PROLONGED VARIABILITY IN PLASMA PROTEIN BINDING OF DISOPYRAMIDE AFTER ACUTE MYOCARDIAL INFARCTION

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1 Disopyramide plasma binding was determined *in vitro* in plasma from 20 patients with acute myocardial infarction (aged 35–79 years) and in 20 age and sex matched healthy subjects. Plasma samples were collected on days 1, 5 and 12 after infarction and when the patient returned to the outpatient clinic.

2 In healthy subjects there was a significant negative correlation between disopyramide free fraction and plasma α_1 -acid glycoprotein (AAG) concentration. A similar correlation was observed in the patients with myocardial infarction, however this correlation was dependent on time elapsed after infarction. Disopyramide free fraction did not correlate with albumin concentration in either group.

3 Mean plasma AAG concentrations were increased by 63% within 5 days after infarction and had returned to initial levels some months later (73.5 ± 7.8 days). On each of the four sampling days, a two to four fold individual variability in plasma AAG concentrations was observed.

4 Maximum increases in disopyramide plasma binding were shown on days 5 and 12 after infarction. These increases were dependent on both drug and AAG concentrations. Increases in fraction bound were greater at the higher drug concentrations. Within the usual therapeutic plasma range for disopyramide (2 to 5 mg/l), the mean increases in fraction bound, compared to day 1 data, varied from 22 to 45% respectively.

5 Sequential alteration in AAG concentration after infarction indicates that disopyramide plasma binding may not reach a steady state until some months after infarction. Prediction of the time to achieve this steady state would be difficult due to inter- and intra-patient variability in binding.

Introduction

Disopyramide is a basic, class 1 antiarrhythmic drug which is used orally in the prophylaxis of various arrhythmias including those following acute myocardial infarction (Heel *et al.*, 1978). At therapeutic drug concentrations the drug exhibits concentration dependent plasma binding (Hinderling *et al.*, 1974; Cunningham *et al.*, 1977, 1978; Meffin *et al.*, 1979; David *et al.*, 1980). Disopyramide clearance is dependent upon the drug free fraction rather than total drug concentrations (Hinderling & Garrett 1976; Cunningham *et al.*, 1977, 1978; Meffin *et al.*, 1979; Bryson *et al.*, 1982b). Predictions of individual free drug fractions, from total drug concentrations, cannot be extrapolated from pooled plasma data, because wide inter-subject variability in plasma binding at constant total drug concentration has been reported both in healthy subjects and patients (Meffin *et al.*, 1979; Giacomini *et al.*, 1982).

Information on disopyramide disposition in disease states is sparse. Disopyramide kinetics are altered in the presence of cardiac failure (Landmark *et al.*,

1981), renal impairment (Johnston *et al.*, 1980), and following acute myocardial infarction (Ward & Kinghorn, 1976; Ilett *et al.*, 1979; Bryson *et al.*, 1982a). In patients with cardiac arrhythmias, there was a two fold variability in disopyramide free fraction, and plasma binding was greater than previously reported values (Meffin *et al.*, 1979). These observations required explanation, especially as earlier work had indicated that disopyramide was bound primarily to albumin (Chien *et al.*, 1974), a plasma protein which is rarely elevated in disease states, and is known to be markedly decreased after acute myocardial infarction (Johansson *et al.*, 1972; Smith *et al.*, 1977).

Recent work in this laboratory and others (Lima & Salzer, 1981; Lima *et al.*, 1981; David *et al.*, 1982) has demonstrated that disopyramide binds mainly to the acute-phase reactant, α_1 -acid glycoprotein (AAG), and to a lesser extent to albumin. Plasma AAG concentrations may be elevated in certain chronic disease states, for example Crohn's disease and

inflammatory arthritis, (Piafsky *et al.*, 1978) and during the acute phase following myocardial infarction (Johansson *et al.*, 1972; Smith *et al.*, 1977). It therefore seemed possible that the previously reported differences in disopyramide binding in patients with cardiac arrhythmias might be related to alterations in its plasma binding proteins. The purpose of the present study was to investigate the effect of acute myocardial infarction on plasma protein binding of disopyramide, with reference to AAG and albumin.

Methods

Subjects

Venous blood samples (12 ml) were collected into standard tubes containing lithium heparin 12.5 iu/ml. Twenty patients (mean age 60 years, range 35–79 years; 17 male, three female), with a provisional diagnosis of acute myocardial infarction were studied. Blood samples were obtained within 24 h of onset of symptoms (day 1), 2–3 h after breakfast on days 5 and 12 after infarction and at a later date (mean 73.5 ± 7.8 days, range 35–150) when the patient returned to the outpatient clinic.

Diagnosis of infarction was retrospectively confirmed by elevation of serum enzymes, clinical signs and electrocardiographic changes (World Health Organisation, 1971). One patient, who was hospitalised for the entire study, suffered a second infarction on day 3 and deceased on day 40. A second patient died after discharge, while three patients were unable to return to the outpatient clinic due to continued ill health. Patients for whom disopyramide was prescribed were excluded from the study.

A healthy control group was also studied. Single venous blood samples were collected from an age and sex matched group of healthy volunteers and blood bank donors (mean age 60 years, range 35–79 years; 17 male, three female).

Plasma protein determinations

Plasma albumin and AAG concentrations were assayed on freshly drawn samples by radial immunodiffusion (Partigen M, Behringwerke A.G., Marburg, West Germany) using Standard-Human-Serum and Control-Plasma (human) as quantitative standards.

Disopyramide plasma binding

[^{14}C]-disopyramide phosphate (58.3 mCi/mmol) and disopyramide were obtained from Hoechst-Roussel Pharmaceuticals, Australia. Radiolabelled disopyramide was purified by thin layer chromatography (David *et al.*, 1980). Fixed amounts of [^{14}C]-

disopyramide in methanol solution (10 $\mu\text{l/ml}$) were added to isotonic phosphate buffer 0.1 M, pH 7.4 containing varying amounts of unlabelled disopyramide, such that total drug concentrations of 2, 4, 6 and 8 mg/l were obtained. For equilibrium dialysis, single freshly drawn plasma samples (1 ml) were dialysed against spiked 1 ml buffer solutions as previously described (David *et al.*, 1980). After dialysing for 5 h, drug concentrations in aliquots of plasma and buffer were measured by liquid scintillation counting, to enable disopyramide binding to be quantified.

Statistical analysis

Results are expressed as mean $\pm$ s.e. mean. The extent of disopyramide binding was expressed either in terms of fraction bound, free fraction (i.e. fraction unbound) or as a binding ratio, which was the ratio of bound compared to free drug (Db/Df) for each observation. Where appropriate, differences between data sets were analysed by two way analysis of variance (subject group and drug concentration) using Genstat (Nelder, 1977). Comparisons of plasma protein concentrations in the infarction group on different days were made using Student's paired *t*-test, and for comparisons between subject groups the *t*-test for unpaired data was used. Correlation coefficients were determined by least square linear regression analysis. In one data set, analysis of variance was used to quantify individual components contributing to the regression of free fraction for disopyramide and AAG concentration.

Results

On average patients received 12.9 ± 4.0 drugs (range 6–22) during hospitalisation, and 3.9 ± 0.4 drugs (range 1–8) during the outpatient period. Anticoagulant therapy was initiated in 17 patients during the first 3 days after infarction; heparin was administered by continuous i.v. infusion at average doses ranging from 10000–31000 iu/day, for periods ranging from 0.5–14 days (Figure 1a). Fifteen patients received lignocaine by i.v. infusion, at average doses which ranged from approximately 1 to 2.7 g/day (Figure 1b). In general, lignocaine infusions were ceased within 48 h after infarction, although one patient continued to receive the drug until day 14.

The time course of changes in both plasma AAG and albumin concentrations after acute myocardial infarction is shown in Figure 2. As previously observed (Johansson *et al.*, 1972) the AAG concentrations were elevated, and the albumin concentrations depressed at day 5. During the study period, both proteins returned slowly to levels which

Figure 1 Relationship between the average daily dose of (a) heparin (■) and (b) lignocaine (▲) administered by i.v. infusion, and the number of patients (●) receiving these drugs during the 2 weeks period after infarction.

Figure 2 Sequential changes in (●) plasma α_1 -acid glycoprotein (AAG) and (■) plasma albumin (HSA) concentrations after infarction. Mean plasma (○) AAG and (□) HSA concentrations for age matched healthy subjects are shown.

were not significantly different from those measured on day 1.

In the infarction patients, there was a wide range of plasma AAG concentrations (0.54–2.43 g/l) and a two to four fold variability in individual levels on each of the four sampling days. The day 1 (0.99 ± 0.07 g/l) and outpatient mean AAG data (1.09 ± 0.12 g/l) were within the normal range for plasma (0.55–1.4 g/l; Putnam, 1975), and were not significantly different from the value for the age matched controls (0.93 ± 0.07 g/l). Compared to day 1 levels, AAG concentrations on day 5 and 12 were significantly increased ($P < 0.001$) to 1.63 ± 0.1 g/l and 1.42 ± 0.13 g/l, an increase of 65% and 44% respectively.

Plasma albumin concentrations remained below the normal range (35–45 g/l; Putnam, 1975), for at least 2 weeks after infarction. The mean albumin concentrations at the outpatient visit (36.82 ± 1.34 g/l) were similar to those for the age matched controls (38.49 ± 1.0 g/l).

Disopyramide plasma binding in the infarction patients and their age matched controls is shown in Figure 3. In both subject groups the extent of binding was dependent on drug concentration. Two way analysis of variance showed that the mean day 1 binding data for infarct patients were not significantly different from data for the age matched controls. Within the usual therapeutic range of 2–5 mg/l, the mean fraction bound varied from 0.68 to 0.46 for the infarction patients and from 0.7 to 0.47 for the control group. Disopyramide binding in infarct patients was similar on days 5 and 12, and the fraction bound on these days was markedly increased compared to the day 1 levels ($P < 0.001$). At each sampling time, the magnitude of these changes was drug concentration

Figure 3 Disopyramide plasma protein binding in healthy subjects (□) and infarction patients on day 1 (●), day 5 (■), day 12 (▲) and at the outpatient visit (○). The shaded horizontal bar indicates the usual therapeutic plasma range for disopyramide.

Figure 4 Inter- and intra-patient variability in disopyramide free fraction (open bars) and plasma AAG concentrations (shaded bars), after acute myocardial infarction. Data relate to an initial total disopyramide concentration of 2 mg/l.

dependent, with the greatest increases associated with higher total drug concentrations. For example, between day 1 and day 5, at disopyramide concentrations of 2 and 5 mg/l, the mean fraction bound increased by 22 and 45% respectively. In the out-patient samples, the fraction bound had decreased towards initial values, but was still significantly elevated compared to data for either day 1 or age matched controls ($P < 0.001$).

Figure 4 shows examples of the inter- and intra-patient variability in AAG concentrations after infarction. All patients showed increases in AAG concentrations, ranging from 10 to 300% within 5 days of infarction. Peak concentrations varied between 1 and 2.43 g/l, with 15 patients achieving concentrations above the normal range. Figure 4 also shows that there was considerable variation in the extent of disopyramide binding in the presence of similar AAG concentrations. Commonly observed changes in disopyramide free fraction are demonstrated in patients KT and DM, where their rapid increases in AAG concentrations were matched with a corresponding fall in disopyramide free fraction. In patient KT, as the AAG protein concentration increased three fold from 0.84 to 2.19 g/l, so the free fraction decreased from 0.32 to 0.10. At day 71 after infarction, the free fraction for this patient was still only 50% of his day 1 level. A similar pattern of

Figure 5 Relationship between disopyramide free fraction (initial total drug concentration 4 mg/l) and plasma AAG concentration, after acute myocardial infarction. The figure shows observations (●) from 13 patients on four separate study days. The least-squares regression line is shown ($y = 0.473 - 0.153x$).

change emerged in patient DM, although his peak AAG concentrations were not above the normal plasma range. Seven patients did not follow any set pattern of drug binding or protein concentrations. For example, in patient VC, the disopyramide free fraction was clearly not directly related to AAG concentration during the first 12 days. Likewise patient EJ had an AAG concentration at day 76 which was 29% greater than on day 5.

Within each subject group, linear regression analysis of the relationship between disopyramide free fraction and plasma AAG concentrations showed similar trends at each drug concentration. Hence only the data related to an initial disopyramide concentration of 4 mg/l is discussed. In healthy individuals, there was a significant negative correlation between the free fraction and AAG concentrations ($r = -0.77$, $P < 0.001$). With the infarction patients, the relationship between AAG and free fraction for disopyramide was examined in 13 patients with complete data for all four sampling days. There was a significant negative correlation between AAG and free fraction (Figure 5, $r = 0.65$, $P < 0.001$). Free disopyramide fractions for each patient were individually regressed against AAG concentrations and the total data was subjected to analysis of variance. This showed that the common regression accounted for 43.8% of the total sum of squares ($F_{1,26}$

= 32.1, $P < 0.001$). Neither the slopes nor the means of the individual regressions were significant in the analysis and hence the regression shown in Figure 5 is an acceptable representation of the data. When all the infarct patient data were plotted for each of the four days on which blood samples were obtained, it was clear that the correlation was dependent on time elapsed after infarction. A poor negative correlation was shown on day 1 ($r = -0.45$, $P < 0.05$) while there was no correlation on day 5 ($r = 0.12$, $P < 0.1$). Significant correlations were obtained using data from day 12 ($r = -0.76$, $P < 0.001$) and the outpatient sampling day ($r = -0.87$, $P < 0.001$).

There was no correlation between albumin concentration and disopyramide free fraction in either healthy subjects or infarct patients. Results similar to those reported above were obtained when correlations between binding ratio (Db/Df) for disopyramide and plasma AAG and albumin concentrations were tested.

Discussion

The results of this study indicate that the wide variability in disopyramide plasma binding, observed in the infarction patients, may be largely explained in terms of two factors, i.e. the relative molar concentrations of disopyramide and the corresponding molar concentration of plasma AAG. Disopyramide binds to plasma AAG with a high affinity, however the molar capacity of the primary binding sites is low (Lima & Salzer, 1981; Lima *et al.*, 1981; David *et al.*, 1982).

In our healthy control subjects, at therapeutic disopyramide plasma concentrations, the molar concentration range for disopyramide (5.9–14.7 μM) and AAG (9.0–40.5 μM) were of the same order of magnitude. The observed concentration dependent decrease in mean fraction bound was confirmation of an increasing saturation of primary protein binding sites as the drug concentration increased. In the infarction patients, with increasing AAG plasma concentrations, the corresponding increases in disopyramide fraction bound were unequal and dependent on the relative molar proportions of drug and protein. In the presence of such saturable binding and increasing AAG concentrations, changes in disopyramide fraction bound were therefore more evident at the higher drug concentrations. Similarly, the maximum mean fraction bound was attained on days 5 and 12 after infarction, when the total drug concentrations were greatly exceeded by the mean peak molar AAG concentrations on these days (40.75 and 35.6 μM respectively).

Disopyramide plasma binding was also influenced by the considerable inter and intra-patient variability in magnitude and duration of changes in plasma AAG

concentrations for many weeks after infarction. Changes in the fraction bound usually followed a similar sequential pattern to the changes in plasma AAG concentrations. However day to day variability in the correlation between the free fraction and this protein suggests that other factors must be considered. Even when a significant correlation existed, as shown for the control and outpatient groups, the correlation coefficients indicated that only 59 to 76% of the variability was explained. Furthermore, although infarction patients had similar mean AAG concentrations on day 1 and several months later, the correlation between disopyramide free fraction and protein concentration in these data was highly variable.

Although the fraction bound on days 5 and 12 was not significantly different, there was a strong correlation between free fraction and AAG concentration on day 12, but no correlation on day 5. This lack of correlation on day 5 may partly reflect the excess plasma AAG available for drug binding, i.e. increases in protein concentration above a certain maximum level might not be reflected in the fraction bound. Alternatively, the binding on days 1 and 5 may be influenced by the plethora of endogenous compounds released into plasma in response to tissue injury. Such compounds would include other acute phase reactants and altered lipoprotein fractions (Johansson *et al.*, 1972; Smith *et al.*, 1977). Increased binding in the presence of increased plasma lipoprotein concentrations was recently shown for quinidine and propranolol (Nilsen *et al.*, 1978; Sager *et al.*, 1981). However, altered lipoprotein binding is unlikely to be a major factor in this study, as the lipoprotein contribution is only 2% of total plasma binding (David *et al.*, 1982).

The effect of heparin and lignocaine administration must also be considered. Lignocaine was administered to the majority of patients within the first 48 h (Figure 1b). Lignocaine binds to AAG (Routledge *et al.*, 1980) and at therapeutic concentrations (3 mg/l) can cause a decrease of some 30% in disopyramide plasma binding, dependent on disopyramide concentrations (David & Ilett, unpublished data). The major effect of lignocaine in this study would be associated with the day 1 infarct patient data since the plasma half-life of lignocaine is short (1.8 ± 0.4 h; Nation *et al.*, 1977), although this may have been prolonged in some patients where lignocaine infusions were continued for longer than 24 h (LeLorier *et al.*, 1977). Heparin administration can cause increases in serum non-esterified free fatty acid concentrations but does not change serum AAG or albumin concentrations (Wood *et al.*, 1979; Sager *et al.*, 1981). The latter authors showed that decreased propranolol binding was associated with increased free fatty acid concentration. As free fatty acids show a high affinity for albumin (Birkett *et al.*, 1977), some

decrease in disopyramide binding to plasma albumin may have occurred. This possibility, together with the decreased plasma albumin concentrations early after infarction, may have contributed to the poor correlation between the resultant disopyramide free fraction and plasma AAG on days 1 and 5.

The observed prolonged variability in disopyramide free fraction is clinically relevant, particularly as the incidence of anticholinergic side effects has been associated with increased free drug concentrations (Lima *et al.*, 1981; Ilett, Tjokrosetio & Benzie, unpublished data). Clinical prediction of the time course to steady state plasma binding would be difficult, due to the demonstrated interpatient

variability in the magnitude and duration of changes in plasma AAG concentrations. Patients who are initiated on disopyramide therapy during the acute phase after infarction, would tend at any constant therapeutic plasma concentration, to display an increasing free fraction for periods as long as several months. Our data suggests that such increases would be proportionately greater at higher disopyramide therapeutic concentrations.

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