Qualitative and Quantitative Tests for Mepivacaine Hydrochloride

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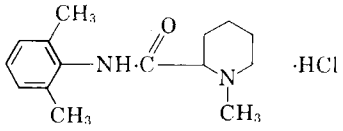
A series of qualitative tests and quantitative methods are presented for mepivacaine hydrochloride. These data result from a cooperative laboratory study by research personnel of the drug firm and the American Dental Association. The methods chosen are discussed, their particular applications noted, and their limitations described.

MEPIVACAINE HYDROCHLORIDE[1] is a local anesthetic agent which is used in dentistry alone or with a vasoconstrictor such as levonordefrin (1). The chemical tests have been developed to provide data on those drugs appearing in "Accepted Dental Remedies." The limits set for these tests seem to be reasonable with expected normal analytical and manufacturing variation for mepivacaine hydrochloride and its preparations. It is to be expected that there may be or will be dosage forms of mepivacaine hydrochloride where these tests will not apply without appropriate modifications.

MEPIVACAINE HYDROCHLORIDE

1-Methyl-2,6-pipecoloxylidide hydrochloride; N-(2,6-dimethylphenyl)-1-methylpiperidine-2-carboxamide hydrochloride; $C_{15}H_{22}N_2O \cdot HCl$; mol. wt. 282.82. The structural formula of mepivacaine hydrochloride may be represented as follows



Physical Properties.—Mepivacaine hydrochloride is a white, odorless, crystalline solid, m.p. 255–262° (decompn.), U.S.P. class 1. It is freely soluble in methanol and water, very slightly soluble in chloroform, and practically insoluble in ether. The pH of a 2% aqueous solution is about 4.6.

Identity Tests.—Dissolve about 100 mg. of mepivacaine hydrochloride in 10 ml. of water and add 2 drops of nitric acid, followed by 1 ml. of silver nitrate T.S.; a white precipitate forms. This precipitate is insoluble in diluted nitric acid but soluble in diluted ammonia solution (presence of chloride).

Dissolve about 100 mg. of mepivacaine hydrochloride in 10 ml. of water, heat almost to the boiling point, and add with stirring 1 ml. of a saturated solution of picric acid in 20% alcohol. Collect the precipitate and wash with a few small portions of water and dry. The picrate melts with decomposition at 197–199°, U.S.P. class I. (Caution! Picrates may be explosive.)

Dissolve about 150 mg. of mepivacaine hydrochloride in 10 ml. of water, and transfer to a small separator. Add 10 ml. of chloroform and 3 ml. of ammonium hydroxide T.S. Shake the separator, allow the layers to separate, and carefully transfer the chloroform layer to a small flask containing 0.5 Gm. of sodium sulfate. Shake the contents until the chloroform solution is clear. Filter the solution and collect the filtrate in a small beaker. Evaporate the chloroform and dry the residue at 60° in vacuum. The yellow-white mepivacaine base melts at 149–153°, U.S.P. class I.

Absorption Characteristics.—A 0.03% solution of mepivacaine hydrochloride in water exhibits ultraviolet absorbance maxima at about 263 and 271 mμ [absorptivity (1%, 1 cm.) about 16.5 and 13.4, respectively] and minima at 254 and 270 mμ.

The infrared absorption spectrum of a 0.3% mixture of mepivacaine hydrochloride in potassium bromide, in a disk of about 0.83 mm. thickness, is shown in Fig. 1.

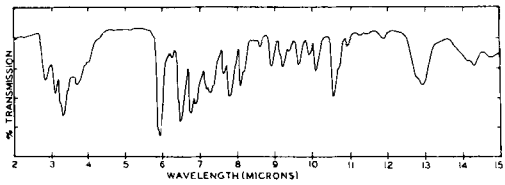


Fig. 1.—Infrared absorption of mepivacaine hydrochloride.

Purity Tests.—Dry about 1 Gm. of mepivacaine hydrochloride, accurately weighed, at 105° for 4 hours: the loss in weight does not exceed 1.0%.

Char about 1 Gm. of mepivacaine hydrochloride, accurately weighed, cool the residue, add 1 ml. of concentrated sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh. The residue does not exceed 0.1%.

Assay.—Transfer to a 200-ml. tall form beaker about 350 mg. of mepivacaine hydrochloride, ac-

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[1] The trade name for mepivacaine hydrochloride is Carbocaine Hydrochloride.

curately weighed. Dissolve in 50 ml. of glacial acetic acid and add 10 ml. of a 6% solution of mercuric acetate in glacial acetic acid. Titrate potentiometrically with 0.1 *N* perchloric acid in glacial acetic acid, or titrate to a green end point using 2 drops of crystal violet in glacial acetic acid as an indicator. A blank should be run on all reagents. Each milliliter of 0.1 *N* perchloric acid is equivalent to 28.28 mg. of mepivacaine hydrochloride. The amount of mepivacaine hydrochloride, $C_{15}H_{22}N_2O \cdot HCl$, is not less than 98.0 nor more than 102.0%.

MEPIVACAINE HYDROCHLORIDE AND LEVONORDEFRIN INJECTION

Identity Tests.—The solution responds to the identity tests for mepivacaine hydrochloride.

Assay.—*Mepivacaine Hydrochloride.*—Transfer to a 60-ml. separator an amount of solution, accurately measured, equivalent to about 40 mg. of mepivacaine hydrochloride. Add 8 ml. of water and 1 ml. of 1 *N* sodium hydroxide and extract the mixture with three 10-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water. Filter the chloroform extracts through a tight cotton plug, using additional chloroform to complete the transfer. Titrate metachromatically to a red end point with 0.01 *N* perchloric acid in dioxane, using 2 drops of 0.1% methyl red in methanol as an indicator. Alternately, add sufficient acetonitrile to the combined, washed chloroform extracts to give a chloroform-acetonitrile ratio of about 4 to 1 and titrate potentiometrically. Each milliliter of 0.01 *N* perchloric acid is equivalent to 2.828 mg. of mepivacaine hydrochloride. The amount of mepivacaine hydrochloride, $C_{15}H_{22}N_2O \cdot HCl$, is not less than 95.0 nor more than 105.0% of the labeled amount.

Levonordefrin.—The concentration of levonordefrin may be determined using the U.S.P. colorimetric assay procedure for epinephrine (U.S.P. XVI, p. 895). When the ferro-citrate solution and the glycine-bicarbonate buffer are mixed with a solution containing levonordefrin and mepivacaine hydrochloride, a fine precipitate forms. This precipitate should be removed by centrifuging before the colorimetric measurements of the iron complex with levonordefrin at 530 mμ are taken. This precipitate does not interfere with the reaction. The amount of levonordefrin is not less than 95.0 nor more than 110.0% of the labeled amount.

DISCUSSION

U.S.P. terminology for solubility, melting points, and reagents have been used wherever feasible.

Identity Tests.—The paper chromatographic R_f values for mepivacaine hydrochloride in hydrochloric acid and acetic acid systems described by Koehler and Feldmann (2) are 0.69 and 0.81, respectively.

Mepivacaine hydrochloride readily forms a reineckate salt in aqueous solutions. Tetraphenyl borate of mepivacaine hydrochloride forms with difficulty, thus it is not included in the identity caine base reacts with cobalt chloride T.S. to give a green color and a fine precipitate (3). A negative test with Millon's mercuric nitrate reagent can be used to determine absence of local anesthetics derived from *p*-aminobenzoic acid or other compounds with a primary amino group. The diazotation reaction with sodium nitrite and hydrochloric acid followed by a coupling reaction with beta-naphthol can be used to determine the presence of any impurities which have a primary aminophenyl group.

Quantitative Methods.—Mepivacaine hydrochloride, being the hydrochloride salt of a basic cyclic tertiary amine, can be determined by a number of the usual methods such as the Kjeldahl nitrogen, volumetric, or other chloride methods, the titration in a water-alcohol or nonaqueous medium of the amine base which has been extracted from an alkaline solution, and the direct perchloric acid colorimetric or potentiometric titration of the hydrochloride salt in a mixture of glacial acetic acid and mercuric nitrate, Fig. 2. This last method does not require a standard and offers a convenient, precise (standard deviation, 0.2%) method for the determination of the active ingredient, mepivacaine hydrochloride.

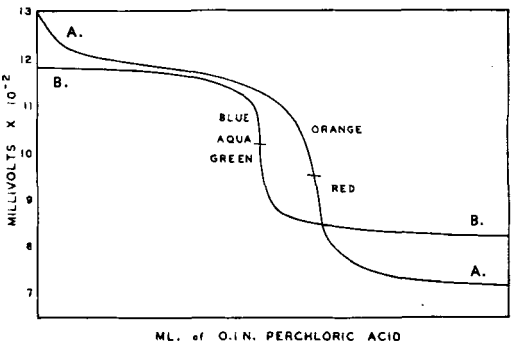

Fig. 2.—Potentiometric titration of mepivacaine base in a 4:1 mixture of chloroform-acetonitrile with 0.01 *N* perchloric acid in dioxane as a titrant and methyl red as an indicator, curve A. Potentiometric titration of mepivacaine hydrochloride in glacial acetic acid with 0.1 *N* perchloric acid in glacial acetic acid as a titrant and with mercuric acetate and crystal violet indicator added, curve B.

The common parenteral forms of mepivacaine hydrochloride used in dentistry are 1.8-ml. cartridges which contain 3% local anesthetic or 2% local anesthetic with a vasoconstrictor at a concentration of 1:20,000. For types of anesthesia other than dental, 1 and 2% mepivacaine hydrochloride solution are available in single and multiple-dose vials containing as much as 50 ml.

The ultraviolet absorption of local anesthetic solutions is frequently a convenient and accurate method of assay. While the ultraviolet absorption of mepivacaine hydrochloride is distinctive (Fig. 3), even the more intense band at 263 mμ with an $E(1\%, 1\text{ cm.})$ of 16.5 is somewhat low for assay purposes. The absorption spectrum of the base and the hydrochloride salt in methanol are essentially identical with that of the hydrochloric salt in

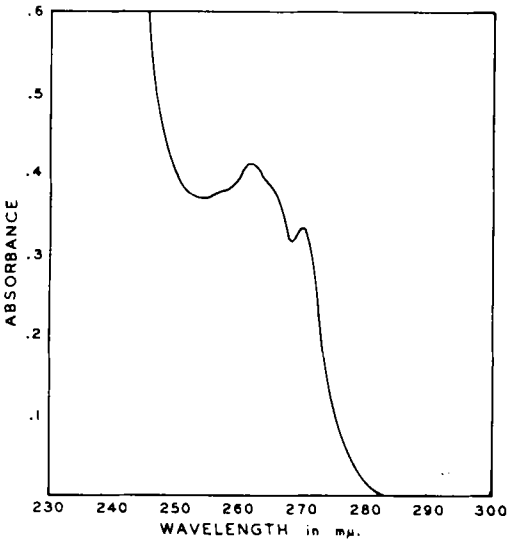

Fig. 3.—Ultraviolet absorption of mepivacaine hydrochloride in water.

The *cis*-aconitic anhydride method for tertiary amines (4) has been used successfully to determine mepivacaine hydrochloride in the usual aqueous solutions as well as blood and serum samples. Mepivacaine base has been used as a standard for this colorimetric procedure. This method may not be suitable for routine analysis, especially for the assay of the usual mepivacaine hydrochloride solutions where the advantages of this method are not fully utilized.

The mepivacaine hydrochloride in the usual local anesthetic solution can be determined gravimetrically as mepivacaine base by extraction with methylene chloride or chloroform of a solution of the hydrochloride which has been made alkaline with sodium carbonate. In such a procedure, the phenolic vasoconstrictors form water-soluble sodium salts which remain in the alkaline aqueous phase while the mepivacaine base is extracted into the organic phase.

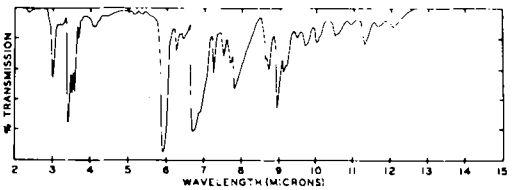

Fig. 4.—Infrared absorption of mepivacaine base in chloroform.

The mepivacaine base obtained from an extraction procedure can be determined by infrared absorption (Fig. 4). The absorption of mepivacaine base in chloroform at 5.97 μ in a 1.0-mm. sodium chloride cell obeys Beer's law in the range 0–6 mg./ml. The method involves the extraction of the base from an alkaline solution with chloroform. The chloroform extract is evaporated in a jet of warm air to less than 10 ml. and then diluted with chloroform to 10 ml. in a volumetric flask. The absorption at 5.97 μ of this solution in a 1.0-mm. cell *vs.* a chloroform-containing reference cell is compared with a standard. This standard, which is a sample of mepivacaine hydrochloride of known purity, is carried through the same procedures as the unknown. Using the baseline technique, the standard deviation of this method is 1.0%.

Mepivacaine base, subsequent to an extraction procedure, can be determined by metachromatic or potentiometric titration with 0.01 *N* perchloric acid in dioxane (Fig. 2). The direct titration of the base in the chloroform extraction solvent makes this a rapid, convenient method. The standard deviation of this titrimetric method is 1.0% and, unlike the ultraviolet and infrared methods, does not require a mepivacaine reference standard.

REFERENCES

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