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MESTINON* (PYRIDOSTIGMINE BROMIDE) IN MYASTHENIA GRAVIS

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RESEARCH aimed at finding synthetic substances for use in place of physostigmine has resulted in the discovery of several preparations. The most active of these is pyridostigmine bromide—Mestinon (dimethyl carbamate of 3-hydroxy-1-methyl pyridium bromide), a heterocyclic agent of the alkylcarbamic group, with the nitrogen atom of the pyridine ring fulfilling the quaternary ammonium function of the molecule. Mestinon is about five times less toxic than prostigmine (neostigmine) and its effect on the intestines is only half as strong, both *in vitro* and *in vivo*, as that of the latter.[1]

In common with other substances of eserine type, Mestinon markedly inhibits the plasma pseudocholinesterase but it shows practically no inhibition of the true cholinesterase of red cells and muscle tissues when given in comparable doses.[2]

It is an excellent curare antidote but its decurarizing effect is quite independent of its inhibitory effect upon the cholinesterases.[2] Because of its anticurare properties and its low toxicity, Mestinon appeared suitable for clinical trial in patients with myasthenia gravis. Seibert[3] was the first to show that Mestinon when given in doses four times larger than prostigmine favourably influenced the myasthenic syndrome and that side-reactions if any were surprisingly mild. Other investigations[4-6] followed, and confirmed Seibert's findings.

In the present study, the effects of Mestinon were investigated over a period of 12 months in a group of patients with myasthenia gravis (Table I).

ILLUSTRATIVE CASE HISTORIES

CASE 1.—W.S. This patient has myasthenia of a bulbar and peripheral type of 25 years' duration. In order to control her weakness, the patient takes 6-8 tablets of prostigmine daily; on this medication she can remain fairly active for limited periods of time. Her clinical picture was characterized by weakness and fatigue in the early morning, prior to prostigmine, and a generalized slump towards the end of the day. When Mestinon, 8 tablets a day, was substituted for 8 tablets of prostigmine the response was most disappointing. Although there was some control of her myasthenic phenomena, the patient was weak and fatigued all day, and felt very depressed. After one week she reverted to prostigmine, and once more was able to lead a fairly active life.

One month later, Mestinon was tried again first in a 1:1 ratio with prostigmine (4 Mestinon and 4 prostigmine tablets); after a time Mestinon was gradually substituted for prostigmine until she was taking 6 tablets of the latter only. This second attempt to treat the patient with Mestinon was gratifying and at the same time most surprising in view of our initial failure with this drug. On this occasion her morning weakness and fatigue was absent when she was on Mestinon. She engaged in more vigorous activities, and at this time did not experience her usual slump towards the end of the day, as observed with prostigmine. At one time, a temporary shortage of Mestinon necessitated renewal of prostigmine. After taking only one tablet of prostigmine, the patient experienced a most violent intestinal colic, a phenomenon that had never occurred in her 20 years of prostigmine therapy. When Mestinon became once more available, she started with 6 tablets daily and she has maintained her improved clinical state.

She has continued on Mestinon for one year, obtaining a steadier and more uniform control of her myasthenic phenomena than on prostigmine, with total absence of side-effects.

CASE 3.—H.LaH. This married woman of 28 has been suffering from a bulbar and peripheral type of myasthenia for the last eight years.

Prior to Mestinon trials, she took 10-12 tablets of prostigmine a day, and on the whole her general condition fluctuated a great deal—up one day, and down the day after. Mestinon was administered to this patient for two days in a 1:1 ratio (5 Mestinon and 5 prostigmine tablets); as her response was very satisfactory, prostigmine was stopped altogether on the third day and she continued with 10 tablets of Mestinon only.

While on Mestinon, she felt remarkably well and strong, and could do a full day's work without getting the least tired. Eventually, she found that she could do with less Mestinon until she reached a dose of three tablets daily, at which level her symptoms were well controlled.

After two months, Mestinon was discontinued and the patient started again on prostigmine. Very surprisingly, it was found that even with increasing amounts of prostigmine it was almost impossible to control this patient's myasthenia adequately. Her condition deteriorated rapidly and she was unable to get out of bed in the morning, climb stairs, or walk for any distance. In order to control the myasthenia, her prostigmine requirement was gradually increased until she was taking as many as 36 tablets a day; even at that her response was very unsatisfactory.

After one month, prostigmine was discontinued and the patient started on 10 tablets of Mestinon daily. In a matter of 24 hours she improved sufficiently to go to work, a feat impossible for the last four weeks of prostigmine therapy. As on the previous occasion, she found that she could control her myasthenia with only 3 tablets of Mestinon a day, and continued on this dose during the following six months. At the end of that time, an attempt to try prostigmine with this patient once more proved entirely unsatisfactory. Her condition deteriorated rapidly and she was resistant to the increasing amounts of the drug.

Once more Mestinon promptly improved her myasthenic state; for the last six months the patient has continued exceedingly well and enjoys a normal life, using only small amounts of the drug (3-5 tablets a day).

CASE 4. L.A. This middle-aged man suffers from myasthenia of two years' duration. The patient's symptoms are chiefly confined to his bulbar musculature but at times there is a fair amount of peripheral weakness as well.

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TABLE I.

RESPONSE TO MESTINON IN 14 PATIENTS WITH MYASTHENIA GRAVIS.

Group A		*Group B*	*Group C*	*Group D*
Mestinon superior to prostigmine		*Mestinon with prostigmine superior to either Mestinon or prostigmine alone*	*No change*	*Mestinon inferior to prostigmine*
Initial response to Mestinon	*Subsequent response to Mestinon*			
1. W.S.—unsatisfactory (bulbar and peripheral)	Good	8. R.W.* (bulbar and peripheral)	11. H.N. (bulbar and peripheral)	13. A.R. (bulbar and peripheral)
2. O.S.—excellent (peripheral)	Excellent	9. G.E.* (peripheral)	12. P.B. (peripheral)	14. L.M. (peripheral)
3. H.LaH.—excellent (bulbar and peripheral)	Excellent	10. B.S. (bulbar and peripheral)		
4. G.A.—unsatisfactory (bulbar)	Good			
5. S.N.—excellent (peripheral)	Excellent			
6. G.G.—excellent (bulbar and peripheral)	Excellent			
7. B.B.—unsatisfactory (peripheral)	Good			

* less than one year follow-up.

At the time of the trial the patient was taking 12 tablets of prostigmine daily and was thus able to relieve some of his muscular weakness, the muscles of the eye and eyelids being the most resistant to treatment. While on prostigmine, he suffered from a troublesome diarrhœa and abdominal colic, which more than offset some of the advantages of prostigmine.

Mestinon, 12 tablets a day, although relieving him of diarrhœa and abdominal colic, was not as effective as prostigmine in controlling muscle weakness. Consequently, his medication was changed to 6 tablets of prostigmine and 6 tablets of Mestinon daily. On this combination he was able to obtain fair control of his myasthenia and at the same time was free of the troublesome intestinal phenomena. In the weeks that followed, prostigmine was gradually replaced by Mestinon; eventually he was able to achieve a satisfactory response with only 8 tablets of Mestinon daily and this was maintained for 12 months. On two occasions attempts were made to treat this patient with prostigmine only; these were entirely unsuccessful because of severe abdominal colic and diarrhœa.

CASE 5.—G.G. This woman, 24 years old, has bulbar and peripheral myasthenia of 3 years' duration. At the time of the trial, the patient was able to control her myasthenia with about 10 tablets of prostigmine daily. When 10 tablets of Mestinon were substituted for prostigmine, the patient observed that not since the onset of her illness had she felt so well and full of vigour. In the weeks that followed, she found that she needed less Mestinon, and reduced the dose to only 3 tablets per day.

To test whether this striking improvement was due to Mestinon and not to the remission of her myasthenia, prostigmine was substituted for Mestinon. This was followed by a surprising deterioration in muscle strength, which was not controlled with increasing amounts of prostigmine. Three days after prostigmine medication, the patient collapsed while getting out of bed and was admitted to hospital in a myasthenic crisis.

As soon as she was able to swallow, the patient again responded very well to Mestinon, 8 tablets a day, and left the hospital requiring only 3-6 tablets. Eventually she found that she could control her myasthenia with only 3 tablets of Mestinon daily, and on this dosage she continued remarkably well for three months. An attempt was then made to test this patient once more with prostigmine only. As on the previous occasion, her strength rapidly declined, and she required increasing amounts of the drug with only partial control of her symptoms. After three days of prostigmine she was once more given Mestinon; symptoms rapidly improved, and on the following day she was able to engage in her normal activities. For the last 12 months she has continued very well on only 3 tablets of Mestinon.

CASE 8.—G.E. This married woman, 35 years of age, has myasthenia of 10 years' duration; her symptoms are chiefly confined to peripheral musculature but occasionally there is a fair amount of bulbar weakness as well.

Prior to Mestinon, the patient obtained only inadequate control of weakness with 8-10 tablets of prostigmine and she led a very restricted life at home. When Mestinon was given to her in conjunction with prostigmine (4 Mestinon and 4 prostigmine tablets daily), a most spectacular improvement was observed. In a single day, she cleaned the bathroom, waxed floors and engaged in all kinds of domestic activities, which before the Mestinon treatment would have been impossible without help. Shopping three times a week did not tire her nearly as badly as had one shopping expedition before, and she

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did not require the afternoon rest previously found essential.

In the weeks that followed she reduced her medication to 3 Mestinon and 3 prostigmine tablets a day, and with this combination she has maintained her improvement.

CASE 9.—R.W. This boy, 15 years old, has myasthenia of 2-3 years' duration; his weakness is bulbar and peripheral in character. Prior to Mestinon, he managed to obtain good but by no means complete control of his myasthenia phenomena with 12 tablets of prostigmine daily. The patient started with 6 tablets of prostigmine and 6 tablets of Mestinon a day; using this combination, he felt so vastly improved that within two months he reduced it to 3 Mestinon and 3 prostigmine a day.

For the past 6 months he has enjoyed perfect health and excels in all kinds of physical activities, such as cycling, football, fishing and hunting. He has largely regained the control of his facial expression, which was not benefited by prostigmine.

CASE 13.—A.R. This woman of 27 has bulbar and peripheral myasthenia of 6 years' duration. She takes about 32 tablets of prostigmine a day and several attempts in the last 12 months to administer Mestinon either singly or in combination with prostigmine have proved entirely unsatisfactory; consequently she continues with prostigmine alone.

COMMENTS

A one-year trial of a new prostigmine analogue, Mestinon (pyridostigmine), has shown this drug to be more effective than prostigmine in 7 of 11 patients (Group A—Table I), because of its superior ability to control myasthenic phenomena and the absence of side-effects after prolonged use.

However, in some of these patients (W.S., L.A. and B.B.—Table I) the beneficial response to Mestinon was not immediately apparent after a first or even second trial with the drug. It is not known whether this was due to the sudden change-over from prostigmine or to some individual tolerance factor in myasthenia. In three patients (G.E., R.W. and B.S., Group B—Table I) who responded fairly well to prostigmine or to Mestinon alone (B.S.), the combination of prostigmine with Mestinon produced a clinical response which by far surpassed the effect of either taken separately. In two patients (H.N. and P.G., Group C—Table I) repeated trials with Mestinon produced no appreciable change in their myasthenic condition as compared with prostigmine. In the other two patients (A.R. and L.M., Group D—Table I) Mestinon was inadequate in controlling the muscle weakness, either when given alone or in combination with prostigmine, and eventually they reverted to the older medication.

In four of our patients (from Group A) in whom Mestinon was found superior to prostigmine abrupt cessation of the drug and its replacement by prostigmine produced severe gastrointestinal upset in two patients (W.S. and L.A.—Table I), and in the other two (H.LaH. and G.G.) sudden deterioration of myasthenia which they were unable to keep in check even with increasing amounts of prostigmine. The latter phenomenon following reinstitution of prostigmine therapy after abrupt cessation of Mestinon has also been reported by others.[4]

In general, it can be assumed that 60 mg. of Mestinon can be safely substituted for 15 mg. of prostigmine, although in patients responding well to the former this ratio is frequently much less.

At no time during our trials was there any evidence of parasympathomimetic stimulation or cholinergic phenomena, even when high doses of Mestinon were given for long periods of time. This relative lack of gastrointestinal stimulation makes Mestinon superior to prostigmine in the treatment of myasthenia gravis. However, it should be borne in mind that any toxic phenomena following Mestinon over-dosage or sensitivity may differ widely from those observed with prostigmine, largely because of the fundamental differences of the two drugs in their effect on the plasma and skeletal cholinesterases.

Our studies with Mestinon extending over a one-year period indicate that, either alone or in combination with prostigmine, it is the drug of choice in the majority of patients with myasthenia gravis: (1) because some patients resistant to prostigmine have shown an excellent response to Mestinon; (2) because the drug appears to be relatively non-toxic.

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RÉSUMÉ

L'auteur rapporte les résultats obtenus chez un groupe de malades souffrant de myasthénie grave, traités pendant une période de douze mois au bromure de pyridostigmine (Mestinon, marque déposée, de Hoffmann-LaRoche Ltée.), préparation synthetique cherchant à remplacer la physostigmine. L'emploi de ce médicament a donné des résultats supérieurs à ceux obtenus par la prostigmine chez sept malades d'un groupe de onze. Les effets secondaires furent minimes ou même absents, mais l'amélioration s'est quelquefois faite attendre. Les deux produits employés simultanément ont semblé produire un effet synergique. Quatre malades ayant bien réagi au Mestinon accusèrent des symptômes gastro-intestinaux marqués à la prostigmine. Chez deux d'entre eux, la myasthénie s'aggrava d'une manière incontrôlable par la prostigmine. La dose habituelle de Mestinon est de l'ordre de 60 mg. M.R.D.