The present findings support the recent suggestion that trazodone causes 5HT-like activities through the formation of mCPP (Maj et al 1979; Caccia et al 1981a). These results raise the possibility that mCPP may be formed in depressed patients treated with trazodone, contributing to its antidepressant activity. It may be relevant to mention that at doses higher than 1 mg kg^{-1} mCPP increases noradrenaline metabolism in the rat brain (Invernizzi et al 1981), an effect which may also contribute to the antidepressant activity. The present data further suggest that trazodone may inhibit some withdrawal syndrome signs in subjects from whom narcotics had been withdrawn.

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Observations on urinary excretion of codeine in illicit heroin addicts

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The metabolism of morphine and heroin in man is still under discussion. Baselt (1978) and Gorrod & Beckett (1978) reported codeine as a minor morphine metabolite via *O*-methylation in man, Boerner & Abbott (1973) during opiate screening of urines of 75 heroin addicts, found codeine and morphine in 85% of the samples, the codeine in amounts between 12 and 15% of the morphine present. To prove that the codeine formed occurred via *O*-methylation of morphine the authors examined 5 subjects (4 non-tolerant and 1 tolerant) given morphine sulphate in various daily doses. Codeine was present in all urines with a significant larger percentage in the tolerant subject (0·7–6% relative to morphine).

Yeh (1974) in a study on urine specimens collected from post-addict volunteers given morphine sulphate (240 mg daily) detected codeine in minute amounts (0·015% relative to morphine), but attributed its presence to it being an impurity (0·04%) in the morphine injected and not to a biotransformation product. The large amount of codeine found in urine samples by Boerner & Abbott (1973) might be the result of either on-column acetylation of the urine extract, or contamination of heroin of illicit source with acetylcodeine. Boerner & Roe (1975) and Yeh (1975) continued their controversy.

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Yong & Lik (1977) report a study of the urinary excretion patterns in opiates addicts: where illicit morphine and heroin had been injected, codeine was also detected in the urines, because codeine was an impurity in illicit morphine and acetylcodeine an impurity in illicit heroin. In cases of licit morphine and heroin intake, codeine was not detected. In 1979, Yeh et al reported new metabolites of morphine in several mammalian species, but did not detect codeine. We have carried out a study on 220 urine samples with previously positive results for opiates by EMIT (DAU—Syva Corp., Palo Alto, California) assay.

The urine specimens were divided in two groups:
Group I: 70 urine samples of subjects known to be receiving morphine only, in doses of 60–120 mg daily (18 in chronic pain treatment and 52 opiates addicts on a controlled deconditioning program on morphine only).
Group II: 150 urine samples of known heroin addicts.

Methods

Each of the urine samples was divided in two aliquots, the first for morphine detection and the second for codeine detection. Morphine extraction and its quantitative determination were carried out according to Felby et al (1974). The codeine was extracted with ether at pH = 14 (NaOH 20%) on acidic hydrolysed urines. The detection was carried out by t.l.c. on silica gel precoated plates with ethanol–benzene–dioxane–ammonia (50:40:5:5) as solvent; iodoplatinate and Marquis as reagents (Clarke 1975).

The quantitative determination of codeine in the remaining extract was by g.l.c. on Carlo Erba, series 4200, equipped with a 2 m × 4 mm glass column packed with 1% OV 17 on anakrom ABS 90–100 mesh, and flame ionization detector. Temperatures for injector, column and detector were 300 °C, 260 °C, and 320 °C respectively. The internal standard (orphenadrine) was previously added to urines, before the hydrolysis, as it does not interfere. Calibration was by use of the codeine/orphenadrine ratio with various concentrations of codeine (0·1–2·0 μg ml^{-1}). The detection limit for codeine was 0·1 μg ml^{-1} by both t.l.c. and g.l.c. The presence of codeine was confirmed by mass-spectrometry on an LKB series 2091: temperatures of ion source and separator were 250 °C and 230 °C respectively; electron energy 20 eV.

Results

Morphine was detected and quantitized in all urine samples. On the other hand codeine was *not present* in urine samples of group I and *present* in those of group II (heroin addicts or users). The amount of codeine in these urine samples was between 4 to 18% of the morphine concentration.

Discussion

This study, in agreement with Yeh's and Yong's observations, has shown that biotransformation of morphine to codeine via *O*-methylation does not occur in man. None of the urine samples of the 70 subjects receiving morphine only (60 to 120 mg daily) contained codeine (the codeine impurity in Italian pharmaceutical morphine HCl is 0·12 to 0·25% and therefore non-detectable with the techniques used). Codeine was present in all urine samples of 150 heroin addicts as a metabolite of acetylcodeine which is an impurity in illicit heroin (in Italy illicit heroin seizures contain 5 to 15% acetylcodeine relative to heroin). During 1980 in our laboratory, of 3500 urine samples from various sources analysed for drugs of abuse (opiates), 65% contained morphine and codeine and always involved heroin addicts or users.

Our findings suggest that it may be possible to differentiate heroin or morphine consumption by the presence of codeine and morphine in urine or in biological specimens if they are in amounts corresponding in our research.

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Morphine antidiuresis in the rat: biphasic effect of the opiate on the excretion of urine electrolytes

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We have recently shown that although both morphine and vasopressin decrease urine outflow in the rat, they have differential effects on the excretion of urinary electrolytes. Morphine, levorphanol, (−)-methadone and the novel opioid-like peptides reduce urine outflow and produce a hypotonic urine characterized by a low concentration of Na^+, K^+ and Cl^-, while the exogenous administration of vasopressin produces antidiuresis with a markedly hypertonic urine due to the large reabsorption of water (for a review see Hays 1980; Huidobro et al 1979; Huidobro & Huidobro-Toro 1979; Huidobro-Toro et al 1979; Huidobro-Toro & Huidobro 1981). When vasopressin is given with morphine the effect is not additive, but rather morphine antagonized the effect of vasopressin on the excretion of urinary electrolytes (Huidobro & Huidobro-Toro 1979), suggesting that the release of antidiuretic hormone may not be the major determinant of the morphine antidiuresis as proposed by de Bodo (1944). The recent finding that Brattleboro rats (animals with severe diabetes insipidus) respond to the full antidiuretic effect of morphine or β-endorphin regardless of their genetic lack of antidiuretic hormone further supports this idea (Huidobro-Toro 1980). Our aim has been to gain further information on the possible involvement of the antidiuretic hormone on the morphine antidiuresis by focusing on the effect of different doses of morphine on urine outflow and electrolyte concentrations in the rat.

Groups of eight adult Sprague Dawley rats (200 ± 15 g)

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