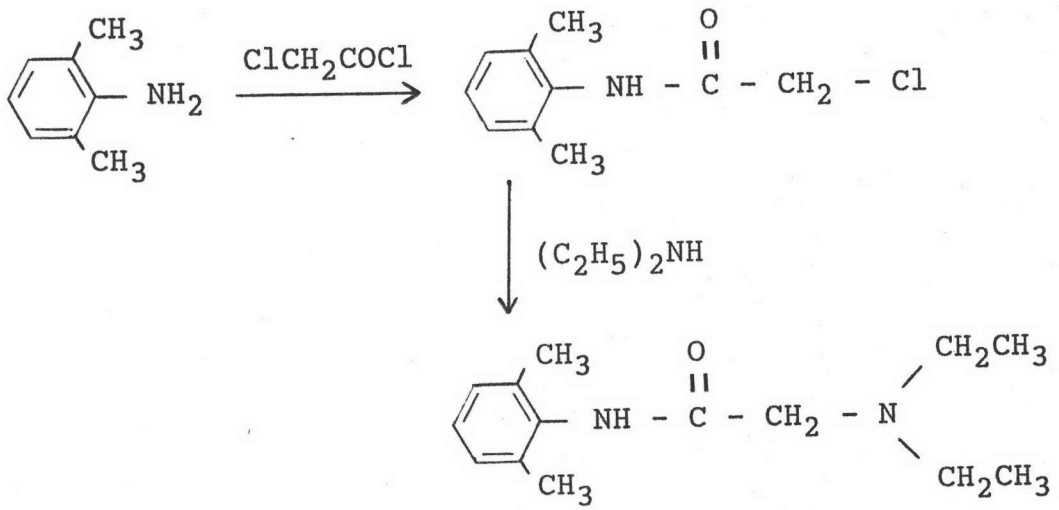
CHAPTER II

HISTORY

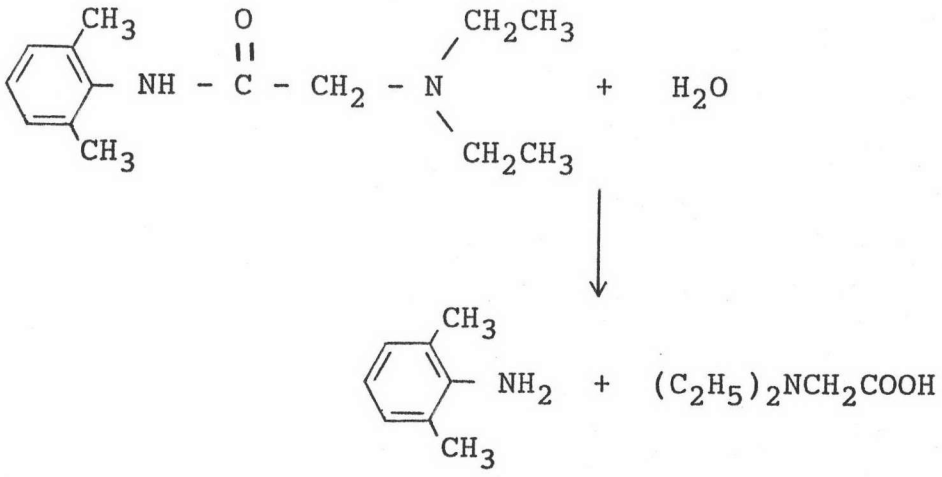
Lidocaine, a synthetic amide drug, was synthesized by a Swedish chemist, Lofgren, in 1943 by acetylation of 2,6-xylidine with chloroacetyl chloride in the presence of a suitable base, and the resulting xylidide reacted with diethylamine (Scheme 1). The product, lidocaine base, was extensively purified and, where appropriated, converted to hydrochloride.



Scheme 1

It appeared that lidocaine in aqueous solution was extremely resistant to heat, acid and alkali, but when decomposition did occur it was by the hydrolysis (Scheme 2). The high stability was due to the sterical hindrance towards attacked on the amido group

exhibited by the two ortho methyl groups. However, lidocaine was more readily hydrolysed by acid than alkali (Groningsson et. al., 1984).



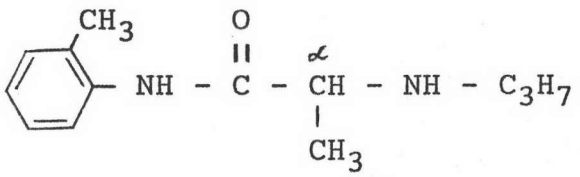
Scheme 2

Antiarrhythmic and local anaesthetic action of lidocaine was due to the sodium channel blocking that resulted in the inhibition of nerve impulse but the true mechanism of action was unknown (Bokesch, Post and Strichartz, 1986; Calahan and Almers, 1979).

In an attempt to develop lidocaine to be more effective and convenient to use, Sarpotdar and Zatz (1986) found that nonionic surfactant such as polysorbate 20 and polysorbate 60 enhanced lidocaine penetration through skin.

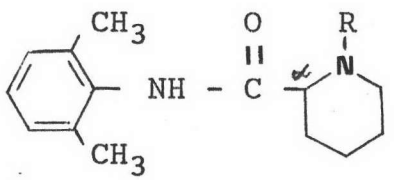
Luben et. al. (1974) introduced anaesthetic patches of 30% lidocaine cream to use in patients for relief of pain before minor operations and intradermal allergen tests. Good effectiveness, adequate duration of action and no side effect were found but the onset of action was not satisfactory.

Transdermal anaesthetic cream (EMLA ^{R}) was launched by Astra for topical anaesthesia of the skin in connection with insertion of intravenous catheters, blood sampling and superficial surgical procedures. The formulation of cream was developed by means of eutectic mixture of local anaesthetics. The eutectic mixture of lidocaine (I) and prilocaine (V) (Broberg and Evers, 1981; Brodin et. al., 1984) was prepared in a ratio of 1 : 1 by weight. The obtained eutectic mixture can be corporated into a cream without first dissolving both drugs in oil, making it possible to attain higher concentration of active drug for each oil droplet than has been previously achieved. The water within the cream enhanced skin penetration by the local anaesthetic (Tregear, 1966). On the basis of these properties, the cream afforded good action (Clarke and Radford, 1986). The content of I and V in EMLA cream was 2.5% (w/w) each which was enough to produce analgesia of the skin. Side reaction was not observed but the onset of action was about an hour (Evers et. al., 1985).



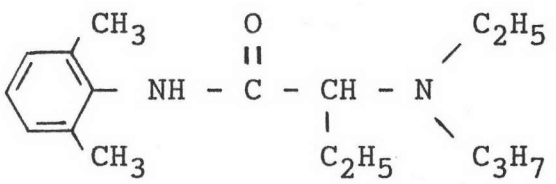
V

In addition to formulation development, chemical modification of lidocaine was also performed to increase drug potency. Concepcion and Covino (1985) reported effect of four analogs, prilocaine (V), mepivacaine (VI), bupivacaine (VII) and etidocaine (VIII) in comparison to that of lidocaine (I).



VI R = CH_3

VII R = C_4H_9

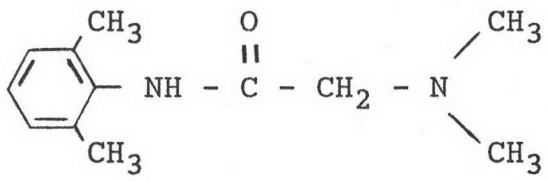


VIII

The chemical structure of prilocaine (V) and mepivacaine (VI) differed from lidocaine (I) by the modification at the amine and the alkyl chain attached to the α-carbon. These structural changes had minor

effect on the physical properties of the compounds so V and VI were nearly similar in biological properties to lidocaine. For bupivacaine (VII) and etidocaine (VIII), it was found that long chain substitution caused great changes in the lipid solubility. The increase in lipid solubility of VII and VIII resulted in their relative higher potency and longer duration of action than that of lidocaine.

Wildsmith et. al. (1987) also studied the relationship between lipid solubility and potency of amide local anaesthetic agents by comparing W-36017 (IX) with etidocaine (VIII) and lidocaine (I). It appeared that VIII which possessed high lipophilicity had the highest potency while IX had the lowest potency. IX had the shortest alkyl chain at the amine that resulted in lower lipophilicity than VIII and I.



IX

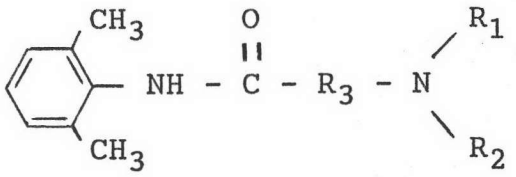
Similar studies were performed by Bokesch, Post and Strichartz (1986) by using lidocaine analogs differed in the length and arrangement of the alkyl groups (R_1, R_2) attached to the tertiary amine portion

of molecule and the added alkyl group (R_3) in the amide-amine linkage (Table 1).

This investigation showed that the increase in the number of carbons at R_1 and R_2 tended to increase drug potency, whereas lengthening of the R_3 chain actually decreased drug potency. Addition of alkyl groups at R_1, R_2 and R_3, not only increased the lipid solubility but also changed other physico-chemical properties of the compound such as pK_a. At the experimental pH of 7.25, analogs with high value of pK_a such as L-30 and W-6603 were in their protonated counterparts which were much less membrane permeant than other analogs with low value of pK_a such as RAD-243. Thus L-30 and W-6603 were less potent than any other analogs. Thus, it was important to take other factors namely pK_a, physiological pH and receptor specificity into account as well as lipid solubility.

In 1984,Loftssen et. al. synthesized lidocaine sulfur analogs in order to test whether the structural requirement for basic or quarternary nitrogen in antiarrhythmic drug was essential. Sulfur was hardly protonated in an ionized form so it was expected that sulfur analog which contained a thio group instead of an amino group would have no activity. The result was contrary to the expectation since two of these analogs, 2-dimethylsulfonic-N-(2,6-dimethylphenyl)

Table 1 : Structure activity relationship of lidocaine analogs.[a]

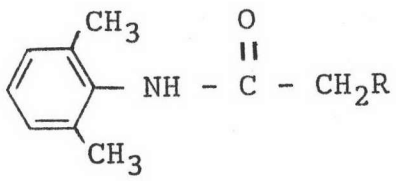


X

Drug	R_1	R_2	R_3	pK_a	Relative Potency
Lidocaine.HCl	C_2H_5	C_2H_5	CH_2	7.7	1.0
RAD-240.HCl	CH_3	C_2H_5	CH_2	7.6	1.20
RAD-241.HCl	CH_3	C_3H_7	CH_2	7.6	1.46
RAD-242.HCl	CH_3	C_5H_{11}	CH_2	7.4	6.66
RAD-243.HCl	CH_3	C_7H_{15}	CH_2	6.9	8.30
RAD-244.HCl	CH_3	C_4H_9	CH_2	7.6	3.18
L-30.HCl	C_2H_5	C_2H_5	C_2H_4	9.0	0.25
L-48.HCl	C_2H_5	C_3H_7	CH_2	8.0	3.20
W-6603.HCl	C_2H_5	C_2H_5	C_3H_6	9.5	0.33

[a]Bokesch, Post and Strichartz, 1986.

acetamide iodide (XI) and 2-ethylthio-N-(2,6-dimethyl-phenyl) acetamide (XII) possessed antiarrhythmic action and lasted much longer than lidocaine. It was possible that antiarrhythmic activity and longer duration of action were due to its active metabolite.



XI R = $-\overset{+}{S}(CH_3)_2 \cdot I^-$

XII R = $-S-C_2H_5$

Permanent cationic quarternary ammonium derivatives of lidocaine, QX-314 (II) and QX-572 (III) were developed by Astra. Connors and Prince (1982) and Frazier, Narahashi and Yamada (1970) showed that both II and III had a mechanism of action via blocking the sodium channel similar to that of tertiary amine local anaesthetic. Charged form of these two derivatives made them difficult to penetrate through nerve membrane. Intracellular injection of II or III allowed selective local anaesthetic action in the neuron being studied only, with negligible effects on the other adjacent neuron. The study was further showed that III had a higher oil in water partition coefficient and its potency was accordingly higher than that of II.

Poor penetration can be overcome by providing an external energy source which facilitate the transport processes. Electrical energy from an electrical current will assist the movement of ions by repulsion between like charges and attraction between opposite charges (Tu and Allen, 1989). This unique drug delivery system by aid of electrical current was called iontophoresis. Siddiqui, Roberist and Polack (1985) studied the effect of iontophoresis on the permeation of lidocaine hydrochloride in various pH of vehicle. The result was that much of lidocaine hydrochloride was in ionized form at pH below 8. Hence, at low pH, iontophoresis had a great effect on membrane penetration of lidocaine and higher skin penetration occurred.

Green, Guy and Hadgraft (1988) studied the effect of fatty acids, namely oleic acid and lauric acid on the transport of drugs. Skin permeation of the cationic drug was enhanced **in vitro** and **in vivo** An increase in lipophilicity through ion-pair of carboxylate ion of the acid and cationic drug was accounted for the enhancement.

Prodrug of lidocaine via ion-pair approach was developed here. Syntheses of organic salts of lidocaine (IV), determination of skin permeability and apparent partition coefficient were reported in this thesis.