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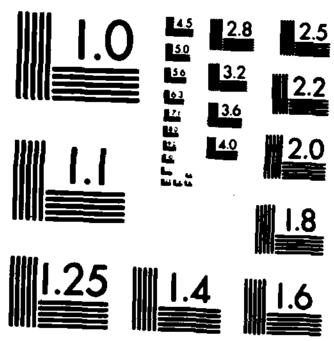

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Aerospace Medical Research Laboratory

HUMAN RESPONSE TO PYRIDOSTIGMINE BROMIDE

JUDITH I. WILLIAMS

MACAULAY-BROWN, INC.

MARCH 1984

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AIR FORCE AEROSPACE MEDICAL RESEARCH LABORATORY
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
WRIGHT-PATTERSON AIR FORCE BASE, OHIO 45433

NOTICES

TECHNICAL REVIEW AND APPROVAL

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This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

CHARLES BATES, JR.
Director, Human Engineering Division
Air Force Aerospace Medical Research Laboratory

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This report reviews the available human exposure to pyridostigmine bromide. Part of this report is an annotated bibliography of the documents reviewed.

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PREFACE

This report was prepared in support of the Human Engineering Division, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio 45433. The literature review was conducted by MacAulay-Brown, Inc., 3989 Colonel Glenn Highway, Fairborn, Ohio 45324. The project was conducted in accordance with the "Technical and Analytical Support for the Air Force Chemical Defense Analysis Program," Task 81-04, "Pretreatment Psychomotor Studies." The work was accomplished during February and March of 1982 under Air Force Contract F33615-80-C-0514.

The contribution of Captain Ronald Yates in reviewing the report is gratefully acknowledged.

SUMMARY

Pyridostigmine is an anticholinesterase agent which has been used in the chronic treatment of myasthenia gravis for more than thirty years. The drug has also been widely used in surgical patients for the reversal of neuromuscular blockade. Currently, pyridostigmine is being tested in military personnel in Great Britian as a pretreatment for protection against nerve agents. Side effects are generally related to overdosage; in treatment of myasthenia gravis, dosage must be adjusted to achieve optimal therapeutic effects with minimal toxicity. In surgical patients side effects are commonly controlled by simultaneous administration of atropine. Only trivial side effects were seen in approximately 100 normal subjects taking low doses of pyridostigmine in studies relating to pretreatment against nerve agents. The drug is poorly absorbed after oral administration and plasma levels are low. Peak plasma levels occur at two to three hours after oral dosing. Elimination occurs almost exclusively in the urine via the kidneys.

The amount of pyridostigmine which can be administered without severe side effects appears to be related to the degree of impairment of neuromuscular transmission. Myasthenic patients may tolerate as much as several grams per day, while surgical patients can tolerate intravenous doses equivalent to oral doses of 300-600 mg. The studies in military personnel indicate that doses of 30 mg at 8 hour intervals produce only trivial side effects in persons with normal neuromuscular transmission. Based on the results of the military studies and the general lack of adverse effects other than overdose symptoms, it can be concluded that administration of pyridostigmine to normal subject is probably safe at low doses, i.e. 30 mg at 8 hour intervals.

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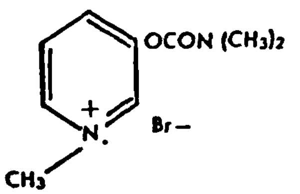
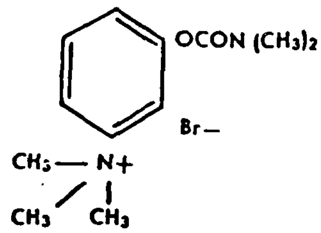
CHEMISTRY

Pyridostigmine bromide is the generic name for the dimethylcarbamate ester of 3-hydroxy-1-methylpyridinium bromide. The compound was first synthesized in the Hoffman-La Roche Laboratories, Basle, Switzerland in 1945 and is sold by Roche Laboratories under the trade name of Mestinon bromide. The drug is the pyridine analogue of neostigmine (Prostigmin) bromide, to which it is often compared.



Pyridostigmine bromide
(Mestinon bromide)



Neostigmine bromide

Pharmacologically, pyridostigmine is classified as an anticholinesterase agent. Acetylcholinesterase is an enzyme which is required in the termination of the transmitter action of acetylcholine at the cholinergic neuromuscular junction. Anticholinesterase agents inhibit or inactivate acetylcholinesterase resulting in increased acetylcholine. Pyridostigmine acts as a "competitive substrate", inhibiting the enzyme by forming a complex with it. Hydrolysis of pyridostigmine then follows in a manner analogous to that of acetylcholine, resulting in the regenerated enzyme. Thus, pyridostigmine is considered to be a "reversible" anticholinesterase agent (1).

Pyridostigmine is one of the quaternary ammonium anticholinesterase agents, which generally do not penetrate cell membranes readily. Hence, compounds in this category are poorly absorbed from the gastronintestinal tract and are excluded by the blood-brain barrier from exerting significant action on the central nervous system after moderate doses (1).

TREATMENT OF MYASTHENIA GRAVIS

Myasthenia gravis is a disorder of neuromuscular transmission, resulting from an autoimmune attack upon the postsynaptic receptor for acetylcholine. The disease is characterized by fluctuating muscular weakness and variable response to anticholinesterases. In mild cases only the eye muscles may be affected causing ptosis, whereas in myasthenic crisis the muscles of respiration are affected and death may ensue. The prevalence rate is 3-4 per 100,000 population, or approximately 6000-8000 cases in the US. (2,3). Treatment with anticholinesterase agents such as pyridostigmine may relieve the symptoms of myasthenia gravis, but does not cure the disease and medication must be taken on a chronic basis.

According to Roche Laboratories, pyridostigmine acts by inhibiting the destruction of acetylcholine and thereby permits freer transmission of nerve impulses across the neuromuscular junction. The average oral dose is 600 mg/day in divided doses, and an injectable form of the drug may be given by intramuscular or intravenous injection at 1/30 of the oral dose. Adverse reactions are stated to be "most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic." Muscarinic reactions due to increased acetylcholine are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, and heavy perspiration. Nicotinic effects are chiefly muscle cramps, fasciculations, and weakness. Extreme overdosage may lead to death through involvement of the muscles of respiration. A skin rash due to the bromide radical may be seen in an occasional patient, but the reaction usually subsides rapidly after withdrawal of the drug.

Pyridostigmine has been used in the treatment of myasthenia gravis for over thirty years. Siebert, 1953 (5), reported that since 1948 pyridostigmine was given a therapeutic trial in 23 myasthenic patients. Undesirable side effects after doses of 240-720 mg/day were mild and rare. Westerberg and Magee, 1954 (6), replaced neostigmine with pyridostigmine in the treatment of 22 patients with myasthenia gravis. After doses of up to 1080 mg/day, side effects were minimal and were associated with overdosage. Symptoms were abdominal aching and cramps, a "burning feeling" in the stomach, and diarrhea. Schwab and Timberlake, 1954 (7), treated with pyridostigmine fifty myasthenic patients who had previously been treated with neostigmine. Pyridostigmine, in doses as high as 1620 mg/day, was found to be free of disagreeable gastrointestinal side effects, but in some cases not so effective as neostigmine. Osserman, Teng, and Kaplan, 1954 (8), treated twenty patients with pyridostigmine, most of whom were monitored for a period of seven months by means of urinalysis, blood counts, and physical examinations. Hemoglobin, red blood cell, and differential counts performed at intervals showed no change. Doses ranged from 300-2160 mg per day. Side effects consisted of diarrhea, abdominal cramps, skeletal muscle cramps, and epigastric distress.

Tether, 1956 (9), reported a study of 165 patients with myasthenia gravis who were treated with pyridostigmine at daily doses of 60-6000 mg per day. Tether stated that "no distressing side-effects were observed even in patients who used it as long as seventeen months." However, pyridostigmine in excess caused the following symptoms; sweating, salivation, mild abdominal symptoms, muscle fasciculations, a peculiar blurring or "jumping" of vision with mild vertigo, and occasionally a "thick tongue" sensation with speech impairment. Schwab et al., 1957 (10), investigated the use of long acting pyridostigmine tablets in the treatment of 109 patients with myasthenia gravis. Daily dosage ranged from 180 to 4320 mg. The authors found "no reaction whatever from the prolonged-action Mestinon tablets, except that when the dosage has been too strong, overdosage symptoms have occurred." In reviewing 282 cases of myasthenia gravis Osserman et al., 1958 (11), stated that pyridostigmine is the drug of choice since it controls two-thirds or more of the patients with minimal side effects. They found no difficulty with toxicity, since the usual muscarinic side effects occurred as soon as overdosage was reached.

REVERSAL OF NEUROMUSCULAR BLOCKADE

Reports of the use of pyridostigmine in reversing neuromuscular blockade in anesthetized surgical patients began to appear in the literature in 1967 and continue to the present (12-26). These studies are of interest since they document the use of intravenous doses in hundreds of patients without reported ill effects. Since Roche Laboratories recommends the use of injectable pyridostigmine at 1/30 of the oral dose, the intravenous doses of 10-20 mg of pyridostigmine commonly used in reversal of blocking are equivalent to single oral doses of 300-600 mg. The neuromuscular blocking agents used in the cited studies include d-tubocurarine, gallamine, curare, pancuronium, and alcuronium. These are competitive blocking agents which compete with acetycholine for receptor sites at the motor end plate. The extent of blocking during surgery is determined by monitoring the muscular response to electrical stimulation of the ulnar nerve.

Katz in 1967 (12) reported the use of pyridostigmine as an antagonist to d-tubocurarine in 104 surgical patients. Atropine was found necessary to prevent excessive salivation and bradycardia. Intravenous administration of 10 or 20 mg of pyridostigmine was found to be effective in promoting recovery from neuromuscular blockade. For example, a patient required only three minutes for recovery after 10 mg of pyridostigmine, while during previous surgery the same patient required 75 minutes to recover spontaneously. McNall et al., 1969 (13), gave repeated 2 mg doses of pyridostigmine to reverse blockade induced by gallamine or curare in 133 patients. The average dose required for reversal after gallamine (7.4 mg) was slightly higher than after curare (7 mg). Zsigmond in 1972 (14) gave 5 mg of pyridostigmine followed by 1 mg increments for reversal of blockade due to d-tubocurarine. The mean dose that reversed blockade was 15.4 mg/70 kg.

In 1973 Fogdall and Miller (15) reported that in a study of thirty patients 11.7 mg of pyridostigmine reversed blockage by d-tubocurarine and 9.1 mg antagonized pancuronium-induced blockade. A second group of forty subjects received either neostigmine (2.5 mg) or pyridostigmine (14.5 mg) for reversal. Miller et al., 1974 (16), continuously infused d-tubocurarine in thirty patients to produce constant ninety percent depression of twitch response. Various doses of pyridostigmine or neostigmine were given to antagonize blockade. Peak effects of antagonism were reached at twelve to seventeen minutes with pyridostigmine, which showed a slower onset and longer duration than neostigmine. Lippmann and Rosoff, 1974 (17), used pyridostigmine to reverse blockade induced by pancuronium in 100 surgical patients, and reported that such side effects as bradycardia and salivation were minimal. Gyermek, 1975 (18), compared the results of a neostigmine-atropine combination in reversal of pancuronium block with those of various pyridostigmine combinations in 119 surgical patients. He found less change in pulse rate and fewer arrhythmias in the pyridostigmine groups.

Ravin, 1975 (19), investigated reversal by pyridostigmine for pancuronium or d-tubocurarine-induced blockade in 84 patients. Doses of pyridostigmine necessary for recovery were 8.3 mg after pancuronium and 11.6 mg after d-tubocurarine. A study of 340 surgical patients with pancuronium block was reported by Gyermek in 1977 (20). For reversal 24 received neostigmine, twelve received edrophonium, and the remainder received pyridostigmine (14 mg/70 kg) or a combination of pyridostigmine and edrophonium. The onset of action of pyridostigmine was accelerated by addition of edrophonium, a rapidly acting anticholinesterase agent. Eriksen et al., 1978 (21), compared the effects of atropine or glycopyrron in combination with neostigmine (2.5 mg) or pyridostigmine (15 mg) in eighty patients relaxed with d-tubocurarine. Arrhythmias occurred less frequently in the pyridostigmine groups. Owens et al., 1978 (22), studied 93 geriatric patients to determine the incidence of arrhythmia following administration of neostigmine or pyridostigmine in reversal of neuromuscular blockade. Neostigmine was associated with a higher incidence of arrhythmia than pyridostigmine, especially when halogenated anesthetics were used. Miller et al., 1979 (23), found that 4-aminopyridine potentiated the antagonism of pancuronium-induced blockade by neostigmine or pyridostigmine in 57 surgical patients. Ferguson et al., 1980 (24), compared the effects of neostigmine, pyridostigmine, and edrophonium on rates of recovery of pancuronium-induced blockade in 36 patients. Recovery was most rapid with edrophonium and slowest with pyridostigmine.

Several investigators have examined serum cholinesterase levels after pyridostigmine administration in surgical patients, since it is the anticholinesterase effect of pyridostigmine that provides the basis for the therapeutically useful antagonism of the competive blocking agents. Barrow and Johnson in 1966 (25) gave doses of pyridostigmine (4-20 mg) to anesthetized dental patients. Inhibition of serum cholinesterase ranged from 58-91 percent. Restoration of fifty percent of the original cholinesterase activity occurred within 15-35 minutes. Stoelting, 1976 (26), reported a study of eighteen patients given pancuronium for blockade and either neostigmine or pyridostigmine for reversal. After a mean dose of 14.6 mg of pyridostigmine, serum cholinesterase was reduced by 85% within one minute and remained significantly reduced for two hours. Barake et al., 1981 (27), investigated the effects of neostigmine and pyridostigmine on serum cholinesterase in twenty surgical patients given alcuronium to maintain neuromuscular blockade. Maximum depression of cholinesterase activity was observed at five minutes after injection of the anticholinesterase agents and depression was prolonged in the pyridostigmine group.

Succinylcholine is a depolarizing neuromuscular blocking agent and, as such, has a different mechanism of action from the competive agents discussed above. Anticholinesterase agents do not antagonize blockade by depolarizing agents, rather it has been found that pyridostigmine prolongs the neuromuscular blocking action of succinylcholine (28). Sunew and Hicks, 1978 (29), found that both neostigmine (5 mg) and pyridostigmine (25 mg) significantly prolonged the blocking effect of succinylcholine in sixteen surgical patients.

PRETREATMENT FOR PROTECTION AGAINST NERVE AGENTS

Since the early 1970's, the Chemical Defence Establishment of Great Britain has been investigating the use of pyridostigmine as a pretreatment for protection of military personnel subject to exposure to nerve agents. The rationale for this use of pyridostigmine is that the drug would protect a percentage of the body pool of acetylcholinesterase from binding irreversibly with the nerve agent. After exposure to a nerve agent, an oxime would be administered which would result in the immediate release of the acetylcholinesterase bound to pyridostigmine and thus allow transmission of nerve impulses.

The study reports of the Chemical Defence Establishment are classified; therefore they were not available for review. A recent journal publication (Gall, 1981), however, summarizes the results obtained from these studies, to date involving about 100 men (30). The projected protective dose of pyridostigmine is 30 mg every 8 hours. After two days of dosing on this schedule, peak blood levels of 35 mg/ml pyridostigmine were measured at 2.5 hours after dosing and inhibition of acetylcholinesterase was 42 percent.

The drug was administered for periods as long as four weeks. Side effects were considered trivial and included a slight increase in flatus, occasional looseness of the bowels, and a slight slowing of the pulse by about five beats/min both at rest and on exercise. No effects were noted in visual parameters including pupil size. There were no changes in physiological or blood parameters, and no changes in psychological tests which, in addition to the usual battery of tests for cognitive and psychomotor skills, memory, manual dexterity, and vigilance, included practical driving tests on a test track both by day and night.

EXCRETION, PLASMA CONCENTRATIONS AND PHARMOKINETICS OF PYRIDOSTIGMINE BROMIDE

The first study of the disposition of pyridostigmine in man was reported by Kornfeld et al., 1970 (31). Pyridostigmine labeled with carbon-14 was administered intravenously to groups of normal and myasthenic subjects. The disappearance of radioactivity from the blood and appearance in the urine was similar in both groups. Pyridostigmine was rapidly eliminated from the body by way of the kidneys. Forty-four to seventy-seven percent of the injected radioactivity appeared in the urine within one hour and an average of 88 percent was recovered within 24 hours. Multiple urinary metabolites were demonstrated; however, most of the radioactive material was in the form of unchanged pyridostigmine and its chief metabolite, 3-hydroxy-N-methyl-pyridinium bromide (31, 32). A subsequent study (33) showed that chronic administration of pyridostigmine to myasthenic patients did not affect the plasma pyridostigmine-14C disappearance curve or urinary excretion patterns. Removal of the thymus gland did not change the metabolism of pyridostigmine in myasthenia gravis patients (34).

The development of sensitive gas chromatographic assays for pyridostigmine bromide allowed the measurement of plasma concentrations which are present in the nanogram range. Cohen et al., 1976 (35), found that pyridostigmine reached peak concentrations in the blood at two hours after oral administration, and demonstrated a relationship between serum concentration and clinical response. Calvey and Chan, 1977 (36), measured plasma concentrations of seven patients stabilized on doses of pyridostigmine bromide ranging from 60-660 mg/day. Plasma concentrations were maintained within a relatively narrow range, usually between 20 and 60 ng/ml. In another study by the same investigators (37), plasma concentrations required to restore neurotransmission to normal in four myasthenic patients ranged from 28-126 ng/ml. A fifth patient suffering from ptosis required less than 10 ng/ml to regain strength in the eye muscles. In contrast, a study by White et al., 1981 (38), of eight well controlled and eight poorly controlled patients failed to show correlation of plasma level and response. The levels varied greatly in the two groups with a definite overlap of values, but were generally higher in the poorly controlled group.

Cohen et al., 1977 (39), studied four myasthenia gravis patients who were under unsatisfactory control while receiving oral pyridostigmine. Each of the patients improved when serum levels of pyridostigmine were increased by intravenous administration, and the disappearance of pyridostigmine in the blood was similar to that of patients under good control. These observations demonstrate that the failure to achieve adequate serum levels after oral administration of pyridostigmine was due to malabsorption rather than increased tissue uptake, degradation, or excretion of the drug. Poor absorption of pyridostigmine was also shown by Aquilonius et al., 1980 (40), who compared the plasma levels of pyridostigmine after oral and intravenous administration and concluded that oral bioavailability of the drug amounted to only 7.6 percent of the dose. They found that bioavailability was not influenced by concomitant food intake, although the appearance of the peak plasma concentration was prolonged from 1.7 to 3.2 hours. The elimination half-life of pyridostigmine in the plasma was found to be 1.7 hours.

The role of the kidney in elimination of pyridostigmine was investigated by Cronnelly et al., 1980 (41), in surgical patients with normal kidney function and in patients without renal function undergoing kidney transplant operations. The half-life of elimination increased from 1.8 hours in normal patients to 3.3

hours in anephric patients, indicating that 75 percent of the plasma clearance of pyridostigmine was due to excretion via the kidney.

ADVERSE EFFECT

Field, 1980 (42), reported the case of a 69 year-old woman who suffered extensive generalized hair loss after pyridostigmine bromide therapy (360 mg/day) for several months. After more than a year had passed, pyridostigmine treatment was reinstated. Striking hair loss occurred after five weeks. Hair regrowth occurred three months after treatment was stopped.

CONCLUSION

The amount of pyridostigmine which can be tolerated without severe side effects appears to be related to the degree of impairment of neuromuscular transmission. Myasthenic patients may routinely ingest as much as several grams of pyridostigmine per day. Surgical patients whose normal nerve transmission is blocked by muscle relaxants can tolerate intravenous doses equivalent to oral doses of 300-600 mg. The studies in military personnel indicate that doses of 30 mg at eight hour intervals are tolerated by persons with normal neuromuscular transmission. Based on the results of the military studies and the general lack of side effects other than overdose symptoms cited in the medical literature after thirty years of extensive use, it can be concluded that administration of pyridostigmine to normal subjects is probably safe at low doses, i.e. 30 mg at 8 hour intervals. Although normal subjects may tolerate somewhat higher doses without excessive side effects and without diminished task performance, there are no published reports of such studies.

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PYRIDOSTIGMINE BROMIDE BIBLIOGRAPHY

PYRIDOSTIGMINE

(1)

Koelle, G. B., Anticholinesterase Agents. In, The Pharmacological Basis of Therapeutics, 5th edition (Goodman, L.S., and Gilman, A., ed.), MacMillan Publishing Co., New York, 445-466, 1975.

Comments:

Acetylcholinesterase (AChE) is required in the termination of the transmitter action of acetylcholine (ACh) at the cholinergic neuromuscular junction. Anticholinesterase (anti-ChE) agents inhibit or inactivate AChE. Pyridostigmine is an anti-ChE agent classified as a "competitive substrate", inhibiting the enzyme by forming a complex with it. Hydrolysis of pyridostigmine then follows in a manner analogous to that of ACh, resulting in the regenerated enzyme. Thus, pyridostigmine is considered to be a "reversible" anti-ChE agent. Pyridostigmine is one of the quaternary ammonium anti-ChE compounds, which generally do not penetrate cell membranes readily. Hence, compounds in this category are poorly absorbed from the gastrointestinal tract and are excluded by the blood-brain barrier from exerting significant action on the central nervous system after moderate doses. All the quaternary ammonium anti-ChE compounds have direct action at some cholinergic sites.

The effects of acute intoxication by anti-ChE agents are manifested by muscarinic and nicotinic signs and symptoms. The cause of death is primarily respiratory failure, usually accompanied by a secondary cardiovascular component.

Pyridostigmine is one of the anti-ChE agents used in treating myasthenia gravis, a disease characterized by weakness and rapid fatigability of the skeletal muscles. The site of the physiological defect in myasthenia gravis is the neuromuscular junction. It is generally agreed that the defect, reversible by anti-ChE agents, is the failure of an appropriate amount of ACh to reach the muscle receptor site.

(2)

Roche Laboratories, Mestinon Injectable: Mestinon, In, Physicians' Desk Reference, Medical Economics Co. Inc., Oradell, NJ, 1609-1610, 1982.

Comments:

Product information supplied by the manufacturer, Roche Laboratories: The side effects of Mestinon are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. A skin rash, due to the bromide radical, may be seen in an occasional patient. Mestinon inhibits the destruction of acetylcholine by acetylcholinesterase and thereby permits freer transmission of nerve impulses across the neuromuscular junction. For myasthenia gravis the average dose is 600 mg/day. To supplement oral dosage pre- and postoperatively, during labor and postpartum, during myasthenic crisis, or whenever oral therapy is impractical, approximately 1/30 of the oral dose may be given by intramuscular or very slow intravenous injection. For reversal of nonpolarizing muscle relaxants, usually 10 or 20 mg of Mestinon Injectable is sufficient for antagonism of the effects of the relaxants.

TREATMENT OF MYASTHENIA GRAVIS

(3)

Merritt, H.H., Myasthenia Gravis, In, A Textbook of Neurology, Lea & Febiger, Philadelphia, 597-606, 1979.

Comments:

Myasthenia gravis is a disease due to a defect of neuromuscular transmission caused by the presence of antibodies to the acetylcholine receptor and characterized by fluctuating weakness that is improved by inhibitors of cholinesterase. The prevalence rate is 3 per 100,000 (or approximately 6,000 cases in the United States). Treatment relies mainly on the short-acting anticholinesterase compounds.

(4)

Penn, A. S., Myasthenia Gravis, In, Neurology (Rosenberg, R.N., ed.) Grune & Stratton, New York, 382-391, 1980.

Comments:

Myasthenia gravis is a disorder of neuromuscular transmission, resulting from an autoimmume attack upon the nicotinic postsynaptic receptor for acetylcholine, in which there is fluctuating weakness, characteristic electrophysiologic alterations and variable response to anticholinesterases. The prevalence rate is 40 per million population. At the present time, most of the abnormalities in myasthenia gravis can be explained by the rapidly accumulating evidence of an autoimmune process that attacks the neuromuscular junction. For therapy pyridostigmine bromide (Mestinon) is most widely used. The response to acetylcholinesterase varies from patient to patient and may vary for the same patient with time of day, exercise, stress, and other factors.

(5)

Seibert, P., Treatment of Myasthenia Gravis: Clinical Experience Concerning Treatment of Pseudoparalytic Myasthenia Gravis with Pyridostigmine (abstract), J.A.M.A. 153, 175, 1953.

Abstract:

Since 1948, a pyridine homologue of neostigmine (Pyridostigmine), was given a therapeutic trial in 23 patients with myasthenia gravis associated with psuedoparalysis. Results of animal experiments, which have not yet been published, showed that pyridostigmine is five times less toxic than neostigmine, while the effect of the new preparation on the isolated intestine in vitro and in situ is only half that of neostigmine. Most of the author's patients had been treated previously with neostigmine, but there was only little improvement and the drug was not well tolerated. Result of the treatment with pyridostigmine showed that the effect of the drug on the muscles was prolonged, so that single doses of the drug could be given at longer intervals. The improvement of the functional capacity of the muscles was definitely superior to that obtained with neostigmine. The muscles of the trunk and of the extremities were most favorably affected by pyridostigmine; the drug was least effective with respect to the external muscles of the eye. Undesirable side effects were rare and mild. It was possible to administer large doses of the drug for prolonged periods. The dose required varied with the individual patient; while in some patients 4 tablets daily were sufficient, 12 tablets daily were required in other patients. Results with pyridostigmine were definitely

superior to those obtained with neostigmine as far as improvement of symptoms was concerned. A cure of the disease, however, could not be accomplished with pyridostigmine.

(6)

Westerberg, M.R. and Magee, K.R., Mestinon in the Treatment of Myasthenia Gravis, Neurology 4, 762-772, 1954.

Conclusions:

1. Twenty-two patients with myasthenia gravis were given Mestinon bromide to replace neostigmine in their treatment.
2. Twenty-one, or 95%, of the patients preferred Mestinon to neostigmine.
3. Mestinon gave more prolonged effect and more even maintenance of strength than did neostigmine.
4. Side effects or toxic reactions to Mestinon were minimal.
5. Mestinon was effective either given alone or in conjunction with ephedrine, potassium, or tetraethylpyrophosphate.

Comments:

Side effects listed for two patients on high doses of Mestinon were constant abdominal aching and cramps, a "burning feeling" in the stomach, and diarrhea.

(7)

Schwab, R.S., and Timberlake, W.H., Pyridostigmine (Mestinon) in the Treatment of Myasthenia Gravis, New England J. Med. 251, 271-272, 1954.

Summary:

An analogue of neostigmine, pyridostigmine, is an effective antimyasthenic compound when 60 mg is used for each 15 mg of neostigmine. It is free of disagreeable gastrointestinal side effects but in some cases is not so effective as neostigmine. In those who cannot tolerate neostigmine without atropine, pyridostigmine is superior to neostigmine. *The danger of masking* overdosage with neostigmine when atropine is taken is discussed.

Comments:

Fifty patients were treated with pyridostigmine after prior treatment with neostigmine. Twenty patients found the pyridostigmine to be superior because of its lack of intestinal stimulation. Fourteen patients believed that pyridostigmine was not as helpful in neutralizing their symptoms, and the remainder saw no difference between the two drugs.

(8)

Osserman, K.E., Teng, P., and Kaplan, L.I., Studies in Myasthenia Gravis: Preliminary Report on Therapy with Mestinon Bromide, J.A.M.A. 155, 961-965, 1954.

Summary:

In a comparative study on neostigmine and Mestinon in equivalent doses (usually one 60 mg Mestinon bromide tablet for each 15 mg neostigmine bromide tablet) made on twenty patients with myasthenia gravis, the results obtained with Mestinon were excellent in nine cases, good in three cases, fair in three cases, and equivalent to those obtained with neostigmine in four cases. The treatment was unsuccessful in one case. The effectiveness of Mestinon is only slightly longer than that of neostigmine. Mestinon beneficially affects small skeletal muscles innervated by cranial nerves more than the limb muscles of patients with myasthenia gravis. A striking feature of Mestinon therapy is the lack of muscarinic and nicotinic side-reactions.

Comments:

Most of the twenty patients were followed for a period of seven months of Mestinon therapy. Patients were monitored with complete blood cell counts and platelet counts, routine urinalyses and physical examinations. Hemoglobin, red blood cell, and differential counts performed at intervals showed no change. The incidence of side effects was four of diarrhea, three of abdominal cramps, one of skeletal muscle cramps, and four of epigastric distress. Four patients required atropine for side effects. Two patients in acute myasthenic crisis were given 10 mg of Mestinon e.v. or i.m. each hour without the development of diarrhea or extreme nausea. When the patients were able to swallow, they were then given 300 mg of Mestinon every hour. The patients were discharged on regimens of 240 mg every three hours and 120 mg every 2 hours, respectively.

(9)

Tether, J.E., Treatment of Myasthenia Gravis with Mestinon Bromide, J.A.M.A. 160, 156-157, 1956.

Abstract:

The diagnosis of myasthenia gravis was made in 165 patients whose symptoms were either aggravated by one-tenth of the minimal curarizing dose of tubocurarine chloride or objectively improved by intravenously administered neostigmine. Most patients satisfied both criteria. Mestinon was compared with neostigmine in these patients. Mestinon was effective in controlling the myasthenic symptoms, particularly the dysphagia. Its action was smoother because more prolonged, and no distressing side effects were observed even in patients who used it as long as seventeen months.

Comments:

Of 165 patients 33 percent took less than 200 mg, thirty percent took 200-399 mg, 29 percent took 400-1399, and eight percent took 1400 mg or more. The author listed the following side effects of Mestinon in excess: sweating, salivation, mild abdominal symptoms, muscle fasciculations, a peculiar blurring or "jumping" of vision with mild vertigo, and occasionally a "thick tongue" sensation, with dysarghia and dysphagia.

(10)

Schwab, R.S., Osserman, K.E., and Tether, J.E., Treatment of Myasthenia Gravis: Prolonged Action with Multiple-Dose Tablets of Neostigmine Bromide and Mestinon Bromide, J.A.M.A. 165, 671-674, 1957.

Summary:

Prolonged-action or slow-release tablets of neostigmine bromide, containing three regular doses of 15 mg each, and a half-strength form, containing three doses of 7.5 mg each, have been tried in the treatment of 85 patients with myasthenia gravis. Prolonged-action or slow-release tablets of Mestinon bromide, containing three regular doses of 60 mg each, and a half-strength form containing three doses of 30 mg each were tried in treating 109 patients with myasthenia gravis. In the case of the neostigmine bromide tablets, 54 of the 85 patients have found them superior to their regular medication and are still taking them. In the case of the Mestinon bromide tablets, 82 of the 109 patients still continue to take these tablets. The greatest value of this type of medication is in eliminating the need of doses during the sleeping hours.

Comments:

Patients were followed for periods ranging from one month to twelve months. There were no reactions whatsoever from the prolonged-action Mestinon tablets, except that, when the dosage was too strong, overdosage symptoms occurred. Seven patients experienced excessive stimulation of the intestinal tract, with other muscarinic side-reactions.

(11)

Osserman, K.E., Kornfeld, P., Cohen, E., Genkins, G., Mendelow, H., Goldberg, H., Windsley, H. and Kaplan, L.I., Studies in Myasthenia Gravis: Review of Two Hundred Eighty-two Cases at the Mount Sinai Hospital, New York, Arch. Int. Med., 102, 72-81, 1958.

Summary:

A review of 282 proven myasthenia gravis patients is presented. A classification of these patients is suggested which aids in prognosis and treatment. Three drugs, neostigmine (Prostigmine), pyridostigmine (Mestinon) and ambenomium (Mytelase), are available for treatment. Pyridostigmine is the drug of choice. New dosage forms of Timespan (prolonged action) tablets of neostigmine and pyridostigmine are shown to be helpful. The medical management of myasthenia can be most gratifying; 64 percent of patients show improvement. The edrophonium (Tensilon) test is an important adjuvant in the management of the myasthenic patient. The indications for thymectomy are modified.

Comments:

The authors reported that no difficulty was found with toxicity, since the usual muscarinic side-reactions occurred as soon as overdosage was reached. Less than one percent of patients showed sensitivity to bromide. Side effects in overtreated patients included increased muscle weakness, fasciculations (visible involuntary contractions or twitching of muscle fibers), lacrimation, excessive perspiration, salivation, nausea, vomiting, diarrhea, and abdominal cramps.

REVERSAL OF NEUROMUSCULAR BLOCK

(12)

Barrow, M.E.H., and Johnson, A Study of the Anticholinesterase and Anticurare Effects of Some Cholinesterase Inhibitors, Brit. J. Anaesth., 38, 420-431, 1966.

Abstract:

The inhibition of serum cholinesterase by neostigmine, tacrine, pyridostigmine and edrophonium has been measured in vivo under clinical conditions. The inhibition by these agents of both serum cholinesterase and red blood cell cholinesterase has been compared in vitro. The anticurare action of neostigmine and of tacrine has been compared myographically. Previous clinical observations have been confirmed, and further support is given to the theory that neostigmine has a direct action on the neuromuscular junction or muscle fibre, apart from its anticholinesterase property. However, the degree of inhibition of the enzyme depends upon the concentrations of enzyme, substrate and inhibitor, and since the concentrations existing at the neuromuscular junction are unknown, they cannot be reproduced for experimental purposes.

Comments:

Six anesthetized dental patients received intravenous doses of pyridostigmine, either 4, 5, 10, Or 20 mg each. Atropine sulfate was given along with the drug. Inhibition of serum cholinesterase ranged from 58-91percent. Restoration of fifty percent of the original level of cholinesterase activity occurred within fifteen minutes after the 4 mg dose and within 25-35 minutes after the higher doses.

(13)

Katz,R.L., Pyridostigmine (Mestinon) as an Antagonist of D-Tubocurarine, Anesthesiology 28, 528-534, 1967.

Abstract:

The effects of pyridostigmine were compared with those of edrophonium and neostigmine in anesthetized patients. Pyridostigmine was superior to edrophonium and equal to neostigmine as an antagonist of d-tubocurarine. Pyridostigmine produced fewer oropharyngeal secretions and decreased the heart rate less then did neotigmine. Further clinical studies of pyridostigmine should be carried out to confirm or deny this initial favorable experience. It is recommended that adequate recovery from neuromuscular block be defined as return of twitch height to the control level and, more important, the restoration of well sustained tetanus (30 cps) to the level seen prior to the administration of any neuromuscular blocking agents.

Comments:

The neuromuscular effects of pyridostigmine were determined in 108 surgical patients by measuring the adduction of the thumb due to ulnar nerve stimulation. In every patient one or two injections of 10 mg of pyridostigmine restored twitch height to the control level. Atropine was not injected prior to pyridostigmine in the first fourteen patients and it was found that two patients had marked outpouring of oropharyngeal secretions. Thereafter, 1 mg of atropine was injected thirty to sixty seconds prior to 10 mg of pyridostigmine.

(14)

McNall, P.G., Wolfson, B., Tuazon, J.G., and Siker, E.S., Use of Pyridostigmine for the Reversal of Neuromuscular Blockade, Anesth. Analg. 48, 1026-1032, 1969.

Summary:

Pyridostigmine bromide was used to reverse neuromuscular blockade induced by curariform drugs during surgery. The degree of paresis was monitored throughout surgery by twitch response to ulnar nerve stimulation in 133 patients. In 39 cases electromyogram tracings of twitch response in the hypothenar muscles were made. The average dose of gallamine used was 0.81 mg/kg/hr; that of curare was 0.11 mg/kg/hr. In the gallamine series the dosage of pyridostigmine necessary to reverse neuromuscular block ranged from 2 to 18 mg, with an average of 7.42 mg. In the curare series the dose of pyridostigmine ranged from 4 to 10 mg with an average of 7 mg. There were no cases of recurarization after reversal. Infrequent side effects of pyridostigmine included salivation and bradycardia, and were minimal when they occurred. Pyridostigmine represents a safe alternative to neostigmine in the reversal of neuromuscular blockade induced by curariform agents.

Comments:

At the end of surgery neuromuscular blockade was reversed according to the following schedule: 0.4 mg of atropine was given intravenously followed in two minutes by 4 mg of pyridostigmine. Additional 2 mg doses of pyridostigmine were given at two to three minute intervals until reversal was complete.

(15)

Zsigmond, E.K., Pyridostigmine: A Safe and Effective Antagonist to D-Tubocurarine in Anesthetized Man (abstract), Clin. Pharmacol. Ther. 13, 155-156, 1972.

Comments:

Forty anesthetized surgical patients were given d-tubocurarine for muscular relaxation. The movements of the fifth finger in response to ulnar nerve stimulation were continuously recorded. After an initial dose of 0.6 mg of atropine and 5 mg of pyridostigmine, 1 mg increments of the latter were given until complete reversal was obtained. Additional atropine was administered as needed. The mean dose of pyridostigmine which reversed blockade was 220 micrograms/kg (or 15.4 mg/70 kg). The author concluded that pyridostigmine should be used in preference to neostigmine for routine reversal of neuromuscular block by nondepolarizing muscle relaxants because of its lower incidence of muscarinic effects.

(16)

Fogdall, R.P., and Miller, R.D., Antagonism of D-Tubocurarine- and Pancuronium-Induced Neuromuscular Blockades by Pyridostigmine in Man, Anesthesiology 39, 504-509, 1973.

Abstract:

Pyridostigmine was administered to thirty unpremedicated adult surgical patients anesthetized with nitrous oxide and halothane to antagonize neuromuscular blockade by d-tubocurarine (dTc) or pancuronium. The mean doses of pyridostigmine necessary for fifty percent recovery of depressed twitch height and for sustained tetanus were 4.9 and 11.7 mg, respectively, for dTc and 4.2 and 9.1 mg, respectively, for pancuronium. Compared with results of a previous study of neostigmine, 5.8 and 5.4 times more pyridostigmine than neostigmine were needed for sustained tetanus during antagonism of blockades by dTc and pancuronium. In forty additional patients, atropine, 0.3, 0.6, or 1.0 mg, was administered concomitantly with neostigmine, 2.5 mg, or pyridostigmine, 14.5 mg, during antagonism of dTc- or pancuronium-induced neuromuscular blockade. The bradycardia following pyridostigmine does not differ significantly from that following neostigmine when combined with these doses of atropine.

Comments:

Neuromuscular transmission was evaluated by quantitating force of thumb adduction in response to ulnar nerve stimulation. The first group of thirty patients received 1 mg of pyridostigmine intravenously every three minutes until neuromuscular blockade was antagonized. The second group of forty patients received a bolus i.v. injection of either 2.5 mg of neostigmine or 14.5 mg of pyridostigmine.

(17)

Miller, R.D., Van Nyhuis, L.S., Eger, E.I., Vitez, T.S., and Way, W.L., Comparative Times to Peak Effect and Durations of Action of Neostigmine and Pyridostigmine, Anesthesiology 41, 27-33, 1974.

Abstract:

In thirty patients anesthetized with halothane and sixty percent nitrous oxide, and in twelve cats anesthetized with chloralose and urethane, d-tubocurarine (dTc) was continuously infused to produce constant ninety percent depression of twitch height prior to injection of neostigmine or pyridostigmine. Mean times from neostigmine, 0.6, 1.2, of 1.8 mg/m^2, or pyridostigmine, 3, 6, or 9 mg/m^2 administration to peak antagonism (onset time) of dTc were 11.1, 8.5, and 7.1 minutes with neostigmine and 15.8, 16.9, and 12.2 minutes with pyridostigmine in man. Mean times from administration of the same doses of neostigmine and pyridostigmine to fifty percent return to the dTc-depressed twitch (duration of action) were 37.8, 41.0, and 57.2 minutes with neostigmine and 51.4, 78.8, and 83.6 minutes with pyridostigmine in man. The onset and duration of action times also were longer with pyridostigmine than with neostigmine in the

cat. The doses of pyridostigmine and neostigmine needed for fifty percent antagonism of the dTc-induced depression of twitch height were 4.0 mg/m^2 and 0.92 mg/m^2. Thus, the potency ratio of pyridostigmine to neostigmine is 4.35 (4.0/0.92) in man and 9.3 (120/13) in the cat. We conclude that pyridostigmine has a slower onset and longer duration than neostigmine.

Comments:

Neuromuscular function was monitored by recording the force of thumb adduction after ulnar nerve stimulation. To avoid an inconsistent background for determining the effect of the antagonist, the muscle relaxant was given by constant infusion. Peak effects of antagonism were reached at twelve to seventeen minutes with pyridostigmine and time to peak varied inversely with dose.

(18)

Lippmann, M., and Rogoff, R.C., A Clinical Evaluation of Pyridostigmine Bromide in the Reversal of Pancuronium, Anesth. Analg. 53, 20-23, 1974.

Abstract:

Pyridostigmine bromide was used to reverse the neuromuscular blockade induced by pancuronium bromide in 100 surgical patients. Throughout the operation, the degree of paralysis was monitored by twitch response to ulnar-nerve stimulation. In doses of 10 to 20 mg, pyridostigmine is an effective antagonist of pancuronium. Such side effects as salivation and bradycardia were minimal. Pyridostigmine bromide appears to be a safe alternative to neostigmine in the reversal of pancuronium bromide.

Comments:

Pyridostigmine preceded by 1 mg of atropine readily antagonized pancuronium in all patients, ninety responding to a 10 mg dose, eight to a 15 mg dose and two to a 20 mg dose. The shortest time to recovery was one minute, the longest was 45 minutes (average 9.4 min).

(19)

Gyermek, L., Clinical Studies on the Reversal of the Neuromuscular Blockade Produced by Pancuronium Bromide: I. The Effects of Glycopyrrolate and Pyridostigmine, Curr. Ther. Res. 18, 377-386, 1975.

Abstract:

On 119 anesthetized surgical patients, divided into four groups, the neuromuscular block produced by pancuronium was reversed by (a) atropine plus neostigmine, (b) atropine plus pyridostigmine, (c) glycopyrrolate plus pyridostigmine and (d) glycopyrrolate plus pyridostigmine plus edrophonium. While all of these combinations were effective in reversing the pancuronium-induced neuromuscular block as judged by the time of return and extent of the sustained tetanic response (ulnar n. stimulation) and of return of adequate spontaneous respiration, reversing regimen (b) was superior to (a) in producing less change in pulse rate and less arrhythmias (sixteen versus six percent). Drug combination (c) was superior to both (a) and (b), eliciting only minimal changes in pulse rate and no arrhythmias. Regimen (d) produced similar effects as (c). Results in this group suggest that the onset of action reversing neuromuscular blockade is faster than with other combinations. Semiquantitative measurement of salivary secretions did not indicate noticeable differences between groups. It is concluded that both components of the generally used atropine-neostigmine combination used for the reversal of curarization can be replaced advantageously by

properly selected doses of other anticholinergic and anticholinesterase agents.

Comments:
The anticholinergic drug, atropine or glycopyrrolate, was mixed in one syringe with the appropriate amount of anticholinesterase. All agents were given at fixed doses based on body weight. Pyridostigmine was given at doses of 0.2 or 0.12 mg/kg, corresponding to 14 or 8.4 mg/70 kg man. The drug mixtures were injected during an interval of approximately two minutes.

(20)
Ravin, M.B., Pyridostigmine as an Antagonist of D-Tubocurarine-Induced and Pancuronium-Induced Neuromuscular Blockade, Anesth. Analg. 54, 317-321, 1975.

Abstract:
In an evaluation of the clinical effectiveness of pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade in patients anesthetized with neurolept-nitrous oxide technic, sixty adults received either d-tubocurarine (dTc) (N=30) or pancuronium (N=30). The pancuronium-dTc potency ratio with neurolept-nitrous oxide anesthesia is 4.85:1. The mean doses of pyridostigmine necessary for fifty percent recovery of control twitch height and sustained tetanus were 5.72 $\pm$ 0.45 (S.E.) mg and 11.6 $\pm$ 0.88 mg, respectively, for dTc, and 4.05 $\pm$ 0.24 mg and 8.27 $\pm$ 0.41 mg, respectively, for pancuronium. There was no correlation between the amount of pyridostigmine necessary for relaxant antagonism and the total dose of relaxant used. In 24 patients, neuromuscular blockade was reversed by an intravenous injection of pyridostigmine and either 0.6 mg or 1 mg of atropine. Within two minutes, patients given 1 mg of atropine had a significantly faster heart rate than those given 0.6 mg of atropine ($p>0.001$).

There was no correlation between control heart rate and maximum changes in heart rate. No cardiac arrhythmia or bronchospasm was observed in patients with either pancuronium or dTc following atropine-pyridostigmine mixtures. The cardiac muscarinic effects of pyridostigmine could be modified by simultaneous administration of 1 mg of atropine.

Comments:
In 36 patients approximately fifteen minutes before the end of surgery, pyridostigmine (1 mg) was given every two minutes until reversal of neuromuscular blockade, as indicated by a response to tetanic current stimulation that was well sustained for five seconds. The mean dose for reversal was 11.6 mg after dTc and 8.27 mg after pancuronium. An additional 24 patients received 10 mg of pyridostigmine i.v. along with atropine for the reversal of blockade.

(21)
Bentz, E.W., and Stoelting, R.K., Prolonged Response to Succinylcholine Following Pancuronium Reversal with Pyridostigmine, Anesthesiology 44, 258-260, 1976.

Abstract: None.

Comments:
An 82 year-old surgical patient received divided doses of 15, 5, and 10 mg of pyridostigmine i.v. administered along with atropine for pancuronium reversal. Surgeons then elected to perform a cystostomy and succinylcholine was given as a muscle relaxant. Prolonged paralysis occurred and was attributed to residual anticholinesterase effects of the pyridostigmine.

(22)

Stoelting, R.K., Serum Cholinesterase Activity Following Pancuronium and Antagonism with Neostigmine or Pyridostigmine, Anesthesiology 45, 674-678, 1976.

Abstract: None.

Comments:

Eighteen surgical patients received pancuronium for neuromuscular block. Reversal was accomplished with either neostigmine or pyridostigmine given as a rapid i.v. injection along with atropine. The dose of pyridostigmine was 0.225 mg/kg (mean dose 14.6 mg). Serum cholinesterase was reduced 85 percent within one minute after pyridostigmine and remained significantly reduced for 120 minutes. After neostigmine, activity was reduced 88 percent at one minute but no longer significantly reduced after ten minutes.

(23)

Gyermek, L., Clinical Pharmacology of the Reversal of Neuromuscular Block, Int. J. Clin. Pharmacol. 15, 356-362, 1977.

Abstract:

In 34C anesthetized surgical patients, the following parameters related to the restoration of skeletal muscle function following pancuronium block were studied: 1) the speed of return of spontaneous respiration; and, 2) the speed of return of sustained contraction of the hand flexors and adductor muscles following tetanic electrical stimulation to the ulnar nerve. In addition, effects on the cardiovascular system and on the secretory system were determined. It was found that pyridostigmine can advantageously replace neostigmine in the reversing regimen. Replacement of atropine with either one of the following three synthetic quaternary ammonium type of parasympathetic blocking

drugs: glycopyrrolate, propantheline bromide, and scopolaminium bromide, potentially eliminates CNS toxicity. Furthermore, glycopyrrolate and propantheline bromide in combination with pyridostigmine produced less abrupt changes in the heart rate than the combination of either atropine and neostigmine or the combination of atropine and pyridostigmine. The moderately long onset of action of pyridostigmine can be accelerated by the addition of edrophonium, a rapidly acting anticholinesterase agent. These two agents, when either 0.004-0.006 mg/kg glycopyrrolate or 0.03-0.06 mg/kg propantheline bromide was added to them produced rapid and permanent reversal of the pancuronium produced neuromuscular block with minimal fluctuations in heart rate and with almost no incidence of arrhythmias. In the case of "over curarization" no known reversing regimen is fully effective in the therapeutically safe dose range.

Comments:
Three hundred and forty surgical patients with pancuronium block were studied. For reversal 24 received neostigmine, twelve received edrophonium, and the remainder received either pyridostigmine or a combination of pyridostigmine and edrophonium. The drugs were administered intravenously during an interval of approximately two minutes. The dose of pyridostigmine was generally 0.2 mg/kg (14 mg/70 kg) while lesser amounts (0.05-0.15 mg/kg) were given in combination with edrophonium.

(24)
Eriksen, K., Hansen, E.K., and Hasselstrom, L., Effects on Muscarinic Receptors of Various Agents in Reversal of Neuromuscular Blockade, Acta Anaesth. Scand. 22, 447-457, 1978.

Abstract:

The effects were studied of various drug combinations, recommended for use in reversal of neuromuscular blockade, on heart rate and salivary secretions in eighty healthy patients anesthetized with nitrous oxide-oxygen-halothane and relaxed with d-tubocurarine. The drug combinations were mixtures of atropine 1 mg-neostigmine 2.5 mg, atropine 1 mg-pyridostigmine 15 mg, glycopyrron 0.5 mg-neostigmine 2.5 mg, and glycopyrron 0.5 mg-pyridostigmine 5 mg, respectively. It was found that administration of the atropine-containing mixtures induced more pronounced initial increases and delayed decreases in heart rate than the mixtures containing glycopyrron. Pyridostigmine-containing mixtures elicited a somewhat more pronounced initial increase in heart rate than neostigmine-containing mixtures, but a less pronounced and delayed decrease in heart rate. Supraventricular arrhythmias occurred less frequently in the pyridostigmine groups than in the neostigmine groups. No such difference was found between the atropine and glycopyrron groups. Glycopyrron caused a more intense dryness of the mouth than atropine. A differential attitude towards the use of drugs for reversal of neuromuscular blockade, based on the cardiovascular state of the particular patient, might be recommendable.

Comments:

Eighty surgical patients with neuromuscular blockade induced by d-tubocurarine received i.v. injections (one minute) of either pyridostigmine 15 mg or neostigmine 2.5 for reversal.

(25)

Sunew, K.Y., and Hicks,R. G., Effects of Neostigmine and Pyridostigmine on Duration of Succinylcholine and Pseudocholinesterase Activity, Anesthesiology 49, 188-191, 1978.

Abstract:

Effects of the anticholinesterase drugs on the duration of action of succinylcholine (SCh) and psuedocholinesterase activity were studied in sixteen adult patients undergoing general anesthesia. Each patient received two doses of SCh, 1 mg/kg, intravenously; the first dose was given before and the second dose, five minutes after neostigmine, 5 mg, or pyridostigmine, 25 mg. Electromyographic determinations were used to measure the duration of SCh-induced block. Prolongation in the neostigmine group (n=8) was compared with that in the pyridostigmine group (n=8). Pseudocholinesterase activities were determined before, during, and at the point of full recovery of neuromuscular blockade by the second dose of SCh.

The effect of SCh, 1 mg/kg, was significantly prolonged from the control value, 11.1 ± 1.43 (mean ± SE) to 35 ± 3.24 minutes following neostigmine, and from 13.1 ± 1.45 to 23.9 ± 2.5 minutes after pyridostigmine. Pseudocholinesterase activities determined five minutes after administration of neostigmine and pyridostigmine were decreased to 21 and 20 percent of control, respectively. Full recovery from the SCh-induced block was observed, while enzymatic activities remained suppressed to 47 and 39 percent of control in the neostigmine and pyridostigmine groups, respectively. The neuromuscular blocking effect of SCh was significantly prolonged by both neostigmine and pyridostigmine, but more by neostigmine. It is concluded that the enzyme may not be the sole factor determining the effect of anticholinesterase drugs on the action of SCh.

Comments:

Eight surgical patients received 25 mg of pyridostigmine along with atropine as a bolus i.v. injection.

(26)

Owens, W.D., Waldbaum,L.S., and Stephen, C.R., Cardiac Cysrhythmia Following Reversal of Neuromuscular Blocking Agents in Geriatric Patients, Anesth. Anald. 57, 186-190, 1978.

Abstract:

Ninety-three patients 65 years of age or older were studied to determine the incidence of dysrhythmia following administration of one of two cholinesterase inhibitors, neostigmine or pyridostigmine. Their ECG was then continuously monitored for ninety minutes. Neostigmine was associated with a higher incidence of dysrhythmia than was pyridostigmine. Neostigmine administered to patients with pre-existing coronary disease and/or conduction defects and to patients with hypertension was associated with a significantly higher incidence of dysrhythmia than was pyridostigmine when administered to patients with the same conditions. The incidence of dysrhythmia in patients who received a halogenated anesthetic was five times greater after neostigmine than after pyridostigmine.

Comments:

Fifty surgical patients received pyridostigmine 0.28 mg/kg (maximum 20 mg) along with atropine for reversal of neuromuscular blockade. Forty-three patients received neostigmine. Fewer cardiac side effects were noted with pyridostigmine.

(27)

Miller, R.D., Booji, L.H.D.J., Agoston, S. and Crul, J.F., 4-Aminopyridine Potentiates Neostigmine and Pyridostigmine in Man, Anesthesiology 50, 416-420, 1979.

Abstract:
To elucidate the interaction of 4-aminopyridine with neostigmine and pyridostigmine, the authors studied 57 anesthetized surgical patients using a technique of constant infusion of pancuronium to quantitate antagonist activity. 4-Aminopyridine, 0.15 or 0.35 mg/kg, produced no antagonism, while 0.5 mg/kg produced a mean 24 + 6 percent (peak) antagonism. The dose that produced fifty percent antagonism (ED_{50}) of neostigmine alone was 22 micrograms/kg; with 0.35 mg/kg 4-aminopyridine, it was 7 micrograms/kg. The ED_{50} of pyridostigmine alone was 110 micrograms/kg; with 0.35 mg/kg 4-aminopyridine, it was 27 micrograms/kg. 4-Aminopyridine prolonged the onset times of both neostigmine and pyridostigmine, but prolonged the duration of action of neostigmine only. At a given level of antagonism of pancuronium, adding 4-aminopyridine 0.35 mg/kg, to neostigmine and to pyridostigmine decreased the amounts of atropine needed to prevent a change in heart rate by 68 and 70 percent, respectively. The authors conclude that 4-aminopyridine potentiates antagonism of a pancuronium-induced neuromuscular blockade by neostigmine or pyridostigmine. Less atropine is needed to prevent cardiac muscarinic stimulation when 4-aminopyridine is used with either neostigmine pyridostigmine.

Comments:
Fifty-seven anesthetized patients were given a constant infusion of pancuronium for neuromuscular blockade which was monitored by determining twitch height after ulnar stimulation. Either neostigmine or pyridostigmine was used for antagonism of blockade. The doses of pyridostigmine used ranged from 20 to 200 micrograms/kg (1.4-14 mg/70 kg).

(28)

Ferguson, A., Egerszegi, P., and Bevan, D.R., Neostigmine, Pyridostigmine, and Edrophonium as Antagonists of Pancuronium, Anesthesiology 53, 390-394, 1980.

Abstract:
This study was performed to compare the effects of three anticholinesterases on rates of recovery from pancuronium-induced neuromuscular blockade. Pancuronium (3 mg/70 kg) was antagonized during nitrous-oxide-halothane anesthesia, in man, with neostigmine (2.5 or 5.0 mg/70 kg), pyridostigmine (10 or 20 mg/70 kg), or edrophonium (50 or 100 mg/70 kg). Reversal was attempted at ten percent spontaneous recovery of muscle twitch, which was measured by use of train-of-four stimulation. Following administration of the antagonist each patient had progressive recovery of neuromuscular function. Recurarization was not observed during the period of study. Recovery was most rapid with edrophonium and slowest with pyridostgmine. Five minutes after administration of the antagonists, mean T4, the height of the fourth twitch as a percentage of the first in each train, exceeded fifty percent only with the larger dose of neostigmine and both doses of edrophonium. Thirty minutes after reversal there was no significant difference in recoveries among the drugs tested, and T4 exceeded seventy percent for all patients. It is concluded that, under the conditions of this study, neostigmine, pyridostigmine, and edrophonium induce sustained antagonism of pancuronium-induced neuromuscular blockade. The antagonism produced by large doses of edrophonium is faster than that produced by neostigmine or pyridostigmine.

Comments:
Thirty-six anesthetized surgical patients were studied, twelve of whom received either 10 or 20 mg/70 kg of pyridostigmine for reversal of pancuronium-induced blockade.

(29)

Baraka, A., Wakid, N., Mansour, R. and Haddad, W., Effect of Neostigmine and Pyridostigmine on the Plasma Cholinesterase Activity, Br. J. Anaesth. 53, 849-851, 1981.

Abstract:

The effect of neostigmine 0.005 mg/kg or pyridostigmine 0.25 mg/kg on serum cholinesterase activity was investigated in twenty adult patients undergoing elective surgery. Both drugs produced marked depression of enzymatic activity. The maximal depression was observed in samples taken five minutes after injection. The maximal percentage depression of enzymatic activity was not significantly different in the two drug groups. However, at thirty to sixty minutes after injection, the degree of depression was less in the neostigmine group. This may be attributed to the different plasma clearances of neostigmine and pyridostigmine.

Comments:

Alcuronium was administered to maintain neuromuscular blockade. The dose of pyridostigmine was 0.25 mg/kg (17.5 mg/70 kg).

PRETREATMENT FOR PROTECTION AGAINST NERVE AGENTS

(30)

Gall, D., The Use of Therapeutic Mixtures in the Treatment of Cholinesterase Inhibition, Fund. Appl. Tox. 1, 214-216, 1981.

Abstract: None.

Comments:

This article summarizes the results of human pyridostigmine studies conducted by the Chemical Defence Establishment of Great

Britain. To date, some 100 men have received the drug. The blood levels of pyridostigmine and of acetylcholinesterase inhibition after a single dose run closely parallel with a peak at three to four hours and maximum levels of 17 ng/ml pyridostigmine and thirty percent inhibition. After two days of 30 mg pyridostigmine eight hourly, peak levels occur at 2.5 hours with 35 ng/ml pyridostigmine and 42 percent inhibition. After four weeks of dosing, cumulative inhibition beyond about forty percent was not seen. Side effects were considered trivial and included a slight increase in flatus, occasional looseness of the bowels, and a slight slowing of the pulse by about five beats/min both at rest and on exercise. No effects were noted in visual paramenters including pupil size. There were no changes in physiological or blood parameters, and no changes in psychological tests which, in addition to the usual battery of tests for cognitive and psychomotor skills, memory, and manual dexterity and vigilance, included very practical driving tests both by day and night on a test track.

PHARMACOKINETICS AND METABOLISM OF PYRIDOSTIGMINE

(31)

Kornfeld, P., Samuels, A.J., Wolf, R.L., and Osserman, K.E., Metabolism of 14C-labeled Pyridostigmine in Myasthenia Gravis, Neurology 20, 634-641, 1970.

Summary:

This report presents the first study of a labeled anticholinesterase drug in human subjects. Five normal and eight myasthenic individuals, all in basal state, participated in this study. Following rapid intravenous injection of 2 mg pyridostigmine-14C (29.2 microcuries), frequent samples of plasma and urine were analyzed. Neither pyridostigmine, its chief metabolite (3-hydroxy-N-methyl-pyridinium bromide), nor other metabolites found in plasma are protein bound. Both groups seem to handle the drug qualitatively similarly, but small, nonsignificant quantitative differences were observed in the excretion of pyridostigmine and its metabolites. About ninety percent of radioactivity is recovered in urine. Traces of pyridostigmine-14C are still detectable in urine 72 hours following a single injection. Multiple urinary metabolites of pyridostigmine were demonstrated.

Comments:

Pyridostigmine-14C administered intravenously is rapidly eliminated from the body via the kidneys. Forty-seven to 77 percent of the injected radioactivity appeared in the urine within one hour and an average of 88 percent was recovered by 24 hours. The disappearance of radioactivity from the blood and the appearance in urine were similar in normal and myasthenic subjects.

(32)

Kornfeld, P., Wolf, R.L., Samuels, A.J., and Osserman, K.E., The Effect of Chronic Pyridostigmine Administration on Pyridostigmine-14C Metabolism in Myasthenia Gravis, Neurology 21, 550-552, 1971.

Summary:

Chronic pyridostigmine administration did not affect the plasma pyridostigmine-14C disappearance curve or urine radiochromatograph patterns of three myasthenic patients representing mild, moderate, and severe forms of the disease. The significance of the prompt clinical myasthenic response to intravenous edrophonium after a therapeutic dose of pyridostigmine, at a time when significant amounts of intact pyridostigmine are being excreted, is discussed.

Comments:

Three myasthenic subjects received 2 mg of pyridostigmine-14C in place of one regular dose of pyridostigmine at the regularly scheduled time. Normal oral doses for these subjects were 30-180 mg every three to four hours. The response to i.v. edrophonium suggests that a threshold blood level exists for pyridostigmine, and clinical effectiveness of the medication ceases when this level is not maintained.

(33)

Somani, S.M., Roberts, J.B., and Wilson, A., Pyridostigmine Metabolism in Man, Clin. Pharmacol. Ther. 13, 393-399, 1972.

Abstract:

Observations of myasthenic patients given oral pyridostigmine and 14C-pyridostigmine by intramuscular injection were designed to determine the excretion in urine of unchanged pyridostigmine and its metabolites. Paper chromatography of urine revealed the presence of three metabolites in addition to pyridostigmine. The unchanged drug and its major metabolite were isolated from the urine of a patient given oral doses with the use of the combined techniques of ion-exchange chromatography, electrophoresis, and paper chromatography. Pyridostigmine and 3-hydroxy-N-methyl pyridinium thus isolated were characterized by ultraviolet spectra and mass spectra and estimated by a reverse isotope-dilution method. It is suggested that the problems of chronic overdosage with pyridostigmine are related to the possible accumulation of some of these substances in patients who are treated for prolonged periods with high doses of pyridostigmine.

Comments:

Urine samples were analyzed from one patient who received an intramuscular dose of 8 mg of 14C-pyridostigmine and from two patients taking oral doses of 720 and 2160 mg daily.

(34)

Kornfeld, P., Mittag, T.N., Genkins, G., Horowitz, S., and Papatestas, A.E., Studies in Myasthenia Gravis: Pyridostigmine-C14 Metabolism after Thymectomy, Neurology 25, 998-999, 1975.

Abstract:

Pyridostigmine-carbon-14 (P-C14) excretion studies in myasthenia gravis patients who had had thymectomies failed to produce any significant difference from results observed in myasthenic patients who had not had thymectomies. Thus, change in P-C14 metabolism cannot help explain decreased anticholinesterase requirements and electromyographic changes observed in some patients following thymectomy.

Comments:

Four myasthenic patients who had had the thymus removed received 2 mg of pyridostigmine-14C intravenously. Metabolism of the drug was not different from that in patients with intact thymus glands.

(35)

Cohan, S.L., Pohlmann, J.L.W., Mikszewski, J., and O'Doherty, D.S., The Pharmacokinetics of Pyridostigmine, Neurology 26, 536-539, 1976.

Abstract:

A simplified gas chromoatographic method for measuring quaternary ammonium compounds has been developed and used to measure the serum concentration of pyridostigmine in human beings.

Pyridostigmine is present in the serum within one hour after oral administration and reaches a peak at two hours. Results in several patients suggest that the serum concentration achieved is related to the size of the dose and that there is a relationship between serum concentration and clinical response.

Comments:
Nine myasthenic patients and four normal volunteers each received 60 mg of pyridostigmine administered orally. Peak concentrations of pyridostigmine in serum were measured at 1.5-2 hours after the dose. Two subjects developed toxicity. One myasthenic patient on a regimen of 60 mg every three hours had decreasing strength in the extremities and decreased pulmonary vital capacity at 1.5 hours after the second dose of pyridostigmine. One normal volunteer who took two doses of pyridostigmine (60 mg), four hours apart, showed nasal speech and difficulty in swallowing at one hour after the second dose.

(36)
Calvey, T.N., and Chan, K., Plasma Pyridostigmine Levels in Patients with Myasthenia Gravis, Clin. Pharmacol. Ther. 21, 187-193, 1977.

Abstract:
Plasma concentrations of pyridostigmine were measured in seven patients with myasthenia gravis. Six subjects on oral pyridostigmine bromide were stabilized on widely different doses of the drug (60 to 660 mg/day). Nevertheless, the concentration of the quaternary amine in plasma was maintained within a relatively narrow range (usually between 20 and 60 ng/ml). In three myasthenic patients, the area under the plasma concentration-time curve was relatively constant for four hours after the same oral dose of pyridostigmine (60 mg). Despite this similarity, there were, in general, considerable interindividual

differences in the bioavailability of pyridostigmine in myasthenic patients. In one subject, the bioavailability of the quaternary amine was increased sixfold by doubling the oral dose from 30 mg to 60 mg. After oral administration of pyridostigmine, the half-life of the drug in one subject (4.25 hr) was almost three times as great as after intramuscular administration in a different patient (1.49 hr).

Comments:
The narrow range of plasma concentrations of pyridostigmine after widely different doses suggests that the differential dosage requirements of myasthenic patients may be partially related to interindividual differences in drug absorption, metabolism, or excretion, as well as the the variable nature of the disease. In one subject who received a 2 mg intramuscular dose of the drug, the maximum plasma concentration was 62.4 ng/ml at thirty minutes.

(37)
Chan, K., and Calvey, T.N., Plasma Concentration of Pyridostigmine and Effects in Myasthenia Gravis, Clin. Pharmacol. Ther. 22, 596-601, 1977.

Abstract:
The relation between the plasma concentration of pyridostigmine and its effects were studied in five patients with myasthenia gravis. In four patients with typical electromyographic decrement in the adductor pollicis, there was a positive correlation between the concentration of pyridostigmine in plasma and the effect on neuromuscular transmission. The plasma concentration of pyridostigmine required to restore transmission to normal (as calculated from the regression line relating plasma concentration to neuromuscular function) varied over a five-fold range, reflecting the variable severity of the disease. In

another myasthenic patient with purely ocular symptoms, there was a significant correlation between the plasma concentration of the drug and the diameter of the palpebral fissure. It is suggested that the routine measurement of the plasma concentration of pyridostigmine may be of value in the management of myasthenia gravis. A method to calculate the optimal daily dose of pyridostigmine in individual myasthenic patients is described.

Comments:

The five subjects studied were stabilized on oral pyridostigmine (dosage range, 60-660 mg/day in divided doses). In four patients the plasma concentration of pyridostigmine required to restore neuromuscular transmission to normal ranged from 27.8-125.7 ng/ml. Muscular response after stimulation of the ulnar nerve was measured. The fifth patient suffered from ptosis, and extremely low plasma concentrations (less than 10 ng/ml) were sufficient to affect the ocular muscles and increase the opening between the eyelids.

(38)

Cohan, S.L., Dretchen, K.L., and Neal, A. Malabsorption of Pyridostigmine in Patients with Myasthenia Gravis, Neurology 27, 299-301, 1977.

Abstract:

Four patients with myasthenia gravis were under unsatisfactory control while receiving oral pyridostigmne. In each of these patients, the serum levels of drug were below those observed in patients with myasthenia gravis who are well controlled. The strength of each of these patients improved when the serum pyridostigmine level was increased by intravenous administration of this agent. Furthermore, the rate of disappearance of pyridostigmine from the serum following intravenous administration was the same as that for control subjects and

patients under good control. This demonstrates that failure to achieve adequate serum pyridostigmine levels following oral administration is due to malabsorption rather than to increased rates of tissue uptake, degradation, or excretion of the drug.

Comments:

In one patient with gastrointestinal hypermotility, the addition of 0.4 mg atropine i.m. to oral pyridostigmine resulted in serum levels comparable to normal controls and clinically responsive myasthenic patients. Addition of atropine did not elevate serum pyridostigmine levels in two other subjects, indicating that failure to absorb the drug is not simply a result of gut hypermotility produced by the muscarinic effects of pyridostigmine.

(39)

Aquilonius, S.M., Eckernas, S.A., Lindstrom, B. and Osterman, P.O., Pharmacokinetics and Oral Bioavailability of Pyridostigmine in Man, Eur. J. Clin. Pharmacol. 18, 423-428, 1980.

Summary:

The pharmacokinetics of pyridostigmine was evaluated after intravenous injection in two healthy male volunteers and after oral administration to five subjects. Plasma concentrations of pyridostigmine were determined after ion pair extraction from plasma and analysis by gas chromotography-mass spectrometry with chemical ionization, using d6-pyridostigmine as internal standard. Degradation of pyridostigmine in vitro was compensated for by use of the deuterated internal standard and by rapid cooling and separation of plasma after blood sampling. After intravenous administration of pyridostigmine 2.5 mg the plasma elimination half-life was 1.52 h, the volume of distribution was 1.43 l/kg and the plasma clearance 0.65 l/kg x h. The pharmacokinetic constants were very similar after oral administration of pyridostigmine 120 mg: the elimination half-life was 1.7 $\pm$ 0.24 h, the volume of distribution 1.64 $\pm$ 0.29 l/kg and the plasma clearance was 0.66 $\pm$ 0.22 l/kg x h. The bioavailability was calculated to be 7.6 $\pm$ 2.4%. When pyridostigmine was taken together with food, the peak plasma concentration was prolonged from 1.7 to 3.2 h. Bioavailability, however, was not influenced by concomitant food intake. "Steady-state" plasma concentrations of pyridostigmine were measured in myasthenic patients on their ordinary dose schedule of cholinesterase inhibitor drugs. More than a seven-fold difference in steady-state plasma concentration was found between patients taking approximately the same daily dose of pyridostigmine.

Comments:

Myasthenic patients on dosages of 360-720 mg of pyridostigmine exhibited a seven-fold difference in plasma concentrations. The authors state that in addition to poor absorption, kidney function may also play a role in disposition of the drug since pyridostigmine is predominantly eliminated unchanged in the urine. One of the patients on maintenance therapy with pyridostigmine had impaired renal function; he showed the highest steady-state concentration of the drug.

(40)

Cronnelly, R., Stanski, D.R., Miller, R.D. and Sheiner, L.B., Pyridostigmine Kinetics With and Without Renal Function, Clin. Pharmacol. Ther. 28, 78-81, 1980.

Abstract:

Pyridostigmine kinetics were examined under conditions of clinical use as an antagonist of nondepolarizing neuromuscular blockade in anesthetized patients with and without renal function. Pyridostigmine serum levels were assayed by gas-liquid chromotography, and data were fitted to a two compartment kinetic model. Pyridostigmine kinetics following renal transplantation (n=5) were not different from those in patients with normal renal function. Renal function (n=5) elimination half-life increased from 112 ± 12 min (mean ± SD) to 379 ± 162 min, and serum clearance decreased from 9 ± 12 ml/kg/min to 2 ± 0.6 ml/kg/min in anephric patients (n-=4). We conclude that renal function accounts for 75 percent of pyridostigmine clearance.

Comments:
The subjects were five surgical patients with normal kidney function, four without kidney function, and five who had kidney transplantion at least one hour before pyridostigmine administration. The results showed that 75 percent of the plasma clearance of pyridostigmine was due to excretion via the kidney and the remainder due to nonrenal mechanisms.

(41)
White, M.C., De Silva, P., and Havard C.W.H., Plasma Pyridostigmine Levels in Myasthenia Gravis, Neurology 31, 145-150, 1981.

Abstract:
Plasma concentrations of pyridostigmine were measured after oral administration in sixteen patients with myasthenia gravis. The levels varied greatly among both well and poorly controlled patients, but were usually higher in the latter group. Absorption of the drug appears to be erratic; its clearance from the plasma is slow and its metabolism could involve an enterohepatic circulation. Drugs such as methylcellulose may prevent absorption. Three poorly controlled patients were studied on a high-dose alternate-day steroid regimen, and a

marked decrease in pyridostigmine bioavailability on the same dose of drug was observed in all three. No such changes were demonstrated in a volunteer group taking a lower dose of steroids.

Comments:
Eight well controlled patients were taking a regular daily dose of 180-360 mg of pyridostigmine, while eight poorly controlled patients took doses of 375-1500 mg daily. Plasma pyridostigmine concentrations varied greatly among both well and poorly controlled patients with a definite overlap in values between the two groups. Peak concentrations in the well-controlled group ranged from 21-155 ng/ml and in the poorly-controlled group from 46-370 ng/ml. The authors conclude that maintenance of adequate plasma levels of anticholinesterase is but one factor determining muscle strength in myasthenia. High fluctuating levels could indicate excessive medication.

ADVERSE REACTION

(42)
Field, L.M., Toxic Alopecia Caused by Pyridostigmine Bromide, Arch. Dermatol. 116, 1103, 1980.

Comments:
A 69 year-old woman experienced extensive generalized hair loss after pyridostigmine bromide therapy (360 mg/day) for several months. Approximately one year later, pyridostigmine bromide therapy was reinstated. Striking hair loss occurred after five weeks. Hair regrowth occurred three months later.

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