J. Pharm. Pharmacol. 1998, 50 (Supplement): 255

Design of ester prodrugs of 3-hydroxypyridin-4-one chelators with clinical potential

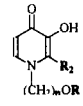
Z. D. LIU, D. Y. LIU, S. L. LU AND R. C. HIDER

Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX

3-Hydroxypyridin-4-ones (HPOs) are currently one of the main candidates for the development of orally active iron chelators (Hider *et al.* 1996). The simple 1,2-dialkyl derivatives are highly effective at removing iron from iron overloaded animals including man but are associated with two disadvantages; (i) they penetrate cells easily and therefore gain ready access to the bone marrow and the brain and (ii) they are rapidly conjugated with glucuronic acid, thereby loosing their iron binding properties (Singh *et al.* 1992). Designing more hydrophilic hydroxypyridinones, for instance hydroxyalkyl hydroxypyridinone can effectively decrease penetration of membranes. Some of 1-hydroxyalkyl derivatives of HPOs such as CP102 and CP41 (**Table**) are not extensively metabolised *via* phase II reactions and therefore their chelating action is more prolonged (Singh *et al.* 1996). Not surprisingly the increased hydrophilicity of such compounds is associated with relatively poor oral absorption and insufficient extraction by the liver, which is the major iron storage organ. A strategy to improve chelation efficacy and hence to minimize drug-induced toxicity can be achieved by the selective delivery of the drug to target organs such as the liver. The development of hydrophobic ester prodrugs of 1-hydroxyalkyl HPO derivatives is one route, which has been considered to improve both drug absorption and hepatic extraction.

In this work, a range of ester prodrugs of 1-hydroxyalkyl HPOs has been synthesized (**Table**). The distribution coefficient (K_{part}) values of these ester prodrugs and the corresponding alcohols in 1-octanol and MOPS buffer (pH 7.4) are also presented. In order to identify a lead prodrug, by which specific drug delivery can be achieved, the stability of these ester prodrugs was monitored under different conditions such as aqueous solution (pH 2.0 and pH 7.4), rat plasma and rat liver homogenate.

Table: The chemical structure of 1-hydroxyalkyl HPOs and their ester prodrugs.

	R_2	n	R	K_{part}
CP40	CH_3	2	H	0.08
CP162	CH_3	2	$COC(CH_3)_3$	4.70
CP41	CH_3	3	H	0.13
CP165	CH_3	3	$COC(CH_3)_3$	8.78
CP102	CH_2CH_3	2	H	0.22
CP117	CH_2CH_3	2	$COC(CH_3)_3$	14.5
CP181	CH_2CH_3	2	COC_6H_4OH-*o*	50.3
CP183	CH_2CH_3	2	COC_6H_5	32.8

In vivo iron mobilization efficacy of these ester prodrugs has been compared with their parent drugs using a ^{59}Fe-ferritin loaded rat model. Most prodrugs provide a clear improvement over their parent compounds in the efficacy model (**Figure**). However, not all the prodrugs provide increased efficacy, thus CP183 is less effective than the parent compound CP102, suggesting that lipophilicity is not the only factor which influences the drug efficacy.

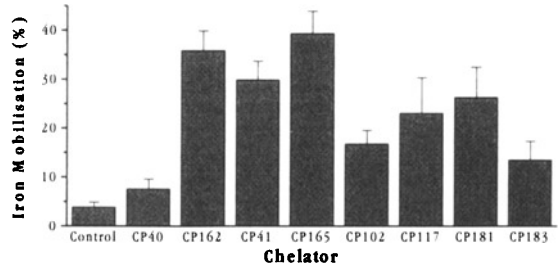


Figure: Iron mobilization comparison between ester prodrugs and their parent compounds.

Hider R.C., Choudhury R., Rai B.L., Dekhordi L.S., Singh S. (1996) Acta Haematol. 95: 6-12.

Singh S., Epemolu R.O., Dobbin P.S., Tilbrook G.S., Ellis B.L., Damani L.A., Hider R.C. (1992), Drug Met. Disp. 20, 256-261.

Singh, S., Choudhury, R., Epemolu, R.O., Hider, R.C. (1996) Eur. J. Drug Metab. Pharmacokinet. 21: 33-41.