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Review Article

Aconite: A pharmacological update

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ABSTRACT

Aconitine (Queen of Poisons) and related alkaloids found in the Aconitum species are highly toxic cardiotoxins and neurotoxins. Aconite is a herbaceous perennial plant, chiefly native of the northern hemisphere, growing in moisture retentive but well-draining soils of the mountain meadows. At present, more than 120 species of the plant have been found. Severe aconite poisoning occurs after accidental ingestion of the wild plant or consumption of an herbal decoction made from aconite roots. This review paper discusses some of the pharmacological activities of the aconite plant and its chief constituent aconitine. The effect of KB-R7943, the sodium-calcium exchange (NCX) blocker, on aconitine-induced arrhythmias in Guinea pigs using the ECG recordings suppressed abnormal electrical activity, but SEA did not show such effects. Aconitine also mediates the phosphorylation status of Cx43 and PKCα in the cultured ventricular myocytes of neonatal rats. These reports collected are very encouraging and indicate that the plant should be studied more expensively for its therapeutic benefits.

Keywords: Aconite; Aconitine; Anti-inflammatory; Arrhythmia; Phosphorylation; Poisoning

INTRODUCTION

Aconitum, known as aconite, monkshood, wolfsbane, leopard's bane, women's bane, Devil's helmet or blue rocket, is a genus of over 250 species of flowering plants belonging to the buttercup family, Ranunculaceae. Aconitine is a highly poisonous alkaloid derived from various aconite species.

Aconite is a herbaceous perennial plant, chiefly native of the northern hemisphere, growing in moisture retentive but well-draining soils of the mountain meadows. Their dark green leaves lack stipules. They are palmate with 5-7 segments, each of which is 3-lobed with coarse sharp teeth. The leaves are spirally arranged, and the lower leaves possess long petioles. The tall, erect stem is crowned by racemes of large blue, purple, white, yellow or pink zygomorphic flowers with numerous stamens. There are 2-10 petals in the form of nectaries.

Aconitine, the chief constituent of *Aconitum* species, is soluble in chloroform or benzene, slightly in alcohol or ether, and very slightly in water. The Merck Index gives LD_{50s} (i.e., median lethal dose 50%) for mice: 0.166 mg/kg (intravenously); 0.328 mg/kg intraperitoneally (injected into the body cavity); approx. 1 mg/kg orally (ingested). In rats, the oral LD_{50} is given as 5.97 mg/kg.

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Oral doses as low as 1.5–6 mg aconitine was reported to be lethal in humans (en.wikipedia.org, 2011).

TAXONOMY (www.zipcodezoo.com, 2011)

Domain: Eukaryotae

Kingdom: Plantae

Subkingdom: Viridaeplantae

Phylum: Tracheophyta

Subphylum: Euphyllophytina

Infraphylum: Radiatopses

Class: Magnoliopsida

Subclass: Ranunculidae

Superorder: Ranunculanae

Order: Ranunculales

Family: Ranunculaceae

Subfamily: Trollioideae

Genus: Aconitum

MORPHOLOGY

Genus Aconitum

Herbs: Perennial; tubers or roots.

Roots: Elongate fascicled.

Leaves: Basal and cauline; proximal leaves petiolate; distal leaves sessile; cauline leaves alternate. Leaf blade palmately divided into 3-7 segments; ultimate segments narrowly elliptic or lanceolate to linear; margins incised and toothed.

Inflorescence: Terminal or axillary; 1-32 racemes or panicles, to 28 cm; bracts leaf like, not forming involucre.

Flowers: Bisexual; bilaterally symmetric; sepals not persistent in fruit; lowersepals (pendents) 2, plane, 6-20mm, lateral sepals 2, round-reniform; upper sepal (hood) 1, saccate, arched, crescent-shaped or hemispheric to rounded-conic or tall and cylindrical, usually beaked, 10-50mm; petals 2, distinct, bearing near the apex a capitate, to be coiled spur, concealed in hood, long-clawed; nectary present, on spur; stamens 25-50; filaments with base expanded; staminodes absent between stamens and pistils; pistils 3-5, simple; ovules 10-20 per pistil; style present.

Fruits: Follicles aggregate, sessile, oblong; sides prominently transversally veined; beak terminally, straight, 2-3mm.

Seeds: Deltoid, usually with small, transverse, membranous lamellae, x=8 (www.zipcodezoo.com, 2011).

Figure 1: ***Aconitum delphinifolium***

Figure 2: ***Aconitum variegatum***

Figure 3: ***Aconitum napellus***

Figure 4: ***Autumn Aconitum***

SPECIES

Aconitum ajanense

Aconitum albo-violaceum

Aconitum altaicum

Aconitum ambiguum

Aconitum angusticassidatum

Aconitum uncinatum (Southern Blue Monkshood)

Aconitum umbrosum

Aconitum variegatum

Aconitum anthora (Yellow Monkshood)

Aconitum anthoroideum

Aconitum album

Aconitum axilliflorum

Aconitum baburinii

Aconitum baicalense

Aconitum barbatum

Aconitum besserianum

Aconitum biflorum

Aconitum bucovinense

Aconitum burnatii

Aconitum carmichaelii' (Carmichael's Monkshood)

Aconitum charkeviczii

Aconitum chasmanthum

Aconitum chinense

Aconitum carmichaelii var. truppelianum

Aconitum cochleare

Aconitum columbianum (Western Monkshood)

Aconitum confertiflorum

Aconitum consanguineum

Aconitum coreanum

Aconitum crassifolium

Aconitum nasutum

Aconitum cymbulatuz

Aconitum czekanovskyi

Aconitum decipiens

Aconitum degenii (syn. A. variegatum ssp. paniculatum)

Aconitum delphinifolium (Larkspurleaf Monkshood)

Aconitum desoulavyi

Aconitum ferox (Indian Aconite)

Aconitum firmum

Aconitum fischeri (Fischer Monkshood)

Aconitum flerovii

Aconitum gigas

Aconitum gracile (synonym of A. variegatum ssp. variegatum)

Aconitum helenae

Aconitum hemsleyanum (Climbing Monkshood)

Aconitum hosteanum

Aconitum infectum (Arizona Monkshood)

Aconitum jacquinii (synonym of A. anthora)

Aconitum jaluense

Aconitum jenisseense

Aconitum karafutense

Aconitum karakolicum

Aconitum maximum (Kamchatka Aconite)

Aconitum miyabei

Aconitum moldavicum

Aconitum montibaicalense

Aconitum nanum

Aconitum nemorum

Aconitum neosachalinense

Aconitum kirinense

Aconitum volubile

Aconitum noveboracense (Northern Blue Monkshood)

Aconitum ochotense

Aconitum orientale

Aconitum paniculatum

Aconitum paradoxum

Aconitum pascoi

Aconitum pavlovae

Aconitum pilipes

Aconitum plicatum

Aconitum podolicum

Aconitum productum

Aconitum pseudokusnezowii

Aconitum puchonroenicum

Aconitum raddeanum

Aconitum ranunculoides

Aconitum reclinatum (Trailing White Monkshood)

Aconitum rogoviczii

Aconitum romanicum

Aconitum rotundifolium

Aconitum rubicundum

Aconitum sachalinense

Aconitum sajanense

Aconitum saxatile

Aconitum sczukinii

Aconitum septentrionale

Aconitum seravschanicum

Aconitum krylovii

Aconitum kunasilense

Aconitum kurilense

Aconitum kusnezoffii (Kusnezoff Monkshood)

Aconitum kuzenevae

Aconitum lamarckii

Aconitum lasiostomum

Aconitum leucostomum

Aconitum longiracemosum

Aconitum lycoctonum

Aconitum macrorhynchum

Aconitum tanguticum

Aconitum tauricum

Aconitum turczaninowii

Aconitum vulparia (Wolfsbane)

Aconitum woroschilovi

Aconitum sichotense

Aconitum smirnovii

Aconitum soongaricum

Aconitum stoloniferum

Aconitum stubendorffii

Aconitum subalpinum

Aconitum subglandulosum

Aconitum subvillosum

Aconitum sukaczevii

Aconitum taigicola

Aconitum talassicum

Aconitum napellus' (Monkshood; type species)

NATURAL HYBRIDS

Aconitum × austriacum

Aconitum × cammarum

Aconitum × hebegynum

Aconitum × oenipontanum (A. variegatum ssp. variegatum × ssp. paniculatum)

Aconitum × pilosiusculum

Aconitum × platanifolium (A. lycoctonum ssp. neapolitanum × ssp. vulparia)

Aconitum × zahlbruckneri (A. napellus ssp. vulgare × A. variegatum ssp. variegatum)

ACONITINE POISONING

It is quickly absorbed via mucous membranes, but also via skin. Respiratory paralysis, in very high doses also cardiac arrest, leads to death. A few minutes after ingestion paresthesia starts, which includes tingling in the oral region. This extends to the whole body, starting from the extremities. Anesthesia, sweating and cooling of the body, nausea and vomiting and other similar symptoms follow (en.wikipedia.org, 2011).

PHARMACOLOGICAL ACTIVITIES

Aconitine-induced arrhythmias

To induce electrical abnormality, a studied was performed in which aconitine (1 μM) dissolved in Tyrode's solution containing 1.8 mM Ca^{2+}, was perfused. Electrical abnormality appeared within 1 min after perfusion of aconitine solution (25.0 g/kg) after treatment with SEA (2-[4-[(2,5-difluorophenyl) methoxy] phenoxy]-5-ethoxyaniline) (1-10mg/kg) & KBR (2-[2-[4-(4-nitrobenzyloxyl)phenyl]ethyl] isothioureamethansulfonate) (1-30 mg/kg) (Shah A *et al.,* 2004; Adaniya H *et al.,* 2004; Ameri A, 1998; Amran MS *et al.,* 2003; Catterall WA, 1980; Catterall WA, 1988; Honerjager P *et al.,* 1983; Iwamoto T *et al.,* 1986).

The effects of Cl^- channel blockers 5-nitro-2-(3 phenylpropylamino) benzoic acid (NPPB) and niflumic acids (NFA) were investigated on Langendorff-perfused rat hearts. Addition of the Na^+ channel agonist aconitine (0.1 μM) to the perfusion solution produced polymorphic ventricular arrhythmias with a latent period of 25.5 ± 6.3 sec NPPB (5-nitro-2-(3-phenyl propylamino) benzoic acid) and NFA (niflumic acid) reversibly depressed the upstroke of the AP in a dose-dependent manner with IC_{50} values of ∼12.3 and ∼73.1 μM, respectively (Zhou S *et al.,* 2005; Accili EA *et al.,* 1996).

Aconitine-mediated phosphorylation

The band intensity of phosphorylated Cx43 & non-phosphorylated Cx43 in cultured and aconitine-treated cardiomyocytes of neonatal rats were determined by Western blot analysis. The changes in phosphorylation status occurring in PKCα in cultures were revealed by quantitative immunofluorescent microscopy. A decreased band intensity (0.37±0.04) of phosphorylated Cx43 (P-Cx43) and a concomitant increased band intensity (3.56 ± 0.65) of non-phosphorylated Cx43 (NP-Cx43) were found, compared to the controls (1.00 for P-Cx43 and NP-Cx43) (Liu Y *et al.,* 2011).

Anti-inflammatory activity

The anti-inflammatory activity of ethanolic root extracts of *Aconitum heterophyllum* (225, 450 and 900 mg/kg p.o) has been evaluated in cotton pellet-induced granuloma in rats. The extract has reduced inflammation as evidenced by decreased weight of cotton pellet in cotton pellet-induced granuloma in rats (Verma S *et al.,* 2010).

Enzyme Immunoassay

A reliable enzyme immunoassay (EIA) method was developed for quantitative determination of aconitine with high sensitivity and specificity. The bovine serum albumin (BSA) and β-galactosidase conjugates as im-

munogens and enzyme-labeled antigens were prepared by coupling of their proteins with succinic acid and hexadecanedioic acid. All combinations of β-galactosidase-labeled antigens LAg1 ($-CH_2$ = 52) and LAg2 ($-CH_2$ = 514) with antisera As1 ($-CH_2$ = 52) and As2 ($-CH_2$ = 514) showed high sensitivity to aconitine in a range of 0.1—1.0 ng, injected into rabbits. The oral administration of aconitine to rats at two doses of 0.1 and 1.0 mg/kg b.w., showed the maximum plasma concentrations (C_{max}) as 0.7360.08 and 3.360.6 ng/ml at times of 45±9 and 150±52 min, respectively (Tazawa T *et al.,* 2003).

CONCLUSION

Some of the pharmacological activities of aconite and its chief constituent aconitine were studied based on various research works done by different scientists worldwide. In aconitine-induced arrhythmia, the effect of KB-R7943(KBR; 10 μM), the sodium-calcium exchange (NCX) blocker, on aconitine-induced arrhythmias in Guinea pigs using the ECG recordings suppressed abnormal electrical activity, but SEA (100 μM) did not show such effects. In aconitine-mediated phosphorylation, after the aconitine treatment the amount of phosphorylated PKCα (P-PKCα) decreased significantly. Similar changes were revealed in phosphorylation status occurring in PKCα in the cultures revealed by dephosphorylation of Cx43 Western blot analysis. These observations suggest that aconitine not only induce, but also alter expression of P-PKCα in cultured cardiomyocyte.

In aconite–induced arrhythmia in rat heart, the Cl^- channel blockers and NFA reversibly depressed the upstroke of the AP in a dose-dependent manner, without significantly affecting the resting potential of rat ventricular myocytes. Both Cl^-channel blockers inhibited I_{Na} and induced a leftward shift of the steady-state inactivation of I_{Na}. This is an attempt to compile and document all possibly found activities of the plant which could prove to be helpful in various research and review aspects.

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