STUDIES ON THE PHARMACOLOGY OF PHOLCODINE, CODEINE AND DEXTROMETHORPHAN IN MAN AND RAT

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by

Zhao Rong Chen, B.M., M.M.

Department of Clinical and Experimental Pharmacology,
the University of Adelaide,
Australia.

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ABSTRACT

The aims of this thesis were to study the pharmacokinetics and pharmacodynamics of pholcodine, codeine and dextromethorphan in humans and in rats.

1. Original sensitive and specific HPLC assays were developed for the determination of (1) pholcodine; (2) codeine-6-glucuronide; (3) codeine, norcodeine and morphine and (4) dextromethorphan and three metabolites in plasma and in urine, which are suitable for the pharmacokinetic and metabolism studies in man and rat.

2. The pharmacokinetics and metabolism of pholcodine after single and chronic dosing were studied in six healthy human subjects. The pharmacokinetics and metabolism of pholcodine were substantially different from those of other chemically related compounds, such as codeine. Pholcodine had a very long plasma half-life which was about 15 times longer than that of codeine. The results indicate that the currently recommended dosage regimens for pholcodine may be inappropriate. Two new metabolites were isolated and one of them, a oxidative product of the morpholine ring, of pholcodine was successfully identified by HPLC, mass spectra and nuclear magnetic resonance spectra.

3. The pharmacokinetics of codeine were comparatively studied in 8 young subjects and 7 elderly patients. Codeine-6-glucuronide, the major metabolite of codeine, was directly determined in plasma and in urine for the first time. The plasma concentrations of codeine-6-glucuronide were 17 times higher than codeine but the plasma half-lives of the two compounds were similar in young subjects. The pharmacokinetics of codeine and codeine-6-
glucuronide in the elderly were altered compared with those in the young subjects. The absorption was delayed and the plasma half-lives for codeine and especially for codeine-6-glucuronide were increased. The plasma concentrations of codeine and codeine-6-glucuronide at steady state increased 2.4 and 3.8 times respectively and the renal clearances of codeine and codeine-6-glucuronide decreased 5.0 and 7.2 times respectively. The plasma concentrations of codeine and codeine-6-glucuronide at steady state were strongly correlated with the clearance of creatinine. All the pharmacokinetic changes were significantly correlated with age. β-glucuronidase, a widely used tool for the studies of glucuronides, is not suitable for the quantitative determination of codeine-6-glucuronide because of the incomplete hydrolysis.

4. The polymorphic metabolism of codeine was demonstrated in humans. The O-demethylation ratio of codeine was strongly correlated with that of dextromethorphan which is known to exhibit genetic polymorphism in the O-demethylation. This finding may have important clinical implications because codeine may not produce analgesia in the poor metabolisers who are unable to metabolise codeine to morphine. The preliminary results of the study on the genetic polymorphism of dextromethorphan suggested that the frequency of deficiency of this polymorphism in an Australian population was 3/52, which was similar to those in European countries (3-9%).

5. The μ-receptor binding affinities of codeine and its metabolites and several other opioids were studied in rat brain using the ligand \(^3H\)-DAGO. The results showed that some of metabolites had similar or higher affinity to the μ-receptor than the parent compound and suggest they may be important in mediating analgesia. Pholcodine and dextromethorphan showed very low
binding affinities to the $\mu$-opioid receptor which supports the previous findings that pholcodine and dextromethorphan have no analgesic effect.

6. Codeine O-demethylation to morphine in the brain was studied in the rat in vitro and in vivo. At 30 minutes after intraperitoneal administration of codeine, morphine was detected in the brain. However, after intraperitoneal administration of morphine, although a similar plasma morphine concentration was achieved, morphine was not detected in the brain. The results indicate a central (brain) conversion of codeine to morphine. The morphine concentrations in the rat brain after codeine administration peripherally were about 20 times that required to displace 50% of the $\mu$-receptor ligand $^3$H-DAGO. After incubation of codeine with NADPH system in vitro, more morphine was found in microvessel rich tissue than in the total homogenate. The results suggest that the O-demethylation of codeine to morphine occurs in microvessel tissue, possibly in endothelial cells. The biotransformation of codeine to morphine in the brain rather than in liver may explain the analgesic effect of codeine.

7. A cough recording system for measuring cough frequency was developed for a clinical study designed to compare the relative antitussive efficacy of codeine, pholcodine and dextromethorphan in patients. In a double-blind, placebo controlled pilot study, the antitussive effect of these agents in patients with chronic cough were studied.