able plasma and urinary salicylate after topical rubefacient application.¹ We performed a study to examine the effect of topical rubefacient on the haemostatic mechanism in man.

Methods

Ten healthy adult volunteers applied 10 g of Bayolin (benzyl nicotinate, glycol salicylate, and a heparinoid) to each calf on two separate occasions. On one occasion 600 mg of aspirin was taken 12 hours earlier, and on a third occasion the effect of 600 mg aspirin alone was examined. The three tests were performed randomly at three week intervals. No drugs were permitted during the study.

A series of studies were carried out before and 45 minutes after Bayolin application: blood count, prothrombin time, partial thromboplastin time, thrombin time, plasma fibrinogen, fibrinolytic screen (plasminogen activator, plasminogen and α_2 -plasmin inhibitor concentrations), platelet studies (aggregation to collagen and serum thromboxane B_2 concentrations), chromogenic substrate assays of heparin and factor Xa, and plasma salicylate concentrations. A subjective score (0-4) of the intensity of the cutaneous response was recorded and compared with an objective assessment of this response.

Results

All volunteers experienced heat, erythema, and paraesthesia in the area of application with a maximal response 20 to 40 minutes after application. Individual variation in the intensity of response was noted. The subjective response correlated well with an objective assessment of severity. Four individuals had a pronounced response (score 3-4), the mean response being 2.4 (SD 1.1). Ingestion of aspirin before the test greatly reduced or abolished the cutaneous response to ointment (mean 0.3 (0.5)).

The blood count, coagulation screen, and fibrinolytic activity were unaltered by topical rubefacient irrespective of aspirin (table). Plasma heparin activity and salicylate were undetectable after rubefacient alone. Topical rubefacient produced no change in serum thromboxane B_2 concentrations, but inhibition of platelet aggregation to a collagen dose of 5 μ g/ml occurred ($p < 0.05$). Aspirin administered before the tests abolished platelet aggregation and reduced the serum thromboxane B_2 concentration.

Inhibition of platelet aggregation after rubefacient was most apparent in the four volunteers with a pronounced cutaneous response. Their mean aggregation to collagen (5 μ g/ml) fell from 84 (9)% to 54 (15)% and the dose giving 50% aggregation (median effective dose) increased from 0.56 (0.37) μ g/ml to 1.17 μ g/ml.

Discussion

Inhibition of platelet aggregation to collagen 5 μ g/ml is the only detectable haemostatic abnormality after application of a single dose of Bayolin. The greater inhibition observed in volunteers with an intense cutaneous response may indicate that after intense erythema greater absorption of salicylate occurred, though this was still below detectable concentrations. This observation is consistent with animal studies showing enhanced epicutaneous absorption of salicylate when nicotinic acid benzyl ester was added.¹

Inhibition of the cutaneous response to rubefacients by oral analgesia has been previously observed.⁵ If these compounds have any analgesic effect it is probably mediated through the cutaneous symptoms evoked. While this study suggests that topical rubefacient does not produce appreciable haemostatic defects in man, it appears that concurrent aspirin may noticeably impair any beneficial local effect.

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Cutaneous amoebiasis: case report

Amoebiasis, whether presenting as colitis, hepatic abscess, or empyema, may be misdiagnosed in Britain, particularly in patients who have never been abroad.¹ The much rarer cutaneous amoebiasis is also likely to be underdiagnosed; this is particularly so when it affects the abdomen after laparotomy, because the spreading gangrene of the skin closely mimics the postoperative synergistic gangrene of Meleney, with which it has been confused.^{2,3} We report a further example of this mistake.

Case report

A 21 year old man who had recently returned from the Far East was admitted on 4 September 1965 with fever (37.8°C) and severe pain in the left hypochondrium and in the back. The white cell count was $13 \times 10^9/l$ with a neutrophil leucocytosis. A fortnight later a tender epigastric swelling was found between the left costal margin and the lateral border of the left rectus abdominis. The history of foreign travel and the leucocytosis suggested an amoebic liver abscess but there had been no diarrhoea or dysentery, repeated examination of stools showed no amoebas, and result of the complement fixation test was negative. Surgical exploration of the swelling produced 250 ml of white pus. The cause of the abscess was obscure. It did not communicate with the liver or spleen and on culture there was no bacterial growth.

Drainage of the abscess relieved the pain but a fortnight later it returned. The white cell count had risen to $19 \times 10^9/l$ and the abscess was therefore re-opened and drained. Subsequently the wound edges became black, exquisitely tender, and intensely painful. The gangrenous process spread outwards across the abdomen, and the triple zonation (a central slough, a raised purplish black margin, and an outer, bright red zone of hyperaemia) of Meleney's bacterial gangrene became apparent. The classical treatment of radical excision of the edges of the ulcerated area failed to halt the spread and the patient's condition deteriorated, owing largely to the intolerable pain.

At this stage the ulceration occupied a large part of the upper abdomen (figure) but *Entamoeba histolytica* (strongly positive result on periodic acid Schiff staining) had been identified in sections prepared from the excised wound margins. The diagnosis was changed to cutaneous amoebiasis. Antiamoebic treatment (dehydroemetine 80 mg daily subcutaneously) was begun and within 48 hours a dramatic improvement occurred. The pain resolved completely and the patient felt and looked much better. The gangrene of the ulcer edges began to fade and healing began, becoming complete some three months later (figure). The patient resumed his occupation and when last seen in August 1984 was well.

Comment

Amoebiasis may affect patients who have never been out of Britain.¹ Cutaneous amoebiasis has often escaped early diagnosis because it

Effects of rubefacient ointment on haemostasis (mean (SD) results in 10 volunteers)

	Coagulation studies			Fibrinolysis studies			Platelet studies			
	Thrombin time (s)	One stage prothrombin time (s)	Activated partial thromboplastin time (s)	Plasminogen activator (fibrin plate mm)	Plasminogen (%)	α_2 -Plasmin inhibitor (%)	Fibrinogen (g/l)	Serum thromboxane B ₂ (ng/ml)	Aggregation (median effective dose) (μ g collagen/ml)	Aggregation to 5 μ g collagen/ml (%) maximum)
Before application	7 (1)	14 (1)	41 (4)	11.8 (3.2)	89.7 (5.7)	93.2 (7.2)	2.5 (0.6)	226 (173)	0.53 (0.26)	84.5 (6.8)
After application	7 (1)	14 (1)	41 (5)	13.4 (2.2)	92.8 (9.5)	94.3 (5.9)	2.5 (0.5)	224 (115)	0.77 (0.59)	71.1 (17.5)*

* $p < 0.05$.

closely resembles Meleney's gangrene in appearance and cause.^{2,3} Several factors contributed to the delay in diagnosing amoebiasis in our patient—the absence of amoebas in the stools, the negative complement fixation test result, the white abscess pus instead of the classical "anchovy" pus, the fact that amoebas are not visible in Gram

Top: Postoperative cutaneous gangrene of abdominal wall due to amoebiasis. Appearance bears striking resemblance to Meleney's gangrene. Bottom: Appearance of abdomen three months after beginning emetine. Healing is complete but with extensive scarring.

stained films of pus, and the recognised difficulty in diagnosing amoebic abscesses in the left lobe of the liver.⁴ The complement fixation test for amoebiasis has now been superseded by the more reliable immunofluorescence test.⁵

In a patient with progressive gangrene of the abdominal wall it is essential to exclude amoebiasis before accepting the alternative diagnosis of synergistic bacterial gangrene of Meleney.

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Antagonism of ceftazidime by chloramphenicol in vitro and in vivo during treatment of Gram negative meningitis

Following the work of Jawetz and his colleagues in the 1950s¹ a considerable body of evidence has accumulated that bacteriostatic and bactericidal drugs may antagonise each other in vitro² and in vivo in both animals^{3,4} and man.⁵ Despite this many authorities believe that antagonism between bacteriostatic and bactericidal drugs is unimportant, and the use of such combination treatment in bacterial meningitis is still widely practised. We have observed definite and clinically important antagonism, both in vitro and in vivo, between chloramphenicol and the cephalosporin ceftazidime during treatment of a young infant with salmonella meningitis. The combination treatment failed to eradicate the infection but subsequent treatment with ceftazidime alone was successful.

Case report

A previously normal 2½ month old boy was admitted in November 1984 with a two day history of fever, diarrhoea, abdominal distension, and poor feeding. Twelve hours after admission he had generalised convulsions and a rectal temperature of 40°C. The cerebrospinal fluid was bloodstained and a cell count could not be performed; the glucose concentration, however, was 2.0 mmol/l (36 mg/100 ml) (blood glucose concentration 6.7 mmol/l; 121 mg/100 ml). Gram staining showed Gram negative rods, and both cerebrospinal fluid and blood cultures yielded *Salmonella enteritidis* group D.

Intravenous treatment was begun with chloramphenicol 75 mg/kg/day, later increasing to 100 mg/kg/day, together with ceftazidime 100 mg/kg/day, in three divided doses. The child showed little response over the next four days, with persistent fever. A second sample of cerebrospinal fluid taken on the fourth day of treatment contained a white cell count of $136 \times 10^6/l$ (89% polymorphs), protein 1.59 g/l, and a glucose concentration of 1.6 mmol/l (29 mg/100 ml) (blood glucose concentration 4.7 mmol/l; 85 mg/100 ml). Gram staining gave a negative result and a blood culture was sterile, but again culture of cerebrospinal fluid grew *S. enteritidis*.

In vitro tests of serum and cerebrospinal fluid taken at that time showed that the serum could inhibit the growth of an inoculum of the salmonella at a dilution of 1/2, and the cerebrospinal fluid at a dilution of 1/16, but that neither fluid could kill the organism at any dilution (table). The minimal inhibitory concentrations of chloramphenicol and ceftazidime for the salmonella were 4 mg/l and 0.5 mg/l, respectively. The minimal bactericidal

Concentrations of ceftazidime and chloramphenicol in serum and cerebrospinal fluid and in vitro bacteriostatic and bactericidal activities of serum and cerebrospinal fluid against isolated strain of salmonella. (Minimal inhibitory concentration and minimal bactericidal concentration of ceftazidime 0.5 mg/l; minimum inhibitory content of chloramphenicol 4 mg/l)

	26 November		30 November	
	Serum	Cerebrospinal fluid	Serum	Cerebrospinal fluid
Growth of salmonella	—	+	—	—
Ceftazidime (mg/l)	1.53	15.3	234.6	31.5
Chloramphenicol (mg/l)	5.4	8.0	—	—
Inhibitory dilution	1/2	1/16	ND	1/32
Bactericidal dilution	—	—	ND	1/32

ND = Not done.

On 26 November treatment was with ceftazidime plus chloramphenicol, each 100 mg/kg/day in three divided doses, and specimens were collected seven hours after last dose. On 30 November treatment was with ceftazidime 150 mg/kg/day alone in four divided doses, and specimens were collected three hours after last dose.

concentration of ceftazidime was 0.5 mg/l, identical with the minimal inhibitory concentration. Concentrations of the antibiotics in serum and cerebrospinal fluid were measured by high pressure liquid chromatography. The cerebrospinal fluid, which had yielded salmonella on culture and failed to kill the organism in vitro, was found to contain 15.3 mg ceftazidime and 8.0 mg chloramphenicol/l (table). This amount of ceftazidime was 30 times greater than the minimal bactericidal concentration and should have been more than enough to kill the organism. This result suggested antagonism of ceftazidime by chloramphenicol in vivo.

Chequerboard titration of all possible concentrations of chloramphenicol and ceftazidime against the salmonella disclosed antagonism in vitro. Titration showed that when used alone ceftazidime at a concentration of 0.5 mg/l (the minimal bactericidal concentration) killed the organism but that when combined with chloramphenicol 4 mg/l or more the combination was bacteriostatic but not bactericidal at concentrations up to 16 mg ceftazidime/l.

In view of these findings chloramphenicol was stopped and treatment continued with ceftazidime alone at 150 mg/kg/day in four divided doses.