I N T R O D U C T I O N

The aminoglycoside antibiotics were known to interfere with a variety of physiological functions including myocardial activity, autonomic ganglionic and neuromuscular transmission (Swain et al., 1956; Adams et al., 1973; Wright and Collier, 1974; and Singh et al., 1978).

The rather unique toxic reaction of acute muscular paralysis and apnea resulting from neuromuscular blockade has been attributed to the various aminoglycosides. A review of 83 reports of prolonged paralysis implicated neomycin as the most frequent cause (Pittinger et al., 1970).

In man, neuromuscular blockade has generally occurred after intrapleural, intraperitoneal instillation of large doses of aminoglycosides. However, the reaction has followed the intravenous, intramuscular and even the oral administration of these agents (Holtzman, 1976). Most episodes have occurred in association with anaesthesia or the administration of other neuromuscular blocking agents. Patients with myasthenia gravis are practically susceptible to this effect.

Animal studies had begun in 1946 when Molitor et al. (1946, 1950) investigated the acute toxicity of streptomycin on several animal species (pigeon, toads, mice, rats, guinea pigs, rabbits, cats and dogs) following the administration of the drug by different routes. In all warmblooded animals which had received a lethal dose of streptomycin, they found that death occurred by respiratory paralysis since the heart continued to beat for several minutes after respiration had ceased. It was observed that prompt initiation and maintenance of artificial respiration could often prevent an otherwise fatal outcome. They reported in addition that frogs do not depend solely upon pulmonary respiration, survived at doses of streptomycin many times larger than those tolerated by mice, provided that they were kept partially in frequently changed water. As signs of acute poisoning caused by venous and subcutaneous administration of streptomycin they reported restlessness, labored respiration, loss of consciousness and coma in larger animals such as cats and dogs, besides these symptoms, nausea, vomiting and ataxia were also observed.

Although these findings indicated that streptomycin may have neuromuscular blocking activity, the

systematic investigation of the neuromuscular effect only started in 1957 by Vital Brazile and Carrado, one year after the first cases of respiratory depression from neomycin-ether interaction were reported by Pridgeon in 1956.

Vital Brazile and Corrado (1957) employed a very high dose (110 mg/kg) to demonstrate the neuromuscular blocking effect of streptomycin in dogs and they stated that when they administered a larger doses (more than 110 mg/kg) streptomycin induced complete myoneural blockade to tetanizing impulses. The muscle responded always to direct stimulation. Nerve tetanization neostigmine and calcium were shown to antagonize streptomycin blockade.

They showed that neuromuscular blockade caused by ether-streptomycin or magnesium was surprisingly alike in the following characteristics:

- Tetanus occurs as a response to indirect stimulation with tetanizing frequency when isolated volleys of impulses were blocked by the drug.
- Post tetanic twitches were maximum immediately after tetanus or after a brief delay when the nerve was

again stimulated with low frequency stimuli (post tetanic facilitation).

- Calcium chloride administration causes complete or mostly complete antagonism to the effect of the drug.

But in 1960, Jindal and Deshponde found that a dose of 40 mg/kg streptomycin produced complete paralysis and smaller doses had proportionately a smaller effects and they stated that:

- The direct excitability of the different muscle preparations (e.g. frog rectus abdominis and dog gastrocneius-sciatic nerve preparation) was never found to be decreased in any of the experiments.
- Neostigmine could antagonize the effect of streptomycin only when there was a partial neuromuscular block.
- In the presence of complete neuromuscular block the effect of neostigmine was negligible.
- Calcium ions could antagonize quickly but less completely the effect of streptomycin on skeletal muscle.

Similar results had been reported by Pittinger and Long (1958) and Corrado et al. (1959) for the neuromuscular blocking action of neomycin. Thus, it was

likely that the neuromuscular blocking action of neomycin and streptomycin involved a common mechanism of action.

Corrado (1963) attributed the mechanism of neuromuscular blockade from streptomycin, neomycin and kanamycin to their ability to reduce the level of ionized calcium in blood. This conceptual relationship between streptomycin and related antibiotics and calcium ionization was based upon:

- An inverse relationship between acute streptomycin toxicity and residual calcium content of the relatively impure early samples of the antibiotic (Keller et al., 1956 a).
- Observations of anticoagulant effect of streptomycin in blood (Keller et al., 1956 b).
- Streptomycin depression of contractions of the isolated frogs heart (Keller et al., 1956 b) which was concomitant with reduction of ionized calcium in Ringer's solution as measured by the bioassay technique of Mc Lean and Hastings (1934).
- Known chelating potentialities of some antibiotics including streptomycin (Chenoweth, 1956).
- The antagonistic action of calcium salts to the

neuromuscular blockade caused by streptomycin and other related antibiotics in addition to the decreased toxicity of neomycin and streptomycin administered with calcium salts (Corrado et al., 1959).

- Decreased streptomycin toxicity when administered as calcium chloride complex and synergism of the neuromuscular blocking activity of neomycin by the chelating agent sodium citrate (Corrado et al., 1959).

As the above evidences were of indirect and non specific nature, they were inferential rather than conclusive. Tetany which is suspected to be developed as a response to the decreasing of ionized calcium in the blood had not been reported as an antecedent of paralysis in clinical situations (Pittinger et al., 1970). Also it had not been observed in laboratory animals whose characteristic response to excessive drug was a progressive flaccid paralysis (Pittinger and Adamson, 1972).

Later on, in 1970, Pittinger proved that streptomycin sulphate in paralyzing concentration did not decrease calcium ionization in human or rabbit sera, using the calcium selective electrode which provides (in his

inappropriate use of the bioassay procedure. Lastly, they said that although there was no quantitative study on the effect of neomycin on ionic calcium there was no clinical or laboratory evidence of depression calcium ionization by neomycin. Paralysis produced by neomycin was progressive and flaccid without evidence of intervening tetany.

Vital Brazile (1961) showed that streptomycin reduced responsiveness of the gastrocnemius muscle of the dog to intra-arterially injected acetylcholine and moreover it depressed contractions of denervated tibial muscle in dogs caused by direct electrical stimulation and in some instances produced a slight elongation of the denervated muscle. Calcium ions synergized the depressant effect on denervated muscle but antagonized the hypotensive and respiratory depressant effect of the antibiotic. Thus, he postulated that the antibiotics stabilized muscle membranes rather than combined with acetylcholine receptors. He speculated that streptomycin blocked the effect of acetylcholine by a dual mechanism, the desensitization of the end plate to the depolarizing action of the transmitter and diminution of membrane excitability in region close to the end plate.