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A New Liquid Membrane Electrode for Determination of Lidocaine in Local Anaesthetic Formulations*

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ABSTRACT. A new lidocaine responsive liquid membrane electrode based on the use of lidocaine reineckate ion pair complex in nitrobenzene solvent is developed. The electrode displays a linear response for $10^{-2} - 10^{-5}$M lidocaine over the pH range of 3–6.5. The response time varies from 35 sec. to one min. depending on the lidocaine concentration. The life span of the electrode is at least 1 month. Excipients and diluents commonly used in local anaesthetic formulations do not interfere. Determination of lidocaine in some pharmaceutical preparations gives results with an average recovery of 99% of the nominal values and a mean standard deviation of 1.7% which compare favourably with those obtained by the United States Pharmacopoeia method.

Lidocaine (lignocaine or xylocaine) is a non ester type of local anaesthetic commonly used in dentistry and locally applied to mucous membranes. Methods used for its determination are very limited. A procedure based on extraction, addition of acid and back titration with alkali has been recommended by the United States Pharmacopoeia (USP XVII 1963). This method is not selective and gives results highly influenced by the presence of many basic substances. Lidocaine has also been spectrophotometrically determined by methods involving a reaction with copper(II) in alkaline medium (DeFreitas 1977). Bromocresol green reacts with lidocaine at pH 4.2 to give a colored complex extractable in chloroform. The complex is measurable either directly at 420 nm or at 625 nm after treatment with tetrabutylammonium hydroxide (Girgis and Mahmoud 1979). Photometric titration with chromogenic reagents has also been proposed (Andersson *et al.* 1978 and Abou-Ouf *et al.* 1979). These methods, however, suffer from severe interferences by many types of anaesthetics and amines.

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Other reports on the determination of lidocaine advocate procedures involving gas-liquid chromatography (Palermo and Lundberg 1978), high performance liquid chromatography (Smith and Nuessle 1981, Waraszkiewcz *et al.* 1981), capillary isotachophoresis (Klein 1982) and enzyme immunoassay (Walberg 1978). In the present work, a new liquid membrane electrode has been developed and satisfactorily used for determination of lidocaine in various anaesthetic formulations. We previously demonstrated the advantages of using such simple and selective monitoring systems for determination of some alkaloids and related drugs (Hassan and Elsayes 1979, Ma and Hassan 1982, Hassan and Tadros 1984, Hassan *et al.* 1985, and Hassan and Rechnitz 1985).

Experimental

Reagents

All solutions were prepared with deionized twice-distilled water and analytical reagent grade substances, unless otherwise stated. Lidocaine hydrochloride monohydrate and ammonium reineckate were obtained from Sigma Chemical Co. (St. Louis, MO). A 10^{-2}M lidocaine stock solution was prepared by dissolving 2.89 g of lidocaine hydrochloride monohydrate in one liter of water. Dilute solutions (10^{-3} – 10^{-5}M) were prepared by appropriate dilutions. Pharmaceutical preparations containing lidocaine were obtained from Astra Pharmaceutical Co., Sweden.

Apparatus

All potentiometric measurements were carried out at 20-27°C and pH 3.0-6.5 using Orion Microprocessor Ionalyzer (Model 901) and lidocaine liquid membrane electrode in conjunction with Orion Ag/AgC1 double junction reference electrode (Model 90-02) with 10% KNO_3 in the outer compartment. The pH adjustment was conducted with an Orion combined glass-calomel electrode (Model 91-02).

Procedure

The lidocaine liquid membrane electrode was prepared as follows: A 20 ml aliquot of aqueous 10^{-1}M lidocaine hydrochloride solution was mixed with a 50 ml aliquot of aqueous 10^{-1}M ammonium reineckate solution. The pink precipitate was filtered with a G-3 sintered glass crucible, washed with deionized water, dried at 100°C for one hour and ground to fine powder. A portion of the precipitate (~ 50 mg) was dissolved in a 10 ml aliquot of nitrobenzene. This solution was used as a liquid ion exchanger membrane. The body of an Orion liquid membrane electrode (Model 92) equipped with Orion 92-05-04 porous membrane was assembled and filled with a mixture of equal volumes of 10^{-2}M aqueous lidocaine hydrochloride and 10^{-2}M potassium chloride as internal reference solution. The

assembled electrode was conditioned by soaking in 10^{-2}M aqueous lidocaine hydrochloride solution for 24 hr before use.

The electrode was calibrated by immersion in conjunction with a double junction Ag//AgCl reference electrode in 15 ml aliquots of $10^{-2}-10^{-5}$M aqueous lidocaine hydrochloride solutions which had been adjusted to pH 3.0 - 6.5. The potential of each solution was recorded after it became stable. A calibration graph was made by plotting the observed potential as a function of logarithm lidocaine concentration. The graph was used for subsequent unknown measurements.

For determination of lidocaine in pharmaceutical preparations, a weighed portion of the preparation containing 0.2-25 mg/ml of lidocaine hydrochloride was dissolved or dispersed in the least amount of deionized water. The pH was adjusted to 3.0 - 6.5 with dilute hydrochloric acid or sodium hydroxide solution and the mixture completed to a total volume of 15 ml with deionized water. The electrode system was immersed in the solution, the potential recorded and compared with the calibration graph.

Results and Discussion

In previous work, we described membrane electrodes for the determination of atropine based on the use of atropine-reineckate ion pair complex in either benzyl alcohol or poly(vinyl chloride) matrix (Hassan and Tadros 1984). In the present work, we found that lidocaine reacts with ammonium reineckate at room temperature to give a water insoluble pink complex (m.p. 210°C) with elemental analysis data that agree with the composition $C_{14}H_{29}N_8OS_4Cr$. This complex readily dissolves in nitrobenzene.

A liquid membrane electrode prepared from 10^{-2}M nitrobenzene solution of the complex as an ion exchanger and a mixture of both KCl and lidocaine hydrochloride (10^{-2}M each) as an internal reference solution displays, relative to a double junction Ag/AgCl reference electrode, a linear response for $10^{-2}-10^{-5}$M (equivalent to 2.89 mg/ml to 8.67 μg/ml) of aqueous lidocaine hydrochloride monohydrate solutions. The slope of the calibration graph is 29 mV/concentration decade, indicating that lidocaine which contains two basic centers behaves as a divalent ion (Fig. 1).

The response time of the electrode to reach a stable potential within ± 1 mV is 35 sec and one min for solutions containing $> 10^{-3}$M and $< 10^{-4}$M lidocaine, respectively. The potential readings of the electrode are independent of the pH over a wide range. For example, a pH-mV profile indicates variation of not more than ± 1 mV over the pH range of 3.0 - 6.5 (Fig. 2). The performance

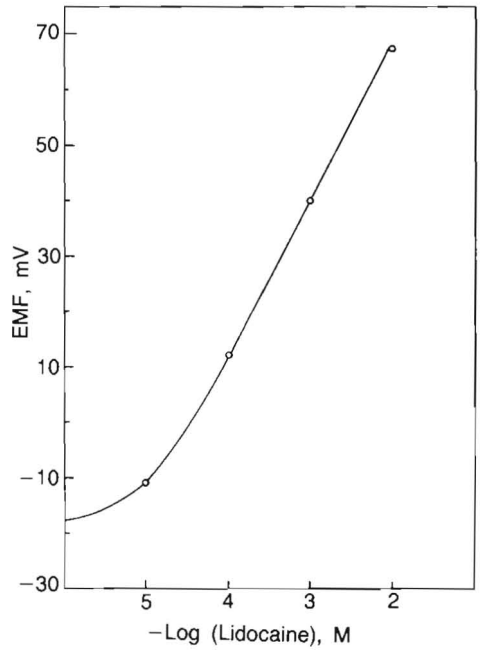

Fig. 1. Potential response graph for lidocaine-reineckate liquid membrane electrode.

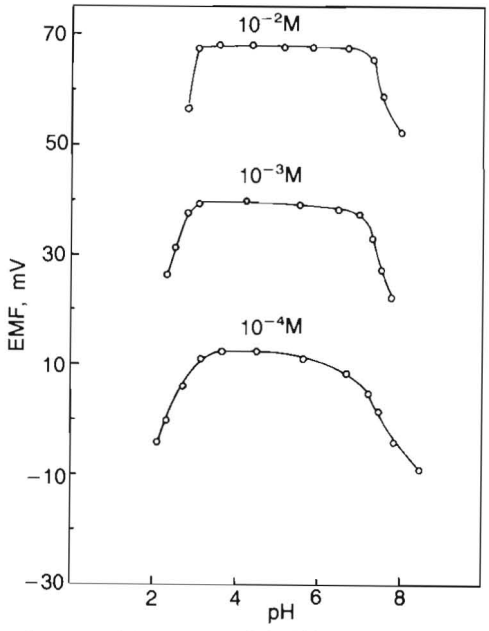

Fig. 2. Effect of pH on the potential response of the lidocaine-reineckate liquid membrane electrode.

characteristics of the electrode remain almost constant for at least 30 days after which the liquid membrane should be renewed.

Determination of lidocaine in aqueous solutions at the concentration levels of 0.3 to 30 mg/ml by direct potentiometry using the lidocaine reineckate liquid membrane electrode and the calibration graph and the known addition (spiking) techniques (Ma and Hassan 1982) shows results with an average recovery of 99.2%. The mean standard deviation (S) is 1.1% (Table 1). The electrode can also be used to monitor potentiometric titration of lidocaine with sodium tetraphenylborate titrant. A sharp inflection break of about 90 mV is obtained at the equivalence point.

Table 1. Determination of lidocaine using lidocaine-reineckate liquid membrane electrode

Lidocaine added (mg/ml)	Calibration graph		Known addition	
	Recovery*%	S%	Recovery*%	S%
0.30	98.3	1.8	97.3	2.1
0.50	99.5	1.2	102.1	1.5
1.00	98.5	0.9	100.3	1.0
5.00	97.9	0.8	99.5	0.8
10.00	98.8	0.8	98.6	0.8
20.00	98.0	0.7	101.9	0.7
30.00	99.2	0.6	100.2	0.8

* Average of 3 measurements

The high selectivity of the electrode for 10^{-2}–10^{-4}M lidocaine is demonstrated by the insignificant effect of as high as 10^{-2}M of many basic substances such as urea and glycine on the electrode response. Furthermore, the electrode shows no response for many of the diluents and excipients commonly used in anaesthetic formulations such as methylparaben, propylparaben, hydroxypropylmethylcellulose, cetylpyridinium chloride, propylene glycol and polyethylene glycol. The average recovery of 10 μg/ml to 5 mg/ml of lidocaine hydrochloride in the presence of up to 100 mg/ml of these excipients is 98.9% and the mean standard deviation being 1.6%.

Some commercially available and widely used local anaesthetic preparations containing lidocaine are determined by direct potentiometry after dilution. The results obtained (Table 2) for determination of lidocaine in some gels, ointments, creams, injections and sprays show an average recovery of 99% of the nominal

Table 2. Determination of lidocaine in some pharmaceutical preparations using lidocaine-reineckate liquid membrane electrode and USP methods.

Preparation	Labelled lidocaine	Electrode method		USP XVII method	
		Recovery*%	S %	Recovery*%	S %
Lidocaine, 2% (ampoule)	20 mg/ml	99.2	1.3	99.0	2.1
Lidocaine, 5% (ampoule)	50 mg/ml	99.8	1.7	98.0	1.9
Lidocaine, 2% (gel)	20 mg/ml	98.3	2.1	102.0	2.5
Lidocaine, 5% (ointment)	50 mg/ml	98.9	1.9	99.0	1.8
Lidocaine, 10% (spray)	100 mg/ml	98.8	1.5	98.1	1.7

* Average of 3 measurements.

lidocaine values. The mean standard deviation is 1.7%. These results are in good agreement with those obtained for comparison using the United States Pharmacopoeia method (USP XVII 1963) which shows an average recovery of 99.2% of the nominal values. The present procedure offers the advantages of high selectivity, simplicity and rapidity. The standard deviation is 0.5% less than that obtained by the USP XVII procedure.

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قطب جديد ذو غشاء سائل لتقدير الليدوكايين في بعض التركيبات المستخدمة في التخدير الموضعي

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استحدث قطب جديد ذو غشاء سائل مكون من محلول رينيكات الليدوكايين في النتروبنزين. ويستجيب هذا القطب استجابة خطية تتطابق مع معادلة نرنست في تركيزات مولارية من الليدوكايين تتراوح بين $١٠^{-٢}$ و$١٠^{-٥}$ في مدى أس هدروجيني ٣ ـ ٦,٥. ويتفاوت وقت استجابة القطب ما بين ٣٥ ثانية ودقيقة واحدة إعتماداً على تركيز الليدوكايين المقاس. ولقد ثبت أن كثيراً من المواد التي توجد في التركيبات الدوائية المستخدمة في التخدير الموضعي لا تتداخل ولا تؤثر على دقة التقدير التي تبلغ ٩٩٪ من القيم الحقيقية بمتوسط حيود قياسي مقداره ١,٧٪. ولقد تطابقت هذه النتائج مع تلك التي حُصِل عليها باستخدام طريقة الفارما كوبيا الأمريكية.