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(71) Applicant *(for all designated States except US)*: **JAMES COOK UNIVERSITY** [AU/AU]; Townsville Campus, Townsville, QLD 4811 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **VINK, Robert** [AU/AU]; James Cook University, Townsville Campus, Townsville, QLD 4811 (AU). **NIMMO, Alan, John** [AU/AU]; James Cook University, Townsville Campus, Townsville, QLD 4811 (AU).

(74) Agent: **FISHER ADAMS KELLY**; Level 13, AMP Place, 10 Eagle Street, Brisbane, QLD 4000 (AU).

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(54) Title: BRAIN, SPINAL AND NERVE INJURY TREATMENT

(57) Abstract: A treatment for brain, spinal and nerve injury comprising use of a substance P receptor antagonist optionally in combination with a magnesium compound. There is also provided a formulation for use in this treatment comprising a substance P receptor antagonist and a magnesium compound.

TITLE

"BRAIN, SPINAL AND NERVE INJURY TREATMENT"

FIELD OF THE INVENTION

THIS INVENTION relates to a method of therapy of brain, spinal and nerve injury. There is also provided a formulation which is particularly useful in the method.

Injury to the brain results in the development of motor and cognitive deficits that contribute to the significant morbidity experienced by survivors of brain injury. Moreover, it is an occurrence that has the highest incidence in younger members of society. Accordingly, injury to the brain is responsible for the greatest loss of productive life as compared to any other disease process. Despite this, there is no effective therapy to improve outcome after brain injury. We disclose the use of a method of therapy as a robust pharmacologic intervention for the treatment of brain injury. Use of this therapy significantly improves both motor and cognitive outcome in mild to severe experimental brain injury and has also been found to have beneficial effect also for the treatment of spinal cord and nerve injuries.

BACKGROUND OF THE INVENTION

It is well known that brain injury results in the development of neurologic deficits through two mechanisms. The first of these is known as primary mechanisms. These occur at the time of the injurious event and include mechanical processes such as laceration, tearing, stretching and compression of nerve fibres. Little can be done for this type of injury once it has occurred. The second mechanism is secondary injury, which includes biochemical and physiological processes, initiated by a primary injury but which manifest with time after the injury. It has been demonstrated that much of the morbidity after brain injury is associated with the development of this secondary injury. Given that the secondary

injury develops from minutes to days after the primary event, there exists a window of opportunity to pharmacologically prevent this type of injury and significantly improve resultant outcome. However, the factors that make up secondary injury must first be identified and then "antifactors" developed to inhibit the injury process.

Our studies have concentrated on identifying secondary injury factors after brain injury and developing interventional therapies. One of the factors that we had previously identified[1-4] as critical to determining outcome after injury was brain magnesium ion concentration. This ion is a regulatory factor in a number of biochemical and physiological processes that are activated after brain injury. Indeed, a decrease in the magnesium ion concentration was observed to exacerbate the injury process while an increase in the concentration of magnesium ion was noted to attenuate the injury process and result in an improved outcome [5]. The treatment of brain injury with magnesium has since been shown to be effective[1,6-10] even when administered up to 24 hours after the primary event, and the success of the treatment in experimental animal studies has subsequently led to clinical trials in human brain injury.

Despite the attenuation of deficits after brain injury with magnesium administration, it was clear that there were still motor and cognitive deficits that persisted after the treatment. Our attention was particularly drawn to the fact that in younger animals, the accumulation of water in the brain (brain swelling) was still present and that this may present a significant risk factor. Indeed, in a recent clinical study[11], delayed brain swelling was responsible for 50% of all deaths recorded in young victims of brain injury.

STATEMENT OF INVENTION

It therefore is an object of the invention to provide a method of therapy in relation to brain injury and a formulation for use in the method.

The formulation in one aspect of the invention comprises a substance P receptor antagonist and a magnesium compound.

The method of the invention includes the step of administration of the formulation to the patient suffering from brain injury. Alternatively each of the components of the formulation are administered separately or separated by a time delay that does not affect the effectiveness of the therapy, e.g. 1-30 minutes.

Substance P is an excitatory neurotransmitter and has a role in pain transmission and is a peptide having the structure RPKPEEFFGLM-NH_2. It is from the hypothalamus, CNS and intestine and increases smooth muscle contraction of the G1 tract.

It is known that substance P binds to a number of receptors inclusive of the NK1 receptor (i.e. neurokinin 1 receptor), the NK2 receptor and the NK3 receptor. These receptors are believed to have a role in blood travelling to the brain.

Therefore a substance P antagonist is a substance that inhibits binding of substance P to any one of the receptors referred to above. A list of suitable substance P antagonists is referred to in Tables 1, 2 and 3 attached herewith.

Reference may also be made to NK1 receptor antagonists as described in US Patent 5990125 which are incorporated herein by reference as constituting substance P antagonists that may be utilized in the formulation of the method of the invention. This has specific reference to compounds of structures Ia, Ib, Ic, Id, Ie, X, XVI, XVII, XVIII, XIX, XX and XXI, as well as other antagonists comprising quinuclidine, piperidine ethylene diamine, pyrrolidine and azabornane derivatives and related compounds that exhibit activity as substance P receptor antagonists as described in column 33 of the US Patent 5990125.

Such receptor antagonists may be employed having regard to the dosages referred to in column 34 of US Patent 4990125

and in various forms of administration i.e. alone or with various pharmaceutically acceptable carriers or diluents by oral administration or parental administration as referred in column 34 of US Patent 5990125.

The activity of various substances as substance P receptor antagonists for use in the invention may also be determined by the assays referred to in columns 35-36 of US Patent 5990125.

Reference also may be made to substance P receptor antagonists described in US Patent 5977104 including the various dosage forms and dosages referred to in this reference which is also totally incorporated herein by reference.

Reference also may be made to US Patent 4481139 which describes various peptide antagonists, which is also totally incorporated herein by reference.

It will also be understood that the term "Substance P" as used herein may also include within its scope various truncated forms or analogues as described in US Patent 4481139, which is totally incorporated herein by reference.

Reference also may be made to US Patent 4985896 which refers to various piperdine and morpholine derivatives for use as substance P antagonists for use in the present invention or piperazino derivatives as described in US Patent 5981520. Each of these references are totally incorporated herein by reference.

Reference also may be made to piperidinyl compounds as NK1 or NK2 antagonists for use in the invention referred to in US Patent 5998444 which is also totally incorporated herein by reference.

It will also be appreciated that tachykinin antagonists referred to in US Patent 4981744 may also be used as substance P antagonists in the invention and thus, this reference is also totally incorporated herein.

Reference may also be made to EP-A-1035115 which is totally incorporated herein by reference, which refers to N-benzyl-4-tolylnicotinamides and related compounds as NK1 receptor antagonists for use in the invention.

Reference may be made to International Publication WO 0050398 which is totally incorporated herein by reference, which refers to various phenyl and pyridinyl derivatives as NK1 receptor antagonists for use in the invention.

Reference is also made to International Publications WO 0050401, WO 0053572, WO 0073278 and WO 0073279, which refer to 3-phenylpyridines, biphenyl derivatives, 5-phenyl-pyrimidine derivatives and 4-phenyl-pyrimidine derivatives respectively which specifications are also totally incorporated herein by reference. These specifications refer to NK1 receptor antagonists for use in the present invention.

Reference also may be made to the 1998 Sigma Catalogue and more particularly pages 1194-1997 which describe modifications of substance P or substance P fragments, which may be used as substance P antagonists, for use in the invention. This publication is also totally incorporated herein by reference.

In relation to the magnesium compound, this may comprise any suitable source of magnesium ion such as magnesium chloride, magnesium sulphate, magnesium oxalate, magnesium gluconate or other non toxic magnesium salt.

The pharmaceutical preparations in accordance with this invention can in addition also contain preservatives, solubilizers, sabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances. Thus the term "comprising" used in the specification should be interpreted in this context. The

dosage can vary within wide limits and can, of course, be fitted to the individual requirements in each particular case. In general, a dosage of 1 to 20000mg per patient, preferably10 to 5000mg and more preferably 50 to 2000mg of the substance P receptor antagonist should be appropriate.

In relation to the development of the inventive concept, it was established by the present inventors that one reason for acute water accumulation in the brain after injury was the result of vasogenic oedema formation. This is caused by an increased permeability of the blood brain barrier thus permitting vascular proteins and water to enter the extracellular space in the brain and cause swelling. Few studies have examined how this increased blood brain barrier permeability contributes to the development of neurological deficits after injury, and no studies have investigated whether inhibition of brain swelling improves outcome. Studies of migraine[12,13] have suggested that the blood brain barrier becomes permeable to vascular components because of substance P. We therefore hypothesised that administration of a substance P receptor antagonist may prevent brain swelling and the development of delayed neurologic deficits after injury. This hypothesis was a result of our discovery referred to above, that water accumulated in the brain as a result of vasogenic oedema formation.

EXPERIMENTAL

A number of commercially synthesised substance P receptor antagonists are currently available from standard scientific chemical suppliers, as is apparent from Tables 1, 2 and 3. We chose to use the compound N-acetyl-L-tryptophan based on its low lipid solubility that limits its ability to naturally cross the blood brain barrier and the fact that it is relatively inexpensive. Administration of N-acetyl-L-tryptophan at an intravenous dose of 246mg/kg (saline vehicle) given at 30 minutes after brain injury resulted in a significant

improvement of cognitive outcome in brain injured animals as assessed by the Barnes Circular Maze. Similarly, there was a significant improvement in motor outcome of animals as assessed by the rotarod test. These improvements in outcome were apparent at 24 hours after brain injury and persisted for the 14 day assessment period. Control (vehicle tested) animals has significantly worse neurologic outcome than treated animals at all time points tested.

Animals treated with N-acetyl-L-tryptophan had a significant reduction in brain water accumulation at 24 hours after injury as compared to vehicle treated controls. This was consistent with the observation that N-acetyl-L-tryptophan reduced brain penetration of Evans blue at 5 hours after injury, the time associated with maximum blood brain barrier permeability after brain injury. Thus N-acetyl-L-tryptophan administered at 30 minutes after brain injury reduced blood brain barrier permeability and reduced vasogenic oedema formation. The fact that these effects were noted with a non-permeable formulation of the NK1 antagonist suggests that the effects were largely mediated by vascular receptors and not dependent upon central receptors.

Administration of N-acetyl-L-tryptophan at 24.6 mg/kg also significantly improved cognitive outcome of brain injured animals. However, the drug had less of a beneficial effect on motor outcome. Moreover, because there was always some residual cognitive and motor deficits noted in all treated animals, the beneficial effects of treatment with the NK1 antagonist were less apparent when injury of mild severity was induced as opposed to injury of a sever nature. This is a major limitation given that mild head injury has the greatest incidence in brain injury patients.

COMBINATION MAGNESIUM AND N-ACETYL-L-TRYPTOPHAN

The most common form of brain injury is mild head injury. Guidelines to be introduced next year (2000) by the World

Federation of Neurological Surgeons will recommend that all cases of minor head injury with any complications such as vomiting, nausea, loss of consciousness or amnesia MUST present to a hospital. This will place considerable pressure on the health system to adequately treat these individuals such that secondary injury does not develop any further. Currently, there is no such therapy.

Our results with N-acetyl-L-tryptophan suggest that this compound closes the blood brain barrier after head injury and reduces brain swelling. This is extremely important in young victims of head injury who are particularly vulnerable to delayed brain swelling. Furthermore, our results with magnesium therapy suggest that magnesium treatment is effective at reducing neurologic deficits not necessarily associated with increased blood brain permeability. We therefore propose that a combination of a substance P antagonist with a magnesium compound or salt will be a particularly effective therapy for the treatment of brain injury irrespective of severity.

Combination administration of 246 mg/kg N-acetyl-L-tryptophan plus 30 mg/kg magnesium sulphate (intravenously) resulted in a profound attenuation of both motor and cognitive deficits that was significantly greater than obtained with either drug in isolation (FIG. 1 and FIG. 2).

Each of the compounds in the combination formulation has a number of properties that make it particularly attractive for use in brain injury.

Substance P (SP) antagonists have been shown to rapidly improve mood by antagonising substance P induced anxiety. Thus they are effective in treating post-injury depression. From the work described above, it is apparent that SP antagonists reduce blood brain barrier permeability and inhibit the formation of vasogenic oedema and post-injury brain swelling. The antagonists also have been shown to inhibit pain. There are high numbers of substance P

receptors in the hippocampus and striatum, those parts of the brain that are known to be associated with learning and memory. Inhibition of binding with SP antagonists may thus prevent substance P induced deficits in learning and memory. Our evidence presented above suggests that this may be the case. This has never been shown previously. Indeed, there has been no literature on the role of substance P, or any neuropeptides, in brain injury.

Magnesium affects over 300 cellular enzymes. It is not surprising, therefore, that magnesium has numerous targets at which it may improve outcome. These include, amongst others, blocking glutamate induced excitotoxicity, improving membrane stability and reducing the production of reactive oxygen species, improving energy status, inhibiting calcium channels, reducing neurotransmitter release, inhibiting mitochondrial transition pore opening, and inhibiting apoptosis. Notably, it also blocks glutamate induced release of substance P. Physiologically, magnesium has been shown[14-17] to improve cerebral blood flow, reduces cerebral vasospasms, and reduces vascular ceramide and prostaglandin production.

The combined use of magnesium and the substance P antagonist results in greater protection against neural injury than either drug used alone.

We have previously shown that magnesium has a beneficial effect in trauma when administered at intravenous doses ranging from 16 to 60 mg/kg. When administered as an intramuscular injection, the effective dose varies form 45 to 90 mg/kg. The target is to increase free magnesium concentration in the blood to approximately 1.0mM, which is double the normal blood free magnesium concentration. Beneficial results are observed irrespective of the magnesium salt used.

Our studies with the substance P antagonist has demonstrated that the effective i.v. dose varies from 24.6 mg/kg to

240.6 mg/kg or higher, with the higher doses having a greater beneficial effect on motor outcome. Moreover, these doses pertain to antagonists that have low lipid solubility and thus limited blood brain barrier permeability. A highly lipid soluble formulation should exact the same beneficial actions, however, there may be centrally mediated side-effect that may be inappropriate.

When used in combination, the formulation may vary in the range described for the individual components. We have achieved excellent results using the maximum i.v. doses described for the individual components.

The combination magnesium/SP antagonists is expected to be useful in the following conditions:

- As a "first-aid" prophylactic treatment following traumatic brain injury
- As a "first-aid" prophylactic treatment following minor head injuries, including concussion
- As a therapy following non-traumatic brain injuries, including stroke, hypoxia and any form of brain injury where oedema is implicated
- As a maintenance therapy following brain injury

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TABLE 1

NK1 Receptor Antagonists

Chemical Code	Chemical Name
CGP49823	(2R,4S)-2-benzyl-1-(3,5-dimethylbenzoyl)-N-[(4-quinolinyl)methyl]-4-piperineamine) dihydrochloride
CP-96,345	2S,3S)-cis-(2(diphenylmethyl)-N-[(2-methoxyphenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine
CP-99,994	((2S,3S)-cis-3-(2-methoxybenzylamino)-2-phenyl-piperidine)dihydrochloride
CP-122,721	(+)-2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine
FK 888	(N2-[(4R)-4-hydroxy-1-(1-methyl-1H-indol-3-yl)carbonyl-L-propyl\-N-methyl-N-phenylmethyl-L-3-(2-naphthyl)-alaninamide
GR203040	(2S,3S and 2R,3R)-2-methoxy-5-tetrazol-1-yl-benzyl-(2-phenyl-piperidin-3-yl)-amine
GR-205171	3-Piperidinamine,N-[[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenyl]methyl]-2-phenyl-, (2S-cis)-
GR 82334	[D-Pro9,]spiro-gamma-lactam]Leu10, Trp11]physalaemin-(1-11)
GR 94800	PhCO-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH2
HSP-117	3-Piperidinamine,N-[[2,3-dihydro-5-(1-methylethyl)-7-benzofuranyl]methyl]2-phenyl-, dihydrochloride, (2S-cis)-
L 703,606	1-Azabicyclo[2.2.]octan-3-amine,2-(diphenylmethyl)-N-[(2-idophenyl)methyl]-, (2S-cis)-, oxalate
L 732,138	N-acetyl-L-tryptophan
L 733,060	((2S,S)-3-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-phenyl piperidine
L 742,694	(2-(S)-(3,5-bis(trifluromethyl)benzyloxy)-3-(S)-phenyl-4-(5-(3-oxo-1,2, 4-triazolo)methylmorpholine
L 754,030	2-(R)-(1-(R)-3, 5-bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine

L 668,169	L-Phenylalanine, N-[2-[3-[[N-[2-(3-amino-2-oxo-1-pyrrolidinyl)-4-methyl-1-oxopentyl]-L-methionyl-L-glutaminyl-D-tryptophyl -N-methyl-L-phenylalanyl]amino]-2-oxo-1-pyrrolidinyl]-4-methyl-1-oxopentyl]-L-methionyl-L-glutaminyl-D-tryptophyl-N-methyl-, cyclic (8->1)-peptide, [3R-[1[S*[R*(S*)]], 3R*]]-
LY 303241	1-Piperazineacetamide, N-[2-[acetyl[(2-methoxyphenyl)methyl]amino]-1-(1H-indol-3-ylmethyl)(ethyl]-4-phenyl-, (R)-
LY 303870	(R)-1-[N-(2-methoxybenzyl)acetylamino]-3-(1H-indol-3-yl)-2-[N-(2-(4-(pi peridinyl)piperidin-1-yl)acetyl)amino]propane
LY 306740	1-Piperazineacetamide, N-[2-'acetyl[(2-methoxyphenyl)methyl]amino]-1-(1H-indol-3-ylmethyl)ethyl]-4-cyclohexyl-, (R)-
MEN 11149	2-(2-naphthyl)-1-N-[(1R,2S)-2-N-[1(H)indol-3-ylcarbonyl]aminocyclohexanecarbonyl]-1-[N'-ethyl-N'-(4-methylphenylacetyl)] diaminoethane
MK-869	3H-1,2,4-Triazol-3-one, 5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1, 2-dihydro-, [2R-[2α(R*), 3α]]-
PD 154075	(2-benzofuran)-CH2OCO]-(R)-alpha-MeTrp-(S)-NHCH(CH3) Ph
R-544	Ac-Thr-D-Trp(FOR)-Phe-N-MeBzl
RP-67580	(3aR, 7aR)-7,7-diphenyl-2[1-imino-2(2-methoxyphenyl)-ethyl]+++perhydroisoindol-4-one hydrochloride
RPR 100893	(3aS, 4S, 7aS)-7, 7-diphenyl-4-(2-methoxyphenyl)-2-[(S)-2-(2-methoxyphenyl)proprionyl]perhydroisoindol-4-ol
Spendide	Tyr-D-Phe-Phe-D-His-Leu-Met-NH2
Spantide II	D-NicLys1, 3-Pal3, D-Cl2Phe5, Asn6, D-Trp7.0, Nle11-substance P
Spantide III	L-Norleucinamide, N6-(3-pyridinylcarbonyl)-D-lysyl-L-prolyl-3-(3-pyridinyl)-L-alanyl-L-prolyl-3,4-dichloro-D-phenylalanyl-L-asparaginyl-D-tryptophyl-L-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-leucyl-
SR140333	(S)-1-[2-[3-(3,4-dichlorphenyl)-1 (3-isopropoxyphenylacetyl) piperidin-3-yl] ethyl]-4-phenyl-1 azaniabicyclo [2.2.2]octane
WIN-41,708	(17beta-hydroxy-17alpha-ethynyl-5alpha-androstano[3,2-b]pyrimido[1,2-a]benzimidazole
WIN-62,577	1H-Benzimidazo[2,1-b]cyclopenta[5,6]naphtho[1,2-g]quinazolin-1-ol, 1-ethynyl-2,3,3a,3b,4,5,15,15a,15b,16,17,17a-dodeachydro-15a,17a-dimethyl-, (1R, 3aS, 3bR, 15aR, 15bS, 17aS)-

TABLE 2

NK2 Receptor Antagonists

Chemical Code	Chemical Name
SR-48,968	(S)-N-methyl-N[4-(4-acetylamino-4-[phenylpiperidino)-2-(3,4-dichlorophenyl)-butyl]benzamide
L-659,877	cyclo[Gln,Trp,Phe,Gly,Leu,Met]
MEN 10627	cyclo(Met-Asp-Trp-Phe-Dap-Leu)cyclo(2beta-5beta)
SR 144190	(R)-3-(1-[2-(4-benzoyl-2-(3,4-difluorophenyl)-morpholin-2-yl)-ethyl]-4-phenylpiperidin-4-yl)-1-dimethylurea
GR 94800	PhCO-Ala-Ala-D-Trp-Phe-D-Pro-Pro-Nle-NH2

TABLE 3

NK3 Receptor Antagonists

Chemical Code	Chemical Name
SR-142,801	(S)-(N)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenylpiperidin-4-yl)-N-methyl acetamide
R820	3-indolylcarbonyl-Hyp-Phg-N(Me)-Bzl
R486	H-Asp-Ser-Phe-Trp-beta-Ala-Leu-Met-NH2
SB 222200	(S)-(-)-N-(a-ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboximide
L 758,298	Phosphonic acid, [3-[[2-[1-[3,5-bis(trfluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5oxo-1H-1,2,4-triazol-1-yl]-, [2R-[2α(R*), 3α]]-
NK-608	(2R,4S)-N-[1-{3,5-bis(trifluormethyl)-benzoyl}-2-(4-chloro-benzyl)-4-piperidinyl]-quinoline-4-carboxamide

FIGURE 1.

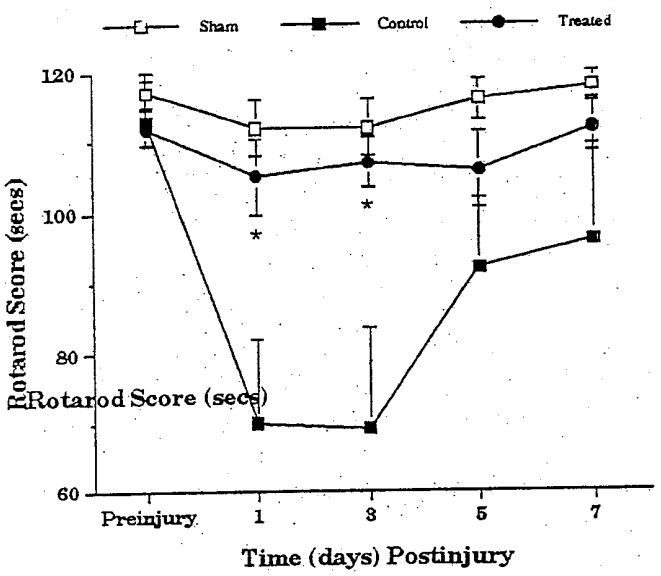
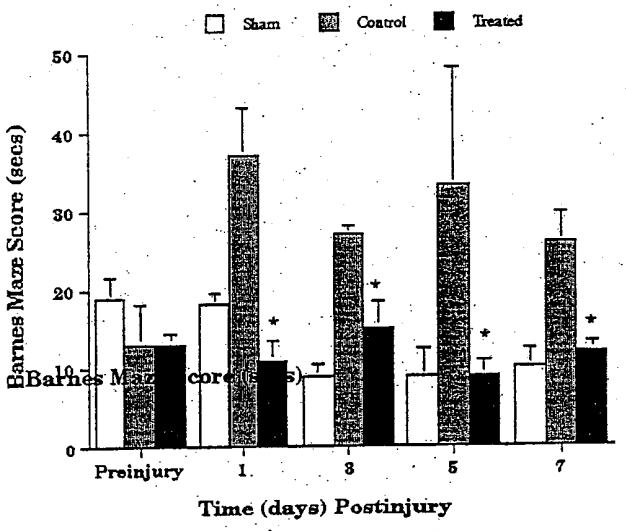


FIGURE 2.



CLAIMS

1. A formulation comprising a substance P receptor antagonist and a magnesium compound.

2. A formulation as claimed in claim 1, wherein the substance P receptor antagonist is an NK1 receptor antagonist.

3. A formulation as claimed in claim 2, wherein the NK1 receptor antagonist is selected from the group consisting of CGP49823, CP-96,345, CP99,994, CP-122,721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-117, L-703,606 oxalate, L-732,138, L-733060, L-742,694, L-745,030, L-668,169, LY-303241, LY-303870, LY306740, MEN-11149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41,7098, WIN-62,577.

4. A formulation as claimed in claim 1, wherein the substance P receptor antagonist is an NK2 receptor antagonist.

5. A formulation as claimed in claim 4, wherein the substance P receptor antagonist is selected from the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800.

6. A formulation as claimed in claim 1, wherein the substance P receptor antagonist is an NK3 receptor antagonist.

7. A formulation as claimed in claim 6, wherein the substance P receptor antagonist is selected from the group consisting of SR-142,801, R820, R486, SB222200, L758,298 and NKP608.

8. A formulation as claimed in claim 1, wherein the substance P receptor antagonist is N-acetyl L-tryptophan.

9. A formulation as claimed in claim 1, wherein the magnesium compound is selected from the group consisting of magnesium chloride, magnesium sulphate, magnesium oxalate, magnesium gluconate or other non-toxic magnesium salt.

10. The use of a substance P receptor antagonist for

treatment of brain, spinal cord and nerve injuries.

11. The use of a formulation comprising a substance P receptor antagonist and a magnesium compound for treatment of brain, spinal cord and nerve injuries.

12. The use of a substance P receptor antagonist for reducing brain barrier permeability and/or reduced vasogenic oedema.

13. The use of a formulation comprising a substance P receptor antagonist and magnesium compound for reducing brain barrier permeability and/or reduced vasogenic oedema.

14. The use according to claim 10 or 11, wherein the injuries are caused by laceration, tearing, stretching or compression of nerve fibres.

15. The use according to claim 10, wherein the substance p receptor antagonist i.v. dose varies from 24.6mg/kg to 240.6mg/kg or higher.

16. The use according to claim 11, wherein the i.v. dose of the magnesium compound ranges from 16mg/kg to 60mg/kg.

17. The use according to claim 11, wherein an intramuscular dose of magnesium compound ranges from 45mg/kg to 90mg/kg.

18. The use according to claim 11, wherein the dosage of magnesium compound is sufficient to increase free magnesium concentration in the blood to approximately 1.0mM.

19. A formulation as claimed in claim 1 substantially as herein described with reference to the Experimental Section.

20. The use of a substance P receptor antagonist as claimed in claim 10 substantially as herein described with reference to the Experimental Section.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/00046

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 31/405, A61K 33/06, A61P 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPAT, MEDLINE, Chemical Abstracts: NK receptor antagonist, substance P receptor antagonist, neurokinin receptor antagonist, magnesium, brain, spinal, nerve, vasogenic o?edema,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 610 165 A (Malcolm MacCoss et al) 11 March 1997. Column 39 lines 9 to 33 (Example 12)	1, 2, 9
X	EP 0 721 778 A2 (Pfizer Inc.) 17 July 1996. Page 40 lines 30-35, page 41 lines 45-46	1, 2, 9, 10, 11, 12, 13, 14
X	US 5 716 979 A (David Christopher Horwell et al) 10 February 1998. Column 32 lines 52-57	1, 2, 9

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 2001	24 April 2001
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	K.G. ENGLAND Telephone No : (02) 6283 2292

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/00046

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Shepheard, S. L. et al, "Comparison of the Effects of Sumatriptan and the NK1 Antagonist CP-99,994 on Plasma Extravasation in Dura Mater and c-fos mRNA Expression in Trigeminal Nucleus Caudalis of Rats" Neuropharmacology (1995) Volume 34 No 3 pp 255-261. See the whole document, in particular page 255.	12
X	Cumberbatch, Michael J. et al, "Reversal of behavioural and electrophysiological correlates of experimental peripheral neuropathy by the NK1 receptor antagonist GR205171 in rats" Neuropharmacology (1998) Volume 37 pp 1535-1543. See the whole document, in particular page 1535.	12
A	Weglicki, W. G. et al "Neuropeptides, free radical stress and antioxidants in models of Mg-deficient cardiomyopathy" in "Magnesium: Current Status and New Developments", [Int. Symp. Magnesium] 1997. T. Theophanides and J. Anastassopoulou Editors, Kluwer, Dordrecht, Netherlands, Publisher. Pages 169-178.	1-20
A	Kramer, J. H. et al, "Magnesium-deficiency-enhanced Post-ischemic Myocardial Injury is Reduced by Substance P Receptor Blockade" Journal of Molecular and Cellular Cardiology (1997) Volume 29 pages 97-110.	1-20
A	WO 99/64009 A (Merck Sharp & Dohme Limited) 16 December 1999. See the whole document in particular page 5 lines 1 to 8.	1-20

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/00046

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
US	5 610 165 A	AU	18429/95 A1	WO	95/22525 A1
EP	721778 A2				
US	5 716 979 A	JP	6189566 A2		

END OF ANNEX