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Study on pyridazinone derivative MCI-154 as a cardiotonic agent

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Abstract

The effect of a cardiotonic agent, MCI-154, 6-[4-(4'-pyridylamino)phenyl]-4,5-dihydro-3(2H)-pyridazinone hydrochloride trihydrate, is a Ca2+ sensitizer on the contractile properties and adenosine triphosphatase ATPase activity on skeletal muscle fibers. As in cardiac muscle, MCI-154 potentiated isometric tension and improved isometric tension cost at full Ca^{2+} activation. However, MCI-154 decreased all the kinetic parameters. The MCI-154 improves not only cardiac systolic function but also diastolic relaxation in CHF. The possible mechanisms are $Ca2^{+}$ transient and cell shortening in ventricular myocytes and also L-type Ca^{2+} current and $Na+/Ca^{2+}$ exchange current. The MCI-154 exhibited hemodynamic, inotropic, mechano-energetic and oxidative metabolic effects.

Keywords: MCI-154; cardiotonic drugs; Ca^{2+} sensitizers sensitizers.

INTRODUCTION

Various pyridazinone compounds are possess various biological activities like antimicrobial, analgesic, anti-inflammatory, antiphlogistics, antipyretics, antifeedant, herbicidal, antisecretory, immunosuppressant, antiulcer, antidepressants, neuroleptics, anxiolytics, sedative-hypnotics, tranquillizers, anticonvulsants, GABA antagonists, anticancer and other anticipated pharmacological properties and also used as intermediates for drugs and agrochemicals. These interesting biological activities prompted us to study of pyridazinone compouns for their biological activities. They include cardiovascular activities such as blood platelet aggregation inhibitors, antithrombotics, antihypertensive, cardiotonics, vasodilatators, antiarrhythmics, cardioselective β-blockers, and hypocholesterolaemic agents [1-5]. Positive inotropic compounds for the treatment of heart failure should act without inducing deleterious arrhythmias such as ventricular tachycardia or ventricular fibrillation. Cardiac glycosides and β-adrenoceptor agonists have been known to increase intracellular Ca^{2+} concentrations they sometimes increase the myocardial oxygen demand and induce ventricular tachycardia and/or ventricular fibrillation in failing hearts. Positive inotropic agents with a new mechanism of cardiotonic action, these drugs increase the Ca^{2+} sensitivity of the cardiac contractile system [6,7]. Calcium (Ca^{2+}) sensitizers, a new class of cardiotonic agents, have been shown to exert positive inotropic effects without increasing intracellular Ca^{2+} transient. They circumvent Ca^{2+} overload that guides to arrhythmias, myocyte injury and do not increase the energy consumption for managing Ca^{2+}. Most of the Ca^{2+} sensitizers may impair cardiac diastolic function by increased Ca^{2+} sensitivity of the myofilaments. Therefore, Ca^{2+} sensitizers are useful for the treatment of CHF.

Calcium sensitizing agent: The Ca^{2+} sensitizers are used treat heart failure without increasing the risk of deleterious arrhythmias or sparing the energy for handling intracellular Ca^{2+}. The 6-[4-(4'-pyridylamino)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride trihydrate (MCI-154) is an orally active positive inotropic agent. MCI-154 exerted dose-dependent vasodilatory and weak positive chonotropic effects. MCI-154 increased the myofibrillar Ca^{2+} sensitivity and the maximal Ca^{2+}-activated force and also to improve the contractile function of depressed canine heart [8]. MCI-154 within the positive inotropic doses did not change the myocardial cyclic AMP levels and the membrane Ca^{2+} current of ventricular cells. If there are no changes in the cardiac depolarizing currents at positive inotropic doses of MCI-154, this drug should not alter the electrical behavior of the heart and hence should not aggravate ventricular arrhythmias. Since deleterious arrhythmias are often present in patients with CHF, it is of great importance to evaluate the proarrhythmic properties of MCI-154. The effects of

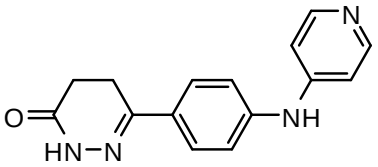
MCI-154 on various types of canine ventricular arrhythmias produce by coronary ligation, digitalis intoxication and halothane-adrenaline interactions. The effects of MCI-154 on membrane ionic currents, especially increased Ca^{2+} currents induced by the β-adrenoceptor agonist, isoprenaline. These agents share an inhibitory effect on the activity of cardiac phosphodiesterase III (PDE-III) besides increasing Ca^{2+} sensitivity of the contractile machinery. For the treatment of heart failure, these Ca^{2+} sensitizers have advantages over conventional cardiotonic agents, like Ca^{2+} channel agonists, since they are capable of improving contractile performance without inducing cellular Ca^{2+} overloading, which could result in arrhythmias and myocardiac injury [9].

Some of these Ca^{2+} sensitizers increase active tension only at submaximal Ca^{2+}levels, but others are also known to increase active tension at a saturating level of Ca^{2+}, suggesting that the latter have a direct action on actomyosin. These potential applications of these Ca^{2+}sensitizers in research for elucidation of the mechanism of actomyosin interaction and its regulation by Ca^{2+}, both in cardiac and in skeletal muscle preparations. The MCI-154 enhances Ca^{2+} binding to troponin C complexed with troponin I and troponin T [10]. However, this effect alone would not explain the potentiating effect at saturating Ca^{2+} levels. It is also unclear whether MCI-154 exerts its potentiating effect only on cardiac muscles, or also on other types of muscles. The MCI-154 is also effective in skeletal muscle fibers. MCI-154 increased the isometric tension of skinned muscle fibers. Contrary to its effect on cardiac muscles, MCI-154 reduced the ATPase rate during isometric contraction at a saturating Ca^{2+} level. In skeletal muscle, MCI-154 increases the number of force- producing actomyosin complexes by inhibiting a reaction step which follows the force-generation event [11-15].

Pyridazinone derivative MCI-154 act as cardiotonic

Positive inotropics are used for the treatment of heart failure should act without inducing deleterious arrhythmias such as ventricular tachycardia or ventricular fibrillation. Cardiac glycosides and/3-adrenoceptor agonists have been known to increase $[Ca^{2+}]i$ concentrations, hence they sometimes increase the myocardial oxygen demand and induce ventricular tachycardia and/or ventricular fibrillation in failing hearts. Positive inotropic agents with a new mechanism of cardiotonic action have been developed. One type of these new drugs increases the Ca^{2+} sensitivity of the cardiac contractile system [7]. These Ca^{2+} sensitizers are expected to treat heart failure without increasing the risk of deleterious arrhythmias or sparing the energy for handling $[Ca^{2+}]i$. MCI-154 in the dose range vasodilatory and weak positive chonotropic effects. MCI-154 has been reported to increase the myofibrillar Ca^{2+}sensitivity and the maximal Ca^{2+} activated force also to improve the contractile function of depressed canine hearts [9]. MCI-154 within the positive inotropic doses did not change the myocardial cAMP levels and the membrane Ca^{2+} current of ventricular cells. If there are no changes in the cardiac depolarizing currents at positive inotropic doses of MCI-154, this drug should not alter the electrical behavior of the heart and hence should not aggravate ventricular arrhythmias. Since deleterious arrhythmias are often present in patients with CHF, it is of great importance to evaluate the proarrhythmic properties of MCI-154. The effects of MCI-154 on various types of spontaneously occurring canine ventricular arrhythmias produced by coronary ligation, digitalis intoxication and halothane-adrenaline interactions, the new inotropic agents with a PDE-III inhibitory action such as amrinone, milrinone, vesnarinone has arrhythmogenic effects [16,17]. The effects of MCI-154 on membrane ionic currents increased Ca^{2+}currents induced by the β-adrenoceptor agonist, isoprenaline, in single ventricular cells of the guinea-pig.

The pyridazinone derivative MCI-154, is a Ca^{2+} sensitizer that has more potent positive inotropic effect than pimobendan, adibendan and sulmazole and exhibited hemodynamic, inotropic, mechano-energetic and oxidative metabolic effects. MCI-154 has been improved not only cardiac systolic function but also diastolic relaxation in CHF. The MCI-154 showed extremely potent inotropic as well as vasodilating activity. However, the mechanisms of inotropic effects of MCI-154 are poorly understood [18]. MCI-154 induced a progressive dose-dependent decrease in systemic vascular resistance (SVR), with a concomitant increase in heart rate and cardiac output. The MCI-154 has minimal inotropic action, induces a significant "oxygen waste", and decreases SVR [19]. In cardiac muscle, MCI-154 potentiated isometric tension and improved isometric tension at full Ca^{2+} activation and showed little Ca^{2+}-sensitizing effect. In contrast to its effect on cardiac muscle, MCI-154 decreased all the kinetic parameters such as shortening velocity, the rate of rise of tension, and actomyosin ATPase activity. MCI-154 acts directly on skeletal actomyosin and inhibits a reaction step of the ATPase cycle later than the force generating event [6].



MCI-154

MCI-154 has no impairment to cardiomyocyte relaxation. The effects of MCI-154 on Ca^{2+} transient and cell contraction and its influence on L-type Ca^{2+} current and Na^{+}/Ca^{2+} exchange current in rat ventricular myocytes. The MCI-154 (1~100 μmol/L) had no effect on L-type Ca^{2+} current; MCI-154 concentration-dependently increased cell shortening, with a slight increase in Ca^{2+} transient amplitude and Ca^{2+} transient restore kinetics. MCI-154 dose dependently increased the electrogenic Na^{+}/Ca^{2+} exchange current both in the inward and the outward directions in ventricular myocytes. The MCI-154 exerted inotropic action without impairing myocyte relaxation. The stimulation of inward Na^{+}/Ca^{2+} exchange current may accelerate the Ca^{2+} efflux. The improvement by MCI-154 of myocyte relaxation is attributed to the forward mode of Na^{+}/Ca^{2+} exchange [20].

The MCI-154 increased heart rate and left ventricular function with no change in rate pressure product and coronary blood flow, with a decrease in cardio vascular resistace (CVR). MCI-154 reversed the decrease in cardiac output and preload recruitable stroke work caused by isoflurane. The MCI-154 increases myocardial contractility and decreases CVR without changing myocardial oxygen consumption. MCI-154 restores the myocardial contractility depressed by isoflurane and enhances the coronary vasodilating effect of isoflurane [21]. MCI-154 had deleterious effects on ventricular arrhythmias, since several PDE-III inhibitors have been shown to aggravate arrhythmias. Continuous infusion of MCI-154 (1 μg/kg/min for 15 min) did not suppress or aggravate the arrhythmias. A bolus injection of 30μg/kg, MCI-154 did not aggravate the adrenaline-induced arrhythmias. The results showed that MCI-154 (10-100 μM) did not increase the inward Ca^{2+} current under the condition where these currents were increased by isoprenaline. The MCI-154 does not aggravate ventricular arrhythmias and does not act on membrane currents associated with arrhythmogenesis. The MCI-154 is a useful positive inotropic agent with little arrhythmogenic effect [22]. The Ca^{2+}-sensitizing action of MCI-154 on

the contractile proteins. MCI-154 enhanced the tension development induced by Ca^{2+} concentration in chemically skinned fiber from right ventricular muscle in a concentration-dependent manner. MCI-154 markedly increased ATPase activities of myofibrils and reconstituted actomyosin. In myofibrils and actomyosin, MCI-154 caused a shift of the Ca-ATPase activity relation curve to the without affecting the maximum activity, an increase in Ca^{2+} sensitivity. MCI-154 had little effect on actin-activated, Mg^{2+}, Ca^{2+} and (K^{+}, EDTA)-ATPase activities of myosin. Ca^{2+} binding to cardiac myofibrils or cardiac troponin were increased by MCI-154. The MCI-154 enhances Ca^{2+} binding to cardiac troponin C to elevate the Ca^{2+} sensitivity of myofilaments and caused a positive inotropic action in cardiac muscle.

MCI-154 enhances Ca^{2+} binding to troponin C complexed with troponin I and troponin T [10]. However, this effect alone would not explain the potentiating effect at saturating Ca^{2+} levels. It is also unclear whether MCI-154 exerts its potentiating effect only on cardiac muscles, or also on other types of muscles. Here we report that MCI-154 is also effective in skeletal muscle fibers. MCI-154 increased the isometric tension of skinned muscle fibers from rabbit psoas in a dose-dependent manner. Contrary to its effect on cardiac muscles, MCI-154 reduced the ATPase rate during isometric contraction at a saturating Ca^{2+} level. In skeletal muscle, MCI-154 increases the number of forceproducing actomyosin complexes by inhibiting a reaction step which follows the force-generation event. MCI-154 potentiates isometric tension but reduces the kinetic parameters of contractile events in skeletal muscle preparations [23]. It is also known that P reduces the sensitivity of the contractile machinery to Ca^{2+} [24]. MCI-154 reverses these inhibitory effects of P [25] in skinned cardiac muscle. MCI-154 was also effective to reverse the inhibitory effects of P in skeletal muscle fiber preparations [26].

The MCI-154-induced potentiation of tension and reduction of shortening velocity were similar to those in-duced by the application of ADP. Although a sufficient amount of creatine phosphokinase had been added to the solutions to keep the ADP level low [11], ADP could still accumulate in the interior of the fibers if the activity of creatine phosphokinase was suppressed by MCI-154. The MCI-154 has little effect on the activity of the creatine phosphokinase. The effects of MCI-154 on the contractile properties were not caused by the accumulation of ADP within the fibers. Since MCI-154 is known to increase the ATPase activity of cardiac muscle preparation at a saturating Ca^{2+} level, it was of interest to test whether MCI-154 also increases the ATPase activity of skeletal muscle preparations. MCI-154 has been shown to reduce the kinetic parameters of contraction measurement in the presence of MCI-154. Both in the presence and absence of MCI-154, the amount of creatine liberated increased linearly with time. The inhibitory effect of MCI-154 on ATPase activity is contrary to reports on cardiac muscle preparations [27].

MCI-154 increases the isometric tension of skinned skeletal muscle fibers at a saturating Ca^{2+} level. MCI-154, 600 mM, enhance the Ca^{2+} sensitivity of the skeletal muscle fibers to a far lesser extent than that for skinned cardiac preparations. The effect of MCI-154 on skeletal muscle fibers is that the tension enhancement at a saturating Ca^{2+} level is accompanied by an overall decrease of kinetic parameters, i.e, decreased velocity, decreased rate of rise of tension and decreased actomyosin Mg ATPase activity. This inhibitory effect of MCI-154, along with its very small Ca^{2+}-sensitizing effect, is not to be expected if MCI-154 increases the affinity of skeletal troponin-C for Ca^{2+}. Instead, all these effects are explainable if MCI-154 has a direct action on actomyosin. The concomitant increase of isometric tension and decrease of ATPase rate are readily explained if MCI-154 decreases the rate constant for a reaction step which limits the rate of dissociation of force-producing myosin heads from actin [28]. The effects of decreasing the rate constant for ADP release. The fraction of associated myosin heads hence tension and stiffness [29]. The influence of MCI-154 is mainly on the dissociation of the force-producing myosin heads of skeletal muscle [30]. These effects of MCI-154 on skeletal muscle fibers are reminiscent of those of ADP. ADP is believed to compete with ATP for the nucleotide binding site on myosin [31]. Since myosin heads with bound ADP have high affinity for actin, addition of ADP is expected to, and actually does, decrease the rate of dissociation of myosin heads from actin [32]. The MCI-154 raises the ADP concentration inside the fiber by inhibiting creatine phosphokinase activity. Therefore, MCI-154 acts as a non-metabolite inhibitor of actomyosin ATPase with effects equivalent to those of ADP. The possibility that MCI-154 binds to nucleotide binding sites in a competitive manner cannot be excluded.

The effect of MCI-154 on skeletal muscle is inhibition in terms of enzymology, but another expression would be that it can improve the tension cost, i.e, the energy consumed to support a given amount of tension [33,34]. MCI-154 is also known to increase Ca^{2+} binding to cardiac troponin C [35]. It is known that an increased level of activation results in an increased rate of rise of tension, probably because of the increased rate constant for the transition from weak binding, rapidly dissociating actomyosin complex to low force, slowly dissociating complex [10, 14]. The effects of MCI-154 on skinned skeletal muscle fibers, potentiates isometric tension at saturating Ca^{2+} levels [29]. The skeletal muscle seems to be less sensitive to these Ca^{2+} sensitizers, probably because only one of the potentiating mechanisms (direct action on actomyosin) is working. It is likely that this difference between skeletal and cardiac muscle preparations reflects the difference in the properties of troponin isoforms [34].

The lack of proarrhythmic effects of MCI-154 on the halothane-adrenaline arrhythmia models. MCI-154 did not suppress or aggravate the arrhythmias when a continuous infusion was applied [8,9]. The MCI-154 does not aggravate ventricular arrhythmias at positive inotropic doses. The PDE-III inhibitors, such as amrinone, milrinone, vesnarinone and OPC-18790, all aggravated the adrenaline-induced ventricular tachyarrhythmias, and only about one tenth of the positive inotropic doses of these drugs could be administered without severely aggravating this arrhythmia [36]. The MCI-154 did not aggravate adrenaline-induced arrhythmias, unlike other positive inotropic agents, strongly indicates that MCI-154 exerts its positive inotropic effect through a pure Ca^{2+}sensitizing property, not by inhibiting PDE-III. The MCI-154 has an inhibitory effect on PDE-III obtained from guinea-pig left ventricular tissues. However, this previous study also clearly suggests that MCI-154 induces a positive inotropic effect though the cAMP-independent mechanism, because the inhibitory effect of MCI-154 on PDE-III is about 1.5-fold less potent than that of milrinone, while the inotropic effect of MCI-154 is about 800-fold more potent than that of milrinone [37]. Moreover, myocardial cyclic AMP levels did not increase when MCI-154 augmented myocardial contractility. The Ca^{2+}sensitizing action of MCI-154 has been extensively demonstrated in skinned cardiac fibers and purified contractile proteins, i.e, troponin C, troponin I and troponin T.

In contrast, another Ca^{2+}sensitizer pimobendan which also has a potent PDE-III inhibitory activity [38,39]. The pimobendan aggravated the non-sustained ventricular tachycardia to sustained ventricular tachycardia or ventricular fibrillation, as does milrinone. The Ca^{2+}sensitizer, sulmazole, at an inotropic dose aggravated the adrenaline-induced arrhythmia. The MCI-154 is not deleterious to halothane-adrenaline-induced arrhythmia, unlike other inotropic drugs of PDE-III inhibitors or Ca^{2+}sensitizers. Milrinone and OPC-18790 also tended to aggravate

48-h coronary ligation arrhythmias. All these agents have high PDE-III inhibitory activity [40,41] and increased the total heart rate and atrial rate. However, a forskolin derivative NKH477, which also increases intracellular cyclic AMP, had no arrhythmogenic effects on 48-h coronary ligation-induced arrhythmias despite there being an acute increase in the total heart rate [42,43]. Therefore MCI-154, which did not increase the total heart rate and atrial rate, can be used safely even with acute myocardial ischemia and infarction. There have been no reports that explain this antiarrhythmic mechanism of MCI-154, such as the Na^+ channel-blocking effect, MCI-154 can be used in combination with digitalis without increasing the risk of arrhythmia.

Amrinone, sulmazole have strong positive chonotropic effects and have antiarrhythmic effects on digitalis arrhythmia by an overdrive suppression mechanism [44,45].

MCI-154 on digitalis arrhythmia is difficult to explain on the basis of our previous results that coronary ligation-induced and digitalis-induced arrhythmias are suppressed by class I Na^+ channel blockers. Since malignant arrhythmias, which may result in sudden death, often occur in the failing heart, it is important that treatment for heart failure should not aggravate the preexisting arrhythmias. MCI-154 does not aggravate ventricular arrhythmias in three canine experimental models. Thus, the practical importance of our results is that MCI-154 can be used as a positive inotropic drug concomitant with catecholamine and/or digitalis, or in patients with myocardial infarction without increasing the risk of arrhythmias and the oxygen demand compared to other recently developed positive inotropic agents. The proarrhythmic effects of other inotropic agents, such as amrinone, milrinone, sulmazole, vesnarinone and OPC-18790, using the halothane-adrenaline-induced ventricular tachyarrhythmia model and bolus injection of the drugs, a bolus injection of MCI-154 (30 µg/kg) was also examined. The 30 µg/kg was a supramaximal dose for the treatment of heart failure [17,42].

With both skeletal and cardiac muscles, addition of inorganic phosphate P to the bathing solution reduces the isometric tension, by reversing the phosphate-release step which is closely associated with force-producing events. It is also known that P reduces the sensitivity of the contractile machinery to Ca^{2+}, MCI-154 reverses these inhibitory effects [46,47]. MCI-154 has little effect on the activity of the creatine phosphokinase. Therefore, it is concluded that the observed effects of MCI-154 on the contractile properties were not caused by the accumulation of ADP within the fibers. Since MCI-154 is known to increase the ATPase activity of cardiac muscle preparation at a saturating Ca^{2+} level, it was of interest to test whether MCI-154 also increases the ATPase activity of skeletal muscle preparations. The creatine quantitation is a valid method for ATPase activity measurement in the presence of MCI-154. This inhibitory effect of MCI-154 on ATPase activity is contrary to reports on cardiac muscle preparations [48,49].

DISCUSSION

The striking feature of the effect of MCI-154 on skeletal muscle fibers is that the tension enhancement at a saturating Ca^{2+} level is accompanied by an overall decrease of kinetic parameters, i.e, decreased velocity, decreased rate of rise of tension after shortening *k* and decreased actomyosin Mg ATPase activity. This inhibitory effect of MCI-154, along with its very small Ca^{2+}-sensitizing effect, is not to be expected if MCI-154 increases the affinity of skeletal troponin-C for Ca^{2+} Instead, all these effects are explainable if MCI-154 has a direct action on actomyosin. The concomitant increase of isometric tension and decrease of ATPase rate are readily explained if MCI-154 decreases the rate constant for a reaction step which limits the rate of dissociation of force-producing myosin heads from actin [12-15]. Thus, increased population of the force-producing myosin heads in the presence of MCI-154 is expected. MCI-154 does not interact with troponin directly. It is believed that the step of force generation is associated with the release of P from myosin [8,9]. In the presence of 20 mM P, parameters of the contractile perfor-mance of the skeletal muscle fibers were affected by MCI-154 to an extent comparable to that in the absence of MCI-154. The influence of MCI-154 is mainly on the dissociation of the force-producing myosin heads of skeletal muscle. The MCI-154 is known to reverse the inhibitory effect of P, their potentiating effect is much greater in the presence of P than in its absence. These effects of MCI-154 on skeletal muscle fibers are reminiscent of those of ADP. ADP is believed to compete with ATP for the nucleotide binding site on myosin. Since myosin heads with bound ADP have high affinity for actin, addition of ADP is expected to, and actually does, decrease the rate of dissociation of myosin heads from actin. Therefore, MCI-154 acts as a non-metabolite inhibitor of actomyosin ATPase with effects equivalent to those of ADP. At present, however, the possibility that MCI-154 binds to nucleotide binding sites in a competitive manner cannot be excluded. The effect of MCI-154 on skeletal muscle is inhibition in terms of enzymology, but another expression would be that it can improve the tension cost, i.e, the energy consumed to support a given amount of tension. At concentrations effective for cardiac muscles; 100 mM, MCI-154 has little effect on skeletal muscle fibers. High concentrations of MCI-154 into skeletal muscle fibers, it may prove beneficial for improving the energetic performance of posture muscles. The effect of MCI-154 is also known to increase Ca^{2+} binding to cardiac troponin C. Increased level of activation results in an increased rate of rise of tension [15-18]. The effects of MCI-154 on skinned skeletal muscle fibers are similar, and distinct from their effects on cardiac muscle preparations, potentiates isometric tension at saturating Ca^{2+} levels. However, even negative MCI-154, this work effects on kinetic parameters including ATPase activity. As a result, tension cost is improved just as in cardiac muscle preparations. Slight or negative kinetic effects imply that, in skeletal muscle, isometric tension is not potentiated through further activation of the thin filament. Absence of the reversal of the inhibitory effect of P in the case of MCI-154 may also support this assumption, since P is known to reduce the sensitivity of the contractile machinery to Ca^{2+}. The two mechanisms of action of MCI-154, the one through troponin seems to be less functional in skeletal muscle preparations. The skeletal muscle seems to be less sensitive to these Ca^{2+} sensitizers, probably because only one of the potentiating mechanisms direct action on actomyosin is working. It is likely that this difference between skeletal and cardiac muscle preparations reflects the difference in the properties of troponin isoforms [41-45].

CONCLUSION

The MCI-154 increases isometric tension of skeletal muscle fibers at a saturating Ca^{2+} concentration, and suggested that this is due to its direct action on the kinetics of the actomyosin ATPase reaction. This property emphasizes the usefulness of MCI-154 as a tool for studying the mechanism of actomyosin interaction, since it acts as a non-metabolite inhibitor to increase the proportion of the force-producing actomyosin intermediates. There is a tendency to focus the action of Ca^{2+} sensitizers on the thin filament regulatory system, but the present results make it essential to focus on their direct action on actomyosin as well, to fully account for their potentiating effects. A positive inotropic agent with Ca^{2+}-sensitizing activity, MCI-154, had deleterious effects on ventricular arrhythmias, since several PDE-III inhibitors have been shown to aggravate arrhythmias. MCI-154 did not aggravate the adrenaline-induced arrhythmias. MCI-154 did not increase the inward

Ca^{2+} current under the condition where these currents were increased by isoprenaline. The MCI-154 does not aggravate ventricular arrhythmias and does not act on membrane currents associated with arrhythmogenesis. Thus, MCI-154 may become a useful positive inotropic agent with little arrhythmogenic effect.

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