applications of various phlogogens. The production of this state is believed to involve the peripheral neurohumoral system.

The author wishes to express appreciation to Dr. B. W. Zweifach for helpful suggestions and criticism in writing this manuscript.

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Received December 20, 1961. P.S.E.B.M., 1962, v109.

Oxethazaine and Related Congeners: A Series of Highly Potent Local Anesthetics. (27300)

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N,N-bis- (N-methyl-N-phenyl-t-butylacetamido)-β-hydroxyethylamine HCl (Oxethazaine, WY-806) is a representative of a new series of highly potent local anesthetics(1). This agent together with the N-substituted congeners prepared from mephentermine* shown in Table I contain a glycine amide moiety and were developed from approximately 300 glycine amides of the mono- and bis-acetamide configuration(2) wherein the features of the procaine and lidocaine types of anesthetics were incorporated in the molecule. Characterization of such molecules show that the mono-acetamides tend to resemble procaine in activity while the bis-acetamides of the oxethazaine type exceed by far the potency of cocaine, procaine, dibucaine, lidocaine or S-650.† Moreover, oxethazaine is unique in that as a weak base it is relatively non-ionized in acid solutions so that its efficacy at pH 1 or gastric pH is high while that of other anesthetics is negligible.

Methods. Topical anesthesia was determined as described by Sollmann(3) and consisted of filling the conjunctival space with 0.4 ml of the test solutions and then holding the eyelids together for 1 minute to bathe the cornea. For *infiltration* effectiveness 0.2 ml was injected into the inner canthus(4). Groups of rabbits were used at each of several concentrations and the opposite eye similarly treated with either distilled water or physiological salt solution served as the control. Anesthesia was determined by testing for presence or absence of the wink reflex by gently stroking either the cornea (topical) or

* Wyamine,® Wyeth Labs., Inc.

† Supplied by Ayerst, McKenna & Harrison Limited (Canada).

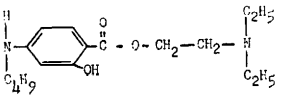
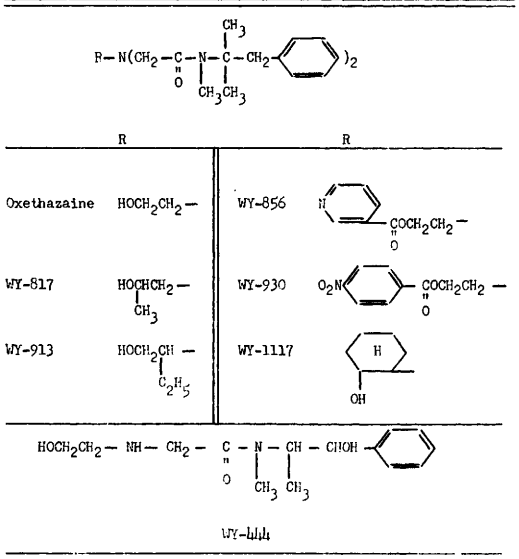


TABLE I. Structure of Mono- and Bis-Acetamide Local Anesthetics.



eyelid (infiltration) at 5-minute intervals with a specially prepared glass rod. Anesthesia following *intraspinal* administration was tested by the technic described by Bieter and his associates(5) and the responses compared with those obtained in rabbits similarly injected with physiological salt solution. Anesthesia was considered effective when complete hind-leg flaccidity (motor paralysis) occurred.

Acute toxicity (LD_{50}) data was obtained in albino mice weighing 16-25 g. Each value was computed according to the method of Bliss(6) using groups of 10 or more mice at 5-6 logarithmically spaced doses. The animals were observed for 14 days and deaths occurring within this period were included in the calculations.

Results. In all studies appropriate concentrations of the hydrochlorides computed in terms of the free base were prepared daily just prior to use. Table II shows the minimal concentrations that produced anesthesia in rabbits lasting not less than 20 nor more than 30 minutes. After topical application oxethazaine, WY-856, 913 and 930 are equipotent and are 500 times more potent than cocaine, 8 to 20 times more active than dibucaine or S-650, and exceed the activity of lidocaine and procaine by 2000 to 4000 times; WY-817, however, is slightly more potent than oxethazaine and WY-1117 is half as potent. Of particular interest is the fact that minimal effective concentrations of these agents, unlike the less potent cocaine, dibucaine, procaine, lidocaine and S-650, have induction periods of varying duration which can be shortened by increasing the concentration of the anesthetics. On the other hand, oxethazaine and WY-856 are 5 times more potent following infiltration than they are after topical application. Moreover, the latency before onset of anesthesia is markedly reduced and is approximately ¼ the time required after topical administration. It is to be noted that WY-856 and 1117 have immediate onset and resemble in this respect, cocaine, dibucaine, procaine, lidocaine and S-650.

WY-444 differs from oxethazaine and the other WY-compounds listed in being a monorather than a bis-acetamide and is the only one in our series of local anesthetics that elevated blood pressure. Intravenous adminis-

TABLE II. Anesthetic Potency—Rabbit Eyes.

Comp.	Conc. sol'n† (%)	Potency ratio*	Induction (min.)
	Topical application		
Oxethazaine	.0005	1	19
Cocaine	.25	1:500	Immed.
Dibucaine	.004	1:8	"
Procaine	2.0	1:4000	"
S-650	.01	1:20	"
Lidocaine	1.0	1:2000	"
WY-817	.0001	1:0.2	15
WY-856	.0005	1:1	18
WY-913	.0005	1:1	17
WY-930	.0005	1:1	20
WY-1117	.001	1:2	12.5
WY-444	>2.0	>1:4000	Immed.
	Infiltration		
Oxethazaine	.0001	1	4.5
Cocaine	.25	1:2500	Immed.
Dibucaine	.001	1:10	"
Procaine	.5	1:5000	"
S-650	.01	1:100	"
Lidocaine	.5	1:5000	"
WY-817	.0005	1:5	2.5
WY-856	.0001	1:1	Immed.
WY-913	.0005	1:5	4.5
WY-930	.0005	1:5	4.5
WY-1117	.0005	1:5	Immed.
WY-444	.5	1:5000	"

* Calculated for avg duration of 20-30 min. at pH 6.5.
† As base.

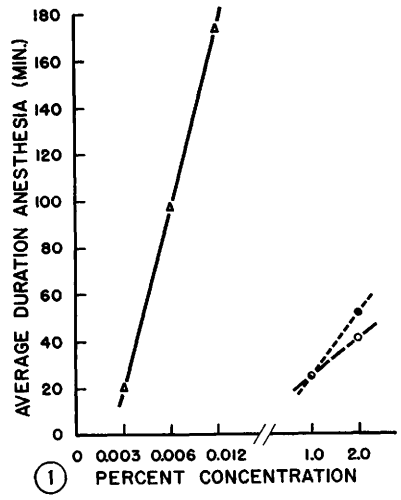
tration to dogs of 3 mg base/kg produces a pressor response approximately equivalent to that obtained with 0.007 mg/kg epinephrine. In studies with both normal and hypodynamic frog hearts WY-444 resembles pressor amines in converting epinephrine induced arrhythmias to normal rhythm(7).

None of the compounds are corneal irritants and there is no evidence of erythema or hyperemia. Prolonged anesthesia causes pseudopitting, a drying effect due to absence of the wink reflex.

Further confirmatory evidence of the anesthetic potency of oxethazaine and its congeners was obtained by the guinea pig wheal method and also after intraspinal administration in rabbits. The results by the former method utilizing the infiltration technic of Rose(8) as modified by Schaffer and Loomis (9) and stimulating with a 751-A, A.E.L. electronic stimulator (20 pulses/sec, 1 msec duration) agree qualitatively with those shown in Table II. Although the potency ratio values are not quite as large the same general ranking persists and oxethazaine remains at least 10 times more potent that dibucaine. Fig. 1 shows the effectiveness of intraspinally administered oxethazaine as compared to similarly administered lidocaine or procaine. Oxethazaine is approximately 300 times more potent and induces immediate and complete motor paralysis of the hind limbs that persists longer than sensory anesthesia. Since the slope for oxethazaine shows a more rapid rate of change per unit dose than lidocaine or procaine, paralysis for 8 or more hours is easily obtained at a level of 0.05%. Despite such prolonged action, recoveries are complete, uneventful and without signs of residual injury.

Oxethazaine is unique in that it maintains a high degree of efficacy even at pH 1 (Fig. 2). For an equivalent duration of anesthesia lasting 28 minutes, lidocaine and procaine must be buffered within the range of pH 5 and 7, respectively, and require concentrations at least 400 times greater than that of oxethazaine.

LD_{50} determinations are summarized in Table III. The intraperitoneal toxicities of oxethazaine and the highly potent congeners



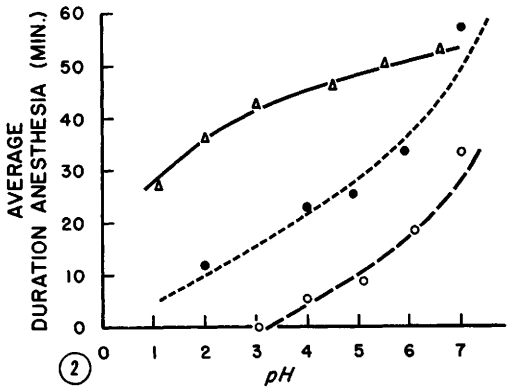


FIG. 1. Anesthetic potency of intraspinally administered oxethazaine (△—△), lidocaine (●···●) and procaine (○--○).

FIG. 2. Effect on corneal (topical) anesthesia following application of 0.005% oxethazaine (△—△), 2% lidocaine (●···●) and 2% procaine (○--○) at various pH.

approximate those of cocaine and dibucaine. The less potent compounds such as lidocaine, procaine and WY-444 are correspondingly less toxic. Symptoms of toxicity at the LD_{50} consist of transient depression with occasionally S-shape erection of the tail, incoordination, tremors, leaping and bounding, some stimulation of respiration followed by gasping (dyspnea) and death by respiratory failure prior to circulatory collapse.

Discussion. Local anesthetic potency of high degree does not occur in those glycine amides wherein the amido N is derived from aralkyl amines; while the use of mephentermine (N-α,α-trimethyl-β-phenethylamine)

TABLE III. Acute Toxicity—Mice.

Comp.	Route	Quant. est. of LD_{50} (mg/kg)*	Range (± 2 S.E.) limits Lower (mg/kg)*	Upper (mg/kg)*
Oxethazaine	Oral	399.9	319.2	500.9
	Intraper.	30.3	27.3	33.6
Cocaine	Intraper.	62.8	57.1	69.0
Dibucaine	"	27.6	24.2	31.8
Procaine	"	192.4	157.8	234.5
S-650	"	79.9	63.2	101.1
Lidocaine	"	141.6	128.6	155.9
WY-817	"	47.3	31.4	61.1
WY-856	"	84.8	71.2	99.5
WY-913	"	48.2	36.7	62.0
WY-930	"	33.2	19.8	42.5
WY-1117	"	77.1	66.4	84.6
WY-444	"	270.6	249.3	293.7

* As base.

which is both sterically hindered and incapable of forming d,l-isomeric derivatives produces the highest activity (oxethazaine, WY-817, 913, 1117). Oxethazaine is therefore unique in this respect since its configuration combines 2 molecules of an adrenergic substance (mephentermine) with a cholinergic substance (ethanolamine) through an amide linkage; but it remains to be established what significance should be attached to the presence of these moities with respect to the pharmacological activity of oxethazaine. Moreover, the number of methylene groups separating the hydroxyl from the tertiary amino group is particularly important. While the 2-hydroxyethyl derivative (oxethazaine) has high order activity, the corresponding 3-hydroxypropyl is practically devoid of effect. Esterification of the terminal hydrogen yields a number of potent members (WY-856, 930), but in no case is this activity greater than that of the alcohols from which they are prepared. Such esterification, however, may reduce or abolish the characteristic time required for induction of anesthesia (WY-856). Finally, formation of monoacetamides such as WY-444 as well as unsymmetrical iminoacetamides, or alterations in chemical type involving replacement of hydroxyl with chloro or amino, or quaternarization of the tertiary amino (acetylcholine analog) yield compounds with little or no anesthetic activity.

Of the N-substituted congeners of oxethazaine applied topically to the cornea all are effective in concentrations ranging from .001 to .0001%. Agents with potency of this order therefore require relatively few molecules to induce anesthesia; however, the lag between the application to this mucous membrane and onset of action represents the time for the molecules of anesthetic to diffuse and reach an effective concentration at the receptors. This delay which is absent following similarly applied equi-effective concentrations (for duration of 20-30 minutes) of cocaine, dibucaine, procaine, S-650 or lidocaine may be undesirable. To compensate, the concentration of the solution can be increased, but this results in unnecessarily long duration of anesthesia. Or, small amounts of hyaluronidase can be added to the anesthetic thereby hastening the onset without affecting the duration of anesthesia(10). By depolymerizing the ground substance of Bowman's membrane (containing the sensory nerve endings), hyaluronidase facilitates penetration of anesthetic so that for a given concentration a larger number of receptors are available. On the other hand high concentrations of enzyme cause excessive depolymerization of the ground substance so that rapid dispersion occurs and only subminimal amounts of anesthetic reach the receptors.

Cutaneous infiltration or intraspinal administration result in almost immediate anesthesia. This difference from topical application is due either to the shorter distance for diffusion between anesthetic depot and the nerve fibers, penetrability of the tissue between these 2 sites, or the inherent ability of the agents to penetrate these tissues. That latency need not be related to potency is demonstrated by compounds WY-856 and 1117.

Although the full clinical utility of oxethazaine has not yet been realized, its high topical anesthetic potency and large margin of safety intragastrically in animals led Deutsch and Christian(11), Jankelson and Jankelson (12), and Hollander(13) to evaluate its usefulness in patients suffering pain from gastritis, duodenal ulcers, hiatus hernia and pep-

tic esophagitis. They found that these conditions were amenable to treatment with this agent and that satisfactory relief was obtained in a large percentage of trials where standard therapy failed.

While the use of topical anesthetics is not new to gastroenterologists none has previously proven satisfactory in the gastric environment because of either toxicity, or inadequate potency and duration of action. The reason for the failure of anesthetic salts such as procaine, lidocaine or dibucaine can be attributed to the fact that these are ionized (dissociated) at gastric pH and that oxethazaine, a weak base, is relatviely non-ionized. Accordingly, the weaker the base the more free base is released and the greater the anesthetic potency(14). Further, the solubility of oxethazaine salts in organic solvents ($CHCl_3$, CCl_4) at gastric pH indicates that it easily penetrates the lipids of nerve sheaths to effect adequate anesthesia of sufficiently long duration.

Summary. 1. Oxethazaine and several N-substituted bis-acetamide congeners constitute a new series of powerful local anesthetics, exceeding by far the potency of either cocaine, procaine, lidocaine or dibucaine. 2. All are effective by topical application to the cornea, cutaneous infiltration or intraspinally. 3. Since oxethazaine is highly effective topically and has a large margin of safety when administered intragastrically, it has proven to be useful clinically for control of pain due to a variety of gastric disorders. 4. Its effectiveness at the acidity of the gastric environment is due to the fact that oxethazaine, a weak base, is relatively non-ionized at pH 1.

Thanks are due to Dr. A. J. Plummer of Ciba Pharmaceutical Products, Inc., Summit, N. J., for supplying dibucaine (Nupercaine®) and to Dr. A. S. Cook of Ayerst, McKenna & Harrison Limited, Canada, for making compound S-650 available for use in these studies. Thanks are also due to the following persons for technical assistance: A. Dervinis, F. Rauzzino, J. McCallum, and A. Blumenthal.

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Received December 20, 1961. P.S.E.B.M., 1962, v109.

Influence of Propylthiouracil and D- and L-Triiodothyronine on Excretion Of Bile Acids in Bile Fistula Rats. Bile Acids and Steroids 118.* (27301)

OVE STRAND (Introduced by O. Wintersteiner)
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It is well known that the thyroid hormones have hypocholesterolemic effects. In the search for agents with hypocholesterolemic properties similar to those of the thyroid hormones but without their undesirable calorigenic effects, different structural analogues have been tried, *e.g.*, D-thyroxine and D-triiodothyronine. These compounds have been

* This work has been supported by a grant from Reservationsanslaget, Karolinska Inst.