Valerian

Species (Family)

Valeriana officinalis L.s.l. (Valerianaceae)

Synonym(s)

All-Heal, Belgian Valerian, Common Valerian, Fragrant Valerian, Garden Valerian

Part(s) Used

Rhizome, root

Pharmacopoeial and Other Monographs

American Herbal Pharmacopoeia[1,G1]
BHC 1992[G6]
BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
EMEA HMPWG proposed core SPC[G23]
ESCOP 1997[G52]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
WHO volume 1 1999[G63]

Legal Category (Licensed Products)

GSL[G37]

Constituents[1–5,G1,G2,G6,G21,G22,G29,G41,G64]

Alkaloids Pyridine type. Actinidine, chatinine, skyanthine, valerianine and valerine.

Iridoids (valepotriates) Valtrates (e.g. valtrate, valtrate isovaleroxyhydrin, acevaltrate, valechlorine), didrovaltrates (e.g. didrovaltrate, homodidrovaltrate, deoxydidrovaltrate, homodeoxydidrovaltrate, isovaleroxyhydroxydidrovaltrate) and isovaltrates (e.g. isovaltrate, 7-epideacetylisovaltrate). Valtrate and didrovaltrate are documented as the major components. Valerosidate (iridoid glucoside).[6] The valepotriates are unstable and decompose on storage or processing; the main degradation products are baldrinal and homobaldrinal. The baldrinals may react further and are unlikely to be present in finished products.

Volatile oils 0.5–2%. Not less than 3 mL/kg of essential oil for the cut drug, both calculated with reference to the dried drug.[G28]

Numerous identified components include monoterpenes (e.g. α- and β-pinene, camphene, borneol, eugenol, isoeugenol) present mainly as esters, sesquiterpenes (e.g. β-bisabolene, caryophyllene, valeranone, ledol, pacifigorgiol, patchouli alcohol, valerianol, valerenol and a series of valerenyl esters, valerenal, valerenic acid with acetoxy and hydroxy derivatives).[7–10]

Other constituents Amino acids (e.g. arginine, γ-aminobutyric acid (GABA), glutamine, tyrosine),[1,11,G21] caffeic and chlorogenic acids (polyphenolic), β-sitosterol, methyl 2-pyrrolketone, choline, tannins (type unspecified), gum and resin.

As with other plants, there can be variation in the content of active compounds (e.g. valerenic acid derivatives and valepotriates) found in valerian rhizomes and roots.[12]

Food Use

Valerian is not generally used as a food. Valerian is listed by the Council of Europe as a natural source of food flavouring (root: category 5) (*see* Appendix 23).[G17] In the USA, valerian is permitted for use in food.[G65]

Herbal Use

Valerian is stated to possess sedative, mild anodyne, hypnotic, antispasmodic, carminative and hypotensive properties. Traditionally, it has been used for hysterical states, excitability, insomnia, hypochondriasis, migraine, cramp, intestinal colic, rheumatic pains, dysmenorrhoea, and specifically for conditions presenting nervous excitability.[G2,G6,G7,G8,G32,G64] Modern interest in valerian is focused on its use as a sedative and hypnotic.

A core Summary of Product Characteristics (SPC) proposed by the European Medicines Evaluation Agency Herbal Medicinal Product Working Group (EMEA HMPWG) states the following indications: the relief of temporary mild nervous tension and temporary difficulty in falling asleep.[G23]

Dosage

Dried rhizome/root 1–3 g by infusion or decoction up to three times daily.[G6]

Tincture 3–5 mL (1:5; 70% ethanol) up to three times daily;[G6,G50] 1–3 mL, once to several times daily.[G3]

Extracts Amount equivalent to 2–3 g drug, once to several times daily;[G3] 2–6 mL of 1:2 liquid extract daily.[G50]

Doses given in older texts vary. For example: Valerian Liquid Extract (BPC 1963) 0.3–1.0 mL; Simple Tincture of Valerian (BPC 1949) 4–8 mL; Concentrated Valerian Infusion (BPC 1963) 2–4 mL.

Clinical trials investigating the effects of valerian extracts on sleep parameters have used varying dosages, for example, valerian extract 400 mg/day (drug:extract ratio of 3:1)[13] to 1215 mg/day (drug:extract ratio of 5 to 6:1).[14]

Pharmacological Actions

It remains unclear precisely which of the constituents of valerian are responsible for its sedative properties.[5] Attention had focused on the volatile oil, and then the valepotriates and their degradation products, as the constituents responsible. However, it appeared that the effects of the volatile oil could not account for the whole action of the drug, and the valepotriates, which degrade rapidly, are unlikely to be present in finished products in significant concentrations. Current thinking is that the overall effect of valerian is due to several different groups of constituents and their varying mechanisms of action. Therefore, the activity of different valerian preparations will depend on their content and concentrations of several types of constituent.[4] One mechanism of action is likely to involve increased concentrations of the inhibitory transmitter GABA in the brain. Increased concentrations of GABA are associated with a decrease in CNS activity and this action may, therefore, be involved in the reported sedative activity.

In vitro and animal studies

Sedative properties have been documented for valerian and have been attributed to both the volatile oil and valepotriate fractions.[15,16] Screening of the volatile oil components for sedative activity concluded valerenal and valerenic acid to be the most active compounds, causing ataxia in mice at a dose of 50 mg/kg by intraperitoneal injection.[15] Further studies in mice described valerenic acid as a general CNS depressant similar to pentobarbitone, requiring high doses (100 mg/kg by intraperitoneal injection) for activity.[17] A dose of 400 mg/kg resulted in muscle spasms, convulsions and death.[17] Valerenic acid was also reported to prolong pentobarbitone-induced sleep in mice, resulting in a hangover effect. Biochemical studies have documented that valerenic acid inhibits the enzyme system responsible for the central catabolism of GABA.[18] An aqueous extract of roots and rhizomes of *V. officinalis* (standardised to 55 mg valerenic acids per 100 g extract) inhibited the uptake and stimulated the release of radiolabelled GABA in isolated synaptosomes from rat brain cortex.[19,20] Further work suggested that this aqueous extract of valerian induces the release of GABA by reversal of the GABA carrier, and that the mechanism is Na^+ dependent and Ca^{2+} independent.[20] The extract contained a high concentration of GABA (about 5 mmol/L) which was shown to be sufficient to induce the release of radiolabelled GABA by this type of mechanism.[21] Aqueous and hydroalcoholic (ethanol) extracts of valerian root displaced radiolabelled muscimol binding to synaptic membranes (a measure of the influence of drugs on $GABA_A$ receptors). However, valerenic acid (0.1 mmol/L) did not displace radiolabelled muscimol in this model.[22] Other *in vitro* studies using rat brain tissue have shown that hydroalcoholic and aqueous total extracts of *V. officinalis* root, and an aqueous fraction derived from the hydroalcoholic extract, show affinity for $GABA_A$ receptors, although far lower than that of the neurotransmitter itself.[23] However, a lipophilic fraction of the hydroalcoholic extract, hydroxyvalerenic acid and dihydrovaltrate did not show any affinity for the $GABA_A$ receptor in this model.

The effects of valerian extracts on benzodiazepine binding to rat cortical membranes have also been explored. Very low concentrations of ethanolic extract of *V. officinalis* had no effect on radiolabelled flunitrazepam binding in this model, although concentrations of 10^{-10} to 10^{-8} mg/mL increased radiolabelled flunitrazepam binding with an EC_{50} of 4.13×10^{-10} mg/mL.[24] However, flunitrazepam binding was inhibited at higher concentrations (0.5–7.0 mg/mL) of valerian extract (IC_{50} 4.82×10^{-1} mg/mL). In other investigations, valerian extract potentiated radiolabelled GABA release from rat hippocampal slices, and inhibited synaptosomal GABA uptake, confirming the effects of valerian extract on $GABA_A$ receptors.[24]

CNS-depressant activities in mice following intraperitoneal injection have been documented for the valepotriates and for their degradation products, although activity was found to be greatly reduced following oral administration.[25] A study explored the effects of a mixture of valepotriates on the behaviour of diazepam-withdrawn male Wistar rats in the

elevated plus-maze test (a measure of the anxiolytic or anxiogenic properties of drugs).[26] Rats were given diazepam (up to 5 mg/kg for 28 days) then vehicle only for three days to induce a withdrawal syndrome. Rats given diazepam or a mixture of valepotriates (dihyritoneally (12 mg/kg) spent a significantly greater proportion of time in the 'open' arms of the maze than did those in the control group.

Another specific valepotriate fraction, Vpt_2, has been documented to exhibit tranquillising, central myorelaxant, anticonvulsant, coronaro-dilating and anti-arrhythmic actions in mice, rabbits, and cats.[27,28] The fraction was reported to prevent arrhythmias induced by Pituitrin vasopressin and barium chloride, and to exhibit moderate positive inotropic and negative chronotropic effects.

Antispasmodic activity on intact and isolated guinea-pig ileum has been documented for isovaltrate, valtrate and valeranone.[29] This activity was attributed to a direct action on the smooth muscle receptors rather than ganglion receptors. Valerian oil has been reported to exhibit antispasmodic activity on isolated guinea-pig uterine muscle,[30] but proved inactive when tested *in vivo*.[31]

In vitro inactivation of complement activation has been reported for the valepotriates.[32]

In vitro cytotoxicity (inhibition of DNA and protein synthesis, and potent alkylating activity) has been documented for the valepotriates, with valtrate stated to be the most toxic compound.[33] Valepotriates (valtrate and didrovaltrate) isolated from the related species *Valeriana wallichii*, and baldrinal (a degradation product of valtrate) have been tested for their cytotoxic activity *in vitro* using cultured rat hepatoma cells. Valtrate was the most active compound in this system, leading to a 100% mortality of hepatoma cells after 24 hours' incubation at a concentration of 33 μg/mL.[34] More detailed studies using the same system showed that didrovaltrate demonstrated cytotoxic activity when incubated at concentrations higher than 8 μg/mL of culture (1.5×10^{-5} mol/L) and led to 100% cellular mortality with 24 hours of incubation at a concentration of 66 μg/mL. The cytotoxic effect of didrovaltrate was irreversible within 2 hours of incubation with hepatoma cells. In mice, administration of intraperitoneal didrovaltrate led to a regression of Krebs II ascitic tumours, compared with control.[34] A subsequent *in vivo* study, in which valtrate was administered to mice (by intraperitoneal injection and by mouth), did not report any toxic effects on haematopoietic precursor cells when compared with control groups.[35] The valepotriates are known to be unstable compounds in both acidic and alkaline media and it has been suggested that their *in vivo* toxicity is limited due to poor absorption and/or distribution.[2] Baldrinal and homobaldrinal, decomposition products of valtrate and isovaltrate respectively, have exhibited direct mutagenic activity against various *Salmonella* strains *in vitro*.[36]

Clinical studies

Numerous studies have explored the effects of valerian preparations on subjective and/or objective sleep parameters.[13,14,37–45] Collectively, the findings of these studies are difficult to interpret, as different studies have assessed different valerian preparations and different dosages, and some have involved healthy volunteers whereas others have involved patients with diagnosed sleep disorders. In addition, other studies have used different subjective and/or objective outcome measures, and some have been conducted in sleep laboratories, whereas others have assessed participants receiving valerian whilst sleeping at home. Overall, several, but not all, studies have documented a hypnotic effect for valerian preparations with regard to subjective measures of sleep quality, and some have documented effects on objective measures of sleep structure. There is a view that subjective measures of sleep quality may be the most appropriate assessment.[45]

A systematic review of randomised, double-blind, placebo-controlled trials of valerian preparations included nine studies.[46] The review concluded that the evidence for valerian as a treatment for insomnia is inconclusive and that there is a need for further rigorous trials. Several of the studies included in the review, and other studies, are discussed in more detail below.

A placebo-controlled study involving 128 volunteers explored the effects of an aqueous extract of valerian root (400 mg) and a proprietary preparation of valerian and hops (Hova) on subjective measures of sleep quality. Each participant took each of the three preparations at night for three non-consecutive nights.[13] On the basis of participants' self-assessment, valerian significantly reduced sleep latency (time to onset of sleep) and improved sleep quality, compared with placebo ($p < 0.05$). Subgroup analysis suggested that the effects of valerian were most marked among participants who described themselves as 'poor' or 'irregular' sleepers.[13] It was reported that Hova did not significantly affect sleep latency or sleep quality, compared with placebo, only that Hova administration was associated with an increase in the number of reports of 'feeling more sleepy than usual the next morning' (i.e. a 'hangover' effect). The authors were unable to explain this discrepancy in the results for the two preparations.

In a subsequent study, eight volunteers with mild insomnia each received aqueous valerian extract

450 mg, 900 mg or placebo, in a random-order experimental design over almost three weeks.[37] The time to the first period of 5 consecutive minutes without movement, measured using wrist-worn activity meters, was used as an objective measure of sleep latency. For this parameter, valerian 450 mg significantly reduced the mean sleep latency, compared with placebo, although there was no further reduction in sleep latency with valerian 900 mg. Subjective assessments indicated that participants were more likely to experience a 'hangover' effect with valerian 900 mg.[37]

The same dosages of aqueous valerian extract were tested for their effects on sleep latency and wake time after sleep onset in healthy volunteers who were either sleeping at home or in a sleep laboratory.[38] Each participant sleeping at home took valerian 450 mg, 900 mg, or placebo, for two consecutive nights on a double-blind, crossover schedule. Participants sleeping under laboratory conditions were randomly assigned to receive valerian 900 mg on the second or third night of the four nights of the study; placebo was taken on the other nights. Under home conditions, valerian 450 mg and 900 mg significantly reduced subjectively measured sleep latency, compared with placebo. Under laboratory conditions, there were no statistically significant differences between valerian 900 mg and placebo on subjective or objective sleep parameters. It was suggested that the 'more stressful' sleep environment of the laboratory may have masked the hypnotic effects of valerian.[38]

A randomised, double-blind, placebo-controlled, crossover study involving 16 patients with previously established psychophysiological insomnia according to International Classification of Sleep Disorders (ICSD) criteria and confirmed by polysomnography assessed the effects of single-dose and longer term administration of valerian root extract on objective parameters of sleep structure and subjective parameters of sleep quality.[39] Participants received valerian root extract (Sedonium; drug:extract ratio 5:1) 600 mg, or placebo, 1 hour before bedtime for 14 days, followed by a wash-out period of 13 days, before crossing over to the other arm of the study. There were no statistically significant effects on objective and subjective parameters of sleep following single-dose valerian administration. After long-term treatment, sleep efficiency (ratio of time spent asleep to time spent in bed) improved in both the valerian and placebo groups, compared with baseline values, although there were no significant differences between groups. There was a statistically significant difference with valerian on parameters of slow-wave sleep, compared with baseline values, which did not occur with placebo. However, it is not clear if this difference was significantly different for valerian, compared with placebo, as no p-value was given.

In a randomised, double-blind, pilot study, 14 elderly women who were poor sleepers received valerian aqueous extract (Valdispert forte; drug:extract ratio 5 to 6:1), or placebo, for eight consecutive days.[14] Valerian 405 mg was administered one hour before sleep for one night in the laboratory, then taken three times daily for the following seven days. There was no difference in sleep parameters between valerian extract and placebo after acute administration. Valerian recipients showed an increase in slow-wave sleep, compared with baseline values. However, valerian had no effect on sleep onset time, rapid eye movement (REM) sleep or on self-rated sleep quality.

Aqueous ethanolic valerian extract (Sedonium) was compared with placebo in a randomised, double-blind trial involving 121 patients with insomnia not due to organic causes.[40] Participants received valerian extract, or placebo, 600 mg one hour before bedtime for 28 days. At the end of the study, valerian extract achieved a significantly higher clinical global impression score than did placebo. Sleep quality improved in both groups, compared with baseline values.

The effects of valerian extracts on sleep parameters have been compared with those of the benzodiazepine oxazepam.[41] This randomised, double-blind trial involving people with non-organic and non-psychiatric insomnia compared valerian root extract 600 mg with oxazepam 10 mg; treatment was taken 30 minutes before going to bed for 28 days. At the end of the treatment period, sleep quality had improved significantly ($p < 0.001$) in both groups, compared with baseline values. There was no difference between the two groups with regard to sleep quality.

An open, uncontrolled, multicentre study assessed the effects of a valerian extract (Baldrian-Dispert) 45 mg daily in 11 168 patients with sleep disorders. Valerian was rated as 'good' or 'very good' in 72% of cases of sleep disturbances, 76% of cases of discontinuous sleep, and in 72% of cases of restlessness and tension.[42]

Several other studies have assessed the effects of valerian extract in combination with other herb extracts, such as hops (*Humulus lupulus*) and/or melissa (*Melissa officinalis*), on measures of sleep.[47–50] A randomised, double-blind trial involving healthy volunteers who received Songha Night (*V. officinalis* root extract 120 mg and *M. officinalis* leaf

extract 80 mg) three tablets daily taken as one dose 30 minutes before bedtime for 30 days ($n = 66$), or placebo ($n = 32$), found that the proportion of participants reporting an improvement in sleep quality was significantly greater for the treatment group, compared with the placebo group (33.3% versus 9.4%, respectively; $p = 0.04$).[48] However, analysis of visual analogue scale scores revealed only a slight, but statistically non-significant, improvement in sleep quality in both groups over the treatment period. Another double-blind, placebo-controlled trial involving patients with insomnia who received Euvegal forte (valerian extract 160 mg and lemon balm extract 80 mg) two tablets daily for two weeks reported significant improvements in sleep quality in recipients of the herbal preparation, compared with placebo recipients.[49] A placebo-controlled study involving 'poor sleepers' who received Euvegal forte reported significant improvements in sleep efficiency and in sleep stages 3 and 4 in the treatment group, compared with placebo recipients.[50]

Some studies assessing combination valerian preparations have compared the effects with those of benzodiazepines.[51,52] A three-week, randomised, double-blind trial reported that a combination of valerian and hops (200 mg and 45.5 mg dry extract, respectively) was equivalent to bromazepam 3 mg with regard to sleep quality in patients with 'environmental' sleep disorders (temporary dyscoimesis and dysphylaxia) according to Diagnostic and Statistical Manual (DSM)-IV criteria.[51] A study assessing the 'hangover' effects of valerian preparations (valerian syrup and valerian–hops tablets) (*see* Side-effects, Toxicity) reported that subjective measures of sleep quality improved in both valerian groups, compared with placebo.[52]

In an open, uncontrolled, multicentre study, 225 individuals who were experiencing nervous agitation and/or difficulties falling asleep and achieving uninterrupted sleep were treated for two weeks with a combination preparation containing extracts of valerian root, hop grains and lemon balm leaves.[53] Significant improvements in the severity and frequency of symptoms were reported, compared with the pretreatment period. Difficulties falling asleep, difficulties sleeping through the night, and nervous agitation were improved in 89, 80 and 82% of participants, respectively.

In a single-blind, placebo-controlled, crossover study involving 12 healthy volunteers, two different single doses of valerian-hops (valerian 500 mg, hops 120 mg; valerian 1500 mg, hops 360 mg) were assessed for their effects on EEG recordings.[54] Some slight effects on the quantitative EEG were documented following administration of higher dose valerian–hops, indicating effects on the central nervous system.

The effects of valerian extract 100 mg (no further details of preparation given) on activation and performance of 48 healthy volunteers under experimental social stress conditions have been assessed, with or without propranolol 20 mg, in a randomised double-blind, placebo-controlled study.[55] Valerian was reported to have no influence on physiological activation and to lead to less intensive subjective feelings of somatic arousal. The effects of a hydroalcoholic extract of valerian have been assessed in a randomised study involving 40 patients with minor symptoms of anxiety and emotional tension.[56] Participants received valerian extract 100 mg three times daily, or placebo, for 21 days. It was reported that valerian was superior to placebo.

Several other studies have assessed the effects of combinations of valerian and St. John's wort (*Hypericum perforatum*) in patients with anxiety or depression.[57–59] In a randomised, double-blind study involving 100 patients with anxiety, a combination of valerian and St. John's wort was reported to be significantly more effective than diazepam according to a physician's rating scale and a patient's self-rating scale.[57] In a randomised, double-blind trial involving 162 patients with dysthymic disorders, the effects of a valerian and St. John's wort combination (Sedariston) were compared with those of amitriptyline 75–150 mg.[58] Another randomised, double-blind trial, involving 100 patients with mild-to-moderate depression compared Sedariston with desipramine 100–150 mg.[59] Pooling the results of these two studies indicated there were 88 (68%) treatment responders in the Sedariston group and 66 (50%) in the group that received standard antidepressants.[60] This difference was not statistically significant.

Several studies have assessed the effects of valerian, or herbal combination products containing valerian, on performance the morning after treatment (*see* Side-effects, Toxicity).[52,61]

Side-effects, Toxicity

Data relating to the safety of valerian have been reviewed.[G21]

Studies assessing the effects of valerian on measures of performance suggest that there may be slight impairment for a few hours following valerian ingestion. However, studies have shown that 'hangover' effects (impairment of performance the morning following valerian treatment) do not appear to be a concern.

In a randomised, double-blind trial involving 102 healthy volunteers, the effects of single-dose valerian

extract (Sedonium) 600 mg on reaction time, alertness and concentration were compared with those of flunitrazepam 1 mg and placebo.[61] The treatment was administered in the evening and psychometric tests were carried out the next morning. After a one-week wash-out period, 91 volunteers continued with the second phase of the study, which comprised 14 days' administration of valerian extract 600 mg or placebo. Single-dose valerian extract administration did not impair reaction time, concentration or co-ordination. A 'hangover' effect was reported by 59% of flunitrazepam recipients, compared with 32% and 30% of placebo and valerian recipients, respectively ($p < 0.05$). At the end of the 14-day study, there was no statistically significant difference ($p = 0.45$) between valerian extract and placebo on mean reaction time (a measure of performance), and valerian recipients showed a trend towards improved sleep quality.

A randomised, double-blind study involving 80 volunteers assessed the 'hangover' effects of tablets containing valerian and hops, and a syrup containing valerian only, given as a single dose, against both placebo and active control (flunitrazepam 1 mg).[52] Performance the morning after treatment, measured both objectively and subjectively, was reported to be impaired only in the flunitrazepam group. Side effects occurred more frequently in the flunitrazepam group (50%), compared with the valerian and placebo groups (10%). A further battery of cognitive psychomotor tests was carried out in another study involving 36 volunteers who received either valerian syrup, valerian–hops tablets, or placebo; tests were conducted 1–2 hours after drug administration to assess acute effects. Compared with placebo, there was a slight, but statistically significant, impairment in vigilance with valerian syrup and impairment in the processing of complex information with valerian–hops tablets.[52]

Few controlled clinical trials of valerian preparations have provided detailed information on safety. Where adverse event data were provided, randomised, placebo-controlled trials involving healthy volunteers or patients with diagnosed insomnia reported that adverse events with valerian were mild and transient, and that the types and frequency of adverse events reported for valerian were similar to those for placebo.[46,61] One study involving small numbers of patients reported a lower frequency of adverse events with valerian than with placebo; the authors did not suggest an explanation for this.[39] Studies comparing valerian preparations with benzodiazepines have reported that valerian root extract (LI-156) 600 mg daily for 14 days[61] or 28 days[41] had a more favourable adverse effect profile than flunitrazepam 1 mg daily for 14 days[61] and oxazepam 10 mg daily for 28 days,[41] respectively.

There is an isolated report of cardiac complications and delirium associated with valerian root extract withdrawal in a 58-year-old man with a history of coronary artery disease, hypertension and congestive heart failure.[62] The man had been taking valerian root extract (530 mg to 2 g, five times daily). It was hypothesised that given the effects of valerian on GABA, withdrawal of valerian root might produce a benzodiazepine-like withdrawal syndrome. However, the man was taking multiple medications and had undergone surgery, and a causal link with valerian could not be made. There have also been isolated reports of hepatotoxic reactions following the use of combination products containing valerian, although these products contained other herbal ingredients, such as scullcap and chaparral, which could have been responsible.[63,G18,G21] Several other reports document hepatotoxic reactions with single-ingredient valerian products, although it is possible that these were idiosyncratic reactions.[64] There is a lack of data on the safety of the long-term use of valerian, and such studies are required.[G21]

Cases of individuals who had taken overdoses of valerian or valerian-containing products have been documented. One case involved an 18-year-old female who ingested 40–50 capsules of powdered valerian root 470 mg, approximately 20 times therapeutic doses.[65] The patient presented 3 hours after ingestion with fatigue, crampy abdominal pain, chest tightness, tremor and lightheadedness. Liver function tests were normal; a urine screen tested positive for tetrahydrocannabinol. The patient was treated with activated charcoal, and symptoms resolved within 24 hours. Several cases ($n = 47$) have been documented of overdose with a combination valerian-containing product ('Sleep-Qik'; valerian dry extract 75 mg, hyoscine hydrobromide 0.25 mg, cyproheptadine hydrochloride 2 mg).[66,67] Individuals had ingested tablets equivalent to 0.5–12 g valerian. Liver function tests were carried out for most patients, all of which were normal.

Toxicological studies documented in the older literature have reported an LD_{50} of 3.3 mg/kg for an ethanolic extract of valerian administered intraperitoneally in rats, and that daily doses of 400–600 mg/kg, administered intraperitoneally for 45 days, did not lead to any changes in weight, blood or urine measurements, compared with controls.[1] Literature cited in a review of the safety of valerian describes an LD_{50} of 64 mg/kg for valtrate, 125 mg/kg for didrovaltrate and 150 mg/kg for acevaltrate in mice after intraperitoneal injection.[G21] Another study in mice reported that valerenic acid 150 mg/kg, given by intraperitoneal

injection, caused muscle spasms and that 400 mg/kg caused heavy convulsions.[17] The latter dose was lethal to six of seven mice.

In vitro cytotoxicity and mutagenicity have been documented for the valepotriates. The clinical significance of this is unclear, since the valepotriates are known to be highly unstable and, therefore, probably degrade when taken orally. Also, they are unlikely to be present in high concentrations in finished products. The volatile oil is unlikely to present any hazard in aromatherapy.[G58]

The EMEA HMPWG proposed core SPC states that the total exposure to valepotriates should not exceed the maximum exposure with herbal tea.[G23] Alkylating and cytotoxic properties of valepotriates are not relevant for finished products as valepotriates decompose rapidly and only traces of valepotriates or their degradation products (in part, baldrinals) are found.

Contra-indications, Warnings

The documented CNS-depressant activity of valerian may potentiate existing sedative therapy.

According to the EMEA HMPWG proposed core SPC, patients should seek medical advice if symptoms persist for more than two weeks, or worsen. Intake of valerian preparations immediately (up to 2 hours) before driving a car or operating machinery is not recommended. The effect of valerian preparations may be enhanced by consumption of alcohol.[G23]

Pregnancy and lactation The safety of valerian during pregnancy and lactation has not been established and should, therefore, be avoided.[68]

A study in rats involved the administration of valepotriates (6, 12 and 24 mg/kg administered orally) during pregnancy up to the 19th day when animals were sacrificed.[69] There were no differences between valepotriate-treated rats and control rats as determined by fetotoxicity and external examination studies, although the two highest doses of valepotriates were associated with an increase in retarded ossification evident on internal examination.

The EMEA HMPWG proposed core SPC states that as data on the use of valerian during pregnancy are not available, use is not recommended as a general precaution. No adverse effects have been reported from the common use of valerian root as a medicinal product, but experimental data are lacking.[G23]

Pharmaceutical Comment

The traditional use of valerian as a mild sedative and hypnotic has been supported by actions documented in studies involving both animals and humans.[G62]

The sedative activity of valerian has been attributed to both the volatile oil and iridoid valepotriate fractions, but it is still unclear whether other constituents in valerian represent the active components. The valepotriate compounds are highly unstable and, therefore, are unlikely to be present in significant concentrations in finished products and probably degrade when taken orally. In view of this, the clinical significance of both the sedative and cytotoxic/mutagenic activities of valepotriates documented *in vitro* is unclear.

The acute toxicity of valerian is considered to be very low.[G21] There are isolated reports of adverse effects, mainly hepatotoxic reactions, associated with the use of single-ingredient and combination valerian-containing products. However, causal relationships for these reports could not be established as the cases involved other factors which could have been responsible for the observed effects. Some studies have compared valerian with certain benzodiazepines; the data available appear to suggest that valerian may have a more favourable tolerability profile, particularly in view of its apparent lack of 'hangover' effects. The safety of valerian in comparison with benzodiazepines requires further investigation and documentation.

References

See also General References G2, G3, G5, G6, G9, G15, G18, G21, G22, G28, G31, G32, G36, G41, G43, G50, G52, G56, G58, G63 and G64.

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