PRODUCT MONOGRAPH

PrTEVA-TIMOLOL
(Timolol Maleate)

5, 10 and 20 mg Tablets

USP

Antihypertensive and
Anti-anginal Agent

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THERAPEUTIC CLASSIFICATION
Antihypertensive and
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ACTION AND CLINICAL PHARMACOLOGY

TEVA-TIMOLOL (timolol maleate) is a beta-adrenergic blocking agent.

The mechanism by which beta-adrenergic receptor blocking agents exert their antihypertensive actions has yet to be determined. Factors which may be involved include:

(a) The ability to reduce cardiac output by competitively antagonizing catecholamine-induced tachycardia at the beta-receptor sites in the heart.

(b) The inhibition of renin release by the kidneys.

(c) The inhibition of the vasomotor centres.

The exact mechanism of the anti-anginal effect of timolol maleate is not established but it may block catecholamine-induced increases in heart rate, systolic blood pressure and the velocity and extent of myocardial contraction, thereby decreasing the oxygen requirements of the heart. However, increases in left ventricular fibre length, end diastolic pressure and the systolic ejection period may increase oxygen requirements. When the net physiological action is advantageous in anginal patients, it delays the onset of pain and decreases the incidence and severity of anginal

attacks during exercise or stress. Therefore, the work capacity and exercise in such patients can be increased by TEVA-TIMOLOL. When treated with timolol maleate, two thirds of the patients in a multiclinic study benefited to some degree. In patients with ischemic heart disease who have survived the acute phase of myocardial infarction, timolol maleate has been found effective in prophylactic use for secondary prevention. The mechanism of this protective effect of timolol maleate has yet to be elucidated.

A comparative two-way, single-dose bioavailability study was performed on TEVA-TIMOLOL (timolol maleate) 10 mg Tablets and Blocadren 10 mg Tablets. The pharmacokinetic plasma data (mean ± standard deviation) calculated for TEVA-TIMOLOL and Blocadren tablet formulations is tabulated below:

Pharmacokinetic Indices for Timolol Maleate:

	TEVA-TIMOLOL (1 x 10 mg Tablet)	**Blocadren (1 x 10 mg Tablet)**
Area Under the Curve: (ng-hours/mL); 0-24 hours	154.29 ± 97.41	150.94 ± 93.99
Peak Concentration: Cmax (ng/mL)	30.90 ± 14.19	30.92 ± 13.97
Time to Peak Level: Tmax (hours)	1.51 ± 0.60	1.58 ± 0.51
Elimination Half-Life: t-½ (hours)	3.11 ± 0.96	3.03 ± 1.02

INDICATIONS AND CLINICAL USE

TEVA-TIMOLOL (timolol maleate) is indicated in the treatment of

(a) Patients with mild to moderate hypertension. Other drugs, particularly a thiazide diuretic, are usually used in combination with timolol maleate. However, in those patients in whom, in the judgement of a physician, a beta-blocker rather than a diuretic should be used to start treatment, timolol maleate may be tried alone as the initial agent.

Compatibility has been proven with the combination of timolol maleate and a diuretic or peripheral vasodilator and the combination has been found to be generally more effective

than timolol maleate alone. No incompatibility has been shown in the limited experience of timolol maleate with other antihypertensive agents.

TEVA-TIMOLOL is not indicated in the treatment of hypertensive emergencies.

(b) Angina pectoris due to ischemic heart disease.

(c) Clinically stable patients who have survived the acute phase of a myocardial infarction to reduce cardiovascular death and the risk of re-infarction. Treatment with timolol maleate was initiated 7 to 28 days after the acute phase in a study which demonstrated these benefits. No data is available to indicate if the benefit would ensue if the treatment is started later.

(d) The prophylactlc treatment of migraine. TEVA-TIMOLOL is not indicated in the treatment of acute migraine attacks.

CONTRAINDICATIONS

TEVA-TIMOLOL (timolol maleate) is contraindicated in the presence of:

(1) Congestive heart failure (see WARNINGS).
(2) Right ventricular failure secondary to pulmonary hypertension.
(3) Significant cardiomegaly.
(4) Sinus bradycardia.
(5) Second and third degree A-V block.
(6) Cardiogenic shock.
(7) Allergic rhinitis, bronchospasm (including bronchial asthma), or severe chronic obstructive pulmonary disease (see PRECAUTIONS).
(8) Anesthesia with agents that produce myocardial depression, e.g., ether.
(9) Hypersensitivity to timolol maleate.

WARNINGS

Cardiac Failure:

In patients with a history of heart failure, TEVA-TIMOLOL (timolol maleate) should be administered with special caution. In congestive heart failure, sympathetic stimulation plays an important role in the support of circulatory function and the potential hazard of further myocardial contractility depression which may precipitate cardiac failure exists through inhibition with beta-blockade.

In some cases, continued myocardial depression for extended periods can lead to cardiac failure in patients without a history of cardiac failure. This has been demonstrated in rare instances during timolol maleate therapy.
Therefore, patients should be fully digitalized and/or given a diuretic and observed closely at the first sign or symptom of impending cardiac failure occurring during therapy with TEVA-TIMOLOL. The action of timolol maleate is selective and the inotropic action of digitalis on the heart muscle is not blocked. However, with the concomitant use of timolol maleate and digitalis, the negative inotropic action of timolol maleate may reduce the positive inotropic action of digitalis. Timolol maleate and digitalis have additive effects in depressing A-V conduction. Therapy with TEVA-TIMOLOL should be discontinued with persistent cardiac failure (see below).

Abrupt Cessation of Therapy with TEVA-TIMOLOL:

Patients with ischemic heart disease should be warned against abrupt discontinuation of TEVA-TIMOLOL. Myocardial infarction, ventricular arrhythmias, or sudden death have been reported in such patients, with or without preceding exacerbation of angina pectoris following abrupt discontinuation of beta-blocker therapy. Therefore, when discontinuation of TEVA-TIMOLOL is intended in a patient with angina or post-myocardial infarction, the dosage should be gradually

reduced over a period of about 2 weeks (maintaining the same frequency of administration) and the patient should be observed closely. If angina markedly worsens, or it acute coronary insufficiency develops, prompt reinstitution of TEVA-TIMOLOL, at least temporarily, is recommended.

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

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild to moderate severity should in general not receive beta blockers, particularly the non-selective beta-blockers such as timolol (see CONTRAINDICATIONS). If timolol must be given to such patients, it should be given with caution and under careful medical supervision since it may block bronchodilation produced by endogenous catecholamine stimulation of beta receptors (see PRECAUTIONS).

Various skin rashes and conjunctival xerosis have occurred with beta-blocking agents including timolol maleate. With the chronic use of one beta-adrenergic blocking agent, oculo-muco-cutaneous syndrome, a severe syndrome characterized by conjunctivitis sicca and psoriasiform rashes, otitis and sclerosing serositis, has occurred. Although this syndrome has not been observed with timolol maleate, physicians should be aware of the possibility of such reactions, and, if they develop, treatment should be discontinued.

Severe sinus bradycardia may develop with TEVA-TIMOLOL due to unopposed vagal activity; in such cases the use of intravenous atropine should be considered, and if no improvement is seen, intravenous isoproterenol should be administered.

By diminishing peripheral manifestations of hyperthyroidism without improving thyroid function, timolol maleate may give a false impression of improvement in patients with thyrotoxicosis. The potential of timolol maleate to aggravate congestive heart failure should be given special consideration. Thyroid function tests are not altered by timolol maleate. Abrupt

withdrawal of beta blockade should be avoided in order to prevent the precipitation of thyroid storm in patients suspected of thyrotoxicosis development.

PRECAUTIONS

Caution should be exercised when TEVA-TIMOLOL (timolol maleate) is given to patients prone to non-allergic bronchospasm *(e.g.,* chronic bronchitis, emphysema) since bronchodilatation produced by the stimulation of beta-receptors by endogenous and exogenous catecholamines maybe blocked.

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 maybe 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.

Caution should be exercised when TEVA-TIMOLOL is given to patients who are subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. The premonitory signs and symptoms of acute hypoglycemia maybe masked by beta-adrenergic blocking agents.

In the concomitant usage of TEVA-TIMOLOL with other antihypertensive agents, dosage should be individually adjusted (see DOSAGE AND ADMINISTRATION).

Patients receiving TEVA-TIMOLOL and catecholamine depleting drugs such as reserpine or guanethidine concomitantly should be monitored closely. An excessive reduction of the resting sympathetic nervous activity may be produced due to the added catecholamine blocking action of this drug.

Caution should be exercised in patients with impaired renal or hepatic function and suitable laboratory tests should be carried out (at appropriate intervals.) A reduction in dosage may be necessary in the presence of renal insufficiency since timolol maleate is excreted mainly by the kidneys. Following oral administration of 20 mg of timolol maleate, patients with severe renal insufficiency undergoing renal hemodialysis have exhibited marked hypotension.

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). In some patients with myasthenic symptoms timolol has been reported rarely to increase muscle weakness.

Due to potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. Consideration should be given to discontinuing these agents if signs or symptoms suggesting reduced cerebral blood flow are observed.

<u>In Patients Undergoing Elective or Emergency Surgery:</u>

The management of patients with angina undergoing elective or emergency surgery while being treated with beta-blockers is controversial. The ability of the heart to respond to beta-adrenergically mediated reflex stimuli is impaired by beta-adrenergic receptor blockade; however, severe complications may result from abrupt discontinuation of therapy with TEVA-TIMOLOL (see WARNINGS). During anesthesia, some patients have been subject to protracted severe hypotension while receiving beta-adrenergic blocking agents. Difficulty in restarting and maintaining the heartbeat has also been reported.

Therefore, TEVA-TIMOLOL should be gradually withdrawn following the recommendation given under Abrupt Cessation of Therapy (see WARNINGS), in patients with angina undergoing elective surgery. Available evidence concludes that 48 hours after cessation of medication, the clinical and physiological effects of beta blockade are no longer present.

If necessary, since timolol maleate competitively inhibits beta-adrenergic receptor agonists, its actions may be reversed by adequate doses of agonists such as isoproterenol or levarterenol during emergency surgery.

Use in Pregnancy:

TEVA-TIMOLOL should not be given to pregnant women as the drug has not been studied in human pregnancy. The anticipated benefit must be weighted against the possible hazards for the use of any drug in patients of child-bearing potential.

Usage in Lactating Women:

Timolol maleate is excreted in human breast milk. The patient should discontinue nursing if the use of the drug is considered essential.

Usage in Children:

Safety and effectiveness in children have not been established.

Drug Interactions:

When timolol is administered to patients receiving catecholamine-depleting drugs such as reserpine, close observation of the patient is recommended because possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Attentuation of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported. When these agents are used concomitantly, patients should be observed carefully to confirm that the desired therapeutic effect has been obtained.

In patients receiving a beta-blocking agent and an oral calcium antiblocker concurrently, the potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur. The nature of any cardiovascular adverse effect tends to depend on the type of calcium entry blocker used. The dihydropyridine derivatives such as nifedipine are more likely to lead to hypotension whereas verapamil and diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker. When cardiac function is normal, oral calcium antagonists may be used with caution in combination with beta-adrenergic blocking agents, but should be avoided in patients with impaired cardiac function. However in exceptional cases, when in the opinion of the physician, concomitant use is considered essential in patients with impaired cardiac function, such use should be instituted gradually, in a hospital setting, under careful observation. In patients receiving beta-adrenoceptor blocking agents, i.v. calcium entry blockers should not be used.

The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging cardiac AV conduction time.

APVERSE REACTIONS

The principal adverse effects experienced with timolol maleate are grouped by system as follows:

Cardiovascular:

Congestive heart failure in 3 to 4% of patients (see WARNINGS). Secondary effects of decreased cardiac output, about 4%, which could include: syncope, vertigo, lightheadedness, postural hypertension and decreased renal perfusion. Severe bradycardia in about 1% of patients. Less frequently occurring side effects include: lengthening of the PR interval, second and third

degree A-V block, sinus arrest (If SA node previously diseased), cold extremities, Raynaud's phenomenon, claudication or paresthesia and hypotension, cardiac arrest, cerebral vascular accident, palpitation, arrhythmia, edema, pulmonary edema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilatation.

Hematologic:

Nonthrombocytopenic purpura.

Respiratory:

Dyspnea has occurred in about 10% of patients and bronchospasm in about 1%; laryngospasm might occur rarely; rales, cough.

Central Nervous System:

Most frequently reported is headache. Less frequently are lightheadedness, drowsiness, vertigo, tinnitus, anxiety, weakness, sedation, insomnia, mental depressions and rarely vivid dreams, nightmares, nervousness, diminished concentration, hallucinations, increased dreaming, decreased libido.

Allergic/Dermatologic: (see WARNINGS)

Occasionally rashes including one case of psoriasiform rash reported to date and pruritus; exfoliative dermatitis was reported in one case; skin irritation, increased pigmentation, sweating.

Gastrointestinal:

Diarrhea in about 5% of patients and vomiting in about 4%; less frequently occurring are constipation, epigastric distress, nausea, dyspepsia, hepatomegaly.

Special Senses:

Tinnitus, visual disturbances, diplopia, ptosis, eye irritation, dry eyes.

Urogenital:

Impotence, micturition difficulties.

Body as a Whole:

Asthenia, fatigue, chest pain, extremity pain, decreased exercise tolerance, weight loss.

Muscoskeletal:

Arthralgia.

Endocrine:

Hypoglycemia, hyperglycemia.

Clinical Laboratory:

Slight increases in BUN, SGPT, serum potassium and serum uric acid and slight decreases in hemoglobin and hematocrit have occurred.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Bradycardia, hypotension, bronchospasm or acute cardiac failure are the most common signs of overdosage. Therapy with timolol maleate should be discontinued in all cases of overdosage and the patient should be carefully observed. The following therapeutic measures are also suggested.

(1) Gastric lavage.

(2) Bradycardia: 0.25 mg to 2.0 mg intravenous atropine sulfate may be used to induce vagal blockade. Isoproterenol hydrochloride should be cautiously administered intravenously if bradycardia persists. The use of a cardiac pacemaker may be considered in refractory cases.

(3) Heart Block (second degree or complete): Isoproterenol or Intravenous cardiac pacemaker.

(4) Acute Cardiac Failure: Conventional therapy should be instituted immediately with digitalis, diuretics and oxygen. Aminophylline given intravenously is suggested for use in refractory cases. If necessary, glucagon hydrochloride, which has been reported to be useful, may also follow.

(5) Hypotension: Therapy with sympathomimetic pressor drugs, such as levarterenol or epinephrine, may be used (see PRECAUTIONS regarding the use of epinephrine). Glucagon hydrochloride has been reported to be useful in refractory cases.

(6) Bronchospasm: Isoproterenol hydrochloride may be used. The addition of aminophylline therapy may be considered.

(7) Hypoglycemia: Glucose given intravenously and/or glucagon given intramuscularly.

Timolol is readily dialyzed from human plasma and whole blood as was demonstrated by an in vitro hemodialysis study using C^{14} timolol. However, a study in patients showed that timolol was not dialyzed in patients with renal failure.

Since TEVA-TIMOLOL (timolol maleate) is a competitive antagonist of isoproterenol, large doses of isoproterenol can be expected to reverse the effects of excessive doses of TEVA-TIMOLOL. However, any complications of isoproterenol overdose, such as tachycardia, headache, flushing of the skin, arrhythmias, nausea, weakness, tremor and sweating, should not be ignored.

DOSAGE AND ADMINISTRATION

Hypertension:

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

The dosage must always be individualized according to the following guidelines.

The initial dose should be 5 to 10 mg twice a day when TEVA-TIMOLOL is administered to patients who are also receiving other antihypertensive agents. Dosage may be increased by increments of 5 mg twice daily at intervals of two weeks if an adequate response is not observed after one to two weeks. Dose should not exceed 60 mg daily.

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

If a daily dose of 20 mg or less is found to sufficiently control the patient, the total dose should be administered in the morning as studies demonstrate adequate response to this dose regimen.

Angina:

The recommended dosage range of TEVA-TIMOLOL is 15mg to 45 mg per day. Most patients respond to a daily dosage of 35 mg to 45 mg. The initial dose should be 5 mg two or three times

a day. It may be necessary, depending on the response, to increase the dosage. The first increase should not exceed 10 mg per day in divided doses and subsequent increases should not exceed 15 mg per day in divided doses. A total daily dosage of 45 mg should not be exceeded. An interval of at least three days should be present between increases in dosages.

Some patients may be maintained on a bid schedule after the titration period.

Preventive Use In Ischemic Heart Disease:

The maintenance dose for long-term preventive use in patients who have survived the acute phase of myocardial infarction is 10 mg twice daily. The initial dose should be 5 mg twice daily and the patient should be closely observed. The dosage should be increased to 10 mg twice daily if no adverse reaction is present after two days. Treatment was Initiated 7 to 28 days after the acute phase of myocardial infarction in the studies evaluating timolol maleate.

Migraine:

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

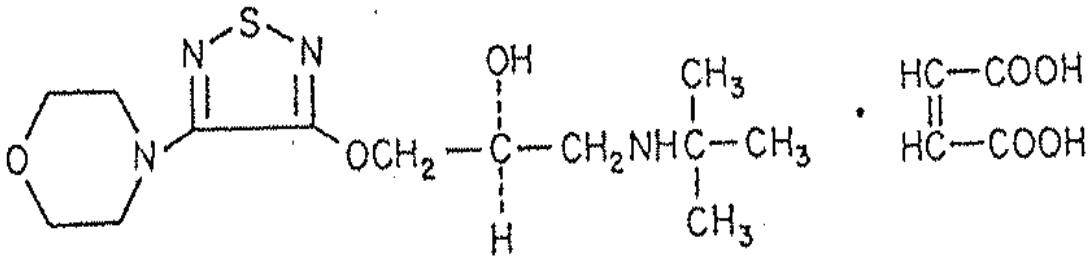
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Timolol Maleate Tablets

Chemical Name: 2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4morpholinyl)-1 ,2 ,5-thiadiazol-3-yl]oxy]-,(S)-, (Z)-2-butenedioate (1:1)

Structural Formula:



Molecular Formula: $C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$ Molecular Weight: 432.49

Description:

White to practically white, odorless or practically odorless, powder which is freely soluble in water; soluble in alcohol and in methanol; sparingly soluble in chloroform and in propylene glycol; insoluble in ether and in cyclohexane. The melting range is 201.5°C - 202.5°C. Timolol maleate has a pka of 9 in water at 25°C.

STABILITY AND STORAGE RECOMMENDATIONS: Store in well-closed, light-resistant containers between 15°-30°C. Unit dose strips should be stored between 15°-25°C and protected from light and high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA-TIMOLOL (timolol maleate) is available as:

5 mg- white, round, flat-faced, bevel-edged, compressed tablets, engraved '**no|vo**' on one side and '**5**' on the reverse containing 5 mg of timolol maleate.

10 mg- light blue coloured, round, flat with beveled edge, compressed tablets; engraved '**no/vo**' on one side and '**10**' on the other side containing 10 mg of timolol maleate.

20 mg- light blue coloured, capsule-shaped, compressed tablets, engraved '**no/vo**' on one side and '**20**' on the other side.

Supplied: Bottles of 100 and 500 and in boxes of 100 as unit dose strips.

PHARMACOLOGY

Pharmacokinetics:

Timolol exhibited rapid absorption, metabolism and effective excretion during animal studies. After both oral and intravenous administration of timolol labeled with C^{14}, urinary and fecal recovery was essentially the same suggesting complete absorption after oral administration. The highest concentrations were found in the small intestine, kidney and liver.

In humans, rapid absorption occurs after oral ingestion of timolol maleate. After one-half hour, timolol can be detected in the plasma and persists for about 6 to 12 hours. Peak plasma concentrations occur in about one to two hours. The plasma half-life of the drug is about 3 to 4 hours. The kidney is the principal organ of excretion of timolol and its metabolites. Plasma concentrations after intravenous administration are approximately twice those following oral administration indicating first pass metabolism of about 50%.

The major metabolites of the extensive metabolism in man are 1-tert-botyl-amino-[4-(N-2-hydroxyethylglycolamldo)-1 ,2,5-thiadiazol-3-yl-oxy]-2-propanol (30%), an ethanolamine derivative (10%) and a lactic acid metabolite (10%). About 20% of a 0.1 mg/kg oral dose was excreted unchanged in the urine. Excretion occurred mainly by way of the kidney and 68% of the drug appeared in the urine within 24 hours. About 5% was eliminated in the feces.

A plasma:amniotic fluid ratio of about 10:1 (1.5 versus 0.17 µg/mL, respectively) resulted from the administration of a 7.3 mg/kg dose of C^{14}-labeiled timolol to pregnant rats (at day 19 of gestation). The concentration was 0.13 µg/g in the placenta and 0.31 µ/g in the whole fetus. A concentration of 1.79 µg/mL (plasma concentration 1.45 µg/mL) of timolol was secreted into the milk of nursing rats who were administered a similar dose.

The passage of timolol through the blood-brain barrier was examined in single and multiple dose drug distribution studies. The metabolites of timolol only slightly Increased in the brain after four consecutive days' dosing in rats. In dogs, the concentrations of timolol in the CSF were observed to be about one-third of the corresponding plasma concentrations.

Effects on the Cardiovascular System:

Intravenous administration of 10 or 40 mg/kg timolol caused a significant reduction in cardiac output and an increase in calculated peripheral vascular resistance without significantly affecting stroke volume in anesthetized dogs. This effect was terminated by the preadministration of a ganglionic blocking agent which suggested that the cardiac output reduction was due to a decrease in sympathetic control of cardiac function rather than a direct depression of the myocardium.

In animals the vasodepressor and cardiac actions (inotropic, chronotropic, or both) of isoproterenol administered intravenously and cardiac accelerans nerve stimulation (endogenously released catecholamines) were effectively antagonized by intravenous administration of timolol.

In man the chronotropic and inotropic effects exerted by exogenously administered isoproterenol were blocked by a single 5 mg oral dose, Similarly there was a reduction in the sympathetic

reflex tachycardia caused by inhalation of amyl nitrate and tachycardia occurring upon completion of the forced expiration of the Valsalva Maneuver. A 20% reduction in heart rate in both the sitting and standing positions resulted within 30 minutes of administration of this dose. At approximately 45 to 90 minutes the effect reached a maximum and at 6 hours recovery was incomplete. A dose dependent reduction in exercise tachycardia also resulted from the administration of intravenous timolol maleate in normal volunteers. After a 1.0 mg dose there was a maximum reduction of 11 %. The increase in forearm blood flow produced by intravenously administered Isoproterenol was effectively reduced by a 0.25 mg dose.

Animal studies demonstrated that hydrocarbon-epinephrine induced arrhythmias were effectively inhibited and ventricular arrhythmias induced by intracoronary administration of a sclerosing agent (tetraflurohexachlorobutane) were effectively controlled by timolol in dogs. There was no alteration in the pattern of arrhythmias or the lethal dose of intravenously administered ouabain and there was no reduction in ventricular arrhythmias in dogs with coronary ligation.

Ouabain-induced arrhythmias are not affected and there is no local anesthetic activity [as evidenced by failure of the highest possible concentration (65 mg/mL) to induce local anesthetic activity in the mouse] which suggests that timolol has no membrane stabilizing (quinidine-like) activity.

No sympathomimetic activity resulted from timolol doses considerably higher than those required to produce beta-adrenergic blockade in the cardiovascular system of the anesthetized dog. Similarly, there was no myocardial stimulation in reserpinized cats after intravenously administered doses capable of completely obliterating the cardioaccelerator effects of isoproterenol.

In rabbits, the plasma renin activity (PRA) was significantly depressed by 49% compared to the control level after the intravenous administration of timolol. There was significant correlation between the fall in mean blood pressure and the changes in PRA. The renin release induced by isoproterenol was also antagonized by timolol maleate.

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

Effects on Respiratory Function:

During bronchoconstriction induced by histamine, the bronchodilator effects of isoproterenol were reduced or abolished by timolol in anaesthetized dogs. The same dose that antagonized the cardiac effects of isoproterenol produced this effect. The forced expiratory volume (FEV_1), was slightly (1.8%), but significantly reduced by a single 10 mg oral dose in 12 normal volunteers. No dyspnea occurred with the decreased FEV_1.

In some patients, an increase in airway resistance due to beta-adrenergic receptor blockade in the bronchi and bronchioles may be potentially dangerous (see CONTRAINDICATIONS and PRECAUTIONS).

Other Effects:

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

TOXICOLOGY

Acute Toxicity:

On the basis of 14 day LD_{50}'s, rabbits were more sensitive than mice or rats and infant rats more sensitive than adult rats. Decreased activity, bradypnea and clonic convulsions preceded death in each of these species. Acute toxicity was found to be influenced by feeding, with lower LD_{50}'s obtained in fasted rats. Mortality data has been summarized below. For each LD_{50} determination there were 10 animals/dose level and a minimum of 5 levels.

SPECIES	SEX	ROUTE	LD_{50} mg/kg
Mouse CFIS	F	p.o.	1190
	F	i.v.	222
Rat CRCD $	M	p.o.	947
	F	p.o.	900
	M	i.p.	390
	F	i.p.	383
Rat CRCD ¢	M	p.o.	1040
	F	p.o.	969
	M/F	i.p.	409
Rat CRCD #	M/F	p.o.	241
Rabbit NZ	M/F	p.p.	485

$ young adult (approximately 5 weeks of age).

¢ weanling (approximately 3 weeks of age).

infant (approximately 24 hours of age).

Mice were 6 to 7 weeks of age and rabbits 12 to 15 weeks of age.

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.

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

Subacute Toxicity:

In Rats:

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

In Dogs

Doses of 200 mg/kg or higher were lethal in some animals. In one of two dogs administered 100 mg/kg/day and in both receiving 400 mg/kg/day, low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred. In some nephrotic areas, small foci of tubular degeneration and regeneration occurred. In a 15-day Intravenous toxicity study, similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs.

Chronic Toxicity:
In Rats:

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

In Dogs:

Fifty-four weeks of oral administration to beagle dogs at doses of up to 25 mg/kg/day resulted in no adverse findings. Criteria for evaluation included physical signs, body weight, food consumption, ECG, hematology, clinical chemistry, urinalysis and results of ophthalmoscopic and post-mortem examinations (organ weights and gross and microscopic examinations of tissues). In one dog receiving 25 mg/kg/day slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis.

Reproduction and Teratology:

In Mice and Rabbits:

At dose levels of 2 to 50 mg/kg/day, teratogenic studies did not reveal evidence of teratogenicity but did suggest embryctoxicity at the highest dose.

In Rats:
At dose levels of 4 to 100 mg/kg/day, oral administration of timolol maleate did not adversely affect the fertility of male or female rats, their reproductive performance, or development of their offspring.

Carcinogenicity:
In Rats:
Two years of oral administration to Charles River CD rats for evaluation of carcinogenic potential resulted in a significantly increased incidence of adrenal medullary pheochromocytomas (malignant or benign and malignant) at the highest test level of 30 mg/kg/day. No adverse effects were observed at or below 100 mg/kg/day.

In Mice:
Two years of oral administration to Charles River CD-1 mice for evaluation of carcinogenic potential resulted in a significantly increased incidence of mammary adenocarcinomas, uterine polyps and pulmonary tumours at the high test level of 500 mg/kg/day. No adverse effects were observed at or below 50 mg/kg/day.

Regarding the mammary tumour finding in the mouse, the increased incidence was associated with a drug related elevation in serum prolactin levels which probably accounts for the excess tumour occurrence. Prolactin is an acknowledged mammary carcinogen in rodents. As prolactin levels were not elevated by therapeutic doses in man, the drug is not expected to place patients at increased risk of mammary cancer.

Regarding the increased rate of pheochromocytoma occurrence in male rats and the increased rates of pulmonary and uterine tumour occurrence in female mice, historical control data suggest that tumour rates observed in the highest dosage groups may have been unrelated to timolol administration.

Mutagenicity:

Mutagenic potential was evaluated in vivo (mouse) in the micronucleus test and cytogenetic assay (oral doses of up to 800 mg/kg in each of these tests) and in vitro in the neoplastic transformation assay (up to 100 µg/mL) and Ames Test (up to 10,000 µg/plate). Only in the Ames Test was there any suggestion of mutagenic potential. In each of seven experiments performed with tester strain TA 100, the highest concentrations of timolol employed, 5000 or 10,000 µg/plate, were associated with statistically significant elevations in numbers of revertants observed. A ratio of test control revertants as high as two was, however, never attained.

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