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# Letters to the Editor

## Pentoxifylline in septic shock

Sir,

Pentoxifylline is known to have pharmacological effects in an animal model of respiratory distress syndrome, multiorgan failure and shock.[1] It blocks the endotoxin-induced synthesis of tumour necrosis factor (TNF) in man.[1] I report a prospective study of the effectiveness of pentoxifylline in the treatment of septic shock.

Six adult patients hospitalized for septic shock and adult respiratory distress syndrome (ARDS) were studied. The patient group consisted of four men and two women; the mean age was 34.2 years (range 19 - 50 years). Antibiotics were administered according to *in vitro* sensitivity of the organism cultured. Routine laboratory tests on blood and urine for haematological, hepatic and renal function, chest X-ray, arterial blood pH, $PO_2$ and $PCO_2$, were done regularly prior to and during treatment. All patients (or their relatives) gave informed consent for invesigation, treatment and follow-up. Pentoxifylline was administered on an empirical basis at 300 mg intravenously every 8 hours for 3 days.

The duration of fever (range 40°C to 41°C) prior to drug administration ranged from 4 to 6 days. The leucocyte count ranged from $14 \times 10^9$/l to $26 \times 10^9$/l with polymorphonuclear leucocyte predominance. Florid picture of septic shock, multi-organ involvement/damage and ARDS was evident in all 6 patients. All had a systolic blood pressure under 90 mmHg, arterial $PO_2$ of 70 mmHg or less and impaired consciousness. Marked clinical improvement occurred in a mean 9.8 hours (range 4 to 14 hours) with disappearance of ARDS (mean 18 hours; range 8 to 24 hours). No appreciable side effects were observed. Patients were discharged after clinical and bacteriological cure and returned for follow-up examination 7, 14 and 28 days after administration of the drug. Patients remained well during follow-up.

Tumour necrosis factor alpha (TNF) a soluble monocyte/macrophage derived mediator may be the essential effector molecule of the pathology of septic shock syndrome[2] by bringing about the shock cascade by way of the production of different interleukins, gamma interferon or arachidonic acid derivatives.[1] Elevated levels of TNF are found in septicaemia.[3] TNF increases the adherence of polymorphonuclear leucocytes to endothelial cells.[1] Increased adherence of activated polymorphonuclear leucocytes in the microvasculature *in vivo* is one of the major causes of vascular injury in ARDS, which is one of the most severe consequences of Gram-negative sepsis in man.[1] Passive immunisation with anti-TNF antibodies has been found to prevent septic shock and critical organ failure due to Gram-negative bacteraemia in baboons.[4] Drugs inhibiting or interfering with the production of TNF may have a beneficial effect in septic shock.

Pentoxifylline [3,7-dimethyl-1-(5-oxohexyl) xanthine] has haemorheological activity and is used clinically in various types of vascular insufficiency.[1] It counteracts the effects of endotoxin in various animal models, reducing extravascular protein accumulation and polymorphonuclear leucocyte sequestration in the lungs[5] protecting from the lethal effects of endotoxin.[6] In macrophage cultures, pentoxifylline inhibits the formation of messenger RNA for TNF[7] and counteracts TNF stimulation of human polymorphonuclear leucocytes.[8] In pigs with induced faecal peritonitis pentoxifylline improved haemodynamic variables as well as pulmonary compliance and reduced the number of pulmonary polymorphonuclear leucocytes and lymphocytes.[9]

Pentoxifylline is rapidly distributed in body tissues after intravenous administration with little potential for tissue accumulation.[10] Its elimination half-life after intravenous administration (200 mg) ranges from 1 to 1.6 hours.[10] It is rapidly metabolized to active and inactive products in the liver.[10] Toxic and adverse reactions to this drug are fairly rare.[10]

The possibility that TNF is an essential mediator of septic shock should encourage a new approach in the treatment of this condition. The removal of TNF[11] or neutralization of its effect might reduce the fatality of septic shock.

Encouraged by the beneficial effects of pentoxifylline in human volunteers who received endotoxin,[1] the author conducted the present prospective study of the effect of pentoxifylline in septic shock particularly when associated with ARDS. The 3-day simple course with pentoxifylline along with specific antibiotic therapy seems beneficial in septic shock with ARDS. The preliminary, albeit uncontrolled, report shows that pentoxifylline counteracts ARDS, multiorgan dysfunction, reduces clinical recovery time, and morbidity and mortality due to septic shock without any appreciable side effects. However, the number of patients studied is small and further larger controlled trials must be done to establish the role of pentoxifylline in septic shock.

TNF modulation may lead to the development of a potentially novel class of anti-shock drugs, reducing the morbidity and mortality, and hospital stay due to severe organ dysfunction in septicaemia.

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## Hypoglycaemia and atrial fibrillation

Sir,

We would like to report a further case of hypoglycaemia-induced self remitting atrial fibrillation. Although 2 similar cases have been previously reported in the *Journal*,[1] we feel that the recent reports of sudden death in young insulin dependent diabetics[2] may make it important to re-emphasize this interesting observation.

A 27 year old male with Type I diabetes of 15 years duration presented to the Accident and Emergency Department following a severe hypoglycaemic reaction. He was taking three daily injections of a Human Velosulin (6 units) and Insulatard (12 units) and claimed good glycaemic control which was supported by a serum fructosamine of 2.95 mmol/l (normal range 1.9–2.7) on admission. He had however been admitted to hospital on two previous occasions following severe nocturnal hypoglycaemia. There was no past medical or family history of cardiac arrhythmias.

At 20.00 h on the day of admission he became weak and confused. His mother recognized his symptoms and recorded a blood glucose of 1.4 mmol/l (BM 1–44 stick read by meter) before giving the patient milk. In the Accident and Emergency Department (21.00 h) he was given a further dose of oral glucose and a subsequent Reflocheck of 14 mmol/l was recorded. Although asymptomatic he was in atrial fibrillation with ventricular rate 100–150 beats/min, confirmed on electrocardiograph. Physical examination was normal and within one hour the rhythm spontaneously reverted to sinus. Subsequent cardiological assessment (auscultation, resting electrocardiogram and echocardiogram), serum potassium and thyroid stimulating hormone levels were all normal.

Hypoglycaemia is common in insulin treated diabetics[3,4] but the incidence of associated cardiac arrhythmias remains unknown. This case supports the view that asymptomatic arrhythmias can be induced by hypoglycaemia and may suggest a possible mechanism for the phenomenon of sudden death in insulin dependent diabetics.

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## Inappropriate secretion of vasopressin, hypopituitarism and corticosteroid therapy

Sir,

A recent report describes five patients with hypopituitarism and severe hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) that improved within a few days after the institution of hydrocortisone therapy, whereas the infusion of normotonic or hypertonic saline had been found to be less effective.[1]

We have observed the association between hyponatraemia due to SIADH and hypopituitarism in a 60 year old previously healthy women who presented with lethargy, weakness and complete absence of axillary and pubic hair. Laboratory features revealed severe hyponatraemia (111 mmol/l), low plasma/urine osmolality ratio (230/298 mosmol/kg) and an increased urinary sodium excretion (50 mmol/l). Chest X-ray, serum creatinine and arterial blood gases were normal. She was treated by restricting fluid intake and with intravenous administration of 5% saline solution that restored serum sodium concentration and plasma osmolality within the first week of admission. A clinical diagnosis of panhypopituitarism was confirmed by means of the LHRH-TRH test as well as both acute and continuous ACTH stimulation performed after a stay of 7 days, at which time hormonal replacement was instituted.

Oelkers emphasize that a response to corticosteroids should be the hallmark of SIADH secondary to hypopituitarism. Although hydrocortisone can restore sodium excretion to normal by inhibiting vasopressin directly[3] there is also evidence that it has mineralocorticoid-like properties and produces renal tubular sodium reabsorption in the absence of ADH.[4] On the other hand, we re-established normal serum sodium levels after conventional therapy without corticosteroids. Probably plasma osmolality improvement itself after saline infusion may