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.

1 Christie AB. Diphtheria. In: Christie AB, ed. *Infectious diseases. Epidemiology and clinical practice.* 3rd ed. London: Churchill Livingstone, 1980:880-1.
2 Miyamura K, Nishio S, Ito A, Murata R, Kono R. Micro cell culture method for determination of diphtheria toxin and antitoxin titres using VERO cells. I. Studies of factors affecting the toxin and antitoxin titration. *J Biol Stand* 1974;2:189-201.
3 Kjeldsen K, Simonsen O, Heron I. Immunity against diphtheria 25-30 years after primary vaccination in childhood. *Lancet* 1985;i:900-2.
4 Ad-hoc working group. Susceptibility to diphtheria. *Lancet* 1978;i:428-30.
5 Topciu V, Babusceau-Plavosin L, Nica A. Titrierung des antidiphterischen Antitoxins auf Zelkulturen, Beziehungen des Antitoxin-Serumtiters und Schick-Reaktion. *Z Gesamte Hyg* 1966;12:377-81.

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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

isolated as the prime pathogens.[1 2] About 95% of strains similar to the *A sobria* that we isolated are enterotoxigenic in the suckling mouse. We found no other cause for our patient's diarrhoea.

Most serious aeromonas infections occur in immunosuppressed hosts. A fatal infection with *P shigelloides* was reported in a patient with sickle cell anaemia.[3] Although our patient had a history of bulimia nervosa, she had been psychiatrically and physically well for over a year before presentation. The pattern of abnormalities of coagulation and liver function was not that seen in patients after overdosage of paracetamol, and the liver showed only minimal necrosis.

We thank Dr P P Brown, consultant microbiologist at this hospital, and Dr J V Lee of the Public Health Laboratory Service Centre for Applied Microbiology and Research, Porton Down, for help in isolating the organisms.

1 Champsaur H, Andremont A, Mathieu D, Rottman E, Auzepy P. Cholera-like illness due to Aeromonas sobria. *J Infect Dis* 1982;**145**:248-54.
2 Rahman AHMS, Willoughby JMT. Dysentery-like syndrome associated with Aeromonas sobria. *Br Med J* 1980;**280**:976.
3 Ellner PD, McCarthy LR. Aeromonas shigelloides bacteraemia: a case report. *Am J Clin Pathol* 1973;**59**:216-8.

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Oral contraceptives and venous thromboembolism: findings in a large prospective study

Data on venous thromboembolism occurring among participants in the Oxford-Family Planning Association contraceptive study were last reported in 1978.[1] We summarise our latest findings here.

Subjects, methods, and results

The methods used in the study have been described.[2] The investigation includes over 17 000 women, who when recruited between 1968 and 1974 were married and aged 25-39; 56% were using oral contraceptives, 25% a diaphragm, and 19% an intrauterine device. During follow up data are recorded on changes in contraceptive methods, hospital referrals, and deaths. Discharge summaries are obtained after inpatient hospital stays.

The present report concerns 105 women suffering their first attack of venous thromboembolism unassociated with pregnancy or the puerperium. They were divided into two categories: those who developed disease within three months after a surgical operation (34) and those who became ill at other times (71). Each case record was assessed by one of us (DM), who as far as possible was blind to the patient's contraceptive practice; the record was allocated to one of three diagnostic groups—namely, certain or probable deep vein thrombosis or pulmonary embolism, or both; possible deep vein thrombosis or pulmonary embolism, or both; or superficial venous thrombosis only. Account was taken of the history, physical signs, results of special investigations (chest radiography, electrocardiography, lung scanning, ultrasound scanning, phlebography, etc) and type of treatment.

Our first series of analyses concentrated on the 71 women suffering thromboembolism unassociated with surgery. In calculating woman years of exposure to risk we omitted periods of observation during pregnancy and during the three months after a delivery or operation. Variables taken into account in the calculation of adjusted incidences were age, smoking history, and history of varicose veins. Several other variables including parity and obesity index had no important influence on risk. There was no significant difference in incidence between women who had never used oral contraceptives and those who had used them only in the past in any of the three diagnostic groups. Accordingly, and because of the small numbers studied, results are given only for those currently using and those not currently using oral contraceptives.

The table shows that there was a strong association between current oral contraceptive use and certain or probable venous thromboembolism (relative risk 7·2, $p<0·001$), a weaker association with possible thromboembolism (relative risk 3·1, $p<0·02$), and little or no association with superficial venous thrombosis (relative risk 1·4, NS). There was no significant association between risk and duration of use of oral contraceptives. Among current users the crude incidence of certain or probable thromboembolism/1000 woman years in those using oral contraceptives containing ≥50 μg oestrogen was 0·62 (20 cases during 32 082 woman years of observation) and in those using preparations containing <50 μg oestrogen it was 0·39 (three cases during 7606 woman years of observation). The corresponding figures for possible thromboembolism were 0·28 (nine cases) and 0. Possible thromboembolism occurred in one woman using a progestogen only oral contraceptive.

Incidence of venous thrombosis and embolism unassociated with surgery related to use of oral contraceptives

	Oral contraceptive use		
	Never or past	Current, ≤36 months	Current, >36 months
Deep vein thrombosis or pulmonary embolism certain or probable			
No of women	6	11	12
Incidence/1000 woman years:			
Crude	0·06	0·63	0·47
Adjusted*	0·06	0·47	0·39
		0·43†	
Deep vein thrombosis or pulmonary embolism possible			
No of women	7	3	7
Incidence/1000 woman years:			
Crude	0·06	0·17	0·28
Adjusted*	0·07	0·16	0·25
		0·22†	
Superficial venous thrombosis			
No of women	17	2	6
Incidence/1000 woman years:			
Crude	0·16	0·11	0·24
Adjusted*	0·15	0·13	0·25
		0·21†	

*Adjusted for age (four groups), smoking history (four groups), and history of varicose veins (two groups).
† Never or past users *v* current users: women with certain or probable thromboembolism $\chi^2_1=22·4$, $p<0·001$; women with possible thromboembolism $\chi^2_1=5·3$, $p=0·02$; women with superficial venous thrombosis $\chi^2_1=0·2$, NS.

We also analysed the data on the 34 cases of postoperative thromboembolism, confining our attention to surgical procedures after which at least one woman suffered the disease. The incidence of postoperative thromboembolism in those using oral contraceptives during the month before surgery (12/1244, 0·96%) was almost twice as high as that in those not doing so (22/4359, 0·5%), but the difference was not significant.

Comment

Our findings agree with those of other major studies in that, firstly, the association between use of oral contraceptives and venous thromboembolism is strongest in those with a certain or probable diagnosis; secondly, the risk is limited to current users; and, thirdly, the risk is unrelated to duration of use.[3-5] Our findings are consistent with the view that the risk is lower with pills containing <50 μg oestrogen, but the data are too few to confirm this.

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1 Vessey MP. Steroid contraception, venous thromboembolism and stroke: data from countries other than the United States. In: Sciarra JJ, Zatuchni GI, Speidel JJ, eds. *Risks, benefits and controversies in fertility control*. Hagerstown: Harper and Row, 1978:113-21.
2 Vessey M, Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception—an interim report. *J Biosoc Sci* 1976;**8**:373-427.
3 Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. *Br Med J* 1969;ii:651-7.
4 Sartwell PE, Masi AT, Arthes FG, Greene GR, Smith HE. Thromboembolism and oral contraceptives: an epidemiologic case-control study. *Am J Epidemiol* 1969;**90**:365-80.
5 Royal College of General Practitioners. Oral contraceptives, venous thrombosis and varicose veins. *J R Coll Gen Pract* 1978;**28**:393-9.

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