TREATMENT OF REFRACTORY HYPOVOLÆMIC SHOCK BY 7·5% SODIUM CHLORIDE INJECTIONS

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Summary Injections of hyperosmotic (7·5%) sodium chloride (100–400 ml) were given to 12 patients in terminal hypovolæmic shock who had not responded to vigorous volume replacement and corticosteroid and dopamine infusions. Hyperosmotic sodium chloride promptly reversed the shock in 11 of these patients. The immediate effects of the NaCl injections were a moderate rise in arterial pressure, the resumption of urine flow, and recovery of consciousness. These effects tended to persist for a few hours. The hyperosmotic infusion also reduced isosmotic fluid requirement by 90%.

Introduction

WHEN shock is prolonged it can become intractable, especially when it ceases to respond to adequate volume replacement combined with corticosteroid and vasoactive drug therapy; in these circumstances, death is very probable. The use of hyperosmotic crystalloid injections in the treatment of severe hæmorrhagic shock is not new;[1] solutions of glucose, NaCl, or mannitol, at concentrations around 600 mmol/l have been extensively used as adjuvants in the treatment of shock, with encouraging results.[2-4] Studies of the use of intravenous injections of $NaHCO_3$, or NaCl, at 1800 mmol/l, have shown significant, but transient, hæmodynamic effects.[5, 6]

Severe hæmorrhagic shock (42% blood loss) produced under rigidly controlled laboratory conditions in dogs can always be reversed by small amounts of 2400 mmol/l NaCl given intravenously as sole treatment.[7,8] Recovery is dramatic and the hæmodynamic effects are permanent; cardiac output recovers to pre-hæmorrhage levels, mesenteric flow overshoots resting levels by at least 50%, mean and pulse arterial pressures return towards normal levels, and heart rate slows down; urine flow resumes and the acid-base equilibrium, which tends to severe metabolic acidosis after blood loss, is gradually restored.

In view of these highly encouraging findings, we decided to study the effects of 7·5% NaCl (2400 mmol/l) injections on patients in terminal, refractory, hypovolæmic shock.

Patients and Methods

Patients

Subjects were 12 consecutive patients (table I) admitted to the intensive care unit of the Hospital do Servidor Público do Estado de São Paulo in refractory hypovolæmic shock during June, 1979, to May, 1980. Hypovolæmic shock was characterised by: (1) fluid loss; (2) arterial hypotension, with a radial systolic pressure of $\leqslant$ 70 mm Hg, inaudible Korotkoff sounds, and diastolic pressure that could not be measured; (3) low central venous pressure; (4) tachycardia; (5) cold limbs; (6) very poor urine flow (8 ml/h in 1 patient, zero in all others); and (7) metabolic acidosis, with raised plasma lactic acid. Respiratory insufficiency ($P_{O_2} < 50$ mm Hg; $P_{CO_2} > 50$ mm Hg; 5 l/min air flow through mask) was also present in 4 of these patients. Patients entered the study when they had been in shock for at least 5 h despite volume replacement and corticosteroid and dopamine infusions. Only 2 patients had been in shock for the minimum time of 5 h; all others had been in shock for considerably longer (up to 22 h). Fluids given before hyperosmotic treatment included glucose, saline, Ringer lactate, and low molecular weight dextran in every case; whole blood was given to all who had lost blood. The saline fluids were given after hyperosmotic treatment; red cells were given to keep the hæmatocrit around 32%.

Procedure

Routine care in the intensive-care unit included continuous monitoring of the electrocardiogram, central venous pressure

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TABLE I—CAUSE OF SHOCK AND OUTCOME OF TREATMENT

Case	Age	Sex	Underlying disease	Ætiology of shock	Outcome
1	45	M	··	Traumatic, due to accident, with ruptured liver, hæmatomas, and femoral fracture	Death
2	27	M	Chronic alcoholism	Acute pancreatitis	Discharge
3	39	F	··	Acute non-infectious gastroenteritis	Discharge
4	39	F	··	Post-cæsarean uterine hæmorrhage	Discharge
5	72	F	Atherosclerosis; iliac artery thrombosis	Post-surgical hæmorrhage (aortic-femoral arterial graft)	Discharge
6	76	M	Prostatic adenocarcinoma	Acute enterocolitis	Death
7	76	F	Diabetes mellitus; hypertension	Acute enterocolitis	Death
8	21	F	··	Postpartum uterine hæmorrhage	Discharge
9	35	M	Hepatic fibrosis	Oesophageal hæmorrhage	Discharge
10	68	M	··	Acute enterocolitis	Discharge
11	65	F	··	Acute enterocolitis	Discharge
12*	24	M	Hepatic fibrosis	Oesophageal hæmorrhage	Discharge Discharge

*Case 12 was treated at Hospital das Clinicas da Universidade de São Paulo with a single injection of 200 ml glucose 50%

determinations through a right atrial catheter (fluid level reading, taking the mid-axillary line as reference level for zero pressure), and urine collection via a catheter. Blood pressure was measured with an aneroid sphygmomanometer; in the absence of audible Korotkoff sounds, systolic pressure was estimated by palpation of the radial pulse. Serial determinations of pH, blood gases, hæmatocrit, hæmoglobin, glucose, lactic acid, urea, creatinine, Na^+, K^+, and Cl^-, were routinely performed. Patients selected for treatment with hyperosmotic injections were given intravenous injections of 7·5% NaCl solutions, pre-heated to 37°C. Injections were given in 50 ml portions, over 3-5 min; they were repeated at 10-15 min intervals. The total volume given ranged from 100 ml, in 30 min, to 400 ml, in 4 h (average, 200 ml in 1 h). After hyperosmotic NaCl, isosmotic fluid infusion was given to maintain normal levels of arterial pressure, central venous pressure, heart-rate, and urine flow.

Results

Shock was reversed in 11 out of the 12 patients, 9 of whom were ultimately discharged from hospital. The immediate effects of hyperosmotic treatment were a rise in arterial pressure, the resumption of urine flow, and an improvement in the level of consciousness (table II). Central venous pressure and heart rate remained unaltered. Long-term effects consisted of a further and sustained increase in arterial pressure, a rise of central venous pressure, and a fall in heart-rate. After the administration of an average 200 ml of 7·5% NaCl isosmotic fluid requirements dropped from 860 ml/h to 90 ml/h, an 89·5% reduction. No consistent or important variations in plasma Na^+ were observed.

3 patients died. 1 of them, case 7, never recovered from shock and died 16 h after hyperosmotic NaCl. 2 others recovered from shock, but died 38 h (case 1) and 60 h (case 6) later. Case 1 was given hyperosmotic fluid 8 h after a successful recovery from a cardiac arrest. His hæmodynamic variables improved, but urine flow did not. He was dialyzed, but this was followed by cardiorespiratory collapse. At recovery there was bilateral rupture of the kidneys. Case 6, who had prostatic carcinoma with pulmonary metastases, completely recovered from shock but died with clinical signs of pulmonary embolism.

TABLE II—IMMEDIATE AND DELAYED EFFECTS OF HYPEROSMOTIC SALINE INFUSION

Variable	Immediately before infusion	30 min after infusion	3-10 h after infusion
Systolic pressure (mm Hg)	47 ± 8	84 ± 10†	116 ± 4†
Diastolic pressure (mm Hg)	··	51 ± 6	74 ± 4†
Heart-rate (beats/min)	109 ± 5	106 ± 9‡	91 ± 6†
Central venous pressure (cm H_2O)	5 ± 1	7 ± 1‡	9 ± 2†
Plasma Na^+ (mmol/l)	134 ± 3	··	137 ± 1‡
Isosmotic fluid administration (ml/h)	860 ± 140	··	90 ± 14†
Hours since treatment for shock started	10 ± 3	··	23 ± 1
Urine flow (ml/h)	3 ± 2	··	100 ± 23†

Values given are mean ± standard deviations (n = 11)
*Values given are stable values, achieved 3-10 h after infusion
†$p \leqslant 0{\cdot}01$ compared with values before infusion (paired t test)
‡$p \geqslant 0{\cdot}1$ compared with values before infusion (paired t test)

9 patients were discharged from the intensive-care unit 3-5 days after the administration of hyperosmotic NaCl, and were later discharged from hospital. In case 5 hæmorrhagic shock following major surgery and lasting 5 h was completely reversed by 200 ml of NaCl 7·5% given over 40 min. Over the next 14 days, however, blood-pressure could only be maintained with intravenous dopamine, despite various attempts to remove the dependence: digitalis derivatives, inosine, sodium-nitroprussiate, isosorbitol trinitrate were tried sequentially or in various combinations, to no avail. On the 14th day after hyperosmotic NaCl the dopamine drip was interrupted for a 10 min test. Hypotension resulted. Immediate treatment with 200 ml 7·5% NaCl restored circulatory function, and the dependence on dopamine disappeared. The patient was discharged from intensive care 5 days later, and from hospital 20 days after that.

Discussion

The use of hyperosmotic infusions for the treatment of hypovolæmic shock is not entirely new and is based on the fact that such infusions cause an increase in myocardial contractility and efficiency,[9] as well as widespread precapillary dilation.[10] It has also been generally assumed that such infusions effect compartmental redistribution by osmotically shifting fluid into the blood vessels. The concentrations of hyperosmotic infusions tested in hypovolæmic patients has been around 600 mmol/l: such infusions produce very slight effects in themselves, but clearly enhance the vascular response to simultaneously infused blood, or other adequate volume expanders.[2-4, 11] In laboratory animals infusions of 1800 mmol/l have produced important hæmodynamic effects, ascribed to increased myocardial contractility, pre-capillary dilation, and fluid shift.[5, 6] The hæmodynamic effects tend to fade in minutes. We found that a concentration of NaCl of 2400 mmol/l produced the same general hæmodynamic response, but the response is more intense and lasts for at least 12 h. We also found that an infusion of NaCl, 2400 mmol/l, in a volume equivalent to 10% of total shed blood, given as sole treatment for short-lasting severe hæmorrhagic shock (40 ml/kg blood loss), permanently reverses the course of shock and produces 100%

survival from an otherwise lethal procedure.[8] We also showed that no important or lasting plasma expansion occurs, because infused particles rapidly disperse to reach an equilibrium between the extravascular and vascular compartments, a result which agrees with the findings of Wolf[12] in normotensive dogs. Another important effect of hyperosmotic infusions, which has been described in normotensive animals, but never mentioned by reports dealing with the use of hyperosmotic infusions in the treatment of shock, is a reduction in venous capacitance, both in the systemic and in the pulmonary circulation.[13,14] We have now found (unpublished data) that hyperosmotic NaCl given to dogs hypotensive from severe hæmorrhage substantially increases mean circulatory pressure, which is a reliable index of venous capacitance. This effect must of course be of paramount importance in the reversal of shock, since it adjusts the vascular capacity to the reduced volume of blood.

Hence, theoretically, hyperosmotic infusions should be useful in the treatment of refractory hypovolæmic shock, because its important actions are chiefly to increase the dynamic efficiency of the cardiovascular system and to adapt it to the reduced volume of blood. The present report entirely substantiates this assumption: 11 out of 12 patients in terminal refractory shock were successfully treated with relatively small volumes of hyperosmotic NaCl.

Clinical situations will probably be different from the physiological set-up under which dogs were made to go into severe but short lasting hæmorrhagic shock which was completely reversed with hyperosmotic NaCl alone. Even so, hyperosmotic NaCl, at 2400 mmol/l, might be useful in the treatment of short lasting shock whenever blood is unavailable. Alternatively, it might enhance the beneficial effects of blood transfusions. Clinical research in this area is required.

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DIMETHYLSULPHOXIDE-INDUCED TOXICITY

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Summary Two elderly people were given intravenous infusions of dimethylsulphoxide (DMSO) as treatment for arthritis. One became seriously ill, the other remained well. Both had similar changes in aspartate transaminase, hydroxybutyrate dehydrogenase, and creatine kinase and evidence of hæmolysis. This is the first report of serum enzyme changes and anæmia after intravenous DMSO in man.

Introduction

DIMETHYLSULPHOXIDE (DMSO) was discovered in 1866.[1] It is a cheap by-product of paper manufacturing. Since the 1960s it has been used as a cryopreservative for platelets and as a transport medium to facilitate transcutaneous drug absorption.[2,3] Topical DMSO has been given for arthritis,[4] sports injuries,[5] scleroderma,[6] and keloid.[7] Intravenous DMSO has been used in cerebral œdema,[8] head injury, and spinal-cord trauma.[9] Intravesicular injection has been used for cystitis.[10]

Irrespective of the mode of administration DMSO is metabolised to dimethylsulphdioxide ($DMSO_2$), an odourless compound excreted by the kidney, and dimethylsulphide (DMS) which is excreted by the lungs and gives a characteristic odour to the breath.[11]

Plasma concentrations of DMSO cannot be directly determined without radioisotopic labelling of the compound.[12] DMSO may be applied cutaneously in dextrose at a concentration of between 10–90%. DMSO is safe for man and animals[13] in an oral dose of 1 g/kg body-weight with plasma concentrations reaching a peak at 4–6 h and detectable levels persisting for 400 h.[14] 30–50% of a single oral dose is excreted as $DMSO_2$ in the urine over 20 days.[15] The same dose of DMSO given intravenously in a 10–40% concentration by weight achieves higher plasma levels and is rapidly distributed throughout all tissues.[11] Over 20 days 80–90% of the compound given by either route is excreted by the kidneys as $DMSO_2$[15] and 3–6% excreted on the breath as DMS.[16,17]

Case-reports

At a private clinic in May, 1979, a husband and wife each received their first course of treatment with DMSO for their painful arthritic knees. They were given three daily intravenous infusions of 100 g of 20% DMSO in dextrose solution apparently without ill effect.

Case 1

A 77-year-old woman weighing 72 kg was known to be hypothyroid and allergic to penicillin. She took thyroxine, nitrazepam, and indomethacin with poor compliance. These drugs were stopped 3 days before a second course of therapy in February, 1980, to prevent adverse interaction with DMSO. After the first infusion of this course of treatment, 300 mg of quinine sulphate was prescribed for night cramps and 12·5 mg of prochlorperazine for vomiting. After the second infusion she became drowsy, vomited blood, and was admitted to the Royal Free Hospital.

On examination she appeared euthyroid and well orientated, but was drowsy, mildly jaundiced, and had a flapping tremor. Her