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3-Hydroxy-2-naphthoates of Lidocaine, Mepivacaine, and Bupivacaine and Their Dissolution Characteristics[1]

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3-Hydroxy-2-naphthoates of lidocaine (I), mepivacine (II), and bupivacaine (III) were prepared as a potential means of prolonging the action of these local anesthetic amines through their sparingly soluble salt forms. The molar ratio of the local anesthetic base to 3-hydroxy-2-naphthoic acid (IV) was 1:1 and the hydroxynaphthoates contained no solvent of crystallization. Dissolution characteristics of these hydroxynaphthoates were determined in water and 0.7 M phosphate buffer, pH 7.46 at 37° and compared with those of the corresponding bases. The hydroxynaphthoates of I and II exhibited lower equilibrium solubilities but their dissolution rates were greater than the corresponding bases in these media. As for III, the hydroxynaphthoate showed higher solubility than the base in water.

Keywords——lidocaine 3-hydroxy-2-naphthoate; mepivacaine 3-hydroxy-2-naphthoate; bupivacaine 3-hydroxy-2-naphthoate; sparingly soluble salts; dissolution study; solubility; local anesthetic salts; long-acting local anesthetics

Long-acting local anesthetic agents are particularly desirable in the management of postoperative pain, in the relief of severe pain associated with terminal states of patients suffering from cancer, and for various nerve blocks carried out in pain clinics. Approach so far taken for prolonging the duration of local anesthesia has been primarily confined to the area of chemical modification of a compound known to have local anesthetic action.[3,4] An anilide type local anesthetic bupivacaine[5] is one of the most long-acting local anesthetics in wide clinical use, and its duration of action is at most 6 to 8 hr. More recently developed etidocaine which is a simple derivative of lidocaine is claimed to have its duration of action approximately of the order of that of bupivacaine.[6] When longer duration of action is required, continuous application of these so called long-acting anesthetics through a catheter left at site is a usual procedure. However, this method demands hospitalization of patients.

Most of local anesthetics have been in the form of hydrochloride salts and surprisingly little effort has been made to prolong the action of these drug through prodrug approach,[7] including complexation, sparingly soluble salts. One of the attempts in this direction is that of Weiner and Zilkha[8] who covalently attached procaine to polyethylene glycol through carbamide linkages and demonstrated the prolonged action of the polyethylene glycol deriva-

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3) J. Büchi and X. Perlia, in "Drug Design," Vol. III, ed. by E. J. Ariëns, Academic Press, New York, 1972, p. 243.
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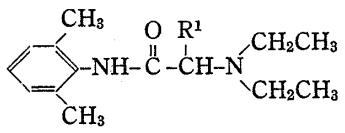
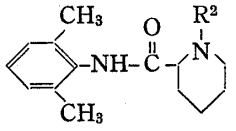
tive over procaine. Another is the preparation of methylsilyl derivatives of lidocaine as lidocaine prodrugs.[9] An implantable device has been studied for controlled release of lidocaine through a silicone membrane.[10] As one of the means of prolonging the duration of action of presently marketed local anesthetic bases we have looked into the possibility of using their sparingly soluble organic acid salts, thereby making the drug slowly available at the injection site. Well-known examples of sparingly soluble salts developed for this purpose are benzathine and procaine penicillin[11] for parenteral use. This approach has been successfully extended to other classes of therapeutic agents such as antimaterials,[12] narcotic antagonists,[13] antibiotics,[14] antidepressants,[15] *etc.*



$R^1=H$: lidocaine (I)
$R^1=C_2H_5$: etidocaine



$R^2=CH_3$: mepivacaine (II)
$R^2=n$-Bu: bupivacaine (III)

Various organic acid salts of lidocaine (I) have been reported, which include the picrate and styphnate,[16] the pamoate,[17] the alkylsulfates,[18] the alkylsulfonates,[19,20] the arylsulfonates,[21] the disulfimidides,[22] *etc.* But, these were prepared not from the standpoint of sparingly soluble salts for prolonging the action of I. For mepivacaine (II) and bupivacaine (III) very few organic acid salts have been reported in the literature. We have prepared 3-hydroxy-2-naphthoates of these three local anesthetics, *i.e.* lidocaine 3-hydroxy-2-naphthoate (V), mepivacaine 3-hydroxy-2-naphthoate (VI), and bupivacaine 3-hydroxy-2-naphthoate (VII) for the purpose of sustained release and compared their dissolution characteristics with those of the corresponding bases. Since 3-hydroxy-2-naphthoic acid (IV) is comparatively nontoxic (LD_{50} 800 mg/kg in mice[23]), and is included in the list of acid components of FDA-approved commercially available salts,[24] the 3-hydroxy-2-naphthoates of these local anesthetic bases may be of clinical value.

Experimental

Materials——The anesthetic bases or their hydrochlorides were supplied by courtesy of the following pharmaceutical companies, I from Fujisawa Pharmaceutical Co., II and III from Yoshitomi Pharmaceutical Inds. Cyclizine hydrochloride was supplied by Burroughs Wellcome Co., and 3-hydroxy-2-naphthoic acid (IV) was purchased from Wako Pure Chemicals Inds. All reagents and solvents used were of reagent grade or chromatographic grade.

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Instrumentation——All melting points were determined on a Shimadzu type MM-2 micromelting point determination apparatus, and the values were uncorrected. Proton magnetic resonance spectra were obtained on a Jeol model PMX 60 NMR spectrometer using TMS as internal reference. Infrared spectra were obtained with a Jasco model IRA-2 spectrophotometer and UV spectra with a Shimadzu UV-300 spectrophotometer. Gas chromatographic assay of I was carried out on a Shimadzu GC-4A gas chromatograph equipped with a hydrogen flame ionization detector using dual glass columns packed with 10% polyethylene glycol 20 M plus 5% KOH coated onto 80—100 mesh Chromosorb W, AW, DMCS.[25] The temperatures of the assay condition were 214.5° in the columns, 235±2° in the injector, and 248±1° in the detector. The flow rate of the carrier gas (He) was 62.2 ml/min and those of H_2 and air were adjusted to give maximum recorder response. The measurements of pH were carried out using a Corning digital pH meter model 112.

Preparation of Lidocaine 3-Hydroxy-2-naphthoate (V)——3-Hydroxy-2-naphthoic acid (IV, 4 g) was dissolved in 120 ml H_2O with about 2 ml 5 N NaOH. The pH of this solution was adjusted to about 6 with 0.1 N HCl. Lidocaine (I, 5 g) was dissolved in about 50 ml H_2O with addition of conc. HCl. The pH of this solution was about 5. The lidocaine solution was added dropwise, under stirring, to the hydroxynaphthoate solution. A sticky mass formed immediately, which solidified upon further stirring. Repeated recrystallization from H_2O–EtOH gave V, mp 133—134°. *Anal.* Calcd. for $C_{25}H_{30}N_2O_4$: C, 71.06; H, 7.16; N, 6.63. Found: C, 70.92; H, 7.14; N, 6.51. Alternatively, 5 g of I was dissolved in 50 ml acetone and 4 g of IV was added under stirring. The precipitate was collected and recrystallized first from acetone-ether. and then from acetone to give V, mp 134—135°. *Anal.* Calcd. for $C_{25}H_{30}N_2O_4$: C, 71.06; H, 7.16; N, 6.63. Found: C, 71.38; H, 7.24; N, 6.55. IR ν_{max}^{KBr} cm^{-1}: 1687 (amide), 1645 (carboxylate). UV λ_{max}^{MeOH} nm (log ε): 353 (3.37), 293 (3.45), 282 (3.73), 271 (3.72). NMR ($CDCl_3$) δ: 1.33 (6H, t, J=7 Hz, N–$CH_2\underline{CH_3}$), 3.18 (4H, q, J=7 Hz, N–$C\underline{H_2}CH_3$), 3.92 (2H, s, $COCH_2N$), 10.08 (1H, br., NH), 2.23 (6H, s, aromatic-CH_3), 7.12 (3H, s, aromatic-H), 8.58 (1H, s, IV-αH), ~12.5 (2H, s, COOH, OH).

Preparation of Mepivacaine 3-Hydroxy-2-naphthoate (VI)——The salt VI was similarly prepared by by mixing equimolar amounts of II and IV in acetone. Recrystallization from acetone–ethanol gave pale yellow crystals, mp 174—179° (subl.>155°). *Anal.* Calcd. for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.69; H, 6.96; N, 6.45. IR ν_{max}^{KBr} cm^{-1}: 1677 (amide), 1640 (carboxylate). UV λ_{max}^{MeOH} nm (log ε): 353 (3.38), 293 (3.45), 282 (3.74), 271 (3.73). NMR ($CDCl_3$) δ: 2.98 (3H, s, N–CH_3), 2.28 (6H, s, aromatic-CH_3), 7.10 (3H, s, aromatic-H), 10.32 (1H, br., CONH), 8.50 (1H, s, IV-αH), ~12 (2H, br., COOH, OH).

Preparation of Bupivacaine 3-Hydroxy-2-naphthoate (VII)——The salt VII was similarly prepared by mixing equimolar amounts of III and IV in acetone. Water was added to the acetone solution so that the final solution became 20% water in acetone and the solution was set aside for crystallization. Four days were allowed for crystallization. The crystals were collected and washed with a little ethanol to give VII, mp 165—168°. *Anal.* Calcd. for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 73.31; H, 7.70; N, 5.82. IR ν_{max}^{KBr} cm^{-1}: 1684 (amide), 1639 (carboxylate). UV λ_{max}^{MeOH} nm (log ε): 353 (3.38), 293 (3.44), 282 (3.73), 271 (3.73). NMR ($CDCl_3$) δ: 2.25 (6H, s, aromatic-CH_3), 7.03 (3H, s, aromatic-H), 10.58 (1H, br., CONH), 8.42 (1H, s, IV-αH), ~12 (2H, br., COOH, OH).

Dissolution Study——Drugs used for dissolution study were triturated with a mortar and pestle and examined under a microscope so that their particle size did not appreciably differ among the lidocaine and mepivacaine series. Dissolution study was carried out in a 50 ml capacity Erlenmyer flask, jacketed and equipped with a glass stopper. Water was circulated around the flask in order to maintain the temperature of the content of the flask at 37.0±0.1°. Dissolution medium (20 ml, either water or pH 7.46 phosphate buffer) was placed in the flask and agitated by means of a magnet bar (2×0.7 cm) at a constant speed of 165 rpm. When temperature equilibrium was attained, approximately 0.1 to 0.15 g of drug was added to start the experiment. Samples were taken at appropriate time intervals and assayed for the dissolved drug spectrophotometrically at 263 nm for the anesthetic bases and at 350 nm for the salts utilizing the absorption maximum of IV under the condition of assay. In the dissolution study of V the samples were simultaneously assayed by GLC for the dissolved I as well, after the following extraction procedure. One milliliter of cyclizine HCl solution (internal standard) was placed in a 15 ml glass-stoppered test tube together with an aliquot of sample, and 0.5 ml of 0.5 N NaOH. Enough water was added so that the total volume of the aqueous phase was maintained to be 2.5 ml in all runs. Water-saturated freshly distilled ether (2 ml) was added and the contents of the test tube was shaken for 2 min. The ether layer (3 μl) was directly injected into the column. The concentration of I was determined from the peak height ratio of I to cyclizine utilizing a previously established calibration curve.

Results and Discussion

In Fig. 1 the NMR spectrum of V in $CDCl_3$ is compared with that of I and most of the protons are assigned as indicated in Experimental. The signal at δ 8.58 is assigned to the

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α-proton to the carboxyl group in IV. Since this signal is observable in the spectrum of IV[26] in DMSO-d_6 as well as in that of pamoic acid[26] which lacks α-proton to hydroxyl group. The signal at δ 12.5 is attributable to the two protons of the carboxyl and hydroxyl group as a result of a rapid exchange of the protons catalyzed by the base (I). Comparison of the signals in I and V reveals that the protons of the 3 methylene groups next to the tertiary nitrogen in V and the amide proton are shifted to lower fields, whereas the signals due to other protons do not significantly differ. These observations indicate that a strong interaction of the carboxyl proton with the tertiary nitrogen in $CDCl_3$. In addition to the NMR spectra, the results of elemental analyses, analyses for the acid component by UV spectrophotometry at 350 nm, analyses for the base by GLC (carried out only for V) support that V, VI, and VII contain the acid and base component in 1: 1 molar ratio without water or solvent molecules of crystallization.

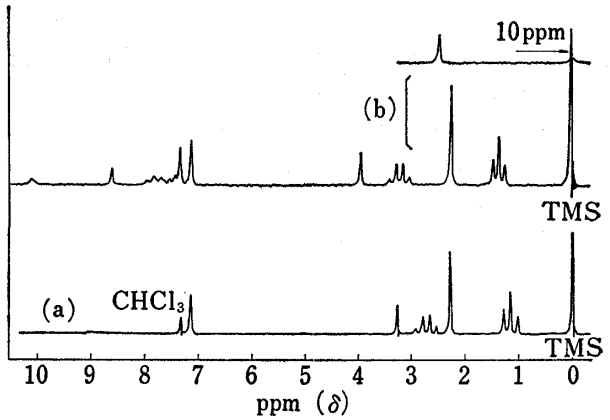

Fig. 1. NMR Spectra of (a) Lidocaine (I), (b) Lidocaine 3-Hydroxy-2-naphthoate (V)

Because these salts have been intended for the slow release of the anesthetic bases at injection site and the availability is primarily governed by the dissolution rate rather than equilibrium solubility[27] the dissolution characteristics of these salts in water and 0.7 M phosphate buffer, pH 7.46, have been determined and compared with those of corresponding bases. A rather unusually high concentration of phosphate buffer was employed since the solubilities of these bases varied greatly among themselves. With I, even 0.7 M phosphate buffer did not have sufficient buffering capacity (the pH at the end of the dissolution study was altered to about 7.5 from 7.46).

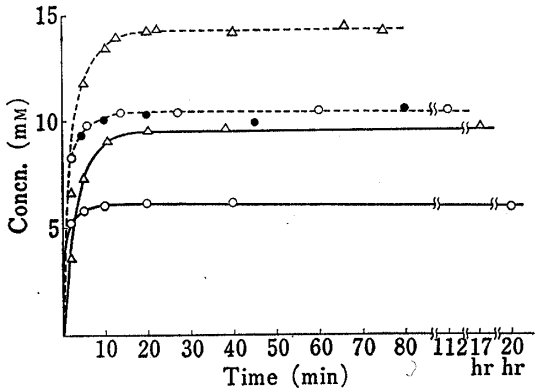

Fig. 2. Dissolution Characteristics of Lidocaine (I) and Its 3-Hydroxy-2-naphthoate (V) at 37°

---△---, I in water; ---○---, V in water; ---●---, V in water (GLC determination of the base); —△—, I in 0.7 M phosphate buffer, pH 7.46; —○—, V in 0.7 M phosphate buffer, pH 7.46.

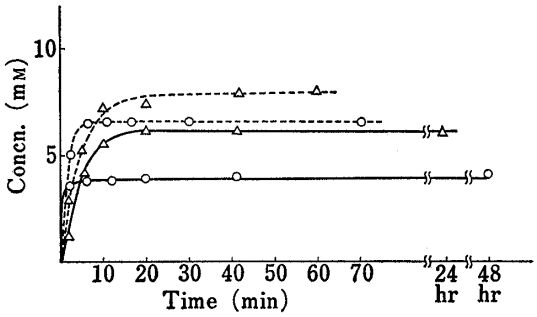

Fig. 3. Dissolution Characteristics of Mepivacaine (II) and Its 3-Hydroxy-2-naphthoate (VI) at 37°

---△---, II in water; ---○---, VI in water; —△—, II in 0.7 M phosphate buffer, pH 7.46; —○—, VI in 0.7 M phosphate buffer, pH 7.46.

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Figures 2 and 3 show the dissolution characteristics of the lidocaine and mepivacaine series, respectively. In the dissolution experiment of V in water, the samples were assayed by GLC for the base as well as by the UV spectrophotometric method for the acid component. Good agreement in these values (Fig. 2) indicates that for every molecule of IV one molecule of I is present in the solution phase. Thus, for other systems samples were assayed for the acid moiety alone. Since the dissolution of VII in 0.7 M phophate buffer showed an anomalous behavior, the dissolution characteristics of bupivacaine series will be reported separately and only equilibrium solubilities for some bupicavaine system are presented in Table I together

Table I. Solubilities (mM)[a] and t_{90} (min)[b] of the Local Anesthetic Bases and Their 3-Hydroxy-2-naphthoates at 37°

		Water		0.7M phosphate buffer pH 7.46	
		Base	Salt	Base	Salt
Lidocaine	Solubility	14.4 ±0.1	10.4 ±0.1	9.86 ±0.14[c]	6.04±0.11
	t_{90}	7.5	4.5	9.5	3.5
Mepivacaine	Solubility	7.97 ±0.04	6.46±0.03	6.05 ±0.03	3.95±0.05
	t_{90}	12.3	3.0	9.5	1.5
Bupivacaine	Solubility	0.417±0.001	1.23±0.02	0.300±0.005	—
	t_{90}	—	—	—	—

a) Average of 2 to 5 determinations ± standard error.
b) Time required to attain 90% of the equilibrium solubility.
c) The pH of the saturated solution was about 7.5.

with the equilibrium solubilities of lidocaine and mepivacaine series studied. In Table I the dissolution rates are tabulated, for convenience, by the time required to attain 90% of the equilibrium solubility. It can be seen from this table that the equilibrium solubilities of V and VI are smaller than those of the corresponding bases in both media, but that the dissolution rates of the salts are greater than those of the corresponding bases. In comparing the dissolution rates of these compounds, the least well controlled factor was the size of the crystals.

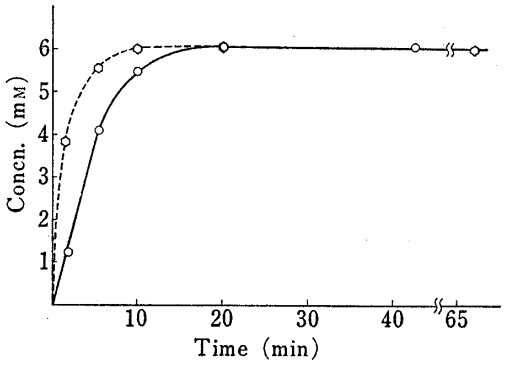

Fig. 4. Effect of Particle Size on the Dissolution of Mepivacaine (II) at 37° in 0.7 M Phosphate Buffer, pH 7.46

---○---, original crystals; —○—, smaller crystals.

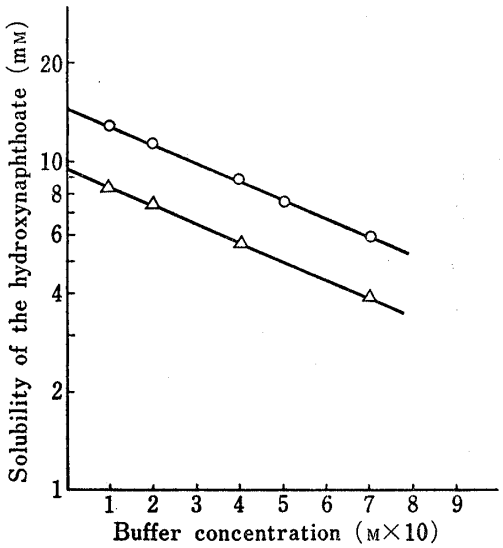

Fig. 5. Effect of Phosphate Buffer Concentration on the Solubilities of Lidocaine 3-Hydroxy-2-naphthoate (V) and Mepivacaine 3-Hydroxy-2-naphthoate (VI) at 37°, pH 7.46

—○—, V; —△—, VI.

Therefore, the effect of particle size reduction was investigated and the result of II is presented in Fig. 4. Contrary to expectation, the reduction in particle size of II decreased the rate of dissolution. This is considered to be due to the hydrophobicity of the base as the base showed a tendency to float on the surface of the dissolution medium. Thus, increase in the surface area by particle size reduction does not afford an increase in dissolution rate, since adsorption of air by the hydrophobic surface reduces the effective surface area for dissolution. The same observation was made by Finholt, *et al.*[28] with phenobarbital, acetylsalicylic acid, and phenacetin. With VI, on the other hand, particle size reduction in the range roughly comparable to II resulted increased dissolution rate. Therefore, the hydroxynaphthoates are considered to be less hydrophobic in nature and give higher dissolution rates than the corresponding bases.

A soluble pharmaceutical salt usually exhibits a greater dissolution rate than the corresponding acid or base at an equal pH.[24] Although these 3-hydroxy-2-naphthoates are less soluble than the corresponding bases, they exhibited greater dissolution rates. The greater dissolution rates together with the lower solubilities of these salts than the corresponding bases would make these salts particularly suitable for sustained action from the physicochemical standpoint, since the loss at the injection site would be expected to be quickly compensated for and the effective therapeutic level would be maintained. A preliminary pharmacological evaluation of V in guinea pigs by the method of Bulbring and Wajda[29] indicated its saturated solution to exhibit the anesthetic activity.

The effect of buffer concentration of the solubilities of V and VI was investigated at 37° and the results shown in Fig. 5. The empirical Setschenow equation [30] to express the extent of salt effect on the solubility of nonelectrolyte was found to adequetly express the effect of buffer concentration on the solubilities of these hydroxynaphthoates; *i.e.*

$$\log \frac{S_0}{S} = kC$$

where S_0 is the solubility of the electrolyte (the hydroxynaphthoates) in the absence of buffer salts and S is the solubility of the electrolyte in molar concentration C of the buffer, and k is the overall salting-out constant. The salting-out constants of V and VI by the buffer were obtained from the slopes of the plots of log S *vs.* C to be 0.54 and 0.56, respectively. Lin, *et al.*[31] have also observed that the Setschenow equation was applicable to an amine hydrochloride.

Unlike V and VI, VII showed a greater solubility in water than the corresponding base. Since the solubilities of these anesthetic bases are not greatly different from those of the hydroxynaphthoates, the advantages of the salts over the bases in parenteral suspensions have to be evaluated *in vivo*.

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