Pseudoephedrine (PSE) [pronunciation: /ˌsuːdəˈfɛdərən/ or /ˌsuː doʊˈefədriːn/] is a sympathomimetic drug of the phenethylamine and amphetamine chemical classes. It is used as a nasal/sinus decongestant and stimulant, or as a wakefulness-promoting agent.
The salts pseudoephedrine hydrochloride and pseudoephedrine sulfate are found in many over-the-counter preparations either as a single ingredient or, more commonly, in combination with antihistamines, guaifenesin, dextromethorphan, paracetamol (acetaminophen), and/or NSAIDs (e.g., aspirin, ibuprofen, etc.).

**Chemistry**

Pseudoephedrine is a diastereomer of ephedrine. Pseudoephedrine is a chiral molecule, meaning it occurs in both "left-handed" and "right-handed" configurations which are not superimposable.

Pseudoephedrine is a precursor of methamphetamine and methcathinone.

**Nomenclature**

The dextrorotary (+)- or d- enantiomer is (1S,2S)-Pseudoephedrine, whereas the levorotating (−)- or l- form is (1R,2R)-Pseudoephedrine.

In the outdated d/l system (+)-Pseudoephedrine is also referred to as l-Pseudoephedrine and (−)-Pseudoephedrine as d-Pseudoephedrine (in the Fisher projection then the phenylring is drawn at bottom).[7][8]

Often the d/l system (with small caps) and the d/l system (with lower-case) are confused. The result is that the dextrorotary d-Pseudoephedrine is wrongly named d-Pseudoephedrine and the levorotary l-Ephedrine (the diastereomer) wrongly l-Ephedrine.

The IUPAC names of the two enantiomers are (1S,2S)- respectively (1R,2R)-2-methylamino-1-phenylpropan-1-ol. Synonyms for both are psi-Ephedrine and threo-Ephedrine.

Pseudoephedrine is the International Nonproprietary Name (INN) of the (+)-form, when used as pharmaceutical substance.[9]

**Synthesis**

Although pseudoephedrine occurs naturally as an alkaloid in certain plant species (for example, as a constituent of extracts from the ephedra species, also known as Ma Huang, in which it occurs together with other isomers of ephedrine), the majority of pseudoephedrine produced for commercial use is derived from yeast fermentation of dextrose in the presence of benzaldehyde. In this process, specialized strains of yeast (typically a variety of *Candida utilis* or *Saccharomyces cerevisiae*) are added to large vats containing water, dextrose and the enzyme pyruvate decarboxylase (such as found in beets and other plants). After the yeast has begun fermenting the dextrose, the benzaldehyde is added to the vats, and in this environment the yeast convert the ingredients to the precursor l-phenylacetylcarbinol (L-PAC). L-PAC is then chemically converted to pseudoephedrine via reductive amination.[10]
The bulk of pseudoephedrine is produced by commercial pharmaceutical manufacturers in India and China, where economic and industrial conditions favor the mass production of pseudoephedrine for export.\[11\]

**Mechanism of action**

Pseudoephedrine is a sympathomimetic amine. Its principal mechanism of action relies on its indirect action on the adrenergic receptor system. The vasoconstriction that pseudoephedrine produces is believed to be principally an α-adrenergic receptor response.\[12\]

While it may have weak or no direct agonist activity at α- and β-adrenergic receptors, the principal mechanism is to cause the release of endogenous norepinephrine (noradrenaline) from storage vesicles in presynaptic neurons. The displaced noradrenaline is released into the neuronal synapse where it is free to activate the postsynaptic adrenergic receptors. These adrenergic receptors are located on the muscles lining the walls of blood vessels. When activated by pseudoephedrine, the muscles contract, causing the blood vessels to constrict (vasoconstriction). The constricted blood vessels now allow less fluid to leave the blood vessels and enter the nose, throat and sinus linings, which results in decreased inflammation of nasal membranes as well as decreased mucus production. Thus, by constriction of blood vessels, mainly those located in the nasal passages, pseudoephedrine causes a decrease in the symptoms of nasal congestion.

**Medical uses**

Pseudoephedrine shrinks swollen nasal mucous membranes. It reduces tissue hyperemia, edema, and nasal congestion commonly associated with colds or allergies. Other beneficial effects may include increasing the drainage of sinus secretions, and opening of obstructed Eustachian tubes. The same vasoconstriction action can also result in hypertension, which is a noted side effect of pseudoephedrine.

Pseudoephedrine can be used either as oral or as topical decongestant. The advantage of oral pseudoephedrine over topical nasal preparations, such as oxymetazoline, is that it does not cause rebound congestion (rhinitis medicamentosa). However, it is more likely to cause adverse effects, including hypertension, sweating, and anxiety.

Pseudoephedrine may be useful as antitussive drug (suppressing of cough).\[13\]

Pseudoephedrine may be administered as a single dose or a regimen of multiple doses. It has been shown in lab testing that the effects of Pseudoephedrine are both immediate and cumulative in nature and effect. While some patients have reported relief of symptoms in as short as 45 minutes after taking the drug, others have reported that continual administration of the drug has a more positive overall effect. That is to say that taking Pseudoephedrine for more than 1 or 2 days will get more noticeable results.

**Indications**

Pseudoephedrine is indicated for the treatment of:

- nasal congestion
- sinus congestion
- Eustachian tube congestion.\[14\]

Pseudoephedrine is also indicated for vasomotor rhinitis, and as an adjunct to other agents in the optimum treatment of allergic rhinitis, croup, sinusitis, otitis media, and tracheobronchitis.\[14\]

Pseudoephedrine is also used as first-line therapy of priapism. Erection is largely a parasympathetic response, so the sympathetic action of pseudoephedrine may serve to relieve this condition.

Treatment for urinary incontinence is an off-label use (a.k.a. "unlabeled use") for these medications.\[15\]
Pseudoephedrine

Adverse effects

Common adverse drug reactions (ADRs) associated with pseudoephedrine therapy include: CNS stimulation, sleepiness, nervousness, excitability, dizziness and anxiety. Infrequent ADRs include: tachycardia and/or palpitations. Rarely, pseudoephedrine therapy may be associated with hallucinations, arrhythmias, hypertension, seizures and ischemic colitis;\textsuperscript{[16]} as well as severe skin reactions known as recurrent pseudo-scarlatina, systemic contact dermatitis, and nonpigmenting fixed drug eruption.\textsuperscript{[17]} Pseudoephedrine, particularly in high doses, may also cause episodes of paranoid psychosis.\textsuperscript{[18]} It has also been reported that pseudoephedrine, amongst other sympathomimetic agents, may be associated with the occurrence of stroke.\textsuperscript{[19]}

Precautions and contraindications

It is recommended that pseudoephedrine not be used in patients with: diabetes mellitus, cardiovascular disease, hypertension, prostatic hypertrophy, hyperthyroidism, closed angle glaucoma, or those who are pregnant.\textsuperscript{[16]} Patients who are prone to anxiety or panic attacks should use pseudoephedrine with caution, as anxiety and restlessness are common side effects, mostly due to the drug’s stimulant properties.

Since nasal congestion is considered to be a relatively minor ailment, alternatives are preferred in patients with these conditions. Appropriate alternatives may include saline sprays/instillations, depending on the patient’s condition. Topical decongestants should be used with caution and for no longer than three days to avoid Rhinitis medicamentosa.

Contraindications for the use of pseudoephedrine include: concomitant or recent (previous fourteen days) monoamine oxidase inhibitor (MAOI), severe or uncontrolled hypertension, and/or severe coronary artery disease.\textsuperscript{[16]}

People with bipolar disorder should use care when taking pseudoephedrine, as it can cause insomnia and thus trigger a manic episode.

Common brand names

Sudafed is a trademark for a common brand that contains pseudoephedrine, although Sudafed PE does not contain it. The following are some brand names of medications that contain pseudoephedrine. Some of them no longer contain it but contain phenylephrine instead.

- Sudafed (Johnson & Johnson [formerly Pfizer])
- Actifed (Burroughs Wellcome)
- Contac (GlaxoSmithKline) - contains pseudoephedrine HCL.
- Claritin-D - contains Loratadine along with pseudoephedrine.
- Zyrtec-D 12 Hour - contains pseudoephedrine HCL as well as cetirizine HCL.
- MucinexD - contains 120 mg pseudoephedrine and 1200 mg guaifenesin, an expectorant.
- Eltor (Sanofi Aventis)
- Allegra D (Sanofi Aventis) - contains fexofenadine along with pseudoephedrine.
Alternative and illicit use

There have been reports of off-label uses of pseudoephedrine for its stimulant properties. Long-distance truck drivers and sports athletes, for example, have reportedly used pseudoephedrine as a stimulant to increase their state of alertness/awareness.

The similarity in chemical structure to the amphetamines has made pseudoephedrine a sought-after chemical precursor in the illicit manufacture of methamphetamine and methcathinone. As a result of the increasing regulatory restrictions on the sale and distribution of pseudoephedrine, many pharmaceutical firms have reformulated, or are in the process of reformulating medications to use alternative, but less effective, decongestants, such as phenylephrine.

Many retailers such as Target, Walgreens, CVS, and Winn-Dixie have created corporate policies restricting the sale of pseudoephedrine-containing products. Their policies restrict sales by limiting purchase quantities and requiring a minimum age with proper identification. These requirements are similar to and sometimes more stringent than existing law. Internationally, pseudoephedrine is listed as a Table I precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

Sports

Pseudoephedrine was on the banned substances IOC list until 2004, when the WADA list replaced the IOC list. Although WADA initially only monitored pseudoephedrine, it is once again on the banned list starting January 1, 2010. Romanian gymnast Andreea Răducan was stripped of her gold medal at the 2000 Sydney Olympics after testing positive. She took two pills given to her by the team coach for a cold. Although she was stripped of the overall gold medal, she kept her other medals, and, unlike in most other doping cases, was not banned from competing again; only the team doctor was banned for a number of years. Ion Țiriac, the president of the Romanian Olympic Committee, resigned over the scandal.

Detection of use

Pseudoephedrine may be quantitated in blood, plasma or urine to monitor possible abuse by athletes, confirm a diagnosis of poisoning or assist in a medicolegal death investigation. Many commercial immunoassay screening tests directed at the amphetamines cross-react appreciably with pseudoephedrine, but chromatographic techniques can easily distinguish pseudoephedrine from other phenethylamine derivatives. Blood or plasma pseudoephedrine concentrations are typically in the 50-300 µg/L range in persons taking the drug therapeutically, 500-3000 µg/L in abusers or poisoned patients and 10–70 mg/L in cases of acute fatal overdosage.

National legislation

Australia

Illicit diversion of pseudoephedrine in Australia has caused significant changes to the way pseudoephedrine products are regulated. As of 2006, all products containing pseudoephedrine have been rescheduled as either "Pharmacist Only Medicines" (Schedule 3) or "Prescription Only Medicines" (Schedule 4), depending on the amount of pseudoephedrine in the product. A Pharmacist Only Medicine may only be sold to the public if a pharmacist is directly involved in the transaction. These medicines must be kept behind the counter, away from public access.

Pharmacists are also encouraged (and in some states required) to log purchases with the online database PROJECTSTOP. This system aims to prevent individuals from purchasing small quantities of pseudoephedrine from many different pharmacies.

As of April 2007, the Australian government is considering the prohibition of all medications containing pseudoephedrine.
Mexico

On November 23, 2007, the use and trade of Pseudoephedrine in Mexico was made illicit, as it was argued that pseudoephedrine was extremely popular as a precursor in the synthesis of methamphetamine.

New Zealand

In New Zealand, from 15 October 2004, as a result of large intercepts of pseudoephedrine and ephedrine, any product containing these substances e.g. cold and flu medicines were classified as Class C Part III (partially exempted) controlled drugs in the Misuse of Drugs Act 1975. New Zealand Customs and police officers are continuing to make large interceptions of precursor substances believed to be destined for methamphetamine production. On 9 October 2009 Prime Minister John Key announced that pseudoephedrine-based cold and flu tablets would become prescription-only drugs and reclassified as a class B2 drug. The Misuse of Drugs Amendment Bill 2010 has not yet been finalised.

United Kingdom

In the UK pseudoephedrine is available on prescription or over the counter under the supervision of a qualified pharmacist. As of 2009 UK pharmacies sell Sudafed (pseudoephedrine hcl) in 12 tablet pack size containing 60 mg per pill. There is not a major problem with pseudoephedrine diversion or methamphetamine use in the UK.

United States

The United States Congress has recognized that pseudoephedrine is used in the illegal manufacture of methamphetamine. In 2005, the Committee on Education and the Workforce heard testimony concerning education programs and state legislation designed to curb this illegal practice.

Congress passed the Combat Methamphetamine Epidemic Act of 2005 ("CMEA") as an amendment to the renewal of the USA PATRIOT Act. Signed into law by president George W. Bush on March 6, 2006, the act amended 21 U.S.C. § 830, concerning the sale of pseudoephedrine-containing products. The law mandated two phases, the first needing to be implemented by April 8, 2006 and the second phase to be completed by September 30, 2006. The first phase dealt primarily with implementing the new buying restrictions based on amount, while the second phase encompassed the requirements of storage, employee training, and record keeping. Though the law was mainly directed at pseudoephedrine products it also applies to all over the counter products containing:ephedrine, pseudoephedrine, and phenylpropanolamine, their salts, optical isomers, and salts of optical isomers. Pseudoephedrine was defined as a "scheduled listed chemical product" under 21 U.S.C. § 802 (45(A)). The act included the following requirements for merchants ("regulated sellers") who sell such products:

- Required a retrievable record of all purchases, identifying the name and address of each party, to be kept for two years
- Required verification of proof of identity of all purchasers
- Required protection and disclosure methods in the collection of personal information
- Required reports to the Attorney General of any suspicious payments or disappearances of the regulated products
- Required training of employees with regard to the requirements of the CMEA. Retailers must self-certify as to training and compliance.
- The non-liquid dose form of regulated products may only be sold in unit dose blister packs
- Regulated products must be stored behind the counter or in a locked cabinet in such a way as to restrict public access
- Daily sales limit—must not exceed 3.6 grams of pseudoephedrine base without regard to the number of transactions
- 30-day (not monthly) sales limit—must not exceed 7.5 grams of pseudoephedrine base if sold by mail order or "mobile retail vendor"
• 30-day purchase limit—must not exceed 9 grams of pseudoephedrine base. (A misdemeanor possession offense under 21 U.S.C. § 844a[36] for the person who buys it.)

In regards to the identification that may be used by an individual buying pseudoephedrine products the following constitute acceptable forms of identification:

• US passport
• Alien registration or permanent resident card
• Unexpired foreign passport with temporary I-551 stamp
• Unexpired Employment Authorization Document
• Driver's License or Government issued identification card (including Canadian driver's license)
• School ID with picture
• Voter's Registration card
• US Military Card
• Native American tribal documents

[34]

Forty-one states also have laws regulating pseudoephedrine.

Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawai'i (as of May 1, 2009) Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana (as of August 15, 2009)[37] Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nevada, New Hampshire, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia and Wisconsin have laws requiring pharmacies to sell pseudoephedrine "behind the counter" and to collect personal information from purchasers.

Oregon and Mississippi require a prescription for the purchase of products containing pseudoephedrine,[38] as do certain pharmacies in Terre Haute, Indiana.[39]

See also

• Ephedrine
• Phenylpropanolamine
• Amphetamine
• Methamphetamine
• Phenylephrine
• Sudafed

References

[2] http://www.whocc.no/atc_ddd_index/?code=R01BA02
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