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Analysis of pathomechanisms involved in side effects of menthol treatment in respiratory diseases

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ABSTRACT

Menthol is frequently used in over the counter medications for common colds and coughs. It was formerly considered to be under the class of herbal medicine, but identification of menthol receptor (TRPM8) moved it from the class of herbal medicine to the molecular pharmacology. It has been documented that menthol reduces dyspnoea and nasal obstruction via stimulation of nasal cold or flow receptors. It has also antitussive and antiirritative effect. Menthol can also induce adverse reactions such as airway irritation, dyspnoea, chest tightness and potentially respiratory failure, mainly in children. The mechanisms responsible for adverse reactions of menthol are not known completely. The adverse reactions of menthol could be due to its effects on TRPA1 channel, relevant to airway irritation. Higher concentrations of menthol stimulate TRPA1 channel causing airway irritation. It also increases mucus production and at the same time reduces cilliary activity leading to mucus stagnation. As the adverse effects were reported mainly at the night it is supposed that suppressed cough reflex during sleep potentiated by menthol induced cough suppression might be responsible for lack of airway mucus clearing and obliteration of small airways. Adverse effects could also be due to consequences of reflexes induced by the menthol action on trigeminal afferents, like apnoea or bronchoconstriction. Menthol is effective in relieving respiratory symptoms, but cough and cold medications should be used with caution. Recommendations are low concentrations of menthol used locally (intranasal) and not combined with camphor or cineole, as they may have additive effects and should be avoided in children under 2 years. Further data are necessary to completely elucidate potential risks of over the counter menthol medication in children but based on the meta analysis of documented case reports, menthol can be used safely if its contraindications for use are followed as with any other over the counter medications.

Keywords: Menthol; TRPM8; Airways; Treatment

1. INTRODUCTION

Recycling of respiratory viruses in the community, seasonal factors, social factors (collective facilities—schools, kindergartens) as well as the fact that the respiratory system is open to environmental influences lead to a high incidence of respiratory diseases in population. Many of these diseases are self limiting viral infections or common colds and they do not require any specific treatment. However symptomatic relief may be necessary in such infections. The most commonly used drugs for symptomatic relief of common colds are nasal decongestants and cough medications as nasal congestion, runny nose and cough are the most limiting symptoms [1].

Over the last couple of years there has been a great deal of attention focused on the potential risk of cough and cold medication in infants and young children, despite the fact that these medicines are widely used with little evidence about their effectiveness [2].

Many of these symptomatic drugs contain essential aromatic volatile substances with a characteristic smell such as camphor, thymol, cineol, but the most common of them is menthol. Identification of the molecular mechanism of the menthol effects (TRPM8 receptor), successfully moved the substance from the class of herbal medicine into the field of molecular pharmacology. Extensive study of menthol action and other TRPM8 agonists could have interesting clinical applications [3].

2. MENTHOL AND ITS USE

Menthol is an aromatic substance, a component of peppermint extract and it has a characteristic flavor and smell. Menthol is cyclic terpene alcohol, which has three asymmetrically situated carbon atoms in the cyclohexane

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ring and the chemical structure allows the existence of four pairs of optical isomers. L-menthol is the isomer that has the strongest biological activity. It has typical peppermint smell and causes cooling sensation when applied topically to the skin or mucous membranes [4,5].

Cooling effects of menthol are not caused by its rapid evaporation from the surface as it was previously assumed, but rather through the effect of menthol on thermosensitive nerve endings via TRPM8 channel, as the receptor for menthol and mild cold are identical [6].

TRPM8 is a non-selective cation channel belonging to the group of melastine TRP channel super family. TRPM8 was successfully cloned from dorsal root ganglia neurons of rats, mice and humans and its expression is not limited only to the primary sensory neurons, but it is expressed by other cell types, such as respiratory or genitourinary epithelium [6,7].

This receptor is sensitive to menthol, eucalyptol, linalol, geraniol, icilin and other substances with cooling effect. Electrophysiological studies have shown that this channel is highly permeable to Ca^{2+} and its activation in turn leads to increased intracellular Ca^{2+} due to influx from the extracellular environment as well as release of calcium from intracellular reserves as well [8].

Application of menthol at low concentrations causes pleasant cooling, analgesic and antiirritant effect. Higher concentrations of menthol can cause irritation, but this mechanism does not depend only on concentration [9,10]. Sensations of burning and irritation after the application of menthol can be explained by a dual mechanism of agonism of menthol, which at higher concentrations activates TRPA1 along with TRPM8 channel. TRPA1 is abundantly expressed in nociceptors [11].

Symptom Relief by Menthol

One of the most common indications for the use of menthol and menthol-containing medicines are the upper respiratory tract diseases regardless of etiology (viral, bacterial), because the symptomatology of these diseases is very similar. They are nasal congestion, impaired breathing through the nose, feeling of airway irritation, sneezing, increased secretion from the nose and cough. For that reason, majority of such medicines are for local intranasal use in form of the nasal drops, sprays or oral use—pastilles, candies and finally ointments that are applied in a thin layer on the front and back of the chest wall.

Application of menthol in combined products, or even alone considerably limits the feeling of nasal congestion. Although menthol/placebo inhalation does not affect objectively measured nasal resistance, it significantly increases subjective perception of nasal patency, which was evaluated by visual analogue scale. So the application of menthol reduces subjective discomfort caused by the presence of this symptom [12,13]. Nerve endings sensitive to menthol were previously known as cold/flow receptors, because their activation occurs due to airflow in upper airways. Each "new" breath of fresh air, colder than the temperature of the mucosal surface activates them, so does the menthol. Information from these receptors is in turn interpreted by brain as "a feeling of improved airflow in the airways" [3].

Intensity of nasal symptoms is also reduced after nerve stimulation on the palate—for example, administration of pastilles or candy containing menthol markedly enhances the feeling of breathing through the nose, but rhinomanometric parameters remain unchanged [14]. These oro-nasal interactions are mediated through palatal nerves and menthol fumes evaporated to the nasopharynx and nasal cavity during expiration [15]. Menthol in the symptomatic treatment of cough is mainly used in the case of acute cough. Antitussive effect of menthol was shown in experimental studies as well as in the adult volunteers, after inhalation of menthol vapors to the lower airways [16,17]. Houghton and Beardmore also documented antitussive effect of menthol vapors in children [18]. However, antitussive activity of menthol is probably mediated through afferent nerves in the upper airways, which abundantly express TRPM8 channels [19]. TRPM8 expression in afferent nerves in animal airways has shown that afferent nerves in the lower respiratory tract express TRPM8 channels significantly less in number than those in the upper respiratory tract, especially trigeminal endings in the nose [20,21].

In addition, antitussive activity of menthol could be enhanced by other mechanisms. Menthol is known to reduce the feeling of irritation and respiratory discomfort. This finding was documented in the study, where 1% *l*-menthol was used as part of premedication before fibrobronchoscopic examination [22]. Menthol is also known to modulate mucociliary transport. Substances modulating mucociliary transport suppress cough by reducing the feeling of irritation of airways, liquefying mucus and facilitate its mobilization in the airways. The other mechanism is that sucking pastilles or sweets containing menthol increases production of saliva and stimulate swallowing. Swallowing is a vagal reflex process that suppresses cough [23].

There are also studies that document the administration of menthol (0.01 to 1 mM) and other TRPM8 agonist icilin (100 μM) inhibits smooth muscle contraction of airways in vitro and the effect on smooth muscle is probably mediated through inhibition of Ca^{2+} entry into cells, as was shown by fura 2 fluorescence procedures. These findings suggest potential use of menthol in reducing symptoms of respiratory illness caused by bronchoconstriction [24].

Based on the available data as mentioned above, there

is pharmacological, clinical and laboratory evidence of its use is alleviation of respiratory symptoms both in children and adult population [25].

3. ADVERSE EFFECTS OF MENTHOL CONTAINING COUGH AND COLD MEDICINES

Although the administration of menthol containing medicines is considered relatively safe and is used quite often, it can lead to serious adverse reactions. Such manifestations may occur in hypersensitive adults. Young children may also experience toxicity of menthol which is underestimated in clinical practice.

It is fully not known about the broad range of cough and cold medicines as their composition is not always exactly defined and we do not know effects of all drug components in detail. There are case reports documenting serious or even life-threatening situations caused by application of cough and cold medications containing menthol. Meta analysis of literature and available case histories suggest that it is not the menthol itself, but the inappropriate use of medicines ignoring the recommendations on product labels could be causing the adverse incidents.

3.1. Disregulation of Breathing Induced by Application of Menthol

It is known, that the control of breathing and airway defensive reflexes in newborns and infants matures progressively with the development of central nervous system. Some works indicate that these mechanisms are not fully functional before reaching the age of 24 months [26]. It is further known that the application of strong chemical stimuli and cold to the nasal cavity and face stimulates the nerve endings of the trigeminal nerve. Relevant stimuli could be chemical, thermal or mechanical. In response to the application of mentioned stimuli such as cold and chemical irritants to the area of baby's nose and face, there is activation of reflex reactions with deceleration of respiratory rate or even respiratory arrest (apnoea) followed by the cardiovascular component of the response in the form of bradycardia and hypertension with blood redistribution—Kratschmer apnoeic reflex [27]. In addition, laryngospasm may occur. These reactions are part of a complex system of airway defensive and protective reflex mechanisms, whose main function is to prevent inhalation of potential hazards deeper into the respiratory tract.

In few cases, all children younger than 1 year, menthol applied to the nostrils caused reflex apnoea. Clinical signs were laryngospasm, spasm of the glottis, instant collapse, dypnoea, unconsciousness, cyanosis and hyperextensive extremities [28]. This mechanism—activation of reflex apnoea, was probably responsible for the situation documented in case reports, where young children were given nasal drops containing menthol. In this particular situation the drops had been stored in refrigerator and activation of trigeminal afferents was not only triggered by the chemical composition of the drops but also by low temperature of it. There have also been documented cases in which parents applied menthol-containing chest lining VapoRub just below the nose in an eighteen months old child and the child immediately went cyanotic and stopped breathing. Parents responded to the situation by turning the child upside down and after a few strokes to back the child coughed out mucus and then breathing went back to normal [29]. In this case that VapoRub was used in the child younger than 2 years (contraindicated according to the product label) and it was not applied on the chest wall, but directly to the proximity of trigeminal nerve endings near the nostrils.

It is documented in experimental works that cold and menthol application directly to the nasal mucosa leads to drop in respiratory rate in experimental animals [30,31] and application of menthol crystals below the nose of a newborn considerably inhibits his/her respiratory rate [26]. Based on this knowledge we can conclude that is not just the pharmacology of menthol inducing apnoea in small children, but the way it is administered contributing to it. Caution should always be taken when applying nose drops or sprays to small children considering possible reflex interactions and immaturity of breathing regulation mechanisms in infants.

Searching for adverse effects of menthol nasal drops also revealed case reports of death of infants who had been treated with certain cough—cold products, but these were ones containing decongestant Pseudoephedrine, which was given in large dose [32], so this result could not be ascribed to the menthol or other natural products.

3.2. Nasobronchial Reflex

Clinical experiences document that menthol containing cough and cold medication triggered wheezing or bronchoconstriction. Exact mechanism of menthol induced airway narrowing causing wheezing is not known. Application of menthol and its superagonist icilin in experimental conditions inhibits bronchial smooth muscle contraction and hence the direct effect of inhaled menthol vapors with the development of bronchoconstriction is unlikely [24].

If we consider the most common application of menthol in the form of nose drops or sprays—the bronchoconstriction could occur in terms of reflex response called nasobronchial reflex. This increased resistance of lower airways caused by bronchoconstriction is by irritation of the trigeminal afferent nerve endings and it is a trigemino—vagal reflex mechanism [33]. Although the

opinions of nasobronchial reflex are often being discussed, the differences of opinion still do exist [34-36]. Some authors have reported bronchoconstriction after irritation of nasal trigeminal afferents, some authors reported bronchodilation and in some cases, the lower airway resistance remained unchanged.

Extensive review by Baraniuk and Merck [33] about nasal reflexes and their implications share that nasobronchial reflex is a component of diving (apnoeic) reflex whose efferent components include bronchoconstriction along with apnoea and laryngeal spasm. Nasobronchial reflex is frequently under debate and it may be elicited by stimulation of trigeminal nasal afferents by mechanical, thermal or chemical stimuli—therefore application of menthol—which is both chemical and thermal channels agonist, might be responsible for such reactions.

3.3. Modulation of Mucociliary Transport

As it has been shown in animal models, menthol inhalation leads to increased production of mucus in the airways, which can be beneficial if the airways contain thick and viscid mucus that is difficult to cough up. Increased mucus production and change of its biophysical qualities may not always be beneficial, because menthol simultaneously inhibits the activity of cilia in the airways, which can lead to stagnation of the mucus in small airways [2]. Cough reflex plays important role in the mucus elimination from the airways, but in case of menthol treatment, cough is usually inhibited due to its antitussive action. Application of ointments and rubs containing menthol on the chest in the night times when the baby does not move can deteriorate the situation further. It is known that during sleep the sense of airway irritation does not occur, cough is inhibited due to sleep and the child may wake up in a paroxysm of cough, dyspnoe, wheezing which may eventually lead to respiratory failure. Mucus plugs obliterate small airways, leading to alveolar hypoventilation, ventilation-perfusion mismatching with impaired oxygenation and ventilation leading to respiratory failure.

3.4. Other Problems Related to Menthol "Toxicity"

Application of menthol on the chest can cause irritation of the skin of the chest, which manifests as redness of the skin with presence of blisters. These effects are probably due to the influence of menthol on TRPA1 channels of skin somatosensitive nociceptors.

Bioavailability and toxicity of menthol and other components present in VapoRubs and ointments after dermal absorbtion is minimal with relatively low systemic exposure to these compounds, even when an unrealistically large number of patches are applied onto the skin for unusually long time [37]. Based on the literature retrieved via MEDLINE and our review of calls to the PIC there have been cases of accidental poisonings with essential oils in children. There have been documented cases of menthol, euclyptol and camphor poisoning in small children after unintentional ingestion of drops, oils, or eating VapoRubs by infants [38].

The main symptoms of poisoning were epigastric pain, nausea, vomiting, dizziness, muscle weakness, miosis, tachycardia, and breathing difficulties. Therefore it is important to be cautious and use common sense when children are surrounded by products containing the mentioned substances.

4. CONCLUSION

From the literature review, it is evident that use of menthol and menthol-containing cough and cold medications is very common in the symptomatic treatment of common respiratory diseases. There has been increasing pharmacological evidence for their use in relief of respiratory symptoms in recent days. The adverse reactions have occurred mostly in cases when the route and mode of administration was breached or when it was used in age range when it was not supposed to be used (children less than 2 years). Accidental poisonings can happen as with any other mediations and caution should be used while these medications are in proximity of children. Overall it can be concluded that over the counter menthol and menthol containing components can be safely used for symptomatic relief in common respiratory illness in children and adults guided by manufacturer guidance and product labels on route and mode of administration and avoiding their use in very young children less than 2 years of age.

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