AMCAB-AT®

एमक्याब-एटी

(Amlodipine Besilate & Atenolol)

DESCRIPTION:

This is a combination of two medicines: Amlodipine and Atenolol, which lowers blood pressure effectively. Amlodipine is a calcium channel blocker which works by relaxing blood vessels while atenolol is a beta blocker which works specifically on the heart to slow down the heart rate. Together, they make the heart more efficient at pumping blood throughout the body.

CLINICAL PHARMACOLOGY:

Mechanism of Action:

Amlodipine:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, AMCAB reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: AMCAB has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of AMCAB in vasospastic (Prinzmetal's or variant) angina.

Atenolol: Atenolol is a beta1-selective (cardio-selective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, Atenolol inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacodynamics:

Amlodipine:

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, Amlodipine (AMCAB) produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with Amlodipine (AMCAB) is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures(+1/–2 mmHg). In hypertensive patients with normal renal function, therapeutic doses of Amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria. Electrophysiologic Effects:AMCAB does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving Amlodipine and concomitant beta-blockers. In clinical studies in which Amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Atenolol:

Beta-adrenoceptor blocking activity of atenolol has been demonstrated by:reduction in resting and exercise heart rate and cardiac output; reduction of systolic and diastolic blood pressure at rest and on exercise; inhibition of isoproterenol induced tachycardia, andreduction in reflex orthostatic tachycardia. A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within 1 hour following oral administration of a single dose. This effect is maximal at about 2–4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an IV dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. The effect on exercise tachycardia of a single 10 mg IV dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration.However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level. Consistent with its negative chronotropic effect due to beta-blockade of the sinoatrial (SA) node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane-stabilizing activity, and increasing the dose well beyond that producing beta-blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

Pharmacokinetics & Metabolism:

Amlodipine:

After oral administration of therapeutic doses of AMCAB, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of AMCAB is not altered by the presence of food. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose. Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Atenolol:

In humans, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the faeces. Peak blood levels are reached between 2 and 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an IV dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose.

Atenolol also differs from propranolol in that only a small amount (6–16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a 4-fold interpatient variation. The elimination half-life of oral atenolol is approximately 6–7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following IV administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to

that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73 m2.

INDICATIONS:
Essential Hypertension; Angina Pectoris

DOSAGE & ADMINISTRATION:
The recommended dosage is one tablet of AMCAB-AT daily. If necessary, the dosage may be increased to two tablets daily. The dosage however should be individualized.
Special Populations:
Patients with Renal Impairment: Dosage of AMCAB-AT should be adjusted in cases of severe impairment of renal function. Dosage of atenolol should not exceed 50 mg/day when creatinine clearance is 15-35 ml/min/1.73 m2. While in patients with creatinine clearance <15 ml/min/1.73 m2, the maximum dosage of atenolol should be 25 mg/day.
Patients with Hepatic Impairment: The recommended initial dose in patients with hepatic impairment is half tablet of AMCAB-AT. Elderly Patients (65 years or above): Dose selection for an elderly patient should be cautious, usually starting at half tablet of AMCAB-AT.

ADVERSE DRUG REACTIONS:
Headache, hypotension, dizziness, breathlessness, fatigue, muscle cramps, bradycardia, palpitations, flushing, oedema, dyspnoea, dyspepsia, cold extremities. Drowsiness, chest pain & impotence rarely. Hypersensitivity reactions.

CONTRAINDICATIONS:
Hypersensitivity to either component, cardiogenic shock, uncontrolled heart failure, sick sinus syndrome, second-or third-degree heart block, untreated phaeochromocytoma, metabolic acidosis, bradycardia (<45 bpm), hypotension, and severe peripheral arterial circulatory disturbances.

DRUG INTERACTIONS:
CYP3A4 inhibitors: Concomitant use of AMCAB-AT Tablets with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may, thus, be required.
CYP3A4 Inducers: The concomitant use of CYP3A4 inducers (e.g. rifampicin, hypericumperforatum) may give a lower plasma concentration of AMCAB-AT Tablets. AMCAB-AT Tablets should be used with caution together with CYP3A4 inducers.
Administration of AMCAB-AT Tablets with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure-lowering effects.
Dantrolene (Infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and IV dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of AMCAB-AT Tablets be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
Sildenafil: Monitor for hypotension when sildenafil is co-administered with AMMCAB-AT Tablets.
Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with AMCAB-AT Tablets but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of AMCAB-AT Tablets in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.
Cyclosporine: No drug interaction studies have been conducted with cyclosporine and the combination in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0–40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on the combination, and cyclosporine dose reductions should be made as necessary.
Simvastatin: Limit the dose of simvastatin in patients on AMCAB-AT Tablets.
Catecholamine-depleting Drugs: Catecholamine-depleting drugs (e.g. reserpine) may have an additive effect when given with the combination. Patients treated with AMCAB-AT Tablets plus a catecholamine depletor should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.
Calcium Channel Blockers: Calcium channel blockers may also have an additive effect when given with atenolol.
Disopyramide: Disopyramide is a type I antiarrhythmic drug with potent negative inotropic and chronotropic effects. Disopyramide has been associated with severe bradycardia, asystole and heart failure when administered with beta-blockers.
Amiodarone: Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with beta-blockers.
Beta-blockers: Beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If the two drugs are co-administered, AMCAB-AT Tablets should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by the combination therapy, the introduction of the combination should be delayed for several days after clonidine administration has stopped.
Prostaglandin Synthase-inhibiting Drugs: Concomitant use of prostaglandin synthase inhibiting drugs, e.g. indomethacin, may decrease the hypotensive effects of AMCAB-AT Tablets.
Aspirin: Information on concurrent usage of the combination and aspirin is limited. Data from several studies, i.e. TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and the combination in the acute myocardial infarction setting.
Digitalis Glycosides: Both digitalis glycosides and the combination slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.
While taking AMCAB-AT Tablets, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental or diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.
Caution must be exercised when using anaesthetic agents with AMCAB-AT Tablets. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of the combination 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.

SPECIAL PRECAUTIONS:
Elderly Patients: Excessive fall of BP may occur.
Caution in patients with COPD, thyrotoxicosis, congestive failure, vasospastic angina, hepatic & renal impairment.
Caution in diabetic patients as beta-blockers may mask tachycardia occurring with hypoglycaemia. Withdrawal should be gradual.
Safety and efficacy have not been established in children.
Not to be used in untreated phaeochromocytoma.

USE IN SPECIAL POPULATION:
Renal Impairment: The dosage of AMCAB-AT Tablets should be reduced in patients with a creatinine clearance <35 ml/min/1.73 m2.
Hepatic Impairment: Caution may be necessary in the use of the combination in patients with severe liver damage because of the prolongation of the elimination half-life of amlodipine.
Pregnancy: The combination should be used during pregnancy only if the expected benefit outweighs the potential foetal risk.
Lactation: The combination should not be used by lactating women. If its use is considered necessary, breastfeeding should be stopped.
Pediatric Use: Safety and effectiveness of this combination has not been evaluated in paediatric patients.
Geriatric Use:
Amlodipine: Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required.

Atenolol: Hypertension and Angina Pectoris due to Coronary Atherosclerosis – Clinical studies of atenolol did not include sufficient number of patients aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. In general, dose selection should be done with caution in elderly patients, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSE:

Amlodipine:Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and, possibly, a reflex tachycardia. Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on an mg/m2 basis) caused a marked peripheral vasodilation and hypotension. If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein-bound, haemodialysis is not likely to be of benefit.

Atenolol: The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic-blocking agent and which might also be expected in atenolol overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycaemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. Atenolol can be removed from the general circulation by haemodialysis. Other treatment modalities should be employed at the physician's discretion and may include the following:

Bradycardia: IV atropine. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

Heart Block (Second- or Third-degree): Isoproterenol or transvenous cardiac pacemaker.

Cardiac Failure: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

Hypotension: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

Bronchospasm: A beta2-stimulant such as isoproterenol or terbutaline and/or aminophylline.

Hypoglycaemia: IV glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

PRESENTATION:

AMCAB-AT:

- Each uncoated tablet contains: Amlodipine Besilate equivalent to Amlodipine 5 mg & Atenolol 50 mg
  Packaging: 30 Tablets X 5 Blisters

ID: 01 pi ATT 20

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