2.0 Entry and exclusion criteria

- 2.1 Name of clinical disorder
- 2.2 Definition and limits of disorder
- 2.3 Age range
- 2.4 Gender
- 2.5 Race
- 2.6 Present therapy
- 2.7 Previous therapy
- 2.8 Other criteria

3.0 Recruitment

- 3.1 Population from which sample drawn
- 3.2 Method of sampling
- 3.3 Referral sources and procedure

4.0 Screening test for admission/retention

- 4.1 First visit
- 4.2 Repeat visits

5.0 Personnel and roles; titles and locations

- 5.1 Clinicians
- 5.2 Controller
- 5.3 Pharmacist
- 5.4 Nursing staff
- 5.5 Manufacturer
- 5.6 Statistician
- 5.7 Other contributors, such as clinical pathologists
- 5.8 Secretary
- 5.9 Personnel substitutions

6.0 Clinic(s)

- 6.1 Addresses, telephones

Trial observations: therapeutic and adverse effects

- 7.1 Symptoms
- 7.2 Signs : validation of observations
- 7.3 Other measured variables, including toxicity
- 7.4 Tablet return or other compliance observations
- 7.5 Patient preferences/treatment identification*
- 7.6 Physician preferences/treatment identification*
- 7.7 Other

8.0 Trial design

- 8.1 Within or between groups
- 8.2 Crossover, block, sequential, etc
- 8.3 Blindness: open, single, double: need for independent assessor
- 8.4 Treatment periods: number, duration, run-in, washouts
- 8.5 Is pilot trial needed?

9.0 Treatment allocation

- 9.1 Stratification/minimisation†
- 9.2 Allocation procedure: randomised, Latin square, other
- 9.3 Form and location of treatment code

10.0 Drugs

- 10.1 Test and comparative
- 10.2 Dosage form
- 10.3 Specification and source
- 10.4 Assurance of comparability, bioavailability
- 10.5 Quality control, stability
- 10.6 Packaging and labelling
- 10.7 Storage and dispensing

11.0 Dosage

- 11.1 Fixed: one or more dose levels
- 11.2 Variable: adjustments, limits
- 11.3 What concurrent treatment permitted or forbidden?

12.0 Statistical design

- 12.1 Hypotheses under test
- 12.2 Tails of comparison
- 12.3 Sample estimates of parameters‡
- 12.4 Probability criteria α , β , θ §
- 12.5 Tests to be used
- 12.6 Handling of dropouts: replacement or not
- 12.7 Action in cases of adverse drug reactions, treatment failure, loss from trial or incomplete records
- 12.8 Probable numbers required
- 12.9 Data handling and computer link
- 12.10 Stopping rules

13.0 Agreement and consent

- 13.1 Patients and volunteers
- 13.2 Service departments
- 13.3 General Practitioner, industrial medical officer
- 13.4 Ethics committees
- 13.5 Committee on Safety of Medicines clinical trial certificate
- 13.6 Confidentiality, disclosure of information
- 13.7 Publication

14.0 Documentation required

- 14.1 Background supporting literature
- 14.2 Protocol
- 14.3 Record form
- 14.4 Treatment allocation procedure
- 14.5 Labelling
- 14.6 Consent forms
- 14.7 Instructions to all collaborators
- 14.8 Emergency code-breaking procedure
- 14.9 Warning notice of trial participation for case notes
- 14.10 Flow sheet

15.0 Other planning matters

- 15.1 Availability of resources: staff and equipment
- 15.2 Finance: payments and other expenditure, income
- 15.3 Foreseen constraints
- 15.4 Target dates
- 15.5 Post-trial drug supply and follow-up

Comment

This list was elaborated from a much simpler one that has been used for some time in this department. The revision reflects the increasing sophistication of trial techniques and the extension of legal and ethical obligations. We are indebted to several colleagues for their help (which, somewhat to our dismay, almost always resulted in the inclusion of additional items rather than in deletions or simplification).

Not every heading will apply in every case, but they all deserve consideration, and their omission from the protocol should be deliberate and not through neglect. It would be virtually impossible for anyone to remember so many points in systematic and logical sequence and, since many of them interrelate, it may be necessary to go through them several times in order to achieve the optimum balance. The wording of the final protocol will obviously not slavishly adhere to the headings as set out and should be as simple as possible.

We have provided this list so that others may send us their comments. We would be particularly grateful to hear from those who put the list to practical test. On the basis of such experience we hope to refine it further.

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¹ Good, C S, (editor), *Principles and Practice of Clinical Trials*. Edinburgh, Churchill-Livingstone, 1976.

² Taves, D R, *Clinical Pharmacology and Therapeutics*, 1974, 15, 445.

(Accepted 25 February 1977)

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The list was compiled by present and past members of the unit.

Isoimmunisation after narcotic addiction

Injection of small volumes of red cells is a technique used for boosting blood group antibodies in programmes designed for the production of anti-D. Gunson *et al*¹ showed that high titres of anti-Rhesus antibodies could be induced in Rhesus-negative male volunteers by repeated injections of Rhesus-positive red cells. It was later shown² that this could be accomplished by volumes as small as 0.01 ml of red cells. We report a case of the production of isoantibodies

*Can the patient or doctor identify the treatment?

†Minimisation: a new method of assigning patients to treatment and control groups.*

‡Forecast estimate of variances and means of groups being compared.

§See Good.¹

in a primigravida, which was thought to be the result of self-injection of autologous blood from a fellow drug addict.

Case report

A 20-year-old primigravida was attending another hospital antenatally. The pregnancy was uneventful until about 25 weeks' gestation (initial testing), when she was found to have atypical antibodies in high titres to the Rhesus and Kell blood group systems. She went into premature labour at 28 weeks and delivered a stillborn baby girl of 140 g at home. After a "flying squad" call for primary postpartum haemorrhage, she was transfused with one unit of uncrossmatched group O Rhesus-negative blood. Nevertheless, she made an uneventful recovery.

She was unmarried, and had a history of mixed addiction to lysergic acid, cannabis, heroin, morphine, cocaine, and amphetamines. Repeated careful histories were taken and she denied any previous operation, blood transfusion, or pregnancy. The only medications given during her pregnancy were topical podophyllin, oral folic acid, and oral iron. The first drugs she had used were cannabis and LSD when aged 16. She became addicted to morphine 18 months before she became pregnant, taking 50 mg of diamorphine or 30 mg of morphine twice a week. Her method of injection was to withdraw blood into the syringe until the solution took on a rosy tinge. After injecting she would flush the syringe by withdrawing about 0.25 ml of blood to reinject, so as to remove the tiniest trace of the drug. This pattern of injection is common among mainlining addicts. She had shared syringes regularly with her boyfriend and other people. She showed no evidence of opiate withdrawal symptoms while in hospital, but has done so since.

Postmortem examination of the small fetus showed no congenital abnormalities. The placenta weighed 169 g with evidence of extensive retroplacental blood clot. Histologically there were primitive villi with a moderately cellular stroma but no evidence of erythroblastic activity. Serological evaluation of the mother, fetus, and putative father is shown in the table.

Results of blood group antigen and antibody titres detected with the antiglobulin technique. Rhesus antibodies were anti-C, D, and E

	ABO	Rhesus	Rhesus genotype	Kell	Rhesus antibodies	Kell (k) antibodies
Mother	A ₁	negative	ċdē/ċdē	negative	1/32000	1/256
Fetus	A	negative	ċdē/ċdē	negative		
Putative father	A ₁	positive	CDē/ċDE	positive		

The actual father of the child was unknown. The blood infused after delivery was group O, Rhesus- and Kell-negative.

Discussion

Our studies show that the antibodies detected in our patient could not have resulted from this pregnancy, as the fetus was Rhesus- and Kell-negative. These antibodies must have arisen after repeated injections of incompatible blood infused during the use of narcotics. While the possibility of sensitisation by one or more previous abortions cannot be absolutely disregarded, our knowledge of the patient and the very high antibody titres detected would tend to exclude this.

To our knowledge this is one of the first reported cases of Rhesus and Kell isoimmunisation arising from contaminated intravenous injections of narcotics. The reason for the premature delivery cannot be accounted for by isoimmunisation and the aetiology of this is at present unknown.

We thank Mr R H T Ward for permission to report this case, and Dr A Taghizadeh for pathological examination of the fetus.

¹ Gunson, H H, *et al*, *British Medical Journal*, 1970, **1**, 593.

² Jakobowicz, R, Williams, L, and Silberman, F, *Vox Sanguinis*, 1972, **23**, 376.

(Accepted 9 February 1977)

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Fulminating haemorrhagic influenza

We describe here a case of fulminating influenza, which was not recognised as such until after the patient had died.

Case report

A 43-year-old Chinese man had lived in England for 16 years. After five days of malaise and sore throat he developed a fever, cough with clear sputum, and exertional dyspnoea and noticed a rash on his lower limbs. There was no relevant medical history. He had not recently travelled abroad.

On admission he was conscious, alert and orientated, flushed (temperature 40°C), tachypnoeic, but not cyanosed. There were no stigmata of liver disease or palpable lymph nodes. Petechial haemorrhages were visible on the hard palate and purpuric lesions on the legs and abdomen. He had sinus tachycardia (120 beats/min) and a blood pressure of 120/75 mm Hg. Coarse rales were audible at the left base. Abdominal examination showed nothing abnormal. There was slight neck stiffness but Kernig's sign was negative. There were no focal neurological signs. Fundoscopy showed nothing abnormal. The haemoglobin was 14.9 g/dl and white cell count $11.9 \times 10^9/l$: 90% polymorphonuclear leucocytes, 7% monocytes, 1% lymphocytes, and 2% metamyelocytes. The platelet count was $71 \times 10^9/l$, and the blood film showed no evidence of fragmented cells. Prothrombin time was 15 seconds (control 14 seconds), fibrinogen titre 1/128 (normal), plasma urea 16.6 mmol/l (100 mg/100 ml), sodium 122 mmol(mEq)/l, and potassium 4.2 mmol (mEq)/l. A chest radiograph showed a normal-sized heart and no evidence of pulmonary consolidation. Urine and cerebrospinal fluid were normal.

Septicaemia of uncertain cause was provisionally diagnosed. He received intravenous antibiotics and corticosteroids. But the purpuric rash started to extend over the rest of his body, becoming frankly haemorrhagic with extensive coalescing ecchymoses developing over all areas except the buttocks. Repeat coagulation studies gave unchanged results. The patient suddenly became centrally cyanosed, requiring intubation and ventilation. Blood-stained secretions were obtained on bronchial suction. Although subsequently well oxygenated, the patient developed a severe and irreversible metabolic acidosis. The electrocardiogram showed non-specific T-wave changes and after repeated episodes of ventricular fibrillation the patient became hypotensive and asystolic. Resuscitation was unsuccessful. Terminally there was bleeding from venepuncture sites, the platelet count falling to $10 \times 10^9/l$.

A necropsy was not performed. Hepatitis B antigen (HBsAg) was present in the blood. Bone marrow examination was normal. Blood cultures, mid-stream specimen of urine, and cerebrospinal fluid were bacteriologically sterile. No organisms were seen on Gram-stain or culture from scrapings taken from the skin lesions. Influenza Victoria/75 virus was isolated from the nasopharynx.

Comment

The correct diagnosis was not made before death. We thought the patient had either a fulminating septicaemia, probably meningococcal, or haemorrhagic smallpox. Nevertheless, the history and clinical course of this patient, with death rapidly after the development of cyanosis, was similar to the descriptions of fulminating influenza that occurred during the 1918 pandemic.¹⁻³ Although rashes were described, purpura was uncommon^{3,4} and haemorrhagic rashes were exceedingly rare. Indeed French³ saw only two cases, both fatal, with haemorrhagic skin lesions but these were confined to the legs.

The cause of the extensive haemorrhagic rash is uncertain. The patient was HBsAg-positive but there were no clinical signs of liver disease and the prothrombin time was normal. When the ecchymoses developed there was no evidence of disseminated intravascular coagulation, although this may have occurred terminally. The skin lesions may therefore have resulted from the effects of the influenza virus on platelet survival and capillary integrity.

We thank Dr F H Scadding for permission to describe this case, and Dr D S Dane and Dr G D W McKendrick for their advice and help.

¹ Rolleston, J, *Medical Annual*, p 202, Bristol, Wright, 1919.

² Hammond, J, *Lancet*, 1917, **2**, 41.

³ French, H, *Ministry of Health Report*, No. 4 Chapter 3, 1920.

⁴ Cole, C, *British Medical Journal*, 1918, **2**, 566.

(Accepted 27 January 1977)

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