INCREASED PLASMA PROPRANOLOL BINDING IN MYOCARDIAL INFARCTION

Although the disposition of propranolol has been extensively studied (Routledge & Shand, 1979), there is little information concerning the kinetics of the drug in patients with myocardial infarction, despite the long-time interest in using the drug in this setting. Plasma propranolol concentrations have been estimated in two studies of patients recently admitted to hospital (Rutherford, Singh, Ambler & Norris, 1976; Norris, Sammel, Clarke, Smith & Williams, 1978) and show the wide variation known to occur in normal individuals. Unfortunately, these studies have confined themselves to measurement of total plasma concentration without regard to possible alterations in plasma drug binding. This is important as the β-adrenoceptor blocking effects of propranolol correlate well with free (unbound) rather than total plasma concentration (McDevitt, Frisk-Holmberg, Hollifield & Shand, 1976). Furthermore, there is reason to believe that plasma propranolol binding may be altered in infarction, because one of its major binding proteins, α_1 acid glycoprotein (AAG) (Piafsky, Borga, Odar-Cederlöf, Johansson & Sjöqvist, 1978) rises above the normal range in patients with infarction (Johansson, Kindmark, Trell & Wollheim, 1972; Bachmann, Weiss & Rapp, 1968).

These studies were performed on six normal subjects and six patients admitted to the coronary care unit who did not receive heparin, as this reduces propranolol binding (Wood, Shand & Wood, 1979). Two consecutive plasma samples were obtained for AAG analysis and drug binding studies and the changes in each compared. In the normal individuals collection of the samples was separated by an interval of at least 8 weeks and in the patients by at least 36 h. Plasma drug binding was measured by equilibrium dialysis as previously described (Wood *et al.*, 1979) after addition of trace amounts of ^{3}H drug (2 ng/ml of propranolol, native drug was added to achieve a plasma concentration of 88 ng/ml). The degree of binding was measured as the molar ratio of bound to unbound drug, (B/F), since this is proportional to the concentration of binding protein when the free drug concentration is small compared with the dissociation constant for the drug-protein complex (Sager, Nilsen & Jacobsen, 1979). The relationship between the change in the binding ratio of propranolol and the change in AAG concentration is shown in Figure 1. Spearman's coefficient of rank correlation (ρ) was 0.867 ($P < 0.01$) suggesting a direct relationship between drug binding changes and AAG concentration changes, and is consistent with the very high correlation between plasma AAG and propranolol B/F in our experience of normal subjects ($r = 0.956$, $n = 24$).

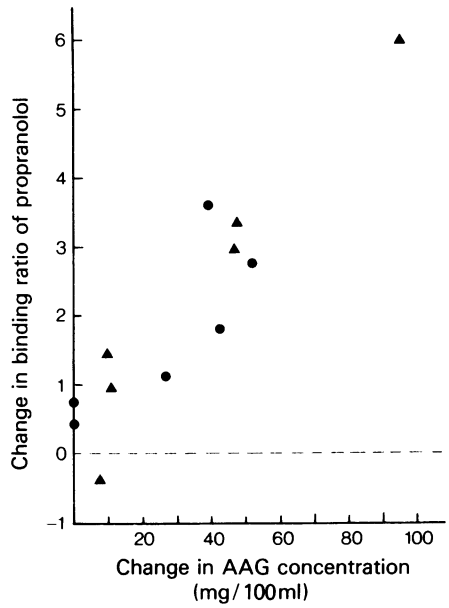

Figure 1 Relationship between the change in the binding ratio for propranolol and the concentration of α_1 acid glycoprotein (AAG) in normal subjects (▲) and patients admitted to the coronary care unit (●).

The fact that one of its major binding proteins rises and falls during the course of infarction and recovery suggests that the plasma binding of propranolol could be continually changing in a clinical situation in which the drug may be administered. Previous conclusions concerning the relationship between AAG concentration and propranolol binding have rested largely on population studies of variation between individuals. The present study has shown that enhanced binding can occur within individuals as a result of myocardial infarction. Marked variation was also seen in the normal subjects, possibly due to minor viral infections not detected clinically since many of the high AAG concentrations in these individuals occurred during the winter months.

Clearly, the increase in propranolol binding during the course of infarction is of potential importance in defining an effective dose of the drug, since the degree of β-adrenoceptor blockade has been shown to correlate with the free (unbound) plasma concentration (McDevitt *et al.*, 1976). The situation is further complicated by the fact that infarction may be associated with reduction in liver blood flow and hepatic enzyme function which could also affect the elimination of propranolol. Despite early enthusiasm

concerning the use of β-adrenoceptor blockers in myocardial infarction several trials in the late 1960's failed to show an effect on mortality (Balcon, Jewitt, Davies & Oram, 1966; Clausen, Felsby, Jorgensen, Nielsen, Roin & Strange, 1966; Multicentre Trial, 1966). Since these negative studies used small doses by modern standards (20 mg, 6 hourly) they may not have achieved adequate therapeutic levels. It is generally agreed that total plasma concentrations of at least 50–100 ng/ml are needed to achieve a reasonable degree of cardiac β-adrenoceptor blockade in normal subjects (Coltart & Shand, 1970). Recently Rutherford *et al.* (1976) measured peak plasma propranolol levels after 20 mg four times daily in patients admitted to the Coronary Care unit. Not only were the levels variable, but most were below 50 ng/ml for at least 48 h. The fact that trough levels would be considerably lower suggests that this regimen would be ineffective during the early, critical hours, especially since any rise in AAG would further reduce the unbound propranolol concentration. This suggestion has some support from the work of Norris, Caughey & Scott (1978) who loaded patients with 0.1 mg/kg i.v. followed by 320 mg orally over the next 27 h. This regimen, which achieved total plasma concentrations in the range of 80–140 ng/ml for 24 hours, appeared to exert a protective effect in both threatened (Norris, Sammel *et al.*, 1978) and established infarction (Peter, Norris, Clarke, Heng, Singh, Williams, Howell & Ambler, 1978). Given that such a regimen may have been effective, individual variability remained high and it would also seem more rational to adjust dosage to achieve a specified plasma concentration. Considering the present findings of altered drug binding in this situation it would be preferable to study unbound rather than total plasma propranolol levels.

In summary we have shown that the rise in AAG following myocardial infarction is associated with an increase in plasma propranolol binding. These findings emphasize that free drug concentrations should be considered in the design of dosage regimens for AAG-bound drugs which may be used in the treatment of myocardial infarction, including alprenolol (Piafsky *et al.*, 1978) and lignocaine (Piafsky & Knoppert, 1978) as well as propranolol.

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