PHARMACOLOGICAL AND CLINICAL STUDY OF THE NEW NON-DEPOLARIZING MUSCLE RELAXANT VECURONIUM (ORG NC 45 NORCURON)

THESIS

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التخدير

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INTRODUCTION
AND AIM OF WORK

Muscle relaxants made general anaesthesia more easy and effective, facilitated surgery and redued post-operative morbidity and mortality. Their universal role in controlled ventilation has contributed to the remarkable improvement in the management and prognosis of diseases associated with respiratory failure, e.g. convulsions { tetanus,status epilepticus }, drug over dosage, head, chest injuries, and in the intensive care units.

The ideal muscle relaxants should have the following properties :- *{Karis and Gissen, 1971}*

1- It should be competitive and non-depolarizing, thus side effects associated with depolarizers should not occur.

2- The cessation of the neuromuscular blockade should not depend on renal or hepatic function, so diseases of one or both of them do not impair its elimination.

3- The breakdown products should not posses neuromuscular blocking effects or other side effects.

4- Relative rapid onset and short duration of action.

5- Non cummulative effects, so when a large duration is desired, repeated or continous administration can be done.

6- Easy reversibility by anticholinesterases.

Up to the present time non of the non-depolarizing neuromuscular blocking agents known has a rapid onset and short duration of action as those of suxamethonium.

Vecuronium bromide is a recently introduced nondepolarizing muscle relaxant (ORG NC 45) which was developed in 1973 by Dr. David Savage of organon. It has short duration of action, non cummulative,allows cardiovascular stability and easy reversibility. Since that time, great attention has been was directed to study it as an ideal neuromuscular blocking drug. {*Crul and Booij, 1980;. Kreig, Crul and Bool, 1980; Agoston et al. 1980; Booij, Edwards .et al, 1980; Booij, Vaqn der pol et al. 1980 and Fahey et al.1981*}.

The aim of this study is evaluation of pharmacological and clinical properties of the new nondepolarizing muscle relaxant vecuronium bromide.

HISTORY

Dale and Feldberg in 1934 demonstrated that Acetyl choline (A - ch) was secreted by the stimulation of motor nerves and its injection close to the neuromuscular junction would cause a muscle contraction. Dale, Feldberg and Vogt in 1936 showed that curare did not prevent the production of acetyl choline. Eccles, Katz and kuffler in 1941 demonstrated a progressive reduction in the electrical responses at the motor end plate on the muscle in the presence of increasing concentration of curare; This revealed that the principal site of action of curare was the acetyl choline receptors, where it blocked the action of the neurotransmitter.

Bennet and his associates in 1940 used d-tubocurarine in man to soften the effects of electroconvulsive therapy. Griffith and Johnson in 1942 used 5 ml of the crud preparation of curare to supplement a cyclopropane anaesthesia for appendicectomy. Once the use of curare was accepted as a muscle relaxant, the search started for alternative drugs with less side effects.

Harold king (1935) suggested that the structural formula for the active compound revealed 2 quaternary ammonium groups.

The staructural similarity of these compound with that of acetyl-choline open the route to study other bis-

quaternary ammonium compounds.Where these two ammonium groups were separated by 10 methyl chain, this will produce a compound with a maximum neuromuscular blocking action" Decamethonium" *Paton and Zaims (1949)*. However decamethonium had properties that differed from those of curare-like action. Suxamethonium was first used in anaesthesia by von Dardel in Stockholm, by Mayerhofer in Vienna and by Scurr in Britain, in 1951.

Bovet and his co-workers described the muscle relaxant action of the synthetic compound, gallamine triethiodide " Flaxedil" in (1947).,its effect in man was firstly described by Huguenared and Boue in (1948) in France and in (1949) in England by Mushin and his colleagues. Pancuronium bromide (ORG NA 97 or Pavulon), a steroid derivative-was first used clinically by Baird and Reid, in 1967 fazadinium bromide (Fazadon or A H 8165) an azo-bis-aryl imidazo-pridinium compound was first studied in humans by *Simpson et al., (1972)*.

Atracurium besylate (Tracrium or BW 33 A) - a bisquaternary ammonium salt- of Wellcome was developed and synthetized by *J.B. Stenlake (1979)*.

Vecuronium bromide (Norcuron or ORG NC 45) was synthetized by Dr. *David Savage* of Organon Technicha Laboratories of Holland in 1973. It was introduced into clinical practice in the U. K. in 1983.

NEUROMUSCULAR TRANSMISSION

ANATOMY

Striated muscles are composed of: muscle cell(muscle fibre). it is 1 to 40 mm. in length, and up to 0.1 mm in diameter. It is multinucleated cells.

The Sarcolemma

It is the cell membrane of the muscle cell, The sarcolemma is electrically polarized during relaxation *(Ganong. 1983)*

Muscle fibrils.

The striated muscle fibre is composed of fibrils (Myofibrils), they have cross striation as the intact fibres. they are packed together with their striations in register. Myofibrils are better seen in cross sections.

Microscopic Picture of the Myofibrils:-(Fig 1)

In the longitudinal section of the striated muscle fibres the cross striations appear as alternating dark and light bands run along the fibres. The dark bands " anisotropic " called A-bands, and the light bands " isotropic" called I- bands. This light bands "I bands " are bisected with a darker thin lines -"Z" lines In the center of each A-bond a paler area can be seen which is termed " H-Zone" *(Hamilton & cormack, 1979)*