women with fractured wrists. Thus the inverse relation between bone mineral density and risk of peripheral fracture that has been observed in postmenopausal women^{1,3,4} apparently also applies to premenopausal women. Whether our patients were compared with their age matched controls or with the larger group of premenopausal women previously reported on² their bone density was significantly reduced. The close agreement between the mean bone mineral density in the controls in this study and in the previously reported group, despite the difference in mean age, also supports our previous conclusion that bone mineral density does not decrease with age in normal premenopausal women.²

An inverse relation between bone density and risk of both vertebral and peripheral fracture has been reported,^{1,3,5} but as far as we know this is the first time that bone density has been measured and found to be low in premenopausal women with fractures. Earlier work on this subject was dominated by the concept of a

fracture threshold and by the high incidence of fractures in postmenopausal women. We suggest that there is no fracture threshold and that the lower the bone density, even if it is within the normal range, the higher the risk of fracture.

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Burn to toddler's penis from an electrochemical battery

I K Mecrow

Musgrove Park Hospital,
Taunton, Somerset TA1
5DA
I K Mecrow, MRCP,
paediatric registrar

There have been several reports of the ingestion of small button batteries by children.^{1,3} To my knowledge burns due to prolonged contact of larger high voltage batteries with the skin have not been reported before.

Case report

A 19 month old toddler was admitted to hospital from the casualty department with a part circumferential full thickness burn to the ventrolateral aspect of the penis. This had been discovered when his nappy (which was damp and had been worn for around five hours), was removed, when a 9 V battery had been found wedged at the base of the penis with both terminals in contact with the skin. Two circular, confluent full thickness burns had been sustained, each measuring 1.5 cm across. A green deposit was seen around one of these, and the penis was inflamed and oedematous. The results of a general examination were normal, and no evidence of abuse, either physical or sexual was found. After surgical debridement

of necrotic tissue the burns were dressed with sulphadiazine. Three months later healing was complete with no deformity of the penile shaft.

Comment

On the day before admission the child's mother had been teaching him to place objects in his trouser pockets. Probably in mimicking this he placed a battery inside his nappy. The battery had both terminals at one end, and when he urinated an electrical circuit was completed and the burn was sustained. He gave no indication of discomfort and apparently had no pain. Although non-accidental injury or sexual abuse seemed unlikely, the parents were interviewed and social work reports compiled. No evidence was found to support these diagnoses.

The risks of ingestion of small objects such as button batteries are generally understood by parents.³ Larger batteries, particularly when worn out, are, however, considered harmless and are occasionally given to small children to play with. These may cause burns if prolonged contact with the skin occurs, and they are therefore unsuitable for this purpose.

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Is injecting air into insulin bottles necessary?

Diana N Lockwood, Michael J Trand,
Hugh M Mather

Ealing Hospital, Southall,
Middlesex UB1 3HW
Diana N Lockwood, MRCP,
medical registrar
Michael J Trand, MIEEIE,
head of medical electronics
Hugh M Mather, MD,
consultant physician

Patients treated with insulin are taught to inject an exact volume of air into the bottle before drawing up insulin to avoid creating a partial vacuum. This complicated manoeuvre may be difficult to master, especially when two bottles are being used. We suspected that it is unnecessary because insulin can easily be withdrawn without adding air despite the vacuum. We therefore monitored serial pressures inside bottles when withdrawing insulin without adding air, and we

measured pressures in bottles used by patients and nurses.

Methods and results

Pressures were measured by inserting into the bottle a needle attached to a Druck PDCR75 transducer through a reservoir of water. The system was calibrated with a precision meter, and readings were within 5% (mean 2.8%) over the range -93 to 93 kPa (relative to atmospheric pressure). Readings were made in duplicate in random order at room temperature. Firstly, we measured serial pressures inside six bottles of insulin after withdrawing aliquots of 0.25 ml (25 units) with a 0.5 ml syringe without adding air. Secondly, we measured the pressure in partly used bottles containing 0.5-9.0 ml (mean 5.0), which were provided by 81 randomly selected patients (aged 9-83).

Correspondence to: Dr
Mather.

Thirdly, we measured the pressure in 31 bottles used by ward nurses at this hospital.

Subsequently 52 patients were specifically asked not to inject air. After using a whole bottle they completed a questionnaire and recorded whether they found this to be easier, whether they found it difficult to draw up insulin, and whether air bubbles were a problem.

In the first study the mean pressure fell rapidly to below -39.9 kPa after 3 ml insulin was withdrawn and subsequently fell more gradually to -58.5 kPa. No difficulty was experienced either in withdrawing the plunger or with air bubbles. In the second study pressures in 31 of the 81 bottles were close to atmospheric pressure (± 0.7 kPa) (figure). The pressure was -13.3 kPa or less in 24 bottles, being below -39.9 kPa in 15, which suggested that air had not been injected before insulin was withdrawn. There was no significant difference in mean age, duration of treatment, or insulin dose between the 24 patients who provided these bottles and the remaining 57. The pressure in the 31 bottles used by nurses was below -13.3 kPa in 23 (figure), and values above -0.7 kPa were found in only four.

The questionnaires from the 52 patients who did not

add air showed that 42 found it easier, 47 found no difficulty in withdrawing insulin, and 40 did not find that air bubbles were a problem.

Comment

About one third of our patients and most nurses did not routinely inject air, presumably because empirically they had found it unnecessary. It proved surprisingly easy to withdraw all the insulin without adding air. Presumably the fine bore of the syringe facilitates withdrawal of the plunger. The answers to the questionnaires showed that most patients did not experience any difficulty when specifically asked not to inject air. A few (12/52) had problems with bubbles when bottles were nearly empty, but several of these patients had similar problems even when air was injected.

This study has potential implications for all patients treated with insulin. As many patients and nurses have already discovered, injection of air may be unnecessary, and further studies are required to confirm this.

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Is there a genetic factor in flecainide toxicity?

J Beckmann, R Hertrampf, U Gundert-Remy, G Mikus, A S Gross, M Eichelbaum

Abteilung für Experimentelle und Klinische Pharmakologie, Bundesgesundheitsamt, D-1000 Berlin 65, Federal Republic of Germany
J Beckmann, MD, senior research fellow
R Hertrampf, MD, research fellow
U Gundert-Remy, MD, professor and head

Dr Margarete Fischer-Bosch Institut für Klinische Pharmakologie, D-7000 Stuttgart, Federal Republic of Germany
G Mikus, MD, research fellow
A S Gross, PhD, research fellow
M Eichelbaum, MD, professor and head

Correspondence to: Professor Dr Eichelbaum.

Treatment of cardiac arrhythmias with the class Ic antiarrhythmic drug flecainide¹ has been associated with several severe adverse drug reactions.² Salerno *et al* reported fatal sustained ventricular tachycardia in two patients, in whom plasma flecainide concentrations were above 2 mg/l, the highest measured in their study.³ In deaths reported to the Federal Health Office (Bundesgesundheitsamt Berlin) as being possibly related to flecainide plasma concentrations of the drug, if available (table), were found to be in excess of the therapeutic range and much higher than expected from the dosage (steady-state concentration (C_{ss}) 0.2-0.6 mg/l).

Flecainide is eliminated by both urinary excretion and hepatic metabolism. The renal tubular secretion of the weakly basic drug ($pK_a=9.3$) depends largely on urinary pH and amounts to 45% at pH 4.4-5.4 and to less than 10% at pH 7.4-8.3. In a study on the kinetics of renal excretion of flecainide the incidental finding of a substantially longer elimination half life in one of the volunteers prompted us to search for factors that might be responsible for the aberrant pharmacokinetic behaviour of flecainide in some patients.

Subjects, methods, and results

The subject with a long elimination half life for flecainide proved to be a poor metaboliser of sparteine (oxytocic), which suggested that the metabolism of flecainide is coregulated by the sparteine-debrisoquine type of genetic polymorphism in oxidative drug metabolism.⁴ Therefore we extended our study by investigating four additional poor metabolisers of sparteine. The elimination half life as well as total and renal clearance of flecainide were determined for five poor and five rapid metabolisers at urinary pH less than 6.0 and after a single oral dose of 50 mg. Metabolic clearance was calculated as the difference between total

and renal clearance. Significance was determined by analysis of variance.

The mean elimination half life was 12.3 (SD 2.8) hours and the metabolic clearance 292 (64) ml/min in poor metabolisers compared with 6.9 (0.9) hours ($p<0.005$) and 726 (112) ml/min ($p<0.01$) respectively in rapid metabolisers. Renal clearance did not differ between the groups (307 (63) v 315 (62) ml/min).

Comment

The data indicate a substantial difference between poor and rapid metabolisers of sparteine with respect to their ability to metabolise flecainide under conditions of low urinary pH. When urinary pH is not controlled a greater proportion of the dose is metabolised. Consequently in patients with impaired renal function the metaboliser phenotype will greatly influence the relation between the dose and the plasma concentration of the drug. Poor metabolisers with renal impairment are at risk as they accumulate the drug to a greater extent than can be predicted from their kidney function alone. Although we have no direct evidence that flecainide toxicity is related to the poor metaboliser phenotype for sparteine-debrisoquine, our findings may help to explain the wide variation in the elimination half life and clearance of flecainide⁵ resulting in unexpectedly high plasma concentrations in some patients. Besides careful clinical monitoring of electrocardiograms³ we recommend that plasma flecainide concentrations are monitored at the beginning of treatment and whenever the dose is increased in patients with impaired kidney or liver function and congestive heart failure. Furthermore, assessment of the sparteine-debrisoquine phenotype in patients with impaired renal function may help to identify patients at risk.

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Dose of flecainide and plasma drug concentrations in patients whose death was possibly related to the drug

Dose of flecainide (mg/day)	No of patients	Plasma concentration (mg/l)
200	6	1.1-2.0
300	1	2.6
400	3	3.4-3.7