view of our findings, however, serial measurements for individual patients should always be taken using the same model, even if it is impracticable to use the same instrument.

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Cerebral venous thrombosis and subarachnoid haemorrhage in users of oral contraceptives

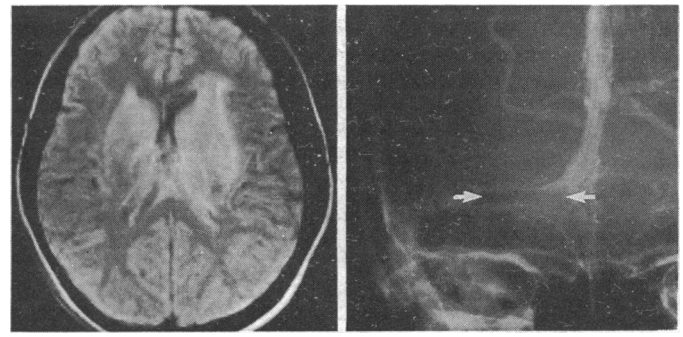
The increased risk of subarachnoid haemorrhage associated with oral contraception is a matter of debate.[1] Most studies indicate that there is a small but significantly increased risk.[2] The reason for this association remains obscure, although Thorogood *et al* proposed that the hypertensive action of the pill has an indirect effect.[3] We report on three patients taking oral contraceptives who developed cerebral venous thrombosis and subarachnoid haemorrhage of varying severity.

Case reports

Case 1—A 30 year old Kenyan woman was found unconscious at home having complained earlier of headache and nausea. Three months previously she had been prescribed Diane (cyproterone acetate 2 mg, ethinyloestradiol 50 μg) for acne. On examination she was obese, comatose, and tachypnoeic with a temperature of 37·6°C. She flexed her arms and legs to painful stimuli and had bilateral extensor plantar responses. Her eyes were deviated to the left, doll's eye movements were present, and her optic fundi were normal. Investigation showed a haemoglobin concentration of 104 g/l, neutrophilia of $15·4 \times 10^9$/l, and blood glucose concentration of 16·6 mmol/l (299 mg/100 ml). Enhanced computed tomography yielded normal results. Examination of cerebrospinal fluid showed 5×10^9 red blood cells/l, 7×10^6 polymorph white cells/l, and a protein concentration of 0·4 g/l. The opening pressure was 400 mm water. After admission her condition deteriorated rapidly; she required artificial ventilation and died three days later. Postmortem examination showed venous infarction of the cerebellum and brain stem secondary to multiple intracranial venous thromboses.

Case 2—A previously healthy woman aged 26 presented with a headache that had worsened progressively over seven days and was associated with unsteady gait, nausea, and vomiting. She had been taking Logynon (ethinyloestradiol 30, 40, 30 μg, levonorgestrel 50, 75, 125 μg) as an oral contraceptive for two years. Examination showed papilloedema, enlargement of her left blind spot and horizontal, vertical, and rotary nystagmus. Enhanced computed tomography showed a filling defect in the superior sagittal sinus. The cerebrospinal fluid had an opening pressure of 370 mm water and contained 8×10^6 red blood cells/l, no white cells, and 0·54 g protein/l. Digital subtraction angiography confirmed thrombosis in the sagittal sinus. The oral contraceptive was stopped and her condition improved rapidly with resolution of her papilloedema by four months.

Case 3—A 26 year old woman with longstanding menorrhagia presented with a two month history of occipital headache, which had begun after she had started taking Marvelon (desogestrel 150 μg, ethinyloestradiol 30 μg) as an oral contraceptive. Two days before her admission the headache had worsened and she had become lethargic and vomited. On presentation she was drowsy, catatonic, and feverish (38·2°C). Examination of the cranial nerve gave normal results. Tone was increased in both arms, more so on the left, with symmetrically brisk reflexes and flexor plantar responses. Haemoglobin concentration was 70 g/l with a microcytic, hypochromic film. Computed tomography showed effacement of the anterior horn of the right ventricle and low density in the region of the basal ganglia. Carotid angiography showed thrombosis of the deep cortical veins and right transverse sinus, and a nuclear magnetic resonance scan showed changes in the basal ganglia and thalamus (figure). The cerebrospinal fluid had an opening pressure of 135 mm water and contained $0·56 \times 10^9$ red blood cells/l, 4×10^6 lymphocytes/l, and 0·16 g protein/l. The oral contraceptive was stopped, and her condition returned to normal over the next 10 days.



Left: Nuclear magnetic resonance image showing increased signal on spin echo sequences in the basal ganglia bilaterally and mass effect on right with compression of the frontal horn. Right: Carotid angiogram showing filling defect (arrows) in right transverse sinus compatible with thrombus.

Comment

Intracranial venous thrombosis is rare in healthy young adults but is a recognised complication of oral contraceptive use and in the puerperium.[4] It commonly results in venous infarction and subarachnoid bleeding, particularly if the thrombosis is extensive.[5] Subarachnoid haemorrhage is the only non-thrombotic vascular complication of oral contraceptives, and its mechanism has never been satisfactorily explained. Though some patients undoubtedly have arterial aneurysms, coagulation defects, and hypertension, we suggest that unrecognised venous thrombosis accounts for some of the excess cases of subarachnoid haemorrhage among women using contraceptives.

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Schick test as a predictor of immunity to diphtheria and of side effects after revaccination with diphtheria vaccine

An outbreak of toxic diphtheria occurred in 1984 in Sweden among chronic alcoholics. No healthy subjects developed the disease, but several contacts of patients became asymptomatic carriers. The prevalence of immunity to diphtheria in Sweden was unknown, and there was no policy for revaccinating adults. In a small study of healthy adults we evaluated the prevalence of immunity and compared the effect of giving a combined diphtheria and tetanus vaccine subcutaneously and intracutaneously. All subjects were Schick tested before immunisation.[1]

Subjects, methods, and results

Thirty nine healthy subjects consented to participate in the study. Only four knew that they had received vaccinations against diphtheria or tetanus, or both, within the preceding 10 years. All but one, however, had probably been immunised during infancy or in school with a combined diphtheria and tetanus

vaccine. The vaccine contained formaldehyde detoxified, aluminium adsorbed diphtheria and tetanus toxins, 25 and 7·5 flocculation units/ml respectively (SBL, Sweden). The subjects were randomised by using sealed envelopes to receive the vaccine subcutaneously (21 subjects) or intracutaneously (18). The mean age was 29·8 (range 23-43) years, with no difference between the groups. Seven of the eight women were randomised to receive the vaccine subcutaneously.

Before vaccination all subjects were Schick tested using standardised reagents (SBL, Sweden). After four days the reactions to the toxin and a heat inactivated control were determined. Induration with a diameter of ≥10 mm at the site of application of the Schick reagent and at least 50% smaller reactions to the control reagent were considered to indicate lack of immunity. Reactions with a diameter <10 mm were interpreted as indicating immunity, and reactions with a diameter >10 mm but no appreciable difference between the reagents were interpreted as pseudoreactions—that is, indicating possible hypersensitivity to an agent in the vaccine.

Serum samples were collected from all subjects before and four weeks after vaccination and analysed for antibodies to diphtheria toxin using a microcell culture technique.[2] Each sample was tested in fourfold dilution from 1:4 to 1:4096, corresponding to antitoxin titres, if positive, from 0·0025 to 2·56 IU. Subjects with titres ≤0·0025 IU were considered to be non-immune, those with titres between 0·001 and 0·004 IU to be partially immune, and those with titres >0·04 IU to be immune.

Correlation between results of Schick test and diphtheria antitoxin titres and side effects to diphtheria and tetanus toxoids (figures are numbers of subjects who provided information)

	Result of Schick test		
	Immunity	No immunity	Pseudoreaction
	Antitoxin titres		
Antitoxin titres before vaccination (IU):			
≤0·0025	5	1	1
0·01-0·04	8		3
>0·04	10	1	8
	Reactions to vaccine		
Erythema (mm):			
None	6		3
<20	7	1	1
20-50	7	1	7
<50	3		
Induration (mm):			
None	4	1	
<20	6		4
20-50	11	1	1
>50	2		7
Body temperature (°C):			
<37·5	17	1	10
37·5-37·9	4	1	1
>37·9	2		1

There was little correlation between serological results before vaccination and the reactions to the Schick test (table). Only one of seven subjects thought to be non-immune serologically had a corresponding Schick reaction. A better correlation was seen among subjects who were serologically immune. The specificity of the Schick test was only 54% when falsely positive and negative reactions and pseudoreactions were excluded. The sensitivity was also low (69%) as 11 of the partially immune or immune subjects had pseudoreactions. Serological findings after vaccination showed that 37 of 38 subjects who were evaluated developed at least fourfold increases in antitoxin titres. The Schick test did not predict adverse reactions to the vaccine (table). The intracutaneous route caused more pronounced local reactions.

Comment

The prevalence of healthy adults without immunity to diphtheria found in this study supports findings in Denmark.[3] The rapid increase in antibody titres indicated that adults aged 40 or under had been immunised previously and developed a booster response that seemed to be independent of the route of administration. Intracutaneous injections, however, caused more pronounced side effects.

The Schick test, a time consuming procedure, was a poor predictor of subjects' immune state and of side effects. In contrast, a group in the United Kingdom found a high correlation between results of the Schick test and antitoxin titres.[4] It did not, however, compare the techniques in the same subjects and excluded subjects with pseudoreactions. Results more closely agreeing with ours were found by Topciu *et al*.[5] A lack of correlation between immunity to diphtheria before vaccination and side effects indicates that the tetanus component of the vaccine may cause the local reactions.

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Fatal infection with Aeromonas sobria and Plesiomonas shigelloides

We report a case of infection with *Aeromonas sobria* and *Plesiomonas shigelloides* that caused a fatal illness similar to cholera.

Case report

A 19 year old woman with a history of bulimia nervosa was thrown into a water fountain while on holiday in Spain. No obvious inhalation of water occurred. Three days later she developed severe diarrhoea. The next day, because of personal problems, she took an overdose of eight paracetamol and eight aspirin tablets. She was admitted to hospital and given ipecacuanha and forced diuresis. Her diarrhoea continued, and three days later she returned to England and was admitted to this hospital. She was lethargic and dehydrated. Her temperature was 37·5°C, pulse 100 beats/min, and blood pressure 60/40 mm Hg. She had generalised abdominal tenderness. Investigations yielded: white cell count $12·7\times10^9$/l (with neutrophilia), prothrombin time 42/13 s, partial thromboplastin time 78/40 s, serum urea concentration 18·9 mmol/l (114 mg/100 ml), serum aspartate transaminase 199 U/l, serum bilirubin 7 μmol/l (409 μg/100 ml), and serum alkaline phosphatase 1570 U/l. Faecal microscopy showed moderate numbers of red cells and profuse white cells. No parasites were seen.

The diarrhoea persisted and her general condition deteriorated despite treatment with intravenous fluids, erythromycin, ampicillin, gentamicin, and hydrocortisone. She developed generalised muscular tenderness. Five days later investigations showed white cell count $6·6\times10^9$/l (with neutropenia) platelet count 76×10^9/l, prothrombin time 124/13 s, partial thromboplastin time 134/41 s, fibrin degradation products 50 mg/l, serum urea concentration 27·5 mmol/l (165 mg/100 ml), serum creatinine 323 μmol/l (3·7 mg/100 ml), aspartate transaminase 1135 U/l, serum bilirubin 20 μmol/l (1·2 mg/100 ml), serum alkaline phosphatase 790 U/l, and creatinine kinase >30 000 U/l. She became drowsy, breathless, and hypotensive and bled from the vagina, rectum, and sites of venepuncture. She died on the ninth day of her illness despite intensive treatment.

Two days before her death stool cultures, by direct plating on desoxycholate citrate medium, yielded a mixed growth of *Aeromonas* spp and *Plesiomonas* spp. These organisms were provisionally identified on the basis of their morphology, motility, and biochemical reactions. They were later identified as *A sobria* and *P shigelloides* by the Public Health Laboratory Service Reference Laboratory, Porton Down. *Aeromonas* spp showed intense β haemolysis in blood agar medium, suggesting production of soluble haemolysin. *Plesiomonas* spp, however, showed only poor haemolytic activity. No other enteric pathogen was isolated. Both organisms were sensitive to cefotaxime and chloramphenicol. Blood cultures yielded negative results.

At necropsy the colon showed mucosal oedema. Histological examination of skeletal and cardiac muscle showed multifocal fibre necrosis. The liver showed swelling, vacuolation, and separation of the hepatocytes without inflammatory infiltration. The marrow was hypoplastic, and the kidneys showed focal tubular atrophy. Fungal hyphas were seen in lung tissue.

Comment

Aeromonas sp and *P shigelloides* are pollutants of water and soil that may produce gastrointestinal, skin, soft tissue, muscle, and bone infections, meningitis, and endocarditis. In 1982 the Public Health Laboratory Service Centre for Microbiology and Research at Porton Down recorded 147 isolates of aeromonas and 24 of plesiomonas from patients with diarrhoea in Britain.

Although early reports suggested that aeromonas are secondary pathogens, this is not always so. Two reports described patients with illnesses similar to dysentery or cholera from whom *Aeromonas* sp producing enterotoxins were