Biochemical Pharmacology, Vol. 34, No. 3, pp. 451–452, 1985.
Printed in Great Britain.

0006-2952/85 $3.00 + 0.00

BIOLOGICAL FATE OF ACYL GLUCURONIDES IN THE RAT
The Role of Rearrangement, Intestinal Enzymes and Reabsorption

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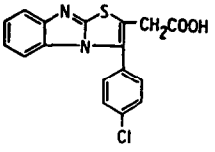
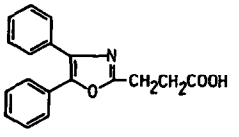
Many exogenous compounds with a carboxylic acid function are metabolized to 1-O-acyl glucuronides (1). These acyl (or ester) glucuronides undergo a pH-dependent rearrangement by which the acyl residue (the "aglycone") migrates from position 1 of the glucuronic acid moiety to positions 2, 3 and 4, thus forming isomeric substituted glucuronic acids (2,3).

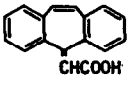
We have examined the rate of rearrangement and nonenzymic hydrolysis of three glucuronides which are metabolites of the antiinflammatory-immunomodifying agents Wy-18,251 (4), oxaprozin (5) and Wy-41,770 (*).



Wy-18,251



Oxaprozin



Wy-41,770

Fig 1 indicates great variability in the rate of decline, i.e. the half-lives of disappearance at pH 7.4 and 37°C are approximately 0.38, 1.3 and 14 hours for the glucuronides of Wy-18,251, oxaprozin and Wy-41,770 respectively. Under these conditions hydrolysis of oxaprozin and Wy-41,770 glucuronides is negligible and only a small amount of Wy-18,251 glucuronide is hydrolyzed. Thus, the 40 fold difference with respect to the rates of disappearance between the glucuronides of Wy-18,251 and Wy-41,770 is primarily due to rearrangement. Therefore, the rate of this reaction depends on the nature of the aglycone (4). In the rat, following iv administration of 52.5 μ moles/kg, the biotransformation products of Wy-18,251 and Wy-41,770 are predominantly excreted in the bile. However, the composition of the biliary excretion products varies in accordance with the difference in the stability of the respective glucuronides described above. In bile collected for 3 minutes at pH 5 to prevent further rearrangement, 24% of total drug related substances is present in the form of the rearrangement products of Wy-18,251 glucuronide, 68% as the glucuronide itself and 8% as free drug (derived from the glucuronide by nonenzymic cleavage). In contrast, bile from Wy-41,770 treated rats contains mostly the acyl glucuronide of the drug (over 85%) and almost no rearrangement products or free drug.

Rearrangement and to a much lesser extent hydrolysis of Wy-18,251 glucuronide continue in the small intestine. Since the rearrangement products are not cleaved by β-glucuronidase nor reabsorbed as such they accumulate in the small intestine until they reach the caecum. There they are hydrolyzed by a hitherto undescribed enzyme of probable

* R.T. Schillings, et al., unpublished data

microbial origin (absent in antibiotic treated rats) which in contrast to β-glucuronidase is not inhibited by saccharolactone. The parent drug regenerated in the caecum is not reabsorbed but is eventually excreted in the feces.

The glucuronide of Wy-41,770 is partially cleaved by the β-glucuronidase(s) present in the small intestine. The liberated parent drug is reabsorbed and reexcreted as acyl glucuronide in bile (enterohepatic recirculation). This is indicated by a secondary peak on the plasma concentration vs time curve, the long half-life of elimination from plasma (10 hrs) and an intestinal transit time of 3 days. In contrast, the plasma half-life of Wy-18,251 is only 2.9 hrs and intestinal transit is much faster (Fig 2). Thus, the disposition of the two anti-inflammatory agents in the rat is quite different despite the fact that both are transformed to acyl glucuronides which are predominantly excreted in the bile. The factors determining the fate of the latter are the extent of rearrangement, cleavage by enzymes specific for glucuronide or rearrangement products, distribution of the enzymes in the various segments of the gut and lastly the capacity of the various segments for reabsorbing parent compound.

Fig 1

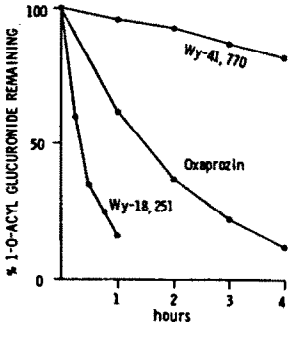


Fig 2

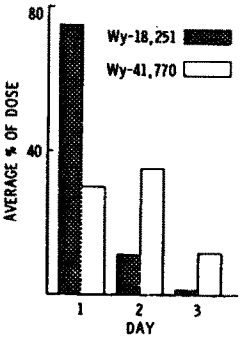


Figure 1: Stability of 1-O-Acyl Glucuronides - The glucuronides were dissolved in 0.1 M phosphate buffer pH 7.4 at 37°C. Remaining glucuronide was determined by HPLC after acidification to stop the reaction.

Figure 2: Fecal Excretion of ^{14}C in Rats Given Labeled Wy-18,251 or Wy-41,770 - Male rats were given intravenous doses of 52.5 μ moles/kg of the respective drug.

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