CLINICAL EVALUATION OF PIPECURONIUM BROMIDE (ARDUAN) IN PATIENTS SUFFERING FROM RENAL AND LIVER FUNCTION DISTURBANCES

THESIS

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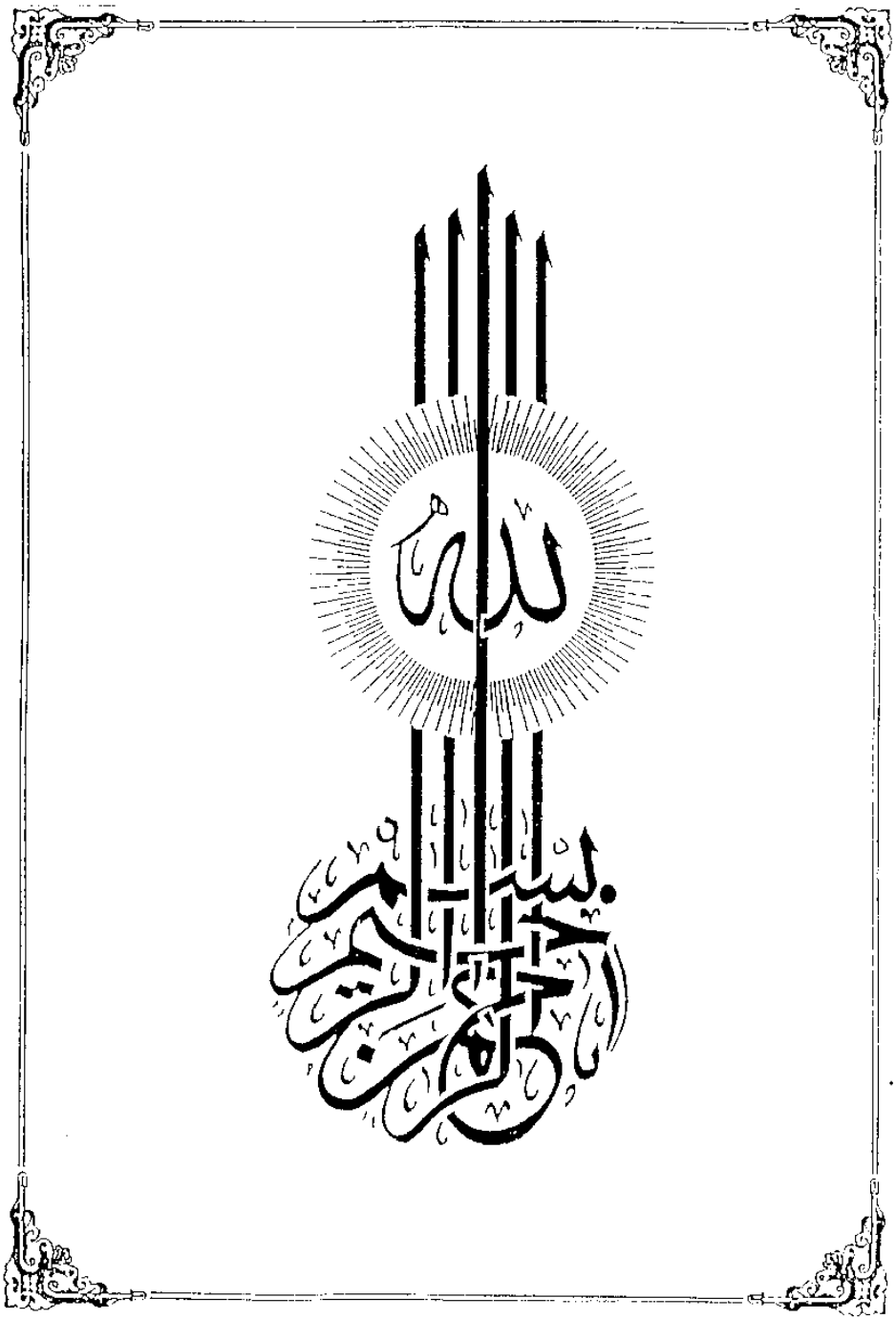

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Introduction

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The introduction of muscle relaxants into clinical anaesthetic practice by *Griffith and Johnson,* in 1942, marked the beginning of a new era in anaesthesia.

During the last 50 years, the use of muscle relaxants has completely changed the practice and scope of anaesthesia and contributed to the most spectacular advances in modern surgery. The relaxants have made general anaesthesia more effective and useful to the advance of surgery, and also reduced intra-operative and post-operative morbidity and mortality. They enabled and allowed many sophisticated and difficult surgical techniques to be easily and successfully done.

With successful application of muscular relaxation in anaesthesia, and in view that curare was not without undesirable properties, new compounds have been studied and introduced in succession into clinical anaesthetic practice in search for the ideal muscle relaxant.

Pipecuronium bromide is a long-acting competitive neuro-muscular blocking agent with a potency and time course roughly similar to those of pancuronium. Like pancuronium, pipecuronium is a bisquaternary compound. This relaxant was developed by Gedeon Richter in Hungary in 1980.

Aim of the Work

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The aim of this work is to evaluate the duration of action of pipecuronium in patients with renal, liver dysfunction in comparison with its duration in normal patients.

Review of Literature

ANATOMY AND PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION

The neuromuscular junction holds particular importance to the anaesthetist with regards to peripherally induced muscle relaxation.

Anatomy of the Neuromuscular Junction

A motor nerve enters a muscle, then branches repeatedly depending on the function of that muscle. For example, muscles that perform fine movements are supplied by nerve fibres that innervate relatively few muscle fibres while muscles that are involved in the control of posture, are innervated by nerve fibres that supply many muscle fibres (*Bowman,* 1980).

In the human body, all muscles, with notable exception of extraocular muscles of the eye and some muscles of the face and neck, are focally innervated. In the muscles in which there are multiple innervation i.e. each muscle fibres passes many myoneural junctions, this muscle type responds to a depolarizing agent by contracture. As the axon forms intimate contact with a single muscle fibre, it loses its

myelin sheath and then branches again to form myoneural junction (*Anis Baraka,* 1980).

The nerve terminals lie in synaptic troughs and are capped with Schwann cells which may serve to mechanically preserve myoneural junction (Fig. 1).

The nerve terminals themselves contain vesicles of transmitter acetylcholine that line up in "active zones" within the nerve terminal. Also present in the nerve terminal are mitochondria which make up about 6.6% of the nerve terminal and cisternae which are thought to be involved in the recycling of the vesicles.

The synaptic cleft, about 50 to 70 nm wide, contains a basement membrane material. The enzyme acetylcholinesterase is also present in the synaptic cleft and is concentrated in the folds. The post-junctional region is immediately recognized by its folded surface the mouth of which be directly opposite the active zone in the nerve terminal. It is also in this region that the acetylcholine receptors and their associated ionic channels are located. Thus the released acetylcholine passes the receptors before being destroyed by acetylcholinesterase within the folds (Fig. 2) (*Heuser,* 1973).

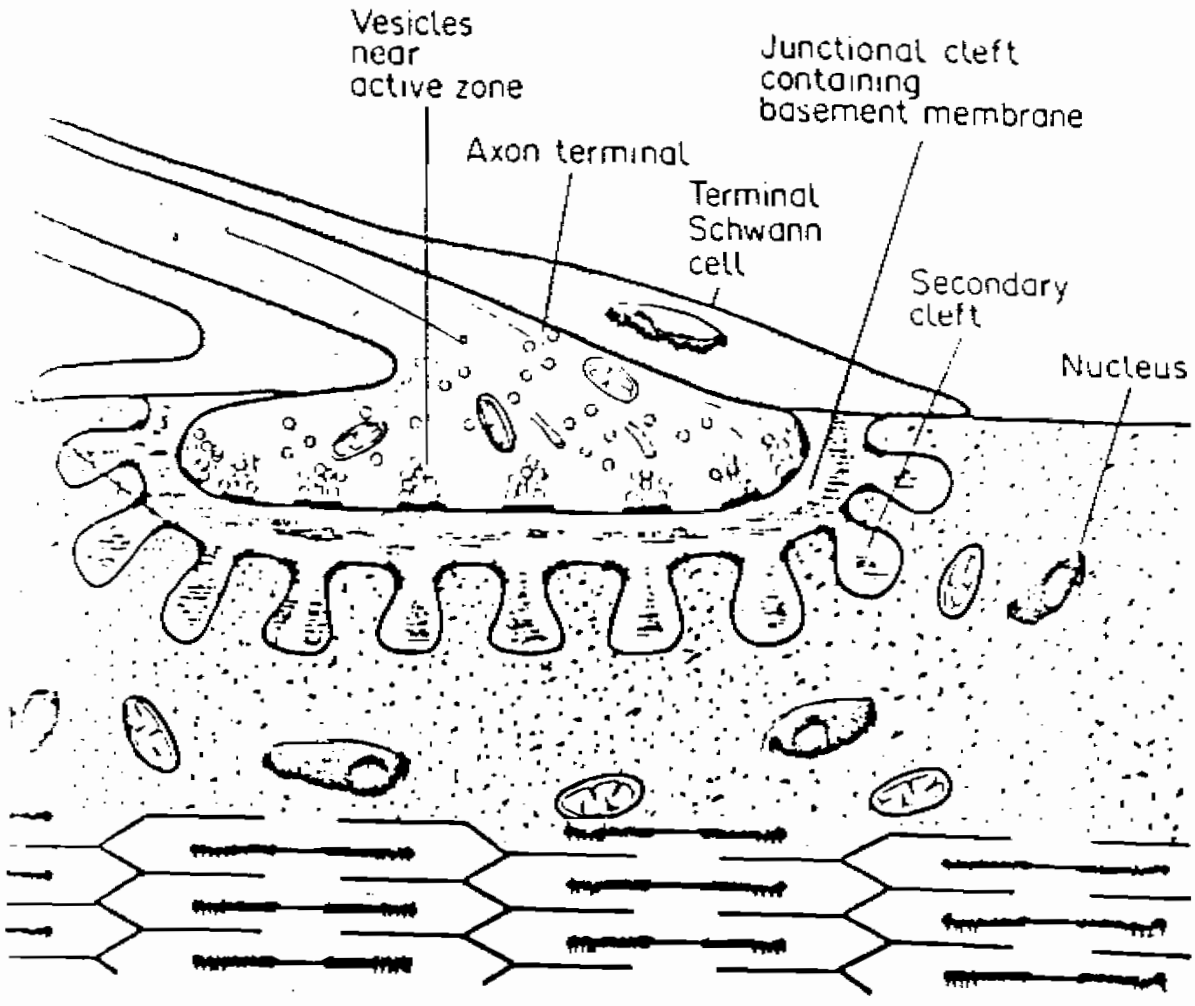

Figure (1): Scheme of the motor nerve ending (*Standaert*, 1986).

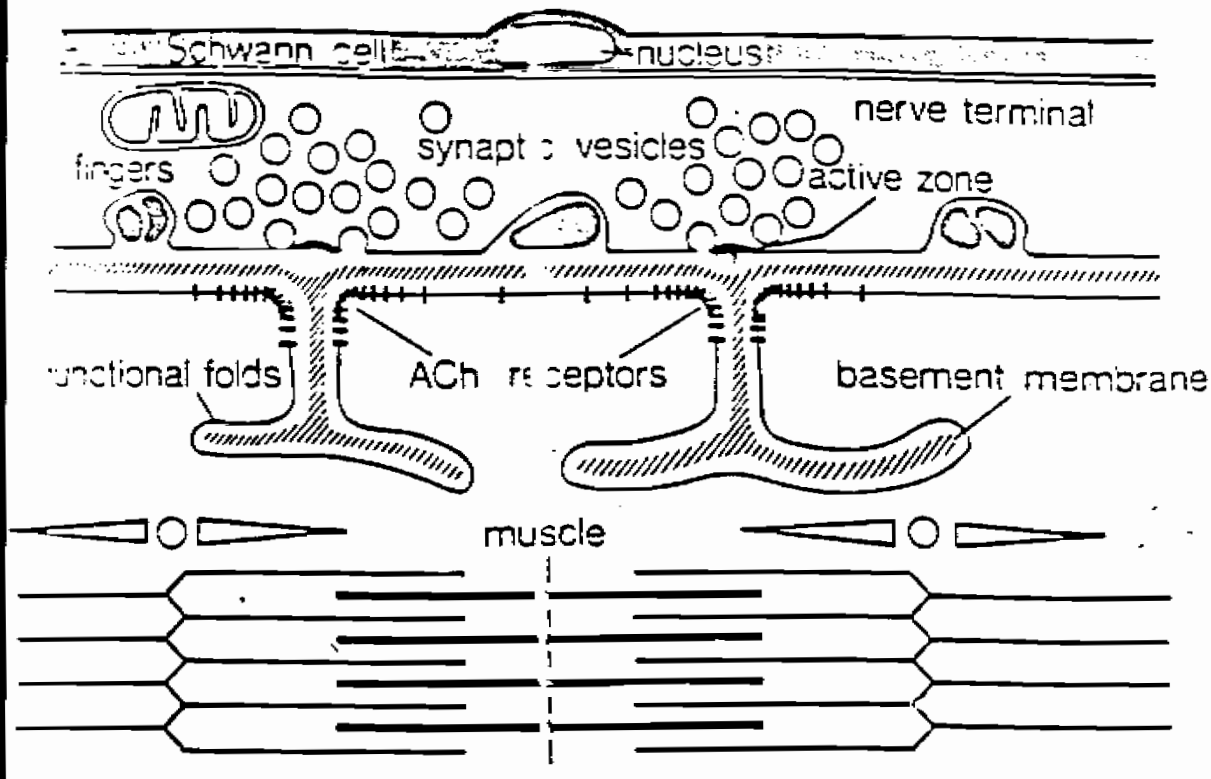

Figure (2): Schematic drawing of the ultrastructure of frog neuromuscular junction in longitudinal section (*Dreger*, 1982).

Function of the Neuromuscular Junction

Neuromuscular transmission starts with the arrival of a nerve action potential at the nerve terminal and concludes with depolarization of the post-junctional membrane. Although the time that elapses between these two events is only a few milliseconds, many different processes take place.

Synthesis of Acetylcholine

The first step is the synthesis of acetylcholine which takes place within the nerve terminal. Acetylcholine is synthesized from choline and acetyl coenzyme, the latter derived from pyruvate which in turn is derived from glucose. Choline is present in the plasma and consequently in the extracellular fluid surrounding motor nerve terminal and the source of approximately of this choline is from enzymatic destruction of acetylcholine (*Collier,* 1974).

Choline undergoes active transportation into the nerve terminal where it accepts the acetyl group carried by acetyl coenzyme and under the catalytic influence of choline acetyl transferase and the resulting bound acetylcholine is then used to refill the vesicles (*Hubbard,* 1973).

Depolarization of Nerve Terminal and Role of K^+, Na^+, Ca^{++}

At rest, most of living cells maintain an ionic concentration gradient across the cell membrane by means of metabolically driven ion pumps. This results in the potassium ion concentration being about 50 times greater inside the cell and the sodium ion concentration being about 30 times outside the cell (*Katz,* 1971).

Depolarization of the nerve terminal follows the arrival of the nerve action potential and is mainly due to the initial influx of sodium ions through sodium ion channels which would take the membrane potential from about -90 mv to about +50 mv. The latter being equilibrium potential for sodium ions. However, at membrane potential of about 0 mv potassium ion channels open and sodium ion channels start to close and in this way the sodium influx gives rise to potassium efflux that prevent the membrane potential from going more positive than about 10 mv and restores the holding potential to -90 mv. Thus the sodium and potassium channels are both sensitive to changes of the membrane potential. Calcium ions enter the nerve terminals during depolarization and then rapidly sequestrated by sarcoplasmic reticulum and the mitochondria (*Miyamoto,* 1978).