HANDBOOK OF TOXICOLOGY
VOLUME IV
TRANQUILIZERS

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EDITOR

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ON THE HANDBOOK OF BIOLOGICAL DATA

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Approved for Public Release
FOREWORD

The Handbook of Toxicology, Volume IV, Tranquilizers, is the eighth of a continuing series of publications*, each containing information, chiefly tabular, in one or more of the biological sciences. These volumes have been prepared under the general direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, National Academy of Sciences-National Research Council.

This handbook was prepared under the general direction of the Aero Medical Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, under Project No. 7165, "Health Hazards of Air Force Materials and Radiation," Task No. 71836, "Evaluation and Control of Toxic Chemical Materials." The project engineer is Dr. George Kitzes, Physiology Branch, Aero Medical Laboratory.

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* Handbooks published 1949-1959

Standard Values in Blood 1951
Standard Values in Nutrition and Metabolism 1953
Handbook of Toxicology, Vol. I, Acute Toxicities 1955
Handbook of Biological Data 1956
Handbook of Toxicology, Vol. II, Antibiotics 1957
Handbook of Respiration 1958
Handbook of Toxicology, Vol. III, Insecticides 1959
Handbook of Toxicology, Vol. IV, Tranquilizers 1959
Handbook of Toxicology, Vol. V, Fungicides 1959
ABSTRACT

This report presents data on physical, chemical, biological, and toxicological properties of 26 tranquilizers, compiled from extensive literature references. The material is as up-to-date as possible at the time of publication. To enhance reliability and, consequently, usefulness, each page of data has been exhaustively reviewed and authenticated by the contributors.

The compilation is as complete as the rapidly changing state-of-the-art in the field of tranquilizer development will permit. Wherever possible, data are presented on molecular formula and weight, structure, physical and chemical properties, pharmacology, clinical aspects, toxicity, and mode and site of action for each compound. This report is a survey and the values presented herein should be considered as "yardsticks" of activity rather than as absolute and definitive.

PUBLICATION REVIEW

This report has been reviewed and is approved.

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Introduction

The modern era of the use of drugs in psychopharmacology began in 1953-1954 with the introduction into the United States of chlorpromazine and the Rauwolfia alkaloids (initially as the ground root). As a result of these and even newer drugs, the population of mental hospitals has stabilized, or even declined, for the first time in this century. No better evidence could be found of the impact of these drugs on mental disease, unless it be the transformation of mental institutions from custodial establishments, with their restraining devices, cold packs, noise, agitation, and confusion, to true therapeutic hospitals.

The Rauwolfia plant, now largely supplanted in therapy by reserpine and other minor alkaloids of the various Rauwolfia species, has a very old history going back to 1000 B.C. in native Indian medicine. In India the plant has long been used for treatment of insomnia, insanity, and hypertension. Its first use in the West was as a hypotensive agent, followed shortly by its application to mental disease problems. The pendulum has now swung back again, and treatment of hypertension is probably the principal current use of reserpine and related alkaloids.

Chlorpromazine was introduced into the United States at about the same time as the Rauwolfia alkaloids; its origin lay in certain antihistaminic phenothiazines. It had been noted that a number of antihistamines produced sedation as one of their undesirable side effects. The potential therapeutic usefulness of an entirely new type of central depressant agent led French investigators to examine structural features of the phenothiazine antihistamines which might be altered so that the effects on the central nervous system would be enhanced. Initial work led to clinical trials as hypothermic agents and anesthetic potentiators. Additional work in the United States and Canada developed utility for the French compounds in treating agitated psychotics. Finally, new series of agents were developed in the United States and abroad; many of these are described briefly in this handbook. Widespread use of the psychopharmacological agents has led to a certain amount of accidental abuse, with occasionally serious consequences; hence it seemed useful to report on the toxicology of these compounds.

Additional clinical data, on the other hand, have necessarily been limited to what some may consider an arbitrary minimum. However, any attempt to review substantially all the literature covering clinical experience would have soon led to an overwhelming of all the other contents and an extension beyond handbook limits. Furthermore, for many of the compounds any summary or survey of experience necessarily partakes of the tentative, conclusions, when they are reached in the future, may well modify certain current optimistic hopes.
The terminology in this, as in any new area, has led to a certain amount of confusion and sometimes some overlapping of meaning.

1. Drugs which influence the state of the mind are known as: Psychopharmacologic agents, phrenotropic drugs.

2. Therapeutic agents employed in treatment of mental disorders are called: Psychotherapeutic drugs;ataractics; tranquilizing agents; psycholytic, psychosolyc, or neuroleptic agents.

3. Agents experimentally useful in producing model psychoses are: Psychosomimetics, hallucinogens.

4. Finally, a new group of non-classical anti-depressants (stimulants) have appeared on the scene, which are characterized as 'psychic energizers,' 'mental mobilizers.'

From among the many substances that may be classified as psychopharmacologic agents, only a very limited number of recent great interest have been chosen. Included are all the so-called tranquilizers of reputed value and present availability, together with a number of other drugs of analogous usefulness.

There may very well shortly be other substances as worthy of consideration as some of those covered herein. However, in a field so live with day-to-day developments, a line had to be firmly drawn across the calendar somewhere, or no such volume as this could ever have been completed.

The form used in presentation of bibliographic references is that suggested in the interim report of the Publications Committee of the American Institute of Biological Sciences and reprinted from the April 1952 A. I. B. S. Bulletin (Vol. 2, No. 2). Abbreviations of journals are taken from the LIST OF ABBREVIATIONS FOR SERIAL PUBLICATIONS, Fourth Series, Army Medical Library, Washington, D. C. (U. S. Government Printing Office, 1948), and the 1955 SUPPLEMENT thereto (except in the rare instances in which no such abbreviations are offered).

NOTE

The following abbreviations have been used to designate routes of administration:

i.m. = intramuscular;
i.p. = intraperitoneal;
i.v. = intravenous;
p.o. = oral;
s.c. = subcutaneous.
Tranquilizers

1. AZACYCLONOL HYDROCHLORIDE

Trademark for α,α-diphenyl-4-piperidinemethanol hydrochloride is Frenquel (Wm. S. Merrell Company).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{18}\text{H}_{21}\text{NO} \cdot \text{HCl} \quad 303.84 \]

STRUCTURE

![Structure of Azacyclonol Hydrochloride](image)

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid [1].
Solubility: S. 2 g/100 g water [1].
PHARMACOLOGY

Man

"Psychosis" induced by lysergic acid diethylamide (LSD) or mescaline has been blocked by azacyclonol. A dose of 10-30 mg daily for 7 days prior to administration of LSD (0.1 mg p.o.) permitted only a fragmentary appearance of the "psychosis" symptoms or prevented them completely. LSD "psychosis" has been abruptly terminated by a single injection of 40 mg (i.v.). 200 mg of azacyclonol given during the 48-hour period prior to mescaline-induced "psychosis" (0.4 g p.o.) prevented most of the hallucinogenic symptoms usually observed [1]. Contrary results have also been reported [2].

Animal

Mice given 17-142 mg/kg of azacyclonol prior to injection of hexobarbital exhibited a moderate increase in sleeping time. Mice also showed a 50% depression of spontaneous activity when given doses of 60% of the LD₅₀ by all routes of administration. At 40% LD₅₀ (142 mg/kg) (s.c.) azacyclonol produced a 60% reduction of the hyperactivity caused by cocaine, dextroamphetamine or morphine. Cats pretreated with 5 mg/kg (p.o.) were protected from convulsions and death induced by morphine sulfate (25 mg/kg). Blood pressure in dogs exhibited a marked fall accompanied by a corresponding rise in respiratory rate when a dose level of 32 mg/kg (i.v.) was maintained [3]. An intraventricular dose of 20 mg produced in cats tachypnea, emesis, tremors, ataxia, relaxation of the nictating membrane and moderate ataraxia. When mescaline (2-3 mg) was administered intraventricularly 2-1/2 hours later, there was no blocking of the autonomic response, but the psychologic effects were changed from catatonia to psychomotor excitement [4]. Azacyclonol does not alter EEG [5] but does restore EEG pattern to normal in curarized rabbits given mescaline or LSD [6].

CLINICAL

Azacyclonol has shown interesting therapeutic properties in some schizophrenic dissociation syndromes when used in the 10-30 mg daily dose range [1]. Reported to alleviate symptoms of postoperative confusional states and acute alcoholic psychoses at a daily dose of 100-300 mg (i.v.)[7].
CLINICAL (Concluded)

Complete recovery claimed in 30-240 minutes of acute toxic hallucination on therapy of 20-100 mg (i.v.) [8] but result not confirmed by other investigators [2]. Acute schizophrenic reactions with delusions and hallucinations showed complete recovery in 1-3 days on 20-400 mg/day [7,9,10]. Inconsistent results reported when drug was used on chronic schizophrenics [2,7,11,12]; azacyclonol seemed to be of benefit if hallucinations and delusions were prominent [13-15]. Chronic arthritis and severe psoriasis improved on a dosage of 120 mg daily (p.o.) [14].

TOXICITY

Man

1200 mg administered daily (p.o.) for 3 weeks [10] and 120 mg daily (p.o.) for 3-7 months [14] showed a complete absence of side effects.

Animal [3]

LD<sub>50</sub> (mouse) 177 mg/kg (i.v.), 220 mg/kg (i.p.), 350 mg/kg (s.c.) and 650 mg/kg (p.o.). Caused convulsions and death in 20-240 minutes. Rats given 86 mg/kg (s.c.) experienced flaccid paralysis of hind legs, depression of spontaneous activity and increased responsiveness to auditory stimulation. Increased irritability and tremor were observed in dogs and cats at doses of 25 and 50 mg/kg (p.o.). Dogs fed 100 mg/kg produced constant activity with a curious rapid alteration of front-foot placement. Monkeys fed 160 mg/kg exhibited no behavioral changes or signs of toxicity.

MODE AND SITE OF ACTION

May inhibit effect of hallucinogens on phosphorylation or on citric acid cycle in glucose metabolism [16].
REFERENCES


REFERENCES (Concluded)


2. BENACTYZINE HYDROCHLORIDE

Trademarks for 2-diethylaminoethyl benzilate hydrochloride are Suavitil (Medicinalco), Parason (Schweizerhull), Surfen (Ayerst Laboratories).

MOLECULAR FORMULA AND WEIGHT

\[ C_{20}H_{25}NO_3 \cdot HCl \]

\[
\begin{array}{cccc}
\text{Analysis} & \text{C} & \text{H} & \text{N} & \text{Cl} \\
\text{Calc.} & 66.01\% & 7.20\% & 3.85\% & 9.75\% \\
\text{Found} & 65.86\% & 7.42\% & 3.87\% & 9.98\%
\end{array}
\]

STRUCTURE

\[
\begin{array}{c}
\text{C} & \text{O} & \text{C} & \text{C} & \text{N} \\
\text{OH} & \text{CH}_2 - \text{CH}_2 & \text{C}_2\text{H}_5 & \text{HCl}
\end{array}
\]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline powder.
Melting Point: 177-178\(^\circ\)C [1].
Absorption Maxima: 268, 264, 258, 252 \(\mu\)m.
Solubility: S. alcohol, 50 mg/ml water.
Stability: 5% aqueous >24 hours.

PHARMACOLOGY [2,3]

Man

A feeling of detachment and muscle relaxation was experienced by subjects given 4-8 mg daily.
2. BENACTYZINE HYDROCHLORIDE (Continued)

PHARMACOLOGY (Concluded)

Animal

Potentiates hexobarbital-induced sleeping time in mice, and at 25 mg/kg (p.o.) gastric secretion was reduced.

Mice show slight stimulation on low doses 2-10 mg/kg and tremors and seizures at high doses. Antispasmodic and antihistaminic action was observed on isolated rabbit and guinea pig intestine. Local anesthetic activity in rabbit eye and mescaline antagonism in mice were observed. Slight apomorphine antagonistic effect reported in dogs.

CLINICAL

Anxiety in psychoneurotics is reportedly relieved by a therapeutic dose of the drug, 1-5 mg 4 times a day [4]. Also reported to abolish neurotic inhibitory avoidance responses engendered by stress and to act as a mild antidepressant in clinical states of depression in both manic depressive and involutional types of psychoses [5]. An antiphobic mood normalizer without sedation or hypnosis.

TOXICITY [2,3]

Man

Acute: On 90 mg (p.o.), single dose, no toxic damage [4].

Chronic: On 15 mg (s.c.) 6 times a day for 6 days, no adverse effects observed [4]. Dryness of mouth, palpitation and loss of concentration experienced on a daily dose of 16 mg for 2 months [4].

Animal

Chronic: Rats receiving 15 mg/kg (p.o.) daily for 5 weeks and dogs 5 mg/kg daily for 4-1/2 weeks showed no significant changes in blood chemistry, liver function, urinalysis or histology. Side effects were alertness, tenseness, dilation of pupils, dryness of mouth and slight ataxia.
2. BENACTYZINE HYDROCHLORIDE (Concluded)

SITE AND MODE OF ACTION

Depresses certain centers in frontal part of thalamus [6]. Inhibits the transmission of nerve impulses between neurons [4,5].

REFERENCES


3. p-Butylmercaptobenzhydryl-2-dimethylaminoethyl sulfide

Trademark for p-butylmercaptobenzhydryl-2-dimethylaminoethyl sulfide is Covatin (Lundbeck, Copenhagen).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{21}\text{H}_{29}\text{NS}_{2} \quad 359.60 \]

STRUCTURE

![Structure Diagram]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid (hydrochloride) [1].
Melting Point: 131-132°C (hydrochloride) [1].
Reactions: With concentrated sulfuric acid, a very strong carmine red color which disappears immediately upon the addition of butylphenyl sulfide [2].

PHARMACOLOGY

Animal

Spasms induced by either acetylcholine $5 \times 10^{-8}$, histamine $5 \times 10^{-8}$ or barium chloride $2 \times 10^{-4}$ g/ml on isolated guinea pig ileum were relaxed 80-100% with $2 \times 10^{-6}$ g/ml of Covatin [2,3]. Dilates coronary arteries in vitro and has a surface anesthetic effect of same order as cocaine [2]. In pretreated mice, prolongs the effect of hexobarbital-induced sleep (50 mg/kg) but has no hypnotic effect [2]. SD$_{50}$ (sedative dose) (mouse) 9.2 mg/kg (i.p.) and CD$_{50}$ (convulsant dose) 247 mg/kg [3].
3. p-Butylmercaptobenzhydryl-2-dimethylaminoethyl sulfide (Continued)

PHARMACOLOGY (Concluded)

In clinical study, was found to inhibit sexual desire of male dogs [4] and to have a calming effect on psychoneurotic race horses [5].

CLINICAL

Daily dose of 150 mg for 25 days relieved nervousness, restlessness and anxiety syndromes in man [6] and also showed good spasmylytic and sedative effect [2,6]. When psychotics were treated with 150-200 mg daily, poor results were obtained; only paranoid delirium case responded to therapy [7].

TOXICITY

Man

20 mg was excreted daily in the urine of subjects given 150 mg daily, showing that the main part of Covatin is broken down in the body [2]. The drug was also administered for 66 days at a dose of 150 mg daily without any observed side effects [6]. Abnormal methemoglobin or other inactive hemoglobin not observed when 300 mg daily was given for 1 week [2], and no side effects were noticed at the same dose for 46 days [6]. However, in another study 300 mg daily for 6 days caused nausea and increased restlessness in some patients [6].

Animal

LD_{50} (mouse) 116 mg/kg (i.p.) [3], 44 mg/kg (i.v.) and 1500 mg/kg (p.o.) [2]. Mice displayed excitation, convulsions, complete exhaustion and finally death, without a specific organ picture [2]. Rats given 1 g/kg (s.c.) exhibited a normal blood picture. Cats injected with 5 mg/kg (i.v.) and 50 mg/kg (s.c.) showed no increase in methemoglobin [2]. 3-4 kg rabbits, injected with 100 mg of Covatin (i.v.) daily for 5 days, excreted 2-20 mg in urine [2].
3. p-Butylmercaptobenzhydryl-2-dimethylaminoethyl sulfide (Concluded)

SITE OF ACTION

Acts on higher centers of CNS, probably in the cerebral cortex [2].

REFERENCES


4. CHLORPROMAZINE HYDROCHLORIDE

Trademarks for 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride are Thorazine (Smith Kline & French Laboratories), Largactil (Rhone-Poulenc), Megaphen (Eayer).

MOLECULAR FORMULA AND WEIGHT [1]

\[ C_{17}H_{19}N_2SCl \cdot HCl \]  \[ 355.32 \]

STRUCTURE [2]

PHYSICAL AND CHEMICAL PROPERTIES [1]

Form and Color: Gray-white crystalline powder.
Melting Point: 194-197°C.
Solubility: S. 1000 mg/ml water at 26°C; v.s. methanol, ethanol, chloroform; i. ether, benzene.
Stability: 5% and saturated aqueous solutions are stable for more than 24 hours. Photosensitive.

PHARMACOLOGY

Man

Chlorpromazine potentiates the action of CNS depressants such as opiates, anesthetics, sedatives and alcohol. Intramuscular route reduces blood pressure in both normotensive and hypertensive patients, but tolerance soon develops to this hypotensive effect. EKG studies show no definite evidence of irregularities resulting from 25-50 mg (p.o. or i.m.). EEG studies show that the drug produces a pattern similar to normal sleep.
PHARMACOLOGY (Concluded)

Animal

Threshold emetic dose of apomorphine was increased 2-1/2 to 4 times in dogs receiving 1.5 mg/kg (s.c.). Protective against morphine and hydergine-(ergot)-induced emesis [3]. Apomorphine emetic response completely abolished on 5 mg/kg [4]. In cats, 0.8-8.5 mg/kg produced a rapid fall in blood pressure [5] and blocked or even reversed the pressor effects of adrenaline [5-7]. Potentiates the anesthetic action of barbiturates [5] and of hypnotics, analgesics, muscle relaxants and general anesthetics [7]. Prevented the muscarinic effect of acetylcholine in the cat [5] and is antagonistic to nicotine-induced tremors and convulsions in the rabbit [7,8]. Also showed a weak spasmolytic and vasodilative activity in rats [7].

CLINICAL

Chlorpromazine controls psychomotor activity in mania, schizophrenia, senile dementia and a number of psychoses resulting from organic lesions. Acute alcoholism, delirium and withdrawal from addicting agents are also greatly controlled [9,10]. It is also used to control severe nausea and vomiting resulting from gastrointestinal disease, uremia, cancer, infections, pregnancy, operative procedures, irradiation and a number of drug therapies [10]. Used adjunctively in psychosomatic indications for relief of stress symptoms [10]. Has been used adjunctively in surgical procedures employing controlled hypothermia [11]. Also used successfully, without untoward effects, for control of anxiety in epilepsy.

TOXICITY

Man

Acute: 390 tablets of 25 mg (9,750 mg) ingested in suicide attempt. After 1 hour, symptoms of drowsiness, confusion, ataxia, shock and visual hallucinations; after 3 hours, respiratory collapse. Liver function, blood pressure and urine remained at normal levels. Patient recovered with symptomatic therapy [12].

15
4. CHLORPROMAZINE HYDROCHLORIDE (Continued)

TOXICITY (Concluded)

**Man**

**Chronic:** Jaundice, without any significant liver abnormalities, was reported in about 1% of patients [10]. Agranulocytosis and leucopenia also occurred in a small percentage of cases. Side effects observed were skin reactions, parkinson-like symptoms, dry mouth and vivid dreams. Some evidence that convulsive threshold lowered in epileptics; such cases required maintenance of an anticonvulsant agent.

**Animal**

**Acute:** LD$_{50}$ (mouse) 50 mg/kg (i.v.) and 75 mg/kg (p.o.); (rabbit) 15 mg/kg (i.v.); (rat) 25 mg/kg (i.v.) [7] and 350 mg/kg (p.o.). Mice and rats given 10-20 mg/kg (s.c.) appeared to be in a central depressive state [7]. Dogs and cats given 2.5-3.0 mg/kg (i.v.) showed marked depression and ataxia [3].

**Chronic:** Daily administration of 20 mg/kg (s.c. or p.o.) for 1 month produced no significant changes in behavior, growth patterns or histopathology [7]. Rats given 10 mg/kg (p.o.) and guinea pigs 10 mg/kg (s.c.) for 90 days showed a slight decrease in liver weight, but only the rat showed an increase in weight of adrenals and testes.

**MODE OF ACTION**

Selective depression of emetic chemoreceptor trigger zone and depression of the ascending reticular activating system of the brain stem; indeterminate effects on certain subcortical nuclei, particularly the hypothalamus [3].

**METABOLISM**

Chlorpromazine is known to be converted, in part, to the sulfoxide, but the major metabolites are still unknown.
4. CHLORPROMAZINE HYDROCHLORIDE (Continued)

ANTIDOTE

10 g chlorpromazine ingested in suicide attempt. Gastric lavage, penicillin and antishock measures (methamphetamine hydrochloride i.v.); respiratory collapse responded to atropine, amphetamine sulfate and picrotoxin [12]. Hypotensive reactions: symptomatic therapy with such agents as amphetamines or caffeine for stimulation, norepinephrine or Neo-Synephrine for pressor effect--epinephrine should not be used since its action may be reversed [2,12,13].

REFERENCES


REFERENCES (Concluded)


5. DEXTROAMPHE TAMINE

Trademark for d-2-amino-1-phenylpropane is Dexedrine (Smith Kline & French Laboratories).

MOLECULAR FORMULA AND WEIGHT

C₉H₁₃N  366.46 (sulfate)

STRUCTURE

\[
\text{NH}_2\hspace{1cm}\text{CH}_2-\text{CH}-\text{CH}_3
\]

PHYSICAL AND CHEMICAL PROPERTIES [1]

Form and Color: White crystalline powder (sulfate).
Taste and Odor: Bitter, odorless (sulfate).
Melting Point: 144-145°C (hydrochloride), above 285°C (sulfate).
Specific Rotation: +20.0-23.5 (400 mg in 10 ml solvent).
Solubility: S. 1 g/10 ml water, 1 g/800 ml alcohol; i. ether.
Identity: Benzoyl derivative MP 155-158°C.

PHARMACOLOGY

Man

Dextroamphetamine at ordinary oral doses did not have sufficient peripheral action to produce any significant change in blood pressure [2]. Patients were given 5-15 mg daily for 2-8 weeks. There was little or no effect on their basal metabolism [3-5] and no significant effect on the blood chemistry [5].

Animal

Dogs administered 10-20 mg (s.c.) of the drug before meals lost appetite and weight for periods up to 3 weeks. Liver, bone marrow and kidney were normal [6]. Dogs and rabbits on therapeutic doses
5. DEXTROAMPHETAMINE (Continued)

PHARMACOLOGY (Concluded)

exhibited very little change in their cardiovascular systems [7]. Rats showed greatest central stimulant activity when administered dextro-amphetamine 2.5 mg/kg (s.c.) as compared with 75 other sympathomimetic amines [8]. Threshold stimulant dose was 0.125 mg/kg (s.c.) [8]. The drug also had a good stimulating effect on respiratory depression produced by dolophine [9]. Effects of epinephrine and acetylcholine on isolated rabbit ileum were inhibited [7]. Convulsive threshold was raised in rabbits [10] and pain threshold raised in dogs [11]. Potentiates morphine analgesia [12,13].

CLINICAL [2]

Dextroamphetamine (5-30 mg daily) has been used successfully in depressive states, obesity, alcoholism, epilepsy, narcolepsy, parkinsonism, enuresis, postoperative and behavioral problems in children.

TOXICITY

Man

Acute: Ingested 42 dextroamphetamine spansules 15 mg (630 mg). Mildly excited but easily calmed, blood pressure normal and pulse 110/minute. Doses of 60-80 mg in 48 hours and 40-110 mg in 72 hours showed no adverse effects [14].

Chronic: Ingested 15 mg daily for 56 days with no effect on kidneys or the liver [6,15]. 15 mg daily for 9 years and 120-240 mg daily for 2-1/2 years given without harmful results [16].

Animal

In rats death occurred on 10 mg/kg (s.c.), LD₅₀ 20 mg/kg (s.c.) [8].

LD₅₀ (mouse), caged in groups, 15 mg/kg (i.p.); caged individually, 110 mg/kg (i.p.) [17].
5. DEXTROAMPHETAMINE (Continued)

MODE OF ACTION

Dextroamphetamine is believed to inhibit the enzyme amine oxidase, thereby keeping CNS partially depressed [18].

ANTIDOTES

Magnesium sulfate (p.o.), phenobarbitone sodium (i.m.) and sodium amytal [19].

REFERENCES


REFERENCES (Concluded)


6. DIETHAZINE

Trademarks for 10-(β-diethylaminoethyl)-phenothiazine hydrochloride are Diparcol (Rhône-Poulenc) (May & Baker); Casantin (Cassella); Latibon (Bayer).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{18}\text{H}_{22}\text{N}_{2}\text{S} \cdot \text{HCl} \quad 334.90 \]

STRUCTURE

![Chemical Structure of Diethazine]

PHYSICAL AND CHEMICAL PROPERTIES

- Form and Color: Crystals [1].
- Melting Point: 183-185°C [1-3].
- Boiling Point: 208-212°C (6 mm Hg), 190-195°C (0.6 mm Hg). (Free base).
- Identity: Pink color with concentrated H₂SO₄, pink to yellow with concentrated HNO₃ and dark red with fuming HNO₃ [4].

PHARMACOLOGY

Gastric secretion reduced markedly by administration (i.p.) of diethazine. Compound reported to have both parasympatholytic and sympatholytic activity [1,4].

CLINICAL

Diethazine may have applicability in the treatment of parkinsonism [5]. However, has been reported too toxic for such use [7].
6. DIETHAZINE (Concluded)

TOXICITY [6]

Animal

\[ \text{LD}_{50} \text{ (mouse)} = 225-250 \text{ mg/kg (i.p.)} \]

SITE AND MODE OF ACTION

Reported to depress the polysynaptic flexor reflex in the thalamic cat [5].

REFERENCES


7. DIMETHYLYN

Trademark for 2,2-diisopropyl-4-hydroxymethyl-1,3-dioxolane is Dimethylane (National Drug Company).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{10}\text{H}_{20}\text{O}_{3} \] 188.26

Analysis: C \( \text{Calc.} \) 63.79\% H \( \text{Calc.} \) 10.71\% [1] C \( \text{Found} \) 63.50\% H \( \text{Found} \) 10.52\%

STRUCTURE

\[ \text{CH}_2\text{OH} \]

\[ \text{O} \]

\[ \text{CH(CH}_3)_2 \]

\[ \text{O} \]

\[ \text{CH(CH}_3)_2 \]

PHYSICAL AND CHEMICAL PROPERTIES

Boiling Point: \( 115^\circ \text{C} (9 \text{ mm Hg}) \).
Density: \( d^{21} = 0.995 \).
Refractive Index: \( n^2_D = 1.4502 [1]. \)

PHARMACOLOGY

Produced transient muscular relaxation and paralysis in the mouse. Mean paralyzing dose, \( \text{ED}_{50} \) 0.82 ± 0.18 mM/kg (i.p.) [2].

CLINICAL

 Reported effective in management of anxiety, tension states in menopause [3] and in dysmenorrhea [4,5]. One report showed reserpine-
7. DIMETHYLYN (Concluded)

CLINICAL (Concluded)

dimethylyn effective in a majority of patients with various mental disorders, particularly those characterized by anxiety and tension [6].

TOXICITY

LD$_{50}$ (mouse) 3.88 ± 0.39 mM/kg (i.p.) [2]. No toxic reactions reported on a daily dose of 1 g.

SITE AND MODE OF ACTION

Depressant action on CNS [2]. Blocks the transmission of abnormal impulses at the spinal interneurons [6].

REFERENCES


8. HYDROXYZINE

Trademark for 1-(p-chlorbenzhydryl)-4-[2-(2-hydroxyethoxy)-ethyl] piperazine is Atarax (Pfizer-Roerig; Union Chimique Belge).

MOLECULAR FORMULA AND WEIGHT [1]

\[ \text{C}_{21}\text{H}_{27}\text{N}_{2}\text{O}_{2}\text{Cl}\cdot2\text{HCl} \quad 477.84 \]

STRUCTURE

![Molecular Structure]

PHYSICAL AND CHEMICAL PROPERTIES [1,2]

Form and Color: White crystalline powder.
Melting Point: 191-194°C.
Solubility: S. water, alcohol; i. ether.

PHARMACOLOGY [1]

**Man**

Effects of hydroxyzine are neurosedation, induction of sleep and muscular relaxation.

**Animal**

Hydroxyzine injected at a dose of 50 mg/kg (i.p.), 60 minutes prior to injection of pentylenetetrazol 125 mg/kg (s.c.), prolonged period of survival of mice but did not prevent crises or eventual death. Drug administered in rats (p.o. and s.c.) provoked an average temperature drop of 1.6°C after 1 hour. Significant analgesic effect observed in
PHARMACOLOGY (Concluded)

rats on doses of 50 mg/kg (s.c.) and 100 mg/kg (p.o.). Prevented apomorphine-induced emetic effect in dogs and also appeared to be a good antifibrillant. Antihistaminic activity was reported, as well as prevention of nicotine-induced trembling in rabbits.

CLINICAL

Conditions accompanied by nervous excitation, insomnia and muscular hypertonia respond well to hydroxyzine. Anguish due to emotional shock and anxiety neuroses of long duration were modified by 10-100 mg fed daily for 1-10 weeks. Controls non-psychotic hyperemotivity and tension. [1,3,4]

On the other hand, it has been reported that hydroxyzine has limited clinical usage [5].

TOXICITY [1,2]

Man

Patients receiving 100-400 mg daily for several months showed no symptoms of renal, hepatic or hematological involvement. No impairment of reflexes was observed, and the drug did not induce hypnosis or torpor. Side reactions occasionally reported were drowsiness, asthenia, nervous restlessness (feeling of unsteadiness, tremor) and dryness of mouth.

Animal

LD₅₀ (rat) 45 mg/kg (i.v.); maximum dose tolerated (p.o.) was 850 mg/kg, average 690 mg/kg. Rats injected daily for 30 days without mortality (10 mg/kg, 100 mg/kg, and 200 mg/kg); 80% survived administration of 200 mg/kg daily (p.o.) for 30 days.
REFERENCES


9. IPRONIAZID

Trademark for 1-isonicotinyl-2-isopropylhydrazine is Marsilid (Hoffmann-La Roche Inc.)

MOLECULAR FORMULA AND WEIGHT [1]

\[ C_9H_{13}N_3O \] 179

Analysis:  
Calc. \( 60.3\% \) 7.3%  
Found \( 60.4\% \) 7.3%

STRUCTURE

![Chemical structure of Iproniazid]

PHYSICAL AND CHEMICAL PROPERTIES [1]

Form and Color: White needles.  
Melting Point: 112-113°C.  
Solubility: V.s. water, alcohol.  
Stability: Stable in dry form.

PHARMACOLOGY

**Man**

Iproniazid acts as a "psychic energizer" [2-5], CNS stimulant producing
9. IPRONIAZID (Continued)

PHARMACOLOGY (Concluded)

A sense of healthy well-being [2,4]. It heightens affective mood and
stimulates mental processes; increases vitality, diminishes sleep
requirements, and raises resistance to fatigue; improves appetite, and
promotes weight gain [6,7] and positive nitrogen balance [2]. Iproniazid
may alter autonomic balance, producing effects of sympathetic excitation,
i.e., constipation, disturbance of salivation, difficulty in starting mictu-
rition and loss of erection [6].

Animal [26,27,33]

In standard pharmacological tests iproniazid is characteristically inert.
In dogs, as high as 8 mg/kg produced no blood pressure changes and no
effect on the pressor response to vagus stimulation, carotid occlusion,
serotonin and acetylcholine. In cats, doses of 8 mg/kg (i.v.) caused
arterial blood pressure depression up to 25 mm Hg of short duration.
It has no blocking effects on ganglionic or neuromuscular transmission
in the cat, does not suppress salivation or diminish lacrimation with
50 mg/kg (s.c.) in rabbits; local application of 1.0% solution (rabbit eye)
produces no mydriasis or local anesthesia. It has less than 1/200 the
activity of atropine in counteracting the increased motility induced by
acetylcholine in isolated rabbit intestine, and approximately 50 times
the activity of atropine in the broncholytic aerosol test. In doses up to 16
mg/kg it has no effect on pyrexia induced in rabbits by Escherichia coli.
In dogs, daily doses of 10-20 mg/kg (p.o.) produce transient CNS hyper-
activity, i.e., muscular twitching and increased amplitude of EEG spikes.

CLINICAL

Iproniazid has been found clinically effective in the treatment of depres-
sive states [2,5,8,9,34], phobic-obessive neuroses [10], depressions
associated with schizophrenia [4,11], senile anxiety and mild depres-
sions [12], as an adjunct in psychotherapy of the depressed, withdrawn
and regressed patients [2,3,5]. Iproniazid is chemotherapeutically effec-
tive in pulmonary tuberculosis, evidenced by sputum conversion, X-ray
changes, reduction of fever, improved physical and mental well-being,
enhanced appetite and weight-gain [7,12,13,20,35-37]. Iproniazid promotes
healing of tuberculous bone and joint lesions [14,15], tubercular wounds
in skin and fascia [16] and bone and draining lesions of nontuberculous
9. IPRONIAZID (Continued)

CLINICAL (Concluded)

origin[17]. Efficacious results have been reported in the control of
distressing symptoms associated with rheumatoid arthritis[12],
rheumatic disease[18] and angina pectoris[19].

TOXICITY

Man

Acute: Symptoms of massive overdosage (2 or more g ingested in sui-
cide attempt) are tachycardia, marked fall in blood pressure, profuse
diaphoresis, pupils unresponsive to light, semi-stupor and insomnia.
Extreme caution should be exercised in administration of barbiturates,
norepinephrine and cortisol because iproniazid potentiates these drugs.

Chronic[15,20-25]: Administration of 4 mg/kg daily in divided doses for
2 months and similarly 10 mg/kg for 40 days produced little change in
hemoglobin levels or erythrocyte count, and slight losses were restored
promptly and spontaneously; leukocyte count and sedimentation rate are
essentially unaffected; cephalin flocculation test revealed no evidence of
liver damage[23]. No significant changes in EKG, icterus indices[23],
blood proteins, albumin-globulin ratio, acid or alkaline phosphatase,
17-ketosteroids, platelets or urine were noted[15]. Untoward reactions
reported -- twitching of extremities, hyperflexia, vertigo, constipation,
drowsiness, mouth dryness and delayed starting of micturition[21-23].
Clonus, psychotic symptoms, withdrawal syndrome, orthostatic hypo-
tension, edema, toxic hepatitis resulting in jaundice, hepatocellular
necrosis and fatalities have all been reported to occur during adminis-
tration of iproniazid[21,22,24,25].

Animal

Acute[26,27]: LD₅₀ (mouse) by various routes ranges from 683 mg/kg
to 968 mg/kg; (rabbit) 125 mg/kg (p.o.), 117 mg/kg (i.v.); (rat) 383 mg/kg
(p.o.). Single doses in acutely toxic range induce signs of CNS stimu-
lation, convulsions terminating in death due to respiratory failure. In
TOXICITY (Concluded)

dogs, no signs of toxicity noted except muscular twitching until doses of 70 mg/kg (free base) were administered. Injected intrathecally, doses of 1.0 and 2.0 cc of 5% solutions of the hydrochloride produced delayed signs of respiratory, cardiac and neurological changes and death after 12 to 22 days.

Chronic: Doses of 5, 20, 80 mg/kg daily (p.o.) added to the diets of rats over 13 weeks produced, at the higher doses, decline in hemoglobin values, increased destruction of erythrocytes, engorgement of spleen and bone marrow hyperplasia. Growth was slightly retarded but there was no effect on survival [26,27].

In dogs, dose levels of 3.5, 7.0, 14.0 mg/kg daily for 13 weeks by, respectively, p.o., i.v. and i.m. routes were well tolerated, but the dogs given the highest dose showed a reduction in erythrocytes, hematocrit and hemoglobin. Grossly, the dogs given the highest dose displayed enlarged, dark purple, firm spleens, and the bone marrows were hemorrhagic. [26,27]

In the Macacus rhesus monkey given 18 mg/kg daily for 12 weeks there was no change in behavior; no weight loss or lowering of hemoglobin occurred. Blood serum, blood cell, bone marrow and urine findings showed that monkeys can tolerate iproniazid in doses comparable with those used in experimental chemotherapy of tuberculosis [28].

MODE AND SITE OF ACTION

Iproniazid affects 9 different enzyme systems, but is chiefly a potent inhibitor of amine oxidase [29], inhibiting the enzyme in brain and liver of animals [30]. Inhibition of the enzyme in the brain may account for CNS excitatory activity. Blocking of the detoxifying function of the liver partly accounts for the toxicity of cumulative doses of the drug and for potentiation [31] of barbiturate hypnosis in animals.

METABOLISM

Iproniazid is rapidly split into isopropyl hydrazine (the active moiety)
9. IPRONIAZID (Continued)

METABOLISM (Concluded)

and isonicotinic acid, the latter being promptly excreted in the urine. The long duration of action of iproniazid as an amine oxidase inhibitor may be accounted for by the attachment of the isopropyl hydrazine moiety to the amine oxidase [27].

REFERENCES


REFERENCES (Continued)


35
REFERENCES (Continued)


36
REFERENCES (Concluded)


10. MEPAZINE

Trademark for 10-[(1-methyl-3-piperidyl)methyl]-phenothiazine is Pacatal (Promonta, Hamburg; Warner-Chilcott Laboratories).

MOLECULAR FORMULA AND WEIGHT

\[ C_{19}H_{22}N_2S \cdot HCl \]

346.93

STRUCTURE

![Structure Diagram]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline.
Melting Point: 180-181°C [1].
Boiling Point: 230-235°C (4 mm Hg) [1].
Solubility: S. 1.4 mg/ml water, 25 mg/ml ethyl alcohol.
Stability: >24 hours in water or ethyl alcohol.
Identity: HNO₃ fuming or NaNO₂ + H₂SO₄ gives red color; Ehrlich's reagent gives white precipitate; 10% chloramin solution + CHCl₃ gives violet color; brown precipitate with bromine water [2].

PHARMACOLOGY

Animal

In dogs parasympathetic and sympathetic systems are inhibited. Spasmyolytic effect observed on isolated guinea pig ileum against barium chloride, acetylcholine and histamine. General sedation; local anesthesia; and a potentiating effect on hypnotics, analgesics (morphine,
PHARMACOLOGY (Concluded)

demerol), muscle relaxant agents, and local anesthetics are some effects [3-6].

Calming effect observed in thoroughbred race horses, which had been very tense and had refused to run. 1 g daily (p.o.) had no hypnotic effect and did not decrease their muscular power. When it was given to vicious and noisy dogs (p.o. and parenterally), they became affectionate and quiet [7].

CLINICAL

Normal rhythm was restored in cardiac disturbances on 100-250 mg daily (p.o.), and 50-150 mg relaxed tenseness [8]. Doses of 200-500 mg daily were beneficial for alcoholics and morphine addicts [9]. Aggressiveness, noisiness and incontinence were reduced on 75-225 mg daily in chronic psychotics [10]; and anxiety, confusion, panic and psychomotor excitement were relieved in psychotics given 50-600 mg (i.m. or p.o.) daily [11].

TOXICITY

Man

On 75-225 mg daily there was 5% jaundice and 40% hypertonia reported [10]. In psychotics, drowsiness, temperature elevation, blurry vision, postural difficulty and atonic bladders and bowels were some of the side effects observed from injections (i.m.)[12]. Agranulocytosis has been reported on an average daily dose of 200 mg [13-15]. In another study a majority of psychotics fed 50-600 mg daily experienced serious side effects [11].

Animal [3,16]

LD₅₀ (mouse) 30 mg/kg (i.v.), 275 mg/kg (p.o.) and 750 mg/kg (s.c.); (rabbit) 20 mg/kg (i.v.) and 1000 mg/kg (p.o.). Daily administration of 20 mg/kg (p.o.) to dogs for 6 months produced no untoward results.
REFERENCES


Untersuchungen über N-aldehyd-piperidyl-phenothiazin Derivate.

l'hibernation artificielle. Presse méd. 60(68):5.

(ihre Vorteile, Grenzen und Gefahren).


65(53):1263.

des Herzens und Fehlsteuernngen des vegetativen Nerveusystems.


18(4):142.

[12] Kline, N. S., and G. M. Jacob. 1955. Use of Pacatal (N-methyl-
piperidyl-(3)-methylphenothiazine) in psychiatric patients.
REFERENCES (Concluded)


11. MEPROBAMATE

Trademarks for 2-methyl-2-n-propyl-1,3-propanediol dicarbamate are Miltown (Wallace Laboratories), Equanil (Wyeth Laboratories) and Oasil (Simes, Milan).

MOLECULAR FORMULA AND WEIGHT [1,2]

\[ C_9H_{18}N_2O_4 \] \hspace{1cm} 218.250

Analysis:  \[ N_2 \]
Calc. 12.8%
Found 12.5%

STRUCTURE

\[
\begin{array}{c}
\text{O} \\

\| \\

\text{H}_2\text{N-C-O-CH}_2\text{-C-CH}_2\text{-O-C-NH}_2 \\
\| \\
\text{C}_3\text{H}_7
\end{array}
\]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid [1].
Melting point: 105-106°C [1].
Solubility: S. water (0.34% at 20°C, 0.79% at 37°C), propylene glycol, most organic solvents [3]; i. base, acid [3].
Stability: Stable in dilute acid and alkali, not broken down in gastric or intestinal juices [3].

PHARMACOLOGY

Animal

Dosages of 350-500 mg/kg administered to rats (p.o.) produced moderate ataxia, marked hypotonia and semi-prostration [3]. Mice given 500-2000 mg/kg showed marked ataxia, prostration, hypnosis and finally death at the higher doses [3]. Dosages of 125 mg/kg of the drug showed
PHARMACOLOGY (Concluded)

a hexobarbital potentiating effect in mice. The emetic response in dogs
given 0.1 mg/kg of apomorphine, followed by dosages of 16, 32, 64 and
128 mg/kg of meprobamate, was reduced by 28%, 34%, 49% and 53%
respectively. Protects animals from death caused by toxic doses of
pentylentetrazol and strychnine and also modifies reaction to electro-
shock treatment [4]. No autonomic effects have been observed [3].

CLINICAL

Doses of 400-2400 mg daily (p.o.) relieved chronic anxiety reactions,
tension states, tension headaches and insomnia in a majority of the
cases treated [5-8]. Drug has sedative and hypnotic qualities as well
as muscle relaxant properties [7]. Also used for petit mal and related
minor epilepsies, skeletal muscle spasms and cerebral palsy. Psych-
otics (mostly schizophrenics) were fed 3200 mg daily for 1-6 months;
80% showed improvement of some kind, but only 3% were completely
rehabilitated [9,10].

TOXICITY

Man

Acute: 20 g ingested by a 40-kg woman and 40 g by a man during a
24-hour period produced drowsiness but no adverse effects [6]. 38 g
resulted in a coma for 40 hours, then complete recovery [11]. Cyanosis
and coma lasting 24 hours resulted from 14 g of the drug [12]. Single
doses of 1600-2000 mg (p.o.) caused a 20-30 second low-voltage activity
in the EEG similar to a phenobarbital reaction [13, v. Pfeiffer et al.,
p 734]. A 400-mg tablet gave rise to nausea, vomiting, redness of skin
and edema [13, v. Waggoner, p 776].

Chronic: No serious side effect observed when 1600-2000 mg was
given daily for 1-15 months [6], but allergic skin rash was exhibited by
a few patients [5,6]. Skin rash also reported in 2-1/2% of 200 patients
fed 800-3200 mg daily for 4-1/2 months [9]. Grand mal convulsion
reported 10 hours after withdrawal[14,15], and in a few cases indications
of drug addiction were observed as well as withdrawal symptoms [6,16].
TOXICITY (Concluded)

Schizophrenics given 3200-4800 mg daily for 21 days showed side effects for first few days of therapy [13 v. Hollister et al., p 789]. Blood pressure changes also reported in a few cases [17]. Drowsiness found in 50% of patients during first 2 weeks of therapy at 1200 mg daily in Borrus [7], but in only 5.3% in Osinski [8] and in none in Seling [6].

Laboratory studies failed to reveal any unfavorable effect on blood, kidneys or liver [18,19].

Animal

Acute: White male mice fed 700-1500 mg/kg of meprobamate showed an LD₅₀ of 1280 mg/kg. Monkeys exhibited complete flaccid paralysis for 7 hours when given 400 mg/kg of drug. Respiration and heartbeat were normal, and all recovered spontaneously [3].

Chronic: Large doses of meprobamate (1200 mg/kg daily p.o.) were administered to mice for 17 days. The mice became tolerant to the anticonvulsant effect of the compound, and upon sudden withdrawal showed symptoms of hyperexcitability similar to that caused by cessation of chronic barbiturate administration [20]. No ill effects were observed in mice fed 0.5-1.0% of drug in food for 90 days, but some suppression of growth occurred at 2% [3]. In rats fed 0.5%, 1.0% and 2.0% of drug in food for 15 months, the blood chemistry was unchanged and urine normal [3]. Dogs given 1 g daily for 60-75 days showed normal blood chemistry during test period, and at autopsy no pathological lesions were observed.

MODE OF ACTION

Selective action on the thalamus and a blocking action on spinal interneurons. Does not affect the autonomic functions but has a marked and prolonged depressant effect on multi-neuronal reflexes [18,21,22].
METABOLIC FATE

A portion of the drug is found in urine as a conjugate with glucuronic acid, and 10% is recovered unreacted [5]. The major metabolites of meprobamate are unknown.

ANTIDOTES

An antihistamine, epinephrine and hydrocortisone for any allergic reaction [6,23]. Amphetamine is used for a fall in blood pressure [17], and 3 ml of 10% Metrazol (pentylenetetrazol) solution has been administered (i.v.) in an attempted suicide (8 g meprobamate in single dose)[24].

REFERENCES


REFERENCES (Continued)


REFERENCES (Concluded)


12. METHYL PHENIDYL ACETATE

Trademark for methyl phenyl-2-piperidyl-acetate hydrochloride is Ritalin (CIBA Pharmaceutical Products Inc.).

MOLECULAR FORMULA AND WEIGHT [1]

\[ \text{C}_{14}\text{H}_{19}\text{NO}_2\cdot\text{HCl} \quad 269.77 \]

STRUCTURE

\[
\begin{align*}
\text{NH} & \\
\text{CH-} & \\
\text{CO-} & \\
\text{O-} & \\
\text{CH}_3 & \\
\cdot\text{HCl} & \\
\end{align*}
\]

PHYSICAL AND CHEMICAL PROPERTIES [1]

Form and Color: White powder.
Melting Point: 208\textdegreeC.
Solubility: S. water, 1 g/15 ml 95\% ethyl alcohol.

PHARMACOLOGY [2]

Animal

Reported to have a pronounced psychomotor stimulating effect in animals and to increase coordinated motility. In unanesthetized animals, shows awakening effect in certain narcotic-induced sleep. Potentiates the increase in motility produced by atropine. Blood pressure and heart rate increased, but no other peripheral sympathomimetic effects noticed.

CLINICAL

Drug is clinically effective in reversing the sedative action of promazine. Patients given 10-30 mg (i.v.) and 75-750 mg of promazine increased
CLINICAL (Concluded)

their psychomotor activity, showed increased alertness, freer verbalization and improved articulation. Effects reversal of subcortical depressions induced by promazine. Antidote for CNS depression inadvertently induced by phenothiazine derivatives [3,4]. A dose of 5-20 mg 3 times a day gave good results when used for chronically ill or convalescent patients. Also effectively relieved fatigue and depression in children administered 5-10 mg 3 times a day [5]. Emotional depression or fatigue states responded to 3-6 mg daily. Author also used drug in combination with analgesics, anticonvulsants, antihistamines, antispasmodics, insulin and sedatives [6]. Abnormal senile behavior was greatly reduced in a majority of over-active and negative patients receiving various combinations of methyl phenidyl acetate and reserpine [7].

TOXICITY

LD$_{50}$ (mouse) 40 mg/kg (i.v.), 150 mg/kg (s.c.) and 300 mg/kg (p.o.); (rat) 70 mg/kg (i.v.), 170 mg/kg (s.c.) and 450 mg/kg (p.o.); (rabbit) 30 mg/kg (i.v.), 170 mg/kg (s.c.) and 900 mg/kg (p.o.) [2].

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REFERENCES


13. PERPHENAZINE

Trademark for 1-(2-hydroxyethyl)-4-[3-(2-chloro-10-phenothiazinyl)-propyl]piperazine is Trilafon (Schering Corporation).

MOLECULAR FORMULA AND WEIGHT

\[ C_{21}H_{26}N_3SOCl \] 403.96

STRUCTURE

![Chemical Structure](image)

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid.
Melting Point: 94-95°C.
Absorption Maxima: 37,000 at 254 m\(\mu\) and 4,500 at 311 m\(\mu\) (methanol).
Solubility: V.s. methanol, ethanol, benzene, chloroform, dimethylformamide, maleic and hydrochloric acids; i. water.
Stability: Stable in dark; photosensitive.
Qualitative: Identifiable by infrared or ultraviolet absorption spectra.

PHARMACOLOGY

Man

In psychological testing, perphenazine (20 mg p.o.) had a combination of inhibitory and stimulant properties. It decreased the critical flicker fusion frequency, increased simple reaction time, increased perception of after-images and improved performance in the digit symbol association test [1]. In chronic schizophrenics, 16 mg 3 times a day (p.o.)
PHARMACOLOGY (Concluded)

for 30 days produced significant improvement in the Wittenborn Rating Scale and in dotting and tapping tests. The digit symbol test was also improved [2].

Animal

Perphenazine produces 50% suppression of conditioned avoidance responses in rats at 1 mg/kg (p.o.) or 0.1 mg/kg (s.c.) without blocking the unconditioned response. A 50% suppression of spontaneous locomotor activity is produced by 1.2 mg/kg (p.o.) or 0.14 mg/kg (s.c.). The ED50 for "taming" monkeys is 1.25 mg/kg (p.o.) or 0.009 mg/kg (i.v.). Slight to moderate overt depression without neurological impairment in the mouse, rat, cat, dog or monkey is produced by 1 mg/kg (p.o.) [3,4]. Perphenazine is 11-56 times more active than chlorpromazine in inhibiting apomorphine-induced emesis in dogs [5,6]. It is also effective against morphine, Hydergine- or deslanoside UPS-induced emesis [6]. Perphenazine is equipotent to chlorpromazine in producing adrenergic block, hypotension, barbiturate potentiation, local irritation or inhibition of gastric secretion. It is one-half as active as chlorpromazine in anticholinergic or antihistaminic activity [7,8]. Perphenazine (2 mg/kg s.c.) produces almost 100% protection of mice administered lethal doses of tetanus toxoid, Brucella endotoxin or various bacterial infections [9]. At 1 mg/kg (i.v.) in the dog it increases hemorrhagic shock survival from 2% to 37%. At 1.5 mg/kg (i.m.) perphenazine increases Noble-Collip shock survival of rats from 31% to 88% [10]. In parabiotic rats perphenazine 0.8 mg/kg (s.c.) produced marked depression of the injected and no depression of the uninjected parabiont [11].

CLINICAL

Perphenazine is a potent and effective phenothiazine tranquilizer. It is useful in controlling anxiety, tension and agitation in a wide variety of mental and emotional conditions. The drug is capable of alleviating psychomotor overactivity and symptoms of emotional stress without apparent dulling of mental acuity [1,12-23]. Perphenazine is a powerful
CLINICAL (Concluded)

antiemetic, and is used for nausea and vomiting due to various causes such as gastrointestinal disease, surgery, radiation therapy, uremia, cancer, pregnancy, drugs and psychogenic factors [24-29]. Total daily dosage is selected according to severity of symptoms, but frequently falls within the range of 6-24 mg daily (p.o.). In severe psychotic disorders, administration of 32-64 mg daily or more (p.o.) may be required. Rapid onset of effect is obtained when perphenazine is given by injection in doses of 5 or 10 mg (i.m.).

VETERINARY

In addition to the human indications of the drug in the treatment of behavioral disturbances, nausea and vomiting, and pre-anesthetic medication, perphenazine (like other of the tranquilizing drugs) is used in domestic animals to reduce the incidence and severity of the pneumonic-shipping fever syndrome, to promote growth, to minimize weight loss in shipment, and to facilitate readjustment to a new environment [30,31].

TOXICITY

Man

Acute: Accidental ingestion of an estimated 120-160 mg by a 2-year-old child resulted in drowsiness followed by excitement, confusion, tachycardia and pseudoparkinsonism. Blood pressure, respiration, temperature and appetite remained within normal limits, and the patient recovered completely with symptomatic therapy [32].

Chronic: 12 subjects received perphenazine in dosages of 12-48 mg daily for 5 to 8 months. No significant changes occurred in blood studies, pulse rate, blood pressure, urinalysis or liver function [32]. Side effects are minimal with dosage not exceeding 24 mg daily (p.o.) [13,14,16,19,20,23]; they have disappeared promptly following withdrawal or reduction of dosage and include such signs as somnolence, restlessness or extrapyramidal reactions, the latter readily controlled by antiparkinson drugs. Allergic phenomena, weakness, dizziness, anxiety or lactation rarely occur; tachycardia, edema or jaundice very rarely; photosensitivity or agranulocytosis have not been observed.

Animal

Acute: LD50 (mouse) 120 mg/kg (p.o.), 37 mg/kg (i.v.); (rat) 318 mg/kg (p.o.), 124 mg/kg (i.p.), 36 mg/kg (i.v.); (dog) greater than 100 mg/kg (p.o.), 51 mg/kg (i.v.). Survival observed over 5 days [3,4].
13. PERPHENAZINE (Continued)

TOXICITY (Concluded)

Subacute: Following perphenazine 5, 10 or 20 mg/kg (p.o.) daily for 30 days in rats of both sexes, no significant changes were noted in the hematological or gross and microscopic state of the tissues. A 20-60% suppression of growth occurred, increasing with dosage. Following 25 mg/kg (p.o.) daily in the dog, no significant changes were noted in the neurological, hematological, blood sugar, non-protein-nitrogen, urinary, renal and kidney function; growth and gross or microscopic state of the tissues [7].

Chronic: No significant histopathologic changes were observed in rats fed 2 and 5 mg/kg or in dogs fed 4 mg/kg of perphenazine daily for 6 months. The initial high doses produced marked suppression of psychomotor activity and slight muscle weakness. There was considerable tolerance development during the course of administration, but no signs of physical dependence following drug withdrawal [7]. Perphenazine (1 mg/kg) fed pregnant rats once daily 12-18 days before delivery and for a total of 36 days produced no significant changes in time for delivery, litter size, growth curves or gross or microscopic pathology [33].

MODE OF ACTION

Selective block of the emetic chemoreceptor trigger zone [6]. Other loci of action unknown.
REFERENCES


REFERENCES (Continued)


REFERENCES (Concluded)


Trademark for 2-p-chlorophenyl-3-methyl butanediol-2,3 is Ultran (Eli Lilly and Company).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{11}\text{H}_{15}\text{O}_{2}\text{Cl} \quad \text{214.5} \]

STRUCTURE

![Chemical Structure](image)

PHYSICAL AND CHEMICAL PROPERTIES

- Form and Color: White crystalline solid.
- Melting Point: 77-78°C.
- Solubility: S. organic solvents; i. water.

PHARMACOLOGY

Animal

Rats or mice given 100-200 mg/kg (p.o.) show a brief period of slight ataxia associated with weakness followed by loss of righting reflex lasting 4-6 hours. Rats given smaller doses (50-80 mg/kg) are protected against the convulsant action of Metrazol (pentylenetetrazol) and against the tonic phase of supramaximal electroshock seizure. Monkeys, dogs and cats have become quiet and less aggressive after adequate doses. EEG and behavioral arousal are easily elicited in these animals [1-4].
CLINICAL

Patients given 300 mg 3 or 4 times daily report reduction in emotional tension and anxiety [5-7]. An unusually high incidence of favorable responses has been reported by patients suffering from premenstrual tension and the menopausal syndrome [8]. The insomnia and extreme nervousness occasionally encountered during steroid therapy can be controlled by 2-3 doses of 300 mg daily [9]. Favorable results have been noted in the treatment of convulsive states [10]. Some clinicians have reported relief of pain related to arthritis and muscle spasm. Therapeutic doses in general do not impair motor or psychic function as measured by standard psychometric tests [11,12].

TOXICITY

Acute: Some patients report lightheadedness, dizziness or sleepiness after doses of 300-600 mg. In a suicide attempt a patient who took 6 g became virtually unresponsive but recovered within 24 hours. Several instances of patients taking 20-30 capsules have been reported without lethal outcome. The highest known dosage was 40-50 pills taken by a woman who then slept soundly for 60 hours with only brief periods of wakefulness.

Chronic: No serious side effects have been reported to date. There have been a few reports of skin rashes which disappeared after the drug was stopped.

MODE OF ACTION

Experiments in decerebrate and spinal cats indicate that phenaglycodol exerts a selective depression of multisynaptic pathways. More detailed studies indicate that some of the effects can be explained on the basis of an action in the anterior portion of the ascending reticular activating system [2,4].
REFERENCES


REFERENCES (Concluded)


15. PHENYLTOLOXAMINE DIHYDROGEN CITRATE

Trademark for N,N-dimethyl-2-(α-phenyl-o-toloyx)ethylamine dihydrogen citrate is PRN (Bristol Laboratories Inc.).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{17}\text{H}_{21}\text{NO} \cdot \text{C}_{6}\text{H}_{8}\text{O}_{7} \quad 447.47 \]

STRUCTURE

\[
\begin{align*}
\text{CH}_2 & \quad \text{phenyl} \\
\text{CH}_3 & \quad \text{O} - \text{CH}_2\text{CH}_2 - \text{N} \\
& \quad \text{CH}_3 \\
& \quad \text{C}_{6}\text{H}_{8}\text{O}_{7}
\end{align*}
\]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid.
Solubility: S. 2 g/100 g water.

PHARMACOLOGY

Man

Phenyltoloxamine is an antihistaminic agent with some anticholinergic and sedative effects. It produces satisfactory daytime sedation at doses of 75-100 mg (p.o.) [1,2] and nighttime sedation at 200 mg [2,3]. 400 mg doses given to healthy college student volunteers produced sedation with a reduction of psychomotor activity and a marked degree of muscle relaxation with no significant alterations of autonomic function [4]. Blood pressure, heart rate, respiration and skin temperature were not significantly altered following 400 mg doses [5].
PHARMACOLOGY (Concluded)

Animal

Phenyltoloxamine is an antagonist of histamine in animals, relaxes intestinal smooth muscle and inhibits spastic responses to cholinergic agents in anesthetized dogs and possesses about the same local anesthetic activity as procaine. Doses of phenyltoloxamine below 10 mg/kg (i.v.) produce only slight transient decreases in blood pressure with little or no effect on respiration in anesthetized dogs. Larger doses cause more pronounced depressor responses accompanied by transient respiratory depression followed by hyperventilation [6]. Phenyltoloxamine decreases spontaneous activity in mice when administered at 50 mg/kg (i.p.). It prevents the tonic extensor component of electroshock in mice at 80 mg/kg (i.p.). Hexobarbital hypnosis is prolonged by the drug. Administration of 5-10 mg/kg (i.v.) to dogs produces some sedation, ataxia and muscle relaxation. Large doses are convulsant [7].

CLINICAL

Phenyltoloxamine produces adequate daytime and nighttime sedation in anxiety states [1-3,8]. Geriatric patients diagnosed as chronic schizophrenics or chronic brain syndrome cases whose behavior and sleeping habits were unacceptable obtained relief from tensions, fears and aggressive features when placed on phenyltoloxamine therapy. The sleep cycle was notably improved as well [9]. Improvement in behavior and appetite, with lessening of depression and withdrawal, was observed in deteriorated and depressed psychotics given phenyltoloxamine [10]. The compound has shown promise of usefulness in the treatment of acute alcoholism ("binge"-type drinkers) [11]. The drug has been reported effective in managing non-neurotic or motivated anxiety and in controlling the manic phase of affective psychosis [8]. In a study of rapidity and accuracy of learning verbal paired associates under drug influence, it was reported that phenyltoloxamine did not depress learning speed and accuracy even at markedly sedative doses (400 mg) [12]. The compound has also been of value in the treatment of pruritus and urticaria [13] and in other dermatologic conditions as well [3].
TOXICITY

Man

Toxicity studies employing daily doses of 200-1600 mg (p.o.) for periods ranging from 1 to 25 weeks showed no alterations in blood count, urinalysis or blood chemistry, and no toxic symptoms were observed other than occasional nausea and excessive sedation at the higher doses [14]. In another study only 5 patients in a total of 2,380 experienced side reactions (principally soporific effects) when given a total of 200-600 mg over a 24-hour period [2].

Animal

Acute: LD$_{50}$ (mouse) 246 mg/kg (i.p.), 55 mg/kg (i.v.), 1127 mg/kg (p.o.); (dog) 50 mg/kg (i.v.). Lower doses consistently cause signs of CNS depression, ataxia and muscle weakness. Toxic doses cause convulsions, emesis and death by respiratory paralysis.

Chronic: Dogs receiving 10, 20 and 40 mg/kg (p.o.) daily for 1 year showed no changes from control animals with regard to weight, blood count, blood chemistry, urinalysis and EKG. Daily administration of 25 and 50 mg/kg (p.o.) to rats for a period of over 1 year has resulted in no obvious toxic manifestations.
REFERENCES


REFERENCES (Concluded)


16. PIPRADOL HYDROCHLORIDE

Trademark for α,α-diphenyl-2-piperidinemethanol hydrochloride is Meratran (Wm. S. Merrell Company).

MOLECULAR FORMULA AND WEIGHT

C₁₈H₂₁NO·HCl  303.84 [1]

STRUCTURE [1]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid [1,2].
Melting Point: 308-309°C (decomposes) [1].
Solubility: S. 1 g/60 g hot water [2].

PHARMACOLOGY

Animal

Showed coordinate hyperactivity and changes in behavior pattern in experimental animals, but convulsions did not occur with less than LD₅₀ doses [2]. Reported to antagonize mild to moderate degrees of barbiturate depression in rabbits [2] and to possess little or no pressor action measured in cats anesthetized with sodium amytal and in atropinized dogs anesthetized with Dial (diallylbarbituric acid) and urethane.
PHARMACOLOGY (Concluded)

solution (CIBA [2]. Large doses in lightly pentobarbitalized rabbits caused a depression of respiration [2].

CLINICAL

Reported useful for narcolepsy [3,4], reactive depressions [4], non-delusive schizophrenia with depressive features, and psychomotor retardation with a blocking of communications [5]. Successfully used in drug-induced lethargy caused by anticonvulsants; antihistamines; chlorpromazine; reserpine; alcoholic hangover; and the depression of parkinsonism, diabetes, and hepatitis [3].

Narcoleptics on 20-100 mg daily were relieved and showed marked improvement [3]. Reactive depression responded well on a daily dose of 5 mg for 6 weeks, and endogenous or psychotic depression responded favorably on 25 mg daily for 6 weeks [4].

Carefully selected cases of alcoholism, precipitated by depression, were helped on 2-8 mg daily for 10 days [6]; 2 mg daily also used in geriatrics to relieve the depression caused by a fear of impending deterioration and death [7].

TOXICITY

Man

Acute: Child, 25 pounds, 2-1/2 years old, ingested 15 mg. An hour later frenzied activity, excitability, continuous vocal expression, voracious appetite, continual brushing of hand across forehead even during sleep that night. Next morning blood pressure was 180/120, pulse was 160, and there was complete recovery [4].

Chronic: Depressed patients have taken 15-25 mg daily and 7 narcoleptics 100 mg daily for a year without untoward effects [3]. Cardiovascular responses, liver function tests, blood counts and urinalyses were reported normal during that period. Anxiety symptoms developed in 15% of cases on 2.5 mg 3 times a day [3].
TOXICITY (Concluded)

Animal

LD$_{50}$ (rabbit) 15 mg/kg (i.v.); (rat) 240 mg/kg (s.c.), 180 mg/kg (p.o.) and 30 mg/kg (i.v.) [2,4]. Lethal doses (i.v., p.o.) to mice, rats, guinea pigs and rabbits cause tremors and convulsions, and death by respiratory depression during convulsions. In dogs (p.o.) and rats (s.c.), lethal doses cause a continuous intense activity and sudden death during hyperactivity [2].

MODE AND SITE OF ACTION

Reported to stimulate reticular substance of upper brain stem tegmentum in rabbit which in turn stimulates the cortex. Possibly a CNS stimulant without action on the autonomic nervous system [3].

ANTIDOTE

Sodium amytal (i.m.) [4].
REFERENCES


17. PROCHLORPERAZINE

Trademarks for 2-chloro-10-[3-(1-methyl-4-piperazinyl)-propyl]-phenothiazine are Compazine (Smith Kline & French Laboratories); Stémét il (Rhone-Poulenc).

MOLECULAR FORMULA AND WEIGHT

\[ \text{C}_{20}\text{H}_{24}\text{N}_{3}\text{SCl} \]
373.96

STRUCTURE

![Chemical Structure of Prochlorperazine]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: Clear, pale amber, viscous liquid with a slight odor.
Boiling Point: 219-222°C (0.3 mm Hg).
Absorption Maxima: 435 m\(\mu\), 605 m\(\mu\), 625 m\(\mu\), 639 m\(\mu\) (dihydrochloride).
Solubility: V. s. ethanol, benzene and chloroform; i water.
Stability: Very stable in dark; slightly photosensitive.
Qualitative: Identifiable by infrared, ultraviolet absorption spectra.

PHARMACOLOGY

**Man**

In a study of psychomotor performance, prochlorperazine (10 mg p.o.) caused a significant decrease in muscular coordination in 18 subjects[1]. In another study in 16 subjects 30-60 mg (p.o.) proved to be a more powerful psychomotor stimulus than caffeine or amphetamine, as shown
PHARMACOLOGY (Concluded)

by decreased reaction time and improved hand steadiness, digit span, digit symbol and cancellation test scores [2].

Animal

In vivo prochlorperazine is 3-6 times as active as chlorpromazine for inhibiting apomorphine-induced emesis in dogs [3-6]. It is also effective against emesis induced by Hydergine and swing [7]. Spontaneous motor activity in mice is depressed 50% by 6 mg/kg (p.o.) [6]. Prochlorperazine blocks conditioned responses in rats without interfering with the responses to unconditioned stimuli [6,8]. It increases the threshold to minimal electroshock seizure in mice [9], and it exhibits a moderate adrenergic blocking activity [10].

CLINICAL

Prochlorperazine was used in 12,000 patients prior to commercial introduction. It has been found useful in mild and moderate mental and emotional conditions in doses of 15-75 mg daily [11-13]. In more severe psychotic disorders, an initial dosage of 30-75 mg daily is increased progressively until the maximum therapeutic response is achieved--300 mg daily in some cases, but more usually 100-150 mg daily [14-20]. As an antiemetic, prochlorperazine is highly effective in doses from 20-80 mg daily [21-23].

TOXICITY

Man

Acute: 5 subjects were given 80-200 mg prochlorperazine daily for 1-3 days. No significant changes occurred in hemogram, urinalysis, liver function, blood pressure or pulse rate. Side effects increased sharply when the dosage was elevated above 80 mg daily. These consisted of somnolence, dizziness, faintness and extrapyramidal reactions [25].
TOXICITY (Concluded)

Chronic: Side effects are minimal as long as the total daily dose does not exceed 60 mg [24]. All side effects disappear promptly on withdrawal or reduction of dosage, and the extrapyramidal reactions may be controlled readily by the concomitant administration of antiparkinson agents.

8 subjects received prochlorperazine 80 mg daily for 9-18 days. No significant changes occurred in hemogram, urinalysis, liver function, blood pressure or pulse rate.

Animal

Acute: LD$_{50}$ (mouse) 46 mg/kg (i.v.); 500 mg/kg (s.c.); 1080 mg/kg (p.o.). In dogs no lethality was observed at dosage < 66 mg/kg (i.v.) [10].

Subacute: No significant changes occurred after 5 weeks in dogs receiving 2.5 mg/kg (s.c.) 5 days a week prochlorperazine ethane disulfonate. In another series the dose was increased progressively from 50 to 200 mg/kg (p.o.) daily in 7 weeks. Albuminuria occurred in 3 out of 7 of the dogs. Respiratory rate and pulse rate were slowed significantly. At the highest level, histopathologic changes occurred in liver and kidney tissue [10].

Chronic: In rats fed 1 and 10 mg/kg 5 days a week for 25 weeks, no histopathologic changes attributable to prochlorperazine were observed. Growth was not depressed significantly. At the higher dosage level, moderate depression, ptosis and hypotonia were observed. In another study the daily consumption of approximately 6 mg/kg (p.o.) did not produce any deleterious effects on mothers or litters through 3 successive generations of rats. Dogs receiving 25 mg/kg 5 days a week for 13 weeks showed no significant changes in urine, liver function, hematology or histology. Side effects were mild depression, diarrhea, dry mouth and relaxation of the nictitating membrane, diminishing in intensity toward the end of the study [10].
REFERENCES


REFERENCES (Continued)


REFERENCES (Continued)


REFERENCES (Concluded)


Trademark for 10-(3-dimethylaminopropyl)-phenothiazine hydrochloride is Sparine (Wyeth Laboratories).

MOLECULAR FORMULA AND WEIGHT

\[ C_{17}H_{20}N_2S \cdot HCl \]

320.89

STRUCTURE

![Chemical Structure of Promazine Hydrochloride]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystalline solid.
Melting Point: 178-180°C.
Solubility: S. water, alcohol.
Stability: Turns slightly pink on standing.

PHARMACOLOGY [1]

Animal

Promazine (1.0 or 3.0 mg/kg i.v.) was given to dogs under pentobarbital anesthesia over a 15-30 second period. Results show it to be a short-acting depressor, blocking or reversing response to epinephrine. Drug given to mice 15 minutes prior to an effective dose of barbiturate prolongs the effect of the latter, and when subhypnotic doses of barbiturates or pentaerythritol chloral are given with promazine to mice and rats, a full hypnotic response is obtained.
CLINICAL

Promazine was effective in about a third of 50 psychotics, most having marked anxiety symptoms, at a dose of 50-600 mg daily [2]. When the same dose was given for 4-7 weeks, it relieved anxiety and depression symptoms and also gave good results in alcoholics when given i.v. [3]. It was of no value in treating chronic schizophrenics [4, 5]. In another study, acutely disturbed psychotics were given promazine (i.v.) until they were calm, quiet, and cooperative; then the drug was continued (i.m.) to maintain effect [6, 7].

Delirium tremens responded to single doses (i.v.) which produced normal sleep [6, 7]. 25-100 mg controlled nausea and vomiting of acute alcoholics in a majority of cases [8] and also had an effect on other withdrawal symptoms [6-8].

600 mg daily for 4-7 days controlled withdrawal symptoms in drug addicts [7]. The drug was also shown to have a potentiating effect on barbiturate therapy [7].

TOXICITY [1]

Man

4 cases of seizures after promazine therapy have been reported on a dosage level of 25-100 mg given every 4-6 hours [4, 9], and a few cases of agranulocytosis occurred after 40 days on a daily dose of 400 mg [10, 11]. Other side effects noted were jaundice, epileptic seizures, fever, hypotonia and (upon autopsy) fatty metamorphosis of the liver [11]. Side effects were also observed when the drug was given for 4-7 weeks at 75-600 mg daily [3], but in another study psychotics fed 100-800 mg daily exhibited no adverse effects [12]. Patients receiving 600 mg daily for 5 months showed no untoward effects, but when the dosage was increased to 1400-1800 mg daily, marked tremors developed [5]. Transient vomiting and marked agitation were observed if the drug was suddenly withdrawn at this high dosage [5]. In 70% of patients on 400-800 mg daily, a mild hypotensive effect was noted [13].
TOXICITY (Concluded)

Animal

The LD$_{50}$ in mice is 216 mg/kg (p.o.), and toxic symptoms are manifested by tremors, occasional running and leaping motions, depression and toleration of the side position. Continuous infusion at dosage levels of 1.0, 2.0, 5.0 mg/kg to dogs produces a gradual depression of blood pressure and a reversal of epinephrine response; respiratory depression with terminal circulatory collapse as the lethal dose of 47 mg/kg in 9.4 minutes is reached. When dogs were fed 20 mg/kg daily and injected with 25 mg/kg 5 times a week for 5 months, no adverse effects were observed, and no gross pathological changes appeared upon autopsy. No gross pathological changes were found in rats fed 0.1-0.2% for 5 months, but there was a slight increase in liver and spleen weights in the males. Hematology was normal.

ANTIDOTE

When acute lowering of blood pressure occurs, oxygen and/or norepinephrine should be used. Epinephrine should be avoided, as it may cause a further lowering [1].

REFERENCES


REFERENCES (Concluded)


19. PROMETHAZINE HYDROCHLORIDE

Trademarks for N-(2'-dimethylamino-2'-methyl)-ethyl phenothiazine hydrochloride are Phenergan Hydrochloride (Wyeth Laboratories, Rhone-Poulenc and May & Baker); Atosil (Bayer, Germany); Lergigan (A. B. Recip Co., Stockholm).

MOLECULAR FORMULA AND WEIGHT

\[ C_{17}H_{20}N_2S\cdot HCl \quad 320.89 \]

STRUCTURE

![Structure of Promethazine Hydrochloride]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White powder [1].
Melting Point: 203-204°C [1].
Maximum Absorption: 248 and 298 m\(\mu\) in aqueous solution [2].
Solubility: V. s. hot water, hot absolute alcohol, chloroform; i. ether, acetone, ethyl acetate [2].
Stability: Slowly oxidized on exposure to air, becoming blue in color [2].
Reactions: Addition of 5 ml HNO\(_3\) to a solution of promethazine hydrochloride (500 mg/15 ml) produces a red precipitate which dissolves on warming, red turning to orange-yellow [3].
Quantitative Determinations: Measure absorbance at 298 m\(\mu\) of a 5.5% aqueous solution, then calculate per cent of the hydrochloride by formula:

\[
\frac{9260 \times \text{Absorbance}}{\text{Weight (mg)}}
\]
PHARMACOLOGY

Animal

Trained rats given 2-25 mg/kg showed muscular incoordination, cerebral depression and prolonged climbing time [4]. A 0.001 M solution has a vasoconstricting action on the precapillary sphincters of the mammalian capillary bed (rat meso-appendix), while histamine has a vasodilating action [5]. Apomorphine-induced vomiting (0.1 mg/kg s.c.) in dogs was reduced 67% by a 20 mg/kg dose of promethazine 30 minutes later [6]. Reported to have a high antianaphylactic shock activity in guinea pigs [7,8], and to antagonize the effects of acetylcholine and histamine [9,10]. In mice the drug potentiates the barbiturates, as evidenced by a prolongation of sleeping time [11].

CLINICAL

Promethazine is used as a psychic sedative, antiemetic, antinauseant, antihistaminic, antitussive and antipruritic agent. Prolonged sedative action was observed on a daily dose of 100-250 mg [12]. Reported useful in surgery and obstetrical preoperative sedation [13-15]. Decreased rigidity and relief of tremors in subjects having Parkinson's disease were obtained on 200 mg daily [16]. Nausea and vomiting of pregnancy were alleviated in 80% of patients [17], and vertigo (instability when standing upright) was relieved in a majority of cases [18]. Sea-sickness has responded to this drug; on 25 mg 3 times a day, 70% protection was afforded [19], and 53% protection was found on a single dose of 35 mg [20]. In large-scale hay fever trials, 70% experienced a complete disappearance of symptoms, while 25% were only partially relieved on, respectively, 25-100 mg and 150-250 mg daily [12, 18]. Serum sickness, pruritus and urticaria improved on promethazine treatment [18].

TOXICITY

Man

150 to 250 mg daily produced dizziness and drowsiness in about 20-25% of subjects [12].

A 2-year-old child ingested 250 mg and experienced agitation, confusion, convulsions and stupor [21].
TOXICITY (Concluded)

Animal

LD$_{50}$ (mouse) 575 mg/kg (p.o.).

ANTIDOTES

Amphetamine and caffeine used to counteract the depressant effect [4].

REFERENCES


REFERENCES (Continued)


upon the sedative action of barbiturates. J. Pharm., Lond. 94:7.

Neogetramine, Trimeton, Antihistaminique RP 3277--An appraisal
of their clinical value. J. Allergy 19:313.

162(8):712.

promethazine for pre- and postanesthetic sedation. Am. Prac-
titioner 7(6):939.

Anaesth. 28(3):126.

zine, Duparcol, Parsidol, Phenergan with respect to the central
effect of nicotine. Correspondence of work with clinical experiments


histamine substance derived from phenoxyazine. Bull. N. York
Acad. M. 25:323.

The effectiveness of various drugs for the prophylaxis of seasick-
REFERENCES (Concluded)


20. PYRATHIAZINE HYDROCHLORIDE

Trademark for 10-[2-(1-pyrrolidyl)ethyl]-phenothiazine hydrochloride is Pyrrolazote (Upjohn Company).

MOLECULAR FORMULA AND WEIGHT [1]

\[ C_{18}H_{20}N_{2}S \cdot HCl \quad 332.91 \]

Analysis: \[ \begin{array}{ccc} \text{C} & \text{H} & \text{N} \\ \text{Calc.} & 64.94\% & 6.36\% & 8.42\% \\ \text{Found} & 65.10\% & 6.18\% & 8.57\% \end{array} \]

STRUCTURE

![Chemical Structure of Pyrathiazine Hydrochloride]

PHYSICAL AND CHEMICAL PROPERTIES [2].

Form and Color: White cubes [1].
Melting Point: 200-201°C [1].
Absorption Maxima: 250 μμ and 300 μμ.
Solubility: S. 1 g/2 ml water, 1 g/8 ml alcohol; i. ether, benzene.
Stability: Photosensitive.
Identity: Pink to brownish-orange color forms when 25 mg is dissolved in 5 ml H₂SO₄.

PHARMACOLOGY

Potent antagonist to many of the pharmacologic responses of histamine and possesses antianaphylactic properties [3]. Long-acting antihistaminic activity observed on isolated smooth muscle [3], and antagonized
PHARMACOLOGY (Concluded)

apomorphine-induced emesis response in dogs [4].

CLINICAL

Found effective in hay fever, asthma, urticaria, headache and pruritus ani [5].

TOXICITY

Man [5]

50 mg 3 times a day (p.o.) produced headaches, drowsiness and nausea.

Animal [3]

Acute: LD₅₀ (mouse) 37 mg/kg (i.v.), 1340 mg/kg (s.c.); (rat) 26 mg/kg (i.v.); (rabbit) 36 mg/kg (i.v.). High doses produced convulsive seizures and rapid respiration.

Chronic: Rats fed 10 mg/kg daily for 10 weeks showed no harmful effects, but on 300 mg/kg for 4 weeks developed distended abdomens caused by liver enlargement. On 25-300 mg/kg fed daily there was fatty infiltration in the liver. A daily dose of 75 mg/kg produced side effects—drowsiness, ruffled coats and difficult breathing.
REFERENCES


J. Pharm. Exp. Ther. 94:197.


 Trademarks for reserpine are Serpasil (Ciba Pharmaceutical Products Inc.),
Rased (E. R. Squibb & Sons), Eskaserp (Smith Kline & French Laboratories).

**MOLECULAR FORMULA AND WEIGHT [1]**

\[ C_{33}H_{40}O_9N_2 \quad 608.666 \]

<table>
<thead>
<tr>
<th>Analysis</th>
<th>O</th>
<th>C</th>
<th>OCH_3</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calc.</td>
<td>23.66%</td>
<td>65.11%</td>
<td>14.82%</td>
<td>6.62%</td>
<td>4.60%</td>
</tr>
<tr>
<td>Found</td>
<td>23.97%</td>
<td>65.38%</td>
<td>14.89%</td>
<td>6.45%</td>
<td>4.80%</td>
</tr>
</tbody>
</table>

**STRUCTURE [2]**

[Chemical structure diagram]

**PHYSICAL AND CHEMICAL PROPERTIES [1]**

- **Color and Form:** White crystalline powder.
- **Melting Point:** 277-278°C.
- **Specific Rotation:** \( \left[ \alpha \right]^{23}_D = -118^\circ \) (chloroform, C = 1).
- **Solubility:** V. s. chloroform, 20% acetic acid; i. water, ethyl alcohol.
PHARMACOLOGY

Man

Drug potentiates action of other hypotensive agents [3]. No consistent effect on renal hemodynamics [4].

Parenteral reserpine (0.50-2.5 mg) usually produced within an hour a marked increase in the free gastric acidity and volume of gastric juice in subjects with and without peptic ulcer [5,6]. This effect also shown after 4-7 days on 2-3 mg daily (p.o.) [6].

Animal [7]

Cat, dog, guinea pig, monkey, mouse, rabbit and rat given reserpine all showed sedation and a reduction in spontaneous activity. Doses of 500-1000 µg/kg (i.v.) in rhesus monkey resulted in calming effect and noticeable lessening of natural curiosity. Dogs given 250-300 µg/kg (i.v.) exhibited a quiescent state; and on a daily dose of 15 µg/kg (i.v.), they showed an increase in both volume and hydrochloric acid content of their gastric juice.

Dogs and monkey fed 25 µg/kg daily for 2 months showed no significant alteration in blood pressure from pre-existing normotensive levels. No evidence of tolerance to drug in dogs given 15-20 µg/kg (i.v.) daily for 10 months. Dogs given 300-500 µg/kg (i.v.) showed an initial slow drop in blood pressure of 20-30 mm Hg, and dog anesthetized with barbital sodium showed a 63 mm blood pressure drop on 500-1000 µg/kg (i.v.)[8]. Cats and rabbits also showed a gradual drop of 100 µg/kg [8].

CLINICAL

Reserpine is used for the treatment of hypertension, insomnia, headache, asthma and dermatological disorders, also, in neuropsychiatry, to relieve anxiety and tension states [9,10]. Drug has proved to be an effective sedative for use in mental hospitals [11].
21. RESERPINE (Continued)

TOXICITY

Man

Acute: 20-month-old male weighing 32 pounds ingested 200 mg reserpine. After 1-1/2 hours, crying, fever 101.4°F., pulse 120, respiration 30, marked lethargy, skin flushed. Slept most of first 36 hours, but could be aroused. Blood count and urinalysis normal when determined after 6 days. Complete recovery [7]. Nasal congestion and postural hypotension noticed in subjects given 3.0-5.5 mg (i.v.). No untoward side effects [12].

Chronic: On 100-3000 µg daily, sedation, nasal stuffiness, weight gain, diarrhea, nightmares and depression were observed [3,13]; and on 0.5 mg daily, lethargy was observed in 35%, nasal congestion in 25%, aching legs in 14%, loose stools in 10% and dreams in 9% [14].

3-6 mg (p.o.) daily for 4-7 days reported to produce bleeding from gastrointestinal tract in subjects with a previous history of duodenal ulcers [15-17]. Hematemesis and melena occurred in subjects on reserpine or Rauwolfia therapy without previous evidence of gastrointestinal disorders [15,18].

Animal [7]

Acute: Rhesus monkeys given 400 mg/kg (p.o.) and rats 1 g/kg (p.o.) showed profound sedation but no untoward effects. Monkeys administered 4 mg/kg (i.v.) and rats 8 mg/kg (i.v.) showed no deaths. Dogs given 0.5 mg/kg (i.v.) got diarrhea.

Chronic: Rats given 4 mg/kg (p.o.), dogs 35 µg/kg (p.o.) and monkeys 3 mg/kg (p.o.) daily for 6 months showed satisfactory sedation but no untoward side effects. No significant change in the hematological picture.

MODE AND SITE OF ACTION

Sedation, reduced emotional response, peripheral autonomic alterations and circulatory changes are explicable on the basis of a change in sympathetic-parasympathetic balance by partial suppression of
MODE AND SITE OF ACTION (Concluded)

sympathetic predominance at the hypothalamic level [7,8] or by central parasympathetic stimulation [19].

REFERENCES


REFERENCES (Concluded)


22. THIOPROPAZATE DIHYDROCHLORIDE

Trademark for 1-(2-acetoxyethyl)-4-[3-(2-chloro-10-phenothiazinyl)propyl] piperazine dihydrochloride is Dartal Dihydrochloride (G. D. Searle & Co.).

MOLECULAR FORMULA AND WEIGHT [1]

\[ C_{23}H_{28}ClN_{3}O_{2}S\cdot2HCl \quad 518.92 \]

STRUCTURE

\[ \text{\includegraphics[width=0.5\textwidth]{structure.png}} \]

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: Gray-white crystalline powder.
Melting Point: 223-229°C.
Solubility: S. water, ethanol, dimethylformamide; i. hydrocarbon solvents.

PHARMACOLOGY

Man

Thiopropazate (10-25 mg p.o.) had a marked inhibiting effect on the reconditioning of a galvanic skin response. Central sympathetic reactivity was reduced in normal or over-reactive subjects and increased in under-reactive individuals [2]. A modest fall in blood pressure occurred in some subjects but no change in heart rate [3]. Significant decrease in acidity of gastric secretion was found from 5-8 hours after a single dose (20 or 40 mg p.o.) of thiopropazate. No effect on volume of secretion or gastrointestinal motility was obtained [4]. Studies of liver function revealed no significant change
PHARMACOLOGY (Concluded)

in phosphatase, serum glutamic oxalacetic and pyruvate transami-
nases, or serum bilirubin in patients receiving daily doses of 40 mg
thiopropazate (p.o.) [5,6]. EEG studies in 1 schizophrenic and 2
normal subjects revealed no alterations except for non-specific ones
associated with general muscle relaxation [7].

Animal
Thiopropazate was 5-10 times more potent than chlorpromazine in
protecting dogs against apomorphine-induced emesis and in inducing
a state of ataraxia [8]. Conditioned responses by rats were reduced
by 88% after injection of 0.25 mg/kg (i.p.), but unconditioned responses
were unimpaired [9]. Rats' learning to avoid or escape shock was
prevented by 0.5 mg/kg [10]. Trained rhesus monkeys showed reduced
excitability but no decrement in immediate or long-term memory after
administration of thiopropazate (1 or 2 mg/kg p.o.) [9].

In dogs anesthetized with pentobarbital, injection of thiopropazate at
0.1-5.0 mg/kg (i.v.) produced variable hypotension. Percentage
fall in blood pressure was not closely correlated with dose. EKG
changes in dogs were restricted to a transient tachycardia [8]. Dur-
tion of sleep induced in mice by hexobarbital (80 mg/kg i.p.) was
increased by pretreatment with thiopropazate at doses of 3 mg/kg or
more [9].

CLINICAL

Thiopropazate is useful in tense, agitated or anxious patients. It
produced improvement in 74-83% of chronic and acute psychoses of
various types, including schizophrenia, manic-depressive and invo-
lutional states, and arteriosclerotic cerebral syndrome [7,11,12].
Suppression of involuntary muscular activity in 10 of 11 cases of
Huntington's chorea has been reported [7]. Thiopropazate is particu-
larly useful in patients with association defect, depersonalization and
anxiety [12]. Optimum dosage for psychotic conditions is 30-40 mg
daily. In patients with duodenal ulcer or psychosomatic gastrointestinal
symptoms, 20-40 mg daily (p.o.) has brought improvement alone and in
conjunction with anticholinergic therapy [5,6,13,14]. Anxiety tension
states are well controlled by 15-30 mg daily [15].

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22. THIOPROPAZATE DIHYDROCHLORIDE (Continued)

TOXICITY

Man

**Acute:** 15 tablets of 10 mg each were consumed in a suicide attempt by a man with an agitated depression. His only response was a period of excitement and irritability without any indication of toxicity or depression [13].

**Chronic:** Sternal bone marrow biopsies performed on 12 patients after 4-6 weeks of treatment (40 mg daily p.o.) with thiopropazate revealed no abnormalities [7]. In another group of patients maintained on the same dose for a 12-week period no signs of abnormality were noted in blood picture, urinalysis, phenolsulfonphthalein, serum bilirubin, alkaline phosphatase, bromsulphalein, thymol turbidity, cephalin flocculation, total serum proteins, EKG or gastrointestinal motility [5,6]. No jaundice or leukopenia has been observed attributable to thiopropazate, but jaundice and leukopenia due to other tranquilizers have been alleviated when thiopropazate was substituted. Pseudoparkinsonism is a common side effect, especially at doses above 40 mg daily. It is readily controlled by withdrawal of the drug, reduction of dosage or antiparkinson therapy. Symptoms of parasympathetic activity are occasionally encountered and, less commonly, generalized skin reactions [16].

**Animal**

**Acute:** $LD_{50}$ (mouse) $197 \pm 20$ mg/kg (i.p.); $279 \pm 40$ mg/kg (p.o.) [8].

**Subacute:** In dogs given 15 consecutive daily doses of 15 to 25 mg/kg thiopropazate (p.o.), signs of central depression and generalized tremors were observed. Appetites remained good, and body weights were stable within narrow limits. Urinalysis, hemoglobin level, red and white blood cell count, serum level of sodium, potassium and chloride ions, serum nonprotein nitrogen, serum bilirubin and bromsulphalein clearance were unaffected. No gross or histological signs of damage to body tissues were found [8].

**Chronic:** Dogs maintained for 6 months on diets containing 1 or 10 mg/kg daily showed good appetites and maintained body weights. Hematological values and urinalyses were normal. 5 of 6 dogs given 10 mg/kg
TOXICITY (Concluded)

developed parkinsonian tremors after 3 weeks [17]. Rats were fed
diets providing daily doses of 1, 3 and 10 mg/kg for periods up to 9
months. Growth retardation was recorded only in the males receiving
the highest dose. Hematological values remained in the normal range.
Some rats in each dosage group were autopsied after 3 months; organ
weights lay in normal ranges, and histological examination revealed no
specific tissue injuries [17].

REFERENCES

9 October 1956.

influenced by amytal, reserpine and chlorpromazine. Psychiat.


Psychiat. 114:1034.

SC-7105, Pharmacological studies.


in avoidance behavior. Presented at American Psychological Associa-
tion, New York City, 20 August - 5 September.
REFERENCES (Concluded)


23. TRIFLUOPERAZINE

Trademark for 10-[3-(1-methyl-4-piperazinyl)propyl]-2-trifluoromethylphenothiazine dihydrochloride is Stelazine (Smith Kline & French Laboratories).

MOLECULAR FORMULA AND WEIGHT [1]

\[ C_{21}H_{24}F_3N_3S \cdot 2HCl \quad 480.44 \]

STRUCTURE [1]

![Structure of Trifluoperazine]

PHYSICAL AND CHEMICAL PROPERTIES [1]

- **Form and Color:** Pale yellow crystalline solid.
- **Taste and Odor:** Odorless.
- **Melting Point:** 236-237°C.
- **Solubility:** S. 50 mg/ml water; sl. s. isopropanol, ethanol.
- **Stability:** Aqueous solution stable more than 24 hours.

PHARMACOLOGY [1]

**Animal**

Trifluoperazine showed 10 times the potency of chlorpromazine in blocking the conditioned escape response in rats and 4 times the potency in depressing spontaneous motor activity in mice. Cataleptic activity in mice was observed to occur at a potency 8 times that of chlorpromazine. Apomorphine-induced emesis in dogs was reduced 50% by 0.05 mg/kg (p.o.) [3]. Doses of 1.0-10.0 mg (p.o.) prior to administration of 7.5 mg/kg of tremorine (p.o.) markedly reduced the number of mice exhibiting tremors. Hexobarbital-induced sleeping time in mice was prolonged 150% by 24 mg/kg. Dogs given 10-20 mg/kg (i.v.) showed no change in their water and electrolyte excretion [3]. No
PHARMACOLOGY (Concluded)

significant effect on blood pressure or glomerular filtration rate was observed in hydrated dogs receiving 1 mg/kg of the drug [3].

CLINICAL [1,2]

Trifluoperazine, tested in more than 3000 hospitalized psychotic subjects, has been found to be the most potent phenothiazine tranquilizer to date. Its principal use has been for treatment of chronic schizophrenics. Improvement was seen in 73% of patients, with a partial or complete remission of symptoms in 55% of subjects. It is notable that beneficial results were seen in chronic schizophrenics who did not respond to other therapy. Hyperactive (agitated, hostile, aggressive or destructive) and hypoactive (withdrawn, apathetic, mute or secretive) types were relieved when given 10-30 mg of the drug daily (p.o.) or 1-3 mg 3 times a day (i.m.). Acute psychotics also responded rapidly to this therapy. Delusions and hallucinations experienced by some of these subjects were reported to be dramatically lessened when they were treated with trifluoperazine. Nausea and vomiting from various causes were alleviated by a dose of 2-5 mg every 6 hours [3].

TOXICITY [1]

Man

Extrapyramidal effects (such as weakness, rigidity, tremor or salivation) and restlessness, agitation, insomnia and jitteriness were observed in certain patients. These side effects were relieved by a reduction in dosage or by the administration of antiparkinson agents. Autonomic-type side effects were virtually non-existent with this drug. Photosensitivity has not occurred, and there is no evidence of any renal, hepatic or cardiovascular toxicity.

Animal

**Acute:** $LD_{50}$ (mouse) 29 mg/kg (i.v.), 1350 mg/kg (p.o.); (dog) 60 mg/kg (i.v.).
TOXICITY (Concluded)

Subacute: Rats were fed 15 mg/kg for 5 weeks. Depression and hypotonia and a slight decrease in their rate of growth were observed. No histopathological changes were seen upon autopsy.

Dogs were given 5 mg/kg (s.c.) or 10 mg/kg (p.o.) daily for 5 weeks. Depression, body sway, head drop, miosis and dry mouth were noticed in animals on 10 mg/kg. Periodic hematological studies were normal except for a slight decrease in leukocytes. No histopathological changes were observed.

Chronic: Rats were fed 1 mg/kg or 5 mg/kg daily for 26 weeks. Growth suppression noticed on latter dosage. Hematological studies were normal, and no characteristic gross pathological findings or histopathological changes were observed. Dogs were fed 1 mg/kg daily for 26 weeks or 5 mg/kg daily for 11 weeks, then 10 mg/kg daily for 15 weeks. Dosage increase made dogs mildly ataxic for a week. Periodic blood, liver, kidney and urine tests were normal. Tissues were normal at autopsy. No difference was found in fluoride content between control and test animals.

ANTIDOTE [1]

If vasopressor therapy is indicated (hypotension), the use of norepinephrine or Neo-Synephrine--not epinephrine--is recommended. Extrapyramidal symptoms may be relieved by antiparkinson agents.
REFERENCES


24. TRIFLUROPROMAZINE HYDROCHLORIDE

Trademark for 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine hydrochloride is Vesprin (E. R. Squibb & Sons).

MOLECULAR FORMULA AND WEIGHT

\[ C_{18}H_{19}F_3N_2S\cdot HCl \quad 388.87 \]

STRUCTURE

![Chemical Structure of Trifluromazine](image)

PHYSICAL AND CHEMICAL PROPERTIES

- Form and Color: White powder.
- Solubility: S. water (> 10 g/100 cc), ethanol, acetone; i. ether.

PHARMACOLOGY

**Man [1-3]**

Administration of 4-12 mg (i.v.) produced CNS depression, evidenced by the induction of light sleep from which the patient could be readily aroused. This dose did not cause orthostatic hypotension. Transient tachycardia (15-30 beats/minute) occurred in 85% of the patients. Doses of 6-10 mg of trifluromazine (i.v.) have proved effective in controlling and preventing nausea and vomiting. Doses of greater than 20 mg (i.v.) may be associated with hypotension.

On administration by i.m. or p.o. routes, trifluromazine exhibited potent antiemetic activity.
PHARMACOLOGY (Concluded)

Animal [4]

Depressant effect in mice: median ataxic dose, 11 mg/kg (p.o.), 3.7 mg/kg (i.p.). On administration (i.p.) in rats, triflupromazine blocked conditioned response to electric buzzer preceding shock stimulus. The drugs antagonized amphetamine in mice, dogs and monkeys. Tranquilizing of monkeys was readily effected on administration (p.o.). Triflupromazine strongly antagonized the pyretic response of rabbits to lysergic acid diethylamide. The drug potentiated the analgesic effect of mor- phine in rats. Injections (i.v.) in anesthetized and unanesthetized dogs depressed pulse rate and blood pressure in the unanesthetized animals; in both groups the carotid pressor reflex was depressed, the reflex tachycardic response to acetylcholine and the bradycrotic reflex re- sponse to epinephrine or the hypotensive response to vagal stimulation was inhibited. Considerable protective action against nicotine-induced death was exerted by triflupromazine injected (s.c.) in mice. Pretreat- ment of dogs with triflupromazine (s.c.) provided highly potent anti- emetic action against apomorphine-induced emesis. Neurological tests in dogs: injections of 30, 45 and 60 mg/kg (i.m.) produced ataxia for 24 hours; no evidence of tremors, extensor rigidity or hypnosis. In monkeys, following administration of 0.5 and 2.0 mg/kg (i.m.), there were no significant changes in EKG patterns, no Babinski sign and no local or generalized tremors. Tranquilization was similar to that ob- served after p.o. administration. A moderate persistent fall in both cardiac rate and blood pressure was observed.

CLINICAL [2,3,5-17]

Triflupromazine has been effectively employed in the treatment of various acute and chronic psychoses. The drug is particularly useful in the management of the psychomotor hyperactivity and overt hostility frequently associated with such conditions as schizophrenia, mania, depression, delirium, senile psychoses and psychoses due to organic brain disease. Triflupromazine has also been extremely valuable in the management of restlessness, anxiety, insomnia and other emotional side effects associated with the withdrawal of alcohol. By virtue of its potent antiemetic property, the drug has been found most useful in the control and prevention of nausea and vomiting associated with a variety
CLINICAL (Concluded)

of clinical disorders. Triflupromazine has been successfully employed in the management of nausea and vomiting associated with certain drugs, acute infections, nitrogen-mustard therapy and pernicious vomiting of pregnancy. The drug has also been found effective in the control of postoperative emesis and for nausea and vomiting following certain neurological procedures such as encephalograms and ventriculograms.

TOXICITY

Man

2 ambulatory patients attempted suicide by swallowing, respectively, 8 and 17 (50-mg) tablets of triflupromazine. Each simply slept for a period no longer than 10 hours. Neither showed any other ill effects from the overdosage [7].

Following daily dosage of 10-300 (p.o.) for 2-52 weeks, and/or 10-30 mg (i.m.) for 2-4 weeks, no significant abnormalities were observed in liver function tests, urinalyses, blood counts, EKG or hepatic function tests [2,5,10].

In most patients, the beneficial effects of the drug are achieved with virtually no sedative effects. Drowsiness or somnolence is seldom intense and generally subsides after the first few weeks of treatment. Allergic phenomena or photosensitivity are infrequently encountered, and are manageable by lowering dosage or discontinuing the drug for a few days; antihistamines are recommended for more severe reactions. Symptoms of weakness, dizziness, anxiety and restlessness have been occasionally reported, but are not generally troublesome and may usually be relieved by moderation of dosage. Marked hypotension has been only rarely reported with p.o. dosage. Orthostatic hypotension and simple tachycardia, both transitory, may occur with parenteral dosage. In some psychotic patients on intensive and prolonged dosage, a reversible parkinsonian syndrome may develop which may be controlled by the use of antiparkinson drugs and/or by reducing or discontinuing therapy temporarily. Extrapyramidal symptoms have not been reported with doses commonly employed against emesis. Jaundice has not been reported. Lactation and edema are occasionally
24. TRIFLUPROMAZINE HYDROCHLORIDE (Continued)

TOXICITY (Concluded)

seen. Weight gain is generally not a problem. A fatal case of agranulocyto-

sis has occurred following triflupromazine treatment [18].

Animal [4]

Acute: LD$_{50}$ (mouse) 44.0 ± 3.3 mg/kg (i.v.), 102 ± 7.7 mg/kg (i.p.),
350 ± 46 mg/kg (p.o.); (rat) 94 ± 6.8 mg/kg (i.p.); (dog) 16.7 ± 4.2 mg/kg
(i.v.).*

Subacute: Daily doses greater than 5 mg/kg (p.o.) in rats on a regimen
of 2.5-80 mg/kg daily for 7 to 16 weeks caused retarded weight
gains of 16-22%. Dogs and monkeys also studied on the above regimen
did not exhibit weight retardation, nor were significant abnormalities
observed in the major organs or in the blood picture. Reduced motor
activity and lethargy were noted initially in dogs and monkeys, diminish-
ing in severity after 6 days but reappearing with increased dosage.

Chronic: Rats given daily doses of 5-80 mg/kg (p.o.) for 37 to 95 days
and dogs receiving 5-40 mg/kg daily for 33 weeks showed no signifi-
cant gross or microscopic findings attributable to the drug. Definite
retardation of growth occurred in all rats except males receiving
5 mg/kg daily and females receiving up to 40 mg/kg daily. In-
creased weight gains followed discontinuance of the drug in the rats
experiencing weight retardation during dosage. All test dogs exhibited
slight-to-large weight gains, a non-sugar-reducing substance in the
urine, and sedative effects. Ataxia was observed on the first day of
dosage in dogs.

SITE AND MODE OF ACTION

The site and mode of action of phenothiazine derivatives are largely
unknown. The drugs are believed to act on the hypothalamus, depress-
ing components involved in the control of basal metabolism, body
temperature, wakefulness, vasomotor tone, emesis and hormonal
balance. They exert a peripheral autonomic effect, and may prolong
and intensify the action of many CNS depressants such as barbiturates,
narcotics and anesthetics.

*± values represent standard error.
REFERENCES


REFERENCES (Concluded)


25. TRIMEPRAZINE

Trademark for dl-10-(3-dimethylamino-2-methylpropyl)-phenothiazine tartrate is Temaril (Smith Kline & French Laboratories).

MOLECULAR FORMULA AND WEIGHT

\[(\text{C}_{18}\text{H}_{22}\text{N}_{2}\text{S})_2\cdot\text{C}_4\text{H}_6\text{O}_6\]

\[747.00\]

STRUCTURE [1]

[Diagram of molecular structure]

PHYSICAL AND CHEMICAL PROPERTIES [1]

Form and Color: White crystalline powder.
Taste and Odor: Faint odor.
Melting Point: 162-163°C (Kofler block).
Solubility: S. 1 g/4 ml water, 1 g/120 ml alcohol, 1 g/75 ml chloroform; i. ether, benzene.
Stability: Powder and aqueous solution photosensitive.

PHARMACOLOGY

Animal [1]

Trimeprazine (p.o.) showed a strong antihistaminic activity: 2.0 mg/kg (p.o.) afforded 100% protection against histamine-induced bronchospasm in guinea pigs. Apomorphine-induced emesis in dogs was reduced 50% by 3.3 mg/kg (p.o.). Spontaneous motor activity in mice was depressed 50% by 10.5 mg/kg (p.o.). Drug showed a mild blocking of conditioned escape response in rats. It increased threshold to minimal electroshock seizure in mice and exhibited a slight
PHARMACOLOGY (Continued)

hypotensive effect without epinephrine reversal when administered (i.v.) to anesthetized dogs.

CLINICAL [1-3]

Trimeprazine, given (p.o.) to more than 4000 subjects suffering from a variety of pruritic conditions, showed a 70% overall incidence of good to excellent results in alleviation of itching at daily doses of 2.5-100 mg. The common skin conditions responsible for the pruritus were neurodermatitis, contact dermatitis, drug eruption, infantile eczema, pruritus vulvae et ani and chronic urticaria. Pruritus resulting from obstructive jaundice, chickenpox and herpes zoster also responded to trimeprazine therapy [4]. The drug relieved the symptoms of hay fever and asthma (sneezing, wheezing, coughing and dyspnea) in 2/3 of subjects treated [5]. In addition to its antihistaminic and antitussive properties, it also exerted a sedative and mild tranquilizing effect [6] and permitted sound, untroubled sleep in subjects with insomnia.

TOXICITY [1,4]

Man

Drowsiness occurred at the recommended dosages of 2.5-20 mg daily in 13% of all subjects. Other side effects, such as gastrointestinal upset, bad taste and dry mouth, occur rarely.

Animal

Acute: LD50 (mouse) 33 mg/kg (i.v.), 580 mg/kg (p.o.).

Subacute: In dogs given 5 mg/kg (i.m.) daily for 30 days, gross and microscopic examination of liver, kidney and bone marrow were normal.

Chronic: Dogs administered daily doses of 2, 5 and 10 mg/kg (i.m.) for 6 months showed no abnormalities.
ANTIDOTE [1,4]

Accidental overdosage can be controlled by dextroamphetamine following induced emesis. Where pressor agents are indicated, norepinephrine may be used. Epinephrine should be avoided, as it may cause a further lowering of blood pressure.

REFERENCES


26. ZOXAZOLAMINE

Trademark for 2-amino-5-chloro-benzoxazole is Flexin (McNeil Laboratories, Inc.).

MOLECULAR FORMULA AND WEIGHT [1]

\[ C_7H_5ClN_2O \quad 168.58 \]

Analysis:

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<td>Calc.</td>
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</table>

STRUCTURE

![Chemical structure of Zoxazolamine](image)

PHYSICAL AND CHEMICAL PROPERTIES

Form and Color: White crystals [1].

Melting Point: 182°C (free base); 229°C (hydrochloride, decomposes) [1].

Solubility: S. 12.5 mg/ml in propylene glycol; i. water.

PHARMACOLOGY [2]

Animal

Flaccid paralysis occurs in mice 1-2 hours after administering of 100 mg/kg (i.p.) or 250 mg/kg (p.o.). Cats fed 300 mg/kg in 6-48 hours and dogs 200 mg/kg in 2-5 hours showed simple flaccidity. Antagonizes effect of strychnine in mice, but does not seem to be protective against Metrazol (pentylenetetrazol)-induced convulsions. Rapid loss of the righting reflex in the rats, hamsters, guinea pigs, rabbits and cats given 25 mg/kg (15-minute loss was reported) [3].
PHARMACOLOGY (Concluded)

Chloralosed dogs showed no sustained changes in blood pressure, heart rate or cardiovascular reflexes. Daily administration (p.o.) to rats and dogs is reported to produce no deleterious hemopoietic, histopathological or pathological changes. Shown to be a potent, long-acting depressant of the mephenesin type.

CLINICAL

Prevents or relieves spasm in voluntary muscles by depressing CNS pathways involved. Prompt relief of stiffness and aching within 30 minutes in 85% of cases [4]. Significant increase of muscular tone noticed in cerebral palsy children given 30-140 mg daily [5]; and in neurological disorders involving involuntary muscles, alleviation of discomfort and spasticity was observed [6].

TOXICITY

Man

Chills and fever, burning and tearing of eyes, rash, gastric burning, nausea, dizziness, drowsiness, lightheadedness and overstimulation reported by patients fed 500 mg 3 times a day [4]. Hypertonia, anorexia and vomiting occurred in children given 30-140 mg daily for 10-210 days [5].

Animal

LD_{50} (mouse) 295 mg/kg (i.p.) [2]. See also PHARMACOLOGY.
REFERENCES


INDEX
# Index

Listed below are the names under which compounds appear in this volume (cf Contents). In addition, commonly used alternative names, synonyms, proprietary and trade names have been included so that this listing may serve as a cross index. Where an entry contains in parenthesis a second name in lower case, the parenthesized name is the one that will be found at the head of the particular chapter.

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<tr>
<td>10-[3-DIMETHYLAMINOPROPYL]-2-CHLORPHENOTHIAZINE HYDROCHLORIDE, (chlorpromazine hydrochloride)</td>
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</tr>
<tr>
<td>10-[3-DIMETHYLAMINOPROPYL]-PHENOTHIAZINE HYDROCHLORIDE, (promazine hydrochloride)</td>
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<tr>
<td>10-[3-DIMETHYLAMINOPROPYL]-2-(TRIFLUOROMETHYL)-PHENOTHIAZINE HYDROCHLORIDE, (trifluromazine hydrochloride)</td>
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<tr>
<td>DIMETHYLATE, (dimethyl)</td>
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<tr>
<td>N, N-DIMETHYL-2-(a-PHENYL-o-TOLOXY)ETHYLAMINE DIHYDROGEN CITRATE, (phenyltolazamine dihydrogen citrate)</td>
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<tr>
<td>DIFAROL, (diethazine)</td>
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<tr>
<td>a, a-DIPHENYL-2-PIPERIDINEMETHANOL HYDROCHLORIDE, (pipradol hydrochloride)</td>
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<td>a, a-DIPHENYL-4-PIPERIDINEMETHANOL HYDROCHLORIDE, (azacyclonol hydrochloride)</td>
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<tr>
<td>EQUANIL, (neprobenzine)</td>
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<tr>
<td>ESKASERP, (reserpine)</td>
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<tr>
<td>FLEXIN, (zoxazoline)</td>
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<td>FRANGUEL, (azacyclonol hydrochloride)</td>
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<tr>
<td>1-(2-HYDROXYETHYL)-4-[3-[2-CHLORO-10-PHENOTHIAZINYL]PROPYL] PIPERAZINE (perphenazine)</td>
<td>51-57</td>
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<tr>
<td>HYDROXYZINE</td>
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[Approved for Public Release]
<table>
<thead>
<tr>
<th>Compound</th>
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<tbody>
<tr>
<td>Proniazid</td>
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<tr>
<td>1-Bononetyl-2-isopropylhydrazine</td>
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<tr>
<td>Largactil (chlorpromazine hydrochloride)</td>
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<tr>
<td>Latibon (dietazine)</td>
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<tr>
<td>Lergigan (promethazine hydrochloride)</td>
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<tr>
<td>Marsilid (proniazid)</td>
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<tr>
<td>Megaphen (chlorpromazine hydrochloride)</td>
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<td>Mepazine</td>
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<tr>
<td>Meprobamate</td>
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<tr>
<td>Mertraan (piradol hydrochloride)</td>
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<tr>
<td>Methyl phenidyl acetate</td>
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<tr>
<td>10-[[3(1-methyl-4-piperazinyl)propyl]-2-trifluoromethyl phenothiazine dihydrochloride, (trifluoperazine)</td>
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<tr>
<td>Methyl phenyl-2-piperidyl-acetate hydrochloride, (methyl phenidyl acetate)</td>
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<tr>
<td>10-[[1-methyl-3-piperidyl)methyl]-phenothiazine, (mepazine)</td>
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<tr>
<td>2-Methyl-2-n-propyl-1,3-propanediol dicarbamate, (meprobamate)</td>
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<td>Milltown (meprobamate)</td>
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<td>Oasil (meprobamate)</td>
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<td>Pacatal (mepazine)</td>
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<tr>
<td>Parason (benactyzine hydrochloride)</td>
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<tr>
<td>Perphenazine</td>
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<tr>
<td>Phenaglycodol</td>
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<td>Phenergan hydrochloride</td>
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<td>Phenyltoloxamine dihydrogen citrate</td>
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<td>Pipradol hydrochloride</td>
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<tr>
<td>Pyrathazine hydrochloride</td>
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<td>Pyrilazote (pyraathazine hydrochloride)</td>
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<td>10-2-(1-pyrolidyl) ethyl-phenothiazine hydrochloride, (pyraathazine hydrochloride)</td>
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<td>Raxed (serpentine)</td>
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<td>Reserpine</td>
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<tr>
<td>Surfen (benactyzine hydrochloride)</td>
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<td>Temaril (trimeprazine)</td>
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<tr>
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