Calcium, vitamin D, and hip fractures

Incidence of falls may have decreased

EDITOR,—Marie C Chapuy and colleagues report that treatment with cholecalciferol and calcium prevents non-vertebral fractures in elderly women and suggest that this is due to an improvement in bone metabolism.[1] As they mentioned in a previous report of this study, however, the resulting increase in bone density is low.[2] A more likely explanation for the results might be a decrease in the incidence of falls in the active treatment group. This incidence, however, was not reported.

A difference in the incidence of falls between the two groups could be explained by the muscular effects of cholecalciferol treatment. Indeed, apart from its action on bone metabolism, a low vitamin D concentration causes muscular weakness, which can be reversed by substitution.[3,4] Chapuy and colleagues mention that the mean serum concentration of 25-hydroxycholecalciferol normalised in the active treatment group but remained low in the controls. In a prospective study that I carried out in 63 elderly women (mean age 82·5 (SD 5·4) years), all living in the community and independent in basic activities of daily living, muscular strength and exercise capacity were related to serum 25-hydroxycholecalciferol concentrations (table).

Serum 25-hydroxycholecalciferol concentration and mean (SD) grip strength for both hands and distance walked in six minute walking test in 63 elderly women

	25-Hydroxycholecalciferol* (nmol/l)		
	<40 (n=50)	≥40 (n=13)	P value†
Grip strength (kPa)	45·5±20·0	59·8±26·6	<0·05
Distance walked (m)	149±111	273±115	<0·01

*Normal value ≥40 nmol/l.
†Student's *t* test.

Other recent reports on the treatment of osteoporosis in elderly people have also failed to mention the incidence of falls.[5] In general, all studies on osteoporotic fractures should mention this incidence as it is essential to the understanding of the dynamics of the intervention.

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Vitamin D alone may be helpful

EDITOR,—Marie C Chapuy and colleagues' recent paper supports their earlier work by showing the beneficial effects of cholecalciferol and calcium supplements in preventing hip fractures.[1] In their comment, however, they note that Heikinheimo *et al,* who gave calciferol injections, showed no significant effect on hip fractures.[2] In Heikinheimo *et al*'s study 341 women were given calciferol by annual injection and were compared with 458 controls. Twenty five hip fractures occurred in the calciferol group and 43 in the controls, yielding rate of hip fracture of 7·3% in the intervention group and 9·4% in the controls. This represents a 22% difference between the two groups ((9·4-7·3)/9·4×100), which is similar to the difference in rates of hip fracture found by Chapuy and colleagues in their intention to treat analysis.

The reason that the difference of 22% observed by Heikinheimo *et al* was not significant was possibly the smaller sample size, which we estimate would have had only an 80% chance of detecting a 58% reduction in hip fractures at the 5% significance level (from 9·4% to 3·9%). Given that this reduction was of a similar magnitude to that observed by Chapuy and colleagues, this suggests that the results of supplementation with cholecalciferol and calcium are primarily due to the vitamin D component rather than calcium.

Calcium supplementation is expensive,[3] but vitamin D is relatively cheap. Thus in economic terms it is important to estimate the independent effects of vitamin D on the incidence of hip fracture.

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Overdose of diltiazem

EDITOR,—T A Roper advocates that in cases of poisoning with the calcium antagonist diltiazem the drug's concentration should be measured, even though the assay is available only in specialised centres.[1] Roper suggests that there is a correlation between clinical sequelae and the diltiazem concentration after overdose. Concentrations of the calcium antagonists do not, however, usually correlate well with clinical outcome after overdose,[2] and routine measurements would be of little value. For example, death has been reported with diltiazem concentrations as low as 1500 μg/l and survival with concentrations as high as 6090 μg/l.[3,4] Similarly, verapamil concentrations have been as low as 1500 μg/l in patients who have died and as high as 4000 μg/l in survivors.[2] Nifedipine is technically difficult to measure as the compound is photosensitive. In addition, peak concentrations of the newer, sustained release preparations of these drugs are delayed, and concentrations on admission may be misleading; these preparations may therefore result in serious toxicity in patients who initially seem well. The laboratory costs of measuring calcium antagonist concentrations on request would be substantial.

Knowledge of the drug concentrations may be even less useful in elderly people and those with underlying heart disease than in others, especially if left ventricular dysfunction and conduction abnormalities such as the sick sinus syndrome are present, as these patients are more susceptible to adverse effects after self poisoning with calcium antagonists. Concomitant treatment with cardiovascular drugs may also potentiate the effects of calcium antagonists. Finally, despite high concentrations of diltiazem the prognosis may be quite good with adequate cardiovascular support.[4] Roper's view is based on analysis of nine reported cases,[3] but if the patient receives adequate supportive treatment it is wrong to assume that any given concentration will be fatal. We therefore suggest caution before advising the routine measurement of drug concentrations in patients with poisoning due to calcium antagonists.

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Overdose of calcium channel blockers

EDITOR,—John Kenny discusses several ways of treating overdose of calcium channel blockers,[1] but reference should also be made to specific antidotes for toxicity due to calcium channel blockers. These antidotes can be very effective, especially in verapamil overdose. 4-Aminopyridine has been used in verapamil toxicity due to renal failure, reverting a third degree heart block to sinus rhythm.[2] Bay K 8644 and RS 30026 (derivatives of dihydropyridine) are experimental drugs that increase the opening time and reduce the closing time of calcium channels[3] and antagonise the effects of blockade of calcium channels in both heart and blood vessels. These drugs have been promising in animal studies of overdose of calcium channel blockers[4] and may soon emerge into clinical practice.

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Safety of thalidomide

EDITOR,—C L Crawford has raised some questions about the prescription of thalidomide on a named patient basis to patients with leprosy in Britain.[1] He wrote to me when I was chairman of the Committee on the Safety of Medicines to ask what information a supplier is required by law to provide with thalidomide when supplying the drug to a doctor for prescription to a named patient. According to the Medicines (Labelling) Regulations 1976 (regulations 11(1)(b)(i) and 11(1)(b)(ii)), suppliers are required to provide information on the containers and packages of a medicine supplied for a named patient prescription but are not required to give details of contraindications, warnings, and precautions. The patient should be told of contraindications, warnings, and precautions by the prescribing doctor, who is entirely responsible for his or her actions when prescribing an unlicensed medicine.

Crawford also asked for advice about the clinical management of patients receiving thalidomide for