

# Recent updates on codeine

## Abstract

Alleviation of pain is a major objective in medicine to increase the quality of life. Analgesics are agents that relieve pain by elevating the pain threshold without disturbing consciousness or altering other sensory modalities. Opium is an isoquinoline alkaloid obtained from poppy plant *Papaver somniferum* (Papaveraceae). Codeine is an alkaloid prepared from opium or morphine by methylation. Codeine is used as a central analgesic, sedative, hypnotic, antinociceptive, antiperistaltic, and is also recommended in tuberculosis and insomnia due to incessant coughing. The literature information relate mostly to the determination of codeine active components using Gas chromatography (GC), Capillary electrophoresis, Thin layer chromatography, High-performance thin layer chromatography, UV-Vis Spectrophotometry, High-performance liquid chromatography and GC in combination with Mass spectroscopy. This contribution provides a comprehensive review of its analytical and pharmacologic profile of codeine.

**Key words:** Analgesic, Codeine, Isoquinoline alkaloid, HPLC, HPTLC Introduction

## INTRODUCTION

Codeine (methyl morphine) is a strong mono acidic base and laevorotatory. It effloresces slowly in dry air and is affected by light. The chemical name of codeine phosphate is 7,8-didehydro-4,5alpha-epoxy-3-methoxy-17-methylmorphinan-6alpha-olophosphate (1:1) (salt) hemihydrate and has the empirical formula of  $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2H_2O$ .<sup>[1]</sup> Codeine phosphate contains not less than 98.5 percent and not more than 101.0 percent of  $C_{18}H_{21}NO_3 \cdot H_3PO_4$  calculated on the dried basis.<sup>[2]</sup> Codeine molecular weight is 406.4. Each soluble tablet contains 30 mg (0.074 mmol) or 60 mg (0.15 mmol) of codeine phosphate. These tablets also contain lactose and sucrose. Soluble tablets of codeine phosphate are freely soluble in water.<sup>[1]</sup>

## MECHANISM OF ACTION

Codeine is a weak narcotic pain reliever and cough suppressant similar to morphine and hydrocodone. A small amount of codeine is converted to morphine in the body. Like morphine, codeine binds to receptors in the brain (opioid receptors) that are important for transmitting the sensation of pain throughout the body and brain. Codeine increases tolerance to pain, decreasing discomfort but the pain still is apparent to the patient. In addition to reducing pain, codeine also causes sedation, drowsiness, and depressed breathing. Codeine frequently is combined with acetaminophen (Tylenol) or aspirin for more effective pain relief.<sup>[3]</sup>

## Analytical and pharmacologic profile of codeine

### *Presence and formation of codeine and morphine in the male Sprague-Dawley rat*

Endogenous codeine and morphine were identified in rat brain by immunologic determination following high-performance liquid chromatography (HPLC). To demonstrate the occurrence of a biosynthetic pathway to morphine in mammals similar to that used by the poppy plant, (+)-salutaridine, (-)-thebaine, and (-)-codeine were administered to rats intravenously. These compounds which are

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intermediates in the synthesis of morphine in *Papaver somniferum* caused a marked increase in the codeine and morphine levels in rat tissues. This provides evidence for a biosynthetic pathway to morphine in mammals.<sup>[4]</sup>

#### Codeine in plasma with fluorescence detection

Determination of codeine in human plasma was based on HPLC for separation and the natural fluorescence of codeine for detection. Codeine was extracted from alkalized plasma with a mixture of hexane and dichloromethane and the extract was further purified and chromatographed. In this method, a stock solution of codeine was prepared by dissolving the amount of codeine phosphate equivalent to 1 mg of codeine in 10 mL of methanol. The stock solution was further diluted with an equivolume mixture of methanol and water to yield a solution containing 1 µg of codeine per milliliter. This solution was used for supplementary drug-free samples of plasma. A stock solution and a working solution of internal standard were prepared in the same way.

*Solutions:* Phosphate buffer solution (50 mmol/L, pH 8), was prepared by dissolving 7 g of monobasic sodium phosphate in 1 L of water and adjusting the pH to 8 with a 1 mol/L solution of NaOH.

*Procedure:* Pipet 2 mL of plasma into a 15 mL test tube and add 200 ng of the internal standard. Alkalinize the plasma with 2 mL of the 50 mmol/L phosphate buffer solution and extract twice with 6 mL portions of hexane/dichloromethane (2/1 by vol) by manually shaking the mixture for 2 min then centrifuging. Combine the organic extracts and wash with 1 mL of NaOH, 50 mmol/L to remove any potentially interfering substances. Transfer the extract to a 15 mL conical test tube and evaporate under a gentle stream of nitrogen to about 1 mL. Wash down the inside wall of the test tube with 1 to 2 mL of methanol and evaporate the entire contents of the test tube to dryness under nitrogen. Dissolve the residue in 200 µL of HPLC mobile phase. Place the test tube in an ultrasonic bath for 30 s, then vigorously vortex-mix. Inject a 50 µL aliquot onto the chromatographic column.

*Chromatographic conditions:* The mobile phase was composed of methanol/water (21/79 by vol), containing 1.5 g of phosphoric acid per liter. Flow rate was set at 2 mL/min and columns were operated at ambient temperature. Column pressure was maintained between 1000 to 2000 psi ( $6.89 \times 10^6$

Pa). The recorder was used at a chart speed of 5 mm/min.

The method can be used for routine assay of codeine at concentrations of 10 µg/L or greater in human plasma. As little as 4 µg/L can be detected. Coefficients of variation for the assay of codeine in the concentration range of 10–100 µg/L were 2.2%–7.4% (n = 6). This method is used to establish a concentration/time profile for plasma from a human volunteer after a 60 mg oral dose of codeine sulfate.<sup>[5]</sup>

#### Determination of morphine and codeine in plasma

A cheap simple and rapid extraction procedure followed by a UV HPLC assay was described for the simultaneous determination of morphine and codeine in plasma. This method was based on the extraction of these opiates from plasma using reversed phase (solid phase) extraction columns followed by HPLC with UV detection at 240 nm. The extraction step provides, respectively, 85% and 80% recovery for morphine and codeine. The response of the detection system was linear for both molecules in the studied range from 50 to 750 ng/mL. No other drugs have been found to interfere with the assay. This method offers a quick, cost-effective, and reliable procedure for specifically determining morphine and codeine from a small sample volume.<sup>[6]</sup>

#### Undeclared codeine in antiasthmatic Chinese proprietary medicine

A rapid and specific liquid chromatography-mass spectrometry-mass spectrometry (LC-MS-MS) method was applied to confirm the presence of codeine by selected reaction monitoring. Codeine was extracted from the capsules by dissolving in sodium dihydrogen phosphate buffer (10 mM, pH = 2.2) and ethanol then made alkaline (pH = 9) and extracted using chloroform. The amount of codeine in AsthmaWan was found to be 61.8 µg/capsule [relative standard deviation (RSD) = 7.9%, n = 9]. Excellent resolution was obtained despite the complexity of the product, which claimed to contain at least nine herbal ingredients, none of which will give rise to codeine. As a further confirmation method, LC-MS-MS was accurate and specific.<sup>[7]</sup>

#### Analysis of codeine and its metabolites in human plasma

The resolving power of high pressure liquid chromatography has been combined with the sensitivity of electrochemical oxidation to develop a method for determination of codeine and its

metabolites, morphine and norcodeine, in plasma. Plasma samples containing Internal Standard (dihydromorphinone) were extracted at pH 8.9 into a 2/98 v/v butanol/methyl tertiary butyl ether organic solvent system and back extracted into 25 mM phosphate buffer pH 2.8. The optimal recovery was greater than 90% for codeine and 70% for morphine and norcodeine. Reverse phase chromatography (5  $\mu$ m phenyl column) with detection by electrochemical oxidation at +1.2 V vs Ag/AgCl was utilized. The method was sensitive, specific, and precise. This method was used to establish a concentration–time profile for plasma codeine and morphine from a human volunteer after a 60 mg oral dose of codeine phosphate. No measurable concentration of norcodeine was found in the plasma. There was no reported method to simultaneously quantitate codeine and its O-demethylated and N-demethylated metabolites in plasma. Radioimmunoassay (RIA) can be used for quantization of codeine and morphine but the assay was not specific due to cross-reaction with the other opiates. Procedures such as GS and thin-layer chromatography (TLC) have also been reported to be used in forensic toxicology studies.<sup>[8]</sup>

#### **Rapid extraction of codeine and morphine in whole blood**

A rapid and efficient procedure was described for the extraction and analysis of codeine and morphine in whole blood. Red blood cells were fragmented by sonication and the blood sample was extracted by passing through a bonded silica column (Bond Elute®, Jone chromatography). The adsorbed drugs were washed and eluted followed by HPLC analysis. Recoveries were between 95% and 100% at 5 ng/mL concentrations.<sup>[9]</sup>

#### **Capillary electrophoresis chemiluminescence detection**

A simple and robust capillary electrophoresis chemiluminescence detection system for the determination of codeine, 6-methoxycodine, and thebaine was described based on the reaction of these analytes with chemically generated tris(2,2A-bipyridyl)ruthenium(iii) prepared in sulfuric acid (0.05 M). The reagent solution was contained in a glass detection cell, which also held both the capillary and the cathode. The resultant chemiluminescence was monitored directly using a photomultiplier tube mounted flush against the base of the detection cell. The RSDs of the migration times and the peak areas for the three analytes ranged from 2.2% to 2.5% and 1.9% to 4.6%, respectively.<sup>[10]</sup>

#### **Simultaneous determination of paracetamol and codeine phosphate in combined tablets dosage form**

Two simple, accurate, and reproducible UV spectrophotometric techniques have been developed for the simultaneous determination of paracetamol and codeine phosphate in combined tablets. The first one was based on the measurement of first-order derivative amplitudes at zero-crossing points 263.5 and 218.4 nm for the assay of paracetamol (5.0–25.0 mg/L) and codeine phosphate (1.25–10.0 mg/L), respectively. The second one uses the amplitudes of ratio spectra first-order derivatives at 255.3 and 221.4 nm to quantify paracetamol (5.0–30.0 mg/L) and codeine phosphate (0.625–10.0 mg/L), respectively. Both the techniques have been extensively validated and compared with an official HPLC method showing their applicability in the routine analysis.<sup>[11]</sup>

#### **Codeine and caffeine in codeine–aspirin–phenacetin–caffeine tablets**

A procedure was reported for determining the codeine and caffeine content of individual codeine–aspirin–phenacetin–caffeine tablets. Codeine was determined fluorometrically; after extraction into dilute sulfuric acid, caffeine was extracted from a chloroform solution of the remaining ingredients with phosphoric acid and determined by UV spectroscopy. Average recoveries with a synthetic mixture were 99.7% and 98.9% for codeine and caffeine, respectively. Assay results were reported for codeine [1–65 mg (1/65 1 grain/tablet)] and caffeine [32 mg 1/2 grain)/tablet] in several different commercial samples.<sup>[12]</sup>

#### **Estimation of uncertainty for measuring codeine phosphate tablets formulation**

Analytical results represent a very important part in a quality control program. Uncertainty estimation was an important step in method validation. The objective of this article was to study the uncertainty of measurement estimation in the quantitative determination of codeine phosphate from pharmaceutical formulations using UV–Vis spectrophotometry. The uncertainty estimation was performed using the Ishikawa diagram. The estimation of uncertainty components proved to be a good way for the experimental model to obtain low contribution of uncertainty to the analytical result.<sup>[13]</sup>

#### **Determination of propyphenazone, paracetamol, caffeine, and codeine phosphate with thin-layer chromatography**

The conditions have been examined for the

determination of propyphenazone, paracetamol, caffeine, and codeine phosphate in caffetin tablets with preparative TLC. The separation of propyphenazone, paracetamol, and caffeine was performed by use of a mobile phase chloroform–acetone–ammonium hydroxide (25%) in volume ratios of 8:2:0.1. Codeine phosphate was separated from the other components with chloroform–ethanol in the volume ratio of 8:2 as a mobile phase. The location of spots on the chromatogram was detected with UV lamp on 254 nm. Every component was eluted from the adsorbent with a solution of 0.1 mol/L hydrochloric acid in ultrasonic bath for 5 min. The solutions were filtered and the absorbency was measured at 240 nm for propyphenazone, 245 nm, for paracetamol, 273 nm for caffeine, and 285 nm for codeine phosphate. The results show that the applied method was fast, reproducible, and suitable for routine analysis.<sup>[14]</sup>

#### Simultaneous determination of acetaminophen and codeine

First derivative UV spectrophotometry has been used for the simultaneous determination of acetaminophen and codeine. Acetaminophen has been assayed by measuring the first derivative absorbances at 263.4 nm and codeine at 251.2 nm. The concentrations of acetaminophen and codeine have been calculated without interference of each other. The procedure was simple and rapid and provides accurate and precise results.<sup>[15]</sup>

#### Simultaneous quantification of morphine and codeine in poppy capsules

TLC–UV densitometric and GS–MS detection (GC–MSD) methods were developed for simultaneous quantification of morphine and codeine in poppy capsules (*P. somniferum*). Morphine and codeine were isolated by extraction with chloroform:isopropanol (3:1, v/v) at pH = 8.5 and by solid-phase extraction on Snap-Cap cartridges at pH = 8.5. The TLC–UV densitometric quantification was performed by external standard method on silica gel plates using ethyl acetate:toluene:methanol:ammonia (68:17:10:5, v/v) as developing solvent and UV detection at 275 nm. For the GC–MSD analysis, the drugs were derivatized with acetic anhydride:pyridine (1:1, v/v) and separated on a 30 m HP5 capillary column. The quantification was performed using nalorphine as internal standard.<sup>[16]</sup>

#### Identification of codeine

A new spray reagent, a 1% (w/v) aqueous solution

of ferric chloride, and a 1% (w/v) acidified alcoholic solution of 2,2'-dipyridyl has been developed for the detection and identification of heroin (diacetylmorphine). A red spot was observed for heroin when the high-performance TLC (HPTLC) plate was sprayed with the reagent and heated at 100°C. Similar spots were observed for morphine, codeine, and thebaine (opiates containing the phenanthrene nucleus). It did not react with papavarine and narcotine (opiates containing the isoquinoline nucleus). The reagent was specific, sensitive, and can be used for the detection and identification of heroin in forensic samples.<sup>[17]</sup>

#### Antistress activity

*P. somniferum* produces secondary metabolites, which have important roles in self-defense processes in plant biochemistry and in allelochemistry. By performing experiments to determine how irregular stress effects changed the alkaloid content of poppies we have shown that different types of stress affect the quantities of alkaloids. *P. somniferum* plants were grown for 2 months from seeds in quartz–sand (natural light, temperature 24°C–28°C, in Knopf's nutritive solution). In this work, the alkaloids in poppies were subjected to two kinds of stress—mycotoxin and drought. The amounts of alkaloids were measured by different separation and detection procedures TLC and HPTLC with fluorescence detection and HPLC. HPLC proved superior for identification and approximate estimation of the morphine alkaloids but the effects of stress on poppy plants can be detected by use of either method. Drought stress resulted in higher levels of the alkaloids, whereas mycotoxin stress did not result in significant difference.<sup>[18]</sup>

#### Chronic cancer pain control

The improved pain control provided by regular dosing of opioid analgesics in patients with severe cancer pain has been well established. This randomized double-blinded study was designed to evaluate the efficacy of controlled-release codeine (Codeine Contin) in patients with cancer pain and to estimate its dose equivalence to a standard combination of acetaminophen plus codeine. Twenty-four patients with at least moderate cancer pain were randomized to codeine contin 100, 200, or 300 mg every 12 h or acetaminophen plus codeine (600 mg/60 mg) every 6 h. On days 1 and 4 of dosing, pain intensity and pain relief were assessed hourly for 12 h. The sum of pain intensity differences from baseline and the total pain relief scores demonstrated a dose–response relationship for codeine contin on days 1 and 4 that

was statistically significant on day 1 and suggested a greater analgesic efficacy on day 4 compared with day 1. Codeine contin 150 mg every 12 h was estimated to be equianalgesic to acetaminophen plus codeine (600 mg/60 mg) given every 6 h. Because a similar equivalence was also demonstrated from analysis of adverse event data, it is concluded that codeine contin 150 mg produces analgesia, and a side-effect profile similar to a 40% lower dose of codeine provided by the combination. These results indicate the need for studies of scheduled every 12-h dosing of codeine contin in comparison with "as needed" dosing of combination preparations in patients with cancer pain.<sup>[19]</sup>

### Hepatotoxic activity

The administration of codeine to freshly isolated rat hepatocytes resulted in cytotoxicity characterized by a dose- and time-dependent leakage of lactate dehydrogenase (LDH) out of the cells. Cytochrome P-450 content and NADPH levels were not changed. Induction and inhibition studies of several potential pathways of codeine biotransformation were carried out to determine if codeine must be metabolized to a reactive intermediate to elicit these hepatotoxic effects. Codeine hepatotoxicity as measured by LDH release was not changed after induction of cytochrome P-450 by phenobarbital and was decreased after cytochrome P-448 induction by B-naphthoflavone. However, codeine hepatotoxicity was inhibited when an inhibitor of cytochrome P-450 metabolism, metyrapone, was added. Inhibition of the other major hepatic oxidative enzyme system, flavin adenine dinucleotide (FAD)-containing monooxygenase, increased the cytotoxicity of codeine. Inhibition of alcohol dehydrogenase had no effect on codeine hepatotoxicity. These results indicate that codeine hepatotoxicity was caused by a cytochrome P-450-generated intermediate of codeine, whereas FAD-containing monooxygenase may metabolize codeine to a nontoxic intermediate.<sup>[20]</sup>

### Antinociceptive activity

Centrally administered codeine glucuronide has been shown to exhibit antinociceptive properties with decreased immunosuppressive effects compared with codeine. In this study, codeine-6-glucuronide was administered to rats and its analgesic effect was compared with that of codeine. The concentrations of codeine and its metabolites in plasma and brain were also determined at the peak response time after administration of each compound. Receptor-binding studies with rat brain homogenates and

affinity profiles were also determined. Intravenous administration of codeine-6-glucuronide resulted in approximately 60% of the analgesic response elicited by codeine itself. Analysis of plasma and brain showed that codeine-6-glucuronide was relatively stable in vivo with only small amounts of morphine-6-glucuronide being detected in addition to unchanged codeine-6-glucuronide. The receptor affinity of codeine-6-glucuronide was similar to that of codeine. It was concluded that intravenously administered codeine 6-glucuronide possesses analgesic activity similar to that of codeine and may have clinical benefit in the treatment of pain.<sup>[21]</sup>

### Antitussive activity

Codeine 10, 20, and 50 mg/kg dose-dependently depressed the coughs caused by larynx stimulation. The antitussive failed to depress the cough caused by stimulation to the tracheal bifurcation although a large dose (50 mg/g) significantly depressed the cough. In capsaicin-treated guinea pigs codeine at 20 mg/g significantly depressed the cough caused by stimulation to the tracheal bifurcation. The present results suggest that cough caused by mechanical stimulation to the larynx might be more sensitive to codeine treatment than cough caused by stimulation to the bifurcation of trachea. It was suggested that coughs caused by mechanical stimulation to both sites might consist of at least two components as regards their pharmacologic nature.<sup>[22]</sup>

## CONCLUSION

From time immemorial, codeine has been widely used as curative agent for a variety of ailments. The codeine possesses significant central analgesic activity so it becomes very popular drug to relieve the pain in patient suffering from the cancer and in head trauma. It also recommended in incessant coughing. Quite a significant amount of work has been done on the analytical evaluation and indications of codeine. Recent evidence relates that it is a combination of four components: propyphenazone, paracetamol, caffeine, and codeine phosphate; in this combination caffeine and codeine phosphate increase the analgesic effect of the paracetamol and the propyphenazone synergistically.

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