Reformulation of injectable vitamin A: potential problems

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A change in the formulation of an established drug may cause unexpected side effects and an important change in bioavailability

Once patients with primary biliary cirrhosis or chronic cholestatic liver disease of any aetiology have entered the cholestatic phase of their disease we give them monthly intramuscular injections of the fat soluble vitamins A (100 000 IU), D (100 000 IU), and K (10 mg) to prevent deficiency of these vitamins.¹ In mid-1989 several of our patients reported pain, swelling, and peeling at the sites of injection. Inquiries to the manufacturer made by the in house scheme for reporting adverse drug reactions showed that the formulation of the injectable vitamin A had been changed and that the bioavailability of the new preparation was 50 times that of the old preparation.

Case reports

Six women (four with primary biliary cirrhosis and two with idiopathic chronic cholestatic liver disease; mean age 59, range 45-65) who were receiving monthly intramuscular injections of vitamin A reported new symptoms between May and October 1989. They had been receiving intramuscular vitamins A, D, and K for six to 120 months (mean 60 months). All reported unusually severe local pain immediately after the injection followed in most cases by local erythema and swelling. One patient reported local itching as the dominant symptom. The pain and erythema lasted for one to three weeks and were followed by peeling of the overlying skin. In two patients light brown discoloration of the skin over the site of the injection was clearly visible six weeks and two months after the injection. In one patient injection of the three vitamins at separate sites with different syringes greatly reduced the symptoms. Two patients, however, had moderately severe local reactions when vitamin A alone was injected at a separate site.

Inquiries showed that the formulation of injectable vitamin A had been changed: the oil base had been changed to a water base, and polyoxyl 40 hydrogenated castor oil (Cremophor RH) had been added as a solubiliser. Data on bioavailability supplied to the Committee on Safety of Medicines by Roche when the product was licensed showed that the bioavailability of the new product was roughly 50% whereas that of the old preparation had been about 1% (personal communication, Roche).

Discussion

This report highlights the problems that can arise from a change in the formulation of a drug, which in this case resulted in a substantial increase in both bioavailability and reactions at the site of injection. The bioavailability of a drug is the proportion that becomes available to the target tissue after administration and exerts its pharmacological effect. A 50-fold increase in bioavailability clearly has important implications for prescribers. This is particularly so in view of the hepatic toxicity associated with hypervitaminosis A.² Patients with primary biliary cirrhosis seem to have impaired release of vitamin A from the liver³ and thus may be at increased risk of toxicity. Furthermore, signs of vitamin A toxicity may be

missed in this group as any deterioration in liver function may be ascribed to the natural course of the disease.

In the light of the bioavailability of the new formulation we now recommend that our patients with chronic cholestatic liver disease receive intramuscular vitamin A 100 000 IU every four months rather than every month. This should overcome the problem of the increased bioavailability but will not prevent the local reactions. It is an empirical recommendation as little information is available on systemic requirements for vitamin A in primary biliary cirrhosis.

The change from an oil soluble to a water soluble preparation also means that vitamins A, D, and K should not be combined in the same syringe or given at the same site. Vitamin A, which is lipid soluble, may become sequestered in the oil base. The datasheet and package insert are now being amended to include data on comparative bioavailability and to emphasise the need to review dosing schedules in patients previously stabilised on long term prophylactic treatment with the previous formulation and to avoid dilution or mixing with other agents before injection (personal communication, Roche). This may help to avoid any inadvertent overdose in patients with cholestatic liver disease and may reduce the incidence of local reactions at the site of injection.

It is disconcerting that we discovered this change in bioavailability almost by chance. The clinical consequences of changes in bioavailability due to changes in the formulation of drugs such as digoxin and phenytoin are well documented.^{4,5} We suggest that major changes in the bioavailability of drugs should as a matter of policy be brought to the attention of prescribers so that prescribing habits may be changed if necessary. Our report also emphasises the value of an in house system for reporting adverse drug reactions, without which these facts might not have been uncovered.

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- 1 Epstein O. The treatment of primary biliary cirrhosis. *Alimentary Pharmacology and Therapeutics* 1988;2:1-12.
- 2 Leo MA, Lieber CS. Hypervitaminosis A: a liver lover's lament. *Hepatology* 1988;8:412-7.
- 3 Nyberg A, Berne B, Nordlinder H, et al. Impaired release of vitamin A from liver in primary biliary cirrhosis. *Hepatology* 1988;8:136-41.
- 4 Anonymous. The bioavailability of digoxin [Editorial]. *Lancet* 1972;ii:311-2.
- 5 Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD. Outbreak of anticonvulsant intoxication in an Australian city. *Br Med J* 1970;iv:271-3.

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Correction

Guidelines for management of asthma in adults: I

Three authors' errors occurred in this statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, and National Asthma Campaign (29 September, p 652). In the last sentence of the paragraph on inhaled anti-inflammatory steroids the step should be 3 and not 4; in the fifth sentence of the paragraph on oral β_2 agonists and xanthines the steps should be 4 and 5 and not 5 and 6; and in the third sentence of the paragraph on step down the steps should be 3 and 4 and not 4 and 5.

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