condition randomly. Group I-E received 250 mg. each of potassium and magnesium aspartate every 12 hours starting within the first hour of the experiment. The drug was administered suspended in 5 ml. distilled water directly into the stomach with a No. 18 catheter and syringe. (The potassium, but not the magnesium aspartate, would dissolve in the quantity of water used; for this reason only potassium aspartate was administered to groups II-E and III-E.) Group II-E received 200 mg. of potassium aspartate intraperitoneally in 1 ml. distilled water every 12 hours. Group III-E received 50 mg. of potassium aspartate i.p. every 12 hours in 0.5 ml. of distilled water. Each control group received an equal amount of distilled water administered by the same route as its experimental group.

The rats were placed in individual 5.5 × 9.5-in. cubicles, on wheels, two-thirds submerged in water, which rotated at a constant speed of approximately 2 r.p.m. Food trays were placed in each cubicle so that the animals could feed at any time. The animals remained on these wheels continuously except when they were removed twice a day for the drug administration. The total distance covered by an animal during the day was 0.7 mile. The rats, when exhausted, fell from the wheel into the water and were unable to remount the wheel. Animals were removed from the experiment when they fell into the water after being replaced on the wheel three times during a 15-minute period. This procedure is the same as that employed by Webb and Agnew.

RESULTS

Figure 1 shows for the experimental and control groups at each age the mean hours at which the criterion of exhaustion was reached. Data for only 34 animals are included in the analysis because six did not learn to walk on the wheel (one in Group I-C, two in Group I-E, one in Group III-C, and two in Group III-E). Three animals were removed from the wheel at 136 hours at they seemed to be interminable walkers (one in Group I-C, one in Group II-E, and one in Group II-C).

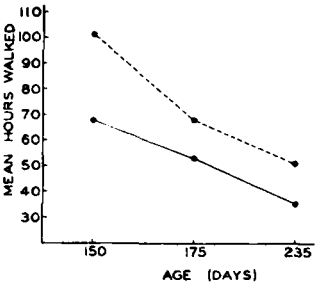

Fig. 1.—Mean hours until exhaustion for the control and experimental groups at three ages. Key: ●---●, control; ●—●, experimental.

DISCUSSION

An analysis of variance resulted in a significant age difference ($p < .01$) and a significant drug effect ($p < .05$).

First it should be recognized that the design is flawed by the changed dosage procedures in the three age groups. Despite this flaw, the consistency of the results across all three conditions supports certain general conclusions.

The previously reported relationship between age and exhaustion time was confirmed for both the experimental and the control groups. On the other hand, the results of the aspartate group (*a*) showed no differential age effect (when compared with the control groups) and (*b*) were contrary to the results reported by Rosen *et al.* (1).

The latter finding suggests a differential action of aspartic acid in a chronic exhaustion situation such as used here in contrast to the acute exhaustion procedure involved in the swim test. It is possible that aspartic acid may result in an overexpenditure of energy in a low requirement situation which reduces the possibility of resisting terminal exhaustion.

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Mineral Acid Salts of Lidocaine

By HENRY M. KOEHLER and JOHN J. HEFFERREN

Some physicochemical properties of the hydrobromide, hydrochloride, nitrate, perchlorate, phosphate, and sulfate salts of lidocaine are reported.

All local anesthetic agents with one or two exceptions are marketed as hydrochloride salts. Since these agents are generally available in aqueous or glycol solutions or ointments for parenteral or topical administration, physical properties such as hygroscopicity are not so important as those of a drug normally formulated as a tablet or capsule. For example, aqueous solutions of lidocaine hydrochloride for pharmaceutical dosage forms are prepared by adding lidocaine base U.S.P. XVI (1) to a slight molar excess of dilute hydrochloric acid, rather than by dissolving the hydrochloride salt in water (2). In his dissertation about the synthesis and characteristics of anilide-type local anesthetics, Löfgren listed the melting points of four salts of lidocaine and the solubility of the hydrochloride salt in the common organic solvents (3). Except for this work, there is little or no published information on the hydrochloride (4) or other salts of lidocaine. This, coupled with the general feeling that lidocaine hydrochloride was difficult to prepare and somewhat hard to handle (5) led to the preparation and study of the mineral acid salts of lidocaine.

The hydrobromide and hydrochloride salts were

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The lidocaine base used in this study was generously supplied by Astra Pharmaceutical Products, Inc.

TABLE I.—SOLUBILITY OF LIDOCAINE SALTS Gm./100 ml. AT 25° C.

	HCl	HBr	HNO_3	H_2SO_4	H_3PO_4	$HClO_4$
Water	100	100	17	25	29	1.7
Methanol	67	67	40	0.8	25	10
Ethanol	11	40	4	0.6	0.7	1.1
Acetone	1.8	2.2	1.2	<0.01	<0.01	14
Chloroform	4	2.5	20	0.02	<0.01	0.03
Carbon disulfide	<0.01	<0.01	0.01	<0.01	<0.01	<0.01
Ether	<0.01	<0.01	<0.01	<0.01	0.06	<0.01
Carbon tetrachloride	0.01	0.01	<0.01	0.01	<0.01	<0.01

prepared in a dry box with a nitrogen atmosphere by passing dry hydrogen bromide and hydrogen chloride into anhydrous ether solutions of lidocaine base. The salts precipitated immediately and were washed thoroughly with ether. After removal of the ether, monohydrates of the halides were obtained in essentially quantitative yield. The anhydrous salts were prepared by drying overnight at 40° in a pumping vacuum. The nitrate, perchlorate, phosphate, and sulfate salts were prepared by adding a slight molar excess of the concentrated mineral acid or an absolute ethanolic solution of the acid to a well-stirred anhydrous ether solution of lidocaine base. The sulfate was an equimolar salt, whereas the phosphate contained 1 mole of base per 2 moles of phosphoric acid. The salts, which were obtained in excellent yield and purity, could be recrystallized from an absolute methanol-ether mixture. The melting points of the lidocaine salts were: HBr, 127–132°; $HBr \cdot H_2O$, 94–103°; HCl, 127–132°, $HCl \cdot H_2O$, 74–78°; HNO_3, 131–133°; $HClO_4$, 204–205°; $2H_3PO_4$, 182–184°; and H_2SO_4, 210–212°. Löfgren (3) reported values of HCl, 128–129°; HNO_3, 133–134°; $HClO_4$, 205°. The $HCl \cdot H_2O$ was reported as 77–80° (4).

All the lidocaine salts prepared were white, odorless, crystalline solids. The solubilities of these salts are tabulated in Table I. All the salts, with the possible exception of the perchlorate, are highly soluble in water and fairly soluble in polar solvents. Unlike most amine halide salts, lidocaine hydrobromide and hydrochloride are relatively soluble in chloroform.

The stability of the salts in atmospheres of various relative humidities was determined by placing the powdered salts in tared aluminum moisture pans in three large desiccators, maintained at 52.9, 71.2, and 93.0% relative humidities. These relative humidities were obtained by placing saturated solutions of $Mg(NO_3)_2 \cdot 6H_2O$, $NH_4Cl \cdot KNO_3$, and $NH_4H_2PO_4$, respectively, in the bottom of the desiccators (6). The aluminum pans were weighed at 12 and 24-hour intervals until constant weight was obtained. The gain in weight of the salts expressed as moles of water per mole of salt is given in Table II. In the 93% relative humidity chamber, the halide salts liquified within 12 hours. In contrast, the monohydrates of the halide salts were relatively stable at the lower humidities.

TABLE II.—HYDRATION CHARACTERISTICS OF LIDOCAINE SALTS

	Relative Humidities at 25° C.		
	52.9%	71.2%	93.0%
Hydrochloride	1[a]	1[a]	>2[a]
Hydrobromide	1	1	>2
Nitrate	0	0	0
Perchlorate	0	0	0
Phosphate	0	0	0
Sulfate	0	0	0

[a] Increase in weight expressed as ratio of moles of water per moles of salt.

The infrared absorption of the lidocaine salts was determined in KBr pellets and in chloroform when the solubility was adequate. The carbonyl band at about 6μ offered an excellent peak for analysis. The base was extracted with chloroform from an aqueous alkaline solution and the chloroform extract dried, evaporated to a convenient volume, and then diluted to known volume. In a 1-mm. sodium chloride cell, the absorbance at 6μ of the lidocaine base was linear from 1 to 7 mg./ml. Perchloric acid titration of the salt in glacial acetic acid or a chloroform extract of the base was also a convenient analytical method.

The mineral acid salts of lidocaine base seemed to be characteristic of the salts of a number of therapeutic agents containing basic nitrogen moieties. It would appear that lidocaine hydrochloride monohydrate would present few problems in essentially dry pharmaceutical dosage forms. If extremes of humidity were anticipated, other salts such as the phosphate could be considered. Thus, with lidocaine as well as any basic drug, the potential availability of other mineral and carboxylic acid salts which may have more desirable physical properties should be considered before limiting work to the hydrochloride salt.

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