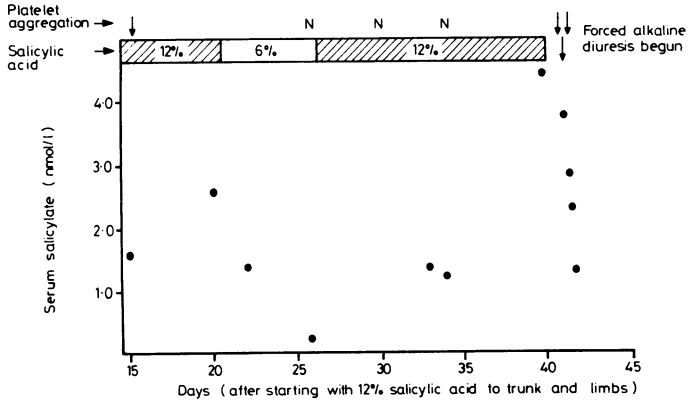
Systemic toxicity from topically applied salicylic acid

Topically applied salicylic acid has enjoyed long and extensive usage as an agent to enhance desquamation in various hyperkeratotic skin diseases. In some of these disorders much of the skin surface may be affected, resulting in the potential for significant percutaneous absorption of the drug. We describe a patient who gradually developed evidence of severe salicylate toxicity while being treated with topical salicylic acid. Consequent on a recent letter in the *BMJ*[1] this report serves as a reminder of a problem which, although recognised,[2] may be unfamiliar to the current generation of dermatologists. It also shows strikingly the systemic absorption that may result from compounds applied to the skin.

Case history

The patient was a 30-year-old man from Mauritius with a history of extensive ichthyosis starting within a few days of birth. Examination showed a small man (weight 46 kg, height 144 cm) with severe generalised ichthyosis, bilateral ectropion, and gross thickening of the horny layer of the palms and soles. Renal function and liver function tests (including serum albumin estimation—48 g/l) were normal. Histologically the skin showed hypergranulosis and pronounced hyperkeratosis. A diagnosis of autosomal recessive non-bullous ichthyosiform erythroderma of the lamellar type was made. Epidermal kinetic studies showed epidermopoiesis to be at the upper limit of normal, and thus the basis for his ichthyosis appeared to be retarded desquamation. He was therefore started on topical salicylic acid in cetomacrogol, initially at a concentration of 4%, daily to the right leg. The rest of his skin was treated with emollients.

The topical salicylic acid was gradually increased to 12% in cetomacrogol applied to the trunk and limbs (except the soles) twice daily (approximate daily dose 150 g). The patient remained on this regimen for 20 days. Serum salicylate concentrations during the second half of this period (see fig) were



Serum salicylate concentrations and results of platelet aggregation tests (n=normal; ↓=moderate impairment; ↓↓=severe impairment) in patient treated with topical salicylic acid. (1 mmol serum salicylate/l≈13·8 mg/100 ml.)

1·6 and 2·57 mmol/l (22·1 and 35·5 mg/100 ml) (upper limit of therapeutic range 2·2 mmol/l; 30·4 mg/100 ml). At this stage the patient's platelets showed impairment of collagen-stimulated aggregation (quantitative in-vitro optical density method). In view of this and since his skin had greatly improved the strength of the topical salicylic acid was reduced to 6%. Serum salicylate concentrations fell. His ichthyosis, however, apparently worsened and after six days 12% salicylic acid was reinstituted. Twelve days later, although the serum salicylate values had twice been reported in the middle of the therapeutic range, he began to complain of malaise, nausea, epigastric discomfort, tinnitus, and slight deafness. Examination disclosed mild sensorineural deafness and he was noted to be hyperventilating. The serum salicylate concentration was 4·55 mmol/l (62·8 mg/100 ml) and the platelet aggregation test showed considerable quantitative impairment. He had a metabolic acidosis (serum bicarbonate 17 mmol (mEq)/l). Topical salicylic acid was stopped and an intravenous infusion forced alkaline diuresis begun. His condition rapidly improved.

Comment

The pronounced percutaneous absorption seen in this patient was undoubtedly related to both the high concentration of salicylic acid used and the fact that it was applied to 85-90% of the body surface. An exacerbating factor would have been a high "skin surface area: body mass" ratio resulting from the patient's small size. In these respects the patient was similar to the case reported by Aspinall and Goel.[1] We expected that appreciable absorption of salicylic acid might occur but were surprised by its delay and severity. The severity may have been due in part to a thinner stratum corneum (at that stage of the treatment) and to decreased renal clearance of salicylate secondary to its induction of a metabolic acidosis. Weiss and Lever[2] cited 13 deaths reported to be due to topical salicylic acid treatment. Patients given frequent high concentrations of salicylic acid topically over a large surface area thus require close clinical and biochemical monitoring.

Our case provides a further reminder that the topical application of drugs, particularly to abnormal skin, may result in toxicity comparable to that seen with systemic administration.

Dr R Marks, Cardiff, conducted the epidermal kinetic studies on this patient.

[1] Aspinall, J B, and Goel, K M, *British Medical Journal*, 1978, **2**, 1373.
[2] Weiss, J F von, and Lever, W F, *Archives of Dermatology*, 1964, **90**, 614.

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Controlled trial of cimetidine in acute upper gastrointestinal bleeding

The histamine H_2-receptor antagonist cimetidine is a potent inhibitor of gastric acid and pepsin secretion.[1] It might therefore prevent peptic digestion of blood clot attached to an eroded vessel in acute upper gastrointestinal bleeding. Prophylactic administration to patients with fulminant hepatic failure reduces the incidence of subsequent bleeding from gastric and oesophageal erosions.[2] We have therefore conducted a prospective, double-blind trial of cimetidine in an unselected series of 69 patients admitted with acute upper gastrointestinal bleeding. Monitoring included central venous pressure (CVP) measurements as a sensitive indicator of recurrent bleeding,[3] because recurrent bleeding is the single most important factor determining mortality.[4]

Patients, methods, and results

All patients admitted with acute upper gastrointestinal bleeding were entered into the trial before they left the casualty department. All gave written informed consent. Patients excluded were (*a*) those whose bleeding was so profuse that immediate surgery was indicated, and (*b*) those whose last evidence of bleeding was more than 72 hours before admission.

Cimetidine (or matching placebo) was given intravenously for 48 hours —200 mg immediately, then 250 mg every six hours—and then by mouth for five days—400 mg thrice daily and 800 mg at bedtime. The trial was terminated at the end of this period, or earlier if there had been evidence of rebleeding. The initial bleed was designated severe if the patient fulfilled any of the following criteria on admission: (*a*) systolic blood pressure below 100 mm Hg, (*b*) pulse rate exceeding 110 beats/min, and (*c*) a haemoglobin concentration below 8 g/dl. Whenever possible patients were admitted to the intensive care unit, where a CVP line was inserted and its position checked radiologically. Pulse rate, blood pressure, and CVP were checked hourly for the first 48 hours. Five criteria were used to diagnose further bleeding: (1) failure of the CVP to reach a sustained level of +1 cm water above the manubriosternal joint after seven units of blood[3]; (2) a fall in CVP from this level to less than −4 cm water over two hours or less[3]; (3) a fresh haematemesis; (4) a sudden rise in pulse rate of over 20 beats/min or a sudden fall in systolic blood pressure of more than 20 mm Hg; and (5) active bleeding detected by endoscopy, which was routinely carried out in the first 24 hours after admission.

Sixty-nine patients completed the trial: 33 received cimetidine, of whom 12 (36%) rebled, and 36 placebo, of whom 10 (28%) rebled. Fifteen patients in the cimetidine group had had a severe initial bleed, and of these 10 rebled. Thirteen patients in the placebo group had had a severe bleed, and of these five rebled. Eighteen patients in the cimetidine group had had a mild initial