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In-vivo metabolism of 1-(3′-hydroxypropyl)-2-methyl-3-hydroxypyridin-4-one (CP41) and 1-(2′-hydroxyethyl)-2-ethyl-3-hydroxypyridin-4-one (CP102) by rat

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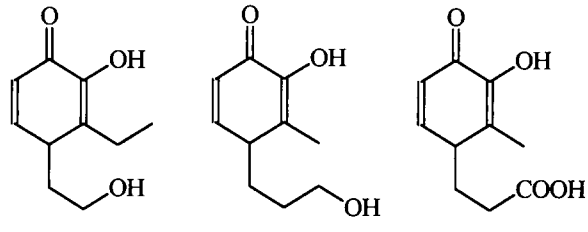
Both 1-(3'-hydroxypropyl)-2-methyl-3-hydroxy-pyridin-4-one (CP41) and 1-(2'-hydroxyethyl)-2-ethyl-3-hydroxypyridin-4-one (CP102) are orally effective iron chelators, which are able to enhance the excretion of iron *in vivo* (Zaninelli *et al.* 1997). Although the pharmacokinetics of CP102 and its metabolic profile in urine has been previously reported (Singh *et al.* 1996), its biliary metabolic profile remains unclear. In addition, a clear understanding of the metabolism of CP41 is needed in order to study its pharmacokinetic characteristics.

The rat bile duct cannulation model was utilised in the present investigation. After the animals were orally administered with a single dose of CP102 or CP41 (450μmol/kg body weight), the bile samples were collected hourly up to a period of 10 hours. The urine samples were also collected using separate animals without bile duct cannulation. The bile and urine samples were analysed using a HPLC method and the amounts of iron excreted in bile and urine were determined utilising a colorimetric method. In order to determine the conjugated metabolites of CP41 and CP102, samples were treated separately in the presence of glucuronidase or sulfatase before being applied for HPLC analysis.

The elimination of CP102 from rat urine showed a similar pattern to that of a previous report (Zaninelli *et al.* 1997), i.e. the unchanged CP102 was the dominant form excreted in urine. Minor amounts of glucuronide and sulfate metabolites of CP102 were also found in urine. In the bile, the unchanged CP102 was only found to be a major elimination form, however, glucuronide and sulfate metabolites were excreted in approximately equal amounts to that of CP102.

Unlike CP102, 1-(3'-hydroxy) group oxidation of CP41 was demonstrated to be the main metabolic pathway. The resulting oxidative metabolite (CP38), was excreted at high levels (~30%) in the urine. Other CP41 elimination forms in urine included the unchanged CP41 (~45%), glucuronide (~10%) and sulfate (~15%) of CP41. The biliary metabolic profile of CP41 was again found to be different to its urinary metabolic profile. CP41 is rapidly oxidised to CP38 in the liver and the latter is excreted in bile forming over 90% of the total recovery of all elimination forms of CP41. Thus unchanged CP41 was excreted in bile to a much lesser extent than in urine. Small amounts of conjugated metabolites of CP41 were also detected in the bile.

In the normal rat, CP102 is found to be more efficient than CP41 at removing iron from the liver. This is surprising, as when CP102 is administered, over 60% of pyridinone secreted in the bile is conjugated (and therefore unable to chelate iron) whereas with CP41 over 90% of the pyridinone secreted is nonconjugated. This may indicate that the negatively charged CP38 can not access the major labile iron pool as efficiently as CP41. Lysosomal compartmentalisation could account for this difference, a factor currently under investigation.



CP102 CP41 CP38

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

Zaninelli, G., Choudury, R., Loreal, O., Guyader, D., Lescoat, G., Arnaud, J., Verna, R., Cosson, B., Singh, S., Hider, R.C., Brissot, P. (1997) J. Hepatol. 27: 176-184