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BRIEF REPORT

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Meningococcal septicaemia: treatment with protein C concentrate

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Abstract Meningococcal septicaemia is a devastating disease with the potential to develop severe vascular complications. The incidence in Northern Ireland has risen from 27 cases notified in 1992 to 56 notified in 1997. We describe the first use of protein C concentrate in addition to antithrombin III infusion in the management of a life-threatening case of meningococcal septicaemia in the Regional Intensive Care Unit, Royal Group of Hospitals, Belfast, UK. The rationale and the evidence to support the use of protein C concentrate are discussed. Despite the apparent efficacy and safety of this treatment, subsequent cases of meningococcal septicaemia have not received protein C concentrate due to a lack of availability.

Key words Meningococcal · Septicaemia · Protein C concentrate

Case report

A 17-year-old male was admitted to a peripheral hospital with a 2-day history of malaise, mild confusion and a headache. Examination revealed a purpuric rash over trunk, arms and face. Initially he was fully orientated, mildly pyrexic (temperature 37.7 °C), with a heart rate (HR) of 130 beats/min and blood pressure (BP) 115/70 mmHg. A presumptive diagnosis of meningococcal septicaemia was made and he was commenced on intravenous benzylpenicillin and cefotaxime. Within 50 min of starting this treatment, his condition deteriorated, necessitating intubation. Despite aggressive fluid resuscitation he required both adrenaline and noradrenaline infusions to establish haemodynamic stability. As part of his resuscitation a pulmonary artery flotation catheter was inserted. A cardiac index (CI) of 8.5 l min m^2 (normal range 2.5–4.0) and systemic vascular resistance index (SVRI) of 200 dyne.s cm^5 m^2 (normal range 1970–2390) were measured. Fulminant pulmonary oedema developed, requiring diuretics. During transfer to the Regional Intensive Care Unit (RICU) the patient required 100 % oxygen, full ventilation and inotropic support.

On admission to RICU (time; 18:30 day 1) he had a blood pressure of 125/74 mmHg and a heart rate of 115/min. Repeat measurements from the pulmonary artery catheter were consistent with severe septicaemic shock (CI 4.8 l min m^2, SVRI 1159 dyne.s cm^5 m^2). He was receiving an adrenaline infusion at 0.033 μg kg min and a noradrenaline infusion at 0.03 μg kg min. He also required 100 % oxygen and 5.5 cm H_2O of positive end-expiratory pressure (PEEP). Despite this high level of support a blood lactate of 6.26 mmol/l (normal range 0–2 mmol/l) was recorded. During the first 24 h he deteriorated; inotropic support was trebled and the level of PEEP was increased to 8 cm H_2O. (time; 07:00 day 2: HR 118 beats/min, BP 135/80 mmHg, CI 4.9 l min m^2 and SVRI of 1446 dyne.s cm^5 m^2, adrenaline 0.1 μg kg min and noradrenaline 0.083 μg kg min).

Clinically, his purpuric rash progressed to the typical pre-gangrenous vascular lesions of meningococcal disease. The most serious lesions were erupting on his lower limbs. His coagulation profile was typically impaired, (Table 1). Previously, similar cases had been routinely managed in the RICU with infusions of antithrombin III to improve anticoagulation of the disseminated intravascular clotting process. Depending on the coagulation profile and the clinical condition of the patient, heparinisation was occasionally indicated. However, this patient was treated with protein C concentrate infusions, eight-hourly, in addition to the routine antithrombin III infusion. The doses of protein C concentrate (Immuno, Vienna) used were given at 100 units/kg body weight, intravenously, eight-hourly. This patient received two doses, 8 h apart, of 7400 units of protein C concentrate. The dose of antithrombin

Table 1

Test	Results			Range
	(on admission)	(day two)	(day three)	
Prothrombin Time	27.4 sec	24.5 sec	15.7 sec	12–17 sec
A.P.P.T.*	68.4 sec	50.6 sec	41.5 sec	24–38 sec
Thrombin Clotting Time	14.7 sec	14.7 sec	15.6 sec	14–22 sec
Claus Fibrinogen	2.96 g/l	3.95 g/l	7.55 g/l	2.0–5.0 g/l
D-Dimer	1000 nano-g/ml	1000 nano-g/ml	250 nano-g/ml	< 500 nano-g/ml
Fibrinogen Degradation Products	> 10 < 40 mcg/ml	> 10 < 40 mcg/ml	> 10 < 40 mcg/ml	< 10 mcg/ml
Protein C (functional)	13 %	25 %	62 %	70–149 %
Antithrombin III	51 %	n/a	85 %	80–120 %

* A.P.P.T. activated partial thromboplastin time

Table 1 shows the coagulation screen initially measured after admission to RICU and those measured on days two and three

III was 3000 i. u., intravenously. Six h after the first dose of protein C concentrate, the patient's inotrope requirements were greatly reduced (time; 17:00 day 2: HR 120/min, BP 100/60 mmHg, CI 6.9 l min m^2 and SVRI of 794 dyne.s cm^5 m^2, adrenaline 0.07 μg kg min, noradrenaline 0.083 μg kg min). After 24 h of treatment, fresh vascular lesions stopped erupting. Repeat estimations of the coagulation profile showed normalisation of the levels of protein C from 13 % through 25 % to 62 % by day 2. The coagulation profile also normalised (Table 1). Antithrombin III levels were 85 % on day 3 (normal). Their replacement was therefore discontinued. Heparinisation was not deemed necessary in view of the dramatic clinical improvement and the normalisation of haemostasis. The patient continued to receive fresh frozen plasma, 300 ml, every 8–12 h. He was extubated on day 2 and discharged to the general ward on the evening of day 3. His recovery was surprisingly rapid and complete with no neurological or vascular sequelae.

The haemostatic infusions were without complications, although it must be noted that the second infusion of protein C concentrate was associated with a blotchy, transient erythematous rash. There was no associated cardiovascular instability. The clinical diagnosis of meningococcal infection was confirmed by the finding of gram-negative cocci on lumbar puncture (no growth) and polymerase chain reaction assay. The patient's improvement was considered to be dramatic in comparison with previously similarly infected patients.

Discussion

Neisseria meningitidis is an encapsulated gram-negative diplococcus which commonly colonises the nasopharynx of healthy individuals. Infection is commonest in young children and adolescents. Meningococcal infection has an overall mortality of approximately 8 % [2]. Meningococcal septicaemia can have mortality rates as high as 54 % [3]. The time from onset of pyrexia to death can be as short as 12 h. The classical purpuric rash, caused by microvascular thrombosis, may be mild initially but can progress to confluent lesions and in some cases, to infarction of digital vessels and even limb amputation. Such changes may occur rapidly within a few hours. Presentation is often with non-specific signs of fever, malaise, vomiting and headache. The early signs of septic shock can be extremely difficult to identify, especially in the young.

Management of meningococcal septicaemia relies on early recognition, parenteral antibiotics, and aggressive resuscitation. Parenteral benzylpenicillin given by the general practitioner is associated with a significant reduction in mortality [4]. However, broad-spectrum third-generation cephalosporins, such as cefotaxime or ceftriaxone, are currently recommended as first-line treatment. Penicillin-resistant meningococci have been identified and the need for broad-spectrum antibiotics to cover other pathogens is the reasoning behind these recommendations [5].

Even those who survive often have significant neurological, orthopaedic or emotional sequelae.

Protein C is a serine protease zymogen and it is vitamin K dependent. It acts as an anticoagulant by inactivating factors V and VIII. In this action it is assisted by protein S and also by thrombomodulin, a surface cofactor on the endothelial cells. Furthermore, and possibly more significantly, it is capable of neutralising inhibitors of tissue plasminogen activator, thus it can enhance fibrinolytic activity. Deficiency of protein C, either congenital or acquired, can be associated with significant intravenous thrombosis. Homozygous congenital protein C deficiency is a serious condition, presenting in neonates with purpura fulminans. Coumarin-induced skin necrosis, an acquired deficiency of protein C, also results in skin lesions which are clinically and pathologically similar to those in congenital protein C deficiency. Meningococcal septicaemia is associated with disseminated intravascular coagulation, often with a profound fall in circulating levels of protein C. A strong correlation between the fall in protein C levels and the severity of thrombotic lesions and poor outcome has been demonstrated [6].

In 1995 Rivard et al., reported on a series of four children aged 3 months to 15 years who required intensive care for meningococcal septicaemia [7]. Treatment with protein C concentrate led to a rise in plasma protein C activity levels to within normal levels in all patients. No adverse effects were noted and reversal of organ dysfunction occurred, and all four survived. Two required

amputations and two had complete recovery. One patient had a concurrent infusion of heparin. The suggested protein C regimen was 100 units/kg body weight infused over 15–20 min, every 6–8 h. This was continued until skin lesions ceased to develop and/or coagulation tests were stable.

In 1997 Smith et al., reported on a series of 13 patients aged 3 months to 27 years with severe meningococcaemia [8]. These patients were treated with a continuous infusion of protein C to maintain normal blood levels. Eleven patients also had a heparin infusion, nine patients had haemodiafiltration and one had peritoneal dialysis. All patients survived despite predicted mortality of 57–80 %. No adverse effects of treatment were noted; two patients required limb amputations, one of whom had a thrombotic cerebrovascular accident. One patient developed chronic renal failure.

In 1998 Rintala et al., reported on three adults (aged 20, 48 and 49 years) who received protein C for meningococcal septicaemia [9]. The administration was of 100 units/kg every 6–8 h (intravenously). All three patients received antithrombin III replacement therapy and haemofiltration for renal insufficiency. One patient died from cerebral oedema. Patient number two had a small sub-arachnoid haemorrhage (no surgery required) but survived with no organ damage. Patient three survived with no organ damage.

Animal work has demonstrated improved outcome with the use of protein C in this disease [10]; however, human trials are hindered by the limited number of patients and the sporadic nature of the disease. The immediate restoration of normal levels of protein C seems a logical step to take in the treatment of severe purpura fulminans. Unfortunately, the unavailability of the concentrate has severely restricted such treatment. Possibly the situation may be improved with the introduction of a recombinant preparation in the future.

On a world-wide basis two pharmaceutical suppliers supply protein C, Immuno (Vienna) – now Baxter Healthcare, USA – and L. K. B. (France). Neither company yet has a license for the treatment of meningococcal disease. A licensed preparation is awaited.

Management and good outcome still rely on early recognition, parenteral antibiotics and aggressive resuscitation. Possibly standard management will soon include early measurement of protein C and early replacement. Certainly we believe protein C and antithrombin III activity should be measured as part of the initial coagulation screen in every patient with the diagnosis of meningococcal septicaemia. These results should then be discussed with a haematologist to plan further management. The use of the combination of protein C and antithrombin III may, in fact, have a better rationale than the utilisation of pure protein C concentrate replacement. The lack of availability of protein C concentrate is a serious restriction in the development of this treatment. As a purified blood product, it is associated with the risks inherent to any blood product but otherwise its use appears relatively safe. Given the severity of meningococcal septicaemia and the clinical data available to date, we believe protein C concentrate should be available on a named patient basis.

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