# DOWNLOAD PDF CALCIUM ENTRY BLOCKERS IN CARDIOVASCULAR AND CEREBRAL DYSFUNCTIONS

## Chapter 1 : Treatment of cardiovascular and cerebral toxicity using calcium modulators - Miles, Inc.

*Calcium Entry Blockers in Cardiovascular and Cerebral Dysfunctions Calcium entry blockers and cerebral function Calcium Entry Blockers in Cardiovascular and.*

For example, calcium modulators can be used as an antidote to the lethal and chronic toxicity of cocaine and related indirectly acting sympathomimetic amines, imipramine and other tricyclic antidepressants, ganglionic stimulating drugs, and other toxic substances such as organophosphorus compounds that cause accumulations of neurotransmitters. Calcium modulators can also be used as an antidote to substances whose toxicity is based upon anticholinesterase activity. In addition, calcium modulators can be used as antagonists to the various types of toxic substances. Calcium modulators are compounds that effect the transport of calcium through cellular membranes. Because of the several mechanisms for calcium transport, and the potential for multiple regulatory sites associated with some of these mechanisms, compounds of diverse structure have been found to be effective as calcium modulators. For example, reported calcium modulators include diphenylpiperazines such as verapamil and its derivatives, lidoflazine, cinnarizine and flunarizine; benzothiazepines such as diltiazem; dihydropyridines such as nifedipine, nitrendipine, nimodipine, nicardipine and BaK; and other structures such as bepridil, prenylamine and perhexiline. As can be seen from the structures of the known calcium modulators shown in FIG. It has been established, however, that compounds that inhibit in vitro constriction of arteries induced by neurotransmitters such as norepinephrine, noradrenaline, and acetylcholine will generally act as calcium modulators in vivo. For example, calcium modulators can be used as an antidote to the lethal toxicity of cocaine and related indirectly acting sympathomimetic amines such as amphetamine and tyramine; as an antidote to tricyclic antidepressants such as imipramine, and ganglionic stimulating drugs such as nicotine; and as an antidote to other toxic substances such as organophosphorus compounds that cause accumulations of neurotransmitters and disrupted neurotransmitter activity. Calcium modulators can also be used as an antidote to substances whose toxicity is related to anticholinesterase activity. In addition, calcium modulators can be used as antagonists to the various types of toxic substances described above. In particular, the toxic effects of substances such as cocaine, imipramine, anticholinesterases, nicotine and organophosphorus compounds whose toxic effect is, at least in part, the result of an accumulation of neurotransmitters can be alleviated by administration of calcium modulators. Suitable calcium modulators for use in the invention are generally those that will inhibit in vitro arterial constriction. Particularly suitable are those compounds, shown in FIG. The preferred compound for use in the treatment of cocaine intoxication according to the invention is nitrendipine. Effective treatment in accordance with the invention requires prompt administration of the calcium modulator following exposure to the toxic material, preferably by intravenous administration. Alternatively, the calcium modulator can be used in accordance with the invention in anticipation of exposure to a toxic substance, such that it acts as an antagonist to the toxic effects. As an antagonist oral administration of calcium modulators is also possible. Calcium modulators may also be combined with other known substances that function as antidotes to provide more effective treatment. In particular, where a toxic substance is known to have more than one mode of toxic effect, e. Furthermore, calcium modulators may help restore normal neurotransmitter activity in the brain of patients recovering from chronic intoxication with cocaine and other dependence producing drugs. Thus the claimed treatment method may be effective in easing the early phase of drug rehabilitation therapy and withdrawal from drug dependence. The utilization of calcium modulators in accordance with the invention is further illustrated by way of the following examples. These results are provided for illustration only, however, and do not limit the scope of the invention. Two calcium modulators, flunarizine and nimodipine were tested for their ability to act as antidotes to lethal imipramine intoxication. The survival time of the five control rats was  Five test rats were given flunarizine at a rate of 0. After the blood pressure of the rats had fallen to 50 mmHg, four control rats were treated with successive bolus of 0. The total dose of flunarizine was 2. The remaining five rats were

similarly treated with nimodipine, the total dosage of nimodipine being 0. The four control rats survived for All four of the rats treated with flunarizine, and four of the five rats treated with nimodipine survived, and were awake and active 24 hours later. Thus, both calcium modulators tested appeared to be effective in the treatment of acute imipramine poisoning. The calcium modulator nitrendipine was tested for its effectiveness as an antidote to lethal doses of cocaine. Five other rats were given the same amount of cocaine followed by nitrendipine 4 to 5 minutes after the cocaine. Nitrendipine was given intra-arterially first in a loading dose of 7. The infusion was stopped when the rat was active and restless. The survival time of the five control rats was 8 min. Death could be attributed to convulsions and respiratory arrest. All five of the nitrendipine treated animals survived and 24 hours later were active and feeding themselves. The recorder permitted monitoring of cardiac arrythmia. These animals exhibited frequent and sustained arrythmias. In addition, marked agitation, tremors and convulsions were observed, followed by death. The heart rate throughout the infusion was stable, and no tremors or convulsions were observed. The cause of death in these five rats was apparently not cocaine intoxication, but rather was probably attributable to excess fluids due to the large infusion volume. Tissue sections prepared from the hearts of the two sets of animals were also markedly different. The animals treated with cocaine alone exhibited disseminated areas of sarcolema disruption with liberation of disorganized myocardial fibers which present an appearance of waviness. Such alterations, which are symptomatic of the necrotic process leading to permanent infarcted lesions, were not observed in the animals treated with both cocaine and nitrendipine. Thus, nirendipine was effective not only to decrease the lethan toxicity of cocaine, but prevented the cardiac morphological lesions irreversibly produced by cocaine. Claims 12 We claim: A method for treating cardiovascular toxicity induced by a tricyclic antidepressant that induces a toxic effect by altering the normal interaction of neurotransmitters with the calcium ion metabolism of myocardial cells, comprising administering to a host intoxicated with the toxic material a compound which inhibits constriction of arteries in vitro in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 1, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. A method for treating cerebral toxicity induced by a tricyclic antidepressant that induces a toxic effect by altering the normal interaction of neurotransmitters with the calcium ion metabolism of cerebral cells, comprising administering to a host intoxicated with the toxic material a compound which inhibits constriction of arteries in vitro in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 3, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. A method according to claim 1, wherein the host is intoxicated with a lethal dose of the toxic material. A method according to claim 3, wherein the host is intoxicated with a lethal dose of the toxic material. A method according to claim 1, wherein the compound administered is nimodipine or flunarizine. A method for treating cardiovascular toxicity induced by imipramine comprising administering to a host intoxicated with imipramine a compound which inhibits constriction of arteries in vivo in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 9, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. A method for treating cerebral toxicity induced by imipramine comprising administering to a host intoxicated with imipramine a compound which inhibits constriction of arteries in vivo in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 11, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine.

## Chapter 2 : Calcium Entry Blockers in Cardiovascular and Cerebral Dysfunctions (eBook, ) [racedaydvl.com

*Calcium Entry Blockers in Cardiovascular and Cerebral Dysfunctions Calcium entry blockers in cardiovascular therapy. Blockers in Cardiovascular and Cerebral.*

Ethanol[ edit ] Ethanol blocks voltage-gated calcium channel Research indicates ethanol is involved in the inhibition of L-type calcium channels. One study showed the nature of ethanol binding to L-type calcium channels is according to first-order kinetics with a Hill coefficient around 1. This indicates ethanol binds independently to the channel, expressing noncooperative binding. Studies conducted by Treistman et al. Voltage clamp recordings have been done on the aplysia neuron. VGCCs were isolated and calcium current was recorded using patch clamp technique having ethanol as a treatment. Results showed calcium current decreased as concentration of ethanol increased. Neurons were exposed to sustained ethanol concentrations of 50 mM for 3 days in vitro. Western blot and protein analysis were conducted to determine the relative amounts of VGCC subunit expression. Thus, sustained ethanol exposure may participate in the development of ethanol dependence in neurons. Perforated patch clamp technique was used having intracellular fluid inside the pipette and extracellular fluid in the bath with added 0. Ethanol inhibits VGCCs and is involved in alcohol-induced relaxation of the urinary bladder. Nondihydropyridine CCBs may produce profound toxicity and early decontamination, especially for slow-release agents, is essential. For severe overdoses, treatment usually includes close monitoring of vital signs and the addition of vasopressive agents and intravenous fluids for blood pressure support. Intravenous calcium gluconate or calcium chloride if a central line is available and atropine are first-line therapies. If the time of the overdose is known and presentation is within two hours of ingestion, activated charcoal, gastric lavage, and polyethylene glycol may be used to decontaminate the gut. Efforts for gut decontamination may be extended to within 8 hours of ingestion with extended-release preparations. Hyperinsulinemia-euglycemia therapy has emerged as a viable form of treatment. Although the mechanism is unclear, increased insulin may mobilize glucose from peripheral tissues to serve as an alternative fuel source for the heart the heart mainly relies on oxidation of fatty acids. Theoretical treatment with lipid emulsion therapy has been considered in severe cases, but is not yet standard of care. Caution should be taken when using verapamil with a beta blocker due to the risk of severe bradycardia. If unsuccessful, ventricular pacing should be used. Embedded in the membrane of some cells are calcium channels. When these cells receive a certain signal, the channels open, letting calcium rush into the cell. The resulting increase in intracellular calcium has different effects in different types of cells. Calcium channel blockers prevent or reduce the opening of these channels and thereby reduce these effects. Several types of calcium channels occur, with a number of classes of blockers, but almost all of them preferentially or exclusively block the L-type voltage-gated calcium channel. CCBs used as medications primarily have four effects: By acting on vascular smooth muscle , they reduce contraction of the arteries and cause an increase in arterial diameter, a phenomenon called vasodilation CCBs do not work on venous smooth muscle. By acting on cardiac muscles myocardium , they reduce the force of contraction of the heart. By slowing down the conduction of electrical activity within the heart, they slow down the heart beat. By blocking the calcium signal on adrenal cortex cells, they directly reduce aldosterone production, which correlates to lower blood pressure. Since blood pressure is in intimate feedback with cardiac output and peripheral resistance, with relatively low blood pressure, the afterload on the heart decreases; this decreases how hard the heart must work to eject blood into the aorta, so the amount of oxygen required by the heart decreases accordingly. This can help ameliorate symptoms of ischaemic heart disease such as angina pectoris. Immunohistochemical analysis of L-type calcium channel Cav1. Marked immunoreactivity was detected in the zona glomerulosa. Immunohistochemistry was performed according to published methods. Slowing down the conduction of electrical activity within the heart, by blocking the calcium channel during the plateau phase of the action potential of the heart see: This can increase the potential for heart block. The negative chronotropic effects of

CCBs make them a commonly used class of agents in individuals with atrial fibrillation or flutter in whom control of the heart rate is generally a goal. Negative chronotropy can be beneficial when treating a variety of disease processes because lower heart rates represent lower cardiac oxygen requirements. Elevated heart rate can result in significantly higher "cardiac work", which can result in symptoms of angina. The class of CCBs known as dihydropyridines mainly affect arterial vascular smooth muscle and lower blood pressure by causing vasodilation. The phenylalkylamine class of CCBs mainly affect the cells of the heart and have negative inotropic and negative chronotropic effects. The benzothiazepine class of CCBs combine effects of the other two classes. Because of the negative inotropic effects, the nondihydropyridine calcium channel blockers should be avoided or used with caution in individuals with cardiomyopathy. Since moment-to-moment blood pressure regulation is carried out by the sympathetic nervous system via the baroreceptor reflex , calcium channel blockers allow blood pressure to be maintained more effectively than do beta blockers. However, because dihydropyridine CCBs result in a decrease in blood pressure, the baroreceptor reflex often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility. Ionic calcium is antagonized by magnesium ions in the nervous system. Because of this, bioavailable supplements of magnesium, possibly including magnesium chloride , magnesium lactate , and magnesium aspartate , may increase or enhance the effects of calcium channel blockade. Ziconotide is a selective blocker of these calcium channels and acts as an analgesic. History[ edit ] Calcium channel blockers were first identified in the lab of German pharmacologist Albrecht Fleckenstein beginning in  He named this herbal drug "Zarnab" and used it as a cardiac remedy. This was the first known use of a calcium channel blocker drug, which were not in wide use in the Western world until the s.

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## Chapter 3 : Calcium channel blocker - Wikipedia

*Get this from a library! Calcium Entry Blockers in Cardiovascular and Cerebral Dysfunctions. [T Godfraind; Arnold G Herman; Donald Wellens] -- 2 The free internal Ca+ concentration in human red cells is set according to the leak 2 and-pump principle: There is a finite passive Ca+ influx at the physiological 2 2 Ca+ -gradient across the.*

A method for treating cardiovascular toxicity induced by a tricyclic antidepressant that induces a toxic effect by altering the normal interaction of neurotransmitters with the calcium ion metabolism of myocardial cells, comprising administering to a host intoxicated with the toxic material a compound which inhibits constriction of arteries in vitro in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 1, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. A method for treating cerebral toxicity induced by a tricyclic antidepressant that induces a toxic effect by altering the normal interaction of neurotransmitters with the calcium ion metabolism of cerebral cells, comprising administering to a host intoxicated with the toxic material a compound which inhibits constriction of arteries in vitro in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 3, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. A method according to claim 1, wherein the host is intoxicated with a lethal dose of the toxic material. A method according to claim 3, wherein the host is intoxicated with a lethal dose of the toxic material. A method according to claim 1, wherein the compound administered is nimodipine or flunarizine. A method for treating cardiovascular toxicity induced by imipramine comprising administering to a host intoxicated with imipramine a compound which inhibits constriction of arteries in vivo in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 9, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. A method for treating cerebral toxicity induced by imipramine comprising administering to a host intoxicated with imipramine a compound which inhibits constriction of arteries in vivo in the presence of a neurotransmitter in an amount effective to treat the toxicity. A method according to claim 11, wherein the compound administered is selected from the group consisting of verapamil, bepridil, nifedipine, diltiazem, cinnarizine, flunarizine, perhexiline, prenylamine, nitrendipine, nimodipine, nicardipine, and lidoflazine. Calcium modulators are compounds that effect the transport of calcium through cellular membranes. Because of the several mechanisms for calcium transport, and the potential for multiple regulatory sites associated with some of these mechanisms, compounds of diverse structure have been found to be effective as calcium modulators. For example, reported calcium modulators include diphenylpiperazines such as verapamil and its derivatives, lidoflazine, cinnarizine and flunarizine; benzothiazepines such as diltiazem; dihydropyridines such as nifedipine, nitrendipine, nimodipine, nicardipine and BaK; and other structures such as bepridil, prenylamine and perhexiline. As can be seen from the structures of the known calcium modulators shown in FIG. It has been established, however, that compounds that inhibit in vitro constriction of arteries induced by neurotransmitters such as norepinephrine, noradrenaline, and acetylcholine will generally act as calcium modulators in vivo. For example, calcium modulators can be used as an antidote to the lethal toxicity of cocaine and related indirectly acting sympathomimetic amines such as amphetamine and tyramine; as an antidote to tricyclic antidepressants such as imipramine, and ganglionic stimulating drugs such as nicotine; and as an antidote to other toxic substances such as organophosphorus compounds that cause accumulations of neurotransmitters and disrupted neurotransmitter activity. Calcium modulators can also be used as an antidote to substances whose toxicity is related to anticholinesterase activity. In addition, calcium modulators can be used as antagonists to the various types of toxic substances described above. In particular,

the toxic effects of substances such as cocaine, imipramine, anticholinesterases, nicotine and organophosphorus compounds whose toxic effect is, at least in part, the result of an accumulation of neurotransmitters can be alleviated by administration of calcium modulators. Suitable calcium modulators for use in the invention are generally those that will inhibit in vitro arterial constriction. Particularly suitable are those compounds, shown in FIG. The preferred compound for use in the treatment of cocaine intoxication according to the invention is nitrendipine. Effective treatment in accordance with the invention requires prompt administration of the calcium modulator following exposure to the toxic material, preferably by intravenous administration. Alternatively, the calcium modulator can be used in accordance with the invention in anticipation of exposure to a toxic substance, such that it acts as an antagonist to the toxic effects. As an antagonist oral administration of calcium modulators is also possible. Calcium modulators may also be combined with other known substances that function as antidotes to provide more effective treatment. In particular, where a toxic substance is known to have more than one mode of toxic effect, e. Furthermore, calcium modulators may help restore normal neurotransmitter activity in the brain of patients recovering from chronic intoxication with cocaine and other dependence producing drugs. Thus the claimed treatment method may be effective in easing the early phase of drug rehabilitation therapy and withdrawal from drug dependence. The utilization of calcium modulators in accordance with the invention is further illustrated by way of the following examples. These results are provided for illustration only, however, and do not limit the scope of the invention. Two calcium modulators, flunarizine and nimodipine were tested for their ability to act as antidotes to lethal imipramine intoxication. The survival time of the five control rats was  Five test rats were given flunarizine at a rate of 0. After the blood pressure of the rats had fallen to 50 mmHg, four control rats were treated with successive bolus of 0. The total dose of flunarizine was 2. The remaining five rats were similarly treated with nimodipine, the total dosage of nimodipine being 0. The four control rats survived for  All four of the rats treated with flunarizine, and four of the five rats treated with nimodipine survived, and were awake and active 24 hours later. Thus, both calcium modulators tested appeared to be effective in the treatment of acute imipramine poisoning. The calcium modulator nitrendipine was tested for its effectiveness as an antidote to lethal doses of cocaine. Five other rats were given the same amount of cocaine followed by nitrendipine 4 to 5 minutes after the cocaine. Nitrendipine was given intra-arterially first in a loading dose of 7. The infusion was stopped when the rat was active and restless. The survival time of the five control rats was 8 min. Death could be attributed to convulsions and respiratory arrest. All five of the nitrendipine treated animals survived and 24 hours later were active and feeding themselves. The recorder permitted monitoring of cardiac arrythmia. These animals exhibited frequent and sustained arrythmias. In addition, marked agitation, tremors and convulsions were observed, followed by death. The heart rate throughout the infusion was stable, and no tremors or convulsions were observed. The cause of death in these five rats was apparently not cocaine intoxication, but rather was probably attributable to excess fluids due to the large infusion volume. Tissue sections prepared from the hearts of the two sets of animals were also markedly different. The animals treated with cocaine alone exhibited disseminated areas of sarcolema disruption with liberation of disorganized myocardial fibers which present an appearance of waviness. Such alterations, which are symptomatic of the necrotic process leading to permanent infarcted lesions, were not observed in the animals treated with both cocaine and nitrendipine. Thus, nirendipine was effective not only to decrease the lethan toxicity of cocaine, but prevented the cardiac morphological lesions irreversibly produced by cocaine.

## Chapter 4 : Calcium paradox and calcium entry blockers

*Calcium Entry Blockers in Cardiovascular and Cerebral Dysfunctions (Developments in Cardiovascular Medicine) [T. Godfraind, A.G. Herman, D. Wellens] on racedaydvl.com *FREE* shipping on qualifying offers. 2 The free internal Ca+ concentration in human red cells is set according to the leakÂ- 2 and-pump principle: There is a finite passive Ca+.*

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## Chapter 5 : Calcium entry blockers in cardiovascular and cerebral dysfunctions (Book, ) [racedaydvl.com]

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