β-Blocker Plasma Concentrations and Inflammatory Disease: Clinical Implications

R.E. Schneider and H. Bishop

Department of Therapeutics and Clinical Pharmacology, Medical School, University of Birmingham, Birmingham

Raised plasma propranolol concentrations in inflammatory disease were found accidentally during a study of drug absorption in patients with coeliac disease (Schneider et al., 1976). At first only patients with Crohn's disease were studied, but later patients with rheumatoid arthritis and a variety of other inflammatory diseases, such as pneumonia, ulcerative colitis and systemic lupus erythematosus were included (Schneider et al., 1981). The mechanism of this phenomenon of raised plasma concentrations was not clear, but it soon emerged that the higher plasma concentrations after an oral dose of propranolol were in some way associated with a raised erythrocyte sedimentation rate, but no quantitative correlation was found (Schneider et al., 1979a).

Mechanism of Raised Plasma Concentrations

Altered Protein Binding

In inflammatory disease there is a rise in the concentration of several plasma proteins, the so-called acute-phase reactants. Amongst these, α₁-acid glycoprotein (orosomucoid) has been shown to bind a number of basic drugs (Sager et al., 1979; Scott et al., 1979) and to affect their pharmacokinetics. Piafsky et al. (1978) found that plasma concentrations of α₁-acid glycoprotein were raised in Crohn's disease and rheumatoid arthritis and correlated positively with the increased binding ratio of propranolol which they found in the plasma of such patients. It has been predicted that total propranolol concentrations would be relatively unaffected (De Leve and Piafsky, 1981; Wilkinson and Shand, 1975). However, a significant positive correlation between the total plasma concentration and α₁-acid glycoprotein levels has been claimed (Schneider et al., 1979b).

Such a rise in the plasma concentration of α₁-acid glycoprotein not only occurs in chronic inflammatory disease, but has also been demonstrated after tissue damage. Thus, Aronsen et al. (1972) have described this occurring after surgery, and in another study it was associated with an increase in propranolol levels after thyroidectomy (Feely et al., 1980). The propranolol concentrations reached a peak 24 hours after
surgery, and then gradually declined over the next fortnight.

Myocardial infarction is another disease entity in which an elevation of α₁-acid glycoprotein has been demonstrated (Johansson et al., 1972; Snyder et al., 1975).

In neonates the reverse phenomenon has been observed: reduced plasma concentrations of α₁-acid glycoprotein were found compared with those in maternal plasma, together with a reduction in the binding ratio of propranolol and thus an increase in the free (unbound) fraction (Wood and Wood, 1981).

Decreased Metabolism

Propranolol is a drug which is extensively metabolised by the liver, and thus only minute amounts of unchanged drug appear in the urine. This clearance is dependent on the hepatic extraction ratio which depends on the activity of liver enzymes as well as liver blood flow. After oral dosage much of the drug is extracted during the first passage through the liver before it reaches the systemic circulation. This first-pass hepatic clearance of drugs is naturally depressed in chronic liver disease, particularly cirrhosis, and in such cases raised plasma levels of propranolol have been shown (Branch et al., 1977). Similarly, in inflammatory disease there is also an indication that some depression of first-pass clearance of propranolol may occur. It would be expected that this depression would be more evident after oral than after intravenous dosing, and in rats with adjuvant-induced arthritis have shown that tissue concentrations are actually lower than those in normal animals, while the total plasma concentrations are raised (Bishop and Schneider, unpublished data). Therefore the estimation of total plasma concentrations of β-blockers like propranolol and alprenolol which are extensively bound to α₁-acid glycoprotein estimation of the total plasma concentrations may give a misleading picture. Preliminary studies with intravenous propranolol in rats with adjuvant-induced arthritis have shown that tissue concentrations are actually lower than those in normal animals, while the total plasma concentrations are raised (Bishop and Schneider, unpublished data).

Feely et al. (1980) suggest that there is decreased hepatic clearance of propranolol in patients after surgery.

Clinical Implications

How do these findings affect the clinical situation? Should dosage regimens of β-blockers be modified in chronic inflammatory disease? Plasma drug concentrations are now widely used for monitoring drug dosage and have been recommended as superior to monitoring of the pharmacological response (Brodie and Reid, 1972), and for the satisfactory administration of drugs such as anticonvulsive agents, digoxin, gentamicin and lithium, their use has been invaluable. However, with drugs such as propranolol and alprenolol which are extensively bound to α₁-acid glycoprotein estimation of the total plasma concentrations may give a misleading picture. Preliminary studies with intravenous propranolol in rats with adjuvant-induced arthritis have shown that tissue concentrations are actually lower than those in normal animals, while the total plasma concentrations are raised (Bishop and Schneider, unpublished data).

As it is generally assumed that it is only the free fraction of a drug which is pharmacologically active, it is the estimation of this fraction which is important. This estimation, however, requires such separation techniques as equilibrium dialysis or ultrafiltration, possibly with the use of labelled drugs. Whether it would be desirable to introduce such sophisticated techniques for the practical management of patients suffering from a chronic inflammatory disease who also require treatment with such β-blockers would depend on the nature of the condition to be treated. In the management of hypertension, for instance, it has been suggested that a stepwise increase in the dose until the desired effect is produced gives satisfactory results (Shand, 1974). On the other hand, it has been claimed that with propranolol, neither the therapeutic response of lowering blood pressure, nor the appearance of toxic symptoms are dose-dependent (Serlin et al., 1980). A sophisticated measurement of the plasma concentration of the free drug would therefore...