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Review

Benefits, limits and danger of ephedrine and pseudoephedrine as nasal decongestants

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ABSTRACT

Due to their vasoconstrictive action on the nasal mucosa, ephedrine and pseudoephedrine are highly efficient amines for relief of nasal congestion. As with any vasoconstrictor and as underscored by the French Society of Otorhinolaryngology in its 2011 guideline, these molecules should not be used in patients under the age of 15. Furthermore, due to unpredictable severe cardiovascular and neurological adverse events that may occur even at low dose and in the absence of any pre-existing pathology, they should not be prescribed for the common cold, and ENT physicians must carefully weigh the risk/benefit ratio in patients with allergic rhinitis. Distribution should be regulated and over-the-counter sales banned.

1. Introduction

Ephedrine and pseudoephedrine are the two oldest molecules known in the treatment of nasal congestion. Their vasoconstriction action on the nasal mucosa makes them highly effective amines in the treatment of nasal congestion. In recent years, however, the French National Pharmacovigilance Commission, first in 2008 and then again in 2012 [1,2], the French Otorhinolaryngology Society, in its 2011 Formalized Consensus Professional Guideline "Use of Vasoconstrictors in Rhinology" [3], and the French national Drug Safety Agency, in its July 2013 action plan [4], have all warned against their use in rhinology. Moreover, in February 2014, the French consumer magazine *60 Millions de Consommateurs*, in a review for the general public of common cold treatments on sale in France, stated that vasoconstrictors "involve a risk of stroke and severe neurological effects" and that they "are often too risky for use against a simple cold" [5]. Despite all of this, while in France nasal ephedrine for nasal congestion (Table 1) is a prescription-only drug, many oral route symptom-relief treatments containing pseudoephedrine are sold over the counter (Table 2).

In view of these facts, we conducted a review of the literature to determine the benefit, limitations and dangers of ephedrine and pseudoephedrine in rhinology.

2. Ephedrine and pseudoephedrine: origins

Ephedrine is one of the 8000 natural compounds of the alkaloid family, the etymology of which comes from the Latin *alcali* ("base"), which in turn comes from the Arabic *al qaliy* ("soda ash" or "burnt ash"), and the suffix -oid ("like"), and which covers all pharmacologically active alkaline heterocyclic nitrous organic compounds [6,7]. Certain alkaloids (conventionally bearing the suffix "-ine"), such as strychnine, are notoriously deadly; many others are used in medicine for their various therapeutic properties: analgesic (morphine, codeine, cocaine), anti-malarial (quinine, chloroquine), anticancer (vinblastine, vincristine, vindesine), bronchodilatory (theophylline), vascular (adrenaline, noradrenaline, atropine, dopamine), sialogogic (pilocarpine), anti-vertigo (scopolamine), or anti-allergic (histamine).

Ephedrine is named for the little bushes of the *Ephedra* genus, extracts of the stem and leaves of which also contain pseudoephedrine and have been used for medical purposes since

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Table 1
Nasal decongestant sprays containing ephedrine on the French market in 2014.

Brand	Ephedrine dose/100 mL	Associated substances	Dosage and maximum treatment duration
Rhino-Sulfuryl®	990 mg	Antiseptic	5 sprays/day/5 days
Rhinamide®	819.2 mg	Antiseptic	5 sprays/day/5 days

antiquity. In the oldest Chinese work devoted to the medicinal virtues of animal, vegetable and mineral drugs, *The Divine Farmer's Materia Medica* (*Shennong Bencao Jing*), *Ephedra sinica* (*Mahuang*) is mentioned for its stimulating and anti-asthmatic virtues [8]. In Europe, the Greek Dioscorides first referred to the therapeutic uses of *Ephedra* (*Ephedra major*) and, in his *Naturalis Historia*, Pliny the elder confirmed these prescriptions. Some believe that this drug may also be the "soma" mentioned in the *Book of Hymns* (*Rig Veda)* of ancient India (and later recycled by Aldous Huxley as a kind of "opium of the people", in *Brave New World*).

Ephedrine was first isolated in the late 19th century, and first synthesized in the 1920s in Japan as a chlorhydrate, and then produced and marketed by Merck [6,9]. Pseudoephedrine was synthesized soon after. By virtue of their molecular structure, these two sympathomimetic amines stimulate the adrenergic receptor system at the junction between the sympathetic nerve and smooth muscle of the vessel walls, thus simulating the vasoconstriction action of norepinephrine, which is physiologically produced by the sympathetic nerve fiber.

In the nasal fossae, regulation of the mucosal vascular network, and in particular the filling and emptying of the cavernous vein plexuses, is fundamental to the regulation of airflow and hence to the sensation of obstruction [10]. The venous plexuses, like the arterioles accompanying them, are surrounded by adrenergic nerve fibers to which they are connected by α and β adrenergic receptors [10]: β receptors are vasodilators, while α receptors are vasoconstrictors and are preponderant [10]. Ephedrine and pseudoephedrine thus exert a vasoconstrictive effect on the vessels, which underlies the relief they procure in nasal congestion.

3. Benefit of ephedrine and pseudoephedrine as nasal decongestants

In rhinology in France, ephedrine is administered nasally and is a prescription drug (Table 1). Pseudoephedrine, on the other hand, whether alone or associated to various other drug classes, is taken orally (Table 2) and is available over the counter.

Ephedrine applied to the nasal mucosa reduces nasal resistance more quickly and strongly than oral pseudoephedrine, but with shorter action time [10,11]. At end of treatment, there may be a rebound effect with increased nasal resistance and recurrence of congestion, for which several hypotheses have been suggested. The 2011 French Society of Otorhinolaryngology guidelines [2] stress that rebound has been described only in experimental contexts with healthy volunteers and might be no more than progression of the disease for which the vasoconstrictor was prescribed. Other hypotheses involve either repeated α-2 receptor stimulation, inducing intense vasoconstriction with mucosal ischemia and interstitial edema, or else α-2 receptor down-regulation, inducing relative dilation and a tachyphylaxic effect leading to increased need of decongestants, or again accessory affinity for β adrenergic receptors which, when stimulated, induce secondary vasodilation once the α effect has worn off [12,13].

Several studies in various pharmaceutical laboratories demonstrated efficacy for oral pseudoephedrine against nasal congestion during common cold [14,15]. In 2004, the Bayer laboratories [14], in a multicenter prospective randomized double-blind trial against placebo including 643 patients with common cold, found reduction of nasal congestion without side-effects 6 hours after oral intake of pseudoephedrine (30 or 60 mg) associated either to acetylsalicylic acid (1 g) or to paracetamol (500 mg or 1 g). Likewise, in 2007, Procter and Gamble [15], in a multicenter prospective randomized double-blind trial against placebo including 485 patients with common cold, found improvement in symptoms (including congestion) 3 hours after intake of syrup containing 8 mg ephedrine associated to 600 mg paracetamol and a steroidal anti-inflammatory. Finally, Eccles et al. [16], in a prospective randomized double-blind trial against placebo including 238 patients with common cold, reported efficacy against nasal congestion without side-effects for 3 days' 60 mg oral pseudoephedrine.

These results in common cold have been backed up by other randomized double-blind studies of associated H1 antihistamines and pseudoephedrine in allergic rhinitis [17–22]. Grosclaude et al. [17] found that the association of an H1 antihistamine (cetirizine 5 mg) and pseudoephedrine (120 mg) for 15 days did not improve nasal congestion more than pseudoephedrine (120 mg) alone but did improve other symptoms. Berkowitz et al. [18,19] found symptomatic efficacy for associated H1 antihistamine (fexofenadine) and pseudoephedrine (60 mg) at 45–60 minutes after intake, lasting 6 hours. Likewise, Chiang et al. [20] found symptomatic efficacy for associations of H1 antihistamines (cetirizine or loratadine) and pseudoephedrine. In allergic rhinitis with moderate asthma, Nathan et al. [21] found efficacy compared to placebo for 4 weeks' associated H1 antihistamine (cetirizine 5 mg) and pseudoephedrine (120 mg). And finally, Mucha et al. [22] found 15 days' oral pseudoephedrine (240 mg) to be more effective against nasal congestion than an oral leukotriene receptor antagonist (montelukast 10 mg).

Table 2
Over-the-counter nasal congestion treatments containing pseudoephedrine in France in 2014.

Brands	Dose per tablet (mg)	Associated substances	Dosage and maximum treatment duration
Humex Rhume®	60	PA	240 mg × 4 days
Dolirhume®	30	PA	180 mg × 5 days
DolirhumePro®	30	PA	90 mg × 4 days
ActifedRhume®	30	PA	180 mg × 5 days
ActifedRhume jour et nuit®	60	PA + AH	180 mg × 4 days
Actifed LP Rhinite Allergique®	120	AH	240 mg × 5 days
Rhumagrip®	30	PA	180 mg × 5 days
Rhinadvil®	30	NSAID	180 mg × 5 days
Rhinureflex®	30	NSAID	180 mg × 5 days
Nurofen Rhume®	30	NSAID	120 mg × 5 days

PA: paracetamol; AH: antihistamine; NSAID: non-steroidal anti-inflammatory drug.