

Efficacy and Safety of Combination of Noscaphine and Chlorpheniramine in Management of Cold and Cough

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ABSTRACT

Cough is one of the most common symptoms for which patients visit the doctor. Because of its broad differential diagnosis, cough is a challenging condition to manage. Antitussives or cough suppressants are indicated if cough interferes with daily activities. Cough suppressants not only provide symptomatic relief by decreasing cough, they also prevent the spread of infection. Noscaphine is a non-narcotic cough suppressant, which relieves cough by acting at the level of the cough center in the brain. It does not cause significant sedative, euphoric, or hypnotic effects, and other side effects such as respiratory suppression and constipation that are typically associated with opioids. Hence, unlike other opioid antitussives such as codeine, noscaphine is nonaddictive.

Keywords: Antitussive, cough suppressant, cough center, non-narcotic, sigma receptors, codeine

Cough is a normal and essential protective reflex that helps clear away secretions or infections or noxious particles from the airways and thus protects the lower airways from the aspiration of foreign materials¹. But cough is also the first overt sign of an underlying disease of the airways and lungs, and is one of the most common symptoms for which people consult their doctors. It can be distressing and severely impair quality of life^{2,3}. Cough therefore has manifold dimensions. It is “a protective mechanism for the lungs, a warning sign of disease, and a detrimental symptom when persistent².”

Cough has multiple etiologies. This broad differential diagnosis makes cough a challenging condition to manage. Categorizing cough according to duration may help in delineating the likely causes⁴.

- Acute cough lasts less than 3 weeks and is most commonly caused by a self-limited viral upper respiratory tract infection or common cold.

- Subacute cough lasts 3 to 8 weeks and is usually post-infectious in origin.
- Chronic cough lasts more than 8 weeks and is caused by cigarette smoking, angiotensin-converting enzyme inhibitors (ACEIs). If chest X-ray is normal, then the most common causes are upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, or gastroesophageal reflux disease.

Cough can also be categorized as dry and wet cough; a wet cough is defined as sputum volume >10 mL/day⁵.

MANAGEMENT OF COUGH

Treating the cause may alleviate cough in most cases, but in some patients, no cause can be identified and cough remains unexplained. Symptomatic treatment is indicated when the cough interferes with the daily activities⁶.

Antitussives or cough suppressants may be used to provide effective symptomatic relief of dry or non-productive cough^{6,7}. Expectorants are used when there are excessive mucous secretions to increase mucus clearance⁷. Based on their site of action, antitussives are of two types: centrally-acting antitussives and peripherally-acting antitussives. The centrally-acting antitussives suppress the responsiveness of the cough reflex by depressing the medullary cough center or associated

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higher centers, and include narcotic antitussives like codeine and non-narcotic antitussives like noscapine⁶.

Another beneficial effect of cough suppressants is their role in preventing the spread of infection. Respiratory viruses and bacteria spread via direct physical contact, through fomites or by inhalation of droplets (>5 µm), and aerosols (<5 µm). Cough as a major symptom of respiratory infections plays a significant role in the human-to-human transmission of infection through production of droplets. Around 3,000 droplets are generated in a cough, whereas a sneeze discharges around 40,000 droplets. The larger droplets fall to the ground and the smaller droplet nuclei travel for longer distances through air. These droplets are also generated during normal breathing and speaking⁸. By decreasing cough, cough suppressants reduce the release of droplets and aerosols containing the infectious pathogens, and thus prevent or interrupt the transmission of infection.

NOSCAPINE: A CENTRALLY-ACTING NON-NARCOTIC ANTITUSSIVE

Noscapine is a phthalide-isoquinoline alkaloid, which is obtained from the latex of *Papaver somniferum* commonly known as the opium poppy⁹. Noscapine has good oral bioavailability as it is rapidly absorbed after oral administration and reaches maximum concentration (C_{max}) of 182 ng/mL after 1 hour. The levels then start declining with a half-life of 124 minutes and become undetectable after 4 hours of administration. This indicates an average total body clearance of 4.78 L/h with an average distribution volume of 5.05 L¹⁰.

Its antitussive potency including the onset and duration of action are comparable to that of codeine¹¹. The onset of antitussive effect is 1 to 2 hours¹². The recommended dose of noscapine is 30 mg 3 or 4 times a day¹³.

Noscapine: Pharmacological Activity

Noscapine is a non-narcotic opioid, chemically related to papaverine, which has cough suppressant activity¹⁴. It is a widely used and highly efficacious antitussive with a central mechanism of action⁹ and has low toxicity¹⁵.

Once regarded as the 'gold standard' cough suppressant drug, codeine is no longer considered so because it has been shown to be no more effective than placebo in cough due to an upper respiratory tract infection^{16,17}.

Dextromethorphan too has been perceived as an effective and safe cough suppressant¹⁶. But it is associated with the risk of misuse and abuse. In high doses, it can cause euphoria and intoxication¹⁷.

Noscapine lacks significant analgesic, sedative, euphoric, and hypnotic effects, and other side effects of opioids such as respiratory suppression and constipation^{9,18}. Therefore, noscapine does not have the potential for addiction unlike codeine, which is often a drug of abuse due to its analgesic and addictive properties⁹. Because of a lack of opioid activity, noscapine is a safe alternative to codeine and dextromethorphan for treating cough^{10,18}.

Noscapine: Mechanism of Antitussive Action Vis-a-Vis Opioids

The antitussive effects of opioids such as codeine are mediated predominantly by their action on the μ - and κ -opioid receptors. In an experimental study, DAMGO, a synthetic opioid peptide with selective μ -opioid receptor agonist activity and U-50,488H, a highly selective κ -opioid receptor agonist, exhibited potent antitussive effects when administered via either intracerebroventricular or intraperitoneal routes¹⁹. In another preclinical study, naloxone, a specific opioid receptor inhibitor, did not block the antitussive effects of noscapine in enalapril or FR190997-treated guinea pigs, which shows that noscapine does not exert its antitussive effect via the μ , κ or δ opioid receptors²⁰. Conversely, pretreatment with rimcazole, a σ -receptor antagonist, significantly and dose-dependently reduced antitussive effects of noscapine suggesting that the antitussive activity was mainly mediated by its σ -receptor agonist activity¹⁹.

The antitussive effect of noscapine has also been attributed to its antagonistic action on bradykinin, a protussive, which induces cough, specifically dry cough caused by ACEIs⁹. The dry cough associated with ACEIs has been hypothesized to be because of their inhibitory effect on degradation of bradykinin and its resultant accumulation in the respiratory tract. Bradykinin leads to sensitization of the airway sensory nerves through the stretch receptors and C-fiber receptors, which release neurokinin A and substance P, causes bronchoconstriction, and production of mucous^{9,21}. Noscapine is a noncompetitive inhibitor of bradykinin. Hence, it exerts its antitussive action by inhibiting the effect of bradykinin in the airways²⁰.

Noscapine Suppresses ACEI-induced Cough

Mooraki et al conducted a study to investigate the cough suppressant effect of noscapine on persistent dry cough induced by ACEIs. For this, they selected 611 hypertensive patients being treated with ACEIs. Of these, 65 patients developed cough following

treatment. Most of them (64.6%) had mild cough and 32.3% had moderate to severe cough. The patients with moderate to severe cough were administered nospapine 15 mg, orally thrice daily concurrent with the ACEI drug. Nospapine effectively resolved the cough in 90% patients within 4 to 9 days of starting treatment and enabled patients to continue with ACEI therapy²².

Nospapine: Safety

Nospapine is well-tolerated and does not cause respiratory depression and addiction. Its large therapeutic window further supports its safety profile compared to other antitussive agents¹⁴.

NOSCAPINE + CHLORPHENIRAMINE: RATIONALE OF COMBINATION

Acute respiratory infections of viral etiology are characterized by coexisting symptoms of irritating dry cough and rhinorrhea. A combination of drugs that can address these symptoms is essential. Nospapine and chlorpheniramine maleate have been widely used for the symptomatic treatment of dry cough associated with cold.

Nospapine acts at the level of the cough center in the brain. It suppresses cough by reducing the activity of the cough center. The frequency as well as intensity of cough is reduced in cases of chronic cough¹⁴. Unlike other opioid antitussives, nospapine is nonaddictive as it lacks significant hypnotic and euphoric effects²³.

Chlorpheniramine is a first-generation antihistamine, which is effective against major allergy symptoms such as rhinorrhea, sneezing, and itching.¹³ It is often used alone or in combination with antitussives in patients with nonspecific cough. They reduce the frequency of cough and also dry up the secretions, which is beneficial in cough along with rhinorrhea⁶. Additionally, the mild sedation caused by chlorpheniramine can be valuable in patients in whom cough is disturbing sleep.

The two drugs when combined show additive response in controlling the dry cough and associated rhinorrhea. Although there are no pharmacokinetic studies of this combination, the existing evidence of use of these drugs in different combinations all over the world, thrice daily and the pharmacokinetic review of nospapine and chlorpheniramine suggests this combination is to be administered 3 times in a day^{24,25}.

CONCLUSION

Cough is a vital protective reflex that helps clear secretions, infections, or harmful particles from the airways.

However, cough is also a common presenting symptom of airway infection and can be distressing and severely impair quality of life. Antitussives or cough suppressants provide effective relief of dry or nonproductive cough by alleviating symptoms and reducing the spread of infection.

Nospapine is a non-narcotic antitussive with effective cough suppressant activity. Its central mechanism of action and low toxicity make it a widely used and safe antitussive option. Due to its lack of opioid activity, nospapine is a safe alternative to other commonly used antitussives such as codeine and dextromethorphan, for treating cough. It has been effective in relieving persistent dry cough including cough induced by ACEIs.

Chlorpheniramine maleate is a first-generation antihistamine drug that has been used for decades to alleviate allergy symptoms. Apart from controlling the rhinorrhea, it also inhibits cough through its peripheral and central effects on histamine and cholinergic stimuli.

The combination of nospapine and chlorpheniramine maleate is not only effective, it also has the potential to increase the patient compliance and reduce the cost of therapy without increasing any adverse effects.

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