Maintenance therapy after i.v. administration of disopyramide with an oral sustained release preparation, a pharmacokinetic study

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The blood levels in 20 patients were studied during the change from parenteral administration of disopyramide to an oral sustained release preparation containing the same active substance. From this study it is concluded that 100 mg i.v. bolus injection of disopyramide can safely be followed by the immediate administration of one sustained release tablet containing 250 mg disopyramide. In case of an i.v. infusion ($0.4 \text{ mg kg}^{-1} \text{ h}^{-1}$) it seems wise not to start earlier with the administration of the sustained release preparation than at the moment of stopping the infusion.

Keywords disopyramide sustained release tablets intravenous administration

Introduction

Disopyramide is an anti-arrhythmic agent with electrophysiological and haemodynamic effects similar to those of procainamide and quinidine. The drug reduces the incidence of arrhythmias, especially those of ventricular origin (Heel *et al.*, 1978).

Oral disopyramide is available as capsules containing an equivalent of 100 mg and 150 mg disopyramide. Due to the relatively short half-life (7–10 h) it has to be administered three to four times daily. Recently a sustained-release tablet formulation of 250 mg disopyramide has become available (Rythmodan Retard (in the Netherlands Ritmoforine Retard) (Roussel)). This study was performed in order to investigate the disopyramide plasma levels when changing from parenteral administration (i.v. bolus or i.v. infusion) to the new sustained release tablets.

Methods

Twenty patients, from either sex, 18–65 years of age, were selected. They were all monitored in a General Hospital for ventricular arrhythmias (runs of > 5 ventricular premature beats, ventricular tachycardia, ventricular flutter or fibrillation). Excluded were patients with renal insufficiency (creatinine clearance < 40 ml/min), congestive heart failure, second or third degree AV block, bundle branch block, and cardiomyopathy.

In 10 patients treatment was started with one i.v. bolus injection of 100 mg disopyramide, followed immediately by the administration of one sustained release tablet of disopyramide 250 mg and subsequently every 12 h one tablet. Blood samples were collected at 1, 4, 12 and 24 h after the bolus injection. The blood samples at 12 and 24 h were taken just before tablets were administered.

Another group of 10 patients were first treated with a disopyramide infusion $0.4 \text{ mg kg}^{-1} \text{ h}^{-1}$ for at least 48 h.

Three hours before the end of the infusion one sustained release tablet of disopyramide 250 mg was administered, followed by one tablet every 12 h. Blood samples in this group were taken during the infusion just before the first tablet was administered, at the moment of stopping the infusion and 1, 4, 9 and 21 h thereafter. Continuous ECG monitoring was done throughout the trial period. Disopyramide levels were measured by h.p.l.c. (Duchateau & Hollander, 1979).

The study was conducted in accordance with the principles of the Declaration of Helsinki. The nature of the study was fully explained to all subjects prior to entry and their verbal consent was obtained. Any participant was free to withdraw at any time. The protocol was passed by an ethical committee.

Results

The patients who received the initial i.v. bolus injection of disopyramide had the following characteristics: age 58 ± 11.8 years, weight 74.6 ± 9.9 kg. At admittance to the hospital their systolic and diastolic blood pressures varied from 95–140 mm Hg and 60–100 mm Hg respectively. Prior to the tachycardia episode the heart rate varied between 60 and 100 beats/min. Six patients were hospitalized for ventricular tachycardia, two patients for ventricular flutter, one for ventricular premature beats and one patient for Wolff

Figure 1 Plasma levels (mg/l) of disopyramide i.v. bolus during change over to sustained release tablets (mean and range shown).

Figure 2 Plasma levels (mg/l) of disopyramide i.v. infusion during change over to sustained release tablets (mean and range shown).

Parkinson White Syndrome. Six of the patients had a history of myocardial infarction.

Of the patients receiving disopyramide in an i.v. infusion the age was 59.4 ± 6.6 years and the weight 74.1 ± 6.8 kg. Systolic blood pressure varied from 90–135 mm Hg, diastolic from 60–90 mm Hg. After treatment the heart rate varied between 80 and 100 beats/min. Two patients were hospitalized for ventricular fibrillation, two for ventricular flutter, five for ventricular tachycardia and one patient had runs of ventricular premature beats. Seven patients had a history of myocardial infarction.

Figure 1 shows the disopyramide concentrations in plasma in mg/l in the group of patients changing from i.v. bolus to sustained release tablets.

Figure 2 gives the results obtained in the group that first was treated with a disopyramide i.v. infusion and then was treated with tablets.

The mean plasma levels were maintained above the minimal therapeutic level of 2 mg/l. Patient 16 died before the end of the 24 h study period due to a myocardial infarction followed by therapy resistant cardiogenic shock.

Discussion

The present study demonstrates that the change from parenteral administration of disopyramide

to oral administration with the new slow release formulation is safe and gives blood levels within the 'therapeutic range' (2–7 mg/l) as far as the bolus injection, directly followed by one sustained release tablet, is concerned. In the other cases where tablets are administered, 3 h before the end of the i.v. infusion, there is a tendency towards too high disopyramide blood levels which could lead to side effects. If the infusion rate(s) had been 'tailored' to the individual so that feedback of concentration information had been used to produce 'steady state' levels strictly

within the 'therapeutic range' then the addition of the sustained release tablet 3 h before the end of the infusion would not have produced unacceptably high concentrations. Therefore we recommend, in case of an i.v. infusion with disopyramide, to change to the oral sustained release formulation using the recently published dose schedule of Lien & Bakke (1983) in this journal. Of course, this study, being a pharmacokinetic study, has the limitation that no correlation was made between plasma levels and therapeutic effect.

References

- Duchateau, A. M. J. A. & Hollander, J. M. R. (1979). Disopyramide: analytical and pharmacokinetic review. *International Congress Series No. 501 The serum concentration of drugs*. Proceedings of a Symposium of the Netherlands Association of Hospital Pharmacists. Amsterdam: Excerpta Medica.
- Heel, R. C., Brogden, R. N., Speight, T. M. & Avery, G. S. (1978). Disopyramide: A review of its pharmacological properties and therapeutic use in treating cardiac arrhythmias. *Drugs*, **15**, 331–368.
- Lien, E. & Bakke, O. M. (1983). Sustained release disopyramide compared to plain capsules after change-over from intravenous infusion. *Br. J. clin. Pharmacol.*, **16**, 71–76.

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