RENIN ANGIOTENSIN SYSTEM AND ITS RELATION TO HYPERTENSION AND DIABETES MELLITUS

ESSAY

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in
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CLINICAL AND LABORATORY STUDIES OF A NEW SHORT ACTING NON-DEPOLARIZER MUSCLE RELAXANT [B.W.-B1090u] [MIVACURIUM] IN CHILDREN AND ELDERLY PATIENTS

THESIS

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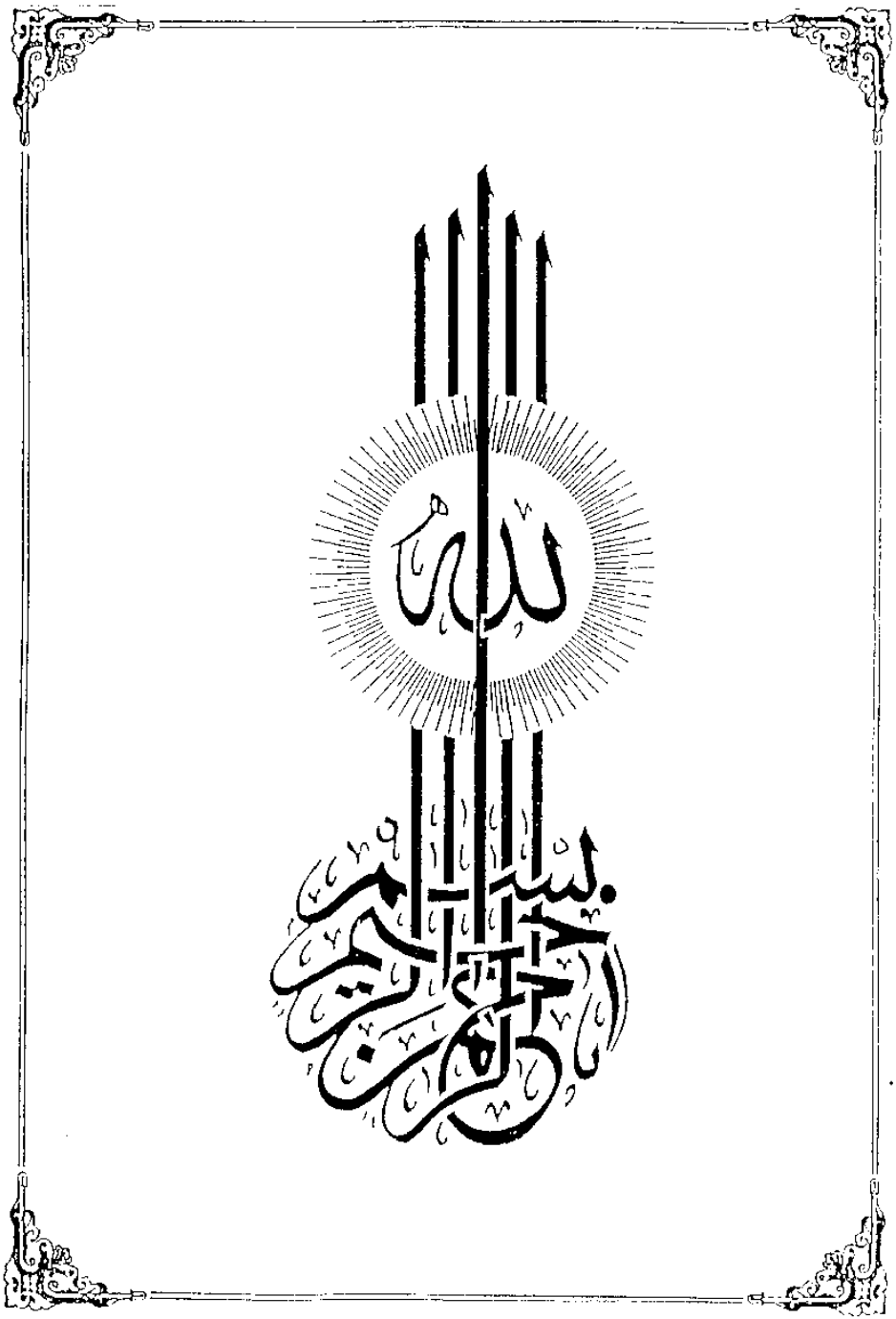

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Contents

INTRODUCTION

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The use of neuromuscular blocking agents to provide skeletal muscle relaxation during surgery has become an integral part of the anesthetic technique to facilitate endotracheal intubation and to provide adequate surgical relaxation with minimal amount of general anesthetic agents. Neuromuscular blocking agents currently available for clinical use are classified as two main groups:

1. Non depolarizing agents that produce neuromuscular blockade by competing with acetylcholine (ACH) for the binding site at the receptor protein.

2. Depolarizing agents that prevent muscle contraction by causing sustained depolarization of the muscle cell membrane.

The relaxant effect of the non-depolarizing agents (e.g. atracurium, vecuronium, d-tubocurarine, metocurine and pancuronium) can be antagonized by the administration of anticholinesterase drugs (neostigmine, edrophonium), while the neuromuscular effects of the depolarizing agents (succinylcholine, decamethonium) can not be reversed.

The importance of neuromuscular blocking drugs in anesthesia is undisputed, and agents of both types have been widely used for many years.

None of the currently available drugs, however, is ideal. Many are associated with significant side effects; d-tubocurarine and metocurarine can cause hypotension because of histamine release (Moss et al., 1981). Pancuronium has been associated with hypertension and tachycardia (Coleman et al., 1972; Marshall and Ojwole, 1979 and Cummings et al., 1983).

Succinylcholine causes a variety of undesirable side-effects owing to its depolarizing action on the skeletal muscle and its agonist effects on nicotinic receptors (Miller et al., 1978 and Brodsky et al., 1979).

The available non-depolarizing agents are often of longer duration of action than desired to meet the need of different surgical procedures. The recommended doses of pancuronium or d-tubocurarine produce complete paralysis of approximately 60-80 m.n., and once recovery has begun, an additional 60-120 minutes may be needed for complete restoration of neuromuscular transmission.

Even with the two new "intermediate duration" drugs-atracurium and vecuronium about 50-60 minutes may be required for full recovery from the recommended relaxant doses. Therefore, for a brief surgery, the duration of paralysis produced by these agents may be longer than clinically desired.

Even in longer surgical procedures, the administration of a non-depolarizing neuromuscular blocking agent close to the end of surgery

can result in prolonged neuromuscular blockade and difficulty in reversal or inadequate clinical recovery. The depolarizing agent -succinyl choline- is frequently used when short duration neuromuscular blockade is desired.

Complete block usually lasts only 5-7 minutes because the drug is quickly metabolized by plasma cholinesterase (pseudocholinesterase). The usefulness of succinylcholine, however, is limited by numerous and potentially serious side-effects. Prolonged apnea can occur in patients with atypical plasma cholinesterase or abnormally low levels of normal pseudocholinesterase (Kalow and Genest, 1957 and Kalow and Davies, 1958). In addition, the agonist action of succinylcholine on other cholinoceptive sites may cause bradycardia (Mathias et al., 1970), muscle fasciculations which may lead to significant post-operative myalgia (Brodsky et al., 1979), and increased intraocular and intra-gastric pressures. Hyperkalemia and malignant hyperthemia may be precipitated in susceptible patients (Tolmie et al., 1967).

The need for an ideal muscle relaxant -without the above mentioned side effects- prompted an extensive search to provide a short-acting non-depolarizing muscle relaxant.

AIM OF THE WORK

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The aim of this work is:

1. To determine the onset, duration and recovery for a single bolus dose of mivacurium (0.08 mg/kg) under N_2O/O_2-narcotic, N_2O/O_2-Isoflurane and N_2O/O_2-Halothane anaesthesia.

2. To demonstrate the relationship between the duration of the neuromuscular blocking effect of mivacurium and the individual subject's plasma cholinesterase activity.

3. Potentiation of neuromuscular blocking effect of the drug when given to patients receiving commonly used inhalational agents (Halothane & Isoflurane). For the assessment of the degree of potentiation we will use relaxograph type "Dalex with NMT monitor".

4. The efficacy of the individual subjects different profiles on the duration of neuromuscular blocking effect of mivacurium through the laboratory studies of:
   a) Liver function tests.
   b) Kidney function tests.
   c) Acid base status.
   d) Serum electrolytes: Na^+, K^+ and Ca^{++}.

5. The efficacy of neostigmine in reversing the drug's neuromuscular blocking effect will be assessed using the relaxograph to monitor the recovery of 95% twitch height and train of four.

HISTORICAL PERSPECTIVE

I. Historical Perspective:

In 1814, Benjamin Prodie (1951) showed that animals poisoned with curare preparation did not die, provided that artificial ventilation was maintained. Claude Bernard's classic studies, in 1851, demonstrated that curare acted peripherally at the junction between the motor nerve and muscle.

West (1932) employed a highly purified fraction of curare in patients suffering from tetanus and spastic disorders. Pure curare was isolated and its chemical structure characterized by King (1935). A standardized preparation of curare (Intocostrin) was first used in a patient to modify the convulsions of electroconvulsive therapy by Bennett (1940). Griffith and Johnson (1942) introduced curare (Intocostrin) into anesthetic practice to provide muscle relaxation. Cullen (1943) reported on 131 cases in which curare was used. Gray and Halton (1946) published a paper entitled: "D-tubocurarine chloride: A milestone in anesthesia". This paper did much to establish the rational use of these drugs. Despite this, however, in the early days, pulmonary ventilation was frequently not assisted. It is no surprise, in retrospect, that hypoventilation proved hazardous. This was probably one of the main factors in the increased mortality rate (up to six-fold) found in patients who were given curare versus those who were not (Beecher and Todd, 1954).

Following the introduction of curare into anesthetic practice, medicinal chemists and pharmacologists began the search for synthetic substitutes. A great many of these substitutes were designed and tasted, but only few have survived. Gallamine triethiodide was first used clinically by Huguenard and Bone (1948) in France.

In the same year, the semi-synthetic curare-dimethyltubocurarine- was introduced into anesthesia by Stoelting et al. (1948). One year later, decamethonium -an intermediate acting depolarizing relaxant- was described by Organe et al. (1949).

Succinylcholine was next introduced (Theslef, 1951 and Foldes-McNal and Borrego-Hinojosa, 1952). Diallybisnortoxiferine (Alcuronium) was introduced by Hugin and Kissling (1961). After that, further pharmacological and clinical interest in the development of new drugs became sporadic until 1968, when pancuronium was introduced. Four years later, AH8165 (Fazadinium) followed, and the semisynthetic curare derivative-metocurine was revived and became more popular in the U.S.A. after a long neglect (Savarese et al., 1977).

Among the efforts to find a short-acting non-depolarizing relaxant was the concept of designing a potent non-depolarizing neuromuscular blocking molecule, which would be a suitable substrate for the enzyme cholinesterase. In collaboration with the Burroughs-Wellcome Company, Kitz and associates, and later Savarese and associates have initiated a program for designing, synthesizing and evaluating pharmacologically

several series of bulky bisquaternary esters of phthalic and related acids (Ginsburg et al., 1971).

One goal of this program was to develop a non-depolarizing neuromuscular blocking agent with rapid onset and short duration that would be particularly useful for brief surgical procedures and to facilitate endotracheal intubation. Ideally, the drug would have no cardiovascular or other side-effects; its blocking action would be non-cumulative, and if necessary, its effects would be readily reversible with anticholinesterase agents. If devoid of cumulative properties, the ideal short-acting agent could be used as an intravenous infusion in procedures of varying duration.

Several compounds evolved from this program, and clinical trials have been performed on some of them. Among these compounds is BW7854 which is a non-depolarizing ester with a rapid onset and short duration of action (Savarese, 1980). Like d-tubocurarine, it had the propensity to release histamine. The latter became so prominent within the clinical neuromuscular blocking dose range that further development was discontinued. The other compound is BWA444U, which is an intermediate acting non-depolarizing relaxant and relatively non-cumulative. It is similar to atracurium in many aspects, except that it is metabolized by plasma cholinesterase. Its margin of safety of histamine release was less than atracurium. In addition, the latter drug has a more desirable degradation mechanism (by Hoffman elimination). Because the