Review Article

Diltiazem

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The purpose of this paper is to review in some detail the pharmacology of diltiazem (a 5-benzothiazepine derivative) (FIGURE), the least well known to Canadian anaesthetists of the calcium antagonist group of drugs. This agent was developed more than ten years ago by Nagao *et al.*¹ The interactions of diltiazem with anaesthetic agents have not been well studied. Because of diltiazem's beneficial myorelaxant effects on myocardial muscle, coronary arteries, aorta and ileum,²⁻⁷ it is expected that it will in future be widely used during anaesthesia for patients with cardiovascular impairment. It is hoped that this review will stimulate further research into the mode of action of diltiazem and its anaesthesia related effects.

In order to better understand the actions of diltiazem a short review of normal functions of calcium in muscle cells and a comparison of the mode of action of diltiazem with other calcium active drugs are warranted.

The function of calcium in muscle cells

The principal contractile proteins of heart and skeletal muscle are myosin, actin and troponin. Troponin is a long polymer which lies within the helices of actin. During relaxation troponin keeps myosin and actin separated from each other. Also during relaxation the concentration of calcium in the cytoplasm of heart and skeletal muscle is much lower than is the concentration of calcium in the extracellular fluid. During contraction of these muscle cells a marked (up to 100-fold) rise in cytoplasmic calcium concentration occurs.⁸ Cytoplasmic calcium then binds to troponin in the presence of adenosine triphosphate (ATP). Union

with calcium breaks long strand-like polymeric troponin into short monomeric troponin. Between these small segments are gaps through which the cross bridges on the head of the myosin molecule are able to attach themselves to receptor sites on the actin. Then in a ratchet-like fashion myosin slides over actin to form a shortened and more rigid molecule called actomyosin. Formation of actomyosin brings about a shortening of the entire muscle cell. A reduction of cytoplasmic calcium causes dissociation of calcium from troponin, resulting in breakage of the actin-myosin cross links with ensuing return of relaxation.⁹⁻¹¹

In vascular smooth muscle contraction is brought about by a different series of events since vascular smooth muscle does not contain troponin. First calcium binds with a low molecular weight protein called calmodulin. The conformationally changed calcium-calmodulin complex then binds and activates myosin light chain kinase. This active complex phosphorylates light chain myosin thereby permitting actomyosin formation with resultant cell shortening. The main source of calcium for vascular smooth muscle contraction is extra-cellular with small amounts perhaps also coming from the mitochondria or from ill-defined sarcoplasmic reticulum.⁹⁻¹¹

Calcium and sodium enter the muscle cell through separate sarcolemmal channels. Sodium is admitted first through "fast" channels. Somewhat later calcium penetrates the muscle cell through "slow" channels. While small amounts of sodium also enter via the "slow" channels, these slow channels are 100 times more selective for calcium than for sodium.⁸ In ventricular heart muscle cells, calcium movement contributes mostly to the plateau of the action potential (phase 2). In the sinus node and in the AV node calcium movement is chiefly responsible for the ascending portion of the action potential (phase 0).^{9,10}

The calcium ions which bring about muscle contraction are derived not only from the extracellu-

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FIGURE Chemical Structure of Diltiazem

lar space but to an even greater extent from the sarcoplasmic reticulum (SR). The relatively small amount of extracellular fluid calcium which traverses the sarcolemma, as described above, then "triggers" the release of much larger quantities of calcium from the SR. This phenomenon, discovered by Endo,¹² is known as "calcium induced calcium release." "Calcium induced calcium release" appears to be the link between the action potential of the sarcolemma and the release of calcium from the SR, i.e., it may be elusive excitation-contraction coupling step. Lesser amounts of calcium may also be derived from the mitochondria from the transverse tubules and from calcium-sodium exchange across the sarcolemma.⁹⁻¹¹

Comparison of diltiazem with other calcium antagonists and agonists

Several pharmacological agents alter movement of calcium and sodium across the sarcolemma. Local anaesthetics such as lidocaine inhibit influx of sodium through the "fast" channels. Beta adrenergic receptor stimulating drugs such as isoproterenol and epinephrine increase calcium influx through the "slow" channels. Three substances, nifedipine, verapamil and diltiazem, have quite different structures but, nevertheless, have the common ability to block the "slow" calcium channels. Nifedipine, an uncharged molecule appears to act by plugging the "slow" channel in the region of its outer voltage dependent gate in an all or nothing fashion. It may

have more pure channel blocking properties than either verapamil or diltiazem. Verapamil and diltiazem appear to act on kinetic phosphorylation of the inner gate of the "slow" channels and by increasing the frequency of contraction, thereby correspondingly reducing the force of contraction. Since the dextro-isomer of verapamil is also a potent "fast" (sodium) channel blocker, some "fast" channel blockade also occurs with high doses of racemic verapamil (the marketed form). Additionally, because calcium channel blocking drugs are lipophilic, intra-cellular sites of action cannot be excluded.⁸⁻¹⁰

Pharmacokinetics and metabolism

Diltiazem is well and rapidly absorbed after oral administration.¹³ It first appears in the blood 15 minutes after ingestion and peak concentrations occur after 30 minutes.¹³⁻¹⁵ The pharmacokinetics of the drug follow a two compartment model, with rapid distribution and elimination with a half-life of four to seven hours.^{13,16} Approximately 80 per cent of the drug is bound to plasma proteins.¹³ Sixty per cent of diltiazem is metabolized in the liver and the remainder is excreted unchanged in the urine.¹³ Several metabolites, also present as conjugates, have been identified by gas chromatography-mass spectrometry. Only desacetyldiltiazem is pharmacologically active, but its activity is only about 40-50 per cent that of diltiazem.¹⁶

In human adults the elimination half time of diltiazem is 4.5 to 4.9 hours after intravenous infusion of 20 mg over ten minutes, an oral dose of 60 to 90 mg, or repeated oral administration of 60 or 90 mg every six hours for four days.¹⁷ After repeated administration, accumulation of both diltiazem and its metabolite, deacetyldiltiazem occur.¹⁷ Most patients show a double peaked time versus concentration curve after oral administration, indicating a possible enterohepatic recirculation.¹⁷

Mode of action of diltiazem on normal heart muscle

The effects of diltiazem on the heart muscle appear to be both direct and indirect. Diltiazem exerts calcium antagonistic actions directly on heart muscle and also indirectly via calcium channel blocking influences on the smooth muscle of the coronary arteries and the peripheral vascular smooth muscle.

Diltiazem has been postulated to act directly on heart muscle mainly by blocking influx of extracellular fluid calcium across the sarcolemma into the myoplasm. In the sarcolemma diltiazem increases the affinity of 1,4-dihydropyridines for the Ca^{2+} channel.¹⁸ However, both Zsoter and Church^{19,20} and Pang²¹ have shown that diltiazem exerts no consistent effect on radioactive calcium uptake into cardiac muscle (rat atrial and chick ventricular muscle) and at certain doses it may even slightly increase calcium uptake into the muscle. Alternatively, diltiazem may act by inhibiting release of sequestered intracellular stores of calcium.²⁰ Diltiazem also inhibits the slow sodium current²² and at high doses depresses the fast sodium current.²² Additionally, Matlib and Schwartz²³ have reported that diltiazem inhibits Na^+ -induced Ca^{2+} release from mitochondria isolated from rabbit hearts. These authors suggest, therefore, that the $\text{Na}^+/\text{Ca}^{2+}$ exchange carrier in mitochondria may be a receptor for diltiazem.²³

Diltiazem depresses calcium-induced tension development in potassium depolarized heart muscle.²² On the other hand the cardiodepressant effects of diltiazem can be overcome by increasing the concentration of the calcium ion in the medium bathing the heart muscle.^{22,24,25}

Catecholamines augment slow channel transport by increasing the number of calcium channels activated at a given voltage²⁶ probably because of a cAMP-induced phosphorylation of specific sarcolemma proteins.^{27,28} However, diltiazem fails to inhibit 3H-dihydroalprenolol (3H-DHA) binding to myocardial β -receptors.²⁹ Additionally, diltiazem, but not propranolol, antagonizes the positive chronotropic responses to calcium in spontaneously beating rat atria.³⁰ Diltiazem, in spite of the absence of β -adrenoreceptor blocking activity, prevents the myocardium from becoming overloaded with calcium in response to the *in vivo* administration of large amounts of isoproterenol.³¹

The effect of diltiazem on normal haemodynamics

In anaesthetized open chest dogs, diltiazem slightly improves venous return and increases right atrial pressure and cardiac output (CO).³² In anaesthetized closed chest dogs diltiazem has no significant effect on pulmonary capillary wedge pressure but does reduce systemic vascular resistance (SVR).³³

Diltiazem increases CO and stroke volumes (SV) of conscious rats during both rest and exercise.³⁴ Magometschnigg found that in healthy male human volunteers diltiazem increased CO and usually also SV but slightly decreased pulmonary wedge pressures.³⁵ These changes appear to be due to a reduction in afterload.^{36,37}

Diltiazem inhibits both papillary and atrial muscle contractility.^{22,24,27,38-43} Diltiazem was shown to exert a negative inotropic effect on: dog hearts,^{24,27,38,42} guinea pig hearts,^{39,40} rat atrial muscle,²⁵ rabbit heart muscle⁴¹ and *in vivo* in human heart muscle.⁴⁴ Diltiazem had no *in vivo* effect on contractility of ventricles of conscious dogs.⁴⁵

Thus in both man and lower animals, diltiazem, in spite of a negative inotropic action, improves both cardiac output and tissue perfusion.

The influence of diltiazem on the rate and rhythmicity of normal hearts

In intact anaesthetized dogs diltiazem reduces sinus node recovery time,³³ prolongs AV conduction time in both the presence and, more particularly in the absence of atropine,⁴⁶ and lengthens the refractory period.³³

Diltiazem suppresses atrioventricular (AV) nodal conduction, prolongs the duration of the plateau of the cardiac action potential,²² and increases refractory periods in AV nodes excised from anaesthetized rabbits⁴⁷ and in normal humans.^{20,48} Diltiazem and digoxin have additive depressant influences on SA and AV node function without significant adverse clinical effects.⁴⁹ On the other hand in awake normal humans diltiazem does not alter sinoatrial (SA) conduction time.⁴⁸

These differences between anaesthetized and awake subjects is reflected in the effects of diltiazem on the heart rate. Thus in healthy male human volunteers diltiazem increases heart rate.³⁵ Diltiazem also slightly increases the heart rate of conscious dogs,⁴⁵ but has no effect on the heart rate of anaesthetized closed chested dogs³³ and actually slows the heart rate of anaesthetized open chested dogs.³²

The effect of diltiazem on normal coronary arteries

Diltiazem, in isolated coronary artery ring segments, reduces the basal tone of the arterial

musculature. It noncompetitively antagonizes the contractile effects of norepinephrine (NE),^{50,51} acetylcholine,^{50,52} serotonin (5HT),⁵¹ histamine,⁵⁰ prostaglandins,^{50,53} potassium,⁵⁰⁻⁵² and a high pH.⁵⁴ This antagonizing effect of diltiazem is more marked against 5HT than against NE.⁵¹ Diltiazem competitively antagonizes the contractile effect of calcium on coronary arterial rings.⁵⁰ The mechanism of this action is still obscure since studies on pig coronary artery skinned muscle fibres have demonstrated that diltiazem does not alter the contractile protein calcium receptor nor caffeine induced calcium release from the SR.⁵⁵

The above inhibiting actions of diltiazem on the coronary arterial musculature would be expected to improve coronary artery flow. Indeed, in unanaesthetized dogs fitted with chronically implanted electro-magnetic flowprobes, diltiazem does increase total coronary flow and decreases coronary vascular resistance while having no significant effect on aortic pressure or on heart rate.⁵⁶

The effect of diltiazem on normal peripheral blood vessels

The vasodilator action of diltiazem is not confined to the coronary circulation. It also lowers mean arterial pressure (MAP), and systemic vascular resistance during rest and exercise by usually, although not always, slightly relaxing the peripheral vascular smooth muscle, and more especially by substantially neutralizing most vasoconstrictor (agonist) substances.^{13,32-34,57-59} This latter effect is more marked in the basilar artery than in other blood vessels.⁵⁹

In the absence of any vasoconstrictor, intravenously infused diltiazem lowers blood pressure,^{45,60} increases total peripheral conductance,⁶⁰ and decreases peripheral resistance. The effect of diltiazem on regional blood flow, as measured by the microsphere method of Hof,^{61,62} significantly increases flow to the brain, slightly increases blood flow to the stomach, small intestine and kidney, has negligible effects on flow to the skeletal muscle, and has no effect or even reduces blood flow to the liver, adrenal gland and spleen.⁶⁰ Organ conductances which reflect the active changes in vascular tone better than blood flow values, show, according to Hof, that there is a tendency toward vasodilatation even in most organs where blood flows tend not to rise or even to fall.⁶⁰

In the presence of vasoconstrictors diltiazem usually has a much more consistent relaxing influence. For instance, in rabbit aortic strips diltiazem inhibits contractions produced by NE.^{63,64} Similarly in the rat mesenteric vascular bed diltiazem attenuates contractions induced by NE.^{63,65} Additionally, in normal male humans diltiazem counteracts the hypertensive action of NE.⁶⁶ This effect of diltiazem, in the presence of NE, is not abolished in a calcium-free medium. Diltiazem, in a dose related manner, attenuates the constricting influence of potassium chloride on rat aortic^{64,67} and mesenteric⁶⁵ arterial strips. In a calcium-free medium this action by diltiazem on potassium induced contractures is abolished.⁶⁵

Contractions of peripheral blood vessels induced by potassium are mainly due to an increased inward movement of calcium from the extracellular space through the depolarized vascular smooth muscle cell membrane.⁶⁸ Contractions induced by NE are due to both slightly increased transmembranal calcium influx and mainly to release of intracellularly bound calcium from the vascular smooth muscle. Kondo *et al.*⁶⁵ claim that the ability of diltiazem to inhibit potassium-induced contractions of rat aortic strips is greater than the ability of diltiazem to inhibit NE induced contractions of these strips. Church and Zsoter,⁶⁴ on the other hand, make the opposite claim. If the former is true it would suggest that the action of diltiazem is principally on the influx of extracellular calcium across the sarcolemma. If the latter is true it would suggest that the action of diltiazem is mainly on the release of intra-cellularly bound calcium into the cytoplasm of the vascular smooth muscle.

The former postulation is supported by the report of Cauvin *et al.*⁶⁹ that diltiazem (1×10^{-6} M) completely inhibits ⁴⁵Ca uptake into rabbit mesenteric resistance vessels. It is also supported by the elegant studies of Kuriyama *et al.*⁷⁰ They found that both potassium containing and NaCl free solutions induced contractions of isolated vascular smooth muscle, both of which are suppressed by the removal of calcium from the bathing solutions. Thus these potassium-induced and NaCl free-induced contractions must be due to acceleration of calcium influx into the muscle by the increase in the K⁺ or by the decrease in the sodium in the bathing solution. Diltiazem competitively suppresses the K⁺ induced contractions but not the contractions

induced by a deficiency of NaCl. The influence of diltiazem, therefore, is on influx of calcium across the sarcolemma and not directly on reduction of Na^+ in the extracellular fluid. Norepinephrine also induces contraction of isolated vascular smooth muscle and this contraction is noncompetitively suppressed by diltiazem. Thus the inhibitory action of diltiazem on the norepinephrine-induced contraction appears to be due mainly to suppression of the norepinephrine receptors in the sarcolemma or to a norepinephrine receptor-modulated release mechanism in the cell and not to a direct action on the internal structures in the cell. This is verified by the observation that diltiazem has no effect on the pCa^{++} -tension* relationship, on calcium accumulation by, or calcium release from the SR of skinned mesenteric or coronary arterial smooth muscle fibres.⁵⁰

The latter postulation is supported by the contrary report of Church and Zsoter⁶⁴ that diltiazem exerts no consistent effect on ^{45}Ca uptake into rat mesenteric veins,⁶⁴ and at one concentration (10^{-7} M) actually increases radioactive calcium influx across the sarcolemma.⁶⁴ Moreover, Flaim and Craven⁷¹ have shown that the influence of diltiazem on ^{45}Ca uptake into vascular smooth muscle may be an indirect rather than a direct effect as they have found that diltiazem inhibits only the NE induced increase in ^{45}Ca uptake into rabbit aortas.⁷¹ Finally, Gauvin *et al.*⁶⁹ have reported that diltiazem (1×10^{-6} M) completely inhibits NE induced contractions of rabbit mesenteric resistance vessels. Essentially similar results using dog femoral arteries have been described by Mullett *et al.*⁵¹ although they note that this anti-NE effect of diltiazem in femoral artery rings is not as potent as in coronary artery rings.⁵¹

Additionally, diltiazem inhibits caffeine-induced contractions of normal rabbit mesenteric arteries⁷² which further suggests that diltiazem, at least in part, acts intracellularly on vascular smooth muscle. This experiment, however, does not elucidate whether diltiazem acts on the intracellular calcium store or on the contractile proteins. This question was answered by Saida and Breeman⁷² who investigated the influence of diltiazem on calcium movements and contractile properties of skinned vascular muscle fibres. They found that diltiazem did par-

tially inhibit caffeine-induced calcium release from the SR.⁷²

It may well be, therefore, that diltiazem acts on vascular smooth muscle at more than one site. Diltiazem may act not only by inhibiting influx of EC calcium across the sarcolemma but also by inhibiting release of calcium from intracellular storage sites.

Diltiazem (10^{-5} M) has been claimed by Sato *et al.*⁵³ not to inhibit prostaglandins ($\text{PGF}_{2\alpha}$ and PGE_2 $1 \times 10^{-5}\text{M}$ to $1 \times 10^{-7}\text{M}$) induced contractions of rabbit aortic strips. However, topical administration of $\text{PGF}_{2\alpha}$ ($30 \mu\text{g}\cdot\text{ml}^{-1}$) or 5-HT to the subdural cavities of Rhesus monkeys has been stated by Murata *et al.*⁷³ to produce a strong vasoconstriction which is completely prevented by the simultaneous addition of diltiazem ($100 \mu\text{g}\cdot\text{ml}^{-1}$) to the subdural cavity and is inhibited by the simultaneous infusion of diltiazem into the femoral vein. These differences may, of course, be due to the differing species and blood vessels examined, but further work should be done in the future to clarify these possibly conflicting experimental results.

Effect of diltiazem on myocardial blood flow with obstructed coronary arteries

In anaesthetized dogs following induction of an acute left circumflex artery stenosis an intravenous bolus of diltiazem improved flow in the normal left anterior descending artery but not in the stenotic circumflex artery, because of the fixed resistance to flow created by the artificial stenosis.⁷⁴ On the other hand, in humans with variant angina pectoris, diltiazem exerts a powerful and longlasting vasodilating action on the coronary vasculature, including the diseased narrowed portions of the vessels.⁵⁶

In dogs in whom an acute total occlusion of the left anterior descending coronary artery has been induced, an intravenous injection of a large bolus of diltiazem⁷⁵ or a four-hour diltiazem infusion⁷⁶ increases regional myocardial blood flow in the control area and in the moderately and mildly ischaemic areas but does not improve myocardial blood flow of the severely ischaemic areas.^{75,76} Flow to, and therefore function of, ischaemic myocardial segments which are not dyskinetic is improved.⁷⁶ Continuous infusion of small doses of diltiazem for 24 hours after coronary occlusion are claimed to cause a significant increase in myocardial blood flow to the circumscribed region at the

* $\text{pCa} = -\log$ of the molar calcium concentration.

ischaemic centre, and thereby a slight reduction in the size of the myocardial infarction.⁷⁵ It has also been found that in pigs in whom the three or four terminal branches of the left anterior descending coronary artery have been acutely ligated and which, therefore, lack collateral circulation, diltiazem improves myocardial blood flow at ischaemic margins without the concomitant myocardial depression typical of other calcium antagonists.⁷⁷

Wartier *et al.*⁷⁸ have reported that in anaesthetized dogs with acute left anterior descending coronary artery occlusion diltiazem (15 and 30 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) reduces arterial blood pressure and increases total coronary blood flow in the patent left circumflex coronary artery, decreases heart rate and increases left ventricular end diastolic pressure. These investigators have also found that diltiazem increases regional myocardial perfusion in non-ischaemic areas but produces no change in total perfusion within the ischaemic zone although the ratio of blood flow in the subendocardium to that in the subepicardium is increased. In awake dogs in whom collateral myocardial circulation has been induced by gradual occlusion of the left circumflex artery, diltiazem is still able to improve perfusion by increasing blood flow through the collateral vessels.^{79,80}

In summary, in focally ischaemic heart muscle, diltiazem produces little improvement in perfusion of the centre of the ischaemic region but does improve perfusion of the margins of the ischaemic area and of the remaining normal areas of heart muscle by increasing blood flow through the unaffected main coronary arteries and then through the collateral vessels.

Mode of action of diltiazem on ischaemic heart muscle

Sudden reperfusion of a severely ischaemic myocardium is accompanied by a rapid and massive influx of calcium ions into the ischaemic heart muscle cells. This calcium is then accumulated within the mitochondrial matrix and precipitated as calcium phosphate. The calcium influx coincides with a large release of creatine kinase, a lesser release of creatine phosphate from the myocardium.⁸¹

Indirect evidence in favour of a reduction by diltiazem of calcium accumulation in ischaemic heart muscle is the observation that in isolated rat

hearts diltiazem reduces the amount of creatine kinase (CK) or lactate dehydrogenase (LDH) released from the ischaemic heart muscle and restores creatine phosphate levels to near normal.⁸¹⁻⁸³ Similarly, in dogs in whom an acute occlusion of the left anterior descending coronary artery has been induced, an intravenous injection of a large bolus of diltiazem reduces ST segment elevation.⁷⁶

The deleterious influx of calcium into the heart muscle can be prevented in isolated cat hearts by the addition of diltiazem to the perfusate.⁸⁴ Bush *et al.*⁸⁴ have shown that when isolated cat hearts are made ischaemic for 60 to 90 minutes and then reperfused pretreatment with diltiazem prevents significant elevations of mitochondrial calcium which reflects inhibition of calcium influx during ischaemia and reperfusion. They also have found that diltiazem inhibits the depression of mitochondrial respiratory activity and uncoupling of oxidative phosphorylation that is seen in similar heart preparations not treated with diltiazem.

Nagao *et al.*⁴² have also reported that in dogs pretreatment with diltiazem reverses the depression of state 3 respiration* of mitochondria induced by ten minutes of occlusion of the coronary arteries. Consequently the claim of Bing⁴³ that diltiazem does not lessen the adverse influence of ischaemia on mitochondrial respiration or on mitochondrial calcium binding must be viewed with caution.

Diltiazem has other beneficial effects on ischaemic heart cell intermediary metabolism. It preserves high energy phosphate reservoirs, decreases the ischaemic-induced inhibition of glycolytic fluxes at the phosphofructokinase level and reverses the ischaemia induced tissue lactacidosis and free fatty acid elevation.⁵⁰

The above data shows that diltiazem exerts its beneficial influences on heart muscle through inhibiting the influx of calcium through the slow channel and possibly also by other as yet not fully defined calcium related intracellular actions.

Effect of diltiazem on myocardial contractility during myocardial ischaemia

During myocardial ischaemia, contractility is reduced⁸¹ with resulting reduction of compliance and rise of left ventricular end diastolic pressure

*State 3 respiration = respiration of mitochondria in the presence of substrate, oxygen, phosphate and ADP.

(LVEDP),^{84,85} decrease of maximal left ventricular pressure (LVP),⁸⁵ cardiac index (CI),^{84,85} stroke volume index (SVI) and stroke work index (SWI).⁸⁵ During sudden reperfusion left ventricular end diastolic pressure rises sharply.⁸¹ Contracture bands develop.⁸¹ Fibrillation may occur.⁸¹

These changes are inhibited by diltiazem.⁸¹⁻⁸⁵ In isolated guinea pig hearts made ischaemic by low flow, diltiazem treatment during the ischaemic period results in a significantly greater recovery of normal contractility than in hearts not treated with diltiazem.⁸⁶ Diltiazem prevents the marked drop in tension of the ischaemic segments of dog myocardia during both short (five to ten minutes)⁴² and longer (20-60 minutes)²⁷ periods of coronary occlusion. Similarly in dogs with coronary stenosis subject to rapid pacing diltiazem inhibits the post stimulation deterioration of segmental shortening.⁸⁷ Diltiazem also prevents in cats the ischaemia induced rise in LVEDP and loss of myocardial compliance.⁸⁴ In dogs given diltiazem during two hours of aortic clamping, post ischaemic falls of CI, SVI and SWI do not occur. Rather these parameters actually rise.⁸⁵

In paced male guinea pig hearts subject to ischaemia and then reperfusion, diltiazem enables the heart to follow the pacing rate for a longer period during ischaemia, significantly reduces reperfusion-induced elevation of diastolic tension and prevents the reduction in recovery of developed tension after reperfusion.⁸⁸

In studies on isolated dog ventricular septapapillary muscle preparations subjected to occlusion and subsequent reperfusion of their coronary arteries, diltiazem selectively reverses the inotropic state of the ischaemic myocardium. In doses that increase coronary blood flow but which do not change developed tension and maximum rate of tension development in papillary muscle before occlusion, diltiazem attenuates tension development at between 40 and 120 seconds of ischaemia. On reperfusion in the absence of diltiazem, an overshoot in developed tension to 22 per cent above preocclusion levels is observed. This overshoot is significantly reduced by diltiazem.⁸⁹

When used as a cardioplegic agent during prolonged ischaemic cardiac arrest in hypothermic dogs diltiazem is superior to KCl.⁸⁵ Thus there is a more complete return to normal of the maximal LVP, maximal rate of rise of LVP, CI and systolic

work index with diltiazem than with KCl following discontinuation of aortic clamping and hypothermia.⁸⁵

We see, therefore, that although diltiazem has a negative inotropic action on normal muscle, in ischaemic muscle diltiazem prevents and reverses loss of contractility, abnormal increases in end diastolic pressures, and decreases in CO and CI. These improvements appear to be due to reduction of calcium influx into the myoplasm of the vascular smooth muscle of the coronary arteries and into the myoplasm of the myocardial cells.

Effect of diltiazem on cardiac rhythm during myocardial ischaemia

In anaesthetized dogs following an acute occlusion of the left circumflex artery the heart rate remains unchanged in the presence of diltiazem.⁷⁴ However, when the systemic hypotension induced by diltiazem is reversed the heart rate declines, illustrating the fact that the negative chronotropic action of the drug may be masked by a reflex increase in heart rate when systemic blood pressure falls significantly.⁷⁴ In intact ischaemic dog heart muscle, diltiazem attenuates ischaemia-induced conduction delay in both the ischaemic myocardium and at the border of the ischaemia.⁹⁰ Patterson *et al.*⁹¹ have recently reported that diltiazem does not prevent the development of electrically stimulated ventricular tachyarrhythmias or ventricular fibrillation in intact ischaemic dog hearts but the onset of fatal arrhythmias is delayed.⁹¹ Even in non-ischaemic dog hearts diltiazem has no significant influence on ventricular fibrillation thresholds.^{91,92}

Theroux has reported that in human patients stabilized after acute myocardial infarcts diltiazem decreases the heart rate.⁹³ Furthermore, in humans with SA node dysfunction or AV nodal block diltiazem provokes a bradycardia, sometimes to the point of asystole.^{46,94} Sugimoto *et al.*⁴⁶ have reported that this bradycardia is due to depression of conduction in the SA or the AV node. However, Valette *et al.*⁹⁴ claim that this bradycardia is not accompanied by significant changes in corrected sinus node recovery time or in atrio-sino-atrial conduction time or in changes in AH or HV conduction. These data suggest that diltiazem may be hazardous in those with SA node dysfunction.^{46,94}

Clinical effect of diltiazem on angina pectoris and myocardial infarcts

In humans suffering from variant or Prinzmetal's angina with ST segment elevation (i.e., unprovoked angina due to spasm of atherosclerotic arteries, accompanied by transient ST segment elevation and relieved by nitroglycerin) diltiazem (240 mg per day) reduces the frequency of angina, increases the number of pain-free days and lowers consumption of nitroglycerin.^{93,96-102} Diltiazem also suppresses the spontaneous rest angina which follows acute myocardial infarction.^{103,104}

Diltiazem prevents coronary artery spasm induced in humans by exercise, cold pressor tests, hyperventilation, Valsalva manoeuvre or by administration of catecholamines, propranolol, methacholine, pilocarpine, and alcohol.¹⁰⁵ In patients with typical variant angina graded doses of ergonovine (0.125 to 0.4 mg) reproducibly induce angina attacks and ST segment elevation.^{106,107} These abnormalities are usually, but not always, prevented by pretreatment with diltiazem.¹⁰⁶⁻¹⁰⁸ Diltiazem suppresses aspirin aggravated attacks of variant angina.¹⁰⁹

Diltiazem given intravenously to humans with stable angina improves left ventricular function in those with angina but reduces left ventricular function in those without angina.⁴⁴ Patients with angina have improved exercise performance on diltiazem.¹¹⁰⁻¹¹⁴ Thus during exercise the time between the first onset of angina and the first appearance of at least 1 mm of ST segment depression is lengthened.^{110,114} Left ventricular ejection fraction, as determined by radionuclide angiography and peak exercise ejection fractions are increased.¹¹⁴ Reduction in both MAP and heart rate with, therefore, a lowering of the pressure-rate product is postulated as the mechanism by which diltiazem enhances the duration of exercise tolerance in patients with angina.⁹³

Diltiazem, therefore, to relieve pain and improve exercise tolerance, is highly beneficial in the long-term therapy of angina pectoris.

Influence of diltiazem on vascular smooth muscle during hypertension

Diltiazem is significantly less effective in inhibiting contractions of mesenteric resistance vessels isolated from hypertensive rats, than contractions of vessels from control rats.¹¹⁵

In patients with essential hypertension diltiazem reduces systolic and diastolic pressures and SVR in most patients.^{36,116} Evaluation of the caliber of the brachial arteries by means of a pulsed Doppler velocimeter studies show that a bolus of diltiazem lowers blood pressure and total peripheral resistance significantly while CI and heart rate remain significantly elevated.^{37,117} After CI and heart rate have returned to normal the blood pressure and total peripheral resistance remain decreased for a further period, providing evidence that the effect on the peripheral blood vessels is a primary one.³⁷ The rise in the CI, CO, stroke index and SWI appear to be secondary to the afterload reduction produced by the reduction in SVR.^{36,37}

The effect of diltiazem on nonvascular smooth muscle

In nonvascular smooth muscle the negative inotropic action of diltiazem is qualitatively similar to that of heart muscle but with only about half the potency.¹⁵ When diltiazem is applied to skinned fibres isolated from guinea pig stomach muscle in a calcium free solution following treatment with calcium, the amplitude of the subsequently generated caffeine-induced contraction is not altered.¹¹⁸ This suggests, but by no means proves, that diltiazem is not acting on intracellular sites in non-vascular smooth muscle.

The influence of diltiazem on normal skeletal muscle

Sato¹¹⁹ has claimed that diltiazem, injected into canine femoral arteries, augments anterior tibial twitch tensions elicited by electrical stimulation of the common fibular nerve. He has observed that diltiazem has little influence on twitch tensions of the dog anterior tibial muscle elicited by direct electrical stimulation of the muscle.¹¹⁹ Sato has postulated that diltiazem increases release of transmitter from presynaptic motor nerve terminals by accelerating release of calcium ions from intracellular calcium stores thereby facilitating neuromuscular transmission.¹¹⁹

In amphibian skeletal muscle diltiazem appears to act by inducing release of calcium from intracellular stores.⁵⁹ In skinned fibres isolated from the iliofibularis muscle of the African clawed toad, diltiazem increases the calcium sensitivity of the contractile system, decreases the maximal tension

developed in a saturating concentration of calcium, inhibits calcium uptake by the SR, inhibits caffeine-induced calcium release from the SR and increases calcium permeability of the SR membrane.⁵⁹

These results suggest that unlike cardiac and smooth muscle, in skeletal muscle diltiazem may act as an agonist rather than an antagonist (except for its ability to inhibit caffeine-induced calcium release from the SR). Work is presently underway in our laboratory to test the validity of these rather surprising findings.

The use of diltiazem in skeletal muscle disorders

In dystrophic hamsters chronic diltiazem therapy reduces the excessively high calcium content of heart muscle and of the diaphragm.¹²⁰ In heart muscle of these dystrophic hamsters the high magnesium content is also lowered by long term diltiazem treatment.¹²⁰

During halothane-induced malignant hyperthermia reactions of pigs diltiazem softens skeletal muscle tone, slows the heart rate and reduces the frequency and severity of multifocal ventricular arrhythmias. If the halothane has been withdrawn before commencement of the diltiazem the hypotensive effect of the diltiazem is compatible with survival of the animal. However, if halothane inhalation is continued during the diltiazem medication then profound and lethal hypotension occurs and the pig dies.*

Much further investigation remains to be done to ascertain whether or not diltiazem will be of any practical benefit in the therapy of skeletal muscle disorders of humans.

Interactions between diltiazem and halothane

A paucity of information exists in the literature regarding the influence of diltiazem on cardiovascular function during anaesthesia. An exception (in the English literature) is a brief report by Zaggy *et al.*¹²¹ These investigators showed that during halothane and oxygen anaesthesia of pigs, diltiazem induced: a slowing of the heart rate, a prolongation of the PR interval, an increase in pulmonary capillary wedge pressure, a reduction in dP/dt and CO, no change in the SVR and a lowering of the MAP.

Complications

McGraw *et al.*¹²² reported that 1.8 per cent of 3,913 patients receiving diltiazem experienced undesirable effects. Others have made similar observations.^{87,106,123-127} Adverse effects most frequently reported include thirst and dryness of the mouth,^{106,122} anorexia,¹²² nausea,^{122,125} vomiting,¹²² constipation,^{122,125} mild gastric fullness,⁸⁷ diarrhoea,¹²² numbness of the tongue,¹²² hypotension,^{122,126,127} bradycardia,¹²² AV block,^{122,126,127} SA block,¹²² other arrhythmias,¹²² ankle oedema,¹²⁵ dizziness,^{87,122} vertigo,¹²² drowsiness, asthenia and fatigue,^{122,125} heaviness of the head and/or chest,¹²² facial flushing, rash and skin eruptions.¹²² However, side effects are less frequent during diltiazem therapy than during treatment with other calcium antagonists.¹²⁴ Sudden withdrawal of diltiazem may induce recurrence of signs and symptoms of myocardial ischaemia.¹²⁸ Until much larger numbers of patients have been treated with diltiazem, great care must be taken in monitoring patients for possible adverse effects.

Conclusions and summary

Diltiazem appears to inhibit calcium influx across the sarcolemma through the slow channels and may also reduce release of calcium from sequestered intracellular stores. It is, therefore, better described as a "calcium antagonist" rather than as a "slow channel blocker." Contrary to previous belief, diltiazem is not a beta adrenergic blocker.

In normal hearts diltiazem: increases venous return, right atrial pressure, stroke volume and cardiac output even though heart muscle contractility is reduced; prolongs the duration of the cardiac action potential and suppresses AV nodal conduction; and in the coronary and systemic blood vessels reduces basal tone and antagonizes the constrictor effect of agents such as epinephrine thereby lowering systemic vascular resistance and mean arterial pressure. In ischaemic hearts diltiazem: reduces CK and LDH release; during reperfusion prevents deleterious influx of calcium into the heart muscle; accelerates the rate of recovery of contractility; and slows the heart rate if hypotension is prevented or if SA or AV nodal dysfunction is present. However, diltiazem does not prevent the development of electrically stimulated ventricular tachyarrhythmias or ventricular fibrillation in either normal or ischaemic hearts. Clinically diltiazem decreases the fre-

*Britt, B.A. Unpublished data, University of Toronto.

quency and severity of variant and resting anginal attacks and prevents exercise induced-coronary artery spasm.

Diltiazem has a negative inotropic action on non-vascular smooth muscle.

The reported effects of diltiazem on skeletal muscle are conflicting and further work needs to be done to clarify the skeletal muscle actions of diltiazem. Nevertheless, it is known that in dystrophic hamsters diltiazem treatment does lower the excessively high calcium concentration of heart and skeletal muscle. During malignant hyperthermic (MH) reactions diltiazem relieves skeletal muscle rigidity and improves ventricular arrhythmias. However, if the diltiazem is given before the halothane is discontinued profound and usually lethal hypotension develops. In normal pigs anaesthetized with halothane diltiazem slows the heart rate, prolongs the PR interval, elevates the pulmonary capillary wedge pressure, lowers left ventricular pressure and cardiac output, does not change systemic vascular resistance but lowers mean arterial pressure.

In conclusion, diltiazem already shows promise of being a drug extremely useful in the management of angina pectoris and myocardial infarction. It may also have a role to play in the treatment of certain aspects of skeletal muscle disorders.

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