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Stevens-Johnson syndrome due to tetracyclines—a case report (doxycycline) and review of the literature

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Summary

A young adult female with Stevens-Johnson syndrome due to doxycycline is described. Other reports of Stevens-Johnson syndrome due to tetracyclines are also reviewed.

Erythema multiforme is an inflammatory skin reaction often recurrent and of unknown cause. It may be precipitated by various agents, including drugs and infections and occur at any age, but is most common in young adults. The lesions present may be of many types but usually one type predominates. It was first described by Hebra in 1860.[1] The most severe form of erythema multiforme was described in 1922 by Stevens and Johnson[2] as an eruptive fever associated with stomatitis and severe conjunctivitis. The best-documented drug association with Stevens-Johnson syndrome is long-acting sulphonamides.[3,4]

Case Report

A 34-year-old woman who had been treated 6 years previously for late secondary syphilis but had not received a full course of treatment because of an allergic reaction to penicillin, was given a 15-day course of doxycycline 300 mg daily, as a precautionary measure in late November–December 1985, in view of unchanged raised serology titres. The titres had been checked during routine pregnancy screening in October 1985. The patient requested a termination of pregnancy and received a 5-day course of tetracycline at that time without ill-effect (the routine post-abortion procedure for all patients at that hospital). The day after completing the 15-day course of doxycycline she developed burning of her eyes and dysuria and, after a further 2 days, the eruption of erythema multiforme. She was admitted urgently to hospital five days after discontinuation of the drug. Large bullae appeared soon after admission in addition to widespread small discrete papular and vesicular skin lesions and extensive mouth, genital, and eye involvement. Investigations revealed a normal full blood count and serum electrolytes, and a normal CXR. A skin biopsy confirmed the diagnosis of erythema multiforme. Paired sera for Herpes simplex, Mycoplasma pneumoniae, and Psittacosis showed no significant increase in titres.

She was treated with intravenous fluid replacement, oral erythromycin, intravenous hydrocortisone 400 mg daily, followed by a tapering course of oral prednisolone, and was nursed on a ripple bed. Eye lesions were treated with chloramphenicol eye ointment and prednisolone/neomycin (Predsol-N) eye drops. Mouth lesions were treated initially with benzydamine hydrochloride oral rinse (Difflam) and later chlorhexidine gluconate (Corsodyl) mouth wash. She made a gradual recovery, and was discharged home 25 days after admission, receiving a mouth wash containing triamcinolone 1 mg t.d.s. for persistent gingival and buccal ulceration. At the time of discharge she showed guttate macular hypopigmented areas over the backs of both forearms, and post-inflammatory hyperpigmentation over her cheeks and back. This was improving when seen at follow-up one, and three months later. She had residual mild conjunctival scarring, and epiphora affecting both eyes due to scarring of the puncta: the latter required minor ophthalmological surgery.

Discussion

Tetracyclines are widely used in dermatology patients in the management of acne and rosacea. Severe adverse reactions are uncommon. The principal side-effects, i.e. nausea, vomiting, and sometimes diarrhoea, are due to retention of the antibiotic in the bowel.[5] Other effects include deposition in calcifying bone, and staining of the deciduous teeth[6], liver damage[7], renal toxicity[8,9], oesophageal ulceration[10] and raised intracranial pressure.[11] Skin reactions are relatively rare. Arndt and Jick predicted a cutaneous reaction rate of not greater than 0·3% for tetracycline (upper confidence limit 95%) compared with an observed rate of 5·9% for co-trimoxazole, and 5·2% for ampicillin.[12] In addition to erythema multi-

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forme, fixed drug eruption[13,14], toxic epidermal necrolysis[15], exanthematic eruptions, urticaria, angioedema and purpura[16] have been reported. Dimethylchlortetracycline and, to a lesser degree, other tetracyclines, are phototoxic.[17,18]

There are scanty reports in the literature of tetracyclines causing Stevens-Johnson syndrome. Up to February 1986 the Committee on Safety of Medicines had reports of five cases of Stevens-Johnson syndrome due to tetracyclines, but this is, of course, likely to be an underestimate because of lack of reporting of adverse effects. Caldwell and Cluff[19], in a 3-year prospective study of adverse reactions to antimicrobial agents, described six cases of Stevens-Johnson syndrome of which two were caused by tetracycline. Ting and Adam[20] reported 34 cases occurring over a 16-year period of which four were attributed to tetracycline. Tetracycline has, in some reports, been given in addition to other drugs. Of the two patients reported by Claxton[21], who had received tetracycline prior to the development of Stevens-Johnson syndrome, one had also received sulphamethoxypyridazine: whether the other patient had also received further drugs is not stated. Gorbachev and colleagues[22] described a patient who developed Stevens-Johnson syndrome after a combination of tetracycline, penicillin, and streptomycin. In addition, patients are often prescribed antibiotics for pre-existing infection, and it is not always possible to decide which is the aetiological factor. Wasserman and Glass[23] described a patient who developed Stevens-Johnson syndrome after taking tetracycline phosphate capsules, but were also able to demonstrate an eight-fold rise in titre of antibodies to type A Influenza virus. Ström[24], in a survey of 266 patients with febrile mucocutaneous syndromes, identified one patient who was treated for an infection with a tetracycline, and two patients who were treated with tetracycline in combination with penicillin or sulphonamide. Prusek and colleagues[25] described a case of Stevens-Johnson syndrome associated with bone marrow aplasia occurring in a child treated for bronchitis with methacycline (Rondomycin).

Doxycycline (6-Deoxy-5β-hydroxytetracycline monohydrate), is a long-acting tetracycline which is readily absorbed from the gastro-intestinal tract and has adverse effects similar to the other tetracyclines. We are unaware of any published reports, in the English literature, of Stevens-Johnson syndrome following use of this antibiotic. Albengres and co-workers[26] described a case of recurrent Stevens-Johnson syndrome which occurred after taking doxycyline which was also precipitated by hexacycline (tetracycline phosphate complex).

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