COMPARATIVE STUDY OF A NEW ANTICHOLINERGIC DRUG GLYCOPYRROLATE (ROBINUL) IN ANAESTHETIC PRACTICE

THESIS

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BY

SOHAIR ABBAS MOHAMED SADEK
M. B. , B. Ch., M. Sc. (Anaesthesia)

Supervised By

Prof. Dr. SADIA ABDEL-HAFIZE
Professor of Pharmacology
Ain Shams University

Prof. Dr. YAHIA HAMIMY
Professor of Anaesthesia
Ain Shams University

Prof. Dr. ABDEL-AZIZ YOUSIF
Professor of Anaesthesia
Ain Shams University

Faculty of Medicine , Ain Shams University

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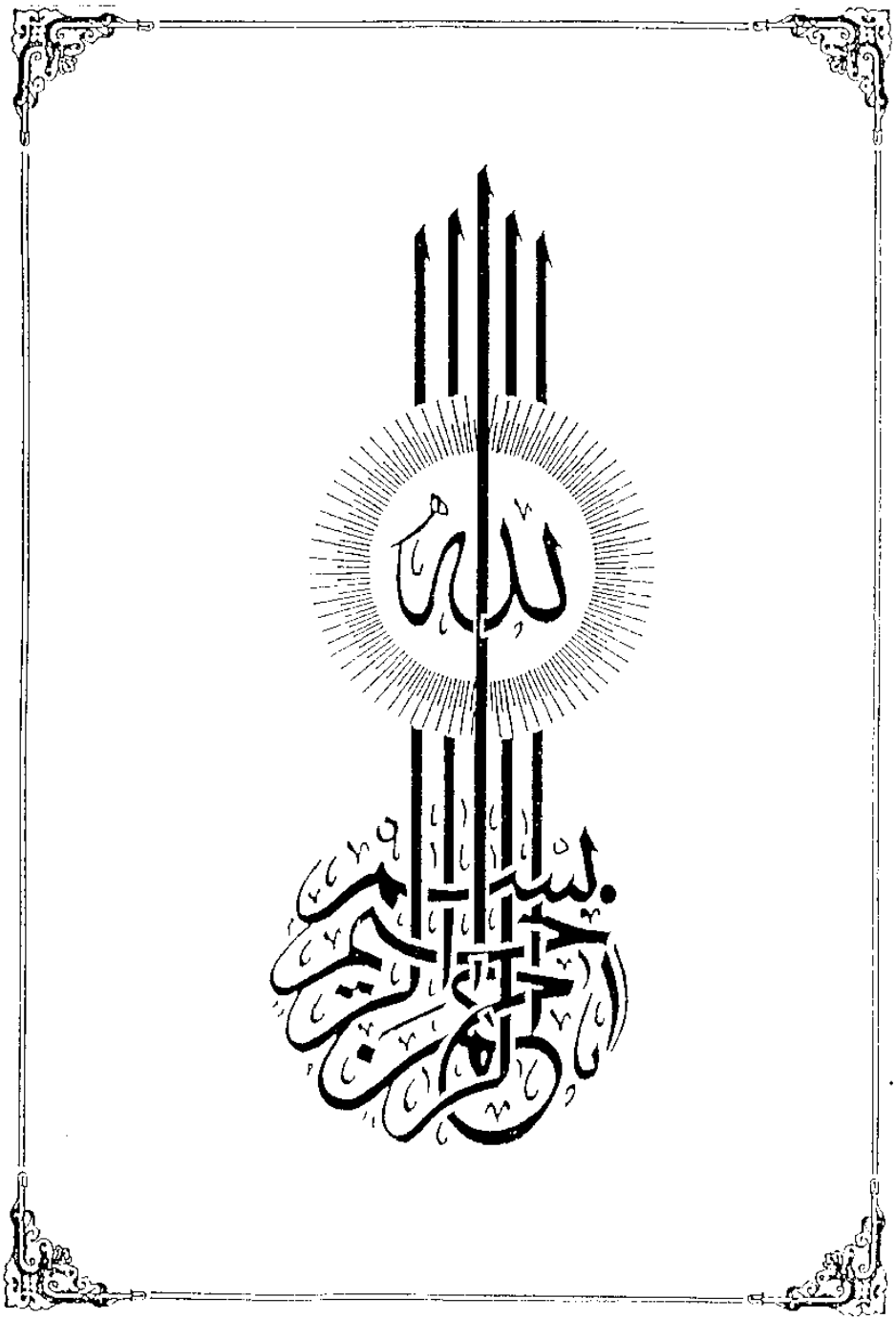

C O N T E N T S

INTRODUCTION

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

Anticholinergic drugs have been used as a part of premedication before induction of anaesthesia, on the account of their antisialagogue actions and their vagolytic effects . They have, also, been shown variously to have some antiemetic effects, they help in prevention of laryngeal spasm, and finally they provide sedation and amnesia (Wyant and Kao, 1974) .

The use of anticholinergic drugs in anaesthesia has also spread, with great help, in counteracting the muscarinic actions of neostigmine at time of reversal of neuromuscular blockade . The most commonly used anticholinergic drugs in anaesthetic practice are atropine and hyoscine , both of them have many disadvantages and untoward effects , such as short duration and the unpredictable antisialagogue action of atropine, and the weak cardiac action of both atropine and hyoscine (Eger , 1962) .

Being tertiary amine compounds with a non-ionized molecule, they cross the blood brain barrier, producing central effects known as central anticholinergic syndrome (Andrews and Belonsky, 1973). From the same aspect, both drugs can also penetrate the placental barrier causing fetal tachycardia and mydriasis (John , 1965) .

Both atropine and hyoscine can produce restlessness, excitement and visual difficulty . Atropine may give rise to dysrhythmias of various types, for example, atrioventricular dissociation, ventricular extrasystoles and even ventricular fibrillation .

Because of the limitations and short comings of these two drugs which were the commonly available anticholinergic premedicants used in anaesthetic practice, studies did not cease in an attempt to meet the requirements of an ideal anticholinergic premedicant drug . In fact, this drug should have the advantages of the already available drugs, and lacking, if possible, their disadvantages . In other words, an ideal anticholinergic drug should be long-acting, with minimal effect on heart rate, that does not cause dysrhythmias, drowsiness, visual disturbances or central effects, and finally with a potent antisialagogue action (Mirakhur , 1979) .

While investigating a number of pyrolidinol derivatives, Franco and Lunsford (1960) found glycopyrrolate to be a potent anticholinergic agent . This drug is a synthetic quaternary ammonium compound which was first used to control gastric acidity (Sun , 1962 and Moellar, 1962).

It was claimed to have a potent antisialagogue action (Mirakhur, Dundee and Jones, 1978), with minimal effects on heart rate (Mirakhur, Clarke, Elliot and Dundee, 1978), beside a long duration of action when given intravenously (Wyant and Kao, 1974) . It was also described to have minimal visual disturbances (Mirakhur, Dundee and Jones, 1978) .

Several recent studies were conducted to investigate the action of glycopyrrolate on cardiovascular system in children (Warran et al., 1981), on heart rate and rhythm in patients with pre-existing cardiac disease (Mostafa et al., 1984) and on post-anaesthetic urinary problems (Orko et al., 1984) .

The comparison of the effect of pre-anaesthetic glycopyrrolate and cimetidine on gastric fluid pH and volume was undertaken by Laxmaiah et al. (1984) . Lately , ocular effects of glycopyrrolate were investigated by Greenan (1985) .

The situation of glycopyrrolate in anaesthetic practice has to be evaluated versus atropine, the standard drug in antimuscarinic field .

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Preparations of belladonna were known to the ancient Hindus , and they have been used by physicians for many centuries . Poisoners of the middle ages frequently used the deadly night - shade plant to cause obscure and often prolonged poisoning; they named it , atropa belladonna . Isolation of atropine in a pure form was carried out by Mein in 1831 .

In 1867 , Bezold and Bloebaum showed that atropine blocked the cardiac effects of vagal stimulation , and five years later , Heidenhoin found that it prevented salivary secretions due to stimulation of chorda tympani. These fundamental observations were quickly followed by many others , and today , there is extensive and secure body of experimental and clinical informations about the pharmacological and clinical aspects of belladonna alkaloids.

In the last years , efforts have been done by chemists to produce drugs , the antimuscarinic properties of which have a different balance of effects on the various organs, for example , to depress salivary secretions without the undesirable antimuscarinic effects on the various organs ,

such as the heart . Many semi-synthetic congeners of belladonna alkaloids , usually quaternary ammonium derivatives , and a larger number of synthetic antimuscarinic compounds with structures often quite unrelated to those of the alkaloids , have been prepared . These have many advantages over the naturally occurring alkaloids and their derivatives , and too many of them have already been marketed for clinical use .

Glycopyrrolate was one of a series of compounds synthesized in the research laboratories of A.H. Robins company . These series included a number of anti-histaminic and anticholinergic compounds , of which was glycopyrrolate (AHR- 504) . It became available first in tablet dosage form in 1961 . The oral dosage form was also available as a combination with phenobarbital under trade name Robinul-PH. A new drug application for the injectable dosage form of glycopyrrolate was submitted for use later on .

The indication for use of the drug was first limited to classical gastrointestinal use for which anticholinergic drugs are indicated . However later , its potential use in anaesthetic practice was then recognized .

The use of anticholinergic drugs in anaesthetic practice is deep rooted and widespread . Atropine the classical representative antagonises all the muscarinic actions of acetylcholine . The drugs of this class may in fact be more appropriately termed " antimuscarinic " drugs , since most show a highly selective antagonism at muscarinic receptors (Eger , 1962 ; Innes and Nickerson , 1975) . Although many drugs with similar properties have been in use from time to time , atropine and hyoscine are still the main stay as revealed by a recent survey (Mirakhur et al. , 1978 a).

Other agents have been studied from the point of view of their gastro-intestinal effects .

A vast number of quaternary compounds , including the quaternary salts of atropine and hyosicne , have been assessed . Scopolamine butylbromide was found to be unreliable antisialagogue , giving rise to excessive increase in heart rate . Methantheline (Banthine) , Propantheline (Probanthine) and oxyphenonium (Antrenyl) have been the most widely studied quaternary drugs . All are more potent and longer lasting than atropine ,but they possess proportionally greater ganglion blocking and

neuro-muscular blocking properties , a relationship shared by other quaternary drugs ; on the credit side , they are relatively longer acting and do not have central or ocular effects . All are poorly absorbed from gastro-intestinal tract. The first two drugs were evaluated clinically and no advantage over atropine could be demonstrated as premedicants and both again produced greater degrees of tachycardia .

More recently another quaternary ammonium compound, glycopyrronium metho-bromide (glycopyrrolate USNF ; Fig.1), has been evaluated for use in anaesthesia , although it had been used in the treatment of peptic ulcer for a number of years .

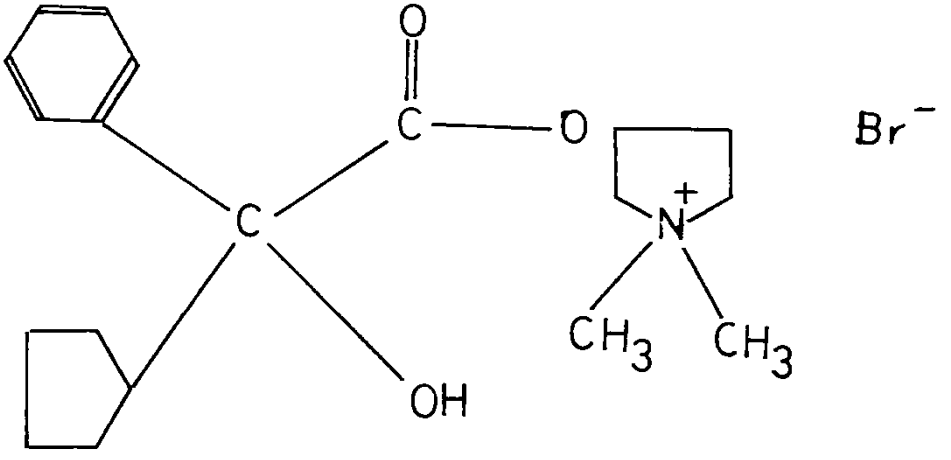

Fig.(1): Structural formula of glycopyrrolate methobromide.

Glycopyrrolate has been shown to posses potent antisialagogue action of long duration . Wyant and Kao (1974) found it to be twice as potent as atropine . However , more accurate assessement showed it to be about four or five times as potent as atropine in its antisialagogue action (Mirakhur , 1978 ; Mirakhur , Dundee and Jones , 1978) .

The penetration of glycopyrrolate across the blood brain and placental barriers is poor and the drug is devoid of undesirable central actions possessed by tertiary compounds . In the clinically useful doses, selectivity of action on salivation and sweating is clearly demonstrated, leaving most other parameters unaffected . As premedicant for minor surgery it showed no advantage over atropine although the drug was less arrhythmogenic than atropine in patients needing intubation (Mirakhur et al.,1978b). Its most consistent superiority over atropine is in terms of cardiovascular stability .

In course of time , this drug will find a place in the anaesthetists' armamentarium . No serious side effects have been reported and the drug could be used with advantage in premedicating elderly patients , with concurrent cardiac disease and in association with neostigmine . Absorption of the drug following oral administration is , however,poor.

The use of anticholinergic drugs for premedicating adults is controversial . Over the past decade , their use has declined considerably . Most anaesthetists still routinely prescribe these drugs , mainly for purpose of reducing secretions , both salivary and bronchial . Although anticholinergic actions were formerly of greater importance , particularly when diethyl ether enjoyed a vogue , the use of non irritant volatile anaesthetic agents , and a smooth unhurried approach to induction of anaesthesia minimize problems induced by excessive secretomotor activity . Moreover, it is well recognized that the dry mouth and paralysis of ocular accomodation produced by atropine are very unpleasant for the patient. In spite of the claimed advantage of anticholinergic premedication in the protection against vagal over-activity, the predominant responses of laryngoscopy, intubation and surgery are sympathetic in origin rather than parasympathetic (Pyrs-Roberts et al., 1971) . There is however , one situation in which there is a good indication for the use of anticholinergic drugs before endotracheal intubation , where repeated doses of suxamethonium are used .

The major anaesthesia-related cause of maternal deaths has consistently been pulmonary aspiration consequent upon vomiting or regurgitation . Vomiting or regurgitation is more