

## Urinary Metabolites of Chloroprocaine

*To the Editor:*—In their recent article, Krohg and Jellum<sup>1</sup> reported no evidence of conjugated 2-chloro-4-aminobenzoic acid (CABA) in either maternal or neonatal urine following epidural anesthesia with 2-chloroprocaine. In addition, they found only small amounts of unmetabolized CABA in neonatal urine. They studied four mothers and one neonate.

In contrast to their data, we are finding on the average 36 per cent of the total excreted CABA to be conjugated. Our data are from a similar ongoing study which presently includes 22 mothers. O'Brien *et al.*<sup>2</sup> have reported similar findings in four subjects. In addition, we have observed that the urine from the resulting infants contains amounts of unmetabolized CABA comparable to those excreted by the mother (data expressed on a  $\mu\text{g}$  drug/mg creatinine basis). In agreement with Krohg and Jellum, we did not find significant amounts of conjugated CABA in neonatal urine during the first 48 h of life. However, on the third day of life, trace amounts of conjugated CABA were detectable.

There are two differences between our methodology<sup>3,\*</sup> and the methodology used by Krohg and Jellum which may explain these conflicting results. First, Krohg and Jellum collected specimens from mothers at the time of delivery and two hours later which corresponds to approximately one and three hours after epidural injection. Only one neonatal urine sample was studied and it was "voided shortly after delivery." In contrast, we collect urine samples from delivery through the first 72 h postpartum in both mother and neonate. Possibly, there was not enough time for sufficient amounts of conjugated CABA to be produced, concentrated, and excreted by Krohg and Jellum's patients. In support of this inter-

\* Technique modified to include 4-amino-3,5,-diiodobenzoic acid as the internal standard and detection by electron capture gas chromatography.

*In reply:*—In reply to the letter from Kuhnert, Kuhnert, and Reese we have the following comments. The above authors claim to find on the average 36 per cent of the total CABA to be conjugated, but they have been unable to identify the conjugate. We have conclusively shown using gas chromatography-mass spectrom-

etry, O'Brien *et al.* reported that the proportion of conjugate to free metabolite increased with time following intravenous administration of chloroprocaine. Secondly, to free conjugated CABA, we pretreat 1-ml aliquots of diluted urine for 20 h at 90°C prior to extraction; O'Brien *et al.*<sup>2</sup> used even harsher hydrolysis conditions. However, no mention is made of conjugate hydrolysis techniques by Krohg and Jellum.

For these reasons, it does not seem reasonable at this time to accept Krohg and Jellum's conclusions regarding maternal levels of conjugated CABA and neonatal levels of unmetabolized CABA.

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etry and reference compound that the major metabolite is N-acetyl CABA.

Whether this should be called a conjugate or not is a matter of definition. One should realize that N-acetyl CABA readily undergoes alkaline hydrolysis to yield free CABA (shown by GC-MS experiments in our labora-

tory). Thus, the conjugate discussed by O'Brien *et al.*<sup>1</sup> and Kuhnert *et al.* may simply be N-acetyl CABA, and that no discrepancy really exists. On the other hand there may also exist additional conjugates, though we failed to find significant amounts of the glycine conjugate.

We agree that the urine sampling period in our experiment is short (3 h) compared to that of Kuhnert *et al.* (72 h). However, O'Brien *et al.*<sup>1</sup> reported a very rapid elimination of CABA and CABA conjugate following a 30-min intravenous infusion of chloroprocaine. In fact, 65 per cent of the administered dose was recovered within 90 min from the onset of the infusion. Thus, it was felt that a three-hour collection period would suffice.

In conclusion, therefore, we feel that only minor conflicting results exist, that N-acetyl CABA is the major metabolite (or conjugate), and that the last sentence in letter of Kuhnert *et al.* is not justified.

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## Pharmacogenetics and Halothane Hepatitis

*To the Editor:*—There is now published evidence in humans that pharmacogenetics may be a factor in human halothane hepatitis.<sup>1</sup> In addition to our recent report of differences in halothane hepatotoxicity among three different strains of rats,<sup>2</sup> we now have evidence within one rat strain (Fischer 344) of considerable variability in hepatic damage following halothane.<sup>3</sup> In a study of the time course of changes in liver function and structure following halothane, maximum values for serum alanine amino-transferase (ALT) varied from 143 IU/l to over 28,000 IU/l. Although mean peak serum ALT was 5,180 IU/l, three of 128 animals studied had values of 28,925; 18,550; 7,650 IU/l, respectively. These high serum ALT values in three animals were accompanied by massive hepatic necrosis, whereas animals with moderate increases in serum ALT had focal necrosis.<sup>3</sup> This provides further evidence of a genetic influence in halothane hepatitis, since the conditions of anaesthesia and oxygenation were identical for all animals.

Clinical studies of repeated halothane anaesthesia report that mild liver injury occurs with a frequency as high as 24-40 per cent of patients; yet severe liver injury is rare. It now seems that pharmacogenetics may provide a key that predisposes a small number of individuals to severe liver injury. Even in such individuals it seems likely that a complex set of factors, such as high rate of

reductive bio-transformation and low oxygen concentration in the liver, may be conditional to the development of massive hepatic necrosis. This is entirely in keeping with a multifactorial etiology of halothane hepatitis as discussed by commentators in both the field of anesthesiology<sup>4,5</sup> and general medicine.<sup>6,7</sup>

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