

Product Monograph

Pr AVA-METOPROLOL
Metoprolol Tartrate Tablets USP
50 & 100 mg

Pr AVA-METOPROLOL (Type L)
Metoprolol Tartrate Film-Coated Tablets USP
50 & 100 mg

β -Adrenergic Receptor Blocking Agent

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DATE OF PREPARATION:
March 4, 2011

Control # 145268

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Name of Drug

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Therapeutic Classification

β -Adrenergic Receptor Blocking Agent

Actions and Clinical Pharmacology

Metoprolol tartrate is a β -adrenergic receptor-blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on the β_1 -adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol tartrate also inhibits β_2 -adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol tartrate has no membrane-stabilizing or partial agonism (intrinsic sympathomimetic) activities. It is used in the treatment of hypertension, angina pectoris and to reduce mortality in patients with myocardial infarction.

The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are:

- a) competitive ability to antagonize catecholamine-induced tachycardia at the β -receptor sites in the heart, thus decreasing heart rate, cardiac contractility and cardiac output;
- b) inhibition of renin release by the kidneys;
- c) inhibition of the vasomotor centres.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, β -adrenergic receptor blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure (preload).

The mechanisms involved in reducing mortality in patients with acute myocardial infarction are not fully understood.

Pharmacokinetics

In humans, absorption of metoprolol is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Intersubject plasma levels achieved are highly variable after oral administration, although they show good reproducibility within each individual. Peak plasma concentrations are attained after approximately 1.5-2 hours with conventional metoprolol formulations, and after approximately 4-5 hours with slow-release formulations. Upon repeated oral administration, the percentage of the dose systemically available is higher than after a single dose and also increases dose dependently. Ingestion with food may raise the systemic availability of an oral dose by approximately 20-40%. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

Metoprolol is extensively metabolised by enzymes of the cytochrome P450 system in the liver. The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Orientals are PMs.

CYP2D6 poor metabolizers exhibit several-fold higher plasma concentrations of metoprolol than extensive metabolizers with normal CYP2D6 activity. However, the cytochrome P450 2D6 dependent metabolism of metoprolol seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol contribute significantly to its β -blocking effect.

Elimination is mainly by biotransformation in the liver, and the plasma half-life averages 3.5 hours (range: 1 to 9 hours). The total clearance rate of an intravenous dose is approximately 1L/min and the protein binding rate is approximately 10%. Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance.

The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects; however metabolite excretion is impaired. Since the resulting metabolite accumulation has no effect on the β -blocking effects, no reduction in dosage is usually needed in patients with chronic renal failure.

Liver impairment may increase metoprolol bioavailability and reduce total clearance.

Pharmacodynamics

Significant β -blocking effect (as measured by reduction of exercise heart rate) occurs within one hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum effect after single oral doses of 20, 50 and 100 mg

occurred at 3.3, 5.0 and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

Pharmacokinetic and pharmacodynamic relationship

Following intravenous administration of metoprolol tartrate, the half-life of the distribution phase is approximately 12 minutes; the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10-minute period, in normal volunteers, maximum β -blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal β -blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of metoprolol tartrate caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery end-diastolic pressure remained unchanged.

Comparative Bioavailability-Ava-Metoprolol Tablets

A randomized, single-dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on eighteen healthy male volunteers. The rate and extent of absorption of metoprolol was measured and compared following a single oral dose of Ava-Metoprolol or Betaloc 100 mg tablets. The results from measured data are summarized in the following table.

Summary Table of the Comparative Bioavailability Data Metoprolol Tablets (A single 100 mg dose: 1 x 100 mg tablets) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Ava–Metoprolol	Betaloc[†]	Ratio of Geometric Means (%)^{##}	90% Confidence Interval (%)^{##}
AUC0-24 (ng•h/mL)	624 817 (82.5)	600 776 (81.3)	100.8	95.2 – 116.5
AUC0-infinity (ng•h/mL)	626 825 (83.9)	602 781 (82.2)	100.8	95.5 – 116.9
Cmax (ng/mL)	115 129 (51.8)	111 124 (51.8)	100.8	94.0 – 115.0
Tmax [#] (h)	1.58 (31.6)	1.76 (35.2)		
t ^{1/2} [#] (h)	3.4 (33.9)	3.3 (35.4)		
[#] Arithmetic means (CV%). ^{##} Based on the least squares estimate. [†] Betaloc is manufactured by AstraZeneca Inc., and was purchased in Canada.				

Comparative Bioavailability-Ava-Metoprolol (Type L) Tablets

A randomized, single-dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on nineteen healthy male volunteers. The rate and extent of absorption of metoprolol was measured and compared following a single oral dose of Ava-Metoprolol Type L or Betaloc 100 mg tablets. The results from measured data are summarized in the following table.

Summary Table of the Comparative Bioavailability Data Metoprolol Tablets - Type L (A single 100 mg dose: 1 x 100 mg tablets) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Ava–Metoprolol Type L	Betaloc[†]	Ratio of Geometric Means (%)^{##}	90% Confidence Interval (%)^{##}
AUC0-24 (ng•h/mL)	839 1113 (78.0)	827 1080 (75.8)	100.2	90.6 – 113.5
AUC0-infinity (ng•h/mL)	853 1158 (83.0)	860 1158 (79.5)	99.9	87.4 – 112.5
Cmax (ng/mL)	147 168 (53.0)	148 171 (54.7)	99.8	89.9 – 109.3
Tmax [#] (h)	1.46 (32.4)	1.54 (39.9)		
t ^{1/2} [#] (h)	4.0 (56.5)	4.7 (84.6)		

[#] Arithmetic means (CV%).

^{##} Based on the least squares estimate.

[†] Betaloc is manufactured by AstraZeneca Inc., and was purchased in Canada.

Indications and Clinical Use

Hypertension

AVA-METOPROLOL / AVA-METOPROLOL (Type L) (metoprolol tartrate) is indicated for mild or moderate hypertension. Usually combined with other antihypertensive agents (thiazide diuretics), it may be tried alone when the physician judges that a beta-blocker, rather than a diuretic, should be the initial treatment.

Combining metoprolol tartrate with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than metoprolol tartrate alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with metoprolol tartrate.

AVA-METOPROLOL / AVA-METOPROLOL (Type L) is not recommended for the emergency treatment of hypertensive crises.

Angina Pectoris

AVA-METOPROLOL / AVA-METOPROLOL (Type L) is indicated for the long-term treatment of angina pectoris due to ischemic heart disease.

Myocardial Infarction

AVA-METOPROLOL / AVA-METOPROLOL (Type L) is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction, to reduce cardiovascular mortality.

In patients with proven myocardial infarction, oral treatment can begin within 3 to 10 days of the acute event (*see Dosage and Administration*). Data are not available as to whether benefit would ensue if the treatment is initiated later.

Clinical trials have shown that patients with unconfirmed myocardial infarction received no benefit from early metoprolol tartrate therapy.

Contraindications

AVA-METOPROLOL / AVA-METOPROLOL (Type L) **should not be used in the presence of:**

- Known hypersensitivity to metoprolol and derivatives, AVA-METOPROLOL / AVA-METOPROLOL (Type L) components, or hypersensitivity to other beta-blockers (cross-sensitivity between beta-blockers can occur)
- Sinus bradycardia.
- Sick sinus syndrome
- Second and third degree A-V block.
- Right ventricular failure secondary to pulmonary hypertension.
- Overt heart failure.
- Cardiogenic shock.
- Severe peripheral arterial circulatory disorders.
- Anesthesia with agents that produce myocardial depression, (e.g., ether).
- Untreated pheochromocytoma
- The intravenous form is also contraindicated in the presence of asthma and other obstructive respiratory diseases (for oral treatment, *see Precautions – Bronchospastic Diseases*).

Myocardial Infarction Patients - Additional Contraindications

AVA-METOPROLOL / AVA-METOPROLOL (Type L) is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (PR interval ≥ 0.24 s); systolic blood pressure < 100 mmHg; or moderate to severe cardiac failure (see Warnings).

Warnings

Cardiac Failure

Special caution should be exercised when administering AVA-METOPROLOL / AVA-METOPROLOL (Type L) to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with β -blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. The positive inotropic action of digitalis may be reduced by the negative inotropic effect of metoprolol tartrate when the two drugs are used concomitantly. The effects of β -blockers and digitalis are additive in depressing A-V conduction. This also applies to combinations with calcium-antagonists of the verapamil type or some antiarrhythmics (*see Drug Interactions*).

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 and/or hypotension (systolic blood pressure ≤ 90 mmHg). Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol tartrate therapy should be reduced or withdrawn.

Abrupt Cessation of Therapy

Patients with angina should be warned against abrupt discontinuation of AVA-METOPROLOL / AVA-METOPROLOL (Type L). There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of β -blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of metoprolol tartrate is planned in patients with angina pectoris or previous myocardial infarction, the dosage should be gradually reduced over a period of about two weeks. The patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, metoprolol tartrate therapy should be discontinued stepwise and with closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with AVA-METOPROLOL / AVA-METOPROLOL (Type L) be reinstated promptly, at least temporarily.

Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it is prudent not to discontinue metoprolol tartrate therapy abruptly even in patients treated only for hypertension.

Oculomucocutaneous Syndrome

Various skin rashes and conjunctival xerosis have been reported with β -blockers, including metoprolol tartrate.

Oculomucocutaneous syndrome, a severe syndrome whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one β -adrenergic receptor-blocking agent (practolol). This syndrome has not been observed with metoprolol tartrate or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Severe Sinus Bradycardia

Severe sinus bradycardia may occur after β_1 -adrenergic receptor blockade with metoprolol tartrate because of unopposed vagal activity. Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated, possibly leading to A-V block. In such cases, dosage should be reduced or gradually withdrawn. Atropine, isoproterenol or dobutamine should be considered in patients with acute myocardial infarction.

Thyrotoxicosis

Although metoprolol has been used successfully for the symptomatic (adjuvant) therapy of thyrotoxicosis, possible deleterious effects from long-term use of metoprolol tartrate

have not been adequately appraised. β -blockade may mask the clinical signs of continuing hyperthyroidism or its complications, and give a false impression of improvement. Therefore, abrupt withdrawal of metoprolol tartrate may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Myocardial Infarction Patients - Additional Warnings

Acute Intervention

During acute intervention in myocardial infarction, intravenous metoprolol should only be used by experienced staff under circumstances where resuscitation and monitoring equipment is available.

Cardiac Failure

Depression of the myocardium with AVA-METOPROLOL / AVA-METOPROLOL (Type L) may lead to cardiac failure (*see general Warnings* above). Special caution should be exercised when administering AVA-METOPROLOL / AVA-METOPROLOL (Type L) to patients with a history of cardiac failure or those with minimal cardiac reserve. Should failure occur, treatment should be as described in *Warnings*.

Severe Sinus Bradycardia

Severe sinus bradycardia may occur with AVA-METOPROLOL / AVA-METOPROLOL (Type L) use (*see general Warnings* above). Acute myocardial infarction (particularly inferior infarcts) may significantly decrease sinus rate. If the rate falls below 40 beats/min, especially with signs of decreased cardiac output, administer atropine (0.25-0.5 mg) intravenously. If atropine treatment is unsuccessful, discontinue AVA-METOPROLOL / AVA-METOPROLOL (Type L) and consider cautious administration of isoproterenol or installation of a cardiac pacemaker.

A-V Conduction

AVA-METOPROLOL / AVA-METOPROLOL (Type L) slows A-V conduction and may produce significant first- (PR interval ≥ 0.24 sec), second-, or third-degree heart block. Acute myocardial infarction may also produce heart block. If heart block occurs, discontinue AVA-METOPROLOL / AVA-METOPROLOL (Type L) and administer atropine (0.25-0.5 mg) intravenously. If atropine treatment is unsuccessful, consider cautious administration of isoproterenol or installation of a cardiac pacemaker. Because of their negative effect on atrioventricular conduction, beta-blockers, including AVA-METOPROLOL / AVA-METOPROLOL (Type L) should only be given with caution to patients with first degree atrioventricular block.

Hypotension

If hypotension (systolic blood pressure \leq 90 mmHg) occurs, AVA-METOPROLOL / AVA-METOPROLOL (Type L) should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or A-V block, treatment should be directed at reversing these (see above).

Precautions

Bronchospastic Diseases

In general, patients with bronchospastic diseases should not receive β -blockers, including AVA-METOPROLOL / AVA-METOPROLOL (Type L). However, because of its relative β_1 -selectivity, metoprolol tartrate may be used with caution in patients with asymptomatic bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since β_1 -selectivity is not absolute, a β_2 -stimulating agent should preferably be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer AVA-METOPROLOL / AVA-METOPROLOL (Type L) in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (*see Dosage and Administration*).

Because it is unknown to what extent β_2 -stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically in patients with proven or suspected acute myocardial infarction. If bronchospasm not related to congestive heart failure occurs, AVA-METOPROLOL / AVA-METOPROLOL (Type L) should be discontinued. A theophylline derivative or a β_2 -agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and β_2 -agonists may produce serious cardiac arrhythmias.

Diabetes and Hypoglycemia

AVA-METOPROLOL / AVA-METOPROLOL (Type L) should be administered cautiously to patient's spontaneously hypoglycemic or diabetic patients, (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. β -adrenergic receptor blockers, including metoprolol tartrate, may mask the premonitory signs and symptoms of acute hypoglycemia.

Liver Function

AVA-METOPROLOL / AVA-METOPROLOL (Type L) should be used with caution in patients with impaired liver function. Liver function tests should be performed at regular

intervals during long-term treatment (*see Actions and Clinical Pharmacology, Pharmacokinetics*).

Allergen Immunotherapy

There may be increased difficulty in treating an allergic type reaction in patients on β -blockers. Whenever possible, β -blockers, including AVA-METOPROLOL / AVA-METOPROLOL (Type L), should be avoided in patients who are at risk of anaphylaxis. In these patients, the reaction may be more severe due to pharmacologic effects of the β -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, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block 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 β -agonists including parenteral salbutamol or isoproterenol, to overcome bronchospasm and norepinephrine to overcome hypotension.

Patients Undergoing Surgery

It is not advisable to withdraw β -adrenoceptor blocking drugs, including AVA-METOPROLOL / AVA-METOPROLOL (Type L), prior to surgery in the majority of patients especially in those with risk of overt or silent coronary heart disease. However, care should be taken to avoid using anesthetic agents that may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg i.v.).

Some patients receiving β -blocking drugs have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

Since metoprolol is a competitive inhibitor of β -adrenoceptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or dobutamine.

Peripheral Artery Disorders

Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect.

Pheochromocytoma

Where a β -blocker is prescribed for a patient known to be suffering from a pheochromocytoma, an alpha-blocker should be given concomitantly.

Occupational Hazards, Reaction Time

β -blockers may adversely affect the patient's reaction time. Patients should be advised to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to metoprolol tartrate therapy has been determined.

Usage in Pregnancy

Metoprolol crosses the placental barrier. Since metoprolol tartrate 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 the possible hazards.

Nursing Mothers

Metoprolol is excreted in breast milk. If drug use is essential, patients should stop nursing.

Usage in Children

The safety and efficacy of metoprolol tartrate in children has not been established.

Usage in the Elderly

Caution is indicated when using metoprolol tartrate in elderly patients. An excessively pronounced decrease in blood pressure or pulse rate may cause the blood supply to vital organs to fall to inadequate levels.

Drug Interactions

Antihypertensives

AVA-METOPROLOL / AVA-METOPROLOL (Type L) dosage should be adjusted to the individual requirements of the patient especially when used concomitantly with other antihypertensive agents (*see Dosage and Administration*).

The following medicinal products may increase the effect or plasma concentrations of metoprolol

Calcium Channel Blockers

As with other β -blockers, metoprolol tartrate should not be given together with verapamil type calcium-antagonists. However, in exceptional cases, when the physician considers concomitant use essential, such use should be instituted gradually in a hospital setting under careful supervision. Negative inotropic, dromotropic and chronotropic effects may

occur when metoprolol is given together with calcium antagonists. Verapamil and diltiazem reduce metoprolol clearance.

Antiarrhythmic Agents

β -blockers may enhance the negative inotropic and negative dromotropic effect of antiarrhythmic agents such as quinidine and amiodarone.

Nitroglycerin

Nitroglycerin may enhance the hypotensive effect of metoprolol tartrate.

Inhalation anesthetics

β -blockers enhance the cardiodepression produced by certain anesthetics (*see Precautions, Patients Undergoing Surgery*).

MAO Inhibitors and Adrenergic Neuron Blockers

Closely monitor patients receiving MAO inhibitors or catecholamine-depleting drugs (such as reserpine or guanethidine). The added β -adrenergic-blockade of metoprolol may excessively reduce sympathetic activity. Metoprolol tartrate should not be combined with other β -blockers.

Prazosin (selective alpha-1-adrenergic antagonist)

The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker.

CYP2D6 inhibitors

Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer. Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine or ranitidine.

The following medicinal products may decrease the effect or plasma concentrations of Metoprolol

Digitalis glycosides

Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time.

α -Adrenergic stimulants (cold remedies, nasal drops)

Exaggerated hypertensive responses can be produced when β -blockers are combined with α -adrenergic agonists.

NSAIDs

Concurrent treatment with indomethacin may decrease the antihypertensive effect of β -blockers.

Hepatic Enzyme-Inducers

Hepatic enzyme-inducing substances may exert an influence on the plasma level of metoprolol. The plasma concentration of metoprolol is lowered by rifampicin.

Effect of metoprolol on other medicinal products

Clonidine Withdrawal Syndrome

The hypertensive crisis which may follow clonidine withdrawal may be accentuated in the presence of β -blockade. Withdrawing the β -blocker several days before the clonidine may reduce the danger of rebound effects.

Oral Antidiabetics

The dosage of oral antidiabetics may have to be readjusted in patients receiving β -blockers (*see Precautions*).

Lidocaine

Metoprolol may reduce the clearance of lidocaine.

Alcohol

Metoprolol may modify the pharmacokinetics (decrease the elimination rate) of alcohol.

Adverse Reactions

The most common adverse events reported are exertional tiredness, gastrointestinal disorders, and disturbances of sleep patterns. The most serious adverse events reported are congestive heart failure, bronchospasm and hypotension.

Reported adverse events according to organ systems are:

Cardiovascular

Secondary effects of decreased cardiac output which include: syncope, vertigo, light-headedness and postural hypotension

Second and third degree A-V block (*see Contraindications*)

Congestive heart failure (*see Warnings*)

Severe bradycardia	Hot flushes	Cardiac arrhythmias
Lengthening of PR interval	Oedema	Palpitations
Sinus arrest	Cold extremities	Chest pains
Claudication	Raynaud's phenomenon	
Gangrene in patients with pre-existing severe peripheral circulatory disorders		
Precordial pain		

In a placebo-controlled study in patients with acute myocardial infarction the incidence of the following cardiovascular reactions were:

	Metoprolol	Placebo
Orthostatic hypotension (systolic BP <90 mmHg)	27.4%	23.2%
Bradycardia (heart rate <40 beats/min)	15.9%	6.7%
Second- or Third-degree heart block	4.7%	4.7%
First-degree Heart block (PR β 0.24 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Central Nervous System

Headache	Weakness
Dizziness	Fatigue
Mental depression	Sedation
Light-headedness	Somnolence or insomnia
Vivid dreams / nightmares	Hallucination
Vertigo	Paresthesia
Anxiety	Personality disorder
Alertness decreased	

Gastrointestinal

Diarrhea	Abdominal pain
Constipation	Heartburn
Flatulence	Dry mouth
Nausea and vomiting	Hepatitis

Respiratory

Shortness of breath	Wheezing
Bronchospasm	Rhinitis
Status asthmaticus	Worsening of psoriasis
Exertional dyspnea	

Allergic/Dermatological (see *Warnings*)

Skin rash (exanthema, urticaria, psoriasiform and dystrophic skin lesions)
Hyperhidrosis
Pruritus
Photosensitivity

Ear, Eye, Nose and Throat (EENT)

Tinnitus	Hearing disorders (e.g. hypoacusis or deafness) when doses exceed those recommended
Dry and/or eye irritation	Blurred vision and non-specific visual disturbances
Conjunctivitis	

Miscellaneous

Muscle cramps	Decreased libido
Exertional tiredness	Peyronie's disease
Weight increase	Arthritis
Alopecia	Retroperitoneal fibrosis

Clinical Laboratory

The following laboratory parameters have been elevated on rare occasions: transaminases, BUN, alkaline phosphatase and bilirubin.

Hematology

Isolated cases of thrombocytopenia and leucopenia.

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of metoprolol tartrate: Confusional state, an increase in blood triglycerides and a decrease in High Density Lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Symptoms and Treatment of Overdose

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms

The most common signs to be expected with overdosage of a β -adrenoreceptor agent are hypotension, bradycardia, congestive heart failure, bronchospasm and hypoglycemia. Atrioventricular block, cardiogenic shock and cardiac arrest may develop. In addition, impairment of consciousness (or even coma), nausea, vomiting and cyanosis may occur.

Concomitant ingestion of alcohol, antihypertensives, quinidine, or barbiturates aggravate the signs and symptoms.

The first manifestations of overdosage set in 20 minutes to 2 hours after drug administration.

Treatment

If overdosage occurs, in all cases therapy with metoprolol tartrate should be discontinued, the patient hospitalized and observed closely. Remove any drug remaining in the stomach by induction of emesis or gastric lavage. In addition, if required, the following therapeutic measures are suggested:

Bradycardia and Hypotension: Initially 1-2 mg of atropine sulfate should be given intravenously. If a satisfactory effect is not achieved, norepinephrine or dopamine may be administered after preceding treatment with atropine. (*See Precaution* concerning the use of epinephrine in β -blocked patients.) In case of hypoglycemia glucagon (1-10 mg) can be administered.

Heart Block (second- or third- degree): Isoproterenol or transvenous cardiac pacemaker.

1. Congestive Heart Failure: Conventional therapy.
2. Bronchospasm: Intravenous aminophylline or a β_2 -agonist.
3. Hypoglycemia: Intravenous glucose.

It should be remembered that metoprolol 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 metoprolol. However, the complications of excess isoproterenol, e.g. hypotension and tachycardia, should not be overlooked.

Dosage and Administration

Special Note to Pharmacist: Splitting AVA-METOPROLOL (Type L) tablets is not recommended since the film coating will be damaged.

Hypertension

AVA-METOPROLOL / AVA-METOPROLOL (Type L) 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.

AVA-METOPROLOL / AVA-METOPROLOL (Type L) treatment should be initiated with doses of 50 mg b.i.d. If an adequate response is not seen after one week, dosage should be increased to 100 mg b.i.d. In some cases the daily dosage may need to be increased by further 100 mg increments at intervals of not less than two weeks up to a maximum of 200 mg b.i.d., which should not be exceeded. The usual maintenance dose is within the range of 100-200 mg daily.

When metoprolol tartrate is combined with another antihypertensive agent which is already being administered, metoprolol tartrate should be added initially at a dose of 50 mg b.i.d. After one or two weeks the daily dosage may be increased if required, in increments of 100 mg, at intervals of not less than two weeks, until adequate blood pressure control is obtained.

Angina Pectoris

The recommended dosage range for AVA-METOPROLOL / AVA-METOPROLOL (Type L) in angina pectoris is 100-400 mg per day in divided doses. Treatment should be initiated with 50 mg b.i.d. for the first week. If response is not adequate, the daily dosage should be increased by 100 mg for the next week. The usual maintenance dose is 200 mg/day. The need for further increases should be closely monitored at weekly intervals and the dosage increased in 100 mg increments to a maximum of 400 mg/day in two or three divided doses. A metoprolol tartrate dose of 400 mg/day should not be exceeded.

Myocardial Infarction

In addition to the usual contraindications:

ONLY PATIENTS WITH SUSPECTED ACUTE MYOCARDIAL INFARCTION WHO MEET THE FOLLOWING CRITERIA ARE SUITABLE FOR THERAPY AS DESCRIBED BELOW:

Systolic Blood Pressure \geq 100 mmHg
Heart Rate * \geq 45 beats per minute
PR Interval $<$ 0.24 seconds
Rales* $<$ 10 cm
Adequate peripheral circulation

*Extreme caution should be exercised when giving intravenous metoprolol to patients with heart rate between 45 and 60 and/or pulmonary rales less than 10 cm.

Therapy should be discontinued in patients if the heart rate drops below 45 or the systolic blood pressure drops below 100 mmHg.

Early Treatment

During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol tartrate each. The injections should be given at approximately 2- minute intervals. During the intravenous administration of metoprolol tartrate, blood pressure, heart rate, and electrocardiogram should be carefully monitored. If any of the injections are associated with adverse cardiovascular effects, intravenous administration should be stopped immediately and the patient should be observed carefully and appropriate therapy instituted.

In patients who tolerate the full intravenous dose (15 mg), AVA-METOPROLOL/AVA-METOPROLOL (Type L) tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (*see Late Treatment* below).

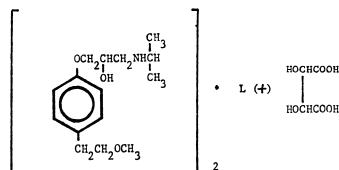
Patients who appear not to tolerate the full intravenous dose should be started on either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with AVA-METOPROLOL/AVA-METOPROLOL (Type L) should be discontinued (*see Warnings*).

Late Treatment (For proven myocardial infarction patients only)

Patients with contraindications to treatment during the early phase of myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on AVA-METOPROLOL/AVA-METOPROLOL (Type L) tablets, 100 mg twice daily, as soon as their clinical condition allows. Treatment can begin within 3-10 days of the acute event. Therapy should be continued for at least 3 months. Although the efficacy of treatment with metoprolol tartrate beyond 6 months has not been conclusively established data from studies with other β -blockers suggest that the treatment should be continued for 1-3 years.

Pharmaceutical Information

Drug Substance



Metoprolol tartrate

Chemical Name:

1. 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, (\pm)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate) (2:1) (salt)
2. (\pm)-1-(Isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt);
3. 1-Isopropylamino-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol (2:1) dextro-tartrate salt.

Molecular Formula: $C_{34}H_{56}N_2O_{12}$

Molecular Weight: 685

Physicochemical properties: Metoprolol is the tartrate salt of an organic base. It is a colourless, odorless, crystalline powder with a bitter taste. At 20°C it is 10% soluble in water. The pH of a 2% aqueous solution is 6.7.

Composition / Stability and Storage Recommendations:

Composition

In addition to metoprolol tartrate, each tablet contains the non-medicinal ingredients lactose monohydrate, microcrystalline cellulose, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide.

In addition to the above, the Type L 50 mg tablet also contains the following non-medicinal ingredients; hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, carnauba wax, D & C Red # 30 Aluminum Lake 30% and Sunset Yellow Aluminum Lake 40%.

In addition to the non-medicinal ingredients listed under Composition, the Type L 100 mg tablet also contains the following; hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, carnauba wax, Indigotine Aluminum Lake 12-14% (Blue #2) and polydextrose.

AVA-METOPROLOL/AVA-METOPROLOL (Type L): Store at room temperature (15° to 30°C) and protect from light.

Availability of Dosage Forms

AVA-METOPROLOL 50 mg: Each white, round, biconvex, scored tablet engraved 'APO' over 'M50' on one side contains 50 mg metoprolol tartrate. Available in bottles of 100 tablets.

AVA-METOPROLOL 100 mg: Each white, round, biconvex, scored tablet engraved 'APO' over 'M100' on one side contains 100 mg metoprolol tartrate. Available in bottles of 100 tablets.

AVA-METOPROLOL (Type L) 50 mg: Each pink, capsule shaped, biconvex, scored, film coated tablet engraved '50' on one side contains 50 mg metoprolol tartrate. Available in bottles of 100 and 1000 tablets.

AVA-METOPROLOL (Type L) 100 mg: Each blue, capsule shaped, biconvex, scored, film coated tablet engraved '100' on one side contains 100 mg metoprolol tartrate. Available in bottles of 100 tablets.

Pharmacology

Effect on the Cardiovascular System

Metoprolol produced dose-dependent reductions in heart rate and contractile force responses to sympathetic nerve stimulation in the anaesthetized cat. The ED₅₀ value for blockade of the chronotropic response to nerve stimulation was approximately 7 times less than that for isoproterenol stimulation. Metoprolol reduced the heart rate in conscious dogs at rest and during exercise. With the exception of PR interval prolongation, ECG complexes were not changed.

In anaesthetized cats, intravenous doses up to 2.0 mg/kg did not significantly influence the pressor response to intravenous epinephrine.

In anaesthetized cats, intravenously-administered metoprolol antagonized the hind limb vasodilating response to intra-arterial isoproterenol in much higher doses (ED₅₀ 5 mg/kg) than required to block the increase in chronotropic response (ED₅₀ 0.4 mg/kg) or increase in contractile force (ED₅₀ 0.2 mg/kg).

In 5 healthy volunteers, intravenously-administered 10 mg doses of metoprolol reduced exercise-induced tachycardia by 13% and systolic blood pressure during exercise by 13%. The decrease in mean blood pressure after epinephrine was abolished by metoprolol, whereas the increase in systolic blood pressure was reduced by 50%; vascular resistance in the forearm was unchanged after metoprolol.

In healthy volunteers, intravenous metoprolol 0.15 mg/kg significantly lowered cardiac output by 1.3 litre/min. at rest, and 3.6 litre/min. during exercise. The mean decreases in heart rate were 9 and 16 beats/min. during rest and exercise, respectively. Right atrial pressure was significantly increased during rest and exercise. Oxygen consumption was not significantly influenced by drug administration. Significant increases in the calculated arteriovenous oxygen differences were observed (6 and 20 mL/litre at rest and during exercise, respectively).

Studies in reserpinized cats showed that metoprolol was devoid of β -receptor stimulating (intrinsic) activity. In cumulative doses up to 0.85 mg/kg, the drug did not significantly influence heart rate or contractile force.

A single oral dose of 40 mg of metoprolol administered to 17 anginal patients 90 minutes before testing, increased total work performed from 5994 to 8462 k.p.m. (40%). Times to onset of pain and appearance of ST depression were similarly increased from 11.8 to 16.9 minutes and 9.9 to 13.9 minutes respectively.

Effects on Pulmonary Function

The effects on specific airways resistance (S_{Raw}) of single oral doses of 100 mg of metoprolol were assessed in 6 healthy volunteers and in 12 patients with bronchial asthma. No bronchodilator was used. Metoprolol did not have a significant effect on S_{Raw} in the normal subjects, but in the asthmatic patients, S_{Raw} was significantly increased. Similar findings were observed with an 80 mg dose of propranolol.

In a controlled study, 17 patients with bronchial asthma received concomitantly a bronchodilator (terbutaline) with 50 or 100 mg b.i.d. of metoprolol. The FEV₁ values fell only in the high dose group, indicating some β_2 -blocking effect.

Other Effects

Metoprolol showed a negligible local anaesthetic effect on the isolated sciatic nerve of the frog and in the intracutaneous wheal test in guinea pigs. The cardiostimulant effects of ouabain, glucagon and theophylline were not affected by doses of 2-3 mg/kg in the anaesthetized cat. The same dosage of metoprolol was found to be devoid of anticholinergic, ganglionic blocking, antihistaminic and alpha-receptor blocking properties in cats.

Metoprolol inhibited the increase in plasma renin activity induced by furosemide. The effects of metoprolol on isoproterenol-stimulated metabolic effects showed inhibition of the increase in liberation of glycerol, glucose, insulin, and free fatty acids.

Toxicology

Acute Toxicity

Species	Sex	Route	Solutions	LD50(mg/kg)
Mouse	male	I.V.	1%	69.4 ± 5.1
Mouse	female	I.V.	1%	79.9 ± 4.5
Mouse	male	P.O.	23%	2460 ± 210
Mouse	female	P.O.	25%	2300 ± 200
Rat	male	I.V.	5%	71.9 ± 4.1
Rat	female	I.V.	5%	74.3 ± 4.4
Rat	male	P.O.	50%	4670 ± 1210
Rat	female	P.O.	50%	3470 ± 580

The toxic symptoms in rats include: sedation, ataxia, piloerection, irritation, spasm, and lacrimation. Rats were unconscious before death, which occurred within 5-10 minutes after intravenous injection and 6-20 hours after oral administration.

In mice the most pronounced symptoms were: sedation, hypersensitivity, irritation, spasms, and ptosis. Convulsions were seen before death, which occurred within 5 minutes after intravenous injection. No symptoms of toxicity were detectable 24 hours after administration in surviving animals.

Long-Term Toxicity (Subacute)

Strain Species	No. of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
Sprague-Dawley Rats	4	10 M 10 F	Saline, 10, 50, 100/day (after 14 days, high dose increased to 200/day).	P.O.	5 Wks	Slight increase in hematocrit and slight decrease in blood sugar in high-dose females.
Beagle Dogs	1	1 M 1 F	40 x 3 days, increased by 20/day to 140 x 6 days to 160/day.	P.O.	3 Wks	Disturbance of balance; increased abdominal muscular tone, mydriasis, hyperemia in visible mucous membranes. One dog died at dose level of 140 mg/kg/day.

Beagle Dogs	2	1 M	80 b.i.d. one day; 2 days later, single dose of 100.	P.O.	3 Days	Disturbance of balance; vomiting, prostration, dyspnea, loss of consciousness, death.
		2 F	20 b.i.d. increased every 5 days by 20 b.i.d. up to 120 b.i.d.	P.O.	4 Wks	Vomiting; increased salivation, tremor, ataxia. One dog died at highest dose.
Beagle Dogs	4	1 M 1 F	0, 5, 20, 40/day	P.O.	4 Wks	None.
Beagle Dogs	3	1 M 1 F	Saline, 0.5, 5 /day	I.V.	2 Wks	Prolonged PR interval in ECG.
Beagle Dogs	2	1 M 1 F	Saline, 5 /day	I.V.	2 Wks	Prolonged PR interval in ECG.

Long-Term Toxicity (Chronic)

Strain Species	No. Of Groups	N per Group	Dose (mg/kg)	Route	Duration	Toxic Effects
Sprague-Dawley Rat	4	15 M 15 F	Saline, 10, 100, 200/day. High dose increased to 200/day after 13 Weeks	P.O.	6 Months	None.
Beagle Dogs	One Control	2 M 2 F	0, 5, 20, 40 b.i.d. After 7 weeks, high dose increased to 50/b.i.d. After 3 months, intermediate dose increased to 30 b.i.d. and high dose to 80 b.i.d.	P.O.	6 Months	Bradycardia, increased PR interval and QT interval in ECG.
	Three Active	3 M 3 F				
Beagle Dog	One Control	6 M 6 F	0, 10, 60 day. High level dogs	P.O.	1 Year	2 high-dose dogs died on day 1,

	Three Active	6 M 6 F	received 120 on day 1, 60 on days 3 to 8; 90/day on days 9 to 22 and 105/day for balance.			otherwise, none.
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Teratology and Reproduction Studies

Rat: (Sprague-Dawley strain) Doses of 10, 50 and 200 mg/kg were administered orally to groups of 20 pregnant rats on days 6-15 of gestation. Treatment with metoprolol did not adversely affect any of the parameters studied.

Rabbit: (New Zealand White strain) Doses of 5, 12.5 and 25 mg/kg were administered orally to groups of 20 pregnant rabbits on days 6-18 of gestation. Parameters studied were not significantly affected, although litter size was lower and fetal loss higher in the high dose group. The incidence of fetal abnormality was unaffected by treatment.

Rat: (Sprague-Dawley strain) Doses of 10, 50 and 200 mg/kg were administered orally to groups of 50 rats from day 15 of gestation, through lactation to 21 days postpartum. Parameters studied in litter and parent animals were not adversely affected.

Rat: (Charles River CD strain) Doses of 50 and 500 mg/kg were administered orally to groups of 10 male and 20 female rats. Males were treated for 63 days prior to mating and during the mating period. The females were treated for 14 days prior to mating, during mating and throughout the gestation and lactation periods to 21 days postpartum, with an interim sacrifice at day 13 of gestation. The only significant finding in this study was a slight reduction of intrauterine growth in rats at 50 and 500 mg/kg/day and a higher frequency of stillbirths in the high dose group.

Carcinogenicity Studies

Metoprolol was administered to 3 groups of 60 male and 60 female Charles River Sprague- Dawley rats at dietary levels of 50, 200 and 800 mg/kg per day for 78 weeks. A fourth group received 2-AAF (positive control) and the fifth was the negative control group. The incidence of nodules and masses observed at necropsy were comparable between the treated and control groups. The only histopathological changes noted were an increased incidence of impaction of pulmonary alveoli by septal cells in the high and intermediate metoprolol-treated groups. The strain of rats was susceptible to the known carcinogen 2-AAF; a statistically higher incidence of neoplasms, primarily hepatomas, was present.

A similar study in Swiss albino mice at doses of 75, 150 and 750 mg/kg per day for 78 weeks showed that the tumors were distributed with equal frequency in the treated and control groups. The strain was susceptible to the known carcinogen.

Selected Bibliography

1. Ablad B, Borg KO, Carlsson E, Ek L, Johnsson G, Malmfors T, and Regardh C-G. A survey of the pharmacological properties of metoprolol in animals and man. *Acta Pharmacol Toxicol* 1975; 36 (suppl V): 7-23.
2. Ablad B, Borjesson I, Carlsson E, and Johnsson G. Effects of metoprolol and propranolol on some metabolic responses to catecholamines in the anaesthetized dog. *Acta Pharmacol Toxicol* 1975; 36 (suppl V): 85-95.
3. Adolfsson L, Areskog N-H, Furburg C, and Johnsson G. Effects of single doses of alprenolol and two cardio-selective β -blockers (H 87/07 and H 93/26) on exercise-induced angina pectoris. *Eur J Clin Pharmacol* 1974; 7 (2): 111-118.
4. Biemann P, Leduc G, Jequier J-C, Davignon J, and Cartwright K. Changes in the lipoprotein composition after chronic administration of metoprolol and propranolol in hypertriglyceridemic hypertensive subjects. *Curr Ther Res* 1981; 30 (6): 956-967.
5. Bodin N-O, Flodh H, Magnussen G, Malmfors T, and Nyberg J-A. Toxicological studies on metoprolol. *Acta Pharmacol Toxicol* 1975; 36 (suppl V): 96-103.
6. Borer JS, Comerford MB, and Sowton E. Assessment of metoprolol, a cardioselective β -blocking agent, during chronic therapy in patients with angina pectoris. *J Int Med Res* 1976; 4: 15-22.
7. Borg KO, Carlsson E, Hoffmann KJ, Jönsson TE, Thorin H, Wallin B. Metabolism of metoprolol-(3H) in man, the dog and the rat. *Acta Pharmacol Toxicol* 1975; 36 Suppl V: 125-35.
8. Boyle DMcC, Barber JM, McIlmoyle EL, Salathia KS, Evans AE, Cran G, Elwood JH, and Shanks RG. Effect of very early intervention with metoprolol on myocardial infarct size. *Br Heart J* 1983; 49: 229-233.
9. Comerford MB, and Besterman EMM. An eighteen months' study of the clinical response to metoprolol, a selective β_1 -receptor blocking agent, in patients with anginal pectoris. *Postgrad Med J* 1976; 52 (610): 481-486.
10. Ekelund L-G, Johnsson G, Melcher A, and Oro L. Effects of cedilanid-D in combination with metoprolol on exercise tolerance and systolic time intervals in angina pectoris. *Am J Cardiol* 1976; 37 (4): 630-634.
11. Epstein SE, and Braunwald E. β -adrenergic receptor blocking drugs. Mechanisms of action and clinical applications. *New Eng J Med* 1966; 275: 1106-1112, 1175-1183
12. Fitzgerald JD. The role of β -adrenergic blockade in acute myocardial ischaemia. IN: Oliver MF, Julian DG, and Donald KW (eds). *Effect of acute ischaemia on*

myocardial function. Churchill Livingstone, Edinburgh and London, 1972, pp. 321-353.

13. Formgren H. The effect of metoprolol and practolol on lung function and blood pressure in hypertensive asthmatics. *Br J Clin Pharmacol* 1976; 3 (6): 1007-1014 The Göteborg Metoprolol Trial in Acute Myocardial Infarction. *Am J Cardiol* 1984; 53 (13): 1D-50D
14. Hansten PD, Horn JR, editors. Principles of beta-adrenergic blocker drug interactions 79-82. Anti-arrhythmic drug interactions 153-8, 162-3, 170-1, 188-9. Antidiabetic drug interactions 373-5. Beta-adrenergic blocker drug interactions 435-57. Drug interactions & updates. Vancouver: Applied Therapeutics Inc., 1993.
15. Herlitz J, Elmfeldt D, Hjalmarson A, Holmberg S, Malek I, Nyberg G, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmsen L, and Wilhelmsson C. Effect of metoprolol on indirect signs of the size and severity of acute myocardial infarction. *Am J Cardiol* 1983; 51: 1282-1288.
16. Hjalmarson A, Ariniego R, Herlitz J, et al. Limitation of infarct size in man by the b1-blocker metoprolol. *Circulation* 1979; 59 and 60 (Suppl II): 164 (Abstr.)
17. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomized trial. *Lancet* 1981 (Oct. 17); 823-827.
18. Hjalmarson A, Herlitz J, Holmberg S, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmsen L, and Wilhelmsson C: The Göteborg Metoprolol Trial; Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983; 67 (suppl I): I26- I32.
19. Imhof P: Les bêta-bloquants et le sport. *Médecine et Hygiène* 1979; 1348.
20. Johnsson G. Influence of metoprolol and propranolol on hemodynamic effects induced by adrenaline and physical work. *Acta Pharmacol Toxicol* 1975; 36 (suppl V): 59-68.
21. Johnsson G, Regardh C-G, and Sölvell L. Combined pharmacokinetic and pharmacodynamic studies in man of the adrenergic b1-receptor antagonist metoprolol. *Acta Pharmacol Toxicol* 1975; 36 (suppl V): 31-44.
22. Johnsson G, Svedmyr N, and Thiringer G. Effects of intravenous propranolol and metoprolol and their interaction with isoprenaline on pulmonary function, heart rate and blood pressure in asthmatics. *Eur J Clin Pharmacol* 1975; 8: 175-180.

23. Kendall MJ, John VA, Quarterman CP, and Welling PG. A single and multiple dose pharmacokinetic and pharmacodynamic comparison of conventional and slow-release metoprolol. *Eur J Clin Pharmacol* 1980; 17: 87-92.
24. Keyrilainen O, and Uusitalo A. Effects of metoprolol in angina pectoris. A subacute study with exercise tests and a long-term tolerability study. *Acta Med Scand* 1976; 199: 491-497.
25. Lennard MS. The polymorphic oxidation of beta-adrenoceptor antagonists. *Pharmacol Ther* 1989;41:461-77.
26. Logan RL, Goldstraw PW, Kiddle GB, Flacks LM, and Watt M. Sustained release metoprolol: a comparison with conventional formulation in the treatment of hypertension. *NZ Med J* 1981; 687: 1- 2.
27. Lorimer AR, Barbour MB, and Lawrie TDV. An evaluation of the effect on resting and exercise blood pressure of some first line treatments in hypertension. *Ann Clin Res* 1983; 15: 30-34.
28. Malek I, Waagstein F, Hjalmarson A, Holmberg S, and Swedberg K. Hemodynamic effects of the cardioselective β -blocking agent metoprolol in acute myocardial infarction. *Acta Med Scand* 1978; 204: 195-201.
29. The Miami Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomized placebo-controlled international trial. *Eur Heart J* 1985; 6: 199-226.
30. Olsson G, Rehnqvist N, Sjogren A, Eerhart L, and Lundman T. Long-term treatment with metoprolol after myocardial infarction: Effect on 3 year mortality and morbidity. *J Am Coll Cardiol* 1985; 5 (6): 1428-1437.
31. Quarterman CP, Kendall MJ, and Welling PG. Plasma levels and negative chronotropic effect of metoprolol following single doses of a conventional and sustained-release formulation. *Europ J Clin Pharmacol* 1979; 15: 97-103.
32. Regardh CG, Borg KO, Johansson R, Johnsson G, Palmer L. Pharmacokinetic studies on the selective β_1 -receptor antagonist metoprolol in man. *J Pharmacokinet Biopharm* 1974;2(4):347-64.
33. Regardh CG, Johnsson G. Clinical pharmacokinetics of metoprolol. *Clin Pharmacokinet* 1980;5:557-69.
34. Richards S. Cutaneous side-effects of beta-adrenergic blockers. *Aust J Derm* 1985;26:25-8.
35. Ryden L, Ariniago R, Arnman K, Herlitz J, Hjalmarson A, Holmberg S, Reyes C, Smedgard P, Svedberg K, Vedin A, Waagstein F, Waldenstrom A, Wilhelmsson C, Wedel H, and Yamamoto M. A double-blind trial of metoprolol in acute myocardial

infarction. Effects on ventricular tachyarrhythmias. *N Eng J Med* 1983; 308: 614-618.

36. Salathia KS, Barber JM, McIlmoyle EL, Nicholas J, Evans AE, Elwood JH, Cran G, Shanks RG, and Boyle D McC. Very early intervention with metoprolol in suspected acute myocardial infarction. *Eur Heart J* 1985; 6: 190-198.
37. Singh BN, et al. Effects of cardioselective β adrenergic receptor blockade on specific airways resistance in normal subjects and in patients with bronchial asthma. *Clin Pharmacol Ther* 1976; 19 (5, Pt 1): 493-501.
38. Stenberg J, Wasir H, Amery A, Sannerstedt R, and Werko L. Comparative hemodynamic studies in man of adrenergic β_1 -receptor agents without (H 93/26 = metoprolol) or with (H 87/07) intrinsic sympathicomimetic activity. *Acta Pharmacol Toxicol* 1975; 36 (suppl V): 76-84.
39. Stockley IH, editor. *Drug Interactions. A source book of adverse interaction their mechanisms, clinical importance and management.* Amiodarone-beta blockers 96-7. Disopyramide + beta-blockers 99-100. Lignocaine (Lidocaine) + beta-blockers 108-9. Quinidine + beta-blockers 121-2. Clonidine + beta-blockers 362-4. Prazosin + beta-blockers 383-4. Beta-blockers + cimetidine 413-4. Beta-blockers + rifampicin 427-8. Beta-blockers + sympathonimetics 429-31. Digitalis glycosides + beta-blockers 506. Hypoglycamic agents-beta blockers 548-550. Anaesthetics, general + beta-blockers 697. Oxford: Blackwell Science, 1992.
40. Trafford JAP, McGonicle R, Bowles J, O'Neal H, Bennet-Jones DN, Halford L, and Evans R. A two year clinical evaluation of atenolol and metoprolol in the treatment of hypertension. *Br J Clin Pract* 1982; 36: 350-352.
41. Van Joost T, Smitt JHS. Skin reactions to propranolol and cross sensitivity to β -adrenoreceptor blocking agents. *Arch Dermatol* 1981;117:600-1.
42. Waagstein F, and Hjalmarson AC. Double-blind study of the effect of cardioselective β -blockade on chest pain in acute myocardial infarction. *Acta Med Scand* 1975; (Suppl 587): 201-208.
43. Waal-Manning, HJ. Hypertension: Which β -blocker? *Drugs* 1976; 12: 412-441.
44. Wagner F, Kalusche D, Trenk D, Jähnchen E, Roskamm H. Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* 1987;24:213-20.
45. Product Monograph – Lopressor (metoprolol tartrate). Novartis Pharmaceuticals Canada Inc. Revised May 2, 2008.