EFFECTS OF 4-AMINOPYRIDINE IN EATON LAMBERT SYNDROME

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SUMMARY

The effects of 4-aminopyridine (a non-anticholinesterase antagonist of curare-like agents) on the evoked muscle action potentials (EMAP) in a patient with Eaton Lambert Syndrome are reported. On two separate occasions the i.v. administration of 0.31 mg kg\(^{-1}\) and 0.62 mg kg\(^{-1}\) was followed by a 300% increase of EMAP for about 2 h without serious side-effects.

The Eaton Lambert Syndrome (Eaton and Lambert, 1957) (ELS) is a rare disorder resembling myasthenia gravis and may be associated with or foreshadow neoplastic disease (Cherington, 1976). For example, small cell bronchogenic carcinoma (Anderson, Churchill-Davidson and Richardson, 1953) is found in about 70% of patients with ELS (Elmqvist and Lambert, 1968). The primary defect is one of neuromuscular transmission (Elmqvist and Lambert, 1968).

THE PATIENT

Recently we observed a 53-yr-old male with a 12-month history of muscle weakness and muscle aching. Depressed tendon reflexes, slow development of maximal voluntary tension in the biceps brachii muscle and normal motor conduction velocity of the median and peroneal nerves were found on examination. Electromyographic recording from the abductor digiti minimi muscle following supra-maximal stimulation of the ulnar nerve revealed: (a) a low amplitude of the evoked muscle action potentials (EMAP); (b) gradual decrease in the amplitude of EMAP at low rates of stimulation (1.0–3.0 Hz) and (c) a facilitation response at high rates of stimulation (10–30 Hz) up to 400% of the initial EMAP. These findings are all consistent with the diagnosis of ELS. Although effective in patients with myasthenia gravis, cholinesterase inhibitors are less effective in ELS (Oh and Kim, 1973). Guanidine acts presynaptically by increasing the number of acetylcholine (Ach) quanta liberated by a single motor nerve action potential, without altering the postsynaptic sensitivity to Ach (Otsuka and Eudo, 1960; Kamenetskaya, Elmqvist and Thesleff, 1975). Although several clinical studies indicate that guanidine improves muscle strength in patients with ELS, severe toxic effects such as interstitial nephritis (Cherington, 1976), severe dermatitis and intractable vomiting (Brown and Johns, 1974), bone marrow depression (Norris, Eaton and Mielke, 1974), gastric distress, paraesthesias and vertigo (Norris et al., 1974) have occurred.

4-AMINOPYRIDINE

4-Aminopyridine antagonizes neuromuscular blockade by curare in animals (Lemeignan and Lechet, 1967) and man (Paskov, Stojanov and Micov, 1973). In a series of *in vitro* (Foldes, Agoston et al., 1976) and *in vivo* (Foldes, Braak et al., 1976) experiments, 4-aminopyridine had no anticholinesterase activity; its antagonistic effect depended on its ability to improve the development of tension in the muscle fibre and to increase presynaptic release of Ach, without affecting the sensitivity of the postsynaptic membrane to Ach or carbachol (Bowman, Harvey and Marshall, 1976). Further observations revealed that 4-aminopyridine not only restores neuromuscular transmission after a block *in vivo* by botulinus toxin (Lundh, Leander and Thesleff, 1977), magnesium sulphate and antibiotics (F. F. Foldes, personal communication, 1976) but it antagonizes the block produced by dantrolene sodium also (unpublished observations).

These considerations prompted us to administer 4-aminopyridine to a patient with ELS on two occasions after the patient's control values were
determined. On the first occasion 0.31 mg kg\(^{-1}\) (total 25 mg) 4-aminopyridine was given i.v. in divided doses over 5 min. On the second occasion 0.62 mg kg\(^{-1}\) (total 50 mg) was administered in 90 s by i.v. injection. Changes in the indirectly evoked MAP were observed before and after the administration of the drug on each occasion separated by 3 days. The results are summarized in table I. There was a significant increase in MAP after the administration of 4-aminopyridine when compared with the results of stimulation without drug treatment. However, there was no difference in the magnitude and duration of the effects after the administration of 4-aminopyridine 25 and 50 mg respectively, which suggests that the maximum effect (300% increase) in MAP could possibly have been obtained with less than 25 mg (0.31 mg kg\(^{-1}\)). There was a slight decrease in the heart rate but no change in the arterial pressure. The patient complained of “tingling” and “pins and needles”, especially of the lips and fingers. These sensations were more pronounced and longer lasting after the administration of the higher dose.

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### REFERENCES


**EFFETS DE LA 4-AMINOPYRIDINE SUR LE SYNDROME D’EATON LAMBERT**

**RESUME**

On signale dans cet article les effets de la 4-aminopyridine (antagoniste non anticholinesterase des agents du type curare) sur les potentiels évoqués de l’action musculaire (EMAP) sur un malade atteint du syndrome d’Eaton Lambert. À deux reprises séparées l’administration intraveineuse de ce produit à raison de 0,31 mg kg$^{-1}$ et de 0,62 mg kg$^{-1}$ a été suivie d’une augmentation de 300% de l’EMAP pendant environ 2 heures, sans qu’il y ait eu d’effets secondaires graves.

**DIE WIRKUNGEN VON 4-AMINOPYRIDIN BEI EATON LAMBERT-SYNDROM**

**ZUSAMMENFASSUNG**

Die Wirkungen von 4-Aminopyridin (ein nicht-Anticholinesterase-Gegenmittel für Curare-Mittel) auf die hervorgerufenen Muskelaktionspotentiale (EMAP) bei einem Patienten mit Eaton Lambert-Syndrom. Bei zwei separaten Gelegenheiten wurde die intravenöse Verabreichung von 0,31 mg kg$^{-1}$ und von 0,62 mg kg$^{-1}$ gefolgt von einem 300%igen Anstieg von EMAP auf etwa 2 Stunden—ohne ernsthafte Nebenwirkungen.

**EFECTOS DE 4-AMINOPIRIDINA SOBRE EL SINDROMA EATON LAMBRET**

**SUMARIO**

Se informa acerca de los efectos que ejerce 4-aminopiridina (un antagonista no-anticolinesterasa de agentes de tipo curare) sobre el potencial de acción muscular evocado (EMAP) en un paciente con el síndrome Eaton Lambert. En dos oportunidades separadas la administración intravenosa de 0,31 mg kg$^{-1}$ y 0,62 mg kg$^{-1}$ fue sucedida por un aumento de 300% de EMAP durante aproximadamente 2 horas, sin sufrir efectos colaterales serios.