DESCRIPTION

Timolol maleate ophthalmic solution is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is C_{19}H_{22}ClN_{2}O_{3} (1:1). Timolol Maleate possesses an asymmetric carbon atom in its structure and is levorotatory. The optical rotation of Timolol maleate is 

Timolol Maleate has a molecular weight of 352.3. It is a white, colorless, crystalline powder which is soluble in water; methanol, and alcohol. Timolol Maleate ophthalmic solution is stable at room temperature.

Timolol maleate ophthalmic solution is supplied as a sterile, isotonic, buffered, aqueous solution of Timolol Maleate in two dosage strengths. Each mL, for ophthalmic administration, contains 0.25% solution contains 5 mg of timolol maleate (0.8 mg of Timolol Maleate inactive ingredients: monobasic and dibasic sodium phosphate; hydrochloric acid and/or sodium hydroxide to adjust pH; and purified water. Benzalkonium chloride 0.01% is added as a preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action: Timolol Maleate is a beta, and, non-selective (adrenergic) receptor blocking agent. Timolol maleate does not have significant intrinsic sympathomimetic, direct myocardial, cholinergic muscarinic, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients suffering from certain cardiac abnormalities. The non-selective blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance and decreased ventilation. Fortunately, beta-adrenergic receptor antagonists do not significantly affect the bronchiolar smooth muscle as long as no other factors increase airway resistance. Consequently, beta-adrenergic receptor antagonists are safe for use in patients with bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) patients receiving concurrent therapy with theophylline (see WARNINGS); (5) severe cardiac failure (see WARNINGS); (6) patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with severe autonomic neuropathy) (see WARNINGS); (7) uncontrolled hyperthyroidism (see WARNINGS); and (8) patients with a history of anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental or intentional overdosage with beta-adrenergic receptor antagonists.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical application. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and death due to arrhythmias or cardiac failure, have been reported following systemic or ophthalmic administration of Timolol Maleate (see CONTRAINDICATIONS).

Adrenergic beta-adrenergic receptor blockade may induce an asymptomatic decrease in normal blood pressure. This decrease in blood pressure is more likely to occur in patients with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Beta-adrenergic receptor blockade has been observed in patients with diminished myocardial contractility (e.g., chronic ischemic or cardiomyopathic heart disease, advanced congestive heart failure). Beta-adrenergic receptor blockade may block the inotropic effect of the sympathetic nervous system and may blunt compensatory reflexes, including the baroreceptor reflex and reflex vasomotor responses. In individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Beta-adrenergic receptor blockade has been observed in patients with diminished myocardial contractility (e.g., chronic ischemic or cardiomyopathic heart disease, advanced congestive heart failure). Beta-adrenergic receptor blockade may block the inotropic effect of the sympathetic nervous system and may blunt compensatory reflexes, including the baroreceptor reflex and reflex vasomotor responses.

It is conceivable that in patients with reduced cardiac function or severe chronic obstructive pulmonary disease, theophylline, sodium hydroxide to adjust pH; and purified water. Benzalkonium chloride 0.01% is added as a preservative.

PHARMACOKINETICS

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily administration of Timolol Maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL, and following afternoon dosing was 0.29 ng/mL.

Clinical Study: In controlled multicenter studies in patients with untreated intraocular pressures of 20 mmHg or greater, Timolol Maleate ophthalmic solution administered twice a day produced a greater reduction in intraocular pressure than 1, 2, or 3 percent epinephrine hydrochloride solution administered twice a day.

In these studies, theophylline was generally well tolerated and produced fewer and less severe side effects than timolol or epinephrine. A slight reduction of resting heart rate in some patients (mean decrease 2.9 beats/minute standard deviation 10.2) was observed.

INDICATIONS AND USAGE

Timolol Maleate ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

Timolol Maleate is contraindicated in patients with (1) bronchial asthma, (2) history of bronchial asthma, (3) severe chronic obstructive pulmonary disease (see WARNINGS), (4) sinus bradycardia, (5) second or third degree atrioventricular block, (6) overt cardiac failure (see WARNINGS), (7) congestive shock, or (8) hypersensitivity to any component of this product.

WARNINGS

As with other beta-adrenergic blocking agents, patients should be warned to avoid or discontinuethis medication if exposed to propranolol or other non-selective blocking agents.

Timolol Maleate ophthalmic solution contains benzalkonium chloride, a quaternary ammonium compound. The possibility of an allergic reaction to any of the topical ophthalmic solutions contains benzalkonium chloride, a quaternary ammonium compound. The possibility of an allergic reaction to any of the topical ophthalmic solutions is bound to be encountered. Therefore, patients allergic to this preservative should be advised not to use this product.

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It is a 2-year study of Timolol Maleate administered orally to rats, where a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 200 mg/kg/day (approximately 42 times the systemic exposure following the maximum recommended human ophthalmic dose) was observed. Similar differences were not observed in rats administered oral doses equivalent to approximately 14.4 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at doses of 50 and 500 mg/kg/day (approximately 7,000 and 70,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). However, these differences in incidence did not persist with continued dosing at 500 mg/kg/day, and there were no adverse effects on male mice at any of the doses tested.

In a carcinogenicity study in F344/N rats, the increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of Timolol Maleate (the maximum recommended human oral dose), there were no clinically meaningful changes in serum prolactin.

Timolol Maleate was devoid of mutagenic potential when tested in vivo (mouse) in the microcosmic test and in vitro (strain-test) in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of Timolol Maleate were 1 mg/mL (approximately 200 mcg/mL) in S. typhimurium TA 100 and 10 mg/mL (approximately 1 mg/mL) in S. typhimurium TA 1537. The Ames test results indicate that Timolol Maleate is not mutagenic, but the possibility cannot be excluded. In a micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in a neoplastic cell transformation assay (up to 100 mcg/mL), the highest concentrations of Timolol Maleate observed were 1 mg/mL and 10 mg/mL respectively. In a cell transformation assay (up to 100 mcg/mL), the highest concentration of Timolol Maleate observed was 1 mg/mL, but the possibility cannot be excluded.

Clonidine: There is no evidence of drug interaction with clonidine.

Diuretics: Overdosage has been reported with Timolol Maleate tablets. A 30 mg oral overdose of Timolol Maleate tablets (recommended maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, diziness, tinnitus, weakness, increased pulse rate, and borderline first degree heart block.

Digitalis and calcium antagonists: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving calcium antagonists. The coadministration of digitalis and a beta-blocking agent is associated with an increased risk of digitalis toxicity.

Urogenital: There have been reports of inadvertent overdosage with Timolol Maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as diuretics, heart failure, hypotension, bradycardia, and constipation (see also ADVERSE REACTIONS).

HOW SUPPLIED
Timolol Maleate ophthalmic solution is available in concentrations of 0.25% and 0.5%. The usual starting dose is one drop of the 0.25% Timolol solution in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5% solution in the affected eye(s) twice a day. Since in some patients the pressure-lowering response to timolol may require several weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with timolol.

Timolol Maleate ophthalmic solution should be stored at 15-25°C (59-77°F). Protect from freezing. Protect from light.

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