PRODUCT MONOGRAPH

TIMOLOL

timolol maleate tablets USP

Tablets 5 mg, 10 mg and 20 mg

Antihypertensive and Anti-Anginal Agent

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Control number: 212835

DATE OF REVISION:

February 19, 2018

NAME OFDRUG

TIMOLOL

(timolol maleate)

Tablets 5, 10 and 20 mg

THERAPEUTIC CLASSIFICATION

Antihypertensive and Anti-Anginal Agent

ACTIONS

TIMOLOL (timolol maleate) is a beta-adrenergic blocking agent.
The mechanism of the antihypertensive effect of beta adrenergic receptor blocking agents has not yet been established. Among the factors that may be involved are:

(i) competitive ability to antagonize catecholamine-induced tachycardia at the beta receptor sites in the heart, thus decreasing cardiac output,
(ii) inhibition of renin release by the kidneys,
(iii) inhibition of the vasomotor centres.

The exact mechanism by which timolol maleate exercises its anti-anginal effect is not certain but it may reduce the oxygen requirements of the heart by blocking catecholamine-induced increases in heart rate, systolic blood pressure and the velocity and extent of myocardial contraction. However oxygen requirements may be increased by such actions as increases in left ventricular fibre length, end diastolic pressure and the systolic ejection period. When the net physiological effect is advantageous in anginal patients it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks. Timolol can therefore increase the capacity for work and exercise in such patients. In a multi-clinic study, two-thirds of the patients treated with timolol maleate benefited to some degree.

Timolol has been found effective in prophylactic use for secondary prevention in patients with ischemic heart disease who have survived the acute phase of a myocardial infarction. At the present time, the mechanism of this protective effect of timolol is unknown.

Bioavailability

TIMOLOL 10 mg Tablet

The bioavailability of a single oral dose of TIMOLOL 10 mg was compared with that of Blocadren 10 mg in normal human volunteers, with results as follows:

Parameter	Blocadren* 10 mg	TIMOLOL* 10 mg	Percent Difference

AUC0-24 (ng hr/ml)	123.5	124.9	+1.1
C_{max} (ng/ml)	24.08	26.42	+9.7
t_{max} (hr)	1.6	1.5	-6.6
$t_{l/2}$ (hr)	3.4	3.2	-5.9

*timolol maleate 10 mg tablet

INDICATIONS

TIMOLOL (timolol maleate) is indicated for:

- Patients with mild or moderate hypertension. Timolol maleate is usually used in combination with other drugs, particularly a thiazide diuretic. However, timolol maleate may be tried alone, as an initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a beta blocker rather than a diuretic. The combination of timolol maleate with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than timolol alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with timolol. TIMOLOL is not indicated in the treatment of hypertensive emergencies.
- Angina pectoris due to ischemic heart disease.
- Patients who have survived the acute phase of a myocardial infarction, and are clinically stable, to reduce cardiovascular mortality and the risk of reinfarction. In the study which showed these benefits, treatment with timolol was begun 7 to 28 days after the acute phase. Data are not available as to whether benefit would ensue if the treatment is initiated later.
- Prophylactic treatment of migraine. TIMOLOL is not indicated in the management of acute migraine attacks.

CONTRAINDICATIONS

Congestive heart failure (see WARNINGS)

Right ventricular failure secondary to pulmonary hypertension

Significant cardiomegaly

Sinus bradycardia

Second and third degree A-V block

Cardiogenic shock

Allergic rhinitis, bronchospasm (including bronchial asthma), or severe chronic obstructive

pulmonary disease (see PRECAUTIONS)

Anesthesia with agents that produce myocardial depression, e.g., ether Hypersensitivity to timolol maleate.

WARNINGS

Cardiac Failure: Special caution should be exercised when administering TIMOLOL (timolol maleate) to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries a potential hazard of further depressing myocardial contractility and precipitating cardiac failure.

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances this has been observed during therapy with timolol.

Therefore, at the first sign or symptom of impending cardiac failure occurring during therapy with TIMOLOL, patients should be fully digitalized and/or given a diuretic, and the response observed closely. Timolol acts selectively without blocking the inotropic action of digitalis on the heart muscle. However, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of timolol maleate when the two drugs are used concomitantly. The effects of timolol and digitalis are additive in depressing A-V conduction. If cardiac failure persists therapy with TIMOLOL should be discontinued (see below).

Abrupt Cessation of Therapy with TIMOLOL
Patients with ischemic heart disease should be warned against stopping TIMOLOL abruptly. Myocardial infarction, ventricular arrhythmias, or sudden death has been reported in such patients following abrupt discontinuation of therapy with beta-adrenergic receptor blocking agents, with or without preceding exacerbation of angina pectoris. Therefore, in angina and post-myocardial infarction, the dosage of TIMOLOL should be gradually reduced over about two weeks (maintaining the same frequency of administration) and the patient should be carefully observed. In patients with angina pectoris, if the angina still markedly worsens, or in any patient if acute coronary insufficiency develops, it is recommended that TIMOLOL be reinstated, at least temporarily.

Since ischemic heart disease may be unrecognized, the above advice should be followed in patients considered to be at risk of having asymptomatic ischemic heart disease.

Various skin rashes and conjunctival xerosis have been reported with beta blockers including timolol maleate. A severe syndrome (oculo-muco- cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis and sclerosing serositis have occurred with the chronic use of one beta adrenergic blocking agent. This syndrome has not been observed with timolol. However physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Severe sinus bradycardia due to unopposed vagal activity may result from the administration of TIMOLOL; in such cases, consider the use of intravenous atropine, and, if no improvement is seen, intravenous isoproterenol.

In patients with thyrotoxicosis, timolol maleate may give a false impression of improvement by diminishing peripheral manifestations of hyperthyroidism without improving thyroid function. Special considerations should be given to the potential of timolol maleate to aggravate congestive heart failure. Timolol maleate does not alter thyroid function tests. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS

TIMOLOL (timolol maleate) should be administered with caution to patients prone to non-allergic bronchospasm (e.g., chronic bronchitis, emphysema) since it may block bronchodilatation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, large doses of epinephrine may be needed to overcome the bronchospasm, while on the other hand these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heartblock and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta-agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

TIMOLOL should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia.

TIMOLOL dosage should be individually adjusted when used concomitantly with other antihypertensive agents (see DOSAGE AND ADMINISTRATION).

Patients receiving catecholamine depleting drugs such as reserpine or guanethidine should be closely observed if TIMOLOL is administered concomitantly. The added catecholamine blocking action of this drug may produce an excessive reduction of the resting sympathetic nervous activity.

Suitable laboratory tests should be carried out at appropriate intervals and caution should be observed in patients with impaired renal or hepatic function. Since timolol is excreted mainly by the kidneys, dosage reduction may be necessary when renal insufficiency is present. Marked hypotension has been observed in patients with severe renal insufficiency undergoing renal hemodialysis following oral administration of 20 mg of timolol.

In Patients Undergoing Elective or Emergency Surgery

The management of patients with angina, being treated with beta blockers and undergoing elective or emergency surgery is, controversial because beta adrenergic receptor blockade impairs the ability of the heart to respond to beta adrenergically mediated reflex stimuli, but abrupt discontinuation of therapy with TIMOLOL may be followed by severe complications (see

WARNINGS). Some patients receiving beta adrenergic blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

For these reasons, in patients with angina undergoing elective surgery, TIMOLOL should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy (see WARNINGS). According to available evidence, all clinical and physiologic effects of beta blockade are no longer present 48 hours after cessation of medication.

In emergency surgery, since timolol is a competitive inhibitor of beta adrenergic receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levarterenol.

Usage in Pregnancy
Since TIMOLOL has not been studied in human pregnancy, the drug should not be given to pregnant women. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against possible hazards.

Nursing Mothers
Timolol Maleate has been found to be excreted in human milk. If use of the drug is deemed essential, the patient should stop nursing.

Usage in Children
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Cardiovascular

Congestive heart failure in 3-4% of patients (see WARNINGS) Secondary effects of decreased cardiac output, about 4%, which could include: syncope, vertigo, lightheadedness, postural hypotension, decreased renal perfusion.

Severe bradycardia in about 1% of patients.

Less frequently:

Lengthening of the PR Interval

2nd and 3rd degree A-V block

Sinus arrest (if SA node previously diseased)

Cold extremities

Raynaud's phenomenon

Claudication or paresthesia

Hypotension

Respiratory

Dyspnea has occurred in about 10% of patients

Bronchospasm in about 1% of patients

Laryngospasm might occur rarely

Central Nervous System

Most frequently reported:

Headache

Less frequently:

Lightheadedness

Drowsiness

Anxiety

Vertigo

Tinnitus

Dizziness

Weakness

Insomnia

Sedation

Mental depression

Rarely:

Vivid dreams

Allergic/dermatologic (see WARNINGS)

Occasionally rashes, including one case of psoriasiform rash reported to date, and pruritus.

Rarely, exfoliative dermatitis.

Gastrointestinal

Vomiting in about 4% of patients

Diarrhea in about 5% of patients

Less frequently:

Constipation

Epigastric distress

Nausea

Eyes

Dry eyes

Clinical Laboratory

Elevation of BUN or SGPT have occurred in some patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The most common signs to be expected are bradycardia, hypotension, bronchospasm, or acute cardiac failure.

If overdosage occurs, in all cases therapy with TIMOLOL should be discontinued and the patient observed closely. In addition, the following therapeutic measures are suggested:

TREATMENT

Gastric lavage

Bradycardia

Use atropine sulfate intravenously in a dosage of 0.25 mg to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a cardiac pacemaker may be considered.

Heart Block (Second degree or complete)

Isoproterenol or intravenous cardiac pacemaker.

Acute Cardiac Failure:

Conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon hydrochloride which has been reported to be useful.

Hypotension

Use sympathomimetic pressor drug therapy, such as levarterenol or epinephrine. (See precaution concerning the use of epinephrine.) In refractory cases the use of glucagon hydrochloride has been reported to be useful.

Bronchospasm

Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

Hypoglycemia

Intravenous glucose and/or intramuscular glucagon.

An *in vitro* hemodialysis study, using C14 timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids, however a study in patients showed timolol was not dialyzed in patients with renal failure.

It should be remembered that timolol maleate is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of TIMOLOL. However, the complications of excess isoproterenol, such as tachycardia, headache, flushing of the skin, arrhythmias, nausea, weakness, tremor and sweating, should not be overlooked.

DOSAGE AND ADMINISTRATION

HYPERTENSION

TIMOLOL (timolol maleate) is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic, but may be used alone (see INDICATIONS).

The dose must always be adjusted to the individual requirements of the patient, in accordance with the following guidelines:

When TIMOLOL is given to patients already receiving other antihypertensive agents, the initial dose should be 5 to 10 mg twice a day. If after one to two weeks an adequate response is not observed, dosage may be increased by increments of 5 mg twice daily, at intervals of two weeks. A 60 mg daily dose should not be exceeded.

When TIMOLOL is used alone the initial dose should be 10 mg twice a day and dosage increased if required, following the regimen described above.

In those patients who are found to be adequately controlled on daily doses of 20 mg or less, the administration of the total dose in the morning should be tried a studies show adequate response to this dose regimen.

ANGINA

The recommended dosage range of TIMOLOL is 15 mg to 45 mg per day. The majority of patients respond to a daily dosage of 35 mg to 45 mg. Therapy should be initiated with 5 mg two or three times a day. Depending on response, increases in dosage may be necessary. The first increase should not exceed 10 mg per day in divided doses. Subsequent increases should not exceed 15 mg per day in divided doses. A total daily dose of 45 mg should not be exceeded. There should be an interval of at least three days between increases in dosage.

After the titration period, some patients may be maintained on a b.i.d. schedule.

PREVENTIVE USE IN ISCHEMIC HEART DISEASE

For long-term preventive use in patients who have survived the acute phase of myocardial infarction, the maintenance dose is 10 mg twice daily. Therapy should be initiated with 5 mg twice daily and the patient observed carefully. If no adverse reaction occurs, the dosage should then be increased after 2 days to 10 mg twice daily. In the studies evaluating timolol following myocardial infarction, treatment was begun 7 to 28 days after the acute phase.

MIGRAINE

Dosage must be individualized. The recommended dosage for prevention of migraine headache is 10 mg twice daily. The dosage range is 10 to 30 mg/day. If a satisfactory response is not obtained after 6 to 8 weeks of the maximum suggested dosage, therapy with TIMOLOL should be discontinued.

AVAILABILITY

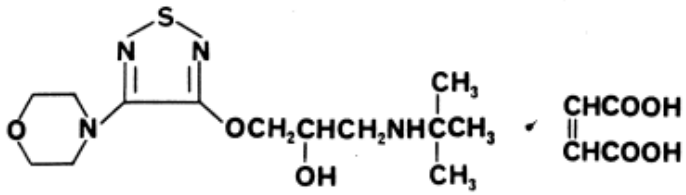
Each white, round, flat, bevelled-edge tablet, scored and engraved T5 on one side, other side plain contains 5 mg of timolol maleate. Available in bottles of 100.

Each light-blue, round, flat, bevelled-edge tablet, scored and engraved T10 on one side, other side plain contains 10 mg of timolol maleate. Available in bottles of 100.

Each light-blue capsule-shaped biconvex tablet, scored and engraved T20 on one side, other side plain contains 20 mg of timolol maleate. Available in bottles of 100.

CHEMISTRY

Timolol Maleate



Molecular Formula: $C_{13}H_{24}N_4O_3S.C_4H_4O_4$

Molecular Weight: 432.50

Chemical Name: (-)-1-(tert-butylamino)-3-((4-morpholino-1,2,5-thiadiazole- 3-yl)oxy) -2-propanol maleate (1:1).

Description: Timolol maleate is a white crystalline compound which melts with decomposition at approximately 198-199°C. It is soluble in water, ethanol and methanol. It is sparingly soluble in chloroform, very slightly soluble in cyclohexane and practically insoluble in isooctane. Timolol maleate is stable in acid and base in a range of pH up to 12 but unstable in strong base (pH 12). The solid is stable when ex ed to air at 105°C for at least one month.

PHARMACOLOGY

PHARMACOKINETICS

In animal studies, timolol was rapidly absorbed, metabolized and effectively excreted. Urinary and fecal recovery was essentially the same after either oral or intravenous administration of C14-labelled timolol, suggesting complete absorption after oral administration. Highest concentrations were observed in the small intestine, kidney and liver.

In humans timolol maleate is rapidly absorbed following oral ingestion. Detectable plasma levels of timolol occur within one-half hour and persist for about 8-12 hours. Peak plasma levels occur in about one to two hours. The drug half-life in plasma is approximately 3-4 hours. Timolol and its metabolites are excreted principally by the kidney. Plasma levels following oral administration are about half those following intravenous administration indicating approximately 50% first pass metabolism. In man, the drug was extensively metabolized with the major metabolites being 1-tert-butylamino-(4-(N-2-hydroxyethylglycolamido)-1, 2, 5-thiadiazol- 3-yloxy)-2-propanol (30%), an ethanolamine derivative (10%) and a lactic acid metabolite (10%). Approximately 20% of a 0.1 mg/kg oral dose was excreted in the urine unchanged.

Excretion occurred primarily via the kidney with 68% of the drug appearing in the urine within 24

hours. Approximately 5% was eliminated in the feces.

A 7.3 mg/kg dose of C^{14}-labelled timolol administered to pregnant rats (at day 19 of gestation) resulted in a plasma: amniotic fluid ratio of approximately 10:1 (1.5 versus 0.17 ug/mL respectively). The concentration in the placenta and whole fetus averaged 0.13 and 0.31 ug/g respectively. A similar dose administered to nursing rats resulted in the secretion of timolol into milk in a concentration of 1.79 ug/mL (plasma concentration 1.45 ug/mL).

Single and multiple dose drug distribution studies in animals were done to investigate the passage of timolol through the blood-brain barrier. After four consecutive days dosing in rats, timolol metabolites in the brain showed only a slight increase. In dogs it was observed that timolol concentrations in the CSF were about one-third of the simultaneous plasma concentrations.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

In anesthetized dogs, timolol at 10 or 40 ug/kg I.V. significantly reduced cardiac output and increased calculated peripheral vascular resistance without a significant effect on stroke volume. Preadministration of a ganglionic blocking agent abolished this effect, suggesting that the reduction in cardiac output was the result of a decrease in sympathetic control of cardiac function rather than a direct myocardial depressant action.

In animals, when administered intravenously, it was effective in antagonizing the vasodepressor and cardiac actions (inotropic, chronotropic or both) of intravenously administered isoproterenol and cardiac accelerans nerve stimulation (endogenously released catecholamines).

In man, a single 5 mg oral dose blocked the chronotropic and inotropic effects of exogenously administered isoproterenol. Similarly the sympathetic reflex tachycardia induced by inhalation of amyl nitrite and the tachycardia occurring after the completion of the forced expiration of the Valsalva maneuver was reduced.

Within half an hour of administration this dose caused a reduction in heart rate of about 20% in both the sitting and standing position. The maximum effect occurred in about 45-90 minutes and recovery was incomplete at 6 hours. Intravenously administered timolol maleate also produced a dose-dependent decrease in exercise tachycardia in normal volunteers. The maximum decrease following a 1.0 mg dose was 11%. A 0.25 mg dose was effective in reducing the increase in forearm blood flow produced by an intravenous infusion of isoproterenol.

In animal studies, timolol was shown to be effective· in inhibiting hydrocarbon-epinephrine induced arrhythmias in dogs as well as controlling ventricular arrhythmias induced by intracoronary administration of a sclerosing agent (tetraflurohexachlorobutane). It was ineffective in reducing ventricular arrhythmias in dogs with coronary ligation and did not alter either the pattern of arrhythmias or the lethal dose of intravenously administered ouabain.

The lack of effect on ouabain-induced arrhythmias coupled with the lack of local anesthetic activity (as evidenced by failure of the highest possible concentration (65 mg/ml) to induce local anesthetic activity in the mouse) suggests that timolol has no membrane stabilizing (quinidine-like) activity.

In dogs, doses considerably above those necessary to produce beta adrenergic blockade did not have sympathomimetic activity in the cardiovascular system of the anesthetized dog. Similarly, intravenous infusions of amounts capable of completely obliterating the cardio-accelerator effects of isoproterenol did not cause myocardial stimulation in reserpinized cats.

When administered intravenously to rabbits, it caused a significant depression in plasma renin activity (PRA) to 49% of control level. Significant correlation emerged between the fall in mean blood pressure and changes in PRA. Timolol maleate also antagonized isoproterenol-induced renin release.

In humans, daily oral doses of 10 to 45 mg significantly reduced the basal plasma renin values of hypertensive patients but not in normal subjects.

EFFECTS ON RESPIRATORY FUNCTION

In the anesthetized dog, the bronchodilator effects of isoproterenol during histamine-induced bronchoconstriction were reduced or abolished by timolol. This effect was evident at the same dose at which it antagonized the cardiac effects of isoproterenol.

In 12 normal volunteers, a single 10 mg oral dose caused a small (1.8%) but statistically significant reduction in forced expiratory volume (FEV 1). The decrease in FEV1 was not accompanied by dyspnea.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance which may be potentially dangerous in some patients (see CONTRAINDICATIONS and PRECAUTIONS).

OTHER EFFECTS

In dogs, the metabolic actions of intravenously infused isoproterenol, such as increases in blood sugar, free fatty acids and lactic acid were effectively blocked by a prior administration of timolol at a dose level which blocked the chronotropic and depressor effects of isoproterenol.

ORAL INTERACTION STUDIES

Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no influence on the toxicity of timolol maleate. Timolol maleate had no effect on the hypoprothrombinemia induced by bishydroxycoumarin in the dog.

TOXICOLOGY

ACUTE TOXICITY (LD 50)

Species and Age	Sex	Route of Administration	LD50 mg/kg
Mouse (YA)*	M	Oral	3600
	F	Oral	2050
Combined		Oral	2580
Mouse (A)	F	Oral	1190
	F	Intravenous	222
	F	Subcutaneous	1040
Rat (YA)	M	Oral	947
	F	Oral	900
	M	Intraperitoneal	390
	F	Intraperitoneal	383
Rat (W)	M	Oral	1040
	F	Oral	969
	M/F	Intraperitoneal	409
Rat (I)	M/F	Oral	241
	M/F	Subcutaneous	143
Rabbit (A)	M/F	Oral	485
	M/F	Subcutaneous	34

(A) = Adult; (YA) = Young Adult; (W) = Weanling; (I) = Infant.

* 6 groups, 5 mice/sex.

Signs of toxicity occurred immediately after intravenous administration and from 10 to 30 minutes following oral, intraperitoneal or subcutaneous administration. The signs observed included lacrimation, ataxia, tremors and bradypnea. Clonic convulsions usually preceded death.

SUBACUTE TOXICITY

In rats treated with 100 to 400 mg/kg for seven weeks, excessive salivation seen 5 to 10 minutes after dosing had a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptyalism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg or higher, were lethal to some animals. Low grade tubular

nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas.

CHRONIC TOXICITY

RATS

Timolol was administered orally to rats at dose levels of 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

DOGS

In a 54-week oral study timolol was administered at doses of 5, 10 and 25 mg/k9/day. Body weight and food normal consumption were and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

TUMORIGENIC TESTS

Lifetime studies with timolol have been completed in rats at oral doses of 25, 100 and 300 mg/kg/day and in mice at oral doses of 5, 50 and 500 mg/kg/day. In male and female rats and male mice at all dose levels, and in female mice at dose levels of 5 and 50 mg/kg/day, timolol demonstrated no carcinogenic effects. There was a slight increase in the incidence of mammary adenocarcinomas in female mice that received 500 mg/kg/day (about 500 times the maximum recommended human oral dose, on a mg/kg basis). Timolol caused dose-related elevations of serum prolactin in female mice at doses of 100 mg/kg or more, but only very slight transient elevations were found in male mice at doses of 500 mg/kg. Since numerous studies have demonstrated that drugs which cause elevations of serum prolactin are associated with mammary tumors in rodents, the mammary tumors in the female mice in the highest dosage group of this study were considered to have resulted from an increased serum prolactin. In adult human female subjects receiving either placebo or oral dosages of up to 60 mg of timolol, the maximum recommended human oral dosage, the range of observed serum prolactin values following drug administration was 4.7 - 10.3 ng/mL for placebo and 5.9 - 9.1 ng/mL for timolol. In humans, no association between serum prolactin and mammary carcinoma has been established.

REPRODUCTIVE STUDIES

Teratogenic studies in the mouse and rabbit at dose levels of 2 to 50 mg/kg/day did not reveal evidence of teratogenicity but did suggest embryotoxicity at the highest dose. Oral administration of timolol maleate to rats at dose levels of 4 to 100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the development of their offspring.

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