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UTILIZATION OF GALANTHAMINE FOR THE TREATMENT OF PATHOLOGIES OF THE CENTRAL NERVOUS SYSTEM OWING TO INTOXICATIONS WITH PSYCHOTROPIC SUBSTANCES

57 **Abstract**

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(54) **Title:** UTILIZATION OF GALANTHAMINE FOR THE TREATMENT OF PATHOLOGIES OF THE CENTRAL NERVOUS SYSTEM OWING TO INTOXICATIONS WITH PSYCHOTROPIC SUBSTANCES

(54) **Bezeichnung:** VERWENDUNG VON GALANTHAMIN ZUR BEHANDLUNG VON KRANKHEITSERSCHEINUNGEN DES ZENTRALEN NERVENSYSTEMS AUFGRUND VON INTOXIKATIONEN MIT PSYCHOTROPEN SUBSTANZEN

(57) **Abstract:** The invention relates to the utilization of galanthamine, as a free base or as acid addition salt, for the treatment of cerebral, central nervous or psychiatric symptoms, dysfunctions or diseases, occurring by the administration of psychotropic substances as a consequence of occasional or chronic misuse of addictive drugs, narcotics or medicaments or as side effect of the prescribed use, especially repeated or protracted use, of medicaments or as the effect of unprescribed use, especially repeated or protracted use of medicaments, or as a consequence of intoxication with psychotropic toxic substances or as a consequence of chronic effect of psychotropic toxic substances in humans and other vertebrates.

(57) **Zusammenfassung:** Die Erfindung betrifft die Verwendung von Galanthamin, als freie Base oder als Säureadditionssalz, zur Behandlung von zerebralen, zentralnervösen oder psychiatrischen Symptomen, Ausfallsserscheinungen oder Krankheiten, die durch die Zuführung von psychotropen Substanzen als Folge von gelegentlichem oder chronischem Suchtmittel-, Rauschmittel- oder Medikamentenmissbrauch, oder als Nebenwirkung bei bestimmungsgemässer, insbesondere bei wiederholter oder länger andauernder Anwendung von Arzneimitteln, oder als Wirkung bei nicht bestimmungsgemässer, insbesondere bei wiederholter oder länger andauernder Anwendung von Arzneimitteln, oder infolge einer akuten Vergiftung durch psychotrope toxische Substanzen, oder infolge chronischer Einwirkung von psychotrop wirkenden toxischen Substanzen beim Menschen oder anderen Wirbeltieren auftreten.

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Use of galanthamine for the treatment of pathological manifestations of the central nervous system based on intoxication with psychotropic substances

The invention relates to the use of galanthamine for the treatment of disorders of the central nervous system such as cerebral, central nervous or psychiatric symptoms, defunctionalization manifestations or disorders which occur as a result of unintentional or intentional intake of psychotropic and/or hallucinogenic agents, e.g. environmental poisons, use and abuse of intoxicants or addictive substances, use and abuse of medicines, especially when there is dependence on addictive substances, especially alcohol dependence, in humans or in vertebrates.

Intake of psychotropic substances, including intoxicants, especially alcohol, is well known to lead to symptoms such as perception disturbances, memory loss, impairment of cognitive ability, general loss of control, aggressiveness, impairment of muscular coordination, etc.
If the substance is deliberately taken as intoxicant, such as, for example, heroin, cocaine or as ethyl alcohol-containing beverage, then although such effects are intended by the intoxicant-consuming person, they are also under certain conditions felt to be disadvantageous. An additional factor is that the severity and the duration of these symptoms may vary and is often difficult for the consumer of the intoxicant to estimate beforehand.

Especially when there is chronic dependence and continued abuse of addictive substances there is not only the generally known organic damage but there is also the occurrence of permanent defunctionalization manifestations which impair, for example, cognitive performance,

especially memory performance. This may also lead to sporadic or permanent dementing states. There may also be chronic manifestations of the previously mentioned psychiatric symptoms such as, for example, a general loss of control. These chronic sequelae of alcohol abuse - which occur in a similar way in other addictive substance dependences - represent a considerable impediment to successful implementation of detoxification therapies. Thus, it is known that the loss of control caused by chronic alcohol abuse makes abstinence impossible for the person affected by alcoholism. This is the main reason why even detoxified alcoholics are prone to relapses, usually with serious consequences. The principle that "controlled drinking" is impossible for dependent people was derived from this observation.

It is additionaly known that there are great individual differences in intoxicant consumption behaviour, which is why, for example, alcoholics are divided into different categories of drinkers.
The problem for certain alcohol consumers is that, after a particular individual threshold dose has been exceeded, there is a rapid general loss of control with the abovementioned adverse side effects. The affected persons are usually unable to recognize in good time that they have reached their individual threshold dose or even their personal risk of relapse. The loss of control brought about thereby, which often leads to further excessive alcohol consumption, is the reason why such people are often referred to as dangerous drinkers. These are frequently people who have already undergone withdrawal therapies and relapse in this way.

It is known that the loss of control caused by chronic abuse of addictive substances, as well as the impairment of

memory performance (and even dementia), often has far-reaching consequences for the affected person and for his surroundings, such as, for example, inability to carry on an occupation, inability to organize daily activities, inability to initiate and maintain social contacts and, resulting therefrom, social isolation.
These defunctionalization manifestations, e.g. the impairment of cognitive performance, often persist even after successfully completed withdrawal therapy. Further psychiatric or cerebral disturbances occurring in association with alcohol abuse or abuse of other addictive substances are, for example: perceptual illusions or hallucinations, amnesia, alterations of consciousness, formal cognitive disturbances, memory deficits, delusions, confabulations, disorientation, states of agitation.

The object therefore was to eliminate or at least alleviate the psychiatric symptoms or symptoms with a central nervous causation, occurring as a consequence of chronic abuse of addictive substances, in particular alcohol abuse, in particular the loss of control, loss of cognitive abilities, dementia, etc.

To solve this problem, the invention proposes using the agent galanthamine for the treatment of people suffering from such sequelae of psychrotropic substances, also based on dependencies on addictive substances. It is possible by administration of galanthamine to at least partially abolish or reverse the psychiatric or cerebral pathological manifestation caused as a result of chronic alcohol or intoxicant consumption, in particular the loss of cognitive abilities or loss of control occurring, so that the said abilities are gradually recovered. It is thus possible according to the present invention to eliminate or at least

alleviate certain chronic symptoms of dependences on addictive substances.

The invention is based on the surprising observation that in animal experiments administration of galanthamine to rats was able to bring about a recovery of cognitive abilities. This restoration did not occur, or occurred only considerably later, in untreated control animals. It was additionally possible to show in clinical studies on chronically dependent alcoholics that galanthamine caused a general improvement in the cognitive performance of the subjects. A further advantage in this connexion is in particular that better control over the addictive behaviour is made possible, so that the risk of relapse is reduced.

Galanthamine (4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6-H-benzofuro-(3a,3,2-ef)-(2)-benzazepin-6-ol) is a tetracyclic alkaloid occurring in certain plants, especially Amaryllidaceea. It can be obtained from these plants by known processes (e.g. as described in DE 195 09 663 A1 or DE patent 1 193 061) or by synthetic routes (e.g. Kametani et al., Chem. Soc. C. 6, 1043-1047 (1971) or Shimizu et al., Heterocycles 8, 277-282 (1977)).

On the basis of its pharmacological properties, galanthamine is included in the group of reversibly acting cholinesterase inhibitors. Galanthamine is used to treat poliomyelitis, Alzheimer's disease and various nervous system disorders, and to treat narrow angle glaucoma. It has also been proposed to use galanthamine to treat nicotine and alcohol dependence (DE 43 01 782 C1, DE 40 10 079 A1), it being said that galanthamine suppresses the addicts' desire for nicotine or alcohol. Use for treating the symptoms or sequelae caused by chronic abuse of intoxicants, especially alcohol, such as loss of

control, loss of cognitive abilities etc., has not previously been described.

According to the invention, galanthamine can be used both in the form of its free base and as acid addition salt for the treatment; preferred salts are galanthamine hydrochloride and galanthamine hydrobromide.

Galanthamine is preferably administered in a pharmaceutical preparation which contains the agent in proportions of from 0.1 to 90% by weight, particularly preferably in proportions of from 2 to 20% by weight, in each case calculated as free galanthamine. The galanthamine - containing pharmaceutical preparations used according to the invention may additionally contain excipients, carriers, stabilizers, etc., in the amounts known to the skilled person.
The dose administered each day is preferably in the range from 0.1 to 100 mg, in particular from 10 to 50 mg.

The preparations which are used according to the present invention for administering galanthamine may contain one or more of the following additives:
- antioxidants, synergists, stabilizers;
- preservatives;
- taste masking agents;
- colours;
- solvents, solubilizers;
- surfactants (emulsifiers, solubilizers, wetting agents, antifoams);
- agents affecting the viscosity and consistency, gel formers;
- absorption promoters;
- adsorbents, humectants, glidants;

- agents affecting disintegration and dissolution, fillers (extenders), peptizers;
- release-delaying agents.

This list is not definitive; the suitable physiologically acceptable substances are known to the skilled person.

Galanthamine can be administered orally or parenterally. It is possible to use known dosage forms such as tablets, coated tablets or pastilles for oral administration. Also suitable are liquid or semiliquid dosage forms, in which case the agent is in the form of a solution or suspension. Solvents or suspending agents which can be used are water, aqueous media or pharmacologically acceptable oils (vegetable or mineral oils). The galanthamine -containing medicaments are preferably formulated as depot medicaments which are able to deliver this agent to the body in a controlled manner over a prolonged period.

It is also possible according to the invention for galanthamine to be administered by the parenteral route. For this purpose it is particularly advantageous to use transdermal or transmucosal dosage forms for the galanthamine administration according to the invention, in particular adhesive transdermal therapeutic systems (agent plasters). These make it possible to deliver the agent in a controlled manner over a prolonged period via the skin to the patient to be treated.

Such systems normally have an agent-containing, contact adhesive polymer matrix which is covered on the side remote from the skin by an agent-impermeable backing, and whose adhesive, agent-delivering surface is covered before application by a detachable protective layer. The manufacture of such systems and the basic materials and

excipients which can be used therefor are known in principle to the skilled person; for example, the assembly of such transdermal therapeutical systems is described in German patents DE 33 15 272 and DE 38 43 239 or in US patents 4 769 028, 5 089 267, 3 742 951, 3 797 494, 3 996 934 and 4 031 894.

It is made possible by the present invention to treat certain concomitant effects or sequelae of occasional or chronic use or abuse of addictive substances, by which means the general wellbeing of these patients is improved and the social reintegration of those chronically harmed by addictive substances is assisted. In addition, the galanthamine treatment proposed according to the invention improves the prospects of success of withdrawal therapies and reduces the risk of relapse. The treatment moreover promotes social reintegration of the persons affected.

The described psychiatric or cerebral disturbances, in particular an impairment of cognitive performance or dementia, may also occur as a result of the intake or the use or abuse of other addictive substances and intoxicants, or as a result of use or abuse of medicines. They may furthermore have been caused by intake or uptake of other agents, e.g. such as environmental poisons (PCB, dioxins, furans, pentachlorophenol, mercury compounds and bromine compounds, amalgam, chlorinated hydrocarbons such as certain solvents).
Besides ethyl alcohol which has already been mentioned, harmful agents also include methanol and other alcohols which may be present for example as impurities in alcoholic beverages.

Addictive substances and intoxicants therefore mean in principle for the purposes of the invention all

psychotropic substances, whether solid, liquid, in vapour or gas form, with which pathological manifestations of the type mentioned occur on single, occasional, frequent or chronic use or abuse.
The invention relates in particular to the following psychoactive drugs: neuroleptics, antidepressants, tranquillizers (especially benzodiazepines), antipsychotics, hypnotics, psychostimulants (especially amphetamines, "fashionable drugs" such as, for example ecstasy, speed with unstandardized mixtures of agents), natural psychotropic drugs and substances, and synthetic derivatives thereof (e.g. based on St John's wort, valerian, hops, melissa, lavender, kava-kava, absinthe, thorn apple (Datura stramonium), angel's trumpet (Brugsmania spp.), deadly nightshade (Atropa belladonna), GHB (gamma-hydroxybutyric acid); also tetrahydrocannabinol (THC) and THC-containing intoxicants such as marihuana and hashish, furthermore cocaine, crack, LSD, psilocybin, mescaline, mixtures of substances as in opium and absinthe, morphine and morphine derivatives such as heroin, codeine, methadone, scopolamine and hyoscyamine), and certain organic solvents such as acetone, petrol, ether, toluene, trichloroethylene, trichloromethane, and other gases and gas mixtures which are "sniffed" or inhaled, e.g. nitrous oxide.

Even on use as intended are some of the aforementioned substances which are employed for therapeutic purposes it is possible for the side effects mentioned to occur during medically prescribed therapy, especially on repeated or prolonged administration, e.g. cognitive disturbances, cerebral defunctionalization manifestations, psychiatric symptoms, etc.
The present invention therefore provides for the administration of the agent galanthamine to treat such

disorders which have been caused by the use as intended or abuse of the aforementioned substances. The same applies to intoxication by the environmental poisons mentioned.

It is also known that the side effects mentioned can be caused not only by use or abuse of psychotropic substances but also as a result of single, multiple or chronic administration of other medicaments. The use according to the invention of galanthamine therefore also extends to the treatment of symptoms or side effects caused in this way.

Cerebral disturbances or psychiatric symptoms, e.g. memory loss or cognitive disturbances, are also observed in the people affected by acute poisoning (e.g. chemical accidents) and in chronic exposure to poisons (e.g. environmental poisons such as wood preservatives, halogenated biphenyls, dioxins, furans, pentachlorophenol, mercury compounds and bromine compounds, mercury, amalgams, halogenated carbon and hydrocarbon compounds, especially chlorinated hydrocarbons, halogenated biphenyls, tributyltin, chromium(VI)-containing wood preservatives, etc.). The use according to the invention of galanthamine therefore also extends to the treatment of people who have been adversely affected by exposure to poisons in the aforementioned way.

Finally, the present application also proposes the administration of galanthamine in the abovementioned cases to other vertebrates, in particular to mammals, suffering from the symptoms or disturbances described above.

Claims

1. Use of galanthamine, as free base or as acid addition salt, for the treatment of disorders of the central nervous system such as cerebral, central nervous or psychiatric symptoms, defunctionalization manifestations or disorders occurring
- as a result of exposure to psychotropic substances
- as a result of occasional or chronic use or abuse of addictive substances, intoxicants or medicines, or
- as side effect of use, especially repeated or prolonged, as intended of medicaments, or
- as a result of acute poisoning, or
- as a result of chronic exposure to poisons
in humans or other vertebrates.

2. Use according to Claim 1, characterized in that the symptoms, defunctionalization manifestations or disorders are cognitive disturbances.

3. Use according to Claim 1 or 2, characterized in that the use or abuse of addictive substances comprises the use or abuse of alcohol.

4. Use according to Claim 1 or 2, characterized in that the use or abuse of addictive substances comprises the use or abuse of hallucinogenic substances.

5. Use according to any of Claims 1 to 4, characterized in that galanthamine is used to treat a general loss of control, of memory loss or of an impairment of memory performance, of cognitive ability, of dementia, of perception disturbances, or impairment of muscular coordination.

6. Use according to any of the preceding claims, characterized in that the dose administered is in the range from 0.1 to 100 mg, preferably 10 to 50 mg, per day.

7. Use according to any of the preceding claims, characterized in that galanthamine is administered in a pharmaceutical preparation which contains the agent in proportions of from 0.1 to 90% by weight, preferably 2 to 20% by weight, calculated as free galanthamine.

8. Use according to Claim 7, characterized in that galanthamine is administered in a pharmaceutical preparation which has a depot effect.

9. Use according to Claim 7 or 8, characterized in that galanthamine is administered orally.

10. Use according to Claim 7 or 8, characterized in that galanthamine is administered parenterally.

11. Use according to Claim 10, characterized in that galanthamine is administered transdermally.

12. Use of galanthamine, as free base or as acid addition salt, for the manufacture of a medicament for the treatment of cerebral, central nervous or psychiatric symptoms, defunctionalization manifestations or disorders occurring
- as a result of occasional or chronic use or abuse of addictive substances, intoxicants or medicines, or
- as side effect of use, especially repeated or prolonged, as intended of medicaments, or
- as a result of poisoning, or
- as a result of chronic exposure to environmental poisons in humans or other vertebrates.

13. Use according to Claim 12, characterized in that the symptoms, defunctionalization manifestations or disorders are cognitive disturbances.

14. Use according to Claim 12, characterized in that the use or abuse of addictive substances comprises use or abuse of alcohol.

15. Use according to Claim 12, characterized in that the use or abuse of addictive substances comprises the use or abuse of psychotropic substances, in particular of hallucinogenic substances.

16. Use according to any of Claims 12 to 15, characterized in that the medicament is used for the treatment of a general loss of control, of memory loss or of impairment of memory performance, of cognitive ability, of dementia, of perception disturbances, or of an impairment of muscular coordination.

17. Use according to any of Claims 12 to 16, characterized in that the medicament mentioned contains the agent galanthamine in proportions of from 0.1 to 90% by weight, preferably 2 to 20% by weight, calculated as free galanthamine.

18. Use according to any of Claims 12 to 17, characterized in that the medicament mentioned has a depot effect.

19. Use according to any of Claims 12 to 18, characterized in that the medicament mentioned is a medicament which can be administered orally.

20. Use according to any of Claims 12 to 18, characterized in that the medicament mentioned is a medicament which can be administered parenterally.

21. Use according to Claim 20, characterized in that the medicament mentioned is a medicament which can be administered transdermally.