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LETTERS TO THE EDITOR

Question about the formation of norcodeine from morphine in man

In studies of metabolism of morphine in man, morphine glucuronide, morphine ethereal sulphate, normorphine and normorphine conjugate were identified as metabolites (Yeh, 1973a). The amounts of free morphine, free normorphine, morphine conjugate and normorphine conjugate were approximately 10, 1, 65 and 3%, respectively, of the administered dose (Yeh, 1973b, 1974a). The biotransformation of morphine to codeine in man reported by Boerner & Abbott (1973) could not be confirmed (Yeh, 1974b). A recent paper reporting the detection, isolation and characterization of norcodeine as a morphine metabolite in man (Boerner, Roe & Becker, 1974) prompts the present communication.

It has been reported recently (Yeh, 1974b) that the amount of codeine found in a morphine sulphate sample, U.S.P. grade was 0·04%. The amount of total (free plus conjugated) codeine found in the urine of men receiving chronic administration of morphine suphate, (60 mg, s.c. q.i.d.), was about 31% of the amount of codeine present as an impurity in the drug administered. Any norcodeine which might have been formed from the codeine was too small to be detectable. Other recent studies have been unable to find codeine in the urine of men (Oguri, Ida & others, 1970; Brunk & Delle, 1974) or rats (Klutch, 1974; Abrams & Elliott, 1974) administered morphine. This discrepancy probably is because either the method of analysis was of limited sensitivity or the morphine sulphate did not contain codeine. Elison & Elliott (1964) previously observed a faint radioactive spot, obtained from the extract of a large amount of urine of rats and dogs administered [N-^{14}C]methylmorphine, having the same R_F as codeine and postulated the *O*-methylation metabolic pathway for morphine. However, the small amount of codeine found could probably be accounted for as a contaminant of the morphine administered.

Using highly sensitive methodology, the metabolism of codeine in man and laboratory animals have been investigated (cf. Way & Adler, 1962; Yoshimura & others, 1970; Yeh, 1974b) and it was found that about 90% of codeine was metabolized. Adler, Fujimoto & others (1955) reported that after [N-^{14}C]methylcodeine administered orally or i.m., the mean urinary excretion was 11% as unchanged codeine, 45% as conjugated codeine, 14% as total norcodeine and 10% as total morphine. Based on the amount of codeine (0·04%) found in morphine sulphate and the amount of codeine biotransformed to total norcodeine (14%), the amount of total norcodeine expected to be excreted in the urine would be about 0·006% of morphine sulphate administered.

The amount of morphine sulphate administered to man by Boerner & others (1974) was about 1200 mg. It would be expected to result in the urinary excretion of approximately 67 μg of total norcodeine. It is not clear from the paper how much norcodeine was isolated. The authors stated that the amount of norcodeine detected with t.l.c. was $>0{\cdot}1$% of administered dose. The authors also stated there was not sufficient sample to obtain an nmr spectrum. The characterization of norcodeine isolated from the urine was performed with a highly sensitive mass spectrometer, requiring less than one μg of sample. Therefore, it is possible that the norcodeine identified in the urine by Boerner & others (1974) could have come from codeine present as a contaminant in the morphine sulphate administered. The authors state that codeine was not detected in the morphine sulphate administered. However, it is not clear whether the method used by the authors is sensitive enough to

detect 0·04% of codeine in the morphine sample and rule out the possibility that the norcodeine could originate from the injected codeine.

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The formation of norcodeine from morphine in man

In answer to the views expressed by Yeh (1975) we affirm that codeine impurities were not detected by mass spectrometry in the morphine used in our studies (Boerner, Roe & Becker, 1974).

We appear to differ over the interpretation of the work of Oguri, Yoshimura & Taukamoto (1970) and Brunk & Delle (1974). Our understanding is that both groups did not administer morphine chronically. Oguri & others administered 10 mg of morphine hydrochloride three times into one patient over a 23 h period and Brunk & Delle administered only one dose of 10 mg radioactive morphine sulphate to their volunteers. Oguri & others determined morphine, normorphine, morphine-3-glucuronide, and morphine-6-glucuronide in the 35 h pooled urine collection; presence or absence of codeine was not reported. Brunk & Delle determined morphine, morphine-3-glucuronide, and morphine ethereal sulphate in the urine of their volunteers. No statements are made of any attempt to determine the presence or absence of codeine or norcodeine.

We agree, however, that animal studies may sometimes serve as useful models in suggesting possible metabolic pathways in man. The study of rats by Abrams & Elliott (1974), which was cited as a recent example of possible metabolic differences between jaundiced Gunn rats and Long Evans rats during prolonged chronic morphine administration and did not show occurrence of codeine as a urinary metabolite, prompts some comments. Even though the investigators of this study claimed a high sensitivity for the detection of codeine, morphine, normorphine, and morphine-glucuronide, the only morphine metabolites found in their analysis of urine were morphine-3-glucuronide and free morphine. These workers specifically stated that they were unable to detect either normorphine or codeine. However, because normorphine is a long-established and generally accepted urinary morphine metabolite in rat studies and is also present in significant quantities, these findings must be