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Generalised allergic reactions to aminophylline

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ABSTRACT Details of three patients who developed allergic responses to aminophylline are presented, together with data on such reactions compiled from reports submitted to the Committee on Safety of Medicines. Two of the patients developed generalised rashes within one day of starting treatment with oral aminophylline. Other symptoms included malaise and confusion. A third patient had severe generalised symptoms and a high fever, which was reproduced on challenge testing. Forty five of 147 reactions to aminophylline reported to the Committee on Safety of Medicines referred to dermatological or allergic reactions and in two instances exfoliative dermatitis was described. In contrast, only seven of 61 reported reactions to theophylline described skin or allergic responses and in none of these was dermatitis or a specified rash mentioned. The available evidence suggests that ethylenediamine rather than the xanthine component of aminophylline may be the principal cause of the reactions.

Theophylline is used as a bronchodilator in obstructive airways disease and has been combined with ethylenediamine (15% by weight) to increase its solubility 20 fold. This combination (aminophylline) is regarded as being ideal for intravenous use and has become popular as an oral formulation of theophylline in Britain. Although the side effects of theophylline are well known, those of ethylenediamine are not. Since the report in 1958 of an industrial pharmacist developing contact dermatitis while working with aminophylline,[1] dermatologists have become increasingly aware of the potential of ethylenediamine for producing rashes. In this initial report the rash affected hand, arms, and face and re-exposure some months later caused it to reappear within eight hours. Subsequently, several other investigations have confirmed the risk of contact dermatitis on exposure to ethylenediamine, which is present in many proprietary drugs, particularly antihistamines and some steroid creams, and in a range of industrial products such as dyes, rubbers, and insecticides.[2–5] The incidence of ethylenediamine sensitivity has been reported to be as high as 13% in patients with contact dermatitis and to represent up to 60% of all positive reactions to skin patch tests.[6–10] The association between systemic (rather than topical) administration of ethylenediamine, however, and allergic skin reactions or other allergic manifestations has received limited recognition.

We report three patients in whom ingested aminophylline produced rashes or allergic reactions and tabulate and review reports to the UK Committee on Safety of Medicines (CSM) of such reactions from 1964 to 1983.

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Case reports

CASE 1

A 13 year old boy with a history of childhood asthma and eczema was admitted to hospital with an exacerbation of his asthma. He had positive skin prick test responses to cat, dog, and grass pollen; the white count was $5{\cdot}9 \times 10^9$ (6% eosinophils) and the IgE level was 400 (normal 85–150) IU/l. His regular medication was inhaled salbutamol and beclomethasone and he took cromoglycate before exercise. While in hospital aminophylline 225 mg twice daily was added to his treatment. No other new drugs were prescribed and no obvious allergens were present. Twenty four hours after taking the aminophylline he developed a generalised erythematous maculopapular rash with a fever, headache, and confusion. Treatment with aminophylline was stopped. Fourteen days later he was rechallenged with an oral dose of aminophylline (225 mg) in hospital and he developed similar symp-

toms within eight hours. He was advised to avoid aminophylline compounds and to continue with cromoglycate treatment for his asthma.

CASE 2

A 52 year old man with mild lifelong atopic asthma presented with increasing cough and dyspnoea of two months' duration. He reported an episode five years earlier when, on the day after taking one 225 mg sustained release aminophylline tablet, he developed a rash affecting the neck and limbs. Two years later he inadvertently took another tablet and developed a similar rash after six hours. His regular medication comprised salbutamol taken by inhaler and as tablets. During admission to hospital theophylline (Nuelin SA 175 mg) was added without adverse effect. Bronchoscopy identified a small cell carcinoma, from which he died seven months later.

CASE 3

A 55 year old woman with asthma was seen in the outpatient clinic and treatment with oral sustained release aminophylline was prescribed. After 48 hours she developed fever, headache, malaise, and muscular pains. At that time her other treatment included salbutamol and beclomethasone by inhalation and oral prednisolone in a dose of 10 mg daily. She had a past history of rashes occurring after the use of both co-trimoxazole and oxytetracycline. Treatment with aminophylline was stopped and her symptoms improved within 24 hours. Four days later she was formally rechallenged with a sustained release aminophylline tablet and her symptoms returned within five hours; she developed a fever peaking at 39°C after 12 hours, which returned to normal within 24 hours. She was advised not to take aminophylline in future.

Data from the Committee on Safety of Medicines

Data from the Committee on Safety of Medicines cannot reflect the true incidence of drug side effects; a comparison of the frequency of adverse reactions to two similar drugs can, however, identify significant differences. If the adverse reaction profiles of aminophylline and theophylline are compared it may be reasonable to assume that any major differences represent reactions to ethylenediamine.

Skin and allergic reactions after the systemic use of aminophylline have been reported infrequently to the Committee on Safety of Medicines. From January 1964 to February 1983 the Committee on Safety of Medicines accumulated a list of 147 adverse reactions to aminophylline products; 45 of these related to skin or allergic reactions (30·6%), of which two were specifically described as exfoliative dermatitis. In contrast, there were 61 reported reactions to theophylline products, of which only seven were related to skin or allergic response (11·5%), none of these being described as "dermatitis" or a specified "rash" (table).

Discussion

Skin and allergic reactions to ethylenediamine given systemically in the form of aminophylline are not well recognised and the Committee on Safety of Medicines data reflect this. In published reports there have been 16 patients reported with skin reactions to xanthine,[3 11–21] all but one being attributed solely to aminophylline.[11] Among the 16 were seven with dermatitis,[3 14 17–20] six with exfoliative dermatitis,[12–16] and three with urticaria[11 17 21]; nine occurred after intravenous administration,[14–19 21] five after oral ingestion,[3 15 17 20] and two after rectal administration.[12 13] It is possible that aminophylline as a compound rather than the ethylenediamine compound is responsible for this difference. Aminophylline, however, dissociates in the body and ethylenediamine is known to be a potent contact allergen, whereas the limited reports and Committee on Safety of Medicines data suggest theophylline to be of low allergenicity. The evidence provided by our patients, the Committee on Safety of Medicines records, the published reports, and results of skin

Adverse skin reactions and allergic responses to theophylline and aminophylline reported to the CSM from January 1964 to February 1983

Reactions	*Aminophylline*	*Theophylline*
Angioedema, facial oedema, and anaphylactic reactions	5	1
Urticaria	9	2
Pruritus	2	2
Photosensitivity	1	—
Dermatitis, including exfoliative dermatitis	5	—
Rash, including erythematous, maculopapular, and non-specified skin disorders	22	1
Erythema multiforme	1	1
Total	45	7
All reported reactions to the CSM (including those above as well as non-allergic and non-dermatological side effects)	147	61

patch testing implicates ethylenediamine as the most likely cause of these adverse reactions. Although in our patients the use of oral aminophylline was sufficient to evoke a response, the fact that only about 30% of ethylenediamine ingested orally is absorbed could explain the lower incidence of reported reactions after oral than after intravenous use.[22] Awareness of reactions may, however, depend upon the route of administration. Acetylation has been identified recently as one of the major metabolic pathways of ethylenediamine, and the incidence of acetylators may be an important determinant of the total incidence of allergic responses to aminophylline.[23] This mechanism has not yet been investigated in those reacting adversely.

In our three patients the time of onset of dermatitis or allergic response after a second exposure to aminophylline was considerably shorter than the first exposure (six to eight hours as opposed to 24 to 48 hours). Rashes occurred over similar time courses in four of the five patients described in published reports as having had more than one challenge.[13 16 18–20] This observation suggests that sensitisation and multiple immunological mechanisms, encompassing both humoral and cell mediated pathways, may be concerned. Consistent with this is the fact that three patients have been reported with a type I immediate hypersensitivity reaction to intravenous or oral aminophylline resulting in urticaria or angioedema.[11 17 23] Attempts to delineate the precise immunological mechanisms concerned have so far proved inconclusive and, although a positive response to a skin patch test may be useful in establishing a diagnosis, false negative results have been reported.[17] Similarly, a past history of contact or allergy to topical ethylenediamine, or both, is useful but not always present.

With the widespread use of ethylenediamine in industry and in pharmaceuticals the risk of exposure is considerable. Physicians should be aware of adverse reactions to ethylenediamine and particularly of its ability to induce asthmatic responses.[1 16 24 25] When patients are given treatment for asthma any deterioration in their asthma may be due to aminophylline rather than a worsening of their primary disease state. Similarly, awareness of potential ethylenediamine sensitivity may avoid confusion with other drug induced rashes and allergic responses, and circumvent rechallenge in a patient with a history of previous rash. This, in some instances, may avert a potentially life threatening exfoliative reaction or asthma. The wide variety of potential sensitisers containing ethylenediamine suggests that avoidance may be difficult and some antihistamines may aggravate the problem. Patients do not, however, need to be deprived of xanthine drugs. A pure oral theophylline formulation may be administered, and in an acute illness either one of its analogues (for example, dihydroxypropyltheophylline)[15] or a salt such as lysine theophylline[26] may be given intravenously.

Addendum

The Committee on Safety of Medicines data are available on the F06S adverse reaction printouts for theophylline and aminophylline brands. We are indebted to Dr JCP Webber, medical officer, Committee on Safety of Medicines, for communications about this material and for permission to quote it. In so doing we acknowledge that any interpretation of these data is that of the authors and not necessarily that of the Committee on Safety of Medicines.

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