117P

ERYTHROCYTES AS A SLOW RELEASE CARRIER SYSTEM FOR PROPRANOLOL AND ITS PRODRUGS

H O ALPAR, E SALT, A JOLLY, K A BELAID & W J IRWIN Drug Development Group, Department of Pharmaceutical Sciences, Aston University, Birmingham B4 7ET

In order to overcome the unwanted side effects, to reduce the extensive hepatic elimination and regulate plasma concentrations attempts were made to encapsulate propranolol and its prodrugs into erythrocytes.

Two prodrugs of propranolol namely O-acetyl propranolol (OAP) and O-pivaloyl propranolol (OPP) have been synthesized (unpublished results) and together with propranolol have been encapsulated into rat erythrocytes using a preswelling technique (Pitt et al 1983).

The results have shown that by increasing the concentration of the drug solution to be loaded (from 3 mg ml^{-1} to 6 mg ml^{-1}) it was possible to increase the efficiency of loading. The loading efficiency was also increased when more lipophilic prodrugs of propranolol were encapsulated and compared to the parent drug. At a 6 mg ml^{-1} loading level encapsulation of propranolol was 46.73 ± 2.2% (n = 10). This value was increased to 58.0 ± 5.0% for OAP and to 68.7 ± 4.2% (n = 5) for OPP. The release of encapsulated and free compounds was tested *in vitro* using dialysis sacs.

In the case of free propranolol and free OAP more than 80% of drug was released in less than 1 h. For encapsulated propranolol and OAP the amount of propranolol released in 3 h was 40% and 32% respectively. There was no release of OAP suggesting that the whole prodrug was converted to parent drug within the erythrocytes. This finding was confirmed by carrying out a degradation study of OAP in plasma, where the half life of OAP was found to be 0.5hr. When the release of free OPP was studied it was found that free OPP was released with propranolol concurrently, possibly due to degradation of OPP in the suspending medium. This was confirmed by degradation studies. At 3h the total OPP released (i.e. OPP and propranolol) was equivalent to 70% of the original concentration.

The encapsulated drug OPP was also shown to degrade to propranolol in dialysis experiments. Propranolol was detected almost immediately in the dialysate but unchanged OPP was only present in detectable amounts in the dialysate 1h after the commencement of the experiment. At 3h the total OPP released (as OPP and propranolol) was only 18% of the total encapsulated (15% propranolol and 3% OPP) prodrug.

The simultaneous release of propranolol and OPP from erythrocytes represents a novel slow release system. Also since the prodrug (OPP) is hydrolysed slowly in plasma to the free drug this provides a "top up" mechanism which would further increase propranolol levels in plasma.

Encapsulated preparations were either used immediately or after storage in a buffer containing 144 mM NaCl, 10 mM NaH_2PO_4, 2 mM $MgCl_2$ and 10 mM glucose at 4°C for up to 3 weeks. No significant loss of viability *in vivo* was observed during this storage period when assessed by phagocytosis as described by Pitt *et al* (1983).

Pitt, E *et al* (1983) Biochem. Pharmac. 32, 3359-3368