SHORT REPORTS

Suspected anaphylactic reaction to Cremophor EL

There have been several reports of anaphylactoid reactions to the intravenous anaesthetic drugs Althesin (alphaxalone and alphadolone) and propanidid (Epontol).[1] The culprit in some of these reactions may have been Cremophor EL, a surfactant common to both drug formulations. Cremophor EL is produced by the epoxylation of castor oil and is actually a complex mixture of compounds. We report a case in which the clinical and laboratory evidence indicated that Cremophor EL was the cause of an anaphylactic (antibody-mediated) response.

Case report

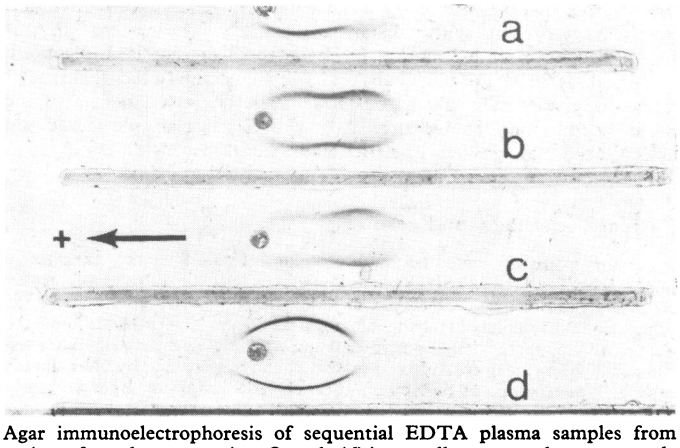
An otherwise fit 14-year-old girl had an ankle fracture reduced on 15 June 1979. The anaesthetic consisted of atropine 0·6 mg, Althesin 4 ml, nitrous oxide, oxygen, halothane, and trichloroethylene. The patient had never previously had a general anaesthetic. The operation was not entirely successful, and the patient presented again on 27 June for internal fixation. Anaesthesia was induced with propanidid injected into an antecubital vein. After the injection of about 20 mg the solution began to extravasate, and the injection was stopped. The anaesthetic was continued with nitrous oxide, oxygen, and halothane. The patient coughed and became cyanosed and then unconscious. Anaesthesia was discontinued. Peripheral vascular shutdown with absent radial pulses was noted; large arterial pulses were present. There was a pronounced expiratory wheeze. About 1·5 l colloid (Haemaccel) and crystalloid (Hartmann's solution) was infused intravenously with dexamethasone and aminophylline. The patient's colour began to improve after about 20 minutes and she recovered consciousness. A salbutamol infusion was begun because she still had an expiratory wheeze. Some two hours after induction she was fully conscious with normal blood gas tensions while breathing room air. Blood was taken for complement and other plasma protein studies and also for haematological tests since she was bleeding extensively from venepuncture sites, suggesting an impaired haemostatic mechanism. Four days later she was given without incident an anaesthetic with no intravenous induction agents.

Concentrations of fibrin degradation products were raised at both two hours (0·16 g/l) and 24 hours (0·04 g/l). Other haematological values were normal. Plasma complement C3 concentration (0·6 g/l) was normal, C4 concentration (0·07 g/l) was very low, and IgE concentration (335 IU/ml) rather high and characteristic of allergy. The plasma samples showed massive (⩾80%) initial C3 conversion (fig), the effects of which would be consistent with the clinical manifestations.

Comment

The patient had no history of allergy or atopy, although her father had had an allergic-type reaction to an injection of phenobarbitone many years previously. Nevertheless, she had a low plasma C4 concentration and an IgE concentration consistent with immunological hypersensitivity, and the interval between exposures to Cremophor EL was short. These three factors are said to predispose to an anaphylactoid response.[1] Evidence is steadily accumulating of the antigenicity of Cremophor EL, which is common to both Althesin and propanidid formulations. Although memory-mediated events after a second exposure to Althesin have been reported in man,[2] Glen *et al*[3] have shown that Cremophor EL alone can cause anaphylactic reactions when readministered to the miniature pig within one to three weeks. They also noted that although an active component of Althesin (alphaxalone) produced the same memory-mediated effect when given to the pig in a different solvent propanidid itself was inert. In addition to anaesthetic reactions clinically severe adverse reactions, with plasma C3 conversion, have been reported[4] in man after intravenous diazepam solubilised in Cremophor EL.

The circumstantial evidence in our patient points to an immunological memory-mediated event directed against Cremophor EL. A direct C3 activation from propanidid but not alphaxalone seems unlikely since the pig experiments indicate that Cremophor and not propanidid is likely to be involved in anaphylactic reactions. More probably Cremophor triggered an immune-mediated reaction in our patient, rapidly reducing the low C4 concentration, and then activated the alternative pathway. If the reaction was not immune-mediated then the Cremophor in Althesin should also have elicited an adverse reaction on the first occasion. A further point of interest was the raised production of fibrinogen degradation products. Although this may have been a non-specific result of vascular collapse, it may have arisen from complement activation.[5]



Agar immunoelectrophoresis of sequential EDTA plasma samples from patient after adverse reaction. Sample (*d*) is a totally converted serum sample used as control. Electrophoresis is towards left of plate: "slits" contain commercial anti-C3 serum. Patient samples taken (*a*) 2 hours, (*b*) 5 hours, (*c*) 20 hours after reaction. Initial high concentration of conversion products in (*a*) (compare control (*d*)) falls gradually since they are biodegraded and replaced with fresh native C3 in (*c*).

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[1] Watkins J. Anaphylactoid reactions to iv substances. *Br J Anaesth* 1979; **51**:51-60.
[2] Watkins J, Clark A, Appleyard TN, Padfield A. Immune mediated reactions to Althesin (alphaxalone). *Br J Anaesth* 1976;**48**:881-6.
[3] Glen JB, Davies GE, Thomson DS, Scarth SC, Thompson AV. An animal model for the investigation of adverse responses to iv anaesthetic agents and their solvents. *Br J Anaesth* 1979;**51**:819-27.
[4] Hüttel MS, Schou Olesen A, Stoffersen E. Complement mediated reactions to diazepam with Cremophor as solvent (Stesolid MR). *Br J Anaesth* 1980;**52**:77-9.
[5] Preston FE. Haematological problems associated with shock. *Br J Hosp Med* 1979;**21**:232-45.

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Diabetic glucose control, lipids, and trace elements on long-term guar

Recent criticism of the effectiveness of high-fibre diets in the treatment of diabetics has, in part, been due to failure to mix the fibre adequately with the carbohydrate portion of the diet. There is, however, also genuine fear that the benefits may wear off with time[1] or that long-term administration of fibre may cause mineral depletion.[2] We therefore present data on the longer-term effects of dietary supplementation with guar.

Patients, methods, and results

Eleven diabetic patients (6 men, 5 women aged 48±SD 5 years and weighing 110±7% of ideal weight) were studied; eight were being treated with insulin (49 U/day), two (cases 2 and 11) with oral agents, and one (case 13) with diet alone. All completed six months of eating 14-26 g guar/day in crispbread form, and eight were followed up into their second year. Of the remaining three, one (case 11) was placed on insulin, while distance from the centre made follow-up of the remaining two (cases 4 and 7) difficult. Urinary