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(54) Benævnelse: **FARMACEUTISK SAMMENSÆTNING OMFATTENDE LACOSAMID OG LEVETIRACETAM MED SYNERGISTISK ANTIKONVULSIV VIRKNING**

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Description

[0001] The present application items the priorities of US 60/813.967 of 15 June 2006, EP 06 021 470.7 of 12 October 2006, EP 06 021 469.9 of 12 October 2006, and EP 06 024 241.9 of 22 November 2006.

[0002] The present invention is directed to a pharmaceutical composition comprising a compound (a) of a class of peptide compounds and at least one further compound (b) for the prevention, alleviation or/and treatment of epileptic seizures wherein this composition has a synergistic effect on the prevention, alleviation or/and treatment of epileptic seizures as compared to the effect of the compounds (a) or (b) given alone.

[0003] Certain peptides are known to exhibit central nervous system (CNS) activity and are useful in the treatment of epilepsy and other CNS disorders. These peptides are described in the U.S. Patent No. 5,378,729 and in U.S. Patent No. 5,773,475.

[0004] EP 1 541 138 is directed to the use of a class of peptide compounds for treating status epilepticus or related conditions, such as acute repetitive seizures and seizure clusters. EP 1 541 138 is further directed to the prevention of generalized tonic clonic convulsions.

[0005] Seizures are the consequence of a paroxysmal brain dysfunction related to excessive neuronal activity that leads to an alteration of behaviour or consciousness. Epilepsy represents the recurrence of two or more unprovoked seizures and represents a chronic brain disease.

[0006] There are two major types of seizures: partial or focal seizures, which originate in a location in the brain, but can spread in the course of the event; and generalized seizures, which can affect both hemispheres simultaneously. Partial seizures are manifested in multiple ways depending on the area that is affected (confusion, automatic body movements, hallucinations, etc), and if they spread in the brain can end up in a generalized tonic-clonic event (a convulsion). There are several types of generalized seizures: convulsive (tonic-clonic, tonic, clonic, myoclonic) and non-convulsive (absences, atonic). Typically all kinds of seizures last a few minutes, usually less than five minutes. Convulsive seizures, particularly tonic-clonic events, typically result in the loss of consciousness.

[0007] Status epilepticus (SE) has been defined as a seizure that lasts for 30 or more minutes, or a series of consecutive seizures that occur for 30 or more minutes during which the subject does not completely recover consciousness. Many clinicians and many recent major research articles, however, consider a patient to be in SE if seizures last more than 5 minutes. There are two main types of SE: generalized SE, which can be convulsive or non-convulsive, and focal SE. Generalized convulsive SE is the most severe type and is associated with high morbidity and mortality. SE can occur in patients with a prior diagnosis of epilepsy. However, the onset of SE is more frequent in subjects without previous epilepsy and is often related to a severe and acute brain disease (for example, encephalitis or stroke) or trauma. In addition to these, a variety of conditions including

hypoglycemia, hyperthermia, drug overdose and alcohol or drug withdrawal can be a cause of SE. Thus, anticonvulsant activity of a compound or combination, for example in models for or patients with complex partial seizures, is not necessarily predictive for activity against SE. SE is not only a life threatening disease but also causes neuronal cell loss and epileptogenesis.

[0008] In spite of remarkable medical advances in the past 50 years, progress in epilepsy therapy has been quite inadequate for a large number of patients. The worldwide prevalence of epilepsy is estimated at between 0.3 and 0.6% (Sander et al., 1987; Schmidt et al., 1986; Loiseau, 1988). About 20-30% of patients suffer from intractable epilepsy or severe side effects despite early treatment and an optimum daily dosage of an adequate antiepileptic drug (Schmidt, 1992; Kramer, 1997; Brodie, 2001). In such cases, an alternative monotherapy may control the seizures; however, a complete suppression of convulsive attacks can be seldom achieved with an AED, even if it is administered at the maximally prescribed dose (Kramer, 1997). When monotherapy with antiepileptic drugs fails, combination therapy is tried in an attempt to improve effectiveness by improving efficacy, tolerability or both.

[0009] Lacosamide (LCM, R-2-acetamido-N-benzyl-3-methoxypropionamide) is a member of a series of functionalized amino acid with anticonvulsant activity. The anticonvulsant activity has been shown in large clinical studies and in animal models of epilepsy, including maximal electroshock seizure [MES], the 6 Hz refractory seizure model, and sound-induced seizure in Frings mice (Bialer et al., 2001, 2002; Hovinga 2003). Further, LCM is active against refractory self-sustaining status epilepticus. In addition to the activity of the drug in electrically induced seizures, it is effective against cobalthomocysteine- and lithium-pilocarpine-induced status epilepticus (Bialer et al., 2001, 2002).

[0010] Initially there was a suggestion that LCM possessed affinity for the strychnine-insensitive glycine site of the NMDA receptor, however, further study suggest that this might not be a direct effect by which the drug exerts its anticonvulsant activity (Bialer et al., 2001, 2002). In receptor-binding studies (on more than 100 different sites), neither LCM nor its metabolites bind to a large variety of neurotransmitter receptors or ion channels (Errington et al. 2006). In cell/tissue culture, LCM had no effects on NMDA-evoked currents or at voltage gated sodium channels. In mouse cortical neurons, the drug increased GABA currents and inhibited glutamate transmission indirectly, most likely through non-specific mechanism (Bialer et al., 2002). Recent data indicate that LCM has a dual mode of action: it enhances slow inactivation of voltage-gated sodium channels and modulates collapsing response mediator protein CRMP-2.

[0011] The preclinical profile suggests that LCM will be useful in the treatment of partial onset and generalized tonic-clonic seizures. New antiepileptic drugs (AED) such as LCM are initially licensed as add-on treatment, often with no evidence to suggest which existing therapies they should be employed with. In addition, approximately 30 % of patients with epilepsy are prescribed polytherapy regimens. There is, thus, a clear need to develop a rational basis for AED polytherapy, i.e. to develop anticonvulsant compositions with improved effectiveness by improving efficacy, tolerability, or both. Effective AED combinations were empirically evaluated in patients with intractable seizures; however, such evaluations were often accompanied with deleterious adverse-effect reactions

(Warner et al., 1992; Luszczki et al., 2003). Thus, preclinical models are used as an alternative for the evaluation of pharmacodynamic drug interactions.

[0012] Pharmaceutical compositions comprising (a) lacosamide and (b) levetiracetam for the prevention, alleviation or/and treatment of epileptic seizures wherein the effect of this composition in the prevention, alleviation or/and treatment of epileptic seizures is synergistic as compared to the effect of the compounds (a) or (b) given alone have not been reported previously. Thus, the present invention concerns a pharmaceutical composition comprising (a) lacosamide or a pharmaceutically acceptable salt thereof, and (b) levetiracetam for the prevention, alleviation or/and treatment of epileptic seizures optionally together with a pharmaceutically acceptable carrier, diluent or/and adjuvant. The effect of this composition in the prevention, alleviation or/and treatment of epileptic seizures may be synergistic as compared to the effect of the compounds (a) or (b) given alone.

[0013] In this application, the compound (a) refers to lacosamide, and the compound (b) refers to levetiracetam.

[0014] The term "synergistic effect on the prevention, alleviation or/and treatment of epileptic seizures" refers to an effect of the pharmaceutical composition according to the invention on the prevention, alleviation or/and treatment of epileptic seizures that is more than additive as compared to the effect of the compounds (a) or (b) given alone.

[0015] The synergistic effect of the present invention may be defined as a synergism of the combination of compounds (a) and (b) in a therapeutically desired effect (synergistic therapeutic effect) in the treatment of epileptic seizures.

[0016] The synergistic effect of the present invention may also be defined as a synergism of the combination of compounds (a) and (b) in reduction of adverse side effect, which may be smaller in the combination of compounds (a) and (b) as compared to the side effects of compounds (a) and (b) given alone.

[0017] According to Deckers et al. (2000) an isobolographic method used to evaluate interactions among AEDs is considered to be the optimal method for detecting synergy, additivity or antagonism among AEDs in animal models of epilepsy, such as the 6Hz seizure model in mice. For isobolographic analysis, the experimental (EDmix) and theoretical additive (EDadd) ED50 values are determined from the dose-response curves of combined drugs. ED50 is defined as a dose of a drug protecting 50% of the animals against 6 Hz-induced seizures. ED50mix is an experimentally determined total dose of the mixture of two component drugs, which were administered in the fixed-ratio combination sufficient for a 50% protective effect. Conversely, ED50add represents a total additive dose of two drugs (calculated from the line of additivity), theoretically providing 50% protection against seizures.

[0018] The term "interaction index α" refers to the ratio of ED50mix/ED50add. This ratio seems to be a good describer of the strength of interaction between two AEDs in isobolographic analysis (Luszczki et al., 2003; Berenbaum, 1989; Tallarida et al., 1999; Tallarida, 2001, 2002). If ED50mix = ED50add, then α = 1. Small derivations of α from 1

may not be considered as significant. If α is smaller than 0.7, this may indicate a synergistic effect. If the index is larger than 1.3, this may indicate an antagonistic effect, and if the index is in between this may indicate purely additive interaction (Luszczki et al., 2003; Kerry et al., 1975; Bourgeois, Wad, 1984, 1988; Bourgeois, 1988).

[0019] In a preferred embodiment, the synergistic effect of the pharmaceutical composition of the present invention is defined as a value of the interaction index α of the composition of up to 0.7, preferably of up to 0.6, more preferably of up to 0.5, wherein α > 0. Examples for the interaction index α are 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, and 0.7.

[0020] A protective index (PI) can be calculated by dividing a given TD50, determined in an animal model quantifying toxic effects of anticonvulsants, by the respective ED50 determined in an animal model for epileptic seizures. The PI is considered a satisfactory margin of safety between AED doses and doses of AEDs exerting sedative, ataxic, or other neurotoxic side effects (Löscher et al., 1991). PI_{mix} is a protective index experimentally determined, and PI_{add} is a protective index theoretically calculated from the lines of additivity in the epileptic seizure model and the model quantifying toxic effects.

[0021] The term "benefit index (BI)" refers to a quotient of PI_{mix} and PI_{add} of respective fixed-ratio combinations, obtained directly from the isobolographic analysis. BI unequivocally estimates advantages of the combination of two drugs applied in various fixed-ratio combinations. Moreover, BI may provide the rationale for combining the respective AEDs in clinical practice if its value is > 1.3, whereas BI < 0.7 may indicate unfavourable combinations of AEDs (Luszczki et al., 2003, Epilepsia 44: 489).

[0022] In another preferred embodiment, the synergistic effect of the pharmaceutical composition of the present invention is defined as a value of the benefit index BI of the composition of at least 1.3, preferably of at least 1.4, more preferably of at least 1.5. Examples for the benefit index BI are 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, and 2.0.

[0023] The term "fixed-dose ratio of compound (b) : compound (a) of 1:1, calculated on the ED50 values of the individual compounds (b) and (a)" refers to compositions comprising both compound (b) and compound (a) in a dose corresponding to 50 % of the respective ED50 dose of the individual compounds (b) and (a) or a multiple of this fixed-dose ratio. Correspondingly, a "fixed-dose ratio of compound (b) : compound (a) of 3:1, calculated on the ED50 values of the individual compounds (b) and (a)" refers to compositions comprising compound (b) in a dose corresponding to 75 % of the respective ED50 dose and compound (a) in a dose corresponding to 25 % of the respective ED50 dose of compound (a) or a multiple of this fixed-dose ratio.

[0024] In general, the "fixed-dose ratio of compound (b) : compound (a) of X:Y, calculated on the ED50 values of the individual compounds (b) and (a)" refers to compositions comprising both compound (b) and compound (a), wherein the dose of compound (b) corresponds to $X\text{-}ED_{50}/(X+Y)$ of compound (b), and the dose of compound (a) corresponds to $Y\text{-}ED_{50}/(X+Y)$ of compound (a), or a multiple of this fixed dose ratio.

[0025] Thus, a composition comprising both compound (b) and compound (a) in a fixed dose ratio of at least X:Y comprises at least X/(at least X+Y) parts of compound (b),

wherein 1 part is an amount corresponding to the ED50 of compound (b), and Y/(at least X+Y) parts of compound (a), wherein 1 part is an amount corresponding to the ED50 of compound (a), or a multiple of this fixed dose ratio.

[0026] The term "multiple" refers to a composition comprising a larger or a smaller amount of compounds (a) and (b) with reference to the amount as defined by the ED50 values, while maintaining the fixed dose ratio. A composition comprising a multiple of the fixed dose ratio as indicated above may thus comprise at least 0.1 times the fixed dose ratio, at least 0.2 times, at least 0.5 times, at least 2 times, at least 5 times, or at least 10 times the fixed dose ratio, or/and at the maximum 100 times the fixed dose ratio, at the maximum 50 times, or at the maximum 20 times the fixed dose ratio.

[0027] In yet another preferred embodiment, compound (b) and compound (a) are present in the pharmaceutical composition of the present invention in a fixed-dose ratio of compound (b) : compound (a) of 1:6 to 6:1, preferably of 1:3 to 6:1, more preferably of 1:1 to 6:1, even more preferably of 3:1 to 6:1, wherein the fixed-dose ratio is calculated on the ED_{50} values of the individual compounds (b) and (a). Examples for fixed-dose ratios of compound (b) : compound (a) according to the present invention are fixed-dose ratios of 1:6, 1:3, 1:1, 3:1, and 6:1. Further examples for fixed-dose ratios according to the present invention are fixed-dose ratios of 1:5, 1:4, 1:2, 2:1, 4:1, and 5:1.

[0028] In a preferred embodiment, compound (b) and compound (a) are present in the pharmaceutical composition of the present invention in a fixed-dose ratio of compound (b) : compound (a) of at least 1:6, at least 1:3, at least 1:1, more preferably at least 3:1, wherein the fixed-dose ratio is calculated on the ED_{50} values of the individual compounds (b) and (a). Examples for fixed-dose ratios of compound (b) : compound (a) according to this more preferred embodiment of the present invention are fixed-dose ratios of 1:1, 2:1, 3:1, 4:1, 5:1, and 6:1.

[0029] In yet another preferred embodiment, compound (b) and compound (a) are present in the pharmaceutical composition of the present invention in a fixed-dose ratio of compound (b) : compound (a) of at the maximum 6:1, wherein the fixed-dose ratio is calculated on the ED_{50} values of the individual compounds (b) and (a).

[0030] The skilled person may determine the ED50 values by methods known in the art. It is preferred that the ED50 values are determined by preclinical or/and clinical trials. Published ED50 values may also be used. ED50 values are published for lacosamide, and levetiracetam. Tables 1, 5 and 6 disclose specific ED50 values obtained in various models of the rat and the mouse. A person skilled in the art knows that in a particular model, among different species, ED50 values show a variation by a factor of up to 5 or even larger.

[0031] In particular, the ED50 of lacosamide is in a range of at least 0.5 mg/kg up to 30 mg/kg body weight p.o. or i.p. More particularly, the ED50 of lacosamide is 10 mg/kg body weight i.p.

[0032] In particular, the ED50 of levetiracetam in a range of at least 10 mg/kg up to 100

mg/kg body weight p.o. or i.p. More particularly, the ED50 of levetiracetam is 20 mg/kg body weight i.p.

[0033] Levetiracetam is the ethyl derivative of piracetam and belongs to the group of racetams. Racetams may have a synergistic effect in the prevention, alleviation or/and treatment of epileptic seizures, as compared to the effect of lacosamide and a racetam alone, wherein epileptic seizures are as defined herein.

[0034] A particularly preferred pharmaceutical composition of the present invention comprises levetiracetam and lacosamide or/and a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier, diluent or/and adjuvant.

[0035] This particularly preferred composition may have a synergistic effect in the prevention, alleviation or/and treatment of epileptic seizures, as compared to the effect of lacosamide and levetiracetam alone, wherein epileptic seizures are as defined herein.

[0036] In this particularly preferred composition, levetiracetam and lacosamide may be present in a fixed-dose ratio of levetiracetam : lacosamide of at least 1:3, at least 1:1, or at least 3:1, wherein the fixed-dose ratio is calculated on the individual ED50 values of levetiracetam and lacosamide. In this particularly preferred composition, the fixed-dose ratio of levetiracetam : lacosamide may be at the maximum 6:1. The fixed dose ratio may be calculated on the basis of a levetiracetam ED50 value or/and a lacosamide ED50 value disclosed herein, or on the basis of ED50 values known in the art.

[0037] This particularly preferred composition may comprise levetiracetam in a dose of at least 1000 mg/day up to 3000 mg/day and lacosamide in a dose of at least of 100 mg/day, preferably at least of 200 mg/day, more preferably at least of 300 mg/day, most preferably at least of 400 mg/day, and in a dose of at a maximum of 6 g/day, more preferably at a maximum of 1 g/day and most preferably at a maximum of 600 mg/day.

[0038] In the particularly preferred compositions described herein, the synergistic effect may also be defined in terms of the interaction index a, as described herein, or in terms of the benefit index, as described herein.

[0039] The particularly preferred pharmaceutical compositions described herein may preferably be prepared for i.v. or oral administration.

[0040] In yet another embodiment of the present invention, the synergistic effect of the pharmaceutical composition of the present invention is defined as a reduced adverse effect of the combination of compound (a) and compound (b) as compared with the compounds (a) and (b) given alone.

[0041] A synergistic side effect reduction may not only be found in those combinations exhibiting a synergistic therapeutic effect, but may also be found in those combinations of compounds (a) and (b) exhibiting an additive therapeutic effect or a non-significant synergistic therapeutic effect in the treatment of epileptic seizures.

[0042] In a preferred embodiment, the epileptic seizures are selected from partial seizures with and without secondary generalisation, primarily generalised seizures, and status epilepticus.

[0043] Yet another aspect of the present invention is the use of the pharmaceutical composition of the invention for the preparation of a medicament for the prevention, alleviation or/and treatment of epileptic seizures, wherein epileptic seizures are as defined herein.

[0044] Yet another aspect of the present invention is a method for the prevention, alleviation or/and treatment of epileptic seizures, wherein epileptic seizures are as defined herein, comprising administering an effective amount of the pharmaceutical composition of the invention to a subject in need thereof.

[0045] Lacosamide is well tolerated, which is an advantage over other commonly used therapeutics for treatment of epileptic seizures.

[0046] Lacosamide and levetiracetam may be formulated in one pharmaceutical preparation (single dosage form) for administration at the same time or may be formulated in two or more distinct preparations (separate dosage forms), which separate dose forms may be administered simultaneously or/and subsequently. The distinct preparations in the separate dosage forms may be administered by the same route or by different routes.

[0047] The pharmaceutical composition of the present invention may thus comprise a single dosage form comprising lacosamide and levetiracetam.

[0048] The pharmaceutical composition of the present invention may also comprise a separate dosage form comprising

(i) lacosamide and

(ii) levetiracetam.

[0049] In yet another preferred embodiment of the present invention, the second composition (ii) may be a commercially available composition.

[0050] Separate dosage forms can optionally be co-packaged, for example in a single container or in a plurality of containers within a single outer package, or co-presented in separate packaging ("common presentation"). As an example of co-packaging or common presentation, a kit is contemplated comprising, in separate containers, lacosamide and levetiracetam. In another example, lacosamide and levetiracetam are separately packaged and available for sale independently of one another, but are co-marketed or copromoted for use according to the invention. The separate dose forms may also be presented to a subject separately and independently, for use according to the invention.

[0051] The pharmaceutical composition of the present invention is preferably prepared for administration in mammals, preferably in humans.

[0052] The pharmaceutical composition of the present invention comprising (a) lacosamide and (b) levetiracetam may be prepared for the prevention, alleviation or/and treatment of epileptic seizures, as defined herein.

[0053] The administration interval of lacosamide and levetiracetam may depend on the dosage forms. Lacosamide may be administered first, or levetiracetam may be administered first.

[0054] It is preferred that lacosamide is substantially enantiopure. As used herein, the term "substantially enantiopure" refers to a content of the R enantiomer of at least 99.5%. This corresponds to an enantiomeric excess (ee) of 99%. The respective quantities of R and S enantiomer may be determined by chiral column chromatography, e.g. by HPLC with "ChiralPak" as chiral, stationary phase.

[0055] Lacosamide can be employed in the form of salts in view of its basic nature by the presence of the free amino group. Thus, lacosamide may form salts with a wide variety of acids, inorganic and organic, including pharmaceutically acceptable acids. The salts with therapeutically acceptable acids are of course useful in the preparation of formulation where enhanced water solubility is most advantageous.

[0056] These pharmaceutically acceptable salts have also therapeutic efficacy. These salts include salts of inorganic acids such as hydrochloric, hydroiodic, hydrobromic, phosphoric, metaphosphoric, nitric acid and sulfuric acids as well as salts of organic acids, such as tartaric, acetic, citric, malic, benzoic, perchloric, glycolic, gluconic, succinic, aryl sulfonic, (e.g., p-toluene sulfonic acids, benzenesulfonic), phosphoric, malonic, and the like.

[0057] The physician will determine the dosage of the present therapeutic combinations which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, the type of malady being treated. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the combinations and increase the dosage by small increments until the optimum effect under the circumstances is reached. When the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The combinations of the present invention are useful in the same manner as comparable therapeutic agents and the dosage level is of the same order of magnitude as is generally employed with these other therapeutic agents.

[0058] In a preferred embodiment, lacosamide is administered in amounts ranging from 1 mg to 100 mg per kilogram of body weight per day, more preferably in amounts ranging from 1 mg to 10 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. Patients in need thereof may be treated with doses of the compound (a) of the present invention of at least

50 mg/day, preferably of at least 200 mg/day, more preferably of at least 300 mg/day, still more preferably of at least 400 mg/day and most preferably of at least 600 mg/day. Generally, a patient in need thereof may be treated with doses at a maximum of 6 g/day, more preferably a maximum of 1 g/day, still more a maximum of 800 mg/day, and most preferably a maximum of 600 mg/day. In some cases, however, higher or lower doses may be needed.

[0059] In a further preferred embodiment, levetiracetam is administered in amounts ranging from 100 mg/day to 4 g/day.

[0060] In another preferred embodiment, the daily doses are increased until a predetermined daily dose is reached which is maintained during the further treatment.

[0061] In yet another preferred embodiment, several divided doses may be administered daily. For example, three doses per day may be administered, preferably two doses per day. It is more preferred to administer a single dose per day.

[0062] In yet another preferred embodiment, an amount of lacosamide may be administered which results in a plasma concentration of 0.1 to 15 µg/ml (trough) and 5 to 18.5 µg/ml (peak), calculated as an average over a plurality of treated subjects, intravenous administration in emergency treatment might result in peak plasmid levels of up to 30 µg/ml.

[0063] The combinations of lacosamide and levetiracetam may be administered in a convenient manner, such as by oral, intravenous (where water soluble), intramuscular, intrathecal, rectal (e.g. suppository, gel, liquid, etc.) or subcutaneous routes. Oral, rectal or/and i.v. administration is preferred. In emergency treatment, i.v. administration is most preferred.

[0064] The pharmaceutical composition of the present invention may be prepared for the treatment regimen as described above, in particular for the treatment with doses as described above, to effect plasma concentrations as described above, for administration periods or/and administration routes as specified in the embodiments of the present invention as described above.

[0065] The combinations of lacosamide and levetiracetam may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly into the food of the diet. For oral therapeutic administration, the combinations of lacosamide and levetiracetam may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1 % of lacosamide. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between 5 to 80 % of the weight of the unit. The amount of combinations of lacosamide and levetiracetam in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g active compound of lacosamide.

[0066] The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier.

[0067] Various other materials may be present as coatings or otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. For example, sustained release dosage forms are contemplated wherein the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to modify the release properties of the resin.

[0068] The pharmaceutical composition may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0069] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin.

[0070] Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle

which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of preparing sterile powders for the manufacture of sterile injectable solutions, the preferred methods of preparation are vacuum drying, or freeze-drying optionally together with any additional desired ingredient.

[0071] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agent, isotonic and absorption delaying agents for pharmaceutical active substances as well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0072] It is especially advantageous to formulate parenteral compositions in dosage unit form or ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifics for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material an the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such as active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

[0073] The principal active ingredients are compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound (a) in amounts ranging from 10 mg to 6 g. Expressed in proportions, the active compound is generally present in from 1 to 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

[0074] As used herein the term "patient" or "subject" refers to a warm blooded animal, and preferably mammals, such as, for example, cats, dogs, horses, cows, pigs, mice, rats and primates, including humans. The preferred patient is a human.

[0075] The term "treat" refers to either relieving the pain associated with a disease or condition, to curing or alleviating the patient's disease or condition.

[0076] The compounds of the present invention are administered to a patient suffering from the aforementioned type of disorder in an effective amount. These amounts are equivalent to the therapeutically effective amounts described hereinabove.

[0077] The present invention is further illustrated by the following example, figures, and tables.

Figure and Table legends

[0078]

Figure 1: Isobologram showing interactions between levetiracetam (LEV) and lacosamide (LCM) for three fixed-ratio combinations in the 6 Hz induced seizure model in mice. Median effective dose (ED50) values for LEV and LCM are placed on the X- and Y-axes, respectively. The straight line connecting these both ED50 values represents the theoretic line of additivity for a continuum of different fixed-dose ratios. The solid points depict the experimentally derived ED50mix values (with 95% confidence limits as the error bars) for total dose expressed as the proportion of LEV and LCM that produce a 50% effect.

Table 1: Effects of LCM and conventional antiepileptic drugs against 6 Hz seizure in mice. Confidence limits are indicated in brackets. AEDs other than LEV and LCM are included as comparisons.

Table 2: Isobolographic characterization of the interaction between LCM and LEV in the 6 Hz seizures tests in mice.

Table 3: The effects of levetiracetam administered alone and in combination with lacosamide on motor coordination in the rotarod test in mice. The results of the rotarod test are expressed as a percentage of animals showing motor co-ordination impairment. Each group consisted of 10 animals. For the testing of levetiracetam alone at its ED_{50}, each group consisted of 20 animals. The Fisher's exact test was used for statistical comparisons.

Table 4: Summary of combined interaction results for LEV+LCM obtained in 6 Hz-induced seizures model in mice.

Table 5: Profile of anticonvulsant activity and minimal toxicity of lacosamide in mice and rats

Table 6: Profile of anticonvulsant activity and minimal toxicity of prototype anticonvulsants in mice and rats

[0079] MES = maximal electroshock, Sc subcutaneous, Met = Metrazol/Chemoconvulsant, Bic = Bicucullin/Chemoconvulsant, Pic = Picrotoxin/Chemoconvulsant, AGS = audiogenic seizures.

Example

[0080] The aim of this study was to investigate potential interactions between LCM and Levetiracetam (LEV) in the 6Hz seizure model in mice using the isobolographic analysis.

According to Deckers et al. (2000) an isobolographic method used to evaluate interactions among AEDs is considered to be the optimal method for detecting synergy, additivity or antagonism among AEDs in animal models of epilepsy. The adverse effects of such combinations were evaluated in the rotarod test.

Animals

[0081] The experiments were performed on adult male CBA mice (University Odessa) weighing between 20 and 28 g. The mice were kept in colony cages with free access to food and water, under standard laboratory conditions with natural light-dark cycle. After 1 week adaptation to laboratory conditions, the animals were randomly assigned to experimental groups consisting of ten mice. Each mouse was used only once. All experiments were performed between 9 am and 4 pm. Procedures involving animals and their care were conducted in accordance with current European Community regulations.

Drugs

[0082] The following AEDs were used in this study: LCM, LTG, VPA, CBZ, PHT, LEV, TPM, GBP donated by SCHWARZ Pharma. All drugs were dissolved in 0.5% methylcellulose and administered intraperitoneally (i. p.) in a volume of 0.2 ml/20 g body weight (CBZ, VPA - 15 min; LCM, LTG - 30 min; LEV, GBP - 60 min; PHT, TPM - 120 min before the test).

[0083] Fresh drug solutions were prepared ex tempore on each day of experimentation. These pretreatment times before testing of AEDs were based on information about their biologic activity from the literature (Barton et al., 2001; Luszczki et al., 2006).

6 Hz seizure test

[0084] "Psychomotor" seizures were induced via corneal stimulation (6Hz, 32 mA, 0.2 ms rectangular pulse width, 3 s duration) using a Grass S48 stimulator (Barton et al., 2001).

[0085] At the time of drug administration, a drop of 0.5% tetracaine was applied to the eyes of all animals. Prior to the placement of corneal electrodes a drop of 0.9% saline was placed on the eyes. Animals were manually restrained and released immediately following the stimulation and observed for the presence or absence of seizure activity, being characterized by stun, forelimb clonus twitching of the vibrissae and Straub-tail. Protection was defined as the absence of a seizure (Barton et al., 2001). In control groups (with vehicle injection) all animals exhibited seizures. The protective efficacy of AEDs was determined as their ability to protect 50% of mice against 6 Hz seizure and expressed as respective median effective dose (ED50) values. To evaluate each ED50 value, at least four groups of 10 mice, after receiving progressive doses of an AED, were challenged with

6 Hz seizure. ED50 values (with 95% confidence limits) were calculated by computer probit analysis (Litchfield, Wilcoxon, 1949) and subsequently transformed into standard errors of mean (SEM).

Rotarod test

[0086] The impaired motor function was quantified by the rotarod test in mice according to Dunham and Miya (1957). The rotarod test was undertaken by use of a rod of 3 cm diameter, rotating at constant speed of 6 rpm. In this test, an acute neurological deficit (adverse effects produced by AEDs) was indicated by the inability of the animals to maintain their equilibrium for at least 120 s on the rotating rod. The dose ratio assessed in this model was always 1:1. For comparison, each AED was tested alone at its ED50 and 50% of its ED50 in the 6Hz model.

Data analysis

[0087] The isobolographic analysis is based on a comparison of equieffective drug doses. In the present study, interactions between drugs, as regards their anticonvulsant efficacy against 6 Hz seizure test were evaluated isobolographically according to the procedure elaborated by Tallarida (1992); Porreca et al. (1990); Luszczki et al. (2006). The experimental (EDmix) and theoretical additive (EDadd) were determined from the dose-response curves of combined drugs (Tallarida et al., 1997). ED50 is defined as a dose of a drug protecting 50% of the animals against 6 Hz-induced seizures. ED50mix is an experimentally determined total dose of the mixture of two component drugs, which were administered in the fixed-ratio combination sufficient for a 50% protective effect. Conversely, ED50add represents a total additive dose of two drugs (calculated from the line of additivity), theoretically providing 50% protection against seizures. The respective 95% confidence limits of EDmix were calculated according to Litchfield and Wilcoxon (1949), and these of EDadd according to Tallarida and Murray (1987), and subsequently transformed to SEM, according to a procedure described in detail by Luszczki, et al. (2003).

[0088] To estimate the types of interactions, three fixed-dose ratios of the drugs were examined as follows 1:3, 1:1, and 3:1 in the 6 Hz-induced seizures. To visualize the types of interactions between LCM and AEDs studied, the isoboles were drawn by plotting the points reflecting the respective doses of LCM (on Y-axis) and doses of an AED on the X-axis. The straight line connecting ED50 values for the two tested drugs administered alone against 6 Hz-induces seizures, represents the theoretic isobole for additivity. If experimentally determined data points, reflecting the combinations of various fixed ratios, lie on this line the drug effects are additive (no interaction). If the points fall significantly below the additive line, the two component drugs act synergistically. Conversely, antagonism may be recognized if these points are localized above the additive isobole.

[0089] Moreover, an interaction index for various fixed-ratio combinations of two AEDs in

the 6 Hz-test was calculated as a ratio ED50mix / ED50add. This ratio seems to be a good describer of the strength of interaction between two AEDs in isobolographic analysis (Luszczki et al., 2003; Berenbaum, 1989; Tallarida et al., 1999; Tallarida, 2001, 2002). If the index is smaller than 0.7, this indicates a synergistic effect. If the index is larger than 1.3, this indicate an antagonistic effect, and if the index is in between this indicates purely additive interaction (Luszczki et al., 2003; Kerry et al., 1975; Bourgeois, Wad, 1984, 1988; Bourgeois, 1988).

[0090] A protective index (PI) can be calculated by dividing a given TD50, obtained in the rotorod test, by the respective ED50 determined in the 6 Hz seizure test. The PI is considered a satisfactory margin of safety between AED doses and doses of AEDs exerting sedative, ataxic, or other neurotoxic side effects (Loscher, W., Nolting, B., The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. IV. Protective indices, Epilepsy Res (1991), 9:1-10).

[0091] A benefit index (BI) is defined as a quotient of PI_{mix} and PI_{add} of respective fixed-ratio combinations, obtained directly from the isobolographic analysis. PI_{mix} is a protective index experimentally determined, and PI_{add} is a protective index theoretically calculated from the lines of additivity in the 6 Hz seizure and the rotorod test. BI unequivocally estimates advantages of the combination of two drugs applied in various fixed-ratio combinations. Moreover, BI provides the rationale for combining the respective AEDs in clinical practice if its value is > 1.3, whereas BI < 0.7 indicates unfavourable combinations of AEDs. (Luszczki JJ, Borowicz KK, Swiader M, Czuczwar SJ, Interactions between oxcarbazepine and conventional antiepileptic drugs in the maximal electroshock test in mice: an isobolographic analysis, Epilepsia (2003), 44:489-99).

RESULTS

1. AED anticonvulsant effects against 6 Hz-induced seizures in mice.

[0092] All studied AEDs (LCM, LTG, VPA, CBZ, PHT, LEV, TPM, GBP) produced dose-dependent anticonvulsant effects against 6 Hz seizure in mice. The ED50 values for the drugs administered alone are presented in Table 1. Among the drugs Lacosamide displayed the highest potency (i.e. lowest ED50).

2. Isobolographic analysis of interactions between LCM and numerous AEDs in the 6 Hz- seizure model.

[0093] Based on ED50 values determined for each AED individually, a theoretical additive ED50 for drug mixtures (ED50add values) was calculated for three fixed-ratios (1:3, 1:1 and 3:1). Subsequently, the experimental ED50mix values were determined for the same fixed-ratio combinations in the 6 Hz seizure test (Table 2). Interaction between LCM+LEV

(Figure 1) were synergistic across all ratios (Table 2), since interaction indices for these combinations were lower than 0.7 (Table 2).

3. Rotarod test

[0094] Detailed results are shown in Table 3. LCM co-administered with LEV in the dose ratio of 1:1 did not produce significant impairment of motor performance in mice.

[0095] Table 4 summarizes the types of interactions observed between LEV and LCM with respect to 6 Hz-induced seizures test.

DISCUSSION

[0096] This study demonstrates that LCM fully protected mice from 6 Hz psychomotor seizures with an ED50 of 10.1 mg/kg. This dose corresponds well with the ED50 (9.9 mg/kg) determined in the anticonvulsant drug screening program of NINDS but is 2-3 times higher than the ED50 needed for protection of maximal electroshock seizures in mice and rats (Stoehr et al., submitted). In general our data are in agreement with those reported by Barton et al. (2001). Lacosamide is the drug with the highest potency in this model when compared to the other tested AEDs. In contrast to the sodium channel modulators phenytoin, lamotrigine and carbamazepine it did not impair rotarod performance at pharmacological doses.

[0097] The 6Hz test is regarded a model for treatment resistant seizures e.g. due to the observation that LEV provides complete protection in this model despite being inactive in a variety of other models (Gower et al., 1993; Klitgaard et al., 1998; Löscher, Honack, 1993; Patsalos, 2004). Our data confirm the differences in the pharmacological profile of the MES and 6 Hz seizure models. Barton et al. (2001) used the immediate early gene c-Fos as a marker of seizure induced neuronal activation and showed that 6 Hz induced seizures result in a clearly different pattern of neuronal activation than that observed following maximal electroshock or PTZ induced seizures. Duncan and Kohn (2004) showed by using the 2-deoxy glucose technique that this specific pattern of neuronal activation was attenuated by lacosamide while the drug had no effect on basal patterns.

[0098] The isobolographic analysis revealed that LCM acts synergistically with LEV across all examined fixed ratios.

[0099] None of the drug combinations studied exhibited infraadditive effects (antagonism between drugs for antiseizure efficacy) or potentiation of toxicities. In no cases in which there was potentiation of antiseizure activities there was also potentiation of acute neurotoxicities. This is, of course, a desirable interaction for any drug combination since the result is an improved margin of safety.

[0100] We can suggest some mechanism underlying the different types of interactions

observed between LCM and LEV. First of all one can exclude pharmacokinetic effects as the reason for the additive or synergistic effects although plasma levels of AEDs have not been determined. LCM does not inhibit or induce a large variety of drug metabolizing enzymes, nor is it metabolized to a significant extent by one of them. Additionally, clinical population pharmacokinetic analysis provided no evidence for any effect of LCM on plasma levels of AEDs or vice versa. Thus the interactions found in the present study are purely of pharmacodynamic nature.

[0101] The mechanisms of action underlying the nature of the synergistic or additive interaction between LCM and LEV are unknown. According to Deckers et al. (2000), synergistic interactions are likely between drugs with different mechanisms of action, and additivity may be expected for drugs sharing similar mechanisms.

[0102] From the analysis of the adverse activity in the rotarod test it may be postulated that the combinations displaying clear-cut synergy or additivity in the 6 Hz seizure test didn't associate with impairment of motor coordination in mice.

[0103] It should be emphasized that the dose ratio may be critical for the final outcome of type of an interaction between AEDs. This is evident from the present result that in some dose ratios, the interactions were simply additive (e.g. LCM+GBP, 1:3) and in other dose ratios were therapeutically synergistic. Results from other studies also point to this problem (Gordon et al., 1993; Borowicz et al., 2000). For instance, Borowicz et al. (2002) by using the MES test in mice it has been observed that GBP in combination with CBZ showed an additive interaction at a dose ratio of 1:1 but for many others very significant synergistic interactions. From this point of view this must be considered by the clinicians when introducing drug combinations in epilepsy patients.

[0104] Theoretically, a drug combination showing only additivity for anticonvulsant actions but not or minimal adverse effects, also is relevant from a clinical point of view (Luszczki et al., 2003), since combinations of low doses can provide the same antiseizure effect while having diminished side effects.

[0105] It is concluded that lacosamide exhibits a synergistic effect together with levetiracetam in the prevention, alleviation or/and treatment of epileptic seizures.

P a t e n t k r a v :

1. Farmaceutisk sammensætning til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor sammensætningen omfatter (a) lacosamid og (b) levetiracetam og/eller et farmaceutisk acceptabelt salt deraf, eventuelt sammen med en farmaceutisk acceptabel bærer, fortyndingsmiddel og/eller adjuvant, og hvor en sådan sammensætning enten foreligger i en enkeltdoseringsform eller i separate doseringsformer, der er samforpakket.

2. Farmaceutisk sammensætning til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald ifølge krav 1, hvor den farmaceutiske sammensætning omfatter (b) levetiracetam og (a) lacosamid i et fast-doseringsforhold af levetiracetam:lacosamid på mindst 1:3, beregnet på ED50-værdierne af de individuelle komponenter (b) og (a).

3. Farmaceutisk sammensætning ifølge et hvilket som helst af krav 1 eller 2 til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor den farmaceutiske sammensætning er formuleret i én farmaceutisk sammensætning (enkeltdoseringsform).

4. Farmaceutisk sammensætning ifølge et hvilket som helst af krav 1 eller 2 til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor den farmaceutiske sammensætning foreligger i separate doseringsformer, der er samforpakket i en enkeltbeholder eller i en flerhed af beholdere i en enkelt ydre emballage.

5. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor den farmaceutiske sammensætning omfatter (b) levetiracetam og (a) lacosamid i et fast-doseringsforhold af levetiracetam:lacosamid på mellem 1:3 og 6:1, beregnet på ED50-værdierne af de individuelle komponenter (b) og (a).

6. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 4 til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske

anfald, omfattende (b) levetiracetam og (a) lacosamid i et fast-doseringsforhold af levetiracetam:lacosamid på mellem 1:1 og 6:1, beregnet på ED50-værdierne af de individuelle komponenter (b) og (a).

7. Farmaceutisk sammensætning til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald ifølge et hvilket som helst af kravene 1 til 4, omfattende (b) levetiracetam og (a) lacosamid i et fast-doseringsforhold af levetiracetam:lacosamid på mellem 1:1 og 3:1, beregnet på ED50-værdierne af de enkelte komponenter (b) og (a).

8. Farmaceutisk sammensætning til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald ifølge et hvilket som helst af kravene 2 og 5 til 7, hvor ED50-værdien af lacosamid er 10,1 mg/kg, og ED50-værdien af levetiracetam er 22,8 mg/kg.

9. Farmaceutisk sammensætning til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald ifølge et hvilket som helst af de foregående krav, hvor den farmaceutiske sammensætning omfatter levetiracetam i en dosis på mindst 1000 mg/dag op til 3000 mg/dag og lacosamid i en dosis på mindst 100 mg/dag og maksimalt 600 mg/dag.

10. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, der er udvalgt fra partielle anfald med eller uden sekundær generalisering, primært generaliserede anfald og status epilepticus.

11. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor den farmaceutiske sammensætning er fremstillet til indgivelse i tre doser per dag, to doser per dag eller som en enkeltdosis per dag.

12. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor den farmaceutiske sammensætning er fremstillet til oral eller intravenøs indgivelse.

13. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse til forebyggelse, lindring og/eller behandling af epileptiske anfald, hvor den farmaceutiske sammensætning er fremstillet til oral indgivelse, og er indeholdt i hårde eller bløde gelatinekapsler eller er presset til tabletter.

14. Anvendelse af den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 1 til 9 eller 11 til 13 til fremstilling af et medikament til forebyggelse, lindring og/eller behandling af epileptiske anfald.

15. Anvendelse ifølge krav 14, hvor de epileptiske anfald er udvalgt fra partielle anfald med og uden sekundær generalisering, primært generaliserede anfald og status epilepticus.

Figure 1

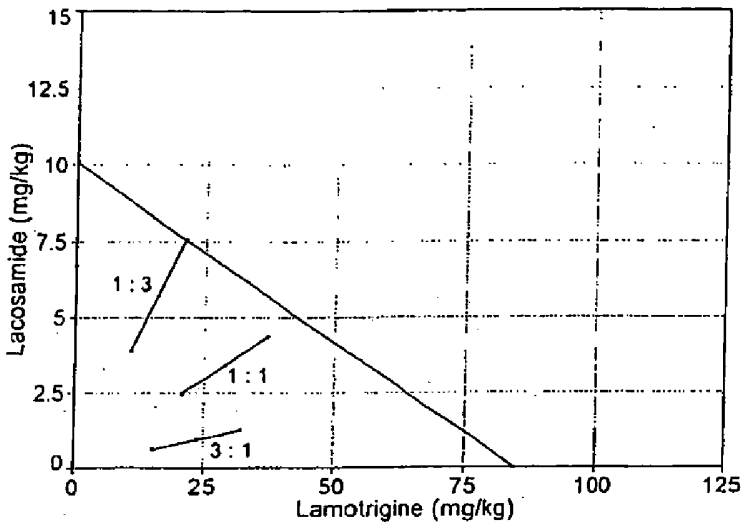

Figure 2

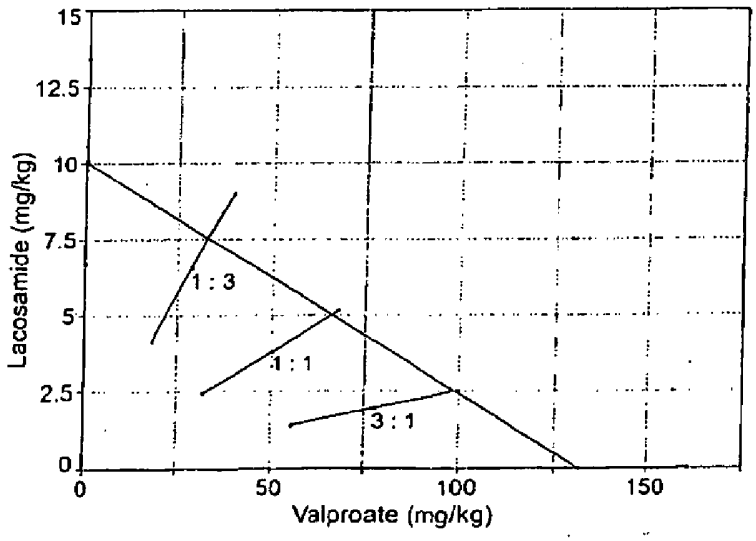

Figure 3

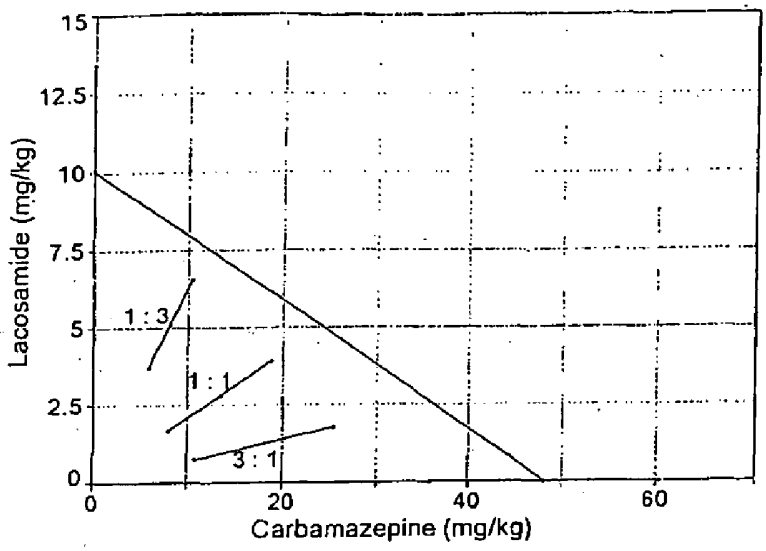

Figure 4

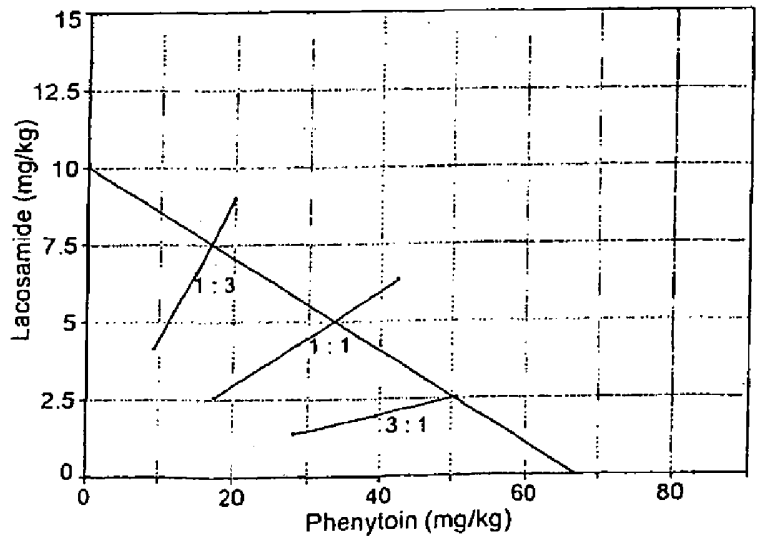

Figure 5

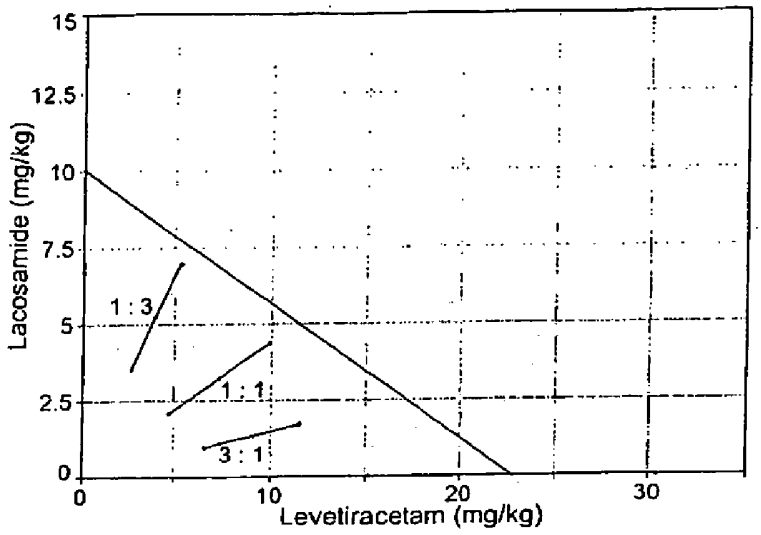

Figure 6

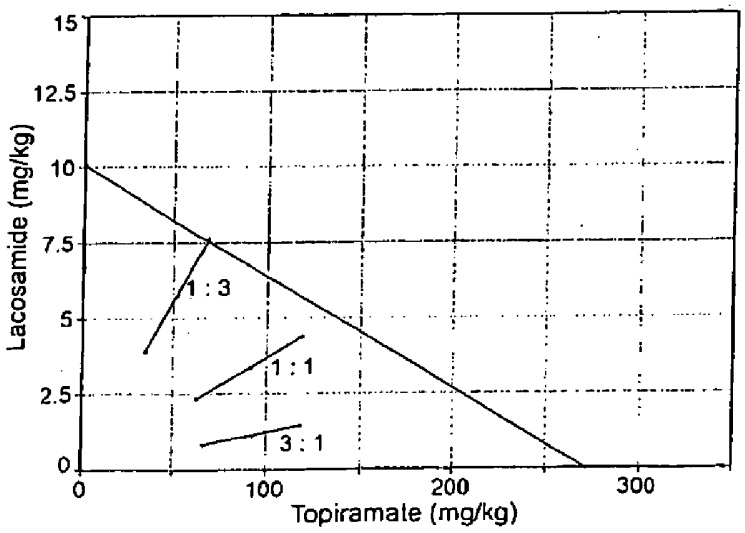

Figure 7

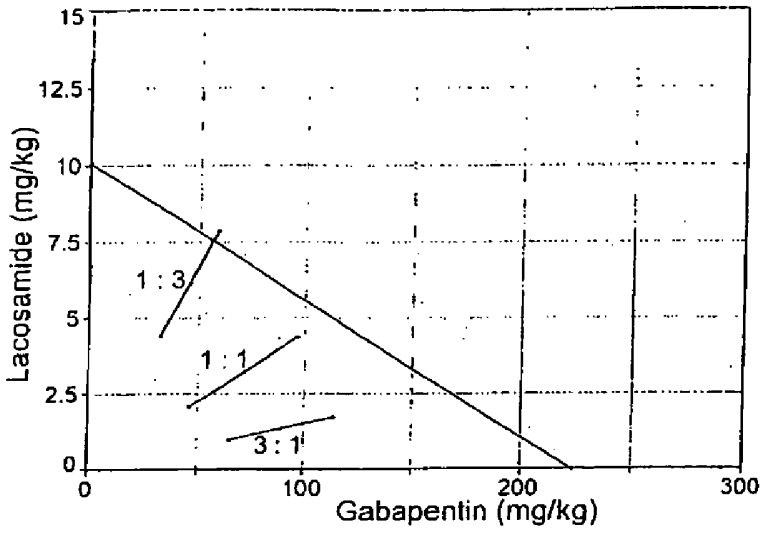

Table 1:

Drug	ED50 (mg/kg i.p.)
LCM	10.1 (4.5 – 19.8)
LTG	85.0 (48.0 – 145.2)
VPA	132.0 (78.7 – 205.6)
CBZ	48.1 (27.4 – 81.5)
PHT	67.0 (39.6 – 111.6)
LEV	22.8 (9.97 – 48.74)
TPM	271,7 (143.0 – 493.0)
GBP	224.0 (108.0 – 428.0)

Table 2:

Drug combination	F	ED_{50add} ± SEM	ED_{50mix} ± SEM	(α)
LTG + LCM	1 : 3	28.8 ± 7.9	21.9 ±7.0	0.76
	1 : 1	47.5 ±12.4	32.3 ±8.9	0.68
	3 : 1	66.2 ± 17.0	24.7 ±8.6	0.37
VPA + LCM	1 : 3	40.5 ±9.7	35.4 ±13.1	0.87
	1 : 1	71.0 ±16.1	53.7 ±19.3	0.76
	3 : 1	101.5 ±22.4	79.6 ±22.5	0.78
CBZ + LCM	1 : 3	19.6 ±5.6	13.3 ±3.7	0.68
	1 : 1	29.1 ±7.8	16.2 ±6.5	0.56
	3 : 1	38.6 ±10.0	19.3 ±7.8	0.50
PHT + LCM	1 : 3	24.3 ±6.5	21.2 ±7.9	0.87
	1 : 1	38.5 ±9.7	34.2 ±14.3	0.89
	3 : 1	52.8 ±12.8	41.4 ±11.7	0.78
LEV + LCM	1 : 3	13.2 ±4.4	9.2 ±3.0	0.69
	1 : 1	16.4 ±5.5	10.5 ±3.7	0.64
	3 : 1	19.6 ±6.6	10.4 ±2.9	0.53
TPM + LCM	1 : 3	75.5 ±21.2	57.7 ±18.7	0.76
	1 : 1	140.9 ±38.9	94.4 ±28.9	0.67
	3 : 1	206.3 ±56.7	93.7 ±25.8	0.45
GBP + LCM	1 : 3	63.6 ±19.2	51.8 ±14.5	0.82
	1 : 1	117.1 ±35.0	74.8 ±26.5	0.64
	3 : 1	170.6 ±50.9	90.4 ±25.0	0.53

Table 3:

Treatment (mg/kg i.p.)	Mice impaired (%)
LCM (5.0) LCM (10)	0 20
LTG (42.5) LTG (85) LCM (5.0) + LTG (42.5)	40 95 50
CBZ (24.0) CBZ (48) LCM (5.0) + CBZ (24.0)	20 50 20
VPA (66.0) VPA (132) LCM (5.0) + VPA (66.0)	0 25 10
PHT (33.0) PHT (67) LCM (5.0) + PHT (33.0)	30 50 20
LEV (11.4) LEV (23) LCM (5.0) + LEV (11.4)	0 0 0
TPM (133.9) TPM (272) LCM (5.0) + TPM (133.9)	0 35 0
GBP (112.0) GBP (224) LCM (5.0) + GBP (112.0)	10 35 20

Table 4:

	1 : 3	1 : 1	3 : 1
LTG + LCM	synergism tendency	synergism	synergism
VPA + LCM	additivity	synergism tendency	synergism tendency
CBZ + LCM	synergism	synergism	synergism
PHT + LCM	additivity	additivity	synergism tendency
LEV + LCM	synergism	synergism	synergism
TPM + LCM	synergism tendency	synergism	synergism
GBP + LCM	additivity	synergism	synergism

Table 5:

Species, Route	Test	Time of Test (hrs)	ED50 (mg/kg)	95% C.I.	P.I.[a]
Mice, i.p.	Rotorod	.25	26.8[b]	25.5-28.0	–
	Frings AGS	.5	0.63	0.37-0.99	43[c]
	MES	.5	4.46	3.72-5.46	6.0
	sc Met	.25	>25		<1
	sc Bic	1	>50		<0.5
	sc Pic	1	>30		<0.9
Rats, p.o.	MMId	–[e]	>500[b]		–
	MES	.5	3.90	2.58-6.20	>128
	sc Met	.5	>250		

[a] Protective Index = TD50/ED50
[b] Median toxic dose (TD50)
[c] P.I. calculated with TD50 obtained in CF#1 mice and ED50 in Frings mice
[d] Minimal motor impairment
[e] Tested at 1/4 through 24 hrs

Table 6:

Profile of Anticonvulsant Activity and Minimal Toxicity of Prototype Anticonvulsants in Mice and Rats

Substance	Mouse, i.p. TD50 or ED50 (mg/kg) and P.I.[a]						Rat, p.o. TD50 or ED50 (mg/kg) and P.I.[a]		
	TD50	MES	sc Met	sc Bic	sc Pic	AGS	TD50	MES	sc Met
valproic acid	483 (412-571)	287 (237-359) P.I. 1.7	209 (176-249) P.I. 2.3	437 (369-553) P.I. 1.1	311 (203-438) P.I. 1.6	155 (110-216) P.I. 3.1	859 (719-1148)	395 (332-441) P.I. 2.2	620 (469-985) P.I. 1.4
felbamate	816 (590-1024)	50.1 (35.8-61.7) P.I. 16	148 (121-171) P.I. 5.5	>300	156 (122-202) P.I. 5.2	10.0 (8.19-12.0) P.I. 82	>3000	47.8 (41.0-57.3) P.I. >63	238 (132-549) P.I. >13
phenytoin	42.8 (36.4-47.5)	6.48 (5.65-7.24) P.I. 6.6	>50	>60	>60	3.88 (2.67-5.50) P.I. 11	>500	23.2 (21.4-25.4) P.I. >22	>250
lamotrigine	48.0 (38.7-57.7)	7.2 (6.1-8.45) P.I. 6.7	>60	>50	>50	2.39 (1.62-3.38) P.I. 20	325 (259-419)	3.21 (2.6-3.69) P.I. 101	>250
carbamaze-pine	47.6 (39.2-59.2)	9.85 (8.77-10.7) P.I. 4.9	>50	>60	28.9 (23.9-41.6) P.I. 1.7	11.2 (7.73-16.2) P.I. 4.3	381 (319-402)	3.57 (2.41-4.72) P.I. 101	>250
gabapentin	>500	78.2 (46.6-127) P.I. >6.4	47.5 (17.9-86.2) P.I. >11	>500	>500	91.1 (61.8-129) P.I. >5.5	52.4 (35.2-76.2)	9.13 (4.83-14.4) P.I. 5.7	>100
ethosuximide	323 (279-379)	>350	128 (101-163) P.I. 2.5	365 (284-483) P.I. 0.9	211 (170-266) P.I. 1.53	328 (263-407) P.I. 1.0	>500	>250	204.2 (160-264) P.I. >2.5
clonazepam	0.27 (0.14-0.43)	23.8 (16.4-31.7) P.I. 0.01	0.017 (0.012-0.025) P.I. 16	0.008 (0.005-0.012) P.I. 34	0.05 (0.03-0.07) P.I. 5.4	0.10 (0.09-0.11) P.I. 2.7	1.99 (1.71-2.32)	2.41 (1.95-2.81) P.I. 0.8	0.77 (0.26-1.52) P.I. 2.6

( ) 95% confidence interval
[a] Protective Index = TD50/ED50