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Report on Appropriate Classification for Aconite (*Aconitum napellus*)

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Summary

An assessment of safety considerations with respect to human usage of complementary medicine preparations made from the substance **Aconite** (any part of the plant ***Aconitum napella***, otherwise known as ***Monkshood***), has been undertaken. The available toxicological data was reviewed, and levels of intake of the known toxic constituents, the alkaloids aconitine, mesaconitine and jesaconitine, known to be associated with adverse effects and possible fatality in humans, were determined.

From this assessment, concentration levels of the known toxic alkaloids below which no toxic effects would normally be associated with their internal ingestion or use, was determined. Levels of ingestion of these toxic components which could normally be deemed as completely safe, were then ascertained. This assessment was then applied to an evaluation of homoeopathic Aconite-containing preparations available in the marketplace, to select 'cut off points' below which general sales classification is deemed appropriate. These calculations were based upon both concentration levels of the toxic alkaloids, as well as the maximum recommended pack size of preparations containing them.

Aconite: an introduction

Aconite (a preparation made from either the roots or herb of the European shrub *Aconitum napellus*, or other *Aconitum* species), has long been used both as a traditional herbal medicine as well as a homoeopathic remedy. As a herbal medicine it is used predominantly for painful conditions such as

neuralgia, myalgia, arthritic complaints and migraine. This herbal use in most countries throughout Europe is restricted to the application of topical preparations, although aconite (*Aconitum sinensis*; *A. coreanum*) is still used internally for various painful conditions and as a 'cardiac tonic' in traditional Chinese Medicine (1). It is also used in experimental pharmacology, due to its ability to trigger cardiac arrhythmia.

In recent years however, aconite has become more used in homoeopathic medicine as opposed to herbal medicine (phytotherapy). Aconite-containing homoeopathic preparations have been extensively available in Europe since the early 1920's, and in New Zealand since the early 1950's. Their main uses include for acute inflammatory illnesses, hypertension, cardiac palpitations with anxiety states, feverish conditions, and for neuralgias (2,34).

Constituents:

Aconitum species contain potent diterpenoid ester alkaloids including aconitine (C₃₄H₄₇NO₁₁), mesaconitine, and jesaconitine. The structure of mesaconitine is closely related to aconitine and differs only from aconitine by a methyl group instead of an ethyl group at the nitrogen atom. N-desethyl aconitine, hyaconitin, oxoaconitine, benzoylaconine, aconine, neopelline, napelline, neoline, songorine, lappaconitine, and talatisamine are also present (3,4). About 30% of the total alkaloid is aconitine. While the diterpenes are of relatively low toxicity, the esterified norditerpene bases have higher toxicity (5).

These norditerpene alkaloids are reported as being present at levels ranging from about 0.3 to 2% of the total plant weight (6,2,3,5). The B.P.C. 1973 specifies not less than 0.5% of alkaloids, calculated as aconitine, and the minimum content specified by pharmacopoeias varies between 0.15 and 0.8% (7).

All parts of the plant contain these alkaloids, and it is likely that there is considerable chemical variation between different varieties of *Aconitum napellus*, as well as other members of the *Aconitum* genus (8,1). Their content and composition varies throughout the year, and alkaloid content is highest in the pre-flowering stage (Myers, 1998). More than 96 spp of *Aconitum* have been studied chemically, resulting in reports regarding over 250 different C19-diterpene alkaloids and a number of C20-diterpene alkaloids.

Coryneine chloride (dopamine methochloride), higenamine (a beta-adrenoceptor agonist), dopamine, noradrenaline and tyramine, have also been reported to occur in various species of *Aconitum* (11,12).

In Asia, Aconite rootstocks are generally processed by drying and soaking or boiling them in water, a process which apparently reduces the toxicity by producing less toxic derivatives (12).

Pharmacology of *Aconitum* alkaloids:

Pharmacokinetics

Aconitine is very rapidly absorbed after ingestion, usually within a few minutes. Dermal contact can also lead to rapid absorption through membranes and intact skin (7,5). Elimination of aconite alkaloids seems to be largely through the liver and kidneys (30).

Pharmacodynamics

Some *Aconitum* alkaloids including lappaconitine increase cardiac vagal afferent nerve activity and reflexly decrease cardiac sympathetic nerve activity, causing a decrease in heart rate and blood pressure (13). Anti-arrhythmic activity has been reported for lappaconitine (18).

Aconitine binds with high affinity to receptor site 2 of the voltage-sensitive Na⁺ channels, thereby causing persistent activation of these channels on cell membranes of different excitable tissues including myocardium, nerve and muscle (14,15,4). This sustained Na⁺ influx eventually leads to permanent depolarisation, inexcitability of the cells, and clinical symptoms of bradycardia, panconduction defect, syncope and ventricular arrhythmias (5,16).

Antinociceptive activity has been demonstrated for aconitine and mesaconitine in rats and mice (17,4), and these two compounds are thought to mainly contribute to the analgesic effect for which *Aconitum spp* are often used (19,4). Analgesic activity, which does not appear to involve interaction with opiate receptors (20), was not considered as suitable for drug development however, due to the narrow therapeutic index of these alkaloids (4,21).

Other central nervous system effects are also seen, including influences on catecholamine and serotonin levels in the cerebral cortex and medulla of rats (22), and inhibition of noradrenaline uptake in rat hippocampal pyramidal cells (23). Evidence of possible anticonvulsant activity has also been reported (24,25.), and hypoglycaemic activity is apparently shown by *Aconitum* roots (5).

Toxicology of aconite alkaloids

Cardiac toxicity and respiratory paralysis are the most serious adverse effects of excessive intake of aconite alkaloids (5,34). Toxicity is normally acute, and chronic toxicity is not expected (5).

Aconitine and mesaconitine appear to be the most toxic alkaloids, each with an LD₅₀ for **intravenous** doses in mice of around 0.1mg/kg, and doses as little as 0.005mg/kg producing toxicologically relevant symptoms (4, 18).

The estimated oral lethal dose of aconitine in a dog is 2 or 3mg, and in a horse, 10-12mg (Myers, 1998). In humans, the reported minimum lethal dose of orally ingested aconitine ranges from 2-6mg in different texts (34,2,5), although a report exists of accidental poisoning of two medical students by 5 to 10mg of aconitine, followed by recovery without treatment (26).

The 1949 edition of the B.P.C. lists an Aconite Tincture which contains 25% v/v *Aconitum napellus* root, and 0.05% w/v of alkaloids. The recommended dose range of this preparation was 0.12 to 0.3ml, which is equivalent to 0.06 to 0.15mg alkaloids. This preparation is no longer listed, and ingestion of levels as low as 0.2mg of aconitine has been associated with the development of severe symptoms (27).

One gram of fresh *Aconitum napellus* may contain 3-15mg of aconitine, and this plant has caused poisoning when eaten in a salad or when mistaken for radishes. Larkspur (*Delphinium* spp) has similar toxicity and contains a number of similar alkaloids, including delphinine and aconitine (18).

Symptoms of aconite poisoning may appear almost immediately and are rarely delayed beyond an hour; in fatal poisoning death usually occurs within 6 hours, although with larger doses it may be instantaneous. The effects produced by aconite poisoning are similar to that of veratrum alkaloids, except paraesthesias are generally more prominent and persistent. A burning sensation and tingling of the mouth, lips, tongue, and throat occur almost instantly, within 10-20 minutes. This is usually followed within 2-6 hours by nausea, salivation, violent emesis, generalised paraesthesias, weakness, and extreme pain. Colicky diarrhoea, skeletal muscle paralysis, cardiac rhythm disturbances and convulsions may follow in up to 8 hours (7,5). Death usually occurs within 6 hours as a result of direct paralysis of the heart or ventricular arrhythmias, but can also occur due to respiratory paralysis. (28,11).

Sinus bradycardia with first degree heart block, supraventricular tachycardia with hypotension, ventricular ectopics, bundle branch block, and junctional escape rhythms, ventricular tachycardia, and *torsade de pointes*, have all been reported (11,5,16,29). Hypotension, conduction delays and dysrhythmias usually begin within six hours of ingestion, but ST-T wave abnormalities and conduction delays may persist for several days (28).

Aconitine also stimulates the medullary centre of the C.N.S., which could contribute to bradycardia and reduction in blood pressure. A central action could also account for the appearance of hyperventilation and respiratory alkalosis in some patients following overdose (11).

The relative toxicity of individual *Aconitum* alkaloids appears to correlate with their affinities for Na⁺ channels, suggesting that Na⁺ channel modulation is responsible for intoxication (4). The aromatic ester group appears to be important for both the antinociceptive and toxic action (4).

Case reports of Aconite toxicity

Several reports of poisoning subsequent to ingestion of *Aconitum*-containing preparations have been documented, mainly from Japan and Hong Kong, but also from India and Italy.

In a recent Japanese case of suicidal ingestion of *Aconitum* tubers, death occurred about 4 hours after ingestion (30).

During a 3 year interval from 1989 to 1991, 17 cases of intoxication from Chinese herbal medicines containing *Aconitum* species were managed in five public hospitals in Hong Kong. Most developed tachyarrhythmias, including ventricular tachycardia and fibrillation from which 2 patients died (27).

Another report which probably includes some of the same cases as that above, documents 8 patients who were admitted over a two year period to a single Hong Kong hospital with features of intoxication (11). Nearly all of these patients experienced adverse effects after taking the first dose. Symptoms generally began within 0.5 to 1.5 hours after aconite consumption, and lasted up to 30 hours. Most subjects experienced a combination of cardiovascular (palpitations, hypotension and ventricular ectopics), gastrointestinal (nausea and vomiting) and neurological (numbness and paraesthesiae and weakness in the extremities) symptoms. Doses ranging from 7 to 11g of roots of *Aconitum carmichaeli* and *A kusnezoffii* had been taken by the subjects. The aconitine content of these has been estimated at 0.4 to 0.6% (8), meaning a total intake of 28 to 66mg aconitine.

An Italian case report documents a man who developed ventricular tachycardia which degenerated into ventricular fibrillation, following ingestion of seeds of *Aconitum napellus* (29). Another case describes self-medication with 8 drops of 'tincture of aconite' (strength unspecified) which resulted in severe bradycardia and reversible panconduction defect (16).

Successful treatment of aconitine induced life threatening ventricular tachycardia with amiodarone has been reported (32). Another paper from Taiwan reported lack of signs of toxicity in patients who received single doses of a formulation which contained 167mg *Aconitum sinensis* (32). Two cases of recovery following ingestion of 5 to 10mg of aconitine, have been reported (26).

No gross or histological cardiac abnormalities have been observed in the few autopsied cases (33), although high levels of alkaloids have been detected in the kidneys, liver and bile in a case of suicidal ingestion (31).

To the author's knowledge, no cases of adverse effects attributable to ingestion of *Aconitum* species have been recorded in New Zealand.

Aconite preparations currently on the New Zealand market:

As far as the author is aware, the only *Aconitum napellus*-containing preparations available on the New Zealand market are homoeopathic in nature. Based upon the documented use of other *Aconitum* species in Asia

and India however, it seems feasible that Traditional Chinese and other Asian Medicine practitioners are in fact using preparations of other *Aconitum* species, in more of a herbal or 'material dose' manner, just as they are for other restricted agents such as *Ephedra sinica*.

According to the submission received by Weleda, the only aconite-containing product(s) being sold as General Sale Medicines (i.e. freely available 'over the counter'), are homoeopathic liquids or powders containing Aconite 4X (i.e. a 0.01% tincture) for internal administration, which contains a maximum of 0.000015% alkaloids, equivalent to 0.15 micrograms per 1ml (15 drop) dose. With pack sizes of 30ml or 100ml being available, a maximum total amount of 4.5 micrograms or 15 micrograms (0.015mg) alkaloids will thus be contained in each pack size respectively. This is less than 1% of the lowest reported fatal adult dose of 2mg.

Other preparations (both stronger or weaker in a conventional pharmacological sense, being less or more 'homoeopathically potentised' respectively), are available through Weleda's dispensary as one-off items where these are requested by registered medical practitioners. These preparations include Aconite 3x (i.e. a 0.1% tincture), and ampoules with strengths up to 2x (i.e. a 1% tincture) for subcutaneous use, suppositories (made from 0.001% fresh plant), and external oils or creams containing a maximum concentration of 10% of dry *Aconitum napellus*. The larger 100ml pack size of Aconite 3X for internal administration will therefore contain a maximum of 150 micrograms or 0.15mg of total alkaloids, which is less than 10% of the lowest reported fatal adult dose.

The proposed Medsafe classification of Aconite:

Medsafe has proposed a reclassification of Aconite to a Prescription Only Medicine classification, for product containing aconite up to the general schedule exemption level of 10mg per litre or per kilogram. Weleda has proposed a lower classification be applied to product containing lower concentrations of the **alkaloids** of aconite.

Previous classifications of Aconite:

Several different previous Medsafe classifications for *Aconitum napellus* have been in operation in the past, including:

Pharmacy Medicine: Aconite; except for external use in medicines containing less than 0.02%.

Restricted Medicine: Aconite; alkaloids of and salts, except in medicines containing less than 0.02% of the alkaloids of Aconite.

Pharmacy-Only Medicine: Aconite; alkaloids of and salts, in medicines containing less than 0.02% of the alkaloids of Aconite.

General Sale Medicine: Aconite; alkaloids of and salts, in medicines for

external use containing less than 0.02% of the alkaloids of Aconite.

Interpretation of the Submission received from Weleda

I have reviewed the Submission for Reclassification of Aconite (*Aconitum napellus*) submitted by Weleda New Zealand Ltd. This submission proposes classification and schedule exemption levels which Weleda claim are based upon active principle concentration, and which fairly reflect the actual risk of the medicine to the consumer.

Given that the levels of original plant or other material found in many homoeopathic medicines are often infinitesimally small, there appears to be a valid case to introduce a classification system which is based upon levels of alkaloids found within Aconite preparations, instead of classifying these (or other such) preparations based upon their name only. Such a system would also help overcome the enormous difficulty in assessing safety parameters for preparations which vary widely in terms of their content of active and toxic constituents. It would of course, rely upon the availability of analytical procedures enabling quantification of these alkaloids as part of the routine quality assurance of Aconite-containing products, but these are already in existence and readily available (30).

As Weleda have pointed out, commercial sources of Aconite tincture (known as 'Aconite Mother Tincture' in Homoeopathy) derive from 2 different pharmacopoeia, the *Homoeopathic Pharmacopoeia of the U.S.*, and the *German Homoeopathic Pharmacopoeia*. The preparation based upon the U.S. Pharmacopoeia, which contains 10% of dry plant material (i.e. a '1 in 10' or a '1x' strength tincture), should therefore contain a maximum of 0.15% total alkaloids. Aconite mother tincture made to comply with the German Homoeopathic Pharmacopoeia method and standard however, is apparently a 50% fresh whole plant juice, and contains not more than 0.075% of alkaloids calculated as aconitine. A '1 in 10' or '1x' strength preparation based upon the juice content of this mother tincture would therefore contain a maximum of 0.015% alkaloids. This 10 fold difference in the alkaloidal content of two different sources of starting material used to prepare all subsequent homoeopathic preparations, highlights a discrepancy that a classification system based upon actual alkaloid levels would resolve.

Conclusions and suggestions for a suitable classification status for Aconite

No case reports of adverse effects associated with the use of homoeopathic preparations containing Aconite were located during a literature search for this agent.

The current classification category for Aconite in New Zealand is a Prescription Only Medicine, with a recommended general schedule exemption for preparations containing less than 10mg per litre or per kilogram of Aconite. In Australia, Aconite (*Aconitum spp*) is classified as a Schedule 4 (Prescription Only) Medicine, with a Schedule exemption for preparations containing less than 10mg per litre or per kilogram.

As Weleda have correctly pointed out however, inconsistencies can arise through use of a Schedule exemption system that applies to levels of raw plant material of *Aconitum spp* contained within a given preparation, due to the fact that Aconite mother tinctures used by homoeopathic product manufacturers, are made using different methods and different starting materials. As such they may contain widely variable levels of actual plant extract as well as active and toxic alkaloids.

As the main consideration regarding the most appropriate classification for this agent is to do with the known toxicity of its alkaloid constituents, a more suitable classification for Aconite would therefore specify 'cut off' levels based upon concentrations of the known active and toxic alkaloid constituents, rather than levels of original plant material from an unspecified source and of an unspecified nature and quality.

Should Aconite remain as a Prescription Medicine, but with the general schedule exemption introduced as recommended, presumably there would be nothing to impair its use in normal homoeopathic dosages by professional homoeopaths. Should the schedule exemption recommended by Weleda restrict access to preparations containing higher concentrations of aconite however, provided such preparations were of a strength and pack size still deemed safe given the toxicological information available, there may be a case for an exemption to be applied to members of an appropriate professional body of homoeopaths, to allow them as well as registered medical practitioners to prescribe this substance. Presumably if this is the case, a submission on this subject will have been made to Medsafe by a professional body(s) representing homoeopaths, and its content noted. It is the view of the author's that prescribing rights for specific complementary medicines with a relatively narrow therapeutic index, should be restricted to those health professionals who have received comprehensive training in the safe and appropriate use of that particular substance(s). In this sense, classification of Aconite as a Prescription Medicine would be most appropriate, provided an exemption was granted to suitably trained and registered homoeopaths.

The consumer's presently unrestricted access to homoeopathic preparations of Aconite which contain infinitesimally small levels of toxic alkaloids however, should not be impaired by any reclassification of this agent. It is the author's opinion that the above restrictions for stronger preparations should therefore not apply to general sales forms of homoeopathic aconite, provided these contain less than 0.02mg of toxic alkaloids (1% the reported lowest fatal dose), per pack size being sold. Ingestion of such levels of aconite alkaloids should not be associated with any adverse effects, and the risk of inappropriate use of such 'OTC' preparations is deemed extremely remote.

For topical aconite-containing preparations, it is suggested that a clear warning be printed on the labelling of all such products, stating that the preparation should not be applied to wounds or abraded surfaces.

What I would therefore propose for a suitable classification of Aconite is as follows:

Prescription Only Medicine:

Aconitum spp, pack sizes of which contain more than 0.2mg total alkaloids, and parenteral or rectal preparations.

Pharmacy Medicine:

Aconitum spp, pack sizes of which contain no more than 0.2mg total alkaloids. External preparations containing not more than 0.02% of total alkaloids.

General Sales Medicine:

Aconitum spp, pack sizes of which contain less than 0.02mg total alkaloids.

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