Hypersensitivity to retinol palmitate injection

Professors W B SHELLEY and E D SHELLEY and Assistant Professor N Y Talanin (Department of Medicine, Medical College of Ohio, PO Box 10008, Toledo, Ohio 43699-0008, USA) write: McCormick reported local inflammatory reactions after intramuscular injections of vitamin A and concluded that the vehicles used to make vitamin A water soluble were responsible.¹ Our observations show that vitamin A (retinol) can itself cause an inflammatory hypersensitivity reaction.

A 66 year old woman with xerosis and lichen sclerosus et atrophicus was first given intramuscular water soluble retinol palmitate in January 1994 with no adverse reaction. Two weeks after receiving a second injection (50000 IU) of retinol palmitate in March 1994 she noted a red itchy area on her right buttock over the second injection site. This grew into an oval erythematous scaly plaque (7.5 cm x 9.0 cm) with a haemorrhagic component, which slowly disappeared over three weeks (figure). Cutaneous hypersensitivity to an ingredient of the retinol injection was suspected.

An intradermal skin test to retinol palmitate (0.1%) was positive at 48 hours, showing a red nodule of 1.2 cm. Similar intradermal tests with all other constituents of the water soluble retinol injection gave negative results, including polysorbate 80, chlorobutanol, butylated hydroxyanisole, butylated hydroxytoluene, and citric acid. Five control patients similarly tested showed no reaction. In our patient a retinol patch test gave negative results and oral challenge with vitamin A was without incident.

To our knowledge, only one case of retinol allergy has been proved: this was an allergic contact dermatitis caused by retinol palmitate in a

cosmetic cream.² No specific sensitivity to injectable retinol has been reported, although retinol injections have been a suspected cause of anaphylactic shock and sudden death.^{3,4} Our patient developed a delayed cutaneous hypersensitivity reaction to retinol injection. Results of skin tests confirmed a specific delayed intradermal hypersensitivity to retinol palmitate, but there was no contact sensitivity or oral intolerance. Although allergy to retinol is rare, our case should alert clinicians using injectable vitamin A.⁵

- 1 McCormick PA, Hughes JE, Burroughs AK, McIntyre N. Reformulation of injectable vitamin A: potential problems. *BMJ* 1990; 301:924.
- 2 Blondeel A. Contact allergy to vitamin A. *Contact Dermatitis* 1984;11:191-2.
- 3 Nagano T, Jimbo M, Hamasaki Y. Sudden death following injection of water-miscible vitamin A. *Wakayama Medical Reports* 1965; 10:105-11.
- 4 Danilov LN, Finogenov LN. Anaphylactic shock following administration of vitamin A. In Russian. *Klinicheskaya Meditsina* 1977; 55:122-3.
- 5 Bates CJ. Vitamin A. *Lancet* 1995;345:31-5.

Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine

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later, were given. Blood pressure decreased to 200/115 mm Hg. The liquid contents of a 10 mg nifedipine capsule were then squeezed on to the patient's tongue while she was lying on her back. After a second dose 10 minutes later inspiratory stridor developed rapidly. Heavy laryngeal swelling made intubation guided by a laryngoscope impossible. After tactile intubation, ventilation was uncomplicated. There were no signs of a systemic allergic reaction. Blood pressure was 200/115 mm Hg.

Computed tomography showed a large intracerebral haemorrhage. The following day the patient was given the same sequence of drugs as before. Initial laryngoscopy showed no oedema. After two sprays of isosorbide dinitrate laryngeal swelling developed. This increased noticeably after the administration of nifedipine. No allergic symptoms occurred. The patient died two days later.

Isosorbide dinitrate in the form of a spray is used to treat angina pectoris.¹ It decreases blood pressure within minutes.² Sublingual nitrates³ and nifedipine^{4,5} are also recommended for treating hypertensive states. Drugs given sublingually are diluted with saliva as patients take them while awake. In our patient the local concentration may have been unusually high when the two drugs were given in this way, causing laryngeal irritation. The reaction may also have been a direct allergic one, but no further testing was possible. Although the indications for reducing raised blood pressure in patients such as ours may be controversial, both drugs are commonly used. Extra caution is called for in cases such as this, when they are given in combination without the patient's cooperation.

- 1 Marmor A, Plich M, Blondheim D, Sharir T, Alpert JS. Increased exercise tolerance and reduced duration of ischaemia after isosorbide dinitrate oral spray in angina pectoris. *Am J Cardiol* 1988;61:4-6E.
- 2 Bijoria K, Wig J, Bajaj A, Sapru RP. Isosorbide dinitrate spray: attenuation of cardiovascular responses to laryngoscopy and intubation. *Anaesthesia* 1992;47:523-6.
- 3 Bussman WD, Kenedi P, von Mengden HJ, Nast HP, Rachor N. Comparison of nitroglycerin with nifedipine in patients with hypertensive crisis or severe hypertension. *Clin Invest Med* 1992;70:1085-8.
- 4 Bertel O, Conen D, Radu EW, Muller J, Lang C, Dubach UC. Nifedipine in hypertensive emergencies. *BMJ* 1983;286:19-21.

Tinnitus and ciprofloxacin

Drs J PAUL (Public Health Laboratory, John Radcliffe Hospital, Oxford OX3 9DU) and N M BROWN (Department of Microbiology, Southmead Hospital, Bristol BS10 5NB) write: Tinnitus is not generally recognised as an adverse reaction to

treatment with ciprofloxacin. An incidence of only three cases per 9473 courses of treatment has been reported,¹ and animal studies have failed to associate ciprofloxacin with ototoxicity.^{2,3} Eleven previous cases of tinnitus linked to ciprofloxacin use have been reported either to the Committee on Safety of Medicines or to the manufacturers (Bayer) since its introduction in the United Kingdom in 1987. We report an association between tinnitus and ciprofloxacin in a 57 year old man whose postoperative infection of a sternal wound was treated with oral ciprofloxacin 750 mg twice daily.

The patient began to experience buzzing and deafness after three days, but he complained to medical staff only on the eighth day of treatment, when he learned to associate his symptoms with ciprofloxacin. Tinnitus started within 10-30 minutes of administration of each tablet and continued for several hours. Ciprofloxacin was stopped on the ninth day, when he again complained of buzzing and deafness after his morning dose. The symptoms resolved within six hours, and he remained well until his discharge 12 days later. He had no pre-existing neurological abnormality and had normal renal function. He had been taking various other drugs, including aspirin, amiodarone, diclofenac sodium, and bumetanide, for several months without side effects. Retrospective analysis of serum samples taken for other reasons showed that ciprofloxacin concentrations about one hour after morning doses on days 2, 3, 5, 7, and 8 were 2.8, 0.7, 1.2, 4.2, and 4.8 mg/l respectively. In healthy volunteers a mean ciprofloxacin concentration of 3.4 mg/l has been found one hour after a single oral dose of 75 mg.⁴ This suggests that tinnitus in our patient was not related to excessive serum concentrations, although symptoms did occur when ciprofloxacin concentrations would have been highest. Tinnitus is an easily overlooked adverse reaction to ciprofloxacin treatment, particularly in elderly patients in whom symptoms may be ignored or confounded with those of a pre-existing condition.

- 1 Schacht P, Arcieri G, Hullmann R. Safety of oral ciprofloxacin: an update based on clinical trial results. *Am J Med* 1989;87 (suppl 5A):98-102.
- 2 Bagger-Sjöbäck D, Spangberg M-L. Does ciprofloxacin affect the inner ear? A preliminary report. *Scand J Infect Dis Suppl* 1989;60:28-34.
- 3 Claes J, Govaerts PJ, Van de Heyning PH, Peeters S. Lack of ciprofloxacin ototoxicity after repeated otological application. *Antimicrob Agents Chemother* 1991;35: 1014-6.
- 4 Catchpole C, Andrews JM, Woodcock J, Wise R. The comparative pharmacokinetics and tissue penetrations of single-dose ciprofloxacin 400 mg iv and 750 mg po. *J Antimicrob Chemother* 1994;33:103-10.

Large erythematous scaly plaque on right buttock at site of injection of retinol palmitate given two weeks before