CHAPTER 1

INTRODUCTION

Local anaesthetics have been known and used in medical field for many years. They became one of the important drugs for some clinical treatments, particularly dentistry and surgery. The dental or other surgery could not have achieved its present standards without effective drugs and methods for the blocking of pain. The first development of local anaesthetics can be traced from Niemann's observation in 1860 on anaesthetizing effect of, the then recently purifield alkaloid, cocaine on the sensitivity of the tongue. Cocaine is the alkaloid contained in large amount, 0.6 - 1.8 %, in the leaves of Erythroxylon coca. This was followed by Koller's application of this substance as an analgesia in ophthalmic surgery in 1884, and followed by Halsted's successful attempt at a mandibular block injection on himself in 1885. This last experiment was carried out because of toothache and is the first dental local analgesia. Clinical local analgesia therefore started in dentistry and was practical all over the world, but frequent accidents and threatened to discredit the new discovery (Goodman and Gilman, 1970).

A purposeful search for synthetic substitutes, however, was very successful. The greatest discovery was procaine (NOVOCAINE^R) in 1950 . Even procaine was the first relatively safe and, to a certian degree, effective agent, but chemical investigators still continue research for

other local anaesthetics which have the ideal properties, such as good stability, high anaesthetic or analgesic efficiency and low toxicity etc. Years after years local anaesthetics have been discovered, for instance chloroprocaine, butethamine, dibucaine, hexylcaine, lidocaine, mepivacaine etc. (Goodman and Gilman, 1970). Lidocaine seems to be widely used for local analgesia or anaesthesia because of its good stability and low toxicity in comparison with available synthesized local anaesthetics (Wilson et al., 1977; Bjorn, 1966). Researchers never stop researching, though the efficiency of lidocaine is very satisfactory, but it is necessary for some surgery to use the local anaesthetic with longer duration than lidocaine. In 1957 Af. Ekenstam et al. had succeeded in synthesizing bupivacaine as the latest local anaesthetic (Moore et al, 1970; Ekenstam et al., 1957). Its pharmacological effects as well as clinical trials have been studied and reported (Reynolds et al., 1968; Moore et al., 1970; Reynolds, 1971). Clinically, its potency is about three to four times of lidocaine and mepivacaine (Kuah et al., 1968; Watt et al., 1964; Henn et al., 1966). Like other amide local anaesthetics, bupivacaine is available in the market as a hydrochloride salt, bupivacaine hydrochloride (Marcaine[@], AB Bofors, Nobelkrut, Sweden)

Bupivacaine Hydrochloride BP, BPC

Chemical and Physical Properties

Molecular structure of bupivacaine hydrochloride is
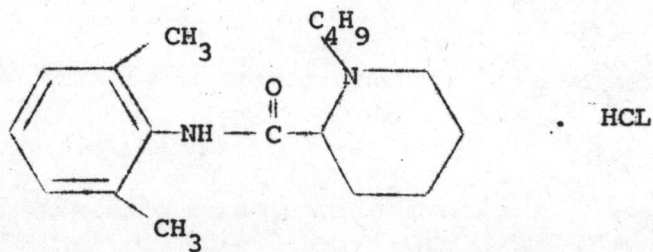
1 - n - butyl - DL - piperidine - 2 - carboxylic acid - 2,

6 - dimethylanilide hydrochloride

Molecular Weight   342.9

Description : A white crystalline powder; odorless, bitter

taste

Solubility : Soluble in 25 parts of water and in 8 parts of

alcohol (95 per cent); slightly soluble in solvent ether and in chloro-

form. pka is 8.1 at room temparature, pH of 0.1 per cent solution is

4.5 to 6.

Melting point : 250° c

Bupivacaine hydrochloride can be steriled by heating in an auto-

clave or by filtration (Wade *et al.*, 1977; Wilson *et al.*, 1977).

Pharmacological Properties

Bupivacaine hydrochloride is a local anaesthetic with an action similar to lidocaine, but on longer duration. Its levo isomer has an even more prolonged action than mepivacaine. Clinically, its prolonged action without nerve damage and tissue toxicity lasts three - four times longer than mepivacaine and lidocaine and 20 to 25 per cent longer than tetracaine. The onset of anaesthesia is comparable to mepivacaine and lidocaine. The occurrence of generalized systemic effect is less than lidocaine or mepivacaine (Wade *et al.*, 1977; Watt *et al.*, 1968; Renynolds, 1971).

Dosage

. Besides being used in local spinal anaesthesia, bupivacaine may be used to produce surface anaesthesia but there are no available preparations. The original manufacturer, Bofors, Sweden, has recommended the infiltration dosage to use for each purpose (Hollman, 1966) (see detail in Table 1) and also suggested that maximum quantity used should not be more than 2 mg per kilogram of body weight to produce a period of four hours anaesthesia.

Undesirable Effects

Like other local anaesthetics, bupivacaine may have quinidine like action (Goodman and Gilman, 1970). The common side effects such as bradycardia, hypotension, headache and respiratory depression, may

occur if minister it over dosage. Clinically, complication is rather rare
if administration is done under the recommended dosage.

Available Preparations

0.25%, 0.5% and 0.75% solution of bupivacaine hydrochloride or
they may be combined with adrenaline or noradrenaline.

TABLE 1

Recommended Dose of Bupivacaine

| Site of blocking	Dose Range (mg.)
Trigeminal block	2.5 - 20
Axillary block, and Epidural Anaesthesia	50 - 150
Intercostal block	15 - 25
Caudal anaesthesia	37.5 - 100
Sympathetic block, lumbar	25 - 100
Stellate block	25 - 50
Epidural block	75 - 100

Lidocaine Hydrochloride USP

Löfgren and his colleagues at the University of Stockholm were awarded by synthesis of lidocaine (Xylocaine®) which appeared to possess intense analgesic action and exceptional stability through wide range pH, Löfgren and Lundquis performed some preliminary tests on themselves, and then finally in 1944, and clinical trials were started by Gordh. Lidocaine was released for general use in 1948 (Ellis and West, 1963).

Physical and Chemical Properties

Lidocaine hydrochloride is one of amide local anaesthetics. The chemical structure is
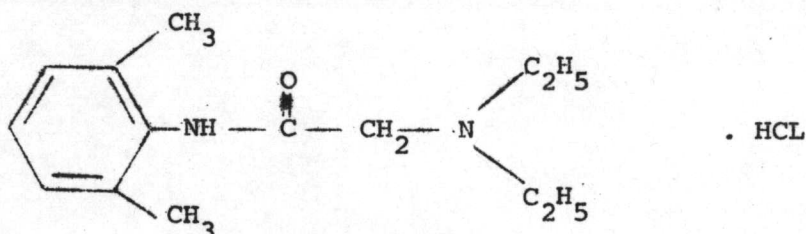
2 - diethylamino - 2, 6 - acetoxylidide monohydrochloride

Description : White crystals with a characteristic oder

Solubility : Freely soluble in water, soluble in alcohol, insoluble in organic solvents and oils. The pKa is 7.9 at room temperature

The free base, an amide, is also a stable solid having the reverse solubility. Lidocaine hydrochloride is very stable can be sterilized by autoclave. For instance, 2% solution buffered at pH 7.3 retained 99.95 per cent of original potency after autoclaving at 115^{c} c for three hours; however the solution became turbid on heating because of changing dissociation constant of water at that temperature and it became clear again if the temperature became cool. Non buffered 2 per cent solution of lidocaine retained 99.98 per cent of the original potency after 84 weeks at room temperatrue (Wade *et al.*, 1977; Wilson *et al.*, 1977).

Dosage

Usual dose range for infiltration up to 60 ml. (100 ml with epinephrine) as a 1 per cent solution; up to 200 mg (400 mg with epinephrine) or 20 ml of a 2 per cent solution. (See detail in Table 11). For external use, topically, up to 250 mg as a 2 - 4 per cent solution or as a 2 per cent jelly, to mucous membranes (Wade *et al*, 1977).

Unesirable Effects

Bradycardia, respiratory depression headache, hypotension
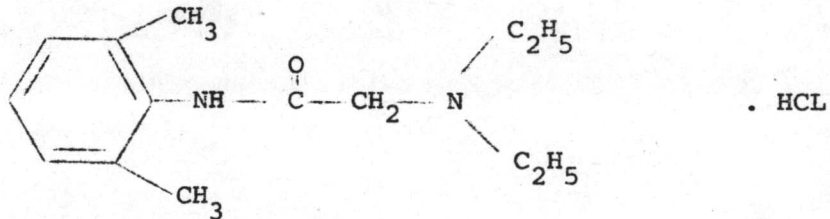
TABLE 11

Reccommended Dose of Lidocaine

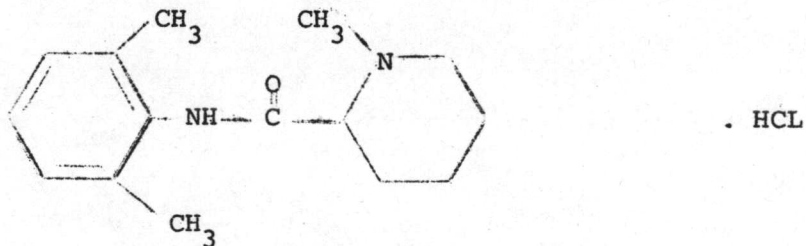| Site of Blocking	Dose Range (mg.)
Dentistry	20 - 100
Digital	20 - 40
Intercostal	30
Paravertebral	30 - 50
Epidural - Thoracic	160 - 200
- Lumbar	300
Caudal - Obstetrical	2200
- Surgical	300
Peripheral nerve (Large)	30 - 75
Pudendal (each side)	100
Spinal	100 - 200
Sympathetic - Stellate ganglion	50
- Lumbar	50 - 100

Avialable Preparation

There are both injectable and topical preparations. The range
of concentration of lidocaine hydrochloride in the injectable form is
I-2 per cent and may be added epinephrine or norepinephrine. Topical
preparations, for external use; are 5 per cent ointment or 4 per cent
jelly (Anderson *et al.*, 1975).

Relative Chemical Structure between Lidocaine Hydrochloride, Bupivacaine Hydrochloride and Mepivacaine Hydrochloride

Lidocaine Hydrochloride (Xylocaine®)

$$
\begin{array}{c}
CH_3 \\
\text{(benzene ring)} \\
CH_3
\end{array}
- NH - \overset{O}{\underset{\|}{C}} - CH_2 - N \begin{array}{c} C_2H_5 \\ C_2H_5 \end{array}
\qquad . \; HCL
$$

Mepivacaine Hydrochloride (Carbacaine®)

$$
\begin{array}{c}
CH_3 \\
\text{(benzene ring)} \\
CH_3
\end{array}
- NH - \overset{O}{\underset{\|}{C}} - \text{(piperidine ring, } N-CH_3 \text{)}
\qquad . \; HCL
$$

Bupivacaine Hydrochloride (Marcaine®)

$$
\begin{array}{c}
CH_3 \\
\text{(benzene ring)} \\
CH_3
\end{array}
- NH - \overset{O}{\underset{\|}{C}} - \text{(piperidine ring, } N-C_4H_9 \text{)}
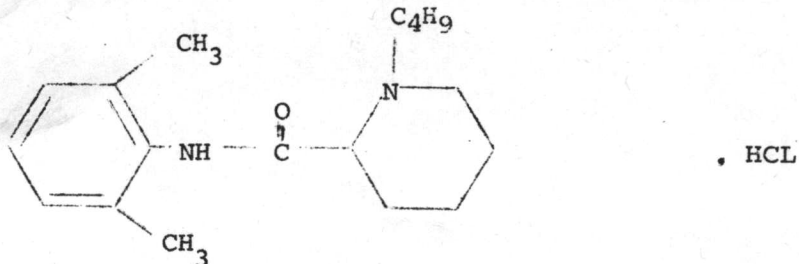\qquad . \; HCL
$$

TABLE 111

Duration of bupivacaine action in lumbar extradural block, double blind study.

| Authors	Definition of duration	local anaesthesia	Duration (min.)
Ekblom and Widman (1966)	First onset of analgesia in any segment to regression in (a) highest segment (definition 3), (b) segment showing earliest recovery	Bupivacaine 0.5% +adrenaline 1 in 200,000	(a) 134 (b) 126
		Prilocaine 2% +adrenaline 1 in 200,000	(a) 94 (b) 90
		Mepivacaine 2% +adrenaline 1 in 200,000	(a) 103 (b) 103
Rubin and Lawson (1968)	Onset (loss of sensation in any segment) to regression of analgesia by at least two segments	Bupivacaine 0.5% +adrenaline 1 in 200,000	288.6
		lidocaine 2% +adrenaline 1 in 200,000	156.6

Mode of Action of Local Anaesthetics

Local anaesthetics can block the impulse conduction along muscle and nerve fibers by inhibiting the increased sodium ion influx to cells. It has been proposed that the resting state of membrane, Na^+-carrier sites are occupied by calcium, the stimuli will cause the removal of this calcium, the carriers are available for carrying Na^+ into cells causing depolarization (Sollman, 1957, Shanes, 1958). The certain mechanism of local anaesthetics have been unknown, but there have been a lot of experiments shown that local anaesthetics can competely act with calcium at cell membranes (Feinstein, 1964)

Chemical Composition and Structure of Cell Menbranes

By analysis of ghosts of red blood cell indicated that cell membranes consisted of lipids and proteins. The ratios of lipids and proteins are varied to each kind of cell membranes. The exact structure of cell membranes has been unknown, but there were the experiments shown that the lipids were arranged in a bimolecular layer, each with hydro-phobic end to the other and hydrophilic turning to the water phases, standing at right angle to the surface, (Lehninger, 1975; Giese, 1963). Moreover, Danielli and Davson also postulated that monolayer of protein might cover, through not necessity completely, on both sides of the membranes. (Giese, 1968; Lehninger, 1979; Davson, 1962) (Fig 1). The lipids are mainly cholesterol and phospholipids, and are bounded toge-ther by protein causing elasticity and strength of the cell membranes (Giese, 1968).

Fig. 1 Arrangement of lipid molecules on water surface.

Polar Head

Non-polar Head

Air

Water

Bimolecular layer
of lipids

Monomolecular layer
of protien
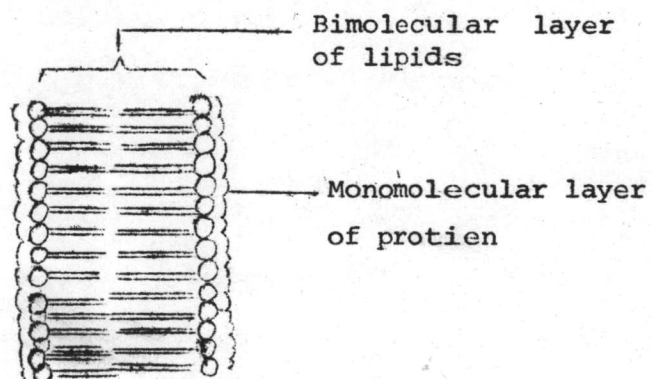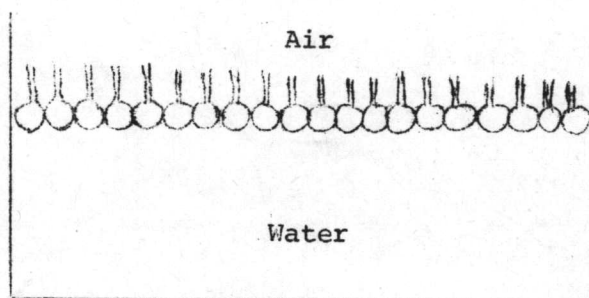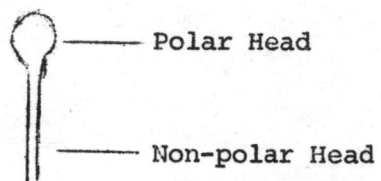
Experimental Model of Lipids

When small amounts of certain slightly soluble oils were placed
on a clear surface of water contained in trough, they would form a layer
one molecular thick called monolayer, monomolecular layer or film, this
phenomenon had shown by Lord Rayleight in 1899. If the area of the film
covering water and the volume of spreading liquid are known, the thick-
ness of the such film or the length of the molecules standing in vertical
position on the surface will be calculated. Furthermore the cross sec-
tional area avaible to the molecules could be easily calculated if the
molecular weight and the density of spreading oil are known (Wade et al.,
1969)

Pockels observed that when the film area or surface area was
reduced by moving the barrier of the trough, the surface tension of
fatty acid was also reduced. He reduced the surface area until the area
per molecule was 20 $\overset{\circ}{A}{}^{2}$ called "Pockels Point". Lord Rayleight, 1899,
also explained that at this point the molecules of the spreading oil
would be contacted and slightly interacted each others. On other words,
the compressive energy will be occurred when film is compressed, the
total free energy as well as surface tension are decreased (Wade et al.,
1969; Langmuir, 1917).

Properties of the film have been quantitatively studied by
Langmuir, Adam, Hankins and others. The film which is spreaded over
the clean surface of substrate (water or aqueous solution) contained
in the trough, can be compressed against a horizontal float by mean of

the movable barrier. The force involved on the film is measured by the apparatus, called "Film Balance" (Fig. 2) with a torsion wire arrangement similar to that employed in ring tensiometer. (Martin *et al* ., 1968). The compressive force per molecule, "Surface Pressure" (¶) is the difference in the surface tension between the pure substrate, r_0, and that with a film covered on it

$$\P \quad = \quad r_0 - r$$

The oil substance under study is dissolved in a volatile solvent and spreaded on the substrate; previously cleaned by means of paraffined or teflon strip. After sperading, the film is permitted for fifteen minutes to completely evaporate volatile solvent before starting measurement. When moving the barrier to various position in the direction of the float, the corresponding film pressure is immediately read from the torsion dial. The film will act as a gas or expanded liquid (expanded film) when it is spreaded over the greatest surface area of the substrate. As the film is being compressed, it acts as a condensed liquid (condensed film) and the film pressure is increased rapidly. If the film is greatly compressed, it will be broken and the molecules will be slipped over each others. The surface pressure will be decreased (Fig. 3)

The surface pressure is plotted against surface area.
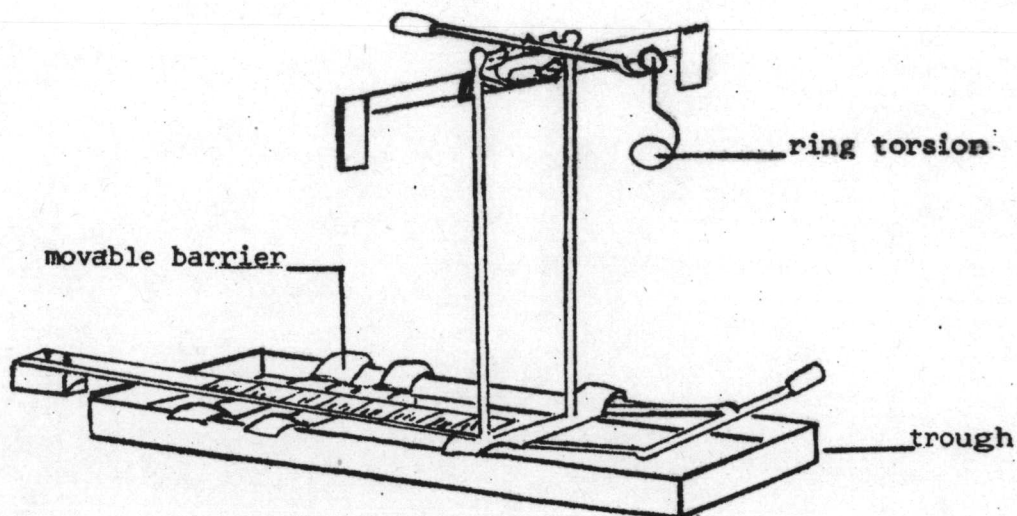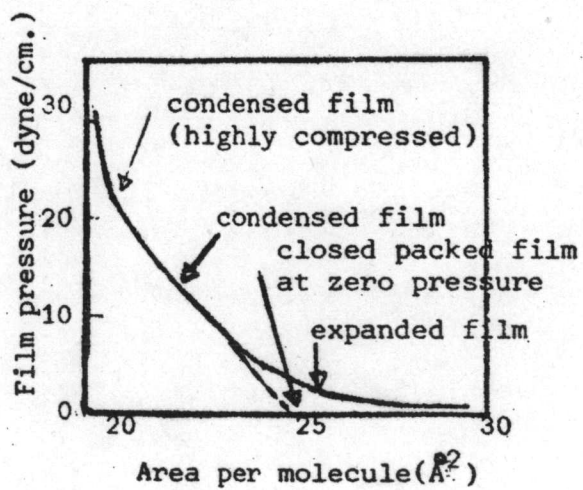
Fig. 2 Langmuir's film balance

Fig. 3 Result of Langmuir's experiment

Monomolecular films have been widely used to elucidate interaction and penetration that occurred between various substance and chemical components of membranes. The mechanism of local anaesthetics and other substances have been studied at the cellular level by the use of monomolecular films (Skou, 1961; Auslander et al., 1975; Weiner and Rosoff, 1972; Sim and Holder, 1974).

Bupivacaine is a new local anaesthetic so there is no report about its penetration and interaction by mean of monomolecular film. Therefore it is the purpose of this investigation to comparatively study the penetration and interaction of two local anaesthetics, lidocaine and bupivacaine in order to suggest bupivacaine dose for topical preparation as its similar action but of longer duration to lidocaine.