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Review

Applications of Higenamine in pharmacology and medicine

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ABSTRACT

Ethnopharmacological relevance: *Aconitum* has been used as local and traditional medicines in many asian regions for the treatment of various diseases such as collapse, syncope, painful joints, oedema, bronchial asthma et al. Higenamine, a plant-based alkaloid, was initially isolated from *Aconitum* and identified as the active cardiotonic component of *Aconitum*. It has been tested as a candidate of pharmacologic stress agent in the detection of coronary artery diseases (CADs) and now researchers have just accomplished the phase III clinical studies successfully in China. Besides, a large number of studies have revealed the various pharmacological properties and potentially multi-spectral medical applications of higenamine. However, to date, no comprehensive review on higenamine has been published.

Aim of the review: This present paper aims to compile a comprehensive update regarding the biochemistry, pharmacokinetic features, pharmacological activities, clinical and potential clinical uses and toxicities on higenamine with the ultimate objective of providing a guide for future research on this drug.

Materials and methods: The selection of relevant data was made through a search using the keyword "higenamine" in "Web of science", "Pubmed", and "China Knowledge Resource Integrated (CNKI)". Information was also acquired from local classic herbal literature, government reports and conference papers.

Results: In addition to *Aconitum*, higenamine also exists in many other plants including *Tinospora crispa*, *Nandina domestica* T$_{HUNBERG}$, *Gnetum Parvifolium* C.Y. Cheng, *sarum Heterotropoides*¸*Nelumbo nucifera*¸*N.nucifera*. The pharmacokinetic studies conducted in animals and humans showed that higenamine conformed to a two-compartment pharmacokinetic model. Studies over the last four decades on higenamine have revealed its various pharmacological properties such as positive inotropic and chronotropic effect, activating slow channel effect, vascular and tracheal relaxation effect, anti-thrombotic, anti-apoptotic and anti-oxidative effect, anti-inflammatory and immunomodulatory effect. This phytochemical constituent has shown its potential therapeutic effects for diseases like heart failure, disseminated intravascular coagulation (DIC), shock, arthritis, asthma, ischemia/reperfusion (I/R) injuries and erectile dysfunction.

Conclusions: Extensive basic and clinical studies on higenamine showed valuable therapeutic effects on different disorders. However, the underlying mechanisms of higenamine have not been established. Therefore, the safety, tolerability and efficacy of higenamine are as yet, not fully understood. Additionally, some of the studies were small sample-sized and unreliable. To sum up, there is a need for deeper investigation in the mechanisms of higenamine action, as well as well-designed preclinical and clinical trials studies to test the safety and clinical value of the drug.

Abbreviations: CAD, coronary artery diseases; DIC, disseminated intravascular coagulation, I/R, ischemia/reperfusion; MPI, myocardial perfusion imaging; SCI, spinal cord injury; ED, erectile dysfunction; AUC, area under the concentration-time curve; cAMP, cyclic adenosine monophosphate; LV, left ventricular; dP/dt_{max}, the maximal rate of pressure rise; TXA_2, thromboxane A_2; TP receptor, thromboxane A_2 receptor; ADP, adenosine 5'-diphosphate dicyclohexylammonium salts; HO-1, heme oxygenase-1; Nrf-2, nuclear factor-erythroid 2-related factor 2; PI3K, phosphatidyl inositol-3 kinase; NO, nitric oxide; iNOS, inducible NO synthase; LPS, lipopolysaccharide; INF, interferon; NF-κB, nuclear factor κB; IL, interleukin; SBP, systolic blood pressure; DPB, diastolic blood pressure; AV, articuloventricular; SSS, sick sinus syndrome; ROS, reactive oxygen species; LPS, lipopolysaccharide; cGMP, cyclic guanosine monophosphate; CC, corpus carvernosum; PDE5, phosphodiesterase type-5; HMGB-1, high mobility group box-1; LD50, lethal dose 50%

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1. Introduction

Plant species are considered to be potential reservoirs for the modern drug discovery due to the effectiveness and safety based on millennia of medical practice and experience (Ngo et al., 2013; Yuan et al., 2016). Higenamine, also known as Norcoclaurine or *dl*-demethylcoclaurine, is a plant-based alkaloid which belongs to the structural class of protoberberines. It was initially isolated as the active cardiotonic component from *Aconitum* by Kosuge in 1976 (Kosuge and Yokota, 1976). In China and Japan, the folk medicine *Aconitum japonicum Thunb. In J.A.Murray (Family Ranunculaceae)*, a source of higenamine, has been a wildly used for centuries to treat collapse, syncope, rheumatic fever, painful joints, gastroenteritis, diarrhea, edema, bronchial asthma, various tumors, and some endocrinal disorders like menoxenia (Singhuber et al., 2009). This alkaloid is also present in many other plants, including *Tinospora crispa (L.) Hook.f. & Thomson belonging to the genus Tinospora of Menispermaceae family,* mainly used as an antipyretic (Ahmad et al., 2016), *Nandina domestica* Thunb (Family Berberidaceae) and *GnetumParvifolium* (Warb.) C.Y. Cheng (Family Gnetum), traditionally applied for the treatment of respiratory disease (Ueki et al., 2011; Xu and Lin, 1999), *Asarum heterotropoides F.Schmidt (Family Aristolochiaceae),* commonly used to treat stomatitis, toothache, gingivitis and rheumatic arthralgia (Li et al., 2010).

Since 1976, higenamine has drawn extensive attention as a potent inotropic and chronotropic agent. At present, higenamine has been demonstrated by clinical investigations to hold promising future as a pharmacological stress agent for myocardial perfusion imaging (MPI) and researchers has successfully accomplished the related phase III clinical trial studies in China (Ma Jixiao, 2011). Interestingly, studies over the years on higenamine have revealed other various pharmacological properties and medical uses that are beneficial in the treatment of acute ailments or diseases, such as bradyarrhythmia, disseminated intravascular coagulation **(**DIC), sepsis, heart failure, ischemia/reperfusion (I/R) injuries, spinal cord injury (SCI) , arthritis , breathing difficulties , erectile dysfunction (ED). Thus, the drug has emerged as a medicinal agent with multispectral activities. However, to date, no comprehensive review on higenamine has been published.

This review attempts to summarize the biochemistry and pharmacokinetic picture of higenamine. The underlying mechanisms and involved pathways reflecting the multispectrum activity of higenamine were also discussed. Central focus has been maintained on the studies conducted to explore the applicability of higenamine in various diseases with the help of continuously growing evidence. The toxic profile of higenamine has also been included in this review.

2. Biochemistry

Higenamine is [1-(4′-hydroxybenzyl)−6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline] (Box 1). Its empirical formula is C16H17NO3, and its molecular weight is 271.272. Higenamine is a chiral compound with one asymmetric carbon, and it is expected that higenamine is actually a racemic mixture of two enantiomers, (S)-(-)-higenamine and (R)-(+)-higenamine. In addition to *Aconitum*, higenamine can be isolated as optically inert racemic mixture enantionmer from *Tinospora crispa* (Praman et al., 2013), *Nandina domestica* $T_{HUNBERG}$(ND)(Ueki et al., 2012), *Gnetum Parvifolium* (Warb.) C.Y. Cheng (Jurong Ye et al., 1980), and *Asarum Heterotropoides* (Chen Zhenzhong et al., 1981), except (R)-(+)-higenamine from embryo of *Nelumbo nucifera* (Lin et al., 2014) and (S)-(-)-higenamine from the leaves of *N.nucifera* (Kashiwada et al., 2005). However, higenamine is now mostly manufactured by chemical synthesis in industry (Huang et al., 1981). And its chloride salt is generally used for clinical purposes since this salt form is relatively more soluble in water. Higenamine hydrochloride is a very stable molecule with an intensive white powder appearance.

3. Pharmacokinetics

The pharmacokinetics of higenamine has been studies in dogs, rabbits and humans (Table 1). One study showed that higenamine exhibited linear pharmacokinetics with a two-compartment open model. After intravenous administration in rabbits, higenamine exhibited a mean residence time of approximately 9 min and a terminal elimination half-life of approximately 22 min that was independent of dose (Lo and Chen, 1996). Peak plasma concentration occurred at the end of the infusion. The means of total body clearance of higenamine was 127.7 mL/min/kg. Area under the concentration-time curve (AUC) increased in proportion with increasing dosage. Their study also demonstrated that plasma protein binding rate of higenamine was about 54%. There did not appear to be any significant differences in pharmacokinetic parameters between single and continuous intravenous infusions (Lo and Chen, 1996). Zheng et al. (Zheng Ying-li et al., 2004) conducted another the pharmacokinetics of higenamine with intravenous infusion in dogs. In their studies, the terminal half-life of higenamine was 8.6 min after intravenous injection, which was different from that in rabbit, suggesting that the pharmacokinetics of higenamine may vary in different animal species.

The oral route pharmacokinetics of higenamine was evaluated by Lo et al. (Lo and Chen, 1996). In a rabbit model, oral higenamine was absorbed rapidly. Time to peak concentrations was about 10 min after oral administration. The terminal half-life of oral higenamine is approximately 20 min, similar to that given intravenously. Poor bioavailability was observed in oral route. The average absolute bioavailability of higenamine after an oral dose calculated by AUC and accumulated urinary excretion were about 21.86% and 2.84%, respectively (Lo and Chen, 1996).

Sheng et al. (Feng et al., 2012b) conducted a pharmacokinetics study of higenamine in ten healthy human volunteers, with intravenous infusion of 22.5 μg/kg. Their results also showed that higenamine conformed to a two-compartment pharmacokinetic model. The distribution volume of higenamine was 18.7 l and 43.0 l (at steady-state), and the estimated clearance was 3.8 l/min, indicating that higenamine could be quickly eliminated from the body. The mean half-life of higenmine was 8.0 min. Ninety-four percent of higenamine can be eliminated from body within 30 min. Their study showed that higenamine was not mainly eliminated through renal excretion (only 9.3% of total elimination), and the liver seemed to play a more important role, but a definite conclusion had to be confirmed by further studies (Feng et al., 2012b). The current data did not show the correlation between the model estimates and various baseline patient demographics. Whether fixed dose administration is suitable for higenamine also needs to be further studied.

The rapid distribution, dose-independent elimination and stable pharmacokinetics of higenamine suggest favorable characteristics of higenamine for intravenous application in some short-term clinical settings.

4. Pharmacology

4.1. Receptor interactions

Higenamine is usually believed to be a partial agonist of β-adrenergic receptor. Evidence to support this opinion includes: (1) Higenamine has showed positive inotropic and chronotropic effect *in vivo* and *in vitro* (Kimura et al., 1994). And the cardiotonic effect of higenamine could be inhibited by β-blocker, propranolol (Park et al., 1984). (2) Higenamine could increase the plasma cyclic adenosine monophosphate (cAMP) content in mice in a dose dependent manner. The increase of cAMP in plasma induced by higenamine could also be blocked by propranolol (Feng et al., 1981). (3) The experiment conducted in turkey erythrocyte membrane showed that higenamine exhibited concentration-depended stimulating effects on adenylate