Ephedrine

Jin-Hua Wang, Xiu-Ying Yang, and Guan-Hua Du

Abstract Ephedrine, also called ephedrine ingot, L-ephedrine, is from dry grass stems of ephedra plants such as ephedra, Zhong ephedra, and Equisetum ephedra. Ephedrine is a white needle-like crystal or crystalline powder and odorless. It is soluble in water and can be dissolved in ethanol but is insoluble in chloroform or ether. Dosage forms of ephedrine are mainly tablets, injections, and eye drops, and they were used widely in clinical practice. Ephedrine was first isolated from the herb "Shuanghui Ephedra" in 1885. Ephedrine was successfully synthesized in 1920. In 1926, ephedrine was approved in clinical practice by the FDA of the United States. Structure of ephedrine was defined in 1926. Ephedrine hydrochloride was used for the treatment of bronchial asthma, hypotension, and central excitation. The side effects of ephedrine hydrochloride are anxiety, insomnia, palpitations, sweating, and other symptoms. Ephedrine is rarely used for asthma treatment now.

Keywords Ephedrine · Asthma · Drug tolerance · Addiction

Alias: Ephedrine, ephedrine ingot, levapedin
Origin: *Ephedra sinica* Stapf (Fig. 1)
Chemical name (Fig. 2)

(R,S)-2-(methylamino)-1-phenylpropan-1-ol

Molecular formula, $C_{10}H_{15}NO$; **MW**, 165; **CAS**, 299-42-3
Ephedrine derivative (Fig. 3)

Molecular formula, $C_{10}H_{15}NO{\cdot}HCl$; **MW**, 201.7; **CAS**, 134-71-4

J.-H. Wang · X.-Y. Yang · G.-H. Du (✉)
Beijing Key Laboratory of Drug Targets Identification and Drug Screening, National Centre for Pharmaceutical Screening, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
e-mail: dugh@imm.ac.cn

G.-H. Du, *Natural Small Molecule Drugs from Plants*,
https://doi.org/10.1007/978-981-10-8022-7_38

Properties

Appearance: a white needle-like crystal or crystalline powder, odorless, and tastes bitter. *Solubility*: soluble in water and can be dissolved in ethanol but insoluble in chloroform or ether. *Melting point*: 217–220 °C.

Dosage Form and Indications

This product was recorded in the *Pharmacopoeia of the People's Republic of China* (2015), the *British Pharmacopoeia* (2017), the *United States Pharmacopeia* (40), the *Indian Pharmacopoeia* (2010), the *European Pharmacopoeia* (9th ed.), and *The International Pharmacopoeia* (5th ed.).

Dosage forms are mainly tablets, injections, and eye drops.

Ephedrine was clinically used in three aspects: (1) prevention for bronchial asthma and relief of mild asthma, (2) treatment for subarachnoid anesthesia or epidural anesthesia caused by low blood pressure and chronic hypotension, and (3) treatment of nasal congestions and swelling caused by nasal congestion.

Literature

Ephedrine is an alkaloid, which is from dry grass stems of ephedra plants such as ephedra, zhong ephedra, or ephedra (麻黄、中麻黄或木贼麻黄). Ephedra is an herb recorded in "Chinese Pharmacopoeia," which can be used for sweating and cold, adjustment of lung function, asthma, and swelling. Ephedrine can treat cold, chest tightness, bronchial asthma, and so on. Ephedra was used as a drug in China for more than 2000 years, which was recorded in history books of materia medica. Ephedra is also known as Longsa recorded in the book *Shen Nong's Herbal Classic of Materia Medica*, Bixiang recorded in the book *Another record by famous record*, and Gougu recorded in the book *Guang Ya*. Ephedra was firstly recorded in the book *Shen Nong's Classic of Materia Medica*. Ephedra tastes bitter and its color is yellow. In the book *Shen Nong's Materia Medica of 100 kinds of herbs*, ephedra was described as no tasteless, and ephedra reveals the pores of the skin, but also deep into the sputum and stop the blood, where the drug can't reach. Ephedra was used as Zuozhi medicine and widely used for the treatment of cold, skin diseases, ulcers, swelling and pain, and injury bruises during the Song, Jin, Yuan, Ming, and Qing dynasty. Ephedra was recorded in many books, such as *Compendium of Materia Medica*, *Synopsis of Prescriptions of the Golden Chamber*, *Treatise on Febrile Diseases Caused by Cold*, *Prescriptions Worth a Thousand in Gold for Every Emergency, Hua Zi all herbal medicine*, and *Theory on Drugs*.

History of R&D

In traditional Chinese medicine (TCM), ephedrine and pseudoephedrine are main active ingredients in "herbal ephedra" [1]. Organic chemist, Changi Changyi (1844–1929), from Japan first isolated ephedrine from the herb "Shuanghui Ephedra" in 1885 [2, 3]. Ephedrine was successfully synthesized by chemist Ernst Späth from Austria (1886–1946) in 1920 [4]. Kehui Chen (1898–1988) and its co-colleague Carl F. Schmidt extracted ephedrine from ephedra in 1923 [5] and then clarified the pharmacological effects of ephedrine, which attracted the attention from Europe and the United States. Ephedrine was approved in clinical practice by the FDA of the United States. Structure of ephedrine was analyzed by Changi Changyi in 1926.

Pharmacology

Ephedrine has a similar effect with adrenaline. Ephedrine can bind α, β receptors and activate the receptor as adrenaline. Ephedrine makes the adrenergic nerve endings release medium and indirectly play the role of adrenaline. Ephedrine is stable and its effect is weaker than adrenaline, and the central excitatory effect is more obvious. Ephedrine can relax bronchial smooth muscle but less durable than adrenaline. Ephedrine can also relieve bronchial spasm, excite the heart, enhance myocardial contractility, and speed up the heart rate. However, its role in increasing the heart rate may be weakened by the vagus nerve excitement caused by increased blood pressure [6]. Ephedrine accelerates heart rate and increases cardiac contractility by stimulating the beta receptor. Ephedrine stimulates the alpha receptor and contracts the arterial effect, but the contraction of the rabbit aorta is dominated by direct action. In recent years, ephedra has been found to have a role inhibiting the formation of acute blood clotting, promote fat synthesis in fat, and scavenge oxygen-free radicals.

Clinical Application

In clinical practice, ephedrine hydrochloride was used for the treatment of bronchial asthma, hypotension, central excitation [7], and toxicity by morphine and barbiturate. Ephedrine hydrochloride was also used to eliminate nasal mucosal congestion. Drug tolerance can occur quickly when ephedrine hydrochloride was used often in a short time. Ephedrine hydrochloride can also be used for hypotension and chronic hypotension caused by subarachnoid anesthesia or epidural anesthesia [8, 9]. The side effects of ephedrine hydrochloride are anxiety, insomnia, palpitations, sweating, and other symptoms by central excitement caused by the long-term use of large doses which can be cured by hypnotic sedative drugs. Acute drug tolerance can be induced by repeated use in short time.

Discussion

Efficacy of ephedrine lasts longer than adrenaline but the effect is poor. Ephedrine may be effective when the symptoms are mild. It is best to choose adrenaline when the symptoms are serious. Tremor, anxiety, insomnia, palpitations, and other symptoms can be caused by long-term repeated use of ephedrine, which can be reduced in combination with phenobarbital. Ephedrine is contraindicated in patients with hyperthyroidism, hypertension, atherosclerosis, and angina. Addiction and tolerance can be induced by long-term repeated use of ephedrine. Bogey, paclitaxel, and other monoamine oxidase inhibitors were forbidden to use with to prevent high blood pressure. As new drugs continue to emerge, ephedrine is rarely used for asthma treatment.

Fig. 1 *Ephedra sinica* Stapf

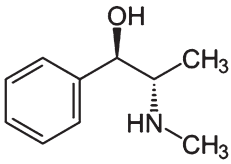

Fig. 2 Chemical structure of ephedrine

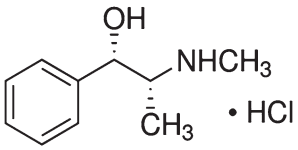

Fig. 3 Chemical structure of ephedrine hydrochloride

References

1. Botanical nomenclature, Shanghai, 1917;1004.
2. Lock M. East Asian medicine in urban Japan: varieties of medical experience. University of California Press; Reprint edition 1984. ISBN 0-520-05231-5.
3. Nagai N, Pharm Z 1887;xxxii: 700.
4. Späth E, Gökring R, Monatsh F. Chemistry. 1920;xli:319.
5. Chen K, Schmidt CF. J Pharmacol Exp Ther. 1924;xxiv:339.
6. Ruben JE, Kamsler PM, Howell WL Jr. The spinal anaesthetic effects of ephedrine sulfate: a preliminary report. Science. 1948;107(2774):223.
7. von Mutius E, Drazen JM. A patient with asthma seeks medical advice in 1828, 1928, and 2012. N Engl J Med. 2012;366(9):827–34.
8. Cannon C, Cowan F, Koppanyi T, et al. Explanation of cocaine desensitization of blood pressure responses to ephedrine. Science. 1961;134(3485):1075–7.
9. Eldaba AA, Amr YM. Intravenous granisetron attenuates hypotension during spinal anesthesia in cesarean delivery: a double-blind, prospective randomized controlled study. J Anaesthesiol Clin Pharmacol. 2015;31(3):329–32.