CHEMICAL MODULATION OF MOTOR CONTROL WITH AND WITHOUT ELECTRICAL STIMULATION OF THE SPINAL CORD IN MULTIPLE SCLEROSIS

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Summary

Pam, a cholinesterase reactivator, has been administered to patients with MS and controls. Oral and parenteral routes of administration were employed with and without electrical stimulation of the spinal cord. The clinical response follows the known time course of the drug and is dose related. Rapid administration of large doses aggravates existing neurological dysfunction. The typical response to 1,000 mgm. intravenously results initially in the appearance of new ophthalmological signs which subside. Thereafter, there is significant improvement in motor control and behavior which gradually subsides. Parenteral administration is superior to oral. Tolerance has been observed. The presence of electrical stimulation of the spinal cord complements the action of the drug. The effect of the drug reproduces the effects of electrical stimulation in patients in whom electrical stimulation has been withdrawn. It is suggested that a defect in CHE and its reactivation in MS patients may have a significant relationship to symptomatology and signs.

Introduction

The pathoanatomical hallmark of Multiple Sclerosis (MS) is segmental demyelination (1). Experimental demyelination has been shown to result in conduction defects (2). The pathophysiologic mechanism of this defect has not been elucidated, but it is presumed in patients with MS that it is such conductive defects which produce symptoms and signs. The fact remains that spontaneous remission and exacerbation of symptoms and signs occurs. Symptoms and abnormal signs can also be induced by a great variety of seemingly unrelated phenomena. In all, the ultimate results are dependent upon membrane polarization phenomenon. The modification of calcium metabolism (3) may cause changes in signs and exposure of the spinal cord in patients with MS to an electrical field may induce improvement in integrated function (4,5,6,7). These phenomena when of short duration can not be reasonably presumed to be associated with return of conduction in demyelinated areas as a result of remyelination. Recent evidence, both in the peripheral and central nervous system after axonal lesions indicates that reconstitution of function is associated with new synapses (8). The possibility exists that in MS in association with segmental demyelination, there is dysfunction at the next appropriate synaptic pool. The sensitivity of such dysfunction to many exogenous agents suggested this may be due to a defect in neuro-transmitter function. Studies of the cerebrospinal fluid (CSF) in MS of catecholamines indicated that the concentration of homovanillic acid (HVA) in CSF with and without electrical stimulation of the spinal cord under probenecid protocol is normal. Hydroxyindol acetic acid (HIAA) is consistently low and not altered by electrical stimulation (9). Some

patients with MS have improved significantly with monoamine oxidase inhibition in association with electrical stimulation of the spinal cord (10). Little information is available in regard to the cholinergic system in MS, except that in the center of plaques of demyelination, an almost selective decrease in pseudo cholinesterase (CHE) is demonstrated (11,12,13). For this reason we felt that replacement therapy related to CHE in MS may be beneficial. Since satisfactory preparations of CHE were not available for human use in the United States, a cholinesterase reactivator 2 Pam Chloride (2-pyridine aldoxime)* (Pam) was employed.

The purpose of this presentation is to describe the efficacy of the administration of this compound in patients with MS with and without electrical stimulation of the spinal cord.

Methods

The patients selected had Multiple Sclerosis. The diagnosis was established by usual criteria. Patients with other neurological disease and pain syndromes were included as controls. Each patient did not know what to expect in terms of change in function. Informed consent was obtained. Knowledge of the effect of the drug in individuals with neurological problems and in organic phosphorus poisoning existed (14,15,16,17). In addition, experience existed with the use of the drug in patients with Myasthenia Gravis in cholinergic crisis (18). Data existed which had established the time course of the effect of the drug.

Pam was administered in varying doses by oral, intramuscular and intravenous routes. In the latter circumstance, single bolus injections and gradual infusion were employed.

Observations were made by the three authors. They were directed primarily to changes in functional capability and neurological dysfunction. Videotape and cinematic records were obtained at specified periods after drug administration. After establishment that a specific effect occurred comparisons were made with and without spinal cord stimulation in different and the same patients. Patients receiving oral preparations were observed under a single blind protocol. Specifically, initially a vehicle was given without drug. Subsequently, the drug was placed in the same vehicle and administered. This procedure was reversed in selected patients. Double blind protocol was followed under other circumstances. Here the physicians engaged in the observations and the patient had no knowledge of whether drug was administered. One of the authors (F.N.) retained control of the preparation of administered compounds. Observation was made by the same principals most often in the same setting, and at the same time of day, after 6:00 p.m.

A number of patients have been treated on a chronic basis with varying dosages according to need. In acute experiments, the usual dose given was 1,000 mgm. within ten minutes. The largest dose administered orally in twenty-four hours was 11,000 mgm. The longest period of chronic administration was one and one-half years. After discontinuance of drug, comparative effects were noted in the same patient.

Material

In Table I, the patient content in the study is indicated. In Table II, the number of patients, the relationship to electrical stimulation of the spinal cord and placebo is outlined. The smallest single dose was 500 mgm; the largest 2,000 mgm, and total I.V., 6,000 mgm. Single doses of 500 mgm. were administered to twenty patients and of 1,000 mgm. to seventeen patients. Multiple doses were given to thirty-two. The degree of dysfunction was graded according to the Kurtzke scale (0-10) (19); ten being most severe. Most patients had had all types of conventional treatment, such as physical therapy, steroids, ACTH, immune suppressive drugs, diet, and vitamins.

Demyelinating disease, in particular, is subject to influence by many specific external and internal environmental influences. Such factors existed persistently. Variations in the temperature inside and outside the hospital room and indolent infection (urinary) was often present. Control of these factors was presumably never absolute. Emotional influences in family situations constantly existed and were not eliminated. Competitive drug antagonism was not eliminated since for a variety of therapeutic reasons these patients had to receive therapy for other problems.

Table I

Contents of Study

	Number of Patients
Total number of patients	61
Type of Disease	
1. Primary demyelinating	
a. M.S.	37
Grade 9	6
Grade 8	4
Grade 7	9
Grade 6	9
Grade 5	9
2. Secondary demyelinating	7
a. ALS	2
Grade 8	1
Grade 7	1
b. Spinal cord trauma	5
1. acute	2
2. chronic	3
3. Others	17
a. Lumbar radiculitis - pain	7
b. Head injury	
1. acute	2
2. chronic	1
c. Metastatic brain tumor - post op.	1
d. Brain tumor - post op.	1
e. Brown - sequard - syphilis	1
f. Tic Douloureux	4

Table II

	Number of Patients
Associated Elements	
1. Without spinal cord stimulation	9
2. With prior spinal cord stimulation	
a. Discontinued	19
b. Continued	26
c. Partial	7
Comparative Elements	
1. Placebo	
a. With spinal cord stimulation	8
b. Without spinal cord stimulation	4
c. Without subsequent administration of Pam	8
d. With subsequent administration of Pam	12

Results

1. Response to single I.V. bolus (1,000 mgm. in ten minutes). Within minutes after termination of the injection and persisting for as long as 30-40 minutes, there is occasional mild nausea without vomiting, a general sense of warmth, and drowsiness and a feeling of "light headedness." There is no change in blood pressure, pulse or respiration. Quite constantly, very shortly, there is blurred vision and horizontal diplopia. At times, a horizontal and vertical component can be specifically identified. Progressively, there is bilateral ptosis (Fig. 1). In the same patient over weekly trials, the ptosis may vary from week to week in severity, but it is always present. Increasingly, it is more difficult for the patient to elevate the upper eyelids and the head may be extended for sight. Ultimately, the patient prefers to keep the palpebral fissures closed because of the marked disorganization of visual perception. Examination at this time, shows the appearance of abnormal ocular mobility patterns which were not present before administration of the drug. Horizontal jerk nystagmus may appear. Classical motility disturbance stimulating internuclear opthalmoplegia has been seen; specifically, the failure of medial deviation of one eye appropriately in saccadic or pursuit horizontal gaze movement. At times, when these abnormalities are at a maximum, the injection of one cc. of Edrophonium chloride (Tensilon) has not reversed the abnormal signs as would be expected if this phenomena were due to hypocholinergic dysfunction at the neuromuscular junction. Gradually, these opthalmological signs disappear, so that there are no complaints referable to vision which were not present before administration of the drug.

Concurrently, with the gradual disappearance of eye signs, a "lightness" is noted in limbs and gradually improved integrated motor function is observed in motor behavior. This is manifested by progressive increased ease and ability to cross the lower limbs while sitting (improved hip flexion). There is increased ability to make circular movements with a foot or carry out rapid flexion - extension movement of a foot and toes which was not possible before. Ataxia becomes less as demonstrated in finger to nose testing, but also in carrying out acts, such as holding a cup and drinking. Tracking movements are done with greater accuracy and projection. During walking, the posture is changed so that a more erect position is maintained. The speed of gait is increased and cadence is more natural and smooth. Individual strides are large and appropriate dorsi flexion of foot, knee flexion and hip flexion may be improved during the walking cycle. While at rest in a supine position, elevation of the lower limbs off the bed will be dramatically increased in force, speed, and ability to sustain a position of elevation (Fig. 2). Carrying out skilled acts such as striking a match are done with greater dexterity and purpose. Under such circumstances,

the patient as a whole addresses himself more appropriately to a specific purpose as would occur under normal circumstances. The timing of associated behavior with skilled acts is more appropriate. The ability to maintain limb position and posture while attention is directed to other specific performance is improved. In patients in whom there have been ophthalmological signs, such as internuclear ophthalmoplegia, the ability of an eye to cross the midline in a medial direction is improved and nystagmus may be modulated (Fig. 3). Ocular dysmetria, if present, may improve.

In any single patient, all these abnormal neurological signs are not present before administration of the drug, and all these changes do not occur in every patient. As neurological phenomena having basic pathophysiological mechanisms, however, they represent distinct entities which change during the time course of action of Pam. To date, we have not seen the initial ophthalmological signs in any patient without MS under the conditions specified. Over a period extending up to one to two and one-half hours, the effects described gradually disappear. The patient's function returns to previous levels and may fall, temporarily, below that level.

2. Effect with and without spinal cord electrical stimulation. The effects described in 1. have been seen in patients who have never had electrical stimulation of the spinal cord. They occur in patients who have electrical stimulation of the spinal cord at the time of administration of the drug. On occasion in such patients, the patient reaches for the transmitter to turn down the voltage because "it becomes more intense." This statement is meant to signify that the perceived sensation by the patient has increased. At a later time, the same patient will spontaneously turn the transmitter back up because the increased "stimulation" is now less. In a patient in whom electrical stimulation of the spinal cord has elevated functional motor behavior, the administration of Pam will increase functional capability, suggesting a complementary action. In patients in whom electrical stimulation of the spinal cord has been carried out, if the electrical stimulation is terminated, function will fall to a certain level. If this patient is now given Pam, function will be returned just as if the transmitter had been turned on, and he describes these events as feeling as if, indeed, electrical stimulation had been re-instituted; "Just like the stimulator."

3. Effects in other disease. Our experience in any specific entity other than MS is not large and represents only isolated instances in many cases. They represent control groups. The fact is in patients with severe head injury in a recovery phase, Parkinson's disease, severe pain from root disturbance, postoperative aphasia, the acute specific response as recorded in MS does not occur. In one patient, during recovery from spinal cord dysfunction, after re-

moval of a meningioma, there was improvement in motor function. This followed oral administration of drug. Force, stride, speed of gait was significantly modified. A patient with motor neuron disease who had dramatic functional improvement with electrical stimulation displayed the same type of response when taking Pam orally with and without the presence of electrical stimulation of the spinal cord. In another patient presumed to have central nervous system syphilis with marked neurological dysfunction and marked paresis of both lower limbs, there was striking change in ability to move the lower limbs after Pam.

Four patients with Tic Douloureux, two of whom had MS, received Pam I.V. In the latter patients, the severe repetitive pain during an acute attack was modulated. The effect lasted two to two and one-half hours. With continuous I.V. infusion, the repetitive attacks were decreased but pain returned after discontinuation of drug. In one patient without MS, recurrent, daily, repetitive attacks of Tic pain prevented the patient from talking and eating for three months. Conventional drugs were used without success. I.V. Pam was administered in doses, 3,000 mgm. on each of two days with no significant effect on pain attacks. On the third day, 7,000 mgm. was given and thereafter, individual attacks ceased and the major bout which had lasted three months was terminated for the first time during this period.

These effects in certain other processes suggests that, rather than this being a non-specific effect, that the drug may have an effect in the presence of demyelinating processes due to other causes besides MS.

4. Effect of varying doses by different routes over different times. The effective dose seems to be 1,000 mgm. Given orally, there is less effect than parenterally. 1,000 mgm. orally may not be tolerated, so 500 mgm. is usually given. This dose has to be given frequently (every two hours) to maintain a level of improved function. It is only after I.V. bolus over ten minutes, that we have observed the opthalmological signs described. This does not occur with oral or with same dose intramuscularly. With 2,000 mgm. I.V. in twenty minutes, there is temporary amelioration of severe neurological signs followed shortly by aggravation of neurological signs. There may also be excessive nausea and vomiting and no other significant improvement after this period of exacerbation of symptoms and signs has occurred. In patients who have taken the drug chronically each day, the dose has to be had titrated and may be in the range of 4,000 and 8,000 mgm. a day. One patient had to take 11,000 mgm. to maintain a level of improved function. Subsequent cessation of chronic ingestion of drug results in regression of improvement to previous levels or below. A more chronic administration of drug by I.V. infusion in contrast to bolus, does not produce

the same effect with same amount of drug. Repeated I.V. or oral administration of drug ultimately will elicit less response (tolerance). However, in a weekly single bolus injection, there is also variability in amount of response which may reflect something other than pharmcodynamics of the drug and be related directly to the disease.

5. Comparative effects single and double blind. After our initial observations, all observations were made under single blind protocol. Placebo was always given initially. In double blind procedure, only one member of team knew of the content of the administered vehicle. The patient had no knowledge. In two specific instances with placebo, there was not only the specific effects of feeling of general well-being, but there was distinct functional improvement in motor behavior up to a point. This did not approach significantly the change with the Pam. However, there is no question that with I.V. placebo, distinct improvement in motor behavior occurred in two different patients even though of limited degree.

6. Toxicity effects. These have been minimal. There is no change in blood count or liver function in patients receiving Pam. Nausea has been a complaint in some with I.V. injection. With oral dose, there is often a change in taste, described as metallic or bitter. Vomiting occurs with too large a dose given too rapidly. Similarly, neurological symptoms of MS can be aggravated by too rapid administration of drug. In one patient, recovering from effects of severe head injury, a severe reaction occurred. This was manifested by rapid, severe hypotension, drowsiness, slowing of pulse, and slight hyperpnea. Impending cardiac standstill was suggested. The latter did not occur. A slow, gradual recovery occurred without subsequent difficulty. Previous cardiac disease was not known to have existed. This patient received 1,000 mgm. I.V. bolus in ten minutes. The reaction occurred precipitously at the end of injection. He became pale, with increased sweating and he wanted to assume a supine position. Recovery took about 30-45 minutes. During the entire reaction, there was no evidence of any of the opthalmological signs mentioned previously in MS patients with same procedures. We have never seen this cardiovascular reaction in MS patients or in any other patient studied.

Comment

The results indicate that the administration of a cholinesterase reactivator, Pam, changes neurological function in MS and other selective demyelinating processes. Inspite of the fact that the evidence is convicing, varied pharmacokinetic and pharmacodynamic factors, particularly in a disease such as MS prohibits the conclusion that, in MS, CHE is at risk. The cause of change in CHE in MS plaques is unknown. The effect of Pam is to reactivate phosphorylated

CHE. Does this mean that in MS there is phosphorylation of this enzyme? There is no evidence for this at present, although it may be true. In addition, there is no data at present to explain how reactivation of CNS CHE may be related to restored function in MS. The function of CHE is still under debate. More recently, Koelle (20,21) has suggested it may be the rate limiting entity in acetycholinesterase production. CHE is known to be present in significant amounts in oligodendroglia. Friede (22) feels it may be a marker for these structures. CHE is involved in fat metabolism (23), blood brain barrier function (24), and primarily has its effect as that of hydrolysis of higher choline esters (25). CHE also hydrolyzes acetycholine but at a slower rate than acetycholinesterase. What effect in neurological disease this may have is unknown. The possibility does exist, however, that in MS there may be a relative hypercholinergic state centrally if CHE is not functioning properly.

Imbalance in monoamine-cholinergic relationships exist in other diseases; Parkinsonism being the classical example. Inhibition of cholinesterase by physostigmine makes Parkinsonism worse. It produces inconstant effects in chorea (26). Our demonstration of change in neurological function by administration of a cholinesterase reactivator suggests that in MS a change in monoamine-cholinergic mechanisms may exist. This may provide a basis for establishing a form of specific pharmacological therapy.

Legend

Fig. 1 Demonstration of induction of bilateral ptosis after I.V. injection of 1,000 mgm. Pam.

Fig. 2 Comparative effects of ability to raise lower extremity before (a), 30-40 minutes after (b), I.M. administration of 1,000 mgm. Pam.

Fig. 3 Improvement of internuclear ophthalmoplegia after I.V. administration of 1,000 mgm. Pam.

Footnote

2 Pam Chloride - Protopam Chloride
Pralidoxime chloride U.S.P., Ayerst Pharmaceutical, New York.

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