LOCAL ANAESTHETIC DRUGS.

Essay

Submitted
In Partial Fulfilment
for the Mastership
in Anaesthesiology

By

DIYA M. NAFIE
M.B., B.Ch.

Supervised By

Dr. Yousry Roubin
Professor of Anaesthesiology
Ain-Shams University

Dr. Mona Halim
Lecturer of Anaesthesiology
Ain-Shams University

1982

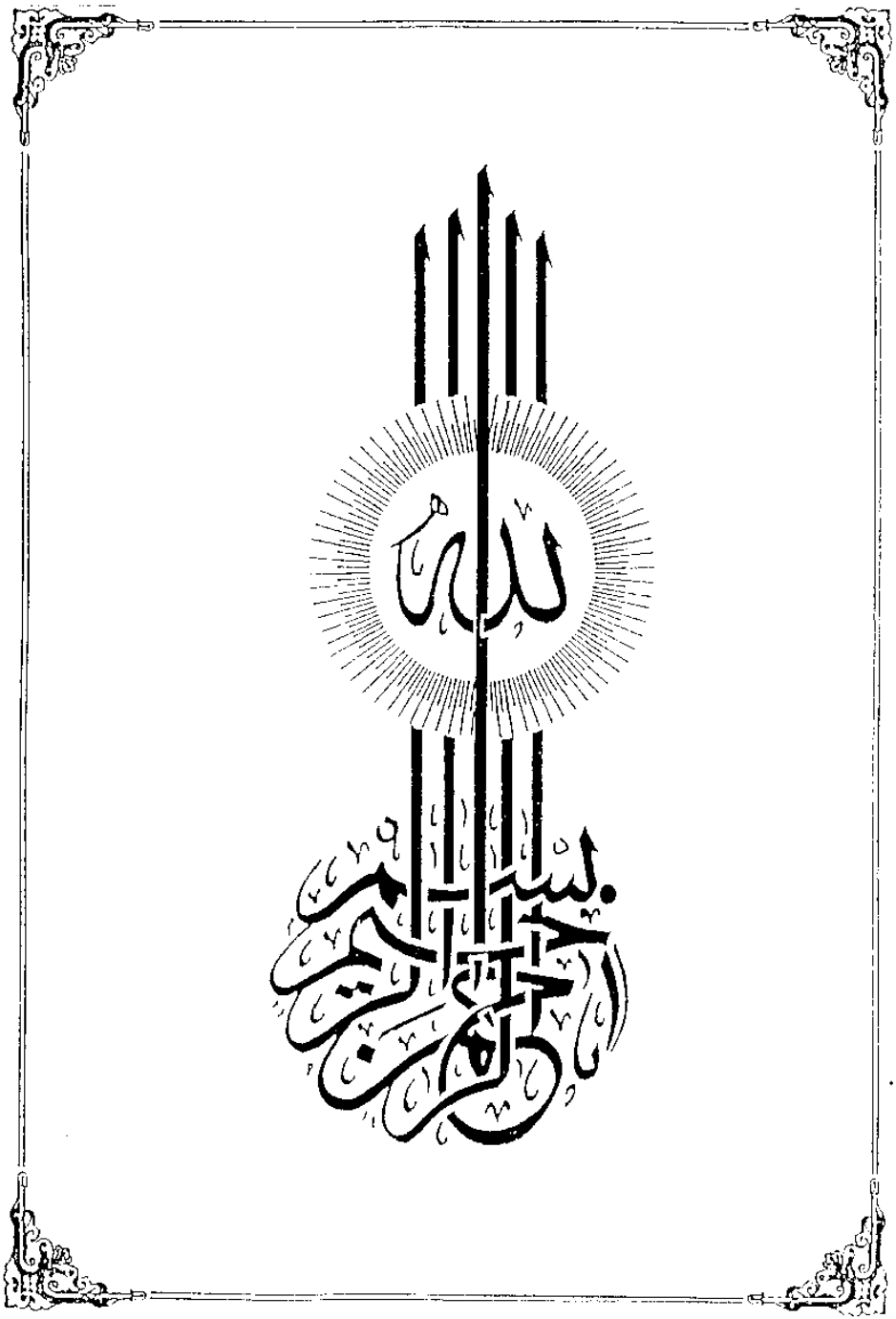
TO :

PARENTS,

WIFE,

&

DAUGHTER.



ACKNOWLEDGEMENT

By all means of gratefulness, I preface my essay to our Head Department of Anaesthesiology Professor Dr. Samir Youakim for his kind supervision and precious instructions.

I wish to express my deepest gratitude to Professor Dr. Yousry Roubin for suggesting and supervising the details of this essay.

My warmest appreciation and heartful thanks go to lecturer Dr. Mona Y. Halim for her kind help and guidance.

Words cannot express how thankful and how grateful I feel towards every member in Anaesthesiology Department, for every moment I have spent with them during this year, for their kind care, teaching and help.

C O N T E N T S

Page

I) HISTORY OF LOCAL ANAESTHETICS 1

II) CHEMISTRY OF LOCAL ANAESTHETICS 2

. Molecular structure of local anaesthetics..... 2

. Structure- activity relationship..... 3

. Behaviour of local anaesthetics in solution. 4

. Desirable characteristics of local anaesthetics.. 5

. Methods of assay of local analgesic drugs..... 6

. Pharmacology of common local anaesthetics..... 8

. Other drugs and agents used for local analgesia..... 14

. Methods of application of local analgesic drugs..... 15

III) MECHANISM OF ACTION 18

. The excitation - conduction process of nerve impulse..... 18

. Proposed mechanisms of action of local anaesthetics..... 20

. Surface- charge theory..... 20

. Membrane-expansion theory 20

. Specific receptor theory... 21

. Interaction between calcium and local anaesthetics..... 24

IV) PHARMAKODYNAMICS AND PHARMACOKINETICS: 25

. Coverings of nerve fibers. 25

. Effect of local anaesthetics on body system..... 26

C O N T E N T S

Page

. Recovery from anaesthetic nerve block.. 28

. Clinical order of nerve block..... 29

V) TOXICITY OF LOCAL ANAESTHETICS 31

. Toxicity due to high blood level..... 31

. Allergic manifestations..... 33

. Methaemoglobinaemia..... 34

. Foetal toxicity..... 34

. Local complications..... 35

. Psychomotor responses..... 35

. Toxicity due to added vasoconstrictors..... 35

. Management of toxic reactions.?..... 35

VI) POTENTIATIO N OF ACTION:.. 41

. Use of vasoconstrictors..... 41

. Alkalanization of solution..... 42

. Use of carbonated compounds..... 42

. Use of hyaluronidase..... 43

. Use of oily solutions and others..... 43

VII) S U M M A R Y 44

VIII) REFERENCES 47

IX) ARABIC SUMMARY . ..... -

HISTORY.

HISTORY OF LOCAL ANAESTHETIC DRUGS

Pain as a result of disease or inflicted as a part of surgery is one of man's most compelling experiences.

Before local anaesthesia came into light, general anaesthesia has been in clinical use for about 38 years. The introduction of cocaine in 1884 by Karl Köller as a local surface anaesthetic for the eye represented an important landmark in starting the history of regional anaesthesia. Thereafter, the field of local anaesthesia expanded quickly to include infilteration, nerve block and later spinal and extradural analgesia.

A number of synthetic local anaesthetics emerged during this period. Because of the recognition of high systemic toxicity and addictive properties of cocaine. Procaine introduced by Einhorn in 1905 proved to be less toxic but less effective and of shorter duration of action.

Numerous related compounds with few advantages over procaine emerged in the years that followed, but the major advance of the period was probably the production of cinchocaine in Germany in the late 1920's.

The next milestone was the introduction of lignocaine in the 1940's: the forerunner of a new generation of chemically related and greatly improved local anaesthetics, aiming to approach the desirable properties of an ideal agent.

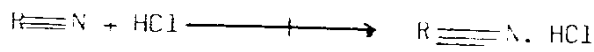
CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIP.

CHEMISTRY OF LOCAL ANAESTHETIC DRUGS AND THEIR STRUCTURE-ACTIVITY RELATIONSHIPS

The most effective local anaesthetics (with few exceptions) are amine derivatives.

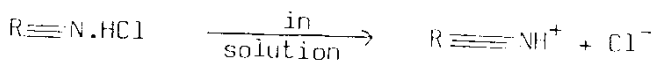
The main features in structure of local anaesthetic drugs is the presence of an aliphatic intermediate chain, which may be an amide (-NH - CO - CH_2-), e.g., Lignocaine or an ester (- C = O - O -) e.g., procaine. To one end of this chain a hydrophilic amino group is attached and to the other end, a lipophilic hydrocarbon residue, usually of aromatic group is attached.

Local anaesthetic drugs are weak bases. They form salts with acids. The salts are water soluble, chemically stable and acidic in solution.



Local anaesthetic base + Hydrochloric acid ⟶ hydrochloric acid salt.

The salts ionise in solution according to the following equation :



Salt $\xrightarrow[\text{solution}]{\text{in}}$ Cation + Anion

In alkaline media, free base is liberated as follows :

Local anaesthetic salt + alkali ⟶ Free base + Salt + Water

Free bases are 4-8 times more potent than the corresponding salts.

Structure - Activity Relationship :

Modification of chemical structure alters the activity and physical properties of the molecule :

- Lengthening of the intermediate chain increases activity up to a maximum after which activity diminishes.
- Increasing the number of carbon atoms on the aromatic or amino group increases activity up to a maximum, after which activity diminishes.
- Addition of butyl group to aromatic end of procaine increases lipid solubility and protein binding.
- Substitution of butyl group for a methyl group of mepivacaine gives bupivacaine.
- Etidocaine is 50 times more lipid soluble, much potent and has greater protein binding than lignocaine because, a propyl group has been substituted for an ethyl group at the amine end. Moreover, ethyl group was added to the intermediate chain.

. Esters are all hydrolysed by plasma pseudocholine estrase. Amides can only be broken down by liver enzymes.

The balance between the hydrophilic amino group and lipophilic hydrocarbon residue is essential for activity. Water solubility is required for transport of the drug to the nerve fiber, while lipid solubility is required for immigration into the axon.

Behaviour of local anaesthetic salts in solution :

The proportion of the non-ionised form of the molecule (base) to the ionised form depends on the pka of the molecule and on the pH of the environment. pka of most local anaesthetic drugs is around 8.

At physiological pH, the concentration of lignocaine base (pka : 7.8) is 10 times that of procaine (pka : 9). Lignocaine has much greater penetrative power than procaine. When the tissues are abnormally alkaline, seperation of the free base is excessive and the base is aggregated into particles suffeciently large to cause precipitation from solution.

If C.S.F. is more alkaline than normal, spinal analgesia may be unsatisfactory or fails due to precipitation of the anaesthetic base from solution.

Local anaesthetic solutions must be kept in alkali free glass and

cleansing of glassware should be meticulous without using soap.

In strong acid medium e.g., pH of pus is 5-6, local analgesic solution will be rendered impotent. Also when epinephrine is added to local analgesic solution, it is acidified and may have a pH as low as 4.0. So they are less effective than non-acidified solutions. Optimum pH for most local anaesthetic drugs is between 7-8.

Desirable characteristics of a local anaesthetic drug :

There can be no such thing as the ideal local anaesthetic drug, because different circumstances require different properties. However certain characteristics are usually desirable. Good penetration tends to promote rapid onset, to eleminate patchy analgesia and to make topical application effective. A local anaesthetic should not produce local irritation. A safe therapeutic ratio is always necessary. For production of prolonged local anaesthesia, long duration of action becomes an advantage. Tachyphylaxis should not occur. Reversibility of action is a must. A local anaesthetic solution should be able to withstand repeated autoclaving and minor pH changes. It should not possess addictive properties It should be chemically and pharmacologically compatible with other drugs used during operation such as adrenaline.

Fiber Type	Function	Fiber Diameter (μm)	Conduction Velocity (m/sec)	Spike Duration (msec)	Absolute Refractory Period (msec)
A α	Proprioception; somatic motor	12–20	70–120	0.4–0.5	0.4–1
β	Touch, pressure	5–12	30–70		
γ	Motor to muscle spindles	3–6	15–30		
δ	Pain, temperature, touch	2–5	12–30		
B	Preganglionic autonomic	< 3	3–15	1.2	1.2
C dorsal root	Pain, reflex responses	0.4–1.2	0.5–2	2	2
sympathetic	Postganglionic sympathetics	0.3–1.3	0.7–2.3	2	2

Classification of nerve fibers

Methods of assay of local analgesic drugs

Most local anaesthetics are fairly satisfactory drugs and improvements gained in the manufacture of new drugs are likely only to be marginal. Therefore careful assessment of a new drug is mandatory if it is to be adopted in preference to a well-tried agent.

Laboratory Investigations in Animals and Man :

Animal studies can be used to compare the acute and cumulative toxicity of drugs by various routes of administration (subcutaneous, intramuscular, intravenous, etc.) and to make a rough assessment of latency, potency and duration of action. The inhibition of the corneal reflex in the rabbit is used to measure surface anaesthetic activity. Inhibition of reaction to pinprick after intracutaneous injection in the guinea-pig can test infiltration analgesia. Conduction anesthesia may be tested by sciatic nerve block in guinea-pig or frog, or by mouse tail root infiltration measuring inhibition of the pain reflex. In man a series of intradermal injections of different concentrations of the new drug, together with a standard drug and a blank (physiological saline) can be given in the forearm. A quantitative assessment of analgesia to pinprick can be made by counting the number of standard pinpricks that are felt as sharp out of a total of, say, five per intradermal weal, at regular intervals. This can give a crude estimate of latency, potency, duration of action and vasoactivity (Morgan and Russell, 1975; Reynolds et al., 1976).

Given a source of willing or needy volunteers, other experimental tests may be carried out in man, such as bilateral ulnar nerve or brachial plexus block. One arm being used as control. Latency, potency, duration and penetration (patchy anaesthesia) of sensory and motor blockade may be tested.