METHOD OF ALLEVIATING SYMPTOMS OF MULTIPLE SCLEROSIS

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References Cited

UNITED STATES PATENTS
2,816,113 12/1957 Wilson et al. ................. 424/263
2,996,510 8/1961 Green .......................... 424/263
3,063,901 11/1962 O'Leary ........................ 424/265

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ABSTRACT

Cholinesterase reactivators are administered to treat the symptoms and signs associated with demyelinating processes or hypercholinergic or other conditions in man characterized by defective neural transmission in association with an acetylcholine-cholinesterase imbalance due to relative decrease in cholinesterase activity.

2 Claims, No Drawings
METHOD OF ALLEVIATING SYMPTOMS OF MULTIPLE SCLEROSIS

This invention relates to new therapeutic uses of cholinesterase reactivators for the symptoms and signs associated with demyelinizing processes or hypercholinergic or other conditions in man characterized by defective neural transmission in association with an acetylcholine-cholinesterase imbalance due to relative decrease in cholinesterase activity.

Cholinesterase reactivators such as 2-PAM (2-formyl-1-methylpyridium oxime or pralidoxime) and salts thereof such as 2-PAM-Cl, 2,3-butanedione-2-oxime (DAM), other 2-oxo-oximes, pyruvaldehyde aldaxime (MINA) and bis quaternary pyridine aldaxime (TMB-4), were originally developed as antidotes for acute nerve gas poisoning and other exogenous organic phosphorous compounds acute poisoning, such as from insecticides. They have found limited usefulness as secondary compounds to be employed in the treatment of patients with Myasthenia gravis in which there had been a crisis produced by primary drugs. The principal action of cholinesterase reactivators is felt to be the reactivation of the enzyme cholinesterase.

According to the present invention, new therapeutic uses are provided for cholinesterase reactivators, including treatment of the symptoms and signs of diseases and other conditions in man which, it is believed, are associated with demyelination as well as other conditions in man characterized by acetylcholine-cholinesterase imbalance due primarily to relative decreased cholinesterase activity and, therefore, defective neural transmission. It is to be understood that the prior art did not recognize any major utility for cholinesterase reactivators apart from the treatment of exogenous phosphorous compounds acute poisoning. Though the use of cholinesterase reactivators for the treatment of exogenous phosphorous compounds acute poisoning has been known for many years, no one had heretofore proposed the use of cholinesterase reactivators for the purposes disclosed in my present patent application.

Cholinesterase has been identified as true cholinesterase or acetylcholinesterase (ACHE) and pseudo or plasma cholinesterase (CHE). The former is distributed throughout various segments of the autonomic, peripheral and central nervous systems and also in other systems outside the nervous system and is felt to be associated with membrane phenomena. Pseudo cholinesterase is also distributed throughout the nervous system and is believed to be primarily in myelin and the glial supporting cells (oligodendroglia). CHE is also distributed throughout various tissues outside the nervous system.

The prime function of cholinesterases in the nervous system is to create the hydrolysis of the protein ester acetylcholine (ACH). Electrical activity of neural tissue is intimately related to ACH and cholinesterases. The precise duration in which ACH is permitted to act is regulated by the timed destruction of ACH by the cholinesterases.

It is known that ACH has various actions described as muscarinic and nicotinic and also central actions in terms of impulse propagation along axons (axon potential) and possibly as a transmitter at some synaptic sites. It is felt by some also that they may be a muscarinic type action in the central nervous system. The precise mechanism of these actions is unknown, but it is related intimately to receptor sites. In the proper amounts, ACH facilitates transmission at these points and in large amounts or when present other longer periods, it inhibits neural function. It has been shown that electrical activity in neural tissues ceases with the absence of cholinesterase because of the failure to destroy ACH which then creates a state of hyperpolarization. In sum, there is a dynamic relationship in terms of function of neural tissue which is related to the proper balance of ACH and cholinesterase in varied areas of the nervous system.

Demyelinizing diseases are associated with pathological processes in which the sheaths of myelin around axons are destroyed wholly or in part. It is known that myelin is a lipid structure containing various chemical compounds such as cholesterol, phospholipids and galactosphingolipids. There are also present in myelin several types of protein, one being the basic protein. It is known that interference with the structure of myelin primarily produces dysfunction of axon conductivity, although anatomically the axon may appear to be relatively intact. This is so called primary demyelination. In secondary demyelination there is alleged to be a primary disorder in the axon with subsequent myelin degeneration around this axon. There are many clinical syndromes associated with demyelination in the nervous system and the symptoms and signs depend upon the location of the process, namely the axons involved and indeed their failure of conduction. In general, the cause of many demyelinating processes is unknown. It is known that demyelination occurs after a rather characteristic response to many noxious agents affecting the nervous system. These agents can be infectious, traumatic or toxic. The outstanding example of a primary demyelinating disease is multiple sclerosis, and the outstanding example of secondary demyelination is amyotrophic lateral sclerosis or motor neuron disease.

I have found that in both categories of demyelinating processes in man electrical stimulation over the dorsum of the spinal cord can reverse or modify many of the symptoms and signs associated with these processes. These include mental deterioration and depression, pain, impaired performance of the voluntary motor system in terms of power and synergy, i.e., abnormal movements, spasticity and peripheral sensory thresholds and, less pronouncedly, cortical seizure activity.

My observations with electrical stimulation in these categories of demyelinating disease, which also include traumatic situations of the central nervous system, suggest that there is indeed an imbalance in cholinergic and adrenergic activity, namely there is a relative central hypercholinergic state.

I believe that when there is destruction of myelin in varying degrees and also varying degrees of axonal destruction, the symptoms and signs are not totally irreversible. This was demonstrated by electrical stimulation over the spinal cord, namely the reversibility of some of the symptoms and signs as enumerated above. It is felt that electrical stimulation reactivates axonal transmission and synaptic function which had been physiologically blocked. It is further felt that this has to do with biochemical events and, of necessity, has to involve the essential elements of acetylcholine and cholinesterase relationships.

I established that in primary and secondary demyelinating disease electrical stimulation could change func-
tion and it is known that with demyelination the biochemical substrates in the diseased area are disturbed. Cholinesterase activity has been demonstrated to be significantly modified in the area of the plaque in association with varying degrees of demyelination, such as in multiple sclerosis. This would result in a relative excess of acetylcholine and a hypercholinergic state relative to axons and, therefore, a hyperpolarization block of conduction, namely, a functional or neurophysiological block which could be reversed under suitable conditions, endogenous or exogenous.

It is known that excess acetylcholine may act as a persistent cathode and result in hyperpolarization and placement of an anode and subsequent stimulation in that area of membrane will reverse the process, and I perceived a similar situation with stimulation of the spinal cord in man. I have concluded that compounds which activate cholinesterase systems, typically oxime compounds such as, for example, 2-PAM and its salts, DAM, other 2-oxo-oximes, MINA, and bis quaternary pyridine aldoxime (TMB-4) should act to mitigate the signs and symptoms of demyelinating diseases and pathological processes which result in a disturbance in ACH-cholinesterase relationships in terms of relative decreased cholinesterase activity.

Apart from 2-PAM and physiologically acceptable salts thereof, DAM, other 2-oxo-oximes, MINA and bis quaternary pyridine aldoxime (TMB-4), other cholinesterase reactivators that may be used according to the present invention to mitigate the signs and symptoms of the aforementioned diseases and processes are the entire class of oximes disclosed in U.S. Pat. No. 2,816,113, the oximes discussed in U.S. Pat. No. 3,063,901 and the oximes disclosed in U.S. Pat. Nos. 2,996,510 and 3,077,476. In the context of the present invention the cholinesterase reactivators may be administered in any dosage form, for example, orally, intravenously, intramuscularly, intraperitoneally or subcutaneously. Moreover, these compounds may be utilized in the present invention in dosages within limits already established as safe and effective in the treatment of poisoning from exogenous organic phosphorous compounds and in dosages given to normal people for prophylactic purposes when they are about to be possibly exposed or may have been exposed to exogenous organic phosphorous compounds such as in the agricultural or horticultural application of organic phosphorous insecticides.

The hereinafter described clinical experiments are illustrative of the present invention.

Initially, 2-PAM-CI was given parenterally and then orally in single doses of 500 to 1000 mg. to persons afflicted with multiple sclerosis. The time course of the effectiveness of the drug was found to be about 15 to about 30 minutes for changes to appear and the changes gradually disappeared over a period of about one to about two hours. Subsequently, repeated daily doses were given to individual patients at different stages of a demyelinating disease and with different demyelinating diseases. Finally, patients received the drug who (1) never had stimulation of the spinal cord before, (2) had previous stimulation of the spinal cord, and (3) while stimulation of the spinal cord was being carried out in a partial or complete manner. Similarly, a group of patients were given a placebo. After their reaction to the placebo was observed, some of the same patients were given 2-PAM-CI. Also, many of these patients had been under observation previously for the effectiveness of another drug, Dantrium, which allegedly modifies spasticity. Observations of the patients to whom a placebo had been given were carried out with and without spinal cord stimulations. Comparative evaluation was therefore permitted.

The results can be summarized as follows:
1. Patients receiving placebo did not show the changes as seen with 2-PAM-CI.
2. Patients receiving Dantrium did not show the total effects as seen with 2-PAM-CI.
3. The administration of 2-PAM-CI repeated the effects seen with spinal cord stimulation in the same patients but also as seen in others.
4. In many instances of a patient receiving stimulation of the spinal cord, administration of 2-PAM-CI required that the power delivered by the stimulator be reduced because the drug plus the stimulation aggravated the parathesiae experienced with stimulation alone. The cumulative effect was too strong.
5. Effects observed repeatedly were:
   a. A sense of alertness; abolition of mental depression and abolition of a feeling of fatigue which in many of these patients is profound. Improved cerebral or mental function also occurred in those in whom the foregoing was a prominent feature.
   b. Impaired function in the voluntary motor system was much alleviated as would occur with stimulation of the spinal cord.
   c. There was a decrease in ataxia, particularly static, postural ataxia, as well as abnormal movements characterized as dystonic or choreic.
   d. There was abolition of visual blurring if this had been present.
   e. There was decreased spasticity and re-operation of reciprocal innervation.
   f. There was relief of pain, if this had been present.
   g. In some, the strength of speech was improved significantly.
   h. Active movements could be carried out for longer periods without fatigue and detrimental dysfunction.

Adverse effects were transitory and observed in only some patients. These effects included nausea and vomiting, visual blurring, an initial sense of fatigue, drying of the mouth and diarrhea.

In some patients I have used both spinal cord stimulation and the cholinesterase reactivator and have found that they complement each other provided that the dosage of the drug and/or the strength of the stimulation delivered are modified when the total effect appears to be too great. In some patients, the drug is simply used alone.

The significant effect in demyelinating diseases of compounds capable of changing the chemical constitution of cholinesterase suggests that a major effect in the symptomatology depends upon the degree of change in the chemistry of cholinesterase. The mitigation of mental deterioration and depression, pain and spasticity, increased function in the voluntary motor system and increased synergy and signs of renewed operation of reciprocal innervation in terms of appropriately timed inhibition and facilitation, i.e., decrease in abnormality or normalization of movements all indicate a fundamental modification of a process having to do with neural transmission and synaptic zones and their connections, axons and dendrites. The almost precise repetition of the effect of spinal cord stimulation by the administration of the drug alone and the complementary function
of both together suggests also the modification of a basic mechanism, that of ACH-cholinesterase. It is known that these relationships are essential for propagation of the axon potential or neural impulse and also at certain synaptic areas, both peripherally and centrally. This evidence also tends to support the conclusion that cholinesterase reactivators such as 2-PAM-Cl indeed have a very significant action in terms of the central nervous system which prior to this time has not been elucidated completely. In addition, it also emphasizes the significance of biochemical change in the cholinesterase systems in relationship to the central nervous system in patients with primary and secondary demyelinating processes and other aforementioned processes and the modification of such biological change by cholinesterase reactivators. It also indicates that such cholinesterase reactivators are effective in processes of long duration since these patients had been diseased for years. This is in sharp contrast to cases of acute organic phosphorous poisoning. In the latter it is felt treatment must be immediate not only for clinical reasons but also because of aging of the phosphorylated cholinesterase. This does not seem to be the case in my applications of cholinesterase reactivators.

The details relating to spinal cord stimulation are described in an article authored by myself and a co-worker and entitled "Chronic Dorsal Column Stimulation in Multiple Sclerosis," New York State Journal of Medicine, Dec. 15, 1973, pp. 2868-2872. In addition to the treatment of the aforementioned conditions, the invention is also useful in the treatment of other conditions in which there are disturbances of acetylcholine-cholinesterase relationships in terms of relative decreased effectiveness of cholinesterase resulting in defective neural transmission. These include injury of the central nervous system (i.e., brain and spine), myelopathy and encephalopathy as may be associated with demyelination as well as diseases associated with focal neural loss in areas of high cholinesterase activity. Moreover, the invention is useful in the treatment of pain, mental deterioration and depression, the latter of which is believed to be essentially a hypercholinergic phenomenon, even in the absence of a demyelinating process. The invention is also useful in the treatment of convulsions.

What is claimed is:

1. Method of alleviating one or more of the symptoms of multiple sclerosis comprising administering to a person suffering therefrom a dose of 2-formyl-1-methylpyridium oxime or a physiologically acceptable salt thereof effective to alleviate said symptoms of multiple sclerosis.

2. Method according to claim 1, in which the cholinesterase reactivator which is administered is 2-formyl-1-methylpyridium oxide chloride.

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