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Pharmacology of the Psychotherapeutic Drug Benactyzine (β-Diethylaminoethyl Benzilate Hydrochloride). (22545)

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Several clinical studies in the European medical literature have indicated that benactyzine* (β-diethylaminoethyl benzilate hydrochloride) may be of value in symptomatic treatment of anxiety and other manifestations of psychoneurosis and psychosomatic disease (3,4,10,13,14). Jacobsen and his associates showed that the drug eliminated experimentally-induced conflict behavior in cats(7) and rats(5,8). Human beings exposed to emotion-provoking stress showed less intense autonomic responses after benactyzine(9).

Benactyzine was first prepared in 1936 (16), but studies of the pharmacological activity of the compound have been limited. *In vitro* anticholinergic and antihistaminic activity were demonstrated by Burtner and Cusic (2) using rabbit intestinal muscle. Lands *et al.*(11) showed that benactyzine has a weaker effect on salivary secretion and on dilation of the pupil than does atropine. The present study describes further pharmacological properties of the compound, and compares it with other psychotherapeutic agents.

Acute toxicity. In mice, benactyzine caused hyperexcitability and convulsions. After intraperitoneal administration of about one-half of an LD_{50} the animals became hypersensitive to sound and touch and had extended S-shaped tails (Straub reaction). Most animals also had clonic convulsions which alternated with periods of exhaustion. Doses higher than 90 mg/kg produced clonic convulsions of great violence. The LD_{50} was 155 ± 9 mg/kg and the mean convulsant dose (CD_{50}) was 86 ± 6 mg/kg. *Effect on behavior.* In adult Rhesus monkeys (*Macaca mulatta*) doses ranging from 1 to 6 mg/kg intravenously caused only minor changes in behavior. After 1 mg/kg there was mydriasis and some decrease in locomotion. Although the animal exhibited less withdrawal from the experimenter there was no real taming effect. At 2 mg/kg the animals became ataxic and occasional convulsive jerks occurred. Six mg/kg put one monkey into frank convulsions. These were clonic, lasting 1 to 5 seconds, and recurred at intervals of 5 to 15 seconds. This stage was present for about 10 minutes and was followed by post-ictal depression lasting over one hour. After intravenous administration, effects were seen within one minute and there was usually some evidence of recovery in one hour. Pupillary dilation was the most persistent effect, sometimes lasting as long as 20 hours.

Potentiation of hexobarbital anesthesia. Groups of mice were given hexobarbital sodium 100 mg/kg and benactyzine hydrochloride simultaneously by the intraperitoneal route and the duration of hexobarbital anesthesia was measured(17). The antihistaminic diphenhydramine (Benadryl), which causes marked prolongation of hexobarbital anesthesia was used for comparison. The results

* Benactyzine is the generic name for β-diethylaminoethyl benzilate hydrochloride accepted by the Scandinavian Pharmacopoeia Commission. The drug is sold in Europe under the trade names Suavitil, Nutinal and Parasan.

TABLE I. Potentiation of Hexobarbital Anesthesia by Benactyzine or Diphenhydramine in Mice. Hexobarbital soluble 100 mg/kg given intraperitoneally simultaneously with other drugs.

Drugs	mg/kg	Duration of anesthesia in mice	t	p
Hexobarbital only		29.0 ± 2.8	—	—
" and diphenhydramine	10	47.2 ± 4.2	3.6	<.01
" " "	20	67.2 ± 6.3	5.5	<.01
" " benactyzine	10	64.9 ± 4.9	6.4	<.01
" " "	20	97.3 ± 4.6	14.5	<.01

are given in Table I. Benactyzine 10 mg/kg more than doubled the duration of anesthesia produced by hexobarbital alone. Furthermore, benactyzine had a markedly stronger effect than diphenhydramine in prolonging hexobarbital anesthesia. *Effect on electroshock seizures.* These tests were carried out in mice by a technic previously described(1). The current intensity of 50 m.a. applied for 0.2 second was about 4 times the convulsive threshold dose. Most mice survived repeated shocks of this kind. After oral administration of small doses of benactyzine electroshock seizures caused death. The oral dose of benactyzine that produced death in 50% of animals after electroshock seizures was 24 ± 3 mg/kg. This dose did not produce any other observable symptom in mice except mydriasis. The latency period between administration of the electric shock and onset of the tonic extensor phase of the convulsion was unchanged after 24 mg/kg benactyzine but was significantly prolonged after 37 mg/kg.

Antispasmodic effect of benactyzine and other drugs was evaluated on the rat colon when acetylcholine and 5-hydroxytryptamine (serotonin) were used as stimulants and on the guinea pig ileum when histamine was used. The spasmogens were used in doses which produced submaximal contractions as follows: acetylcholine chloride 5 γ/100 ml, 5-hydroxytryptamine creatinine sulfate 10 γ/100 ml, histamine diphosphate 50 γ/100 ml. After several reproducible responses were obtained, the drugs were given and permitted to remain in contact with the organ for 3 minutes before addition of the spasmogen. Table II which summarizes the results of these experiments confirms the previously-reported marked anticholinergic action of benactyzine (2,11,12). In this respect the drug is about 20 times more potent than chlorpromazine. The antagonistic action of benactyzine to 5-hydroxytryptamine *in vitro* is of approximately the same order as that of chlorpromazine. Benactyzine is a relatively poor histamine antagonist being 10 times less active than chlorpromazine and 20 times less active than diphenhydramine.

Excretion of 5-hydroxyindoleacetic acid. Benactyzine in doses of 5 mg/kg did not increase excretion of 5-hydroxyindoleacetic acid in the urine of the rat. Under similar conditions, reserpine 5 mg/kg markedly increased excretion of this metabolite of serotonin(15). Thus, it appears unlikely that benactyzine affects 5-hydroxytryptamine metabolism. *Anticholinergic action on blood pressure.* Cats anesthetized with chloralose 60 mg/kg dissolved in 25% aqueous urethane were utilized in these experiments. After uniform blood pressure responses to acetylcholine 2 γ/kg and stimulation of the peripheral vagal stump (0.5 v. for 15 seconds) were obtained, benactyzine was injected and the tests repeated. Benactyzine 1 mg/kg reduced the depressor effect of both vagal stimulation and acetylcholine by about 30% while 3 mg/kg reduced the effects of both by more than 70%. *Potentiation of epinephrine.* The pressor effect of epinephrine in chloralosed cats was markedly greater after administration of benactyzine.

TABLE II. Concentrations of Benactyzine and Other Agents in γ/ml Required to Completely Antagonize Effects of Acetylcholine, 5-Hydroxytryptamine and Histamine on Smooth Muscle.

	Acetylcholine	5-Hydroxytryptamine	Histamine
Benactyzine	.05	1.0	5.0
Chlorpromazine	1.0	.5	.5
Reserpine	4.0	4.0	2.5
Meprobamate	10.0	10.0	100
Diphenhydramine	—	—	.25

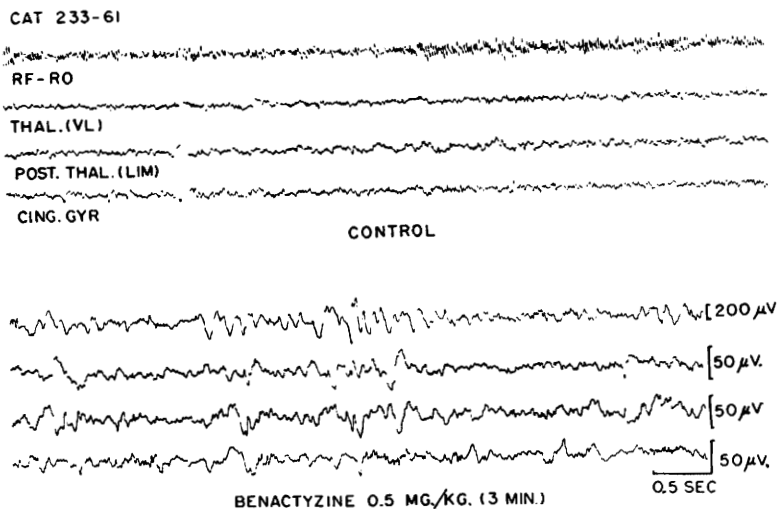

FIG. 1. Effect of benactyzine on electrical activity of brain. Recordings are from right motor to occipital cortex (RF-RO), nucleus ventralis lateralis of thalamus (VL), posterior border of thalamus, in nucleus limitans (LIM), and posterior cingulate gyrus (CING. GYR.).

Thus, benactyzine 1 mg/kg almost doubled the response previously obtained from epinephrine 5 γ/kg. Benactyzine 24 mg/kg in mice reduced the LD_{50} of epinephrine from 7.0 ± 1.3 mg/kg to 5.0 ± 0.3 mg/kg.

Effect on spinal reflexes. The knee jerk and flexor reflex in chloralosed cats showed no characteristic changes after benactyzine 3 mg/kg. After doses of 10 mg/kg both reflexes disappeared and respiration stopped.

Effect on brain waves. In curarized cat preparations, benactyzine 1 mg/kg broke up the regular fast activity of the cortex (40/sec.). In its place, irregular slower outbursts with a predominant frequency of 8 to 15/sec. and higher than usual amplitude became apparent. A similar slowing and increase in amplitude was also noted in recordings from subcortical areas (Fig. 1). The drug also blocked EEG arousal from sensory or thalamic stimulation. Recruiting responses evoked in the cortex by thalamic stimulation were not affected. The records obtained were indistinguishable from those obtained after suitable doses of atropine under similar conditions.

Discussion. Benactyzine is closely related in chemical structure to several drugs that have been used in therapeutics for many years. The spasmolytic adiphenine (Trasentine) differs from benactyzine only in lacking the hydroxyl group in the benzilic acid portion of the molecule. Benactyzine is also similar to the benzilic ester of choline and the cycloplegic Lachesine(6) which differs from benactyzine only in that the nitrogen is quaternary. Benactyzine differs from other psychotherapeutic agents such as chlorpromazine, reserpine and meprobamate not only in chemical structure but also in pharmacological properties. The only action that these 4 psychotherapeutic agents have in common is the potentiating effect on hexobarbital anesthesia. This action, however, is not specific as it is shared by many other drugs, notably the antihistaminics. Benactyzine does not share with meprobamate the taming effect on monkeys, nor does it produce insulation from the environment and catatonia as do chlorpromazine and reserpine in this species. Its effects on spontaneous electrical potentials of the brain are like those of atropine. The ability of benactyzine to normalize stress-induced behavior in animals is of great interest but is not specific since similar effects can also be produced by alcohol(7). However, chlorpromazine appears to be ineffective when evaluated by this technic(7). The frequent occurrence of deaths in benactyzine-treated animals after normally non-lethal electroconvul-

sive shocks appears to make it inadvisable to give electroconvulsive treatment to patients taking benactyzine.

Summary. Benactyzine (β-diethylaminoethyl benzilate hydrochloride) an antispasmodic that has been used in the treatment of psychoneuroses causes hyperexcitability and clonic convulsions in animals. A taming effect was not observed. Hexobarbital anesthesia was markedly prolonged, the effects of acetylcholine on the isolated gut and blood pressure diminished and the action of epinephrine on blood pressure enhanced by this compound. Spinal reflexes were not affected and cortical and subcortical electrical activity was slowed. Mice receiving benactyzine often died during electroshock seizures which were tolerated by normal animals.

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The Development *in vitro* of an Avirulent, Immunogenic Variant of *Mycobacterium tuberculosis* var. *hominis*.* (22546)

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Youmans and Youmans(1) reported that the virulent H37Rv strain of *Mycobacterium tuberculosis* var. *hominis* would multiply in a modified synthetic Proskauer and Beck medium from which the nitrogen source, asparagin, had been omitted, at a rate similar to that obtained in the complete medium. During the course of subsequent investigations, the H37Rv strain was subcultured serially once a week for approximately 6 years onto the surface of the Proskauer and Beck medium from which the nitrogen source had been omitted. It was found that the virulence of these cultures, when tested at intervals in mice and in guinea pigs, had decreased markedly. This variant of the parent H37Rv strain has been designated H37RaN, which stands for strain H37, rough, avirulent, nitrogen.

This study is concerned with a) the virulence of H37RaN as compared with the parent H37Rv, b) metabolic differences between the 2 strains, and c) the immunogenic activity of H37RaN as compared with the well known immunogenic mycobacterial strains, H37Ra and BCG.

Methods. The strains of mycobacteria employed were the 3 human strains, H37RaN, H37Rv, H37Ra, and the one bovine strain, BCG. The H37Rv and H37Ra strains were maintained as pellicle cultures on the modified synthetic Proskauer and Beck (P & B)

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