CONTINUOUS NEOSTIGMINE INFUSION IN A PATIENT WITH MYASTHENIA GRAVIS UNDERGOING CYTOREDUCTIVE SURGERY COMBINED WITH HYPERThermIC INTRAPERITONEAL INTRAOPERATIVE CHEMOTHERAPY (HIPEC)

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ABSTRACT

The successful use of continuous intravenous infusion of neostigmine methylsulfate as a replacement therapy in a patient with myasthenia gravis that underwent cytoreductive surgery combined with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is reported. Continuous intravenous infusion of neostigmine replaced successfully oral pyridostigmine bromide therapy until oral intake was possible for the prevention of myasthenic crisis and permitted uneventful extubation.

Key words: Neostigmine, cytoreductive surgery, hyperthermic intraperitoneal intraoperative chemotherapy, myasthenia gravis

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune chronic disease of the motor endplate. Pyridostigmine orally is the standard treatment of MG. Patients with MG, undergoing major abdominal surgery, are unable to receive per-os medication and medications must be given parenterally. Pyridostigmine has been successfully used by continuous infusion for the prevention of myasthenic crisis 1. Neostigmine methylsulfate has not been reported as a replacement therapy of pyridostigmine. The purpose of the study is to report the prolonged successful use of neostigmine in a patient with MG that underwent extensive cytoreductive surgery in combination with HIPEC for recurrent ovarian cancer.

CASE REPORT

A 54-year old woman, ASA III, who had undergone total abdominal hysterectomy and bilateral oophorectomy 5 years ago for ovarian cancer and had been treated with systemic chemotherapy with carboplatin and taxol presented with peritoneal recurrence. She had a
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history of myasthenia gravis (Class IIa) for which she had undergone thymectomy 3 years ago. Her daily medication included prednisolone 5 mg and pyridostigmine 300 mg. Prednisolone was tapered and stopped preoperatively. She was also treated with intravenous immunoglobulin bimonthly. There was no history of cardiac, renal, or hepatic disease. Vascular access included a subclavian central line, and a 16-G intravenous catheter. Monitor consisted of ASA standard monitors along with invasive blood pressure monitor. Lumbar epidural was possible preinduction at L1-L2 level. General anesthesia was induced with propofol 200 mg and fentanyl 0.25 mg. No muscle relaxant agent was used. Anesthesia was maintained with sevoflurane in oxygen/air mixture (end-tidal concentration 1%-2%). Analgesia was achieved epiduraly with an initial dose of ropivacaine 40 mg with 0.05 mg fentanyl followed by continuous infusion of ropivacaine 2% with fentanyl 3mcg/ml at 8 ml/h. Cytoreductive surgery included pelvic peritonectomy procedure (resection of the pelvic peritoneum en bloc with the sigmoid colon and the upper rectum), resection of the greater and lesser omentum, right lateral peritonectomy procedure and was assessed as complete cytoreduction (CC-0), once no macroscopically tumor was left behind. HIPEC was possible using cis-platin plus doxorubicin in 42.5-43°C for 90 min. The continuity of the gastrointestinal tract was reconstructed after the termination of HIPEC with end-to-end colo-rectal anastomosis. The patient was transferred sedated with propofol in the ICU. She was adequately rewarmed, hemodynamically stabilized with no inotropic support and was left to wake up in approximately two hours. Prior to extubation she was given neostigmine intramuscularly 1.25 mg with atropine 0.5 mg. Initially breathing was adequate with pH=7.4, pO₂=125 mmHg, pCO₂=35 mmHg, BE=-2.6, SpO₂=99% with faced mask. One hour later she complained of respiratory weakness that was treated successfully with intravenous neostigmine 1.25 mg and atropine 0.5 mg. At that point continuous infusion of neostigmine 0.2 mg/h was started. On postoperative day 7, bowel function returned and the patient was given half the dose of the normal medication of pyridostigmine while the infusion neostigmine was decreased. The next day the patient was back to the normal preoperative medications and was discharged to the ward. She had an uneventful recovery and was discharged from the hospital on day 12.

DISCUSSION

The life time prevalence of MG is estimated between 5 and 40/100.000 people with male/female ratio 1/3. The disease is marked by exacerbations and remissions and is characterized by easy fatigability of skeletal muscle due to autoimmune destruction or inactivation of postsynaptic acetylcholine receptors at the neuromuscular junction. Muscle strength improves with rest but deteriorates rapidly with exertion. Infection, stress, surgery, and pregnancy have unpredictable effects on the disease but often lead to exacerbations. Patients with myasthenia may present for thymectomy, unrelated surgical or obstetric procedures. Treatment modalities include immunosuppressants (corticosteroids, azathioprine or cyclosporine), plasmapheresis, high-dose intravenous immunoglobuline, and thymectomy. Over the last 50 years medical therapy has remained the cholinesterase inhibitor pyridostigmine. Pyridostigmine per-os shows low bioavailability (5-10%), plasma elimination half-time of 200 min compared to 97 min when given intravenously,
and 75% renal clearance. As a consequence the inter-dose interval to achieve steady-state plasma concentration within therapeutic range is between 2 and 4 hours. The pharmacokinetic profile of intravenous neostigmine provides a rational basis for continuous infusion. Onset of action is faster, plasma elimination half-time is smaller (77 min) which makes it more easily titratable and relies less on renal clearance (50%), so accumulation is less in cases of renal impairment. Patients with MG undergoing surgery should restart normal medications as soon as possible for the prevention of postoperative respiratory failure. Cholinesterase inhibitors can be given parenterally if oral intake is not possible. A commonly used treatment is neostigmine 1-2.5 mg IV or IM every 2-4 hours titrated to effect the 1/60 of the oral dose of pyridostigmine at the same time intervals. In our case oral intake was impossible for a long period because of paralytic ileus. Continuous IV infusion was preferred because it was required to avoid the discomfort of repeated IM injections. In addition intermittent IV injections would lead to increased serum concentrations with corresponding fluctuation in response. The patient remained under continuous monitoring in the ICU. No further episodes of muscle weakness and respiratory compromise were recorded. No signs of neostigmine overdose were recorded (bradycardia, hypotension, arrhythmias, headache, nausea, vomiting or salivation) and no other dose of atropine was required throughout her stay in the ICU. Liver and renal function remained normal and the daily dose of neostigmine (4.8 mg) remained stable.

CONCLUSION

Continuous IV administration of neostigmine has not been recommended so far for prolonged time for the prevention of myasthenic crisis. It appears that if the patient is adequately monitored the IV administration of neostigmine is safe and well tolerated.

COMPETING INTERESTS

The author certifies that the author does not have any actual or potential conflict or competing interest.

REFERENCES