PROCAINAMIDE ABSORPTION STUDIES TO TEST THE FEASIBILITY OF USING A SUSTAINED-RELEASE PREPARATION

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1 Using *in vitro* techniques it was confirmed that whilst the release of procainamide from the conventional formulation (Pronestyl) was rapid, that from the sustained-release preparation (Cardiorytmin Retard^R) occurred over a prolonged period.

2 The peak plasma procainamide concentrations after single doses of Cardiorytmin Retard^R were relatively lower and occurred later than those after single doses of Pronestyl. Furthermore, after reaching a peak, the fall in plasma procainamide concentration was less rapid after the sustained-release preparation. Early urinary recovery of procainamide in patients and in healthy volunteers was greater after Pronestyl than after Cardiorytmin Retard^R, though overall recovery in urine was similar. These findings indicate that the absorption of the sustained-release preparation is slower, though the overall bioavailabilities of the two preparations are almost the same.

3 These results confirm the feasibility of using a sustained-release procainamide preparation, such as Cardiorytmin Retard^R, since it would be possible to administer the same amount of drug in fewer daily doses without plasma concentrations becoming ineffective towards the end of each dosing interval.

Introduction

In the last decade there has been a rapid increase in the understanding of how pharmaceutical formulation affects drug absorption. As a result the formulations of a number of drugs have been modified so as to alter the time-profile of their concentration in the body.

Procainamide is an effective agent against cardiac arrhythmias, especially those associated with myocardial infarction (Bigger & Heissenbuttel, 1969; Koch-Weser, Klein, Foo-Canto, Kastor & DeSanctis, 1969; Giardina, Heissenbuttel & Bigger, 1973), and since it is well absorbed from the gastrointestinal tract it is often administered to patients in the convalescent period after infarction. The conventional tablet formulation of procainamide (Pronestyl) is rapidly and well absorbed in man (Koch-Weser & Klein, 1971) with peak plasma levels usually occurring at 30-90 min after taking the drug. The elimination half-life of procainamide is short (about 3.5 h when renal

function is normal), and to ensure that the plasma concentration remains effective at all times without reaching the toxic range, it has been found necessary to administer Pronestyl every 3 or 4 h (Koch-Weser & Klein, 1971; Shaw, Kumana, Royds, Padgham & Hamer, 1974). Such frequent administration is unsuitable for convalescing patients since it disturbs their sleep and doses may be accidentally omitted.

By prolonging the time over which each dose would be absorbed, effective, though still non-toxic, plasma concentrations could be achieved by administering larger doses less frequently. For this reason sustained-release formulations of procainamide have recently been developed.

This paper describes the feasibility of using one of these (Cardiorytmin Retard^R) in comparison to Pronestyl, by assessing their rates of dissolution, plasma levels during absorption, and their cumulative urinary excretion. Each tablet of Pronestyl contains procainamide hydrochloride (250 mg) which is rapidly released, whilst each tablet of Cardiorytmin Retard^R contains procainamide chloride (400 mg) in a lipophilic matrix

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which is designed to release the drug slowly at an even rate.

Methods

The investigation involved four healthy volunteers (aged 19-32 years) and ten patients (aged 44-81 years), each of the latter having experienced cardiac infarction or symptoms of ischaemic heart disease within the previous twelve months. Six of the patients took part in the absorption studies and the other four patients took part in the urinary recovery studies. The six patients in the absorption studies received either Pronestyl (1 g) or Cardiorhythm Retard^R (1.2 g) by a randomized cross-over design. Doses were given with water (40 ml) at 11.00 h after an overnight fast and lunch was given 1.5 h later. Two days elapsed between doses to allow elimination of the first dose. Venous blood samples were obtained before and at intervals up to 8 h after drug administration. Plasma procainamide concentration was determined fluorimetrically by the method of Koch-Weser *et al.* (1969) except that ethyl acetate replaced benzene, a modification of Hicks (1971, personal communication).

Percentage cumulative urinary excretion of procainamide over 48 h was determined in four of the patients and in the four healthy volunteers following the oral administration of each of the two treatments (Pronestyl, 750 mg; Cardiorhythm Retard^R, 800 mg), which were given at least one week apart by a randomized cross-over design. The urinary procainamide was determined spectrophotometrically by the method of Mark, Kayden, Steele, Cooper, Berlin, Rovenstine & Brodie (1951). Neither the fluorimetric method nor the colourimetric method measures the main metabolite of procainamide in man, which Dreyfuss, Bigger, Cohen & Schreiber (1972), Karlsson, Kolin, Norlander & Sjöqvist (1974) and Karlsson, Åberg, Collste, Molin, Norlander & Sjöqvist (1975) showed to be *N*-acetylprocainamide, and which Drayer, Reidenberg & Sevy (1974) and Elson, Strong, Lee & Atkinson (1975) showed to be pharmacologically active. In the present study no attempt was made to control urine pH since it has been shown (Meyer, Kaye & Turner, 1974) that the renal excretion of procainamide in man is not influenced by urine pH.

The *in vitro* dissolution rate of each formulation was measured by the United States Pharmacopoeia dissolution rate rotating basket method. Two tablets were allowed to dissolve into water (1 litre) at 37°C. Aliquots were removed at intervals up to 4 h and assayed for procainamide content by the same method as for urine.

Figure 1 Dissolution profiles of the two procainamide preparations, Pronestyl (●) and Cardiorhythm Retard^R (■).

Figure 2 Within patient comparison of plasma procainamide concentrations ($n = 6$, $\pm$ s.d.) following oral Pronestyl (1 g ●) or Cardiorhythm Retard^R (1.2 g ■).

Results

The results of the *in vitro* tests are summarized in Figure 1, and show that whilst procainamide is rapidly released from Pronestyl its release from Cardiorhythm Retard^R is more sustained.

The plasma procainamide levels obtained after administering Pronestyl and Cardiorhythm Retard^R to the cardiac patients are shown in Figure 2. The peak of the mean plasma levels was 6.3 µg/ml and

Figure 3 Within patient comparison of procainamide recovery in urine ($n = 4$, $\pm$ s.d.) following oral Pronestyl (750 mg $\bullet$) or Cardiorytmin Retard^R (800 mg $\blacksquare$).

Figure 4 Comparison of procainamide recovery (mean $\pm$ s.d.) in the urine of four healthy volunteers who were each given oral Pronestyl (750 mg $\bullet$) or Cardiorytmin Retard^R (800 mg $\blacksquare$).

occurred 1 h after administration of Pronestyl, but after Cardiorytmin Retard^R the peak was only 4.2 μ g/ml and was reached slightly later. Using Student's paired t -test the mean peak levels

produced by the two formulations (even without correction for the higher dose given with Cardiorytmin Retard^R) were significantly different ($P < 0.05$). From 2-8 h after Pronestyl the plasma levels declined more rapidly than after Cardiorytmin Retard^R.

The cumulative urinary recoveries, expressed as percentages of the administered dose of procainamide base, can be seen in Figure 3—mean values for the four patients, and in Figure 4—mean values for the four healthy volunteers. In both groups early urinary recovery was greater after Pronestyl than after Cardiorytmin Retard^R, though by 48 h the overall urinary recovery was very similar, being 52% and 57% for Pronestyl in the healthy volunteers and patients, respectively, compared to 47% and 53% for the sustained-release preparation. These differences between the percentage urinary recoveries of the two procainamide preparations were not statistically significant in either the healthy volunteers or the patients.

Discussion

The results of the dissolution rate study confirm that Pronestyl rapidly disintegrates and dissolves *in vitro*, with 100% being released within 10 min, whereas the release of procainamide from the Cardiorytmin Retard^R preparation was prolonged, 35% still remaining undissolved after 4 hours.

The peak plasma levels of procainamide were higher and occurred sooner after Pronestyl than after the sustained-release preparation (see Figure 2), and were usually well into the therapeutic range of 4-8 μ g/ml (Koch-Weser *et al.*, 1969). Furthermore, after peaking the levels declined rapidly after Pronestyl, whereas with Cardiorytmin Retard^R they declined slowly. These findings indicate that Pronestyl is rapidly absorbed whilst the absorption of Cardiorytmin Retard^R is slower and appears to occur over several hours. In keeping with this, the early urinary recovery of procainamide was much greater after Pronestyl than after the sustained-release preparation, whereas between 12 and 24 h relatively more procainamide was recovered following Cardiorytmin Retard^R. The pattern of procainamide recovery in the urine was similar in the patients and in the healthy volunteers (see Figures 3 and 4). By 36 h about 50% of the dose had been recovered in the urine, and in the subsequent 12 h further recovery was trivial. This indicated that the remainder of the dose was eliminated by other means, the most important of which was likely to be metabolism.

The overall percentage urinary recovery of procainamide following either preparation was

almost the same, both in patients and in healthy volunteers. This finding indicates that the total bioavailability of the two preparations were very similar.

These findings parallel those of Ruosteenoja, Torsti & Sothmann (1973) who have also investigated Cardiorhythm Retard^R, and those of Fremstad, Dahl, Jacobsen, Lunde, Nådland, Marthinsen, Waaler & Landmark (1973) and Karlsson (1973) who studied other sustained-release procainamide preparations.

The ability to administer procainamide less frequently can be especially useful when patients with myocardial infarction leave the coronary-care unit to enter medical wards. At this stage they are unlikely to have intravenous infusions and the extent of their medical supervision is relaxed, so that eight hourly dosing, rather than three or four hourly dosing, becomes a simpler and more practical way of giving the same daily dose. It should be realised that when a sustained-release procainamide preparation is to be prescribed, a

loading dose of a rapidly absorbed preparation, such as Pronestyl, becomes more important so as to achieve therapeutic concentrations quickly. In conclusion, it is hoped that by using a sustained-release procainamide preparation in a regimen that is both convenient and effective, the mortality and morbidity associated with cardiac arrhythmias occurring in the first few weeks of convalescence from myocardial infarction (Denborough, Lovell, Nestel & Goble, 1968; Norris, Bensley, Caughey & Scott, 1968; Lawrie, 1969; Sloman, Dowling, Thompson, Hunt, Brown & Ferguson, 1970) might thus be influenced.

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