DRUG CORNER

Codeine: A Relook at the Old Antitussive

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Abstract

Cough is the most frequent complaint of patients seeking medical attention in general and hospital practice. Cough is controlled by treating the cause, however, when no cause can be found, symptomatic relief of cough must be considered. Treatment of dry cough resulting from increased sensitivity of the cough reflex remains a challenge in some subjects. Codeine in combination with other medicines has been a mainstay for the effective short-term symptomatic relief of dry or nonproductive cough in clinical practice. This article focuses on the current status of codeine as an antitussive formulation in the treatment of dry cough. Codeine is one of the centrally acting narcotic opioids approved for use as an antitussive, a prodrug that is bioactivated by CYP2D6 into morphine in the liver. The opioid effects of codeine are related to plasma morphine concentrations. Codeine is one of the most frequently used antitussive in clinical practice and has been widely regarded as the standard cough suppressant against which newer drugs are being evaluated. Codeine has an advantage as an antitussive because of its multifaceted effect as an analgesic and sedative along with cough suppression. However, codeine may have efficacy to suppress cough in humans only in specific situations. Caution is also needed to limit its use only when and as long as it is clinically necessary, particularly in children.

Introduction

Cough is an important defensive reflex for clearing the airways of excess secretions and foreign material.[1] It is the most frequent of patient complaints encountered in general and hospital practice, and can be the presenting symptom of more than 100 clinical conditions of the respiratory system.[1,2] The incidence of cough is reported to vary from 5% to 40%.[1] The prevalence and etiology of cough depends on various factors such as geographical location, history of exposure to offender agents or drugs, seasonal variation, and concomitant respiratory and nonrespiratory illnesses.[3] Dry cough results from increased sensitivity of the cough reflex and its treatment remains a challenge in some subjects.[2] Cough is controlled by treating the cause of cough; however, when no cause can be found, symptomatic relief of cough must be considered.[2] The mainstay of treatment in non-specific cough are cough preparations available without prescription as over-the-counter (OTC) drugs which are also used as an adjuvant in case of cough associated with other conditions.[2] The ingredients of OTC cough preparations (based on their modes of action) include cough suppressants (antitussives), expectorants, mucolytics, demulcents, and bronchodilators.[4] Effective symptomatic relief of dry cough is provided using antitussives.[2] Most of the cough suppressant preparations are used for short-term relief of dry cough and are available as a combination of codeine or dextromethorphan with other medicines.[4,5] In the present article, we focus on the current status of codeine as an antitussive in the treatment of dry cough.

Mechanism of Cough

The components of the cough reflex arc include the afferent, central, and the efferent pathway. Cough is initiated by irritation of cough receptors present all along the respiratory tract. Laryngeal and tracheobronchial receptors respond to both mechanical and chemical stimuli, whereas receptors in external auditory canals, eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium, and stomach are probably mechanical receptors.[3,6]

Impulses from the stimulated cough receptors take the afferent pathway via the vagus nerve to the "cough center" in the medulla oblongata. Efferent signals travel down the vagus, phrenic, and spinal motor nerves to the expiratory musculature to produce cough.[3,7]

Etiologies of Cough

Cough is classified as productive or dry cough depending on the presence or absence of expectoration, respectively, and as acute, subacute, or chronic based on the duration of cough. A dry or nonproductive cough

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is usually caused by viral upper respiratory tract infections (URTIs), smoky environment, air pollution, and dry atmosphere or change in temperature. Dry cough can also be a symptom of asthma, gastroesophageal reflux disease (GERD), drug-induced cough, allergic cough, acute bronchitis, and lung abscess.[4]

Cough with expectoration can be a symptom of URTI, smoking, post-nasal drip, chronic bronchitis, pneumonia, tuberculosis, lung cancer, bronchiectasis, heart failure, and nocardiosis. Colour of the sputum can be indicative of the diagnosis (eg, yellow or brown in bacterial chest infection such as bronchitis or pneumonia, blood in sputum in tuberculosis or cancer).[4]

Acute cough is cough less than 3 weeks in duration. The causes of acute cough include common cold, URTI, bacterial rhinosinusitis, allergic rhinitis, pneumonia, exacerbation of asthma, or chronic obstructive pulmonary disease (COPD). Lower respiratory tract infections, bronchiectasis, and pneumonia also cause acute cough, but they usually progresses to subacute cough. Non-respiratory causes like GERD also cause acute cough.[3,8,9]

Subacute cough is cough lasting for 3 to 8 weeks. Following specific infections (eg, *Mycobacterium*), an increase in bronchial hyperresponsiveness may persist, which can cause or maintain subacute cough that can remain bothersome for a period of weeks even after the inciting infection has completely resolved. *Bordetella pertussis* causes subacute cough that is paroxysmal and disabling.[10]

Chronic cough is cough lasting for more than 8 weeks. The most common cause of chronic cough in adults is chronic cigarette smoking.[1] Other causes include COPD, asthma, GERD, tuberculosis, lung cancer, non-asthmatic eosinophilic bronchitis, drug-induced cough (angiotensin converting enzyme [ACE] inhibitors, beta-blockers, non-steroidal antiinflammatory drugs [NSAIDs]), and drugs causing pulmonary fibrosis.[3,4,6]

Over 90% of the cough episodes are temporally related to reflux episodes.[11] The esophageal-tracheobronchial reflex is triggered from refluxate within the esophagus and the laryngopharyngeal reflux is triggered from refluxate extending beyond the esophagus into the larynx where sensory afferent cough receptors reside.[8]

Cough is one of the commonest symptoms of lung cancer at presentation to clinics.[1] A cumulative experience of 650 patients entering the UK Medical Research Centre's multicenter lung cancer trials showed that, overall, cough was the fourth commonest symptom reported at presentation with a frequency of 70% to 80%. A survey of patients with a variety of other cancers attending a large US cancer hospital found that cough was a troublesome symptom for 22% of patients with colon cancer, 26% with prostate cancer, 28% with ovarian cancer, and 37% with breast cancer. The overall prevalence of cough in patients with cancer was 29% and most palliative care units use codeine-based drugs for relieving cough.[1]

"Cough-variant" asthma presents with nocturnal cough from reversible airflow limitation and bronchial hyperresponsiveness and is a common type of asthma in children. A history of cough prior to a diagnosis of asthma is usually present in elderly asthmatics. Worsening of asthma may present with cough usually occurring first at night with other symptoms such as wheezing and shortness of breath towards early morning.[1]

A variety of viruses cause cough after an acute infection through increased production of neuropeptides and leukotrienes, altered expression of neural receptors, and increased airway mucus production.[12] Drug-induced cough from ACE inhibitors and beta-blockers usually occurs within the first few days after initiation of treatment, but can occur even after prolonged periods of previous therapy.[10] The possible mediators include bradykinins and prostaglandins.[13]

Genuine unexplained cough exists in a group of patients, and recent investigations have allowed the description of a particular phenotype of such individuals.[8] Patients with apparent true unexplained chronic cough are often middle-aged (perimenopausal) women with prolonged dry cough and demonstrable cough reflex hypersensitivity. Additional studies have shown that such patients tend to have airway inflammation characterized by increased numbers of mast cells.[8]

Management of Cough

Cough can be a presentation of some trivial or some serious diseases.[1] Development of persistent cough can be avoided by initiating treatment of cough early and thereby decreasing the spread of infection and many related complications, such as fatigue, sleep deprivation, hoarseness, musculoskeletal pain, sweating, and urinary incontinence.[10]

Management of cough involves identifying the cause of cough and treating the cause. In the present article we focus the discussion on management of dry cough. A detailed history (smoking, occupational, and drug), duration and type of cough, physical examination, and clinical investigations will indicate the diagnosis.[1] A thorough evaluation including relevant diagnostic tests and therapeutic trials with appropriate medications at adequate doses and for sufficient duration needs to be performed before coming to a diagnosis of unexplained cough.[8] The underlying cause of cough requires therapeutic interventions;

however, when the cause cannot be established symptom-focused approaches are required to treat cough.[10] Antitussives are often used for effective symptomatic relief of dry or nonproductive cough and are sometimes helpful in cases of otherwise untreatable cough.[2,14] Antitussives may be centrally or peripherally acting. The most commonly used centrally acting antitussives are dextromethorphan and codeine.[2] Other centrally acting nonnarcotic antitussives include chlophedianol, levopropoxyphene, and noscapine; and centrally acting narcotic antitussives include hydrocodone, hydromorphone, methadone, and morphine.[2] Antitussives should not be given as first-line treatment as they may prevent proper diagnosis.[14] Nonspecific antitussives are used to suppress troublesome cough by inhibiting the cough reflex regardless of the cause of cough when the specific etiology of cough cannot be established (idiopathic); when severe cough needs to be suppressed while awaiting the effect of specific therapy or the resolution of postinfectious cough; and when the cause of cough is irreversible, such as inoperable lung cancer or pulmonary fibrosis.[1] The initiating event may have disappeared, leaving a persistent cough with or without apparent cause.[10] Centrally acting opioid derivatives such as codeine are often used alone or in combination in the management of nonspecific cough.[2] Sedation caused by these is valuable, particularly if the cough is disturbing the sleep.[2]

The American Academy of Pediatrics do not recommend using centrally acting antitussives for treating any type of cough in children because of the lack of evidence of efficacy and safety in controlled clinical trials,[5] whereas the American College of Chest Physicians "Guidelines on Cough" in 2006 include the use of levodropropizine and moguisteine in acute or chronic bronchitis.[9]

Codeine: An Antitussive

Codeine is one of the centrally acting narcotic opioids approved for use as an antitussive. Centrally acting antitussives inhibit or suppress the cough reflex by depressing the medullary cough center or associated higher centers and reduce the discharge of nerve impulses to the muscles that produce coughing.[2]

Codeine is a naturally occurring opium alkaloid and is a constituent of the opium poppy, *Papaver somniferum*.[15] Codeine was isolated from opium in 1833 by Pierre Jean Robiquet and constitutes about 0.5% of opium. Bulk of codeine used medicinally is prepared by the methylation of morphine. Codeine is less potent than morphine, with a potency ratio of 1:10.[15] Codeine is rapidly and well absorbed following oral administration, approximately 50% undergoing presystemic metabolism in the gut and liver.[15] Peak plasma concentration occurs after approximately 1 hour and the plasma half-life is 33.5 hours. Codeine is principally metabolized in the liver in one of the three ways: glucuronidation which is the principal route, *N*-demethylation to norcodeine (10%-20%), and *O*-demethylation to morphine (5%-15%). Between 5% and 15% of the drug is excreted unchanged in the urine. The efficacy of the prodrug is dependent on the amount of active metabolite formed.[15] Codeine produces its antitussive effect primarily via the μ-opioid receptor in the central nervous system.[16]

Codeine in the Treatment of Dry Cough

Evidence suggests that RAR or "cough receptor"-mediated coughs are sensitive to codeine but coughs triggered by neurokinin-containing nociceptive nerves are resistant to it.[16] In support of this suggestion, there is a finding that the expression of transient receptor potential vanilloid-1 (TRPV-1) is increased in the airway nerves of patients with chronic cough. In addition to TRPV-1, it has recently been reported that acid-sensing ion channels (ASICs) were localized in Aδ-fibers of guinea pigs. Therefore, differences in codeine sensitivity to acid-induced coughs may depend on the pH level at the cough induction site. Further studies are needed to determine a final conclusion.[16] Coughs mediated by mechanical stimulation of RARs or "cough receptors" are attenuated by narcotic antitussives primarily at the NTS level via inhibition of glutamatergic transmission. Presynaptic μ-opioid receptors probably contribute to this inhibition. Conversely, neurokinin release in the NTS from nociceptive C and Aδ-fibers, and also from RAR fibers under airway inflammation, causes cough resistant to antitussives including opiates. It is very important to characterize opiate-resistant coughs in experimental animals, and to determine the extent to which such experimentally-induced coughs correspond to the various types of cough in humans.[16]

Eddy et al opine that a multimodal action of codeine, including antitussive, analgesic, and sedative effects is an advantage in special cases: an analgesic effect when the cough is associated with pain and a sedative action helps if the patient is apprehensive or if the cough was initiated or enhanced by central stimuli (nervous cough).[17]

A study in India compared pholcodine plus promethazine (CS1) with dextromethorphan plus chlorpheniramine (CS2) and codeine plus chlorpheniramine (CS3) in the pediatric population. A greater percentage of patients in the CS3 group achieved the clinical end-point for cough episodes by day 7 compared to those in the CS1 group.[18]

Codeine has been shown in randomized double-blind placebo-controlled studies to have antitussive

activity against pathological cough as well as induced cough in healthy volunteers. However, codeine has been demonstrated to be ineffective against cough associated with acute respiratory tract infections. The minimal effective dose of codeine appears to be 20–30 mg.[1]

Codeine was tested in two trials and appeared no more effective than placebo in reducing cough symptoms in adults.[19,20] One of these studies tested codeine in a two phase study (laboratory and home) at a dose of 30 mg four times daily for four days (n = 81), and codeine was no more effective than placebo either as a single dose or in a total daily dose of 120 mg, reported on a five-point cough severity score ($p > 0.2$).[19] The second study (n = 82) of codeine only tested the effect of a single 50 mg dose and cough was assessed via microphone using cough sound pressure levels 90 minutes after drug administration, cough frequency counts, and subjective scores. The mean subjective score on a five-point rating scale was reduced from 2.0 to 1.0 recorded 90 minutes after treatment (P = 0.8) in both treatment groups.[20] One study involving 57 children with night cough compared a single dose for three nights of dextromethorphan and codeine with placebo.[21] Mean cough and composite scores decreased in each of the three treatment groups on each day of the study. Neither dextromethorphan (cough score reduction of 2.1, P = 0.41) nor codeine (cough score reduction of 2.2, P = 0.70) was more effective than placebo (cough score reduction of 2.2) on day 3.[21] A metaanalysis of five studies with dextromethorphan and codeine in adults concluded that these central antitussives drugs were marginally superior to placebo.[22]

Codeine can cause physical dependence, but on a smaller scale than morphine.[1] The danger of development of dependence to codeine at doses used to suppress cough is very small and addiction is uncommon in individuals with no existing vulnerability to addiction.[2]

Cough and cold preparations containing promethazine, codeine, or dextromethorphan are frequently abused since they are psychoactive at high doses and produce a pleasurable feeling or a sensation of being "high." There have been reports of codeine cough syrup abuse from India, Japan, China, and the United States since the early 1990s.[23] A recent 2011 study by Hou et al associated chronic codeine cough syrup abuse to alterations in the dopaminergic system in the brain's reward pathway.[24] This can lead to addiction. Chronic use of high doses of opioids can have damaging consequences on a person's health.

Codeine at therapeutic doses is less toxic to humans than animals possibly because it produces less respiratory depression.[2] Nevertheless, codeine in antitussive doses can cause sedation, nausea, vomiting, and constipation.[1] Codeine should be used cautiously in patients with hepatic or renal impairment, or a history of drug abuse.[4] Rarely allergic cutaneous reactions such as erythema multiforme have been described. Codeine has a better side-effect profile than the other narcotic opiods.[6]

Pharmacogenetics and Codeine

Codeine is a prodrug that is bioactivated by cytochrome P450 (CYP)2D6 into morphine in the liver which then undergoes further glucuronidation.[25] Various genotypes of the CYP2D6 subfamily of CYP450 enzymes correlate with phenotypic subgroups with differing rates of drug metabolism. A person with two nonfunctional alleles at CYP2D6 is considered to have poor drug metabolism, whereas a person with one or two functional alleles is considered to have extensive metabolism, and one who has duplicated or amplified active CYP2D6 genes is considered to have ultrarapid metabolism.[25] The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation usually represents 80% of codeine clearance, and conversion of codeine into morphine by CYP2D6 represents only 10% of codeine clearance.[25] The opioid effects of codeine are related to plasma morphine concentrations produced after codeine intake.[25] Among persons who have ultrarapid metabolism, codeine intake may result in an increase in morphine production. Determination of genotype and phenotype is important in elucidating serious adverse drug reactions and in preventing subsequent inappropriate selection or doses of drugs.[25] An increase in awareness and attention to patients' symptoms is important while prescribing codeine, particularly for children.

Conclusions

Codeine is one of the most frequently used antitussives in clinical practice and has been widely regarded as a standard cough suppressant against which newer drugs are evaluated.[1,2] Codeine has an advantage as an antitussive because of its multifaceted effect as an analgesic and a sedative along with the cough suppression. However, codeine may have efficacy to suppress cough in humans only in specific situations. Caution is also needed to limit its use only when and as long as it is clinically necessary.

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