R_{11}: 33 kilohms, ½ w
R_{12}, R_{15}, R_{26}, R_{29}: 10 kilohms, ½ w
R_{13}, R_{36}: 10 kilohms, trim pot
R_{14}: 1.5 megaohms, ½ w
R_{16}: 2.5 megaohms, ½ w
R_{17}: 500 kilohms, ½ w
R_{21}, R_{22}: 47 kilohms, ½ w
R_{23}, R_{33}, R_{41}: 470 kilohms, ½ w
R_{28}, R_{37}: 4.7 kilohms, ½ w
R_{31}: 1 megaohm, ½ w
C_1: 100 μf, 16 v
C_2: 22 μf, 35 v
C_3: 10 μf, 35 v
C_4: 4.7 μf, 35 v
D_1–D_5: 1 N 4154
Q_1: TIS69 (N channel J F.E.T.)
Q_2, Q_4: 2 N 3903
Q_3: 2 N 3905
L_1, L_2: G.E. 344
S_1, S_2: Push button N.O.
S: Sonalert
AMP.1–AMP.6: μA 741

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Muscle Relaxants, Myasthenia, and Mustards?

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A search of the medical literature failed to reveal any connection between muscle diseases, neoplasms and the nitrogen mustards. This case suggests that the combination of nondepolarizing neuromuscular blocking drugs, alkylating drugs, and myasthenia gravis may be hazardous. In this case, the nitrogen mustard used was triethylene thiophosphoramide (thio-tepa, Lederle).

Report of a Case

A 58-year-old woman, weighing 68 kg, was admitted for laparotomy, at which a malignant cystadenoma of the ovary was found, with metastatic seeding of the peritoneal cavity, omentum, bowel and liver. She had a positive diagnosis of myasthenia gravis, Group IIa,[1] of 6 months' duration, treated with pyridostigmine, 120 mg orally, *q.i.d.* Mild adult-onset diabetes mellitus was present, controlled by diet. Thyroid function was normal, clinically and biochemically. For anesthesia, the early morning dose of pyridostigmine was omitted, and atropine, 0.4 mg, im, given an hour preoperatively. A nerve stimulator (Block-Aid Monitor, BW), using needle electrodes along the ulnar nerve, was placed with the patient awake. While the patient was breathing 100 per cent oxygen, pancuronium bromide was injected iv, an initial dose of 0.5 mg, then increments of 0.25 mg at intervals of 1–2 minutes until the twitch response disappeared. The total dose was 1 mg. Then a sleep dose of thiopental was administered, and control of respiration achieved using N_2O, 70 per cent in oxygen. After topical administration of 4 per cent lidocaine, the trachea was intubated with a cuffed endotracheal tube. Anesthesia was maintained with 70 per cent N_2O, 30 per cent oxygen, and controlled ventilation with Pa_{CO_2} 35 torr. Muscular paralysis was monitored by single-twitch nerve stimulation. Pulse, blood pressure, ECG, arterial blood gases, and temperature were also monitored. After 50 minutes, the twitch response returned and slowly increased, but no more pancuronium was given. One and a half hours after the initial administration of pancuronium, thio-tepa, 60 mg, was instilled into the peritoneal cavity and allowed to remain. Within a minute, the twitch response disappeared. The instrument was checked for proper function. After a further 45 minutes, at the end of the operation, atropine, 1.2 mg, and neostigmine 5, mg, were administered iv, with no effect. The endotracheal tube was left in place and the patient was taken to the recovery room, where mechanical ventilation was instituted. Four hours after the intraperitoneal instillation, edrophonium, 20 mg, was given, without effect. Eight hours after this, there was a slight twitch response, and reversal with neostigmine was again attempted, but this also was not effective; gross fade and posttetanic facilitation were demonstrable. The next morning, the patient could open her eyes, but grip strength was only fair and the respiratory variables were borderline. Neostigmine was given again, the patient's condition improved considerably, and the tracheal tube was removed. Neostigmine was begun, 1 mg, im, every four hours. Because of fatigue,

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this was increased to 2 mg every four hours, but at this level, secretions became a problem. Reintubation of the trachea was carried out. A pulmonary infection ensued. Gentamicin was administered and almost immediately, muscle weakness occurred. During the remainder of the hospital course the patient had recurrent myasthenic crises, interspersed with cholinergic crises, and finally a pulmonary embolus, from which she could not be resuscitated.

Discussion

Alkylating drugs, used in the treatment of malignancies, have not been shown to have additive or synergistic activity when used with nondepolarizing neuromuscular blocking drugs. The molecular conformation of these drugs is one of many tertiary ammonium groups, which undergo intramolecular cyclization with formation of quaternary ammonium groups as a transformation product.[2] This is an ethylenimonium intermediary.

In this case, any of a number of possibilities could have occurred: a) Addition or synergism of pancuronium and thio-tepa. b) Addition or synergism of myasthenia gravis and thio-tepa, a myasthenic crisis.[1] c) The anticholinesterase effects of three substances, residual pyridostigmine,[2] pancuronium,[3] and thio-tepa,[4] being synergistic, a cholinergic crisis.[1] d) An acetylcholine block due to thio-tepa alone, a cholinergic crisis.[2] e) A hexaflurenium type of blockade due to thio-tepa. f) A syndrome similar to the Eaton-Lambert syndrome but associated with cystadenoma of the ovary.[5] g) A carcinoma neuropathy as a pre-existing condition, accentuated by drugs that may interfere with neuromuscular transmission.

Pancuronium has been used in management of myasthenic patients[6] and was chosen for use in this case. As is our custom with myasthenics, the muscle relaxant was titrated into the patient to the desired endpoint before anesthesia was induced, this having been previously explained to the patient.

While there is no proof which of these suppositions was the cause, various drugs each of which by itself or in combination could have accentuated the myasthenic state were used. It is also possible that while the patient was diagnosed as having Group IIa myasthenia, her myasthenia was really of Group III–IV, a fulminant disease where a fatal outcome could be expected.[1] This is very likely when the six-month history is considered.

The use of succinyldicholine in combination with anticancer drugs has been investigated, and reports of prolonged apnea resulting from this can be found. Thio-tepa has an ID_{50} of 7.9×10^{-3} M with benzolycholine as the substrate.[4] Progressive muscular paralysis may follow the administration of drugs in the nitrogen-mustard group.[2] It has been suggested that these drugs, which are similar to acetylcholine in structure, may produce this paralysis by prolonged depolarization of the motor endplates. Irreversible chemical bonding between the transformed mustard and the receptor substance could also occur.[2] Absorption of thio-tepa from mucosal surfaces is known to occur.[2] Peritoneal absorption has not been studied, but it is known to occur with many other drugs. This case report suggests that thio-tepa may have caused or potentiated neuromuscular blockade from pancuronium, and that alkylating drugs (nitrogen mustards) be considered a possible hazard when given to patients during anesthesia involving the use of muscle relaxants. The presence of myasthenia gravis may have been the predisposing and critical factor in this complication.

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