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Review

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

O. Laccourreye[a,c,*], A. Werner[b], J.-P. Giroud[c], V. Couloigner[d], P. Bonfils[a], E. Bondon-Guitton[e]

[a] *Université Paris Descartes Sorbonne Paris Cité, hôpital européen Georges-Pompidou, AP–HP, service ORL et chirurgie cervico-faciale, 20, rue Leblanc, 75015 Paris, France*
[b] *18, rue de la Ferme, 92200 Neuilly-sur-Seine, France*
[c] *Académie nationale de médecine, 16, rue Bonaparte, 75272 Paris cedex 06, France*
[d] *Université Paris Descartes Sorbonne Paris Cité, hôpital Necker-Enfants malades, AP–HP, service ORL, 143, rue de Sèvres, 75015 Paris, France*
[e] *Université Paul-Sabatier, CHU de Toulouse, Inserm U 1027, service de pharmacologie médicale et clinique, crpv, 37, allée Jules-Guesde, 31000 Toulouse, France*

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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

* Corresponding author. Université Paris Descartes Sorbonne Paris Cité, hôpital européen Georges-Pompidou, AP–HP, service ORL et chirurgie cervico-faciale, 20, rue Leblanc, 75015 Paris, France.
E-mail address: ollivier.laccourreye@egp.aphp.fr (O. Laccourreye).

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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.

Table 3
Articles (PubMed search) published in the last 15 years reporting adverse effects for pseudoephedrine as nasal decongestant (*n*: number of cases).

Authors	*n*	Side-effects
Cantu et al. [25]	4	Stroke
Browning et al. [26]	1	Angina pectoris
Manini et al. [27]	1	Myocardial infarction
Pederson et al. [28]	1	Myocardial infarction
Lopez Lois et al. [29]	1	Myoclonia and trembling
Roberge et al. [30]	1	Psychosis and ataxia
Sotullo C.A. et al. [31]	1	Psychosis
Gunn et al. [32]	1	Unexplained death
CDC [33]	3	Unexplained death
Rimsza & Newberry [34]	3	Unexplained death
Weingert et al. [35]	13	Unexplained death
Soyer et al. [36]	1	Acute urinary retention
Bektas et al. [37]	1	Supraventricular tachycardia
Olivier et al. [38]	58	22 cases of hypertension, 4 of stroke, 9 of headache, 15 of vasomotor disorder of the limbs, 8 of convulsion

4. Dangers and limitations of ephedrine and pseudoephedrine

Ephedrine and pseudoephedrine belong to the amphetamine family. Their psychotropic effect, well-known since their widespread use by belligerents on all sides of the Second World War, is one of stimulation with increased aggression and higher fatigue threshold. They are amines categorized as class A narcotics, listed in Table I of the convention against narcotic and psychotrope trafficking since 1988. In France, in 2008 and again in 2012, the National Pharmacovigilance Commission [1,2] highlighted their psychotropic action and cardiovascular side-effects.

The vasoconstriction effect these molecules exert when administered orally or directly on the nasal mucosa considerably increases blood pressure and vasospasm [22–25]. This effect, which on average lasts 5 to 6 times as long as that of adrenaline, may induce hypertension episodes, myocardial infarction, stroke and various neurological symptoms (Table 3) [10,25–38]. The various cardiovascular adverse effects may occur with both oral and nasal administration and after a single dose or prolonged (5 days) treatment, without dose-effect and independently of vascular status and age [25–28,37]. A French study in 2003 analyzed adverse events related to nasal decongestant vasoconstrictors reported to regional pharmacovigilance centers by health-care professionals between their market launch in France and 2001 [38]. The study noted 22 episodes of arterial hypertension, 15 of convulsion and 4 cases of stroke after oral intake of medication containing pseudoephedrine (Table 3) and 1 episode of arterial hypertension and 1 case of stroke after nasal intake of ephedrine [38]. In the USA, the Centers for Disease Control (CDC) reported that common cold treatments based on nasal decongestants, H1 antihistamines, cough treatment and/or expectorants in under 2-year-olds had led to several hundred emergency hospital admissions and at least 3 deaths over the period 2004–2005 [33]. The report confirmed a case study published in 2001 by Gunn et al. [32], warning physicians and parents against uncontrolled use of these products in under 2-year-olds [33]. The danger was confirmed by two North American studies: in 2007, Wingert et al. [35], in a postmortem analysis of samples from 13 cases of unexpected death in under-2 year-olds taking common cold treatments in the Philadelphia region, systematically detected pseudoephedrine; likewise, in 2008, Rimsza and Newberry [34], in a review of the files of cases of unexpected death in children taking common cold treatments in 2006 in Arizona, reported that the majority of victims were from socially disadvantaged families and that postmortem toxicology, when performed, found pseudoephedrine taken for common cold in 3 cases. In 2013, Santé Canada confirmed the government's 2002 decision to limit single and maximum daily doses of pseudoephedrine as nasal decongestant to 32 mg and to withdraw all products with higher doses from the Canadian market [39]. It can be seen from Table 2 that the pseudoephedrine doses contained in the various nasal decongestants freely available in France at the present time are considerably higher than recommended 15 years ago by Santé Canada [39]. It should also be borne in mind that users of over-the-counter pseudoephedrine do not respect the recommended doses and treatment durations and/or may associate this amine to another class of vasoconstrictor, either over-the-counter such as phenylephrine (Hexarhume®, Humoxal®) or on prescription such as oxymetazoline (Aturgyl®, Déturgylone®, Pernazène®), tuaminoheptane (Rhinofluimucil®) and naphazoline (Derinox®)[3,38].

The adrenergic effect of these amines also induces hypolipidemia by reducing blood lipid concentrations. Combined with their appetite suppressant effect, this led several manufacturers to include ephedrine and *Ephedra* in the formulae of various diet supplements available on the North American market in the 2000s. However, adverse effects of the order of schizophrenia and bipolar disorder [23,40] and the recycling of some of these amphetamines to synthesize very easily and cheaply, methamphetamine, which is highly addictive, led to a ban on over-the-counter sale as dietary supplements in Canada and then, in 2006, by the US FDA [41]. The same danger led the French national health products safety agency (Agence nationale de sécurité du médicament) in 2013 to reclassify preparations containing only pseudoephedrine (Sudafed®, Humex Rhinite Allergique®) as prescription drugs [4]; the manufacturers subsequently withdrew both from the market in France.

5. Conclusion

The present review of the literature tends to show that their vasoconstrictive action on the nasal mucosa makes both ephedrine and pseudoephedrine highly effective against nasal congestion. Like any vasoconstrictor, as stressed by the 2011 guidelines of the French Society of Otorhinolaryngology [2], they should not be prescribed for children under the age of 15 years. It further seems that the severe adverse cardiovascular and neurological effects reported with these amines, of unpredictable onset and potentially associated with low doses in the absence of any relevant history, should lead ENT physicians not to resort to them to treat common cold and to exercise the greatest rigor in assessing the cost/benefit trade-off in prescribing them for allergic rhinitis. Given these risks, distribution should be regulated and over-the-counter sale should be avoided.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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