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(54) COMBINATION OF N-ACETYL-L-TRYPTOPHAN AND MAGNESIUM SULPHATE FOR THE TREATMENT OF BRAIN, SPINAL AND NERVE INJURY

KOMBINATION VON N-ACETYL-L-TRYPTOPHAN MIT MAGNESIUMSULFAT ZUR BEHANDLUNG VON GEHIRN-, SPINAL- UND NERVENSCHÄDEN

COMBINAISON DU N-ACETYL-L-TRYPTOPHANE AVEC DU SULFATE DE MANGNESIUM POUR LE TRAITEMENT DE LESIONS CEREBRALES ET SPINALES ET DE DEFICITS NEUROLOGIQUES

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

FIELD OF THE INVENTION

[0001] 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 themethod.

[0002] 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. 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

[0003] 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.

[0004] 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.

[0005] 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

[0006] 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 this method.

[0007] The formulation in one aspect of the invention comprises a NK1 receptor antagonist which is N-acetyl-L-tryptophan and a magnesium compound which is magnesium sulphate, wherein the combined use of the magnesium compound and the NK1 receptor antagonist results in greater protection against injury than either of the magnesium compound or the NK1 receptor antagonist used alone.

[0008] 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.

[0009] Substance P to which the NK1 receptor antagonists belong 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, CSN and intestine and increases smooth muscle contraction of the G1 tract.

[0010] It is known that neurokinin 1 receptor, is believed to have a role in blood travelling to the brain.

[0011] 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, preferably 10 to 5000mg and more preferably 50 to 2000mg of the substance P receptor antagonist should be appropriate.

[0012] 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 case 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.

[0013] We further hypothesised that administration of a Nk1 receptor antagonist 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 edema formation.

EXPERIMENTAL

[0014] 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 otarod 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.

[0015] 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.

[0016] 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 severe 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

[0017] 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.

[0018] Our results with N-acetyl-L-tryptophan suggest that this compound closes the blood brain barrier after head injury and reduces brain swelling or cerebral oedema. 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.

[0019] 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).

[0020] Each of the compounds in the combination formulation has a number of properties that make it particularly attractive for use in brain injury.

[0021] 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.

[0022] The combined use of magnesium and the substance P antagonist results in greater protection against neural injury than either drug used alone.

[0023] 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 approxi-

mately 1.0mM, which is double the normal blood free magnesium concentration. Beneficial results are observed irrespective of the magnesium salt used.

[0024] 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.

[0025] 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.

[0026] 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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Claims

1. N-acetyl-L-tryptophane and magnesium sulphate.

2. N-acetyl-L-tryptophan and magnesium sulphate for use in medicine.

3. The use of a combination of N-acetyl-L-tryptophan and magnesium sulphate for the preparation of a medicament for the treatment of brain, spinal cord and nerve injury.

4. The combination of N-acetyl-L-tryptophan and magnesium sulphate for use in the treatment of brain, spinal cord and nerve injury.

Patentansprüche

1. N-Acetyl-L-tryptophan und Magnesiumsulfat.

2. N-Acetyl-L-tryptophan und Magnesiumsulfat zur Verwendung in der Medizin.

3. Verwendung einer Kombination von N-Acetyl-L-tryptophan und Magnesiumsulfat zur Herstellung eines Medikaments zur Behandlung einer Hirn-, Rükkenmark- und Nervenverletzung.

4. Kombination von N-Acetyl-L-tryptophan und Magnesiumsulfat zur Verwendung bei der Behandlung einer Hirn-, Rückenmark- und Nervenverletzung.

Revendications

1. N-acétyl-L-tryptophane et sulfate de magnésium.

2. N-acétyl-L-tryptophane et sulfate de magnésium en vue d'une utilisation en médecine.

3. Utilisation d'une combinaison de N-acétyl-L-tryptophane et de sulfate de magnésium pour la préparation d'un médicament destiné au traitement d'une lésion cérébrale, spinale et nerveuse.

4. Combinaison de N-acétyl-L-tryptophane et de sulfate de magnésium en vue d'une utilisation pour le traitement d'une lésion cérébrale, spinale et nerveuse.

FIGURE 1.

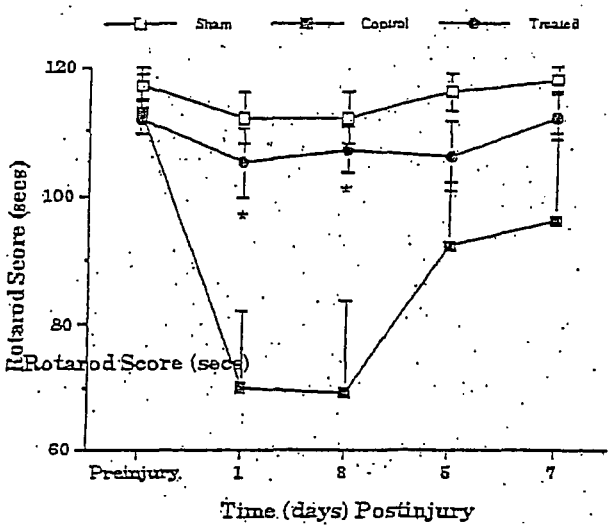
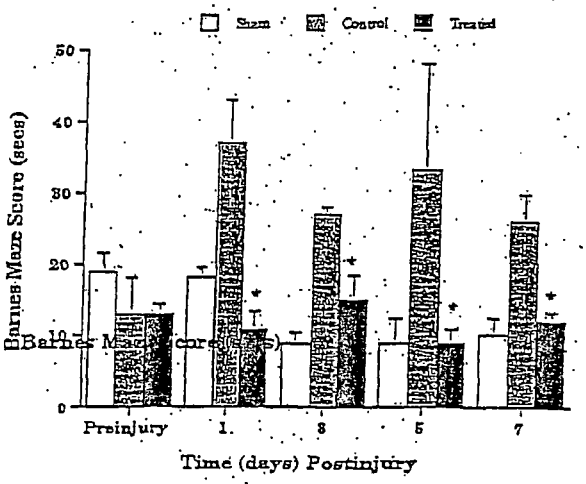


FIGURE 2.



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