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Management of iron overload in anaemia

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Thalassemia and sickle cell anaemia are two hereditary diseases associated with the abnormal synthesis of haemoglobin. The WHO estimate that by the year 2000, 7% of the world's population will be carriers of one or more of these disease states. The reason for the high carrier rate is that they are associated with a degree of resistance towards malaria infection (Flint et al 1986). β-Thalassaemia is associated with a decrease in the rate of production of β-globin chains and severe states of the disease require regular blood transfusions. As the human is unable to increase the basal rate of iron excretion, such treatment leads to iron overload and associated damage to endocrine organs, the liver and heart. The iron chelator Desferal has been used successfully to remove this excess iron but due to poor absorption from the intestine and rapid renal clearance, this chelator has to be given subcutaneously to patients over 8-12-h periods, 5-6 times per week. Compliance is not good and an orally active iron chelator would be of considerable benefit to such patients.

For reasons outlined by the King's College group, bidentate chelators are likely to be the most effective orally active iron scavengers (Hider et al 1996) and of these, 3-hydroxypyridin-4-ones have been established as possessing outstanding potential (Tilbrook & Hider 1998). Indeed one of the compounds 1,2-dimethyl-3-hydroxypyridin-4-one (Deferiprone) is currently in clinical trial in Italy. Unfortunately this compound suffers from a low toxicity/efficacy ratio and has to be given at high doses (75 mg kg^{-1}), which are sometimes associated with side effects (Brittenham 1992). Over the past decade the group at King's College has been systematically modifying the pyridinone structure and thereby increasing the ligands' affinity for iron and selectivity for iron over zinc, optimising the disposition of the ligands, controlling the predominant metabolic pathways and minimising the toxicity of both the free ligand and the iron complex. We have now identified vastly superior chelators to Deferiprone and are currently selecting compounds for more detailed toxicological investigation.

These aspects of medicinal chemistry and toxicology will be discussed, together with a background to thalassaemia as found in the United Kingdom.

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