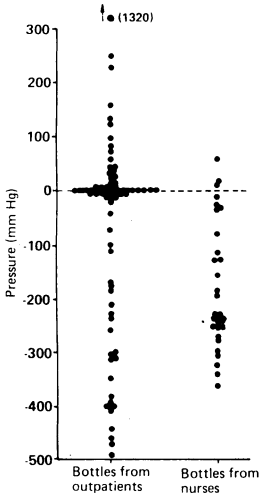

Pressures within 81 insulin bottles from outpatients and 31 bottles from ward nurses

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In the first study the mean pressure fell rapidly to below −39·9 kPa after 3 ml insulin was withdrawn and subsequently fell more gradually to −58·5 kPa.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or less in 24 bottles, being below −39·9 kPa in 15, which suggested that air had not been injected before insulin was withdrawn.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.

We thank Teresa Honey, Alison Hetreed, and Joan Welch. Nordisk Ltd provided financial support.

(Accepted 2 August 1988)

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 flecainide[1] 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 (pKa=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.

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

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 flecainide[5] resulting in unexpectedly high plasma concentrations in some patients. Besides careful clinical monitoring of electrocardiograms[3] 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.

1 Anderson JL, Stewart JR, Perry BA, *et al.* Oral flecainide acetate for the treatment of ventricular arrhythmias. *N Engl J Med* 1981;**305**:473-7.
2 Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. *Am J Cardiol* 1984;**53**:89-94B.
3 Salerno DM, Granrud G, Sharkey P, *et al.* Pharmacodynamics and side effects of flecainide acetate. *Clin Pharmacol Ther* 1986;**40**:101-7.
4 Eichelbaum M. Polymorphic drug oxidation in humans. *Fed Proc* 1984;**43**: 2298-302.
5 Conard GJ, Ober RE. Metabolism of flecainide. *Am J Cardiol* 1984;**53**:41-51B.

(Accepted 6 June 1988)