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TERNOLOL TABLET

VITER06-var (MY)

20054

DESCRIPTION

Ternolol 50 mg
8mm, round, orange film-coated tablet with shallow convex faces, bevel-edged and heart-shaped protrusion.

Ternolol 100 mg
10mm, round, orange film-coated tablet with shallow convex faces bevel-edged and heart-shaped protrusion.

COMPOSITION

Ternolol 50 mg
Atenolol 50 mg per tablet.

Ternolol 100 mg
Atenolol 100 mg per tablet.

PHARMACODYNAMICS

Atenolol is a beta-blocker which is beta1-selective (i.e. acts preferentially on beta1-adrenergic receptors in the heart). Selectivity decreases with increasing dose. Atenolol is without intrinsic sympathomimetic and membrane stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear. It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina. It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Ternolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Ternolol is compatible with diuretics, other hypotensive agents and antianginal agents (see Interactions). Since it acts preferentially on beta-receptors in the heart, Ternolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

PHARMACOKINETICS

Following intravenous administration, the blood levels of atenolol decay tri-exponentially with an elimination half-life of about 6 hours. Throughout the intravenous dose range of 5-10 mg the blood level profile obeys linear pharmacokinetics and beta-adrenoceptor blockade is still measurable 24 hours after a 10 mg intravenous dose.

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40- 50%) with peak plasma concentrations occurring 2-4 hours after dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered. The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

INDICATIONS

For treatment of hypertension, angina pectoris, acute myocardial infarction and cardiac arrhythmias.

CONTRAINDICATIONS

Ternolol, as with other beta-blockers, should not be used in patients with any of the following: known hypersensitivity to the active substance, or any of the excipients; bradycardia (<45 bpm); cardiogenic shock; hypotension; metabolic acidosis; severe peripheral arterial circulatory disturbances; second or third degree heart block; sick sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure.

WARNINGS AND PRECAUTIONS

Ternolol as with other beta-blockers:

- should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7-14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.
- when a patient is scheduled for surgery, and a decision is made to discontinue beta- blocker therapy, this should be done at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.
- although contraindicated in uncontrolled heart failure (see Contraindications), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Ternolol is a beta1-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- although contraindicated in severe peripheral arterial circulatory disturbances (see Contraindications), may also aggravate less severe peripheral arterial circulatory disturbances.
- due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.
- may mask the symptoms of hypoglycaemia, in particular, tachycardia.
- may mask the signs of thyrotoxicosis.
- will reduce heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate and the pulse rate drops to less than 50-55 bpm at rest, the dose should be reduced.
- may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.
- may cause a hypersensitivity reaction including angioedema and urticaria.
- should be used with caution in the elderly, starting with a lesser dose (see Dosage and Administration).

Since Ternolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.7 m^2.

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all, beta-blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Ternolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients, however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

Effect on ability to drive and use machines
Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However it should be taken into account that occasionally dizziness or fatigue may occur.

PREGNANCY AND LACTATION

The use of Ternolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters. In general, β-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour.

There is significant accumulation of Ternolol in breast milk.

Neonates born to mothers who are receiving Ternolol at parturition or breast-feeding may be at risk of hypoglycemia and bradycardia.

Caution should be exercised when Ternolol is administered during pregnancy or to a woman who is breast-feeding.

SIDE EFFECTS

Ternolol is well tolerated. The following side effects may occur:

Cardiac disorders:
Common : Bradycardia.
Rare : Heart failure deterioration, precipitation of heart block.

Vascular disorders:
Common : Cold extremities.
Rare : Postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon.

Nervous system disorders:
Rare : Dizziness, headache, paraesthesia.

Psychiatric disorders:
Uncommon : Sleep disturbances of the type noted with other beta blockers.
Rare : Mood changes, nightmares, confusion, psychoses and hallucinations.

Gastrointestinal disorders:
Common : Gastrointestinal disturbances.
Rare : Dry mouth.

Investigations:
Uncommon : Elevations of transaminase levels.

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BACK

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Very rare : An increase in ANA (Antinuclear Antibodies) has been observed.

Hepatobiliary disorders:
Rare : Hepatic toxicity including intrahepatic cholestasis.

Blood and lymphatic system disorders:
Rare : Purpura, thrombocytopenia.

Skin and subcutaneous tissue disorders:
Rare : Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.
Not Known : Hypersensitivity reactions, including angioedema and urticaria.

Eye disorders:
Rare : Dry eyes, visual disturbances.

Reproductive system and breast disorders:
Rare : Impotence.

Respiratory, thoracic and mediastinal disorders:
Rare : Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

General disorders and administration site conditions:
Common : Fatigue.

Discontinuance of the drug should be considered if, according to clinical judgement, the well- being of the patient is adversely affected by any of the above reactions.

DRUG INTERACTIONS

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects e.g. verapamil, diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Digitalis glycosides, in association with beta-blockers, may increase atrio-ventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped (see also prescribing information for clonidine).

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see Warnings and Precautions).

Concomitant use of prostaglandin synthetase inhibiting drugs (e.g. ibuprofen, indomethacin), may decrease the hypotensive effects of beta-blockers.

Caution must be exercised when using anaesthetic agents with Ternolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

OVERDOSE

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blocker blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

DOSAGE AND ADMINISTRATION

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines.

Adults

Hypertension:
One tablet daily. Most patients respond to 100 mg daily given orally as a single dose. Some patients, however, will respond to 50 mg given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining Ternolol with other antihypertensive agents. For example, co-administration of Ternolol with a diuretic, provides a highly effective and convenient antihypertensive therapy.

Angina:
Most patients with angina pectoris will respond to 100 mg given orally once or 50 mg given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac Arrhythmias:
Having controlled the arrhythmias with intravenous Ternolol, a suitable oral maintenance dosage is 50-100 mg daily, given as a single dose.

Myocardial Infarction:
Early intervention after acute myocardial infarction: For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of chest pain Ternolol 5-10 mg should be given by slow intravenous injection (1 mg/minute) followed by Ternolol 50 mg orally about 15 minutes later, provided no untoward effects have occurred from the intravenous dose. This should be followed by a further 50 mg orally 12 hours after the intravenous dose and then 12 hours later by 100 mg orally, once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, Ternolol should be discontinued.

Late intervention after acute myocardial infarction: For patients who present some days after suffering an acute myocardial infarction an oral dose of Ternolol (100 mg daily) is recommended for long-term prophylaxis of myocardial infarction.

Elderly

Dosage requirements may be reduced, especially in patients with impaired renal function.

Children

There is no paediatric experience with Ternolol and for this reason it is not recommended for use in children.

Renal Failure:
Since Ternolol is excreted via the kidneys the dosage should be reduced in cases of severe impairment of renal function.

No significant accumulation of Ternolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2).

For patients with a creatinine clearance of 15-35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300-600 micromol/litre) the oral dose should be 50 mg daily and the intravenous dose should be 10 mg once every two days.

For patients with a creatinine clearance of <15 ml/min/1.73 m^2 (equivalent to serum creatinine of >600 micromol/litre) the oral dose should be 25 mg daily or 50 mg on alternate days and the intravenous dose should be 10 mg once every four days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Storage:
Store below 30°C. Protect from light and moisture.

Presentation/Packing:
Blisters of 3 x 10's and 10 x 10's.

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