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Literature Survey

Physical and Biological Properties of Pyrilamine

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Keyphrases □ Pyrilamine—antihistamine, chemistry, pharmacology, metabolism, toxicology, mutagenicity, teratogenicity, carcinogenicity, literature survey □ Antihistamine—pyrilamine, chemistry, pharmacology, metabolism, toxicology, mutagenicity, teratogenicity, carcinogenicity, literature survey □ Structure–activity relationships—pyrilamine, chemistry, pharmacology, metabolism, toxicology, mutagenicity, teratogenicity, carcinogenicity, literature survey

When metapyrilene was found to be an animal carcinogen a search was begun to obtain another drug for use in nonprescription sleeping aids (1). It appeared that a related compound, pyrilamine, an antihistamine with sedative properties, could be used (2). This resulted in pyrilamine, which is structurally related to methapyrilene, being nominated for a National Toxicology Program carcinogenesis bioassay. As a result the chemistry, pharmacology, metabolism, toxicology, mutagenicity, teratogenicity, and carcinogenicity of pyrilamine was reviewed.

CHEMISTRY

Background—Production of antihistamines in the United States in 1976 was 217.2×10^3 kg, but data on pyrilamine production is unknown (3).

Pyrilamine has not been found in U.S. drinking water supplies (4), industrial effluents (5), or European water supplies (6).

It has been used as an antihistamine in treatment of allergies (7).

Synthesis—Table I (2, 8–10) gives the structure and physical and chemical properties of pyrilamine. This chemical is prepared by condensing 2-(*N*-*p*-methoxybenzyl)aminopyridine with dimethylaminoethyl chloride or by condensing *N*,*N*-dimethylaminoethyl-α-aminopyridine with *p*-methoxybenzyl chloride in the presence of sodamide or lithamide (11–14).

Analysis—Pyrilamine was separated by TLC on silica gel G plates using benzene–dioxane–diethylamine–absolute ethanol (50:40:5:5) as a solvent system, and several identifying agents (15). It was determined using silica gel G plates, 18 different solvent systems, and 8 chromogenic reagents (5). Another technique used the following solvent systems containing 0.1 *M* NaBr: methanol–butanol (60:40); chloroform–methanol (90:10); and ethyl acetate–cyclohexane–methanol (70:15:5). The use of these ion-paired adsorption systems gave improved, more reproducible separations (16). Celite columns acidified with tosic acid, 0.1 or 1.0 *M* HCl, 10.0 *M* H_2SO_4, or 1.0 *M* H_3PO_4 were used in ion-pair extraction followed by partition chromatography to separate pyrilamine and codeine (17). Other inorganic ions such as Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SCN^-, and SO_4^{2-} were also used (18).

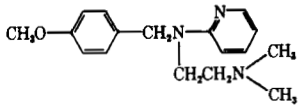
Chromatographic columns[1] were used as anion and cation exchangers to separate pyrilamine from other amines (19). Thin-layer plates composed of silica $60F_{254}$[2], silica $60F_{254}$[2] sprayed with 0.1 *N* NaOH, silica G-25, alumina[2] $F_{254}E$, and cellulose type F[2] sprayed with 5% sodium dihydrogen citrate were used to separate pyrilamine from other amines and to determine recovery percentages (20). TLC was systematized by relating R_f values and solvent systems of five to seven test substances and coding the results into tables for rapid identification (21). This approach was applied to 76 prescription drugs (22) and other therapeutically significant organic bases (23).

TLC using plates[3] and extraction with 1,2-dichloroethane was used to identify 32 basic poisons (24). Pyrilamine was identified using nine color reagents (25), silica gel microfiber sheets[4] and the following solvent systems:

[1] Sephadex SPC 25 or QAE 25.
[2] Merck.
[3] Keiselgel.
[4] ITLC type SA.

0022-3549/83/0100-0003$01.00/0

Table I—Structure and Physical and Chemical Properties of Pyrilamine[a]



Physical State	Oily liquid
Boiling Point	201°(5 mm); 168–172°(0.06 mm)
Solubility	Soluble in acids
Refractive Index	n_D^{25} 1.5760–1.5765
CAS Number	91849
Molecular Weight	285.58
Spectroscopic Data	IR spectra 2940, 2780, 1590, 1520, 1490, 1450, 1350, 1320, 1250 1180, 1040, 980, 760, 730; UV spectra 310, 247; pH 0.1 316, 238; pH 1.0 314, 238; pH 4.1 308, 239; pH 5.7 306, 244 nm.
Volatility	Slightly volatile
Stability	Turns brown on exposure to light
Reactivity	Reacts with acids to form salts
Synonyms	*N*-[(4-methoxyphenyl)methyl]-*N'*,*N'*-dimethyl-*N*-2-pyridinyl-1,2-ethanediamine; 2[(2-dimethylaminoethyl-*p*-methoxybenzyl)amine] pyridine; *N*-*p*-methoxybenzyl-*N'*,*N'*-dimethyl-*N*-α-pyridylethylenediamine; Mepyramine; Pyranisamine; Neo-Antergan.

[a] References 2–5.

ethyl acetate–cyclohexane–ammonia–methanol–water (70:15:2:7:0.5); ethyl acetate–cyclohexane–methanol–ammonia, (50:40:0.7:0.4); ethyl acetate–cyclohexane–methanol–ammonia (70:15:10:5); ethyl acetate–cyclohexane–ammonia (50:40:0.1). Correlations between R_f values from five systems and chemical groups indicated that steric hindrance around the group responsible for the bonding to silica in a particular system, compound basicity, and the presence or absence of a pyridyl group influenced the R_f values to the greatest extent (26).

Carboxylmethylcellulose ion exchange paper (CM82) and the solvent system of water–acetone–formamide (10:1:1) easily separated pyrilamine from other antihistamines (27). Thin-layer electrophoresis on silica gel G plates was used to separate 23 basic drugs (28). Using chromatographic sheets[5] pyrilamine was separated with methanol and identified with Dragendorff's reagent or 0.3% aqueous sodium nitrate (29). Separation on silica gel $60F_{254}$ plates was reported (30) using the following solvent systems: chloroform–methanol (9:1); methanol–concentrated ammonium hydroxide (100:1.5); and chloroform–acetone (9:1); and identified under UV light (254 nm) followed by spraying with either iodine in methanol, modified Ludy–Tenger reagent, or iodine in methanol and copper chloride. Colorimetric determination of pyrilamine was performed using the pyrocatechol violet method (31). The drug was allowed to react with aniline and cyanogen bromide reagent and then was determined at 410 nm (32). Pyrilamine has been spectrophotometrically determined using the Δpi method at 236 nm with an accuracy of 100.2 ±0.8% (33). Various pharmaceutical preparations were analyzed by UV spectrophotometry to determine the pyrilamine content (34). After separation on a cation-exchange resin, alginic acid, pyrilamine was determined by UV spectrometry with an accuracy of 98.97% (35). Difference spectrophotometry at 320 nm (36) and by GC using a column[6] with a flame ionization detector were used in another study (37). Pyrilamine was determined by GC using columns of 20% GESF-96 on 45–60 mesh Chromosorb P and 5% SE-30 on 80–100 mesh Chromosorb A with cyclohexanedimethanol succinate and a thermoconductive detector (38).

A column of 1% cyclohexanedimethanol succinate on 100–120 mesh silanized GC P and a flame ionization detector were also used to determine pyrilamine after acetone–ether extraction of blood (39). A column of 200 mg of cyclohexanedimethanol succinate and 2.0 g of methylphenyl silicone on 80–100 mesh diatomaceous earth was used (40) and columns of OV-1 and OV-17 were employed under isothermal conditions (41). Retention indexes for 230 chemicals including pyrilamine were reported for analyses on SE-30, OV-1, and OV-17 columns under isothermal conditions at 180° (42). Discriminating power analysis for GC showed that columns of either SE-30 or OV-17 possessed the highest discriminating powers for separation and determination of 62 basic drugs (43). GC analysis using a column of 3% OV-17 on high-performance Chromosorb W was used to separate pyrilamine from other street drugs (44).

Columns of either 2.1 or 4.1 g of Dexsil 300 on 18 g of 80–100 mesh Chromosorb W (HP) with a flame ionization detector and an automatic sample injector were used to determine pyrilamine in pharmaceutical preparations (45). Detection in blood from cases of overdosage was possible using columns of 3% OV-17 on 100–200 mesh screens or 1% SP-1000 on 100–200 mesh screens[7] using a nitrogen–phosphorus detector (46).

GC analysis of stored blood samples indicated that the drug was stable for at least 7 months (47). Gas chromatography–mass spectrometry (GC–MS), was used to detect pyrilamine in blood plasma (48), and it was found (49) for pyrilamine and its deuterated analogs that single-ion monitoring at *m/z* 121 gave more precise ratios than multiple-ion monitoring at *m/z* 121 and 124 (49).

Direct thin-layer chromatography–mass spectrometry (TLC–MS) was applied to pyrilamine and 30 μg was detected (50). Isocratic multi-column HPLC with a variable wavelength UV detector was found useful to characterize pyrilamine eluted from columns of silica, silica treated with 3-mercaptopropyltrimethoxysilane, or a strong aliphatic cation exchange (51). A phenyl column[8], using a UV detector set at 254 nm, could detect 18 ng of pyrilamine (52). Use of a column consisting of a monomolecular layer of octadecyltrichlorosilane permanently bonded to Si—C, and a UV detector set at 254 nm, enabled the HPLC separation of pyrilamine from various other drugs (53). HPLC was used to separate pyrilamine from pentobarbital in polyethylene glycol-based suppositories (54).

After testing 15 HPLC systems, it was found that the best separations were obtained with acetonitrile–water–propylamine[9] (90:10:0.01) and CN-10, heptane–methylene chloride–acetonitrile–propylamine (50:50:25:0.1) using commercially available columns[10] (55).

METABOLISM AND STRUCTURE-ACTIVITY RELATIONSHIPS

Metabolism and Metabolic Products—One study suggested that pyrilamine can be *N*-demethylated but that

[5] Eastman 6061.
[6] 15% Dexsil 300 on Chromosorb W.
[7] Supelcocort.
[8] μBondapak.
[9] Micropak CN-10.
[10] Micropak CN-10.

more information is needed on cellular distribution, metabolism, and excretion (56). Intravenous injection of pyrilamine in rabbits did not increase the urinary excretion of histamine but did significantly increase the excretion of histamine metabolites (57). Pyrilamine increased brain histamine by blockade of central histaminergic receptors and the inhibition of histamine-*N*-methyltransferase (58) but was ineffective in decreasing histamine uptake in the heart and stomach of rats (59).

In rats, intraventricular injection of histamine affected dopamine metabolism by increasing the amount of homovanillic acid in the striatum. This effect was blocked by pyrilamine (60). Pyrilamine inhibited the activity of histamine-*N*-methyltransferase in the brain, ileum, atrium and stomach of the guinea pig *in vivo* and *in vitro* (61). Histamine-*N*-methyltransferase from pig atrium was inhibited by pyrilamine when the substrate was histamine but not when the substrate was *N'*-methylhistamine (62). Purified guinea pig histamine-*N*-methyltransferase was inhibited by pyrilamine (63). It inhibited rat liver phosphatidate phosphohydrolyase but had no effect on glycerol phosphate acyltransferase or diacylglycerol acyltransferase (64).

In another study, pyrilamine inhibited rat liver phosphatidate cytidylyltransferase, glycerol phosphate acyltransferase, and phosphatidate phosphohydrolyase (65). This inhibition had a marked effect on lipid metabolism (66). Pyrilamine blocked guinea pig adenylcyclase activity induced by tolazoline and to a lesser extent that induced by histamine (67).

Structure–Activity Relationships—Pyrilamine is a derivative of ethylenediamine and modifications in this moiety can cause extreme changes in antihistaminic potency. The terminal nitrogen atom must be tertiary; replacement of the dimethyl group with a diethyl group decreased potency as did quaternization; the chain between the nitrogen atoms must be two carbon atoms and it should not be branched; the replacement of the pyridyl group with pyrimidyl or halogenated phenyl groups did not affect potency, but substituting an additional pyridyl group for the benzyl group decreased potency, while substituting a *para*-methoxy group increased potency (68).

Pharmacodynamics and Kinetics—Pyrilamine blocked the hypotensive action of both histamine and 5-hydroxytryptamine in the rat (69). It markedly potentiated the depressor response of isoproterenol in the dog, had no effect on the isolated rat seminal vesicle preparation but antagonized epinephrine and norepinephrine, reduced the inhibitory effects of these latter drugs on the guinea pig tracheal chain, and relaxed the isolated rabbit ileum. Pyrilamine had no effect on the hind limb preparation of the rat and potentiated the positive inotropic and chronotropic effects of isoproterenol on the rabbit heart *in situ* (70). Pyrilamine was shown to be a noncompetitive antagonist to epinephrine and norepinephrine when tested on the rabbit aortic strip, rat seminal vesicle, and dog blood pressure. It reduced the response of the dog retractor penis muscle and the rat fundal strip to catecholamines (71). When applied topically (72), pyrilamine was a potent constrictor of the mammalian capillary bed of the rat. Pyrilamine significantly attenuated the baroreceptor reflex vasoconstrictor and the vasoconstrictor effect of intra-arterial histamine, but had no effect on such responses induced by intra-arterial norepinephrine in the isolated, perfused gracilis muscle of the dog (73).

Pyrilamine blocked the pressor response and potentiated the depressor response in rabbits given intravenous histamine (74). It also blocked the constrictor response of the isolated rabbit ear artery but had no effect on the perfused human temporal artery (75). Intra-arterial histamine caused a dose-dependent vasodilatation in the carotid vascular bed of the dog which was only partially blocked by pyrilamine (76, 77). In monkeys, pyrilamine only partially blocked the histamine response in the external carotid circulation but had a greater effect on the internal carotid circulation (78). The histamine depressor response in the monkey was partially blocked (79). Increases in blood flow in the left circumflex coronary artery of the dog induced by histamine infusion were only partially blocked by pyrilamine (80). Perfusion of pyrilamine from the lateral ventricle to the cisterna magna in dogs gave a hypertensive followed by a hypotensive response (81). Pyrilamine did not block the hypotension induced by venom from the green mamba (*Dendroaspis angusticeps*) in the cat, dog, rat, and guinea pig (82). Injection of histamine into the pulmonary artery circulation of the isolated perfused guinea pig lung caused increases in pulmonary perfusion pressure which were converted into decreases upon injection of pyrilamine (83, 84). Pyrilamine added to the perfusion fluid used in isolated cat lung perfusions prevented histamine and anoxia pressor responses but greatly increased the resistance of the lungs to air flow (85). Pyrilamine noncompetitively inhibited the positive ionotropic effect of histamine on the isolated guinea pig papillary muscle (86). Using the isolated spontaneously beating rabbit atria, pyrilamine was shown to have antimuscarinic and antinicotinic effects and to have a cocaine-like effect unrelated to local anesthesia (87). Pyrilamine blocked the typical cardiovascular responses, hyperkalemia and hyperglycemia, induced by histamine (88).

Pyrilamine reversed the airway constriction of the isolated guinea pig trachea and bronchus induced by histamine and honey bee venom (89), but relaxation of isolated cat tracheal rings caused by histamine was only partially inhibited (90). Pyrilamine prevented the bronchoconstrictor effect of histamine and increased bronchial motility in the gallamine paralyzed unanesthetized rabbit (91). It had no effect on the preconvulsion time in guinea pigs exposed to aerosolized propranolol (92), but it elevated the total blood carbon dioxide and decreased the blood pH in dogs (93). Histamine-induced modifications of airway resistance, respiratory frequency, pulmonary blood volume, alveolar tensio-active substances for pulmonary compliance, P_aO_2, P_aCO_2, blood pressure, and pulmonary compliance for respiratory frequency in dogs and guinea pigs were all blocked by pyrilamine (94). In the isolated perfused guinea pig lung preparation, pyrilamine inhibited the pressor response to histamine but not that of prostaglandin $F_2\alpha$, and it blocked the histamine induced contraction of guinea pig pulmonary artery strips (95). Aerosolized pyrilamine attenuated the histamine induced nasal airway resistance in the dog (96), but aerosolized histamine or sulfur dioxide inhalation increased airway resistance in humans and only the former was blocked by pyrilamine (97).

Rhythmic contractions in the isolated vas deferans of the guinea pig and rat with or without intact intramural nerves (98) were induced by pyrilamine, and it blocked the responses of the neonatal rabbit ileum to histamine (99). The acetylcholine induced contraction of the isolated toad rectus abdominalis muscle was blocked by pyrilamine (100). While the drug had no effect on the synthesis of prostaglandin E_2 from arachidonic acid by bull seminal vesicle homogenates (101), it blocked the peristaltic reflex induced by increasing the intraluminal pressure in the isolated frog stomach and guinea pig ileum (102). It did not antagonize the acid secretion induced by histamine in the isolated guinea pig gastric fundus (103), but it inhibited the responses in the fundus and antrum of isolated guinea pig stomach to histamine, cholecystokinin, and gastrin and partially inhibited the antral response to acetylcholine (104).

Pyrilamine did not antagonize gastric acid secretion induced in rats and guinea pigs by gastrin, bethanechol, and histamine (105), failed to inhibit histamine stimulation, but did suppress aminopyrine accumulation in histamine stimulated isolated rabbit gastric glands (106). Pyrilamine counteracted the inhibitory effect of supramaximal doses of histamine on gastric acid secretion in conscious gastric fistula cats (107), but failed to protect guinea pigs from histamine induced duodenal ulceration (108). In pylorus ligated rats, pyrilamine failed to prevent aspirin plus hydrochloric acid gastric ulcerations (109). It prevented the fall in diastolic blood pressure but did not prevent gastric secretion induced by histamine in dogs (110).

Histamine stimulation of gastric acid secretion and mucosal blood flow in dogs was not prevented (111), production of gastric lesions by stress in rats was inhibited (112), and gastric lesions produced by cold-restraint stress in rats were not antagonized by the drug (113). The activation of adenylate cyclase in broken-cell preparations of guinea pig gastric mucosa by histamine, sodium fluoride, or 5-guanylylimidophosphate was inhibited by pyrilamine (114). It was shown that pyrilamine had no real effect in treating gastric hyperacidity and peptic ulcers in humans (115).

Pyrilamine blocked the histamine mediated vascular exudation response to mild but not strong cold injury to rat skin (116). Intramuscular injection in sheep prevented the vascular permeability produced by intradermal injection of histamine, hyaluronidase, adenosine, guanosine, inosine, or xanthosine (117). It was reported to release histamine and as a result increased the permeability of sheep skin (118). Compound 48/80 was used to deplete histamine stores in sheep but resulted in a biphasic response in which the first phase could be blocked by pyrilamine (119). Pyrilamine blocked the vascular permeability evoked in sheep by histamine and 5-hydroxytryptamine but not that evoked by bradykinin (120). Pulmonary exudation and histamine release was induced in rats by intrapleural injection of turpentine, silver nitrate, or carrageen, and pyrilamine decreased both parameters for turpentine and silver nitrate but had an irregular effect on carrageen (121). Pyrilamine had no influence on rat mast cell histamine release mediated by cyclic adenosine phosphate or cyclic 5′-guanylic acid (122), however, it released 5-hydroxytryptamine from rat peritoneal mast cells (123) as well as from cow enterochromaffin granules *in vitro* (124). It caused a large release of histamine and stimulation of salivary secretion in the submaxillary gland of the dog (125).

Pyrilamine was used to identify two histamine binding sites in the isolated guinea pig ileum (126), and was identified as an H_1-receptor antagonist through its histamine blocking effects on guinea pig atria and ileum *in vitro* and on rat stomach contractions *in vivo* (127). It only partially antagonized the effects of histamine on the isolated cat tracheal rings and did not affect isolated sheep bronchial strips indicating very few H_1-receptors in the former and none in the latter (128). It was used to identify the histamine H_1-receptors in the cardiovascular system of the chicken (129). One study showed that pyrilamine had no effect on the microcirculation of the dog's synovial membrane, which indicated a lack of histamine H_1-receptors (130).

Pyrilamine appears to have a pseudo-dualist effect on the histamine H_1-receptors of the guinea pig ileum and trachea *in vitro* (131). [^{3}H]Pyrilamine was shown to bind specifically to guinea ilial histamine H_1-receptors *in vitro* (132). Brain membranes from rats, calves, and guinea pigs specifically bind [^{3}H]pyrilamine *in vitro* indicating the presence of histamine H_1-receptors (133), which has been confirmed in the guinea pig brain (134).

Pyrilamine did not bind to γ-aminobutyric acid receptors in the rat brain synaptosomal membrane (135), but it did bind to the histamine H_1-receptors in cultured mouse neuroblastoma cells (136). Pyrilamine was used to block H_1-receptors and had a slight immunosuppressive effect when combined with an H_2-receptor blocker in rat heart allografting (137). [^{3}H]Pyrilamine binds with high affinity to brain membranes from humans, rats, guinea pigs, rabbits, and mice indicating an association with H_1-receptors (138). Differences in [^{3}H]pyrilamine binding in guinea pig and rat brains has been attributed to an actual difference between the H_1-receptors or the presence of a relatively large number of secondary binding sites in the rat (139). Pyrilamine exhibited a noncompetitive binding to the histamine H_1-receptors in the rabbit coronary artery (140) but was only weakly bound to the tricyclic antidepressant binding sites in the rat brain (141). The binding sites in the guinea pig brain have been localized by autoradiography (142). Specific and nonspecific binding of [^{3}H]pyrilamine was studied in the brain, lung, adrenal, heart, aorta, and ileum of the guinea pig, rat, and rabbit and in the lung of the mouse and monkey. There were significant differences in the number of high affinity binding sites in the lung and adrenal gland depending upon species.

In the bovine adrenal gland, it was shown that binding was more abundant and had a higher affinity in the medulla than in the cortex (143). The H_1-receptor involved in hypotension is only partially attenuated by pyrilamine in the dog (144). [^{3}H]Pyrilamine was used to label the H_1-histamine receptors in the hypothalamus, midbrain, cortex, brain stem, cerebellum, striatum, and hippocampus of the mouse *in vivo* (145). The potencies of H_1-antihistamines in reducing [^{3}H]pyrilamine binding *in vivo* corresponded with their pharmacological activities and their affinities for [^{3}H]pyrilamine binding sites in isolated brain membranes (146). The positive inotropic effects of histamine in the dog were unmasked by injection of both H_1-

and H_2-histamine receptor antagonists (147).

Pyrilamine had an inhibitory effect on human platelet aggregation and adhesiveness *in vitro* (148), but had no effect on rubidium-86 uptake by erythrocytes (149). Pyrilamine caused red cell agglutination *in vitro* (150), but had no influence on digitalis toxicity in cats and guinea pigs (151). Histamine-induced sleepiness in chicks was counteracted by pyrilamine (152), and it inhibited development of physical dependence but not tolerance to morphine, in mice (153). Histamine potentiates the sedative action of chloral hydrate in mice and pyrilamine counteracted this effect (154). Pyrilamine had no effect on the *in vitro* hydroxylation of protocollagen by protocollagen proline hydroxylase (155) but antagonized the release of Ca^{2+} from skeletal muscle induced by scorpion venom (156). When administered alone the drug had no effect on the lipolysis of rat adipose tissue *in vitro*, but in the presence of epinephrine, it stimulated or inhibited lipolysis depending upon dose (157). Whereas pyrilamine suppressed turpentine induced pleural exudate in adult rats, it had little effect in 7-day-old rats (158).

Pyrilamine blocked the decrease in patency in the eustachian tube of the dog caused by topical or intra-arterial histamine (159), accelerated wound healing in the rat when given in conjunction with a histamine liberator, 48/80 (160), but did not antagonize reserpine induced hypothermia in mice (161). It antagonized the hypothermia produced in mice by oxotremorine, but when administered in a high dose also produced hypothermia (162). Pyrilamine antagonized posthistamine catalepsy in rats (163). Pyrilamine reduced the mortality from tourniquet shock in rats from 75 to 35% (164), but only partially reduced the edema and vascular permeability changes produced by prostaglandin E, in the rat paw (165). The binding of spleen cells[11] to beads[12] was inhibited *in vitro* (166). It did not modify the pituitary production of prolactin in patients with Parkinson's disease (167), but did reduce the tremor (168).

No information is available on the pharmacokinetics of pyrilamine (169).

TOXICOLOGY

Acute Toxicity in Animals—The acute LD_{50} in the mouse is 30 mg/kg iv; 102 ± 11 mg/kg ip (68); 150 mg/kg sc (170); 36 mg/kg orally in the rat. Symptoms of acute toxicity include generalized tremor, increased activity, incoordination of movement, Straub tail phenomenon, squeaking, restlessness, chronic convulsions, and death by asphyxia (68). Pyrilamine did not counteract lantana poisoning in buffalo calves (171). Pyrilamine and antischistosomal agents released histamine from the rat's mesentary (172). It only partially counteracted the hypotension produced by quinuronium in sheep (173), did not prevent brain edema in rats induced by intra-arterial injection of ^{85}S-microspheres (174), and not only did not protect against paracetamol-induced hepatic necrosis in rats but actually increased mortality (175).

Chronic Toxicity in Animals—Subcutaneous injection of 35 mg/kg of pyrilamine twice daily in rats arrested growth by the 7th day and normal growth ensued when the drug was discontinued. Daily subcutaneous injections of 20 mg/kg had no effect on weight gain in weanling mice. Rats receiving 10 mg/kg daily for 6 months or 200 mg/kg daily for 32 days showed no signs of chronic toxicity nor was there any evidence of gross or histological abnormalities due to the drug. Similar results were obtained in dogs receiving 20 mg/kg five times weekly for 6 months, and in monkeys receiving 50 mg/kg daily for 35 days (68). Pyrilamine, 50 mg/kg sc daily, caused leukocytosis after 14–23 days, and rupture and enlargement of the gall bladder and common duct in guinea pigs (176).

Acute Toxicity in Humans—Subcutaneous injections of pyrilamine in humans produced a 6–12-fold increase in blood histamine levels for 24 hr. Symptoms of acute toxicity included dizziness, jitteriness, somnolence, dry nose, nausea, weakness, palpitation, insomnia, abdominal cramping, numbness, cold extremities, fatigue, tendency to hemorrhage, chloroform taste, faintness, acute hysterical reaction, mydriasis, narcolepsy, sore tongue, hot flushes, early menses, and dermatitis medicamentosa (68).

Immunotoxicology—Pyrilamine completely blocked the acute inflammatory response induced in the rat skin by histamine but only partially blocked that induced by bradykinin, 5-hydroxytryptamine, and prostaglandin E_1 (177). The acute pinnal inflammation induced in mice by intravenous dextran was blocked (178). It did not inhibit the inflammatory response in hairless mice induced by photosensitization (179). The passive cutaneous anaphylactic reaction evoked in mice and rats by injection of immunoglobulin antibody was only partially blocked (180). The estradiol induced edematous response in the immature rat uterus was not inhibited (181) but pressure induced edema in the rat foot was reduced by 13% (182). It inhibited the paw edema elicited in rats and guinea pigs by local injection of histamine (183), and blocked the 4-hr passive cutaneous anaphylactic reaction in rats injected with rabbit antirat mast cell antiserum (184).

The drug inhibited the active bronchial anaphylactic response in the rat elicited by reagin-type antibodies (185), and completely antagonized the histamine released when carrageenin was injected into the rat's paw and prevented the inflammatory response (186). It reduced the volume of the rat's paw induced by injection of Freund's complete adjuvant only between days 1 and 4 (187). Pyrilamine protected rats against anaphylactic shock evoked by sensitization to egg albumin (188), but had no effect on the direct Arthus reaction elicited in the hind paw of the rat (189). Rats were not protected from horse serum induced anaphylactic shock at 10 days and only protected 20% at 20 days (190). Pyrilamine blockade of histamine's effect on the guinea pig tracheobronchial muscle and ileum *in vitro* was abolished by slow reacting substance of anaphylaxis (191). It protected against the liberation of histamine *in vivo* and *in vitro* by chloroplatinate (192), but did not inhibit the response to ovalbumin in tracheal strips from sensitized guinea pigs (193). Histamine, inhibited by pyrilamine, evoked contractions of ovalbumin sensitized guinea pig lung parenchymal strips, but was only weakly active against ovalbumin (194). The antigen–antibody reaction of the isolated guinea pig ileum was not inhibited by pyrilamine (195), and there was no effect on the rise of cyclic adenosine phosphate and 5′-guanylic acid in the

[11] BALB/c.
[12] HRS.

sensitized guinea pig lung stimulated with antigen (196). Cyclic adenosine phosphate release was suppressed in normal and sensitized guinea pig lung slices when stimulated by either histamine or antigen (197). These results have been confirmed (198).

Anaphylactic response in sensitized guinea pigs is not modified by the drug (199). Pretreatment of guinea pigs with pyrilamine and papaverine to prevent death from anaphylactic shock showed that the histaminolytic activity of the liver and plasma increased under such conditions (200). Pretreatment with pyrilamine prevented anaphylactic death in guinea pigs and increased the time before the appearance of dyspnea and cough (201). Pyrilamine suppressed the histamine-induced bronchoconstrictor component of the anaphylactic response in sensitized guinea pigs (202), but had no effect on slow-reacting substance of anaphylaxis induced bronchoconstriction in the sensitized guinea pig (203). It inhibited the increase in potassium in the blood of guinea pigs in histamine shock and anaphylaxis but not in Forssman shock (204). It prevented death in guinea pigs from anaphylatoxin and histamine and at high doses from anaphylactic shock, and also inhibited bronchoconstriction and emphysema formation from antigen (206–207).

In isolated perfused hearts of sensitized guinea pigs, pyrilamine did not affect the coronary dilating, heart stimulating, and antianaphylactic effects of released histamine or prevent anaphylaxis (208). It reduced cardiac output in the heart–lung preparation of guinea pigs and histamine, injected or antigen released, counteracts this effect (209). Pyrilamine had little effect on anaphylactic bronchospasm in the guinea pig heart–lung preparation or on the increased pulmonary vascular resistance. However, when histamine caused the above effects, pyrilamine completely counteracted them (210). In the isolated perfused sensitized guinea pig lung, pyrilamine was effective in counteracting the bronchospastic effect of antigen (211).

Pyrilamine prevented early shock death in acute anaphylaxis in guinea pigs and this effect could be abolished by propranolol (212). It significantly reduced the lipid-mobilization and hyperlipoproteinemia induced in rabbits by endotoxin (213). In horse serum sensitized rabbits, it antagonized the vasoconstrictor action of histamine on the pulmonary vessels and the right ventricular vasoconstriction caused by the administration of antigen (214). It counteracted the increased vascular permeability produced by histamine in the monkey but had no effect against prostaglandin E vascular effects (215).

Pyrilamine inhibited the skin reaction to histamine in the monkey but had no effect on the *Ascaris* antigen reaction (216). It had only a small effect against the capillary damaging effects of passive cutaneous anaphylaxis in sheep (217) and did not prevent the changes in the lymph nodes, spleen, and intestinal lymphoid tissues of sensitized sheep injected with antigen (218). Pyrilamine selectively inhibited responses to histamine and raised the threshold antibody required to elicit a passive cutaneous anaphylactic response in calves (219). It incompletely blocked depressor changes in carotid blood pressure elicited in calves by histamine and anaphylaxis (220). Pyrilamine had no effect in blocking the photobiologic increase in blood content of the pig skin sensitized to anthracene and long-wave UV radiation but inhibited the increased vascular permeability to [^{125}I]albumin (221).

Pyrilamine had little effect in causing histamine release from human leukocytes *in vitro* and little activity against antigen induced histamine release (222). It relaxed human bronchial muscle contracted by histamine or antigen *in vitro* (223). Histamine release induced by antigen in sensitized human lung mince *in vitro* was inhibited by pyrilamine (224). Intradermal injection inhibited the histamine evoked wheal and flare reaction in human skin (225). The drug had no protective effect in fog provocation of bronchoconstriction in bronchitis patients but had some protective effect against inhaled allergen in asthmatics (226).

Chloroplatinate exposure gives rise to pruritis, erythema, urticaria, eczema, mild lymphocytosis, cough, dyspnea, conjunctival vasodilatation, and asthma. All of these symptoms were successfully treated with pyrilamine, aminophylline, and corticoid therapy (227). The wheal and flare reaction induced by histamine and kallikrein were reduced (228). Pyrilamine inhibited the histamine skin reaction induced by pollen in skin testing for allergies (229).

Neurotoxicology—Injection of histamine into the endonerium of the rat sciatic nerve resulted in a markedly increased permeability of the endoneural blood vessels. This effect was blocked by pretreatment with pyrilamine. The permeability changes caused by compound 48/80, a histamine liberator, could be only partially inhibited by pyrilamine (230). Histamine caused both stimulation and inhibition of the spontaneous electrical activity of neurons in the isolated brain of the snail (*Helix asperse*) and both actions were blocked by the drug (231). Pyrilamine blockade of the motor action of histamine on the guinea pig plexus containing longitudinal muscle preparations from the ileum could still be electrically stimulated into tetanic spasms which were inhibited by histamine (232). Pyrilamine reduced potassium ion permeability in the sartorius muscle of *Rana pipiens* in a chlorine ion-free medium and increased the electrical potential change (233).

The drug did not abolish neuromuscular transmission or decrease the lingui-mandibular reflex in dogs treated with cannabis resin, tetrahydrocannabinol, or parahexyl (234). When injected into the preoptic/anterior hypothalamic nuclei, the lateral ventricle, or the third ventricle it did not block the hypothermic response elicited by systemic injection of histamine in rats (235). It reduced the contractions of the stomach of *Rana temporaria* induced by vagal stimulation (236) and the uptake of [^{3}H]γ-amino-*n*-butyric acid by the rat cerebral cortex *in vitro* (237). The postganglionic action potential of the isolated rabbit superior cervical ganglion *in vitro* was depressed in the presence of histamine and further depressed by the addition of pyrilamine (238). Pyrilamine blocked the calcium ion-related hyperpolarization of *Amphiuma* erythrocyte membrane (239).

Pyrilamine blocked the atropine-resistant responses elicited by electrical stimulation of an area located ventrally in the anterior hypothalamus and rising dorsally toward the optic tegmentum (240). Intraventrical injection of pyrilamine in cats blocked the pressor response induced by intraventricular histamine. Pyrilamine alone produced

a depressor response and blocked both reflex as well as direct excitability of the medullary vasomotor center (241), but had no effect on toothpulp nociceptive thresholds in conscious dogs (242). Pyrilamine had no effect on the biphasic response evoked by transmural stimulation of the guinea pig distal colon *in vitro* (243).

CARCINOGENICITY

Animal Carcinogenicity—No information is available on short term tests on the carcinogenicity of pyrilamine (169), but it is scheduled for a National Toxicology Program carcinogenesis bioassay (244).

Human Carcinogenicity—No epidemiological studies or case reports relating pyrilamine to human neoplasia were found in the literature (169).

MUTAGENICITY

Pyrilamine caused unscheduled DNA synthesis in primary adult rat hepatocytes in culture (245). Mitosis was inhibited 68% by histamine in human keratinocytes in culture, pyrilamine blocked this effect (246). No information is available on *in vivo* mutagenesis (247).

TERATOGENICITY

Pregnant mice given pyrilamine in their drinking water produced resorptions, abortions, premature parturitions, decreased weight of the neonates, decrease in survival rate at 44 days, alterations in skin and fur, delayed eye opening, pneumoperitoneum, and delayed opening of the external auditory meatus and vagina (248). Pyrilamine was not teratogenic in the rat (249). It caused stromal edema to be inhibited but increased the number of blastocytes recovered from the uterus of the pregnant rat on day 5 (250). Injection of histamine into the right ventricle of the rat brain produced hypokinesis and catalepsy, and pyrilamine reduced these effects (251). Pyrilamine significantly decreases motor activity in mice (252). No information is available concerning pyrilamine with the production of human malformations (253).

CONCLUSIONS

The chemistry, metabolism, structure–activity relationships, pharmacology, toxicology, mutagenicity, teratogenicity, and carcinogenicity of pyrilamine have been reviewed. More mutagenic studies using cells in culture are required to establish the drug's mutagenicity potential. Teratogenic and three generation studies employing both mice and rats are necessary to understand pyrilamine's effects on the reproductive process. A chronic toxicology study is necessary to determine the long-term effects of pyrilamine. A pharmacokinetic study coupled with *in vitro* metabolism would assist in showing the exact metabolic pathways used in biotransformation of pyrilamine.

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RESEARCH ARTICLES

Diffusion of Phenol in the Presence of a Complexing Agent, Tetrahydrofuran

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Abstract □ The effect of a complexing agent, tetrahydrofuran, on the diffusion of phenol across a stagnant fluid layer has been studied. At a given activity of free phenol, the steady-state flux of phenol appearing in an acceptor phase was greatly enhanced. However, as the fraction of phenol associated with the complexing agent increased, the flux of phenol decreased, since the transport was then controlled by the diffusion of the complex, a larger structure. A mathematical model of simultaneous association and diffusion was derived to determine whether the diffusional behavior of two associating species could be accounted for in terms of the association equilibrium constant and Fick's second law. Experimental results supported the model. It was concluded that the presence of a complexing agent tends to reduce the rate of diffusion, the effect being more pronounced at high concentrations of complexing agent.

Keyphrases □ Phenol—diffusion in a complexing agent, tetrahydrofuran □ Diffusion—phenol in a complexing agent, tetrahydrofuran □

The purpose of this study was to investigate the influence of complexing agents on the diffusional behavior of drugs. The ability of most drugs to undergo association interactions is intrinsically related to their activity, since most drugs exert their action by complexing to a receptor site. Some dosage forms are designed to take advantage of this associative tendency by using a complexing agent to increase the solubility of the drug in the formulation (1, 2). In other cases, complexing agents are used to modify the dissolution rate of a drug at the site of administration (3, 4), as it is known that the dissolution rate can be greatly affected by association in the diffusion layer (5).

In a previous study (6), the importance of associative interaction on mass transport of drugs was exemplified by the case of simultaneous self-association and diffusion of phenol through an immobilized layer of isooctane. The results of this analysis showed that the self-association of phenol can significantly alter the rate of transport of phenol. The case of simultaneous complexation and diffusion has also been investigated (7). However, those results relied on accurate determination of the forward and reverse rate constants for the associative interaction, parameters which may prove difficult to obtain. It was also assumed that for association equilibrium to be attained within the diffusion layer, it was necessary for the con-

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