Letters to the Editor

Comments on “Shift from Biliary to Urinary Elimination of Acetaminophen-Glucuronide in Acetaminophen-Pretreated Rats”

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We read with great interest the article on the impact of pretreatment with acetaminophen on acetaminophen disposition in rats (Ghanem et al., 2005). The authors found strong arguments in favor of a shift from biliary to urinary elimination of acetaminophen-glucuronide (APAP-G) during repeated administration. This shift from biliary to urinary elimination was associated with increased expression of basolateral multidrug resistance-associated protein 3 (Mrp3) relative to canalicular Mrp2 and decreased enterohepatic recirculation in the absence of alterations in UDP-glucuronyltransferase (UGT) activity. Such a switch is biologically sound since this results in the reduction of enterohepatic recirculation during repeated administration of acetaminophen. It is still unclear whether these observations can be extrapolated to acetaminophen disposition in humans.

However, based on a limited number of studies on acetaminophen metabolism in neonates, infants, and adults during repeated administration, we feel that this concept should at least be investigated in humans. Key observations on the maturational disposition of acetaminophen are most frequently represented by the ratio of APAP-G to APAP-sulfate (APAP-S), i.e., G/S ratio. Following single dose administration, a maturational increase in urinary molar G/S ratio is observed (Levy et al., 1975; Miller et al., 1976; Hendrix-Treacy et al., 1986). Although much more limited in number, observations on the urinary G/S ratio during repeated acetaminophen administration in neonates, infants, and adults more recently also became available (Hendrix-Treacy et al., 1986; Van der Marel et al., 2003; Allegaert et al., 2005) (Table 1).

We recently reported observations on intra- and interindividual variability of glucuronidation of acetaminophen during repeated intravenous administration in preterm and term neonates (Allegaert et al., 2005). Based on urine collections in 23 neonates, a significant increase in urinary G/S ratio was observed with postnatal and postconception age and with repeated administration. Repeated administration remained a significant contributor of urinary excretion of APAP-G to overall APAP excretion after correction for postnatal and postconception age in a multiple regression model.

Van der Marel et al. (2003) described acetaminophen disposition in 47 infants with a mean age of 11 months based on urine and blood samples collected following major craniofacial surgery. Acetaminophen was repeatedly administered either by oral or rectal route. Median G/S ratio was 0.69, and the adult G/S ratio that is usually described at 12 years of age following single dose administration was already reached at about 1 year. Finally, Hendrix-Treacy et al. (1986) documented in a study in nine adults that the fraction eliminated as sulfate conjugate decreased while the fraction excreted as glucuronide increased when multiple dose was compared with the single dose administration (molar G/S ratio, 2.8 versus 2). Serum sulfate levels could not explain this observation since patients on chronic acetaminophen therapy even exhibited elevated serum sulfate levels.

We postulated that the increased glucuronidation reflected enhanced maturation (“induction”) of glucuronidation activity—either hepatic or extrahepatic in its origin—during repeated administration in neonates (Allegaert et al., 2005). Based on the present observations in rodents, a switch from biliary to renal elimination of glucuronidated metabolites should also be considered.

The evaluation of these processes in humans will need simultaneous collection of blood, urine, and bile samples, but the availability of an intravenous formulation of acetaminophen might thereby enable us to discriminate between biliary excretion and variability of bioavailability. In an experimental design, it was appropriate to repeat the same animal experiments in rats of various developmental ages to assess maturational aspects in this switch of biliary to urinary elimination, to evaluate the contribution of extrahepatic (renal) UGT activity on acetaminophen disposition, and to exclude an inductive effect of acetaminophen. More than 100 years after the introduction of acetaminophen into clinical practice, still new observations on its disposition and pharmacodynamic profile are unveiled, and relevant questions can be formulated.

ACKNOWLEDGMENTS

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ABBREVIATIONS: APAP, acetaminophen; Mrp, multidrug resistance-associated protein; UGT, UDP-glucuronyltransferase.
TABLE 1
The molar urinary G/S ratio during single and repeated dose administration in neonates, infants, children, and adults
All G/S ratios were reported by their molar urinary ratio to make results of different populations comparable.

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<td>Allegaert et al. (2005)</td>
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**References**


