MITSUBISHI TANABE PHARMA CORPORATION

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SEA

Standard Commodity Classification No. of Japan
872171

- Ca-ANTAGONIST -

HERBESSER® Injection 10 mg
HERBESSER® Injection 50 mg

<Diltiazem hydrochloride>

Storage
At room temperature.

Expiration date
Indicated on the package and container.

Caution: Use only pursuant to the prescription or directions of a physician, etc.

CONTRAINDICATIONS (HERBESSER Injection is contraindicated in the following patients.)

1) Patients with severe hypotension or cardiogenic shock [The symptoms may be exacerbated.]
2) Patients with 2nd or more degree atrioventricular block or sick sinus syndrome (continuous sinus bradycardia less than 50 beats/minute, sinus arrest, sinoatrial block, etc.) [Excessively inhibitory effect of the drug on cardiac stimulus-formation and conduction may occur.]
3) Patients with severe congestive heart failure [The symptoms of heart failure may be exacerbated.]
4) Patients with severe cardiomyopathy [The symptoms of heart failure may be exacerbated.]
5) Patients with a history of hypersensitivity to any of the ingredients in the drug
6) Pregnant women or women who may possibly be pregnant [See PRECAUTIONS -Use during Pregnancy, Delivery or Lactation.]

DESCRIPTION

The drugs are lyophilized preparations and products for injection to be dissolved in physiological saline or glucose solution for injection before use.

Brand name	HERBESSER Injection 10 mg	HERBESSER Injection 50 mg
Ingredient・content (per ampoule)	Diltiazem hydrochloride	
	10mg	50mg
Inactive ingredient	D-Mannitol	
	70mg	75 mg
Container	Ampoule	
Appearance	White masses or porous solid	
Description of the solution dissolved the content in one ampoule of the drug in 5 ml of water for injection		
Appearance	Colorless and clear	
pH	5.5	5.1
Osmotic pressure ratio (to physiological saline)	0.30	0.44

INDICATIONS

・Tachyarrhythmia (supraventricular)
・Emergency treatment for abnormal hypertension during operation
・Hypertensive emergency
・Unstable angina

DOSAGE AND ADMINISTRATION

The drug (10 mg or 50 mg as diltiazem hydrochloride) is dissolved in at least 5 ml of physiological saline or glucose solution for injection before use and administered as follows:

・Tachyarrhythmia (supraventricular)
Usually for adults, 10 mg of diltiazem hydrochloride as a single dosage is intravenously injected slowly for about 3 minutes. The dosage may be adjusted depending on the patient's age and symptoms.
・Emergency treatment for abnormal hypertension during operation
Intravenous bolus injection:
Usually for adults, 10 mg of diltiazem hydrochloride as a single dosage is intravenously injected slowly for about one minute. The dosage may be adjusted depending on the patient's age and symptoms.
Intravenous drip infusion:
Usually for adults, 5 to 15 μg of diltiazem hydrochloride/kg body weight per minute is intravenously injected in drip infusion. After blood pressure is lowered to the target level, adjust the drip infusion rate while monitoring blood pressure.
・Hypertensive emergency
Usually for adults, 5 to 15 μg of diltiazem hydrochloride/kg body weight per minute is intravenously injected in drip infusion. After blood pressure is lowered to the target level, adjust the drip infusion rate while monitoring blood pressure.
・Unstable angina
Usually for adults, 1 to 5 μg of diltiazem hydrochloride/kg body weight per minute is intravenously injected in drip infusion.
The dosage should be started with a low dose and may be adjusted depending on the patient's symptoms. The maximum dosage should be 5 μg of diltiazem hydrochloride/kg body weight per minute.

PRECAUTIONS

1.Careful Administration (HERBESSER Injection 10mg and 50mg should be administered with care in the following patients.)

1) Patients with congestive heart failure [The symptoms of heart failure may be exacerbated.]
2) Patients with cardiomyopathy [The symptoms of heart failure may be exacerbated.]
3) Patients with acute myocardial infarction [The symptoms of heart failure may be exacerbated.]
4) Patients with bradycardia or 1st-degree atrioventricular block [Excessively inhibitory effect of the drug on cardiac stimulus-formation and conduction may occur.]
5) Patients with hypotension [The blood pressure may be further lowered.]
6) Patients with atrial fibrillation or atrial flutter accompanied with WPW or LGL syndrome [Increased heart rate due to hypotension and ventricular fibrillation may occur.]
7) Patients receiving β-blocking agents [Bradycardia and excessively inhibitory effect on cardiac conduction may occur.]
8) Patients with severe hepatic and renal dysfunction [The effect of the drug may be enhanced by its delayed metabolism and excretion.]

2.Important Precautions

1) **Electrocardiogram and blood pressure should be continuously monitored.**
2) Since the drug may lead to complete atrioventricular block, severe bradycardia and cardiac arrest, pay attention to the followings adequately. [See PRECAUTIONS.]
   (1) Limit the dosage to a bare minimum in the treatment and the administration time to a bare minimum in the intravenous drip infusion
   (2) Observe the patient's conditions during and after administration adequately, and try to detect these symptoms at an earlier stage.
   (3) Prepare adequately to deal with these symptoms in the administration. When abnormalities are confirmed, discontinue the administration immediately and take appropriate measures.
3) It has been reported that the concomitant use of other antiarrhythmic agent (disopyramide phosphate) and terfenadine caused QT interval prolongation and ventricular arrhythmia.
4) In the severe attack such as anginal attack sustaining more than 15 minutes, other therapy (PTCA, CABG, etc.) should be considered, according to need.

3.Drug Interactions

Precautions for coadministration (HERBESSER Injection should be administered with care when coadministered with the following drugs.)

Drugs, etc.	Clinical symptoms and Treatment	Mechanism and Risk Factors
Drugs with hypotenseive effect (anti-hypertensives, nitrates, etc.)	Hypotensive effect may be enhanced. Measure the blood pressure and adjust the dosage	It is considered that the combination additively enhances the effect (hypotensive effect).
β-blocking agents (bisoprolol fumarate, propranolol hydrochloride, atenolol, etc.),	Bradycardia, atrioventricular block, sinoatrial block, etc. may occur. Perform ECG monitoring. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that the combination additively enhances the effects (inhibitory effect on cardiac stimulus-formation and conduction, negative inotropic effect and hypotensive effect). Special caution should be paid in triple combination therapy (diltiazem hydrochloride, β-blocking agents, and digitalis preparations).
Rauwolfa preparations (reserpine, etc)		
Digitalis preparations (digoxin, methyldigoxin)	Bradycardia, atrioventricular block, etc. may occur. Toxic symptoms (nausea, vomiting, headache, dizziness, abnormal vision, etc.) due to the increased blood concentration of digitalis preparations, including these arrhythmias, may occur. Perform ECG monitoring and observe the presence or absence of digitalis toxicity periodically. If necessary, measure the blood concentration of the digitalis preparations. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that the combination additively enhances the effect (inhibitory effect on cardiac stimulus-formation and conduction). Special caution should be paid in triple combination therapy (diltiazem hydrochloride, β-blocking agents and digitalis preparations). Also it is considered that diltiazem hydrochloride increases the blood concentration of digitalis preparations.
Antiarrhythmic agents (amiodarone hydrochloride, mexiletine hydrochloride, etc.)	Bradycardia, atrioventricular block, sinus arrest, etc. may occur. Perform ECG monitoring. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that the combination additively enhances the effect (inhibitory effect on cardiac stimulus-formation and conduction).
Aprindin hydrochloride [antiarrhythmic agents]	Symptoms (bradycardia, atrioventricular block, sinus arrest, tremor, dizziness, light-headed, etc.) due to the increased blood concentration of both drugs may occur. Perform ECG monitoring and observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that the combination affects the common metabolic enzyme (cytochrome P450) of both drugs, which results in the increased blood concentration of both drugs.
Dihydropyridine calcium antagonists (nifedipine, amlodipine besilate, etc.)	Symptoms (enhanced hypotensive effect, etc.) due to the increased concentration of dihydropyridine calcium antagonists may occur. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that diltiazem hydrochloride inhibits the metabolic enzyme (cytochrome P450) of these drugs, which results in the increased blood concentration of these drugs.
Triazolam [hypnogenesis-inducing agents]	Symptoms (prolongation of sleeping time, etc.) due to the increased blood concentration of triazolam may occur. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that diltiazem hydrochloride inhibits the metabolic enzyme (cytochrome P450) of these drugs, which results in the increased blood concentration of these drugs.
Midazolam [hypnogenesis・sedation-inducing agents]	Symptoms (enhanced sedative/hypnotic effect, etc.) due to the increased blood concentration of midazolam may occur. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	
Carbamazepine [psychotropic agents for epilepsy and manic state]	Symptoms (sleepiness, nausea, vomiting, vertigo, etc.) due to the increased blood concentration of carbamazepine may occur. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	
Selegiline hydrochloride [agents for parkinsonism]	The effect and toxicity of selegiline hydrochloride may be enhanced. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	
Theophylline [bronchodilators]	Symptoms (nausea, vomiting, headache, insomnia, etc.) due to the increased blood concentration of theophylline may occur. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	
Cilostazol [antiplatelets]	The effect of cilostazol may be enhanced. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	
Vinorelbine tartrate [antineoplastic agents]	The effect of vinorelbine tartrate may be enhanced. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	
Cyclosporin [immunosuppresants]	Symptoms (renal disorders, etc.) due to the increased blood concentration of cyclosporin may occur. Observe clinical symptoms periodically and measure the blood concentration of cyclosporin. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	

Tacrolimus hydrate [immunosuppresants]	Symptoms (renal disorders, etc.) due to the increased blood concentration of tacrolimus may occur. Observe clinical symptoms periodically and measure the blood concentration of tacrolimus. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that diltiazem hydrochloride inhibits the metabolic enzyme (cytochrome P450) of these drugs, which results in the increased blood concentration of these drugs.
Phenytoin [antiepileptics]	Symptoms (ataxia, dizziness, nystagmus, etc.) due to the increased blood concentration of phenytoin may occur. Observe clinical symptoms periodically. When abnormalities are confirmed, reduce the dosage or discontinue the administration. Also the effect of diltiazem hydrochloride may be reduced.	It is considered that diltiazem hydrochloride inhibits the metabolic enzyme (cytochrome P450) of phenytonin, which results in the increased blood concentration of phenytonin. Also it is considered that phenytonin accelerates the metabolism of diltiazem hydrochloride, which results in the decreased blood concentration of diltiazem hydrochloride.
Cimetidine [H_2-antagonists]	Symptoms (enhanced hypotensive effect, bradycardia, etc.) due to the increased blood concentration of diltiazem hydrochloride may occur. Measure the blood pressure and perform ECG monitoring. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that these drugs inhibit the metabolic enzyme (cytochrome P450) of diltiazem hydrochloride, which results in the increased blood concentration of diltiazem hydrochloride.
HIV Protease inhibitors (ritonavir, saquinavir mesylate, etc.)		
Rifampicin [antituberculotics]	The effect of diltiazem hydrochloride may be decreased. Observe clinical symptoms periodically, and measure the blood concentration of diltiazem hydrochloride if possible. When abnormalities are confirmed, take appropriate measures such as alteration to other drugs or increase in the dosage of diltiazem hydrochloride.	It is considered that rifampicin induces the metabolic enzyme (cytochrome P450) of diltiazem hydrochloride, which results in the decreased blood concentration of diltiazem hydrochloride.
Anesthetics (isoflurane, enflurane, halothane, etc.)	Bradycardia, atrioventricular block, sinus arrest, etc. may occur. Perform an ECG monitoring. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that the combination additively enhances the effect (inhibitory effect on cardiac stimulus-formation and conduction).
Muscle relaxants (pancuronium bromide, vecuronium bromide, etc.)	The effect of muscle relaxants may be enhanced. Pay attention to the effect of muscle relaxants. When abnormalities are confirmed, reduce the dosage or discontinue the administration.	It is considered that diltiazem hydrochloride inhibits the release of acetylcholine from the presynaptic nerve terminals at the neuromuscular junction.

4.Adverse Reactions

Adverse reactions with HERBESSER Injection were reported in 266 (4.1%) of 6,543 patients treated. The main adverse reactions were bradycardia (1.1%), blood pressure decreased (0.7%), 1st-degree atrioventricular block (0.4%), 2nd-degree atrioventricular block (0.3%), atrioventricular junctional rhythm (0.3%), etc. (At the latest reexamination)

1) Clinically significant adverse reactions (Infrequently: 5%> ≧0.1%, rarely: <0.1%)

(1) Since **complete atrioventricular block, severe bradycardia** (initial symptoms: bradycardia, dizziness, light-headed, etc.), etc., may occur infrequently and may lead to cardiac arrest, administer the drug under adequate arrangement for these symptoms. When such abnormalities are confirmed, discontinue the administration immediately and take appropriate measures such as the followings.
For complete atrioventricular block, severe bradycardia:
Administer atropine sulfate, isoproterenol, etc., and /or apply cardiac pacing, etc., according to need.
For cardiac arrest: Conduct the treatment for resuscitation such as cardiac massage or administration of a cathecolamine such as epinephrine, etc.

(2) **Congestive heart failure** may occur rarely. When symptoms of congestive heart failure are observed, discontinue the administration and take appropriate measures.

2) Other adverse reactions

When adverse reactions are confirmed, take appropriate measures such as discontinuing the drug.

	Incidence unknown	5% > ≧0.1%	<0.1%
Cardiovascular		Bradycardia, atrioventricular block, blood pressure decreased, atrioventricular junctional rhythm, extrasystoles, sinus arrest, facial hot flushes	Sinoatrial block, bundle branch block, palpitation, dizziness, transient tachycardia,
Psychoneurologic			Headache, nausea, vomiting
Hepatic		Increased AST(GOT), ALT(GPT), LDH	Increased Al-P
Renal			Decreased urine volume, increased serum creatinine and BUN
Hypersensitivity	photo-sensitivity*		Rash, pruritus
Other			Local injection site redness

*From clinical reports with oral preparations

5.Use in the Elderly

Since the reduced physiological function is generally observed in the elderly patients, therapy should therefore be instituted with special care, starting at a low dosage while carefully monitoring the patient's condition.

6.Use during Pregnancy, Delivery or Lactation

1) HERBESSER Injection is contraindicated in pregnant women or women who may possibly be pregnant. [Animal studies have shown that the drug has teratogenic effects (mice, rats, rabbits :skeletal abnormalities, dysplasias) and embryotoxicity (mice, rats, rabbits: death).

2) It is advisable to avoid using the drug in lactating mothers. When use of the drug is judged to be essential, the breast-feeding should be discontinued during treatment. [It has been reported that diltiazem hydrochloride is excreted in breast milk.]

7.Pediatric Use

The safety of HERBESSER Injection in children has not been established.

8.Overdosage

Symptoms:

Overdosage may cause bradycardia, complete atrioventricular block, heart failure, hypotension, etc. These symptoms are also reported as adverse reactions.

Treatments:

In the event of overdosage, discontinue the administration of HERBESSER Injection and take the following appropriate measures.

1) Bradycardia, complete atrioventricular block:
Administer atropine sulfate, isoproterenol, etc., and/or apply cardiac pacing.

2) Heart failure, hypotension:
Administer an inotropic agent, a pressor agent, intravenous fluids, etc., and/or institute assisted circulation.

9.Precautions concerning Use

(1) Precautions on preparation:

Since diltiazem may be crystallized above pH 8, attention should be paid in preparation of a mixed solution of HERBESSER Injection with other drug preparations.

(2) Precautions on cutting the ampoule:

A "one point-cut ampoule" is used for HERBESSER Injection. After wiping the cut point of the ampoule with an alcohol swab, break off the tip of the ampoule by pressing it into the direction opposite the round mark, not using a file.

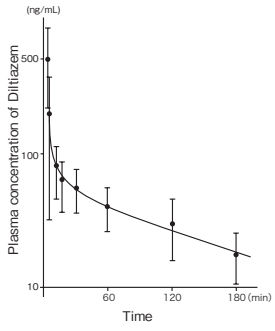
PHARMACOKINETICS

Plasma concentration

The elimination half-life (the elimination phase) of diltiazem hydrochloride after single intravenous injection was about 1.9 hours. In case of intravenous drip infusion, the plasma concentration reached a steady state 5 to 6 hours after the start of administration.

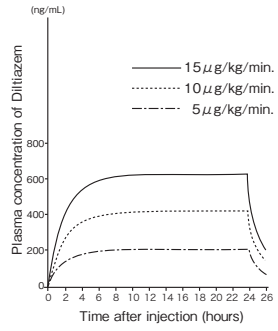
Single intravenous injection[1]

Ten mg of diltiazem hydrochloride was intravenously administered in a period of 1 minute in 8 patients with heart disease.



Intravenous drip infusion[2]

Simulation curves based on the measured values of diltiazem concentration obtained in 5 patients, not undergoing open heart surgery, who received intravenous drip infusion of diltiazem hydrochloride at an injection rate of 5, 10, or 15 μg/kg/min.



CLINICAL STUDIES

1.Tachyarrhythmia (Supraventricular)

Usefulness of HERBESSER Injection on paroxysmal supraventricular tachycardia, tachycardiac atrial fibrillation, and tachycardiac atrial flutter was proven by clinical studies, including a placebo-controlled double blind comparative clinical trial.[3] The efficacy rate (more than effectiveness) of HERBESSER Injection on paroxysmal supraventricular tachycardia was 86.4% (184/213), and that on tachycardiac atrial fibrillation and flutter was 87.2% (130/149).

2.Emergency treatment for abnormal hypertension during operation

Usefulness of HERBESSER Injection on the emergency treatment of abnormal hypertension during operation was proven by the clinical studies, including a nitroglycerin (injection)-controlled single blind clinical trial.[4] The efficacy rate (more than effectiveness) was 94.0% (315/335).

3.Hypertensive emergency

The efficacy rate (more than effectiveness) of HERBESSER Injection on hypertensive emergencies such as malignant hypertension, hypertensive encephalopathy, dissecting aortic aneurysm, acute left ventricular failure, etc., was 100.0% (28/28).[5]

4.Unstable angina

Usefulness of HERBESSER Injection on unstable angina was proven by a randomized single blind clinical trial.[6] The efficacy rate (more than moderate improvement) was 80.0% (32/40).

PHARMACOLOGY

Diltiazem hydrochloride dilates blood vessels and prolongs atrioventricular node conduction time by inhibiting calcium ions influx into the cells in the vascular smooth muscle of peripheral and coronary vessels, etc. and in the atrioventricular node, which shows the effect on hypertension, arrhythmia and angina pectoris.

1.Action on blood pressure

1) Diltiazem hydrochloride lowers elevated blood pressure under both anesthetic and unanesthetic conditions. But the antihypertensive effect is more marked under the anesthetic than unanesthetic condition,[7] and the hypotensive effect is more marked on the elavated than normal blood pressure (rats).[8,9]
2) Diltiazem hydrochloride decreases peripheral resistance and myocardial oxygen consumption and increases cardiac output while lowering blood pressure (dogs).[10]
3) Diltiazem hydrochloride lowers blood pressure without decreasing the cerebral, coronary and renal blood flow, and also has a natriuretic effect (dogs, monkeys).[10-12]

2.Action on arrhythmia

1) Diltiazem hydrochloride prolongs the atrioventricular node conduction time, effective refractory period, and functional refractory period, thus showing efficacy on supraventricular tachyarrhythmia (dogs).[13]
2) Diltiazem hydrochloride suppresses the supraventricular tachyarrhythmia induced by electrical stimulus of the atrium (rabbits).[14]

3.Action on myocardial ischemia

1) Improving action on the balance of myocardial oxygen supply and demand
   (1) Diltiazem hydrochloride increases blood flow to the myocardial ischemic region by dilating the large coronary artery and the collateral channels (dogs).[12, 15-17]
   (2) Diltiazem hydrochloride inhibits coronary artery spasm (pigs, human).[18,19]
2) Myocardial protective action
   Diltiazem hydrochloride maintains cardiac function and myocardial energy metabolism and reduces the infarct size by inhibiting excessive calcium ions influx into the cells under myocardial ischemia (dogs, cats).[20,21]

PHYSICOCHEMISTRY

Nonproprietary name:

Diltiazem hydrochloride (JAN)
Diltiazem (INN)

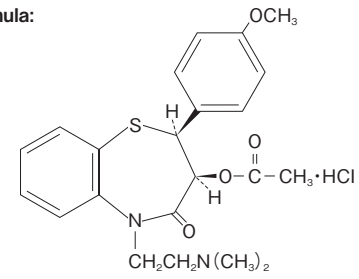
Chemical name:

(2S,3S)-5-[2-(Dimethylamino)ethyl]-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl-acetate monohydrochloride

Molecular formula:

$C_{22}H_{26}H_2O_4S \cdot HCl$: 450.98

Structural formula:



Description:

- Diltiazem hydrochloride occurs as white crystals or crystalline powder, and it is odorless.
- It is very soluble in formic acid, freely soluble in water, in methanol and in chloroform, sparingly soluble in acetonitrile, slightly soluble in acetic anhydride and in ethanol (99.5), and practically insoluble in diethyl ether.
- Optical rotation $[\alpha]_D^{20}$: +115 - +120° (after drying, 0.20 g, water, 20 mL, 100 mm)
- Melting point: 210 - 215℃ (decomposition)

PACKAGING

HERBESSER Injection 10 mg:

10 mg × 10 ampoules, 10 mg×50 ampoules

HERBESSER Injection 50 mg:

50 mg × 10 ampoules, 50 mg×50 ampoules

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Manufactured by
Mitsubishi Tanabe Pharma Corporation
3-2-10, Dosho-machi, Chuo-ku, Osaka, 541-8505, Japan

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