CONTINUOUS INFUSION OF PYRIDOSTIGMINE IN THE MANAGEMENT OF MYASTHENIC CRISIS: A CASE REPORT

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Abstract - Myasthenia crisis is the most dangerous complication of myasthenia gravis. We report one case in which a continuous infusion of pyridostigmine resulted in successful management of myasthenia exacerbation in a 50 year old myasthenic female following thymectomy.
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Key words: Myasthenia gravis, myasthenia crisis, pyridostigmine

INTRODUCTION

Myasthenia crisis (defined as respiratory failure with the need for mechanical ventilation) is the most dangerous complication of myasthenia gravis (early thymectomy, and immuno- suppression). There are a group of patients with myasthenia gravis that suffer from crisis. As myasthenia crisis is a rare illness, accounts about its causes, frequency, duration, and course are scarce. Antibodies to acetylcholine receptor protein are detected in the serum of patients which combine with the alpha - subunits and lead to destruction of a large percentage of receptors. Thymus contains muscle - like cells that have acetylcholine receptors and these cells may be the source of antigen in the development of antibodies (1). A number of different courses of therapy are used, e.g. the intravenous administration of pyridostigmine, prednisolone, plasma exchange, immunoadsorption, and high - dose intraveneous immunoglobuline (2). Pyridostigmine, a competitive inhibitor of cholinesterase enzymes, has been used for many years in the treatment of myasthenia gravis. Symptomatic improvement results from an increased duration of interaction between acetylcholine and the decreased number of functional neuromuscular receptors. In clinical situations where oral administration is not possible or absorption is questionable, parenteral administration of pyridostigmine has been accomplished by intermittent intramuscular or intravenous injection (2). These approaches have several limitations, including slow rates of infusion required for intravenous injection and the discomfort associated with frequent intramuscular injections. However, the most disconcerting aspect of intermittent parenteral therapy is the tendency of the drug effect to wane over the dosing interval, often unpredictably. In the critical care population, this tendency may result in significant difficulty in effects to wean patients from mechanical ventilation. As with many therapeutic agents, widespread clinical use of pyridostigmine preceded the definition of its pharmacokinetic profile. As the differences between serum concentrations during oral vs. parenteral dosing become clear, new dosing strategies will be implemented to accommodate these characteristics.

Case

A 50-yr-old myasthenic female experienced acute non-cardiogenic pulmonary edema post thymectomy secondary to aspiration of gastric acid. Before hospital admission, she had been managed on oral pyridostigmine, prednisone, and azathioprine. She underwent emergent endotracheal intubation and was admitted to the Intensive Care Unit (ICU) for treatment of respiratory failure secondary to myasthenic crisis and pulmonary edema. Pyridostigmine

was initially withheld, and cautiously reinstituted on day 3 of hospitalization at a dose of 0.5 mg IM every 6 hr. Low dosages were used due to the risk of cholinergic side-effects and increased pulmonary secretions. This dosage was later increased to 1 mg, IM every 6 hr. Efforts to wean the patient from mechanical ventilation were limited by progressive fatigue. In addition, the patient complained of discomfort from repeated injections. A continuous intravenous infusion of pyridostigmine was instituted on day 5 of hospitalization. The initial rate of administration was 2 mg/hr, which was increased to 3 mg/hr on the following day.

Her prompt response to therapy was demonstrated by resolution of ptosis and marked improvement in respiratory strength that allowed her to tolerate weaning from mechanical ventilation. Thirty-six hrs later, the patient was changed over to oral pyridostigmine (360 mg/day) and transferred to medical floor for final evaluations.

DISCUSSION

The pharmacokinetic profile of intravenously administered pyridostigmine provides a rational basis for the use of a continuous infusion. In a study on normal volunteers (2), the apparent elimination half-life of pyridostigmine averaged 200 mins after an oral dose, while this value was only 97 mins after an intravenous dose. Similar serum concentration profiles have been observed in myasthenic patients (3, 4).

This apparent paradox results from an unusual situation in which the rate of absorption is slower than the rate of elimination. As a consequence, the absorption rate, rather than the elimination rate, exerts a primary influence on serum concentration during oral dosing. Analogous to a sustained-release dosage form, this phenomenon limits intra dose fluctuations in serum concentration to allow oral dosing at 4-to 6-hr intervals. In contrast to oral administration, the serum concentrations of pyridostigmine after intravenous dosing are not influenced by the absorption rate.

Intravenously administered pyridostigmine has an onset of action with in 2 to 5 mins (5-7). Since the elimination half-life of parenterally administered pyridostigmine averages less than 2 hrs. wide serum concentration fluctuations may occur during intermittent dosing, with corresponding fluctuation in response (8,9). Current recommendations for intravenous administration emphasize slow administration when administered as a bolus dose to limit excessive cholinergic stimulation and concurrent muscarinic effects(9). A continuous infusion allows improved control of myasthenic symptoms while minimizing the potential for serum concentration-related adverse effects.

The use of a continuous infusion may be reserved for patients in whom a response to pyridostigmine has been previously established. In our patient, pyridostigmine was initially administerd by intramuscular injection. This administration allowed an assessment of response and guided the selection of an initial continuous infusion dose. Consistent with the brief duration of action and rapid elimination outlined above, institution of continuous infusion allowed effective continuos control of respiratory function after an inconsistent response to intramuscular pyridostigmine has limited the weaning process. Without this degree of control, cholinergic responses and fluctuations in response may complicate the evaluation of adjustments in ventilator settings.

Our patient exhibited a clear temporal relationship to the implementation of pyridostigmine infusion and improved control of myasthenic symptoms. No evidence of tachyphylaxis was observed during the continuous infusion intervals.

Pyridostigmine is eliminated primarily by renal mechanisms, and elimination half-life has been noted to be prolonged during the state of renal insufficiency (4).

The patient described above had normal renal function. The presence of renal impairment may cause accumulation during prolonged dosing and warrants caution. In addition to exhibiting slow absorption, oral pyridostigmine bioavailability is poor, averaging 14.3% (3). Parenteral anticholinesterase therapy by intravenous bolus injection is routine anesthetic management for the reversal of nondepolarizing muscle relaxants. Edrophonium, neostigmine and

pyridostigmine have similar pharmacological profiles and efficacy (10). However, the elimination half-life for these drugs is less than 2 hr., making intravenous bolus therapy impractical for patients with myasthenia gravis. Many centers in the United States and Europe use an intravenous infusion of neostigmine when parenteral therapy is indicated, particularly in the postoperative period after thymectomy (10, 11). The recommendation of a continusous infusion of neostigmine calculated at 1/60 of the daily oral dose of pyridostigmine to run over 24 hrs. Pyridostigmine is similarly efficacious when converted to 1/30 of the daily oral dose by continuous infusion. Although neostigmine has a shorter elimination half-life (77 mins) compared with 113 mins for pyridostigmine, and lesser reliance on renal clearance (50% renal clearance for neostigmine compared with 75% for pyridostigmine) (10), both drugs seem to be equally efficacious when used as a continuous infusion. As myasthenic crisis approaches, the boundary between cholinergic crisis narrows. Too much anticholinesterase also cause muscle weakness. Conversely, it may be difficult to provide a high enough dose of anticholinesterases in some patients to prevent myasthenic crisis. The conversion from oral therapy to continous intravenous one must be approached with caution and with an appreciation for rapid changes in drug clearance common in critical illness. With these concerns in mind, the best indication for using continous infusion anticholinesterase therapy remains the maintenance of a myasthenic patient who requires anticholinesterase therapy but who can not tolerate enteral administration. In our patient this method of administration resulted in rapidly titrable means of achieving stable control of symptoms during myasthenic crisis.

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