

RHINOLOGY

Update on the pathophysiology and treatment of rhinogenic headache: focus on the ibuprofen/pseudoephedrine combination

Aggiornamento sulla fisiopatologia e sul trattamento della cefalea rinogena: focus sull'utilizzo combinato di ibuprofene e pseudoefedrina

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SUMMARY

Rhinogenic headache is frequently encountered in clinical practice. Treatment of this condition should be based on a proper evaluation of its underlying pathophysiology. Fixed-dose combinations of two or more active agents, and specifically the combination of ibuprofen plus pseudoephedrine, have been shown to be more efficacious than either monotherapy. At present, an ibuprofen/pseudoephedrine fixed-dose combination is available as an over-the-counter drug. This paper reviews in detail the pathophysiology of rhinogenic headache and discusses the rationale for treatment of this condition with a fixed-dose ibuprofen/pseudoephedrine combination.

KEY WORDS: Combination therapy • Ibuprofen • Pathophysiology • Pseudoephedrine • Rhinogenic headache

RIASSUNTO

La cefalea rinogena è frequente nella pratica clinica. Il trattamento di questa patologia dovrebbe essere basato su un'appropriate valutazione della sottostante fisiopatologia. La combinazione di due o più farmaci, ed in particolare ibuprofene e pseudoefedrina, a dosaggi fissi si è dimostrata più efficace delle monoterapie. Al momento la combinazione ibuprofene/pseudoefedrina a dosaggio fisso è commercializzata quale farmaco da banco. Questo lavoro si focalizza sulla revisione in dettaglio della fisiopatologia della cefalea rinogena e discute il razionale del trattamento mediante la combinazione ibuprofene/pseudoefedrina.

PAROLE CHIAVE: *Terapia combinata • Ibuprofene • Fisiopatologia • Pseudoefedrina • Cefalea rinogena*

Introduction

Rhinogenic headache represents a major health issue that is frequently encountered in clinical practice ¹. The results of a worldwide survey in 2007 showed that rhinogenic headache is among the most common complaints among those seeking medical care. In addition to general practitioners, otolaryngologists see a large number of patients with rhinogenic headache ². Most patients with this condition are males aged 10-30 years ²⁻⁵.

Rhinogenic headaches have their primary pathophysiology centred in the nose, with headache and/or facial pain as a result of complex neurohumoral reflexes. The most common rhinogenic headache is that associated with acute rhinosinusitis ^{4 6}. Most cases of rhinogenic headache are caused by viral infections (up to 98%), and only 2% are complicated by bacterial sinusitis ^{1 7}. However, primary care physicians often treat sinusitis as an acute

bacterial infection, prescribing antibiotic therapy and hence contributing to the onset of resistance ¹. In addition, rhinogenic headache is frequently misdiagnosed as other conditions such as migraine ².

Therefore, it is important to identify and appropriately manage this common condition ¹. Treatment should be based on a proper evaluation of the underlying pathophysiology. Fixed-dose combinations of two or more active agents, and specifically the combination of ibuprofen plus pseudoephedrine, have been shown to be more efficacious than either monotherapy. At present, an ibuprofen/pseudoephedrine fixed-dose combination is available as an over-the-counter product ⁸.

This paper reviews in detail the pathophysiology of rhinogenic headache and discusses the rationale for treatment of this condition with a fixed-dose ibuprofen/pseudoephedrine combination.

Pathophysiology and clinical features of rhinogenic headache

The paranasal sinuses are lined with pseudostratified columnar epithelium, and under physiological conditions, the sinuses are normally sterile. Their function depends on regular transport of the mucus layer into a common area, the osteomeatal complex, in the middle meatus of the nasal cavity. This area is the focal point of sinus drainage; from the nasal cavity, the mucus then drains into the oropharynx¹. Acute rhinosinusitis begins as a viral infection of the nose leading to inflammation of the sinuses. Inflammation leads to mucosal oedema, osteomeatal complex obstruction and development of negative atmospheric pressure within the sinuses cavities and decreasing partial pressure of oxygen. Excessive mucus production, with or without transudation of plasma, also occurs. Collectively, these events result in malfunction or complete cessation of movement of the cilia in the sinuses, leading to stasis of the mucus. Inevitably, this creates an environment that promotes the growth of pathogenic organisms¹. In addition, specific anatomic variations, smoking, immunodeficiency disease, allergic rhinitis and exposure to increasing levels of humidity or irritants promote decreased ciliary function, sinus obstruction and superinfection^{1,9}.

Mucosal inflammation represents the central pathophysiological mechanism underlying most of the specific and interrelated factors that contribute to congestion, such as increased venous engorgement, increased nasal secretions and tissue swelling/oedema¹⁰. Inflammation diminishes the physical size of the nasal passages by inducing vasodilatation and increasing blood flow as well as vascular permeability. The result is engorgement of the nasal venous sinusoids, swelling of the anterior and inferior turbinates and obstruction of nasal airflow. Ultimately, this engorgement leads to nasal congestion¹⁰.

Given the contribution of inflammation, it is not surprising that the levels of inflammatory cytokines (interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF)- α) in patients with acute rhinosinusitis are significantly increased in nasal lavage fluid compared with healthy controls¹⁰⁻¹². Kinin levels are markedly increased in nasal secretions of patients with acute viral rhinosinusitis: these polypeptides act on blood vessels to cause vascular leakage and/or engorgement, and also stimulate afferent nerve fibres leading to hyperresponsiveness of the mucosa^{13,14}. In addition, acute rhinosinusitis is associated with increased infiltration of inflammatory cells, including neutrophils and T cells, in the nasal epithelium and lamina propria¹⁰. Sterile inflammation (so-called neurogenic inflammation) may result from neurologic responses involving a

wide range of neurotransmitter systems¹⁰. In particular, the nasal mucosa has sensory, parasympathetic and sympathetic nerves. Sensation to the nasal cavity is provided primarily via the maxillary and ophthalmic branches of the trigeminal nerve. Parasympathetic innervation controls nasal secretions and mucus gland production; moreover, it increases blood flow to the nasal cavity by release of NO. On the other hand, sympathetic innervation decreases the blood flow to the nasal cavity and nasal mucosa. In the presence of mucosal inflammation, parasympathetic and sympathetic tone is dysfunctional, and therefore changes in both glandular and vascular function in the nose occur.

The hypothesis of polymodal receptors in the nasal mucosa suggests that different heat, chemical and mechanical irritants (such as pressure on the mucosa) may cause antidromic release of neuropeptides including substance P and calcitonin gene-related peptide¹⁵ from the peripheral terminals of nociceptive sensory nerve fibres¹⁰, as well as vasoactive neuro-gasotransmitters (noradrenalin, acetylcholine, NO, adenosine) involving sympathetic and parasympathetic terminals. This leads to neurogenic inflammation and peripheral neural sensitisation, which bring about a complex cascade of neurohumoral signalling that is mainly sustained by reflex mechanisms¹⁰. Specifically, the perivascular release of the above-mentioned powerful vasodilators causes increased vessel permeability, plasma extravasation and tissue oedema, which further activate afferent trigeminal sensory fibres and, in turn, continuous antidromic release of vasoactive and inflammatory molecules. Inevitably, this leads to a vicious cycle of neurogenic inflammation that sustains rhinorrhoea, nasal congestion, sinus pain and upper respiratory symptoms^{6,10,16}. With regard to rhinogenic headache, it is now known that this originates both by classic mechanisms of painful stimuli converging at the level of the trigeminal nucleus (the trigeminocervical complex) and activation of the parasympathetic loop, which plays a crucial role not only in sustaining mucosa vasodilation but also in intracranial spreading of neurogenic inflammation. Specifically, painful stimuli reaching the trigeminal nucleus activate direct signalling to the superior salivatory nucleus, which sends preganglionic parasympathetic fibres to the sphenopalatine ganglion. Postganglionic fibres close the reflex arch by sending fibres traveling together with the trigeminal fibres and innervating not only the nasal and sinus mucosa but also intracranial structures, such as the meninges and pial vessel. Hence, parasympathetic activation caused by sustained nasal mucosa inflammation triggers perivascular release of vasodilating compounds at the meninges and cerebral vessels, which activates and then sensitizes the terminals of trigeminal nociceptors with development of rhinogenic headache^{17,18}.

Rhinogenic headache and facial pain develop simultaneously with the onset or exacerbation of rhinosinusitis and usually resolve after remission or successful treatment of acute rhinosinusitis². Sudden onset of two or more symptoms, including nasal discharge/rhinorrhoea, nasal blockage or congestion, facial pain/pressure/frontal headache and disorder of olfaction, of less than 10 days duration, is considered to be caused by a virus (common cold)¹⁹. Treatment should be initiated immediately for patients with rhinogenic headache².

Treatment optimisation for rhinogenic headache

Given the particular pathophysiology of rhinogenic headache, optimal therapy should induce prompt resolution of oedema/mucosa compression, suppression of inflammation, safe analgesia and stimulation of the central nervous system (CNS) within specific hypothalamic and brainstem nuclei to restore neurovegetative homeostasis¹.

Current treatments for rhinogenic headache include decongestants, anticholinergics, anti-histamine, corticosteroids, analgesics and anti-bacterial agents¹. The different therapies used in this setting are sustained by different levels of evidence. Given that each of the above-mentioned drugs acts only against a subset of symptoms, fixed-dose combinations of two or more active ingredients are frequently used in clinical practice¹⁹.

Analgesics, and especially ibuprofen, have a major role in the treatment of rhinogenic headache¹⁶. In this regard, it is worth remembering that the updated guidelines (2015) of the AAO-HNS (American Academy of Otorhinolaryngology - Head and Neck Surgery) for treatment of acute rhinosinusitis give a recommendation to analgesic for relief of both viral and bacterial ARS (Acute RhinoSinusitis) symptoms²⁰.

The main mechanism of action of ibuprofen is non-selective, reversible inhibition of cyclooxygenase enzymes COX-1 and COX-2. COX-1 and COX-2 catalyse the first step in the synthesis of proinflammatory prostanoids from arachidonic acid. These prostanoids enhance oedema formation, increase vascular permeability and promote leukocyte infiltration; they also reduce the threshold of nociceptor sensory neurons to stimulation. Ibuprofen exerts its anti-inflammatory and analgesic effects mostly by inhibiting the formation of these prostanoids²¹. Moreover, ibuprofen has inhibitory effects on polymorphonuclear leukocyte migration and function^{22,23}. It also inhibits the release and biological effects of kinins and inflammatory mediators such as TNF- α and IL1, which are involved in the recruitment of neutrophils, thus exerting an immu-

noregulatory effect²⁴. In addition, ibuprofen is reported to scavenge reactive oxygen and nitrogen species and to inhibit NO synthesis²¹.

Ibuprofen has an excellent safety/tolerability profile even after multiple doses; the frequency of gastrointestinal adverse events is comparable with placebo²⁵. In patients with cold and flu symptoms enrolled in a large study (n = 2815), ibuprofen was as well tolerated as paracetamol and much better tolerated than aspirin²⁶. In a clinical trial on 80 patients with naturally acquired upper respiratory tract infections, ibuprofen 400 mg three times daily significantly reduced the severity of headache-associated symptoms, earache, muscle/joint pain, and sneezing, and also reduced body temperature²⁷.

Oral decongestants are another commonly used class of medications for the treatment of rhinogenic headache¹. They are prescribed usually on a short-term basis to provide fast-acting relief. Oral decongestants have a weaker effect on nasal obstruction than topical intranasal decongestants; however, they do not cause a rebound phenomenon. After oral administration, the effect of nasal decongestion occurs within 30 minutes and persists for up to 6 hours. Decongestants contain sympathomimetic agents, which mimic the actions of norepinephrine. Pseudoephedrine mainly exerts its vasoconstrictive effects by promoting noradrenaline release, thereby behaving as an indirect vasoconstrictor. It has indirect agonist activity, particularly on peripheral α 1 and cardiac β receptors through displacement of noradrenaline from the vesicle pool. Displaced norepinephrine is then released from the sympathetic prejunctional nerve terminal and subsequently binds to post-junctional α -adrenergic receptors on nasal venous sinusoids, thereby producing vasoconstriction, plasma extravasation and mucosal congestion²⁸.

Pseudoephedrine at the low dose used in over-the-counter medicines may cause nasal decongestion with minimal cardiac effects²⁹. Small, but statistically significant increases in pulse and systolic blood pressure occurred after supramaximal doses of pseudoephedrine (120 mg and 180 mg). Conversely, pseudoephedrine at 60 mg is the optimal, single adult dose leading to prompt, maximal nasal decongestion without cardiovascular or other unwanted effects³⁰.

Role of the fixed-dose combination of ibuprofen and pseudoephedrine in clinical practice

According to the available evidence, a fixed-dose combination of ibuprofen and pseudoephedrine may be particu-

larly effective in the treatment of rhinogenic headache³¹. It combines two molecules with complementary mechanisms of action, namely reduction of pain and inflammation with ibuprofen and decrease of nasal oedema, mucous production and congestion with pseudoephedrine. Moreover, pseudoephedrine reduces compression on nociceptive terminals, thus boosting the analgesic effects of ibuprofen. Lastly, pseudoephedrine can help restore neurovegetative homeostasis. Indeed, by enhancing the sympathetic tone, it counteracts hyperactivation of the parasympathetic component that sustains vasodilation and neurogenic inflammation.

The clinical evidence supports effective management of the nasal and paranasal congestion syndrome with the ibuprofen/pseudoephedrine combination. Specifically, in a randomised study, 58 patients were assigned to receive pseudoephedrine 60 mg alone, pseudoephedrine 60 mg plus ibuprofen 200 mg, or placebo, four times daily for 4.5 days beginning 30 h after intranasal inoculation of rhinovirus under double-blind conditions³¹. The frequencies of infection, colds and viral shedding did not differ significantly between groups. Total symptom scores were significantly reduced by 59% by pseudoephedrine plus ibuprofen and 48% by pseudoephedrine alone, compared with placebo. Cumulative nasal scores and systemic scores were significantly reduced in patients receiving pseudoephedrine plus ibuprofen compared with those assigned to placebo, whereas pseudoephedrine alone was not better than placebo in reducing nasal congestion. Combination therapy was well tolerated, with an inci-

dence of adverse events comparable to placebo (Table I). In a recent study, data from an anonymous survey among 1770 pharmacy customers purchasing a product containing 200 mg ibuprofen plus 30 mg pseudoephedrine for treatment of common cold symptoms were reviewed⁸. Scores of symptoms responsive to ibuprofen (headache, pharyngeal pain, joint pain and fever), responsive to pseudoephedrine (congested nose, congested sinus and runny nose), and considered non-specific (sneezing, fatigue, dry cough, cough with expectoration) were analysed. After the first intake, the greatest improvement in a specific symptom (+ 63% vs baseline) was reported for headache, which was also the most bothersome symptom. Nasal and sinus congestion improved by more than 50% (Table II). More than 50% of participants reported symptom relief within 30 min (Fig. 1). The duration of overall symptom relief was reported to be up to 6 h in 54.4% and up to 12 h in 22.6% of patients. Statistical analysis showed that two tablets for the first dose were more effective than one. More than 95% of participants rated global tolerability as excellent or good.

Conclusions

Rhinogenic headache is frequently encountered in clinical practice. Given the particular pathophysiology of this condition, optimal therapy should target multiple pathogenic events and lead to resolution of oedema/mucosa compression and inflammation, as well as promote analgesia and CNS stimulation within specific hypothalamic and brainstem nuclei to restore neurovegetative homeostasis.

Table I. Adverse events with the ibuprofen/pseudoephedrine combination. Pseudoephedrine only and placebo, as reported by Sperber et al.³¹.

	Number (percent) of patients						
	Number of patients	Any adverse event	Light-headedness	Difficulty Sleeping	Lethargy	Indigestion	Other
Pseudoephedrine plus ibuprofen	23	6 (26)	2 (9)*	1 (4) [§]	0	0	4 (17) ^{§^}
Pseudoephedrine alone	23	4 (17)	2 (9)*	0	1 (4)	1 (4)	0
Placebo	10	2 (20)	0	1 (10)	1 (10)	0	0

* Sum of all pseudoephedrine recipients (4/46) was not significantly different from placebo (0/10); [§] One patient reported difficulty sleeping and dry mouth; [^] One patient reported dry mouth, feeling hyper, feeling more awake, flushed face and increased heart rate. Increased pulse rate was not documented in this patient.

Table II. Scores for typical ibuprofen-responsive symptoms at baseline and after intake of the first dose of the combination 200 mg ibuprofen plus 30 mg pseudoephedrine (irrespective of taking 1 or 2 tablets) as well as intra-individual change after first intake.

Score	Baseline	After first intake	Reduction	% Reduction
TIRS	4.62 ± 2.19	1.87 ± 1.69	2.75 ± 1.89	60.0 ± 33.2
TPRS	4.89 ± 2.33	2.50 ± 1.74	2.39 ± 1.93	46.3 ± 64.6
NSS	3.33 ± 2.03	1.81 ± 1.58	1.52 ± 1.53	45.4 ± 41.0
TSS	4.22 ± 1.65	2.02 ± 1.42	2.20 ± 1.41	52.8 ± 29.7

TIRS, typical ibuprofen-responsive symptoms consisting of headache, pharyngeal pain, joint pain and fever; TPRS, typical pseudoephedrine-responsive symptoms consisting of congested nose, congested sinus and runny nose; NSS, non-specific-symptoms consisting of sneezing, fatigue, dry cough, cough with expectoration; TSS < total symptoms consisting of all 11 symptoms. Data are means ± SD on a scale of 0 (smallest extent) to 10 (greatest extent) or % change (reproduced from Klimek et al., 2017⁸).

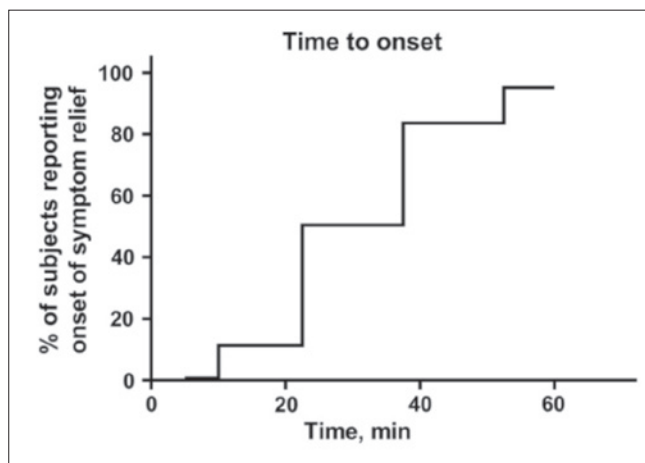


Fig. 1. Time to onset of action after ingestion of the first dose. Data are shown as cumulative % of survey participants reporting onset of symptom relief after ingestion of a combination of 200 mg ibuprofen plus 30 mg pseudoephedrine at a given time point (reproduced from Klimek et al., 2017⁸).

Due to their mechanism of action, ibuprofen and pseudoephedrine may represent a suitable therapeutic strategy for the treatment of rhinogenic headache. In particular, ibuprofen reduces pain and inflammation, and pseudoephedrine contributes to decrease nasal oedema, congestion and neurovegetative dysregulation. Although current clinical evidence is still limited, the effects of the combination are significant with regard to clinical and safety/tolerability aspects. The fixed-dose combination of ibuprofen and pseudoephedrine has potential to have a major role in clinical practice for the management of rhinogenic headache.

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Conflict of interest statement

None declared.

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