RBF = renal blood flow. RVC = renal vascular conductance. SE = standard error. SV = stroke volume. TPC = total peripheral conductance.

Figure 2. Renal blood flow, renal vascular conductance and fraction of cardiac output delivered to the kidney during the observation period according to fluid therapy with sodium octanoate solution or normal saline

Baseline data were collected during a 6-hour control period and a 6-hour intervention period in eight conscious sheep. Results are presented as means \pm SDs.

were similar, and only TPC in the SOct group increased significantly from baseline (Table 2).

Renal haemodynamics

RBF increased from baseline only in the SOct group, reaching a maximum of 213.4 ± 34.3 mL/min at about 100 minutes after the start of infusion (Figure 2). This was associated with a similar simultaneous increase in RVC (peak value at 2.58 ± 0.58 mL/min/mmHg). The fraction of CO delivered to the kidney did not change significantly from the baseline in either the SOct or NS groups (Figure 2).

RBF and RVC were significantly ($P < 0.001$) and persistently higher after SOct (Figure 2). Renal haemodynamic changes were different from systemic haemodynamic changes, with separation developing between the two

groups after 60 minutes, reaching a peak effect at about 2 hours followed by a sustained difference for up to 6 hours.

Discussion

Key findings

In comparing the systemic and renal haemodynamic effects of a fluid bolus of a novel balanced solution containing SOct as buffer and a physiological (100 mmol/L) chloride concentration with those of NS, we found similar systemic haemodynamic effects, but different renal haemodynamic effects. SOct induced an early and sustained increase in RBF and RVC. In contrast, despite producing a similar increase in CO and a decrease in TPC, NS was associated with no change in RBF.

Relationship with previous studies

Previous human and animal studies have found that intravenous infusion of NS can result in a short-lived reduction of global RBF,⁶ renal cortical tissue perfusion⁴ and glomerular filtration rate,⁸ and changes in RVC⁸ and renin activity.⁹ None of these studies, however, measured the effects of NS continuously, and over several hours, with highly accurate transit-time flow probes. In our study, we found that the rapid infusion of a solution with a physiological concentration of chloride (SOct) has different and more favourable effects on RBF and RVC compared with NS. Our findings are consistent with and add to the literature showing that balanced solutions (with the addition of SOct in this case) affect RBF differently from NS.

Excess chloride administration associated with NS may explain the differential effect on renal haemodynamics compared with chloride physiological solutions,¹⁰ possibly triggered by tubuloglomerular feedback and macula densa-induced mesangial contraction⁵ or increased renal vascular responsiveness to angiotensin II.¹¹ Moreover, NS is associated with longer time to first micturition¹² and less urine output compared with balanced solutions.¹³ Finally, in patients undergoing renal transplantation, NS lowered postsurgical urine output, induced metabolic acidosis and reduced creatinine clearance.¹⁴

Octanoate or octanoic acid is also known as caprilate or caprylic acid. It is an 8-carbon saturated fatty acid (C₈H₁₆O₂). It has a pKa of 4.9. Due to its relatively short chain length, it penetrates fatty cell wall membranes, and has some effectiveness in combating certain lipid-coated bacteria, such as *Staphylococcus aureus* and various species of *Streptococcus*. It is used as a food contact surface sanitiser and disinfectant. The octanoic acid breath test is used to measure gastric emptying. Balanced octanoate-containing solutions for infusion are not commercially available, but octanoate (6 mmol/L) is already a component of some commercial albumin solutions.¹⁵

Implications for clinicians

Our study provides further evidence that alternative balanced solutions can maintain better RBF than NS. Replacement of excess chloride with octanoate led to improved RBF in the same way as replacement with lactate, acetate and gluconate had in previous experiments. Our results do not support the use of NS boluses during fluid resuscitation, especially in patients at risk of acute kidney injury. They also suggest that the differing RBF effects of NS compared with balanced solutions may not be secondary to the specific anions in such solutions (lactate, gluconate, acetate, and now octanoate) but rather represent a property of excess chloride.

Strengths and limitations

Our study has several strengths. It is a double-blind randomised controlled trial with a crossover design to decrease the confounding effect of animal-to-animal biological variability. In addition, we compared the effects of NS with those of a novel solution containing an anion currently used as an additive in some commercial albumin preparations.¹⁵ We also measured CO and RBF with each heart beat using highly accurate chronically placed transit-time flow probes. Thus, the accuracy of our measurements and their reproducibility is high.

Our study was, however, confined to assessing the systemic and renal haemodynamic effects of the study solutions over 6 hours. Thus, we can make no comments on urinary output, creatinine clearance, biomarkers,^{16,17} sodium retention,^{18,19} or other physiological implications of the two fluids or on longer-term haemodynamic changes with additional fluid boluses.

Conclusions

A chloride-physiological sodium octanoate solution led to an early and sustained increase in RBF and renal vasodilatation, while NS had no effects. These observations provide yet more evidence that chloride-physiological solutions have more favourable renal haemodynamic effect than NS.

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Author details

Lu Ke, Research Fellow, Cardiovascular Physiology Laboratory¹
 Paolo Calzavacca, PhD Fellow, Cardiovascular Physiology Laboratory¹
 Michael Bailey, Biostatistician²
 Clive N May, Head, Cardiovascular Physiology Laboratory¹
 Wei-qin Li, Head³
 Joseph Bertolini, Research Scientist⁴
 Rinaldo Bellomo, Co-Director²

1 Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC, Australia.

2 Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia.

3 Surgical Intensive Care Unit, Department of General Surgery, Jinling Hospital, Nanjing, China.

4 CSL Behring, Melbourne, VIC, Australia.

Correspondence: rinaldo.bellomo@austin.org.au

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