PILOCARPINE (Systemic)

Category

Cholinergic.

Indications

Accepted

Xerostomia (treatment)¾Pilocarpine is indicated for the treatment of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck. 2, 4, 5, 6, 7, 8, 9, 10, 11, 12 Pilocarpine is also indicated for the treatment of symptoms of xerostomia in patients with Sjogren's syndrome. 19, 20

[Xerophthalmia (treatment)]¾Pilocarpine is indicated for the treatment of xerophthalmia in patients with Sjogren's syndrome. 19

Pharmacology

Mechanism of action/Effect:

Pilocarpine is a cholinergic parasympathomimetic agent that exerts a broad spectrum of pharmacologic effects with predominantly muscarinic action, including stimulation of exocrine function. This stimulation results in increased secretion by the exocrine glands, including the salivary glands. 2, 19, 20

Other actions/effects:

Other exocrine glands, such as the sweat, lacrimal, gastric, pancreatic, and intestinal glands, may be stimulated. 2, 15, 19, 20

Pulmonary effects may include stimulation of the mucous cells of the respiratory tract, increased airway resistance, and increased bronchial smooth muscle tone and secretions. 2, 15

Cardiovascular effects may include changes in hemodynamics and cardiac rhythm. However, pilocarpine may have paradoxical effects. Instead of the expected muscarinic effect of vasodepression occurring, pilocarpine may produce short-lived hypotension followed by hypertension. In addition, both bradycardia and tachycardia have been reported. 2, 15

Gastrointestinal effects include smooth muscle stimulation of the intestinal tract that may result in increased tone and motility, spasm, and tenesmus. The tone and motility of the urinary tract, gallbladder, and biliary duct smooth muscle may be enhanced. 2, 15

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to ophthalmic pilocarpine may be sensitive to oral pilocarpine also.

Carcinogenicity

Studies have not been done. 2, 20

Mutagenicity

Pilocarpine did not cause genetic toxicity in bacterial assays (Salmonella andE. coli) for reverse gene mutations, in vitrochromosome aberration assay (micronucleus test) in Chinese hamster ovary cell line, in vivochromosome aberration assay (micronucleus test) in mice, and primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures. 20

Pregnancy/Reproduction

Fertility¾Studies have not been done in humans. 2, 20

Oral administration of pilocarpine to male and female rats at a dosage of 18 mg/kg/day (approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates) resulted in impaired reproductive function including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to male animals, female animals, or both. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day (approximately 3 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area mg/m2for 6 months) resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair fertility in male and female humans. 20

Pregnancy¾Studies have not been done in humans. 2, 20

Fetuses of pregnant rats given 90 mg/kg per day of pilocarpine (approximately 26 times the maximum recommended human dose) had reduced mean body weight and an increased incidence of skeletal variations. However, these effects may have been secondary to maternal toxicity. 2, 15, 20

FDA Pregnancy Category C. 2, 20

Breast-feeding

It is not known whether pilocarpine is distributed into breast milk. 2, 19, 20

Pediatrics

Appropriate studies on the relationship of age to the effects of oral pilocarpine have not been performed in the pediatric population. Safety and efficacy have not been established. 2, 15, 19, 20

Geriatrics

Appropriate studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of oral pilocarpine in the elderly.

Clinical trials were conducted in both men and women under and over 65 years of age. The adverse events reported by these 4 groups were comparable. In addition, pharmacokinetic studies were done in young men and men and women over 65 years of age after administration of 5 or 10 mg oral pilocarpine 3 times daily for 2 days. The pharmacokinetics were comparable in men under and over 65 years. However, all 5 of the women over 65 years of age in the study had mean maximum concentrations (C max) and trapezoidal values of the areas under the curve (AUC) that were approximately twice as high as the men's values. The men's C max values were 15 and 41 nanograms per mL (72 and 196.8 nanomoles per L) after the 5 and 10 mg dosage, respectively. The men's AUC trapezoidal values were 33 and 108 h (nanograms per mL) after the 5 and 10 mg dosage, respectively. 2, 15

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Anticholinergics or other medications with anticholinergic activity (See Appendix II)

(concurrent use may cause an antagonism of pilocarpine's therapeutic cholinergic effect 14, 19, 20)
(concurrent use may cause an antagonism of the anticholinergic drug's anticholinergic effects; this may be important not only when the drug is being used therapeutically for its anticholinergic effects, but also when the drug has other therapeutic effects and its anticholinergic side effects are being used as indicators of impending adverse effects 2, 13, 14)

>> Antiglaucoma agents, cholinergic, long acting, ophthalmic or

>> Antiglaucoma agents, cholinergic, short acting, ophthalmic or

>> Bethanechol or

>> Cholinergics, other, or other medications with cholinergic activity, such as antimyasthenics

(concurrent use with pilocarpine may result in additive cholinergic effects 2, 13, 19, 20)

>> Beta-adrenergic blocking agents, systemic and ophthalmic

(concurrent use with pilocarpine may increase the possibility of conduction disturbances 19, 20)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Asthma, uncontrolled

(pilocarpine may stimulate the mucous cells of the respiratory tract and may increase airway resistance and bronchial smooth muscle tone 2, 19, 20)

>> Glaucoma, angle closure or

>> Iritis, acute

(pilocarpine may cause miosis 2, 19, 20)

>> Sensitivity to pilocarpine 2, 19, 20

Risk-benefit should be considered when the following medical problems exist

>> Asthma, controlled or

>> Bronchitis, chronic or

>> Chronic obstructive pulmonary disease

(pilocarpine may stimulate the mucous cells of the respiratory tract and may increase airway resistance and bronchial smooth muscle tone 2, 19, 20)

>> Biliary tract disease or

>> Cholelithiasis, known or suspected

(pilocarpine may cause contractions of the gallbladder or biliary smooth muscle and cholecystitis, cholangitis, or biliary obstruction may occur 2, 17, 20)

>> Cardiovascular disease

(patients with significant cardiovascular disease may be unable to compensate for the transient changes in hemodynamics or heart rhythm that are induced by pilocarpine; pulmonary edema has occurred as a complication of pilocarpine toxicity from high ophthalmic doses and may occur with oral pilocarpine also 2, 19, 20)

>> Cognitive disturbances or

>> Psychiatric disturbances

(pilocarpine may have central nervous system effects, which may exacerbate these conditions 2, 19, 20)

Nephrolithiasis

(pilocarpine may increase ureteral smooth muscle tone and may theoretically precipitate renal colic, especially in patients with nephrolithiasis 2, 19, 20)

Peptic ulcer disease, acute

(pilocarpine may increase acid secretion 19)

>> Retinal detachment, predisposition to or

>> Retinal disease

(an association between use of ophthalmic pilocarpine and retinal detachment has been reported in patients with pre-existing retinal disease; it is not known whether this association may occur with oral pilocarpine 2, 15)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Fundus examination

(should be performed periodically in patients with pre-existing retinal disease, since an association between use of ophthalmic pilocarpine and retinal detachment has been reported in patients with pre-existing retinal disease; it is not known whether this association may occur with oral pilocarpine 2, 15)

Side/Adverse Effects

Note: Pilocarpine toxicity is characterized by an exaggeration of its parasympathomimetic effects. 2

The following side/adverse effects have occurred in less than 1% of patients treated with pilocarpine; however, the causal relationship is unknown: anorexia, anxiety, deafness, depression, dysuria, electrocardiogram abnormality, esophagitis, eye pain, glaucoma, hyperkinesia, hypoesthesia, hypothermia, leukopenia, lymphadenopathy, metrorrhagia, paresthesias, seborrhea, speech disorder, stridor, syncope, and urinary impairment. In addition, 1 patient experienced a myocardial infarction, and 1 patient had an episode of syncope; both patients had underlying cardiovascular disease. 2

The following side/adverse effects have occurred rarely in patients treated with ophthalmic pilocarpine: agitation, atrioventricular block, ciliary congestion, confusion, delusion, depression, dermatitis, iris cysts, macular hole, malignant glaucoma, middle ear disturbance, shock, and visual hallucination. 2

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Chills; diarrhea; flu-like syndrome (cough ; fever ; joint pain; muscle aches and pains ; unusual tiredness or weakness); dyspepsia (indigestion); nausea; rhinitis (runny nose); sweating 2, 4, 5, 19; urinary frequency 19 (increased need to urinate; passing urine more often); vasodilation 19 (feeling of warmth or heat; flushing or redness of skin especially on face and neck)

Incidence less frequent or rare

Amblyopia (trouble seeing); asthenia (unusual weak feeling); dysphagia (trouble swallowing); edema (holding more body water; swelling of face, fingers, ankles, or feet); epistaxis (nosebleeds); headache; hypertension; tachycardia (fast heartbeat); tremors (trembling or shaking); voice change; vomiting 2, 4, 5

Overdose

For specific information on the agents used in the management of systemic pilocarpine overdose, see:
· Atropine in Anticholinergics/Antispasmodics (Systemic) monograph; and/or
· Epinephrine in Bronchodilators, Adrenergic (Systemic) monograph.
For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).
Pilocarpine toxicity is characterized by an exaggeration of its parasympathomimetic effects. 2 One hundred mg of pilocarpine is considered to be potentially fatal.

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Acute and chronic

Arrhythmia (irregular heartbeat, continuing or severe); atrioventricular block (chest pain or fainting); bradycardia (slow heartbeat, continuing or severe); confusion ; diarrhea, continuing or severe; gastrointestinal spasm (stomach cramps or pain); headache, continuing or severe ; hypertension; hypotension (tiredness or weakness, continuing or severe); nausea, continuing or severe; respiratory distress (shortness of breath or troubled breathing); shock (fainting or tiredness or weakness, continuing or severe); tachycardia (fast heartbeat, continuing or severe); tremors (trembling or shaking, continuing or severe); visual disturbance, continuing or severe (trouble seeing, continuing or severe); vomiting, continuing or severe 2, 17
Treatment of overdose

0.5 to 1 mg of atropine should be administered subcutaneously or intravenously. 2

Supportive measures to maintain respiration and circulation should be used. 2

For severe cardiovascular depression or bronchoconstriction, 0.3 to 1 mg of epinephrine should be administered subcutaneously or intramuscularly. 2

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Pilocarpine (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to ophthalmic or oral pilocarpine
Use in children¾Safety and efficacy have not been established
Other medications, especially anticholinergics or other medications with anticholinergic activity; antiglaucoma agents, cholinergic, long acting, ophthalmic; antiglaucoma agents, cholinergic, short acting, ophthalmic; beta-adrenergic blocking agents, systemic and ophthalmic; bethanechol; or cholinergics, other, or other medications with cholinergic activity
Other medical problems, especially asthma, controlled; asthma, uncontrolled; biliary tract disease; bronchitis, chronic; cardiovascular disease; cholelithiasis, known or suspected; chronic obstructive pulmonary disease; cognitive disturbances; glaucoma, angle closure; iritis, acute;; psychiatric disturbances; retinal detachment, predisposition to; or retinal disease
Proper use of this medication

>> Taking medication only as directed; not taking it more often and not taking larger dose than directed; doing so may increase chance of side/adverse effects

Importance of seeing dentist regularly to prevent dental and other mouth problems, which are more likely to occur in patients with xerostomia

>> Proper dosing
Missed dose: Taking as soon as possible; skipping missed dose if it is almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

>> Caution if difficulty in reading or other vision problems occur; 17 caution if dizziness or lightheadedness occurs; not driving, using machines, or doing anything else that could be dangerous if not alert or able to see well; checking with physician if reactions are especially bothersome

>> Importance of drinking enough liquids to offset the sweating that medication may cause 2, 15

Side/adverse effects

Signs of potential side effects, especially signs of overdose

General Dosing Information

The lowest dosage that is effective should be used, since the incidence of side/adverse effects is dose dependent. 2, 19, 20

To achieve maximum benefit, pilocarpine tablets may need to be used for 12 weeks or more. The onset and degree of symptom relief varies among patients. 19

Oral Dosage Forms

PILOCARPINE HYDROCHLORIDE TABLETS

Usual adult and adolescent dose

Xerostomia (treatment)¾
Oral, 5 mg three times a day for patients with head and neck cancer. Dosage may be increased up to 10 mg three times a day for patients who do not respond to lower doses; however, increasing the dose also increases the incidence of side/adverse effects. The lowest dose that is tolerated and effective should be used for maintenance. 2, 20 The Canadian manufacturer recommends 5 mg three or four times a day. 19

Xerostomia (treatment)¾
Oral, 5 mg four times a day for patients with Sjogren's syndrome. 20 The Canadian manufacturer recommends 5 mg three or four times a day. 19

[Xerophthalmia (treatment)]¾
Oral, 5 mg three or four times a day for patients with Sjogren's syndrome. 19

Usual adult prescribing limits

Up to 10 mg per dose 19 , 30 mg per day. 19, 20

Usual pediatric dose

Safety and efficacy have not been established. 2, 19, 20

Usual geriatric dose

See Usual adult dose 19

Usual geriatric prescribing limits

See usual adult prescribing limits 19

Strength(s) usually available

U.S.¾5 mg (Rx)[Salagen (carnauba wax) (hydroxypropyl methylcellulose) (iron oxide) (microcrystalline cellulose) (stearic acid) (titanium dioxide) 20]

Canada¾5 mg (Rx)[Salagen (microcrystalline cellulose) (stearic acid) (hydroxypropyl methylcellulose) (titanium dioxide) (polyethylene glycol) (polysorbate 80) (shellac) (ethanol) (synthetic black iron oxide) (N-butyl alcohol) (propylene glycol) (ethylene glycol monoethyl ether) (lecithin) (methyl alcohol) (carnauba wax) 19]

Packaging and storage:

Store at controlled room temperature between 15 and 30 °C (59 and 86 °F). 2, 18, 19, 20