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CALCIUM ANTAGONISTS: EFFECT ON SKELETAL MUSCLE FUNCTION AND WORKING CAPACITY IN NORMAL MALES

The Ohio State University

Ph.D. 1984

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CALCIUM ANTAGONISTS: EFFECT ON
SKELETAL MUSCLE FUNCTION AND WORKING
CAPACITY IN NORMAL MALES

DISSEPTION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

by

Robert A. Lehnhard

**********

The Ohio State University
1984

Reading Committee:
Dr. Robert L. Bartels
Dr. Timothy E. Kirby
Dr. William Muir

Approved by:

Department of Health,
Physical Education,
and Recreation
DEDICATION

To Holly Jo, my wife. Whose understanding goes beyond friendship. Whose patience, support and caring go beyond love.
ACKNOWLEDGEMENTS

I am deeply grateful to my advisor, Dr. Robert L. Bartels, for affording me the opportunity to study and work with himself and his colleagues. His unfailing enthusiasm for his profession and his students served as a fine example and support for my work.

My thanks to Dr. Timothy E. Kirby seem terribly inadequate in light of the support he has given me both in personal time and professional guidance. His unselfishness contributed much to the fulfillment of this work.

I would also like to thank Dr. William Muir and Dr. Stephen F. Schaal, without much needed and considerate effort on their part, this investigation would not have been realized.

My subjects deserve special thanks for putting out tremendous effort for few rewards. Nothing would have been accomplished without their sacrifice of time and great effort.

I am eternally grateful to my parents for instilling in me the value of learning and for their unrestrained support and encouragement of my endeavor.
VITA


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PRESENTATIONS

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CHAPTER 1

INTRODUCTION

The importance of intracellular calcium concentration to excitation-contraction coupling in muscle cells is well known. Within the past two decades a number of different compounds have been discovered and developed which interfere with intracellular calcium levels. These compounds include metals such as cobalt, manganese, lanthanum, and nickel (15), as well as pharmacological agents such as verapamil, nifedipine, diltiazem, D 600, tiapamil, prenylamine, fendiline, and perhexilene (15, 22, 26, 41). Structurally heterogeneous, but apparently similar in their physiological effects, the aforementioned agents have been grouped together and labeled "calcium antagonists", "calcium channel blockers", or "slow channel blockers".

These calcium antagonists act to inhibit the normal rise in intracellular calcium concentration which is necessary for muscle contraction. Although specific mechanisms of action of these agents are still under investigation, research predominantly indicates that these calcium antagonists block the flow of extracellular Ca++
across cardiac and smooth muscle cell membrane into the intracellular space (14, 16, 44, 55). However, there is also evidence that points toward an intracellular site of action of some of these agents (8, 25, 39, 57).

From the group of compounds which fall into the category of calcium antagonists, three, verapamil, nifedipine, and diltiazem are currently receiving wide use clinically. Although long known for its vasodilatory effects, verapamil also prolongs atrio-ventricular conduction and is now considered a drug of choice for treating reentry forms of supraventricular arrhythmias (48). Nifedipine, on the other hand, has little effect on A-V conduction and is used primarily for its potent vasodilatory effects in treating various forms of angina pectoris (3, 12). Diltiazem, though exhibiting similar A-V conduction effects to those produced by verapamil, is primarily used, like nifedipine, for its vasodilation properties and the treatment of angina pectoris (25, 26, 30, 55).

In human models, research to date has principally explored the central and peripheral changes (i.e. slowed A-V conduction and vasodilation) induced by calcium antagonists, and how these changes may aid in the treatment of certain abnormal physiological conditions. Little has been done
with humans to determine the possible effects of these agents on physiological work parameters such as skeletal muscle strength and oxygen consumption. With increasing possibilities for the use of calcium antagonists, it is likely that a growing number of individuals will be treated with this class of drugs. With this in mind, it will be important to know not only what these drugs are able to do to improve certain cardiac and systemic disorders, but also what effect, if any, they may have on an individual's capability to perform various types of work.

**Purpose Of The Study**

The purpose of this study was to determine if therapeutic doses of three different calcium antagonists; verapamil, nifedipine, and diltiazem will produce effect on four physiological parameters in healthy adult males. These parameters are: 1) skeletal muscle strength, 2) skeletal muscle endurance, 3) anaerobic power, and 4) aerobic power.

**Statement Of The Problem**

Research has shown clear benefits from the use of calcium antagonists in the treatment of various cardiac and systemic disorders. Among these benefits is generally an increase in exercise tolerance in subjects with stable
angina pectoris. In light of the proposed mechanisms by which these drugs provide such benefits, it is reasonable to believe that they may also influence an individual's ability to perform various types of work due to an effect on skeletal muscle. Therefore, it is important to determine if calcium antagonists have any effect on skeletal muscle strength, skeletal muscle endurance, anaerobic power, and aerobic power in a person free of angina imposed limitations.

Research Questions

1. Does verapamil, nifedipine, or diltiazem produce effect on skeletal muscle strength in healthy adult males?

2. Does verapamil, nifedipine, or diltiazem produce effect on skeletal muscle endurance in healthy adult males?

3. Does verapamil, nifedipine, or diltiazem produce effect on anaerobic power in healthy adult males?

4. Does verapamil, nifedipine, or diltiazem produce effect on aerobic power in healthy adult males?
Research Hypotheses

1. Verapamil, nifedipine, and diltiazem will not produce effect on skeletal muscle strength in healthy adult males.

2. Verapamil, nifedipine, and diltiazem will not produce effect on skeletal muscle endurance in healthy adult males.

3. Verapamil, nifedipine, and diltiazem will not produce effect on anaerobic power in healthy adult males.

4. Verapamil, nifedipine, and diltiazem will not produce effect on aerobic power in healthy adult males.

Delimitations

1. Subjects were all volunteers. Therefore, they do not represent a random sample.

Limitations

1. Measurement error in gas analysis for determining VO2 max can occur. The extent of such error cannot be determined absolutely.
2. The reliability of the Cybex II isokinetic machine is uncertain.

3. The subjects' performance may possibly be influenced by a "learning effect" with repeated use of the testing equipment.

4. Serum levels of the calcium antagonists were not determined. The extent to which it varied among the subjects is not known.

Definitions

1. Aerobic power - The maximum rate at which an individual is able to consume oxygen.

2. Anaerobic power - The maximum rate at which an individual can convert energy to work.

3. Calcium antagonist - An agent which inhibits the normal rise in intracellular Ca++ concentration during the excitation-contraction coupling process in muscle cells.

4. Congestive heart failure - The state in which abnormal circulatory congestion occurs as a result of heart failure.
5. Diltiazem - A calcium antagonist. A strong vasodilator used primarily for the treatment of various forms of angina pectoris.


7. Heart failure - The condition in which the heart is no longer able to pump an adequate supply of blood for the metabolic needs of the body, despite adequate venous return to the heart.

8. Hypertrophic cardiomyopathy - Degeneration of the myocardium due to disease, accompanied by enlargement of ventricular muscle mass.

9. Isokinetic contraction - The muscle develops maximal tension through the full range of motion as it shortens at a constant speed.

10. Myocardial infarction - A localized death of cardiac muscle cells usually due to a sudden insufficiency of arterial or venous blood supply.

11. Myocardial ischemia - Inadequate circulation of blood to the myocardium.

12. Myocardium - Heart muscle.

14. Oxygen consumption - The volume of oxygen removed from the blood, by the tissues of the body, to meet metabolic energy requirements.

15. Primary pulmonary hypertension - High arterial blood pressure in the pulmonary circuit without preexisting renal disease or known cause.

16. Muscular strength - The force or tension a muscle, or muscle group, can exert against a resistance in one maximal effort.

17. Stable angina pectoris - (Effort Induced Angina) Constricting pain in the chest associated with an increase in myocardial oxygen demand.

18. Supraventricular arrhythmias - Abnormal contractions of cardiac muscle initiated by a source located superior to the ventricles, other than the sinoatrial node.


20. Vasodilation - Dilation of the blood vessels.

21. Vasospasm - Abnormal contraction of the muscular coats of the blood vessels.
22. **Vasospastic angina pectoris - (At Rest Angina)**
Constricting pain in the chest due to vasospasm in the coronary arteries.

23. **Verapamil - A calcium antagonist.** Effects include vasodilation and decreased cardiac tissue excitability. Used in the treatment of hypertension and supraventricular arrhythmias.
CHAPTER II

REVIEW OF LITERATURE

This review of literature will cover the following areas of concern with calcium antagonists. 1) Mechanisms of action of verapamil, nifedipine, and diltiazem. 2) Calcium antagonists and skeletal muscle. 3) Therapeutic application of calcium antagonists. 4) The effects of calcium antagonists on exercise capacity in man.

Mechanisms of Action of Verapamil, Nifedipine, and Diltiazem

To date, specific mechanisms of action of calcium antagonists have not been identified. What has been identified is the binding of these agents to calcium channels in the cell membrane, the effects these agents have on Ca++ influx and efflux in cardiac, smooth, and skeletal muscle, and the electrophysiological effects of these agents.

Verapamil is made up of two structural enantiomeres or compounds having the same chemical formula but different chemical structures. These are the (R) or (+) enantiomer and the (S) or (-) enantiomer. These two different
structures of the same compound create different electrophysiological effects in muscle cell membrane. Bayer et al found that the (R) enantiomere significantly slows the rate of rise of the initial action potential in cardiac muscle cells. This effect is increased with increasing frequency of depolarization (5). This suggests that the (R) enantiomere of verapamil has a sodium (fast) channel blocking ability. The same study also found that the (S) enantiomere of verapamil depresses the plateau phase of the cardiac muscle action potential. This depression occurs also in a frequency dependent manner (5). This finding suggests that the (S) enantiomere of verapamil has a calcium (slow) channel blocking ability. The observed effects of the racemic mixture of verapamil, of depressed excitability and negative inotropism, support the interpretation of these findings.

Voltage clamp experiments by Ehara et al and others, which show depressed plateau phases of the cardiac action potential with verapamil, also lend support to the site of the mechanism of action of this drug as being at the cell membrane (14, 34, 36). Importantly, these studies show that verapamil slows recovery of the membrane following depolarization. This differs from other calcium antagonists which have no apparent effect on the rate of activation or reactivation.
There are other studies which indicate a possible intracellular site of action for verapamil. Separate studies by Lullman et al and Church et al found that verapamil can be concentrated in the intracellular space (8, 39). Church et al also found that Ca++ uptake in cardiac and smooth muscle was not reduced by verapamil (8). In two separate studies, Vaghy et al found that verapamil, as well as nifedipine and diltiazem, prevents the mitochondrial swelling associated with Ca++ uptake seen in ischemic cardiac muscle (57), and that these compounds also inhibit the sodium induced release of calcium from mitochondria (56). These findings indicate that verapamil may act by mechanisms, other than the blocking of Ca++ influx through the cell membrane, to cause the inhibition of the excitation-contraction coupling process in cardiac and smooth muscle.

An in vitro study by Gallant determined that verapamil also has an effect on skeletal muscle contractility (18). It was found that after 30 minutes, 25 uM of verapamil depressed twitch and tetanic force in soleus muscle by more than 50%. In addition, verapamil slightly depolarized the cell membrane, but twitch kinetics were unaltered. All these effects slowly reversed themselves when verapamil was removed.
Nifedipine, unlike verapamil, has no apparent effect on the rate of depolarization-repolarization of the cell membrane. Voltage clamp studies by Bayer et al and others showed that nifedipine did not effect the kinetics of either the Na+ (fast) membrane current, or the Ca++ (slow) membrane current (4). They found nifedipine does depress the slow inward current, and increasing doses will increase the inhibition of this current. It is now believed that nifedipine shows little selectivity as far as blocking the Ca++ channel when it is in either the depolarizing, repolarizing, or resting state. This differs from verapamil which is believed to preferentially block the Ca++ channels when in either the depolarized or repolarizing state (46). These results support the hypothesis that the cell membrane is the site of action for calcium antagonists.

However, Church et al found that nifedipine has no effect on the uptake of Ca++ by cardiac or smooth muscle, and that it enhances the efflux of Ca++ from intracellular stores in smooth muscle (8). And Vaghy et al shows evidence of nifedipine inhibiting the Na+ induced release of Ca++ from heart mitochondria (56), thus accounting for a possible intracellular site of action for this drug.

Diltiazem also appears to have its mechanism of action at the cell membrane. Saikawa et al and others found diltiazem depresses the plateau phase of the cardiac action
potential, and in higher concentrations it acts like the (R) enantiomere of verapamil in depressing the initial or fast phase of the cardiac action potential (41, 42, 44). Lee and Tsien have demonstrated the depolarization frequency dependence of diltiazem (as well as verapamil and nifedipine) and its inhibition of Ca++ influx through the membrane channels (37). Inhibition by this agent increases with increased frequency of membrane depolarization. This is evidence which would account for a cell membrane site of action for diltiazem. Again, however, Vaghy et al have shown that diltiazem inhibits the Na+ induced release of Ca++ from mitochondria (56), which may indicate an intracellular site of action for this compound as well.

Calcium Antagonists and Skeletal Muscle

For a number of years, calcium channels in skeletal muscle membrane have been studied with voltage clamp techniques (1, 45). More recently, the calcium channels in skeletal muscle have been purified and the binding sites for calcium antagonists investigated (10, 19). It is known that these compounds demonstrate a high affinity binding to calcium channels in skeletal muscle (31, 46). And although they show less affinity for skeletal muscle than they do for smooth or cardiac muscle, they bind in sufficient
concentrations to effectively "block" the Ca++ channel in skeletal muscle (31, 46).

In vitro studies by Gonzales-Serratos et al and others have investigated the effects on skeletal muscle excitation-contraction coupling that the blocking of the Ca++ channels by calcium antagonists produce (13, 20, 58). Besides effectively "blocking" the inward current of Ca++ in isolated skeletal muscle fibres, these agents also potentiated twitch, tetanus, and contractures (13, 20, 58). These findings indicate that extracellular Ca++ and its influx through the cell membrane channels has no role in the contraction of skeletal muscle. The mechanism by which these agents increase mechanical activity of the fibres is currently under investigation.

Therapeutic Application of Calcium Antagonists

By whatever mechanism they are achieved, the resulting effects of vasodilation and decreased cardiac tissue excitability with the administration of calcium antagonists, have a wide range of possible clinical applications.

Current approved uses of these agents include treatment of vasospastic angina (2), stable (effort induced) angina (50), myocardial ischemia (11), and supraventricular arrhythmias (48).
Potential applications of calcium antagonists include; reducing the size of myocardial infarcts when administered immediately following the infarct (7), enhancing myocardial preservation during cardio-pulmonary by-pass surgery (9, 24, 35), treatment of systemic hypertension (49), treatment of primary pulmonary hypertension (33), treatment of congestive heart failure (40), and treatment of hypertrophic cardiomyopathy (38, 43).

The Effects of Calcium Antagonists on Exercise Capacity in Man.

Review of the literature in this area found studies primarily concerned with non-healthy individuals. In general, results indicate that the action of calcium antagonists improve exercise tolerance in man with various cardiac disorders. Nothing was found concerning possible effects of these agents on exercise performance as it relates to skeletal muscle strength, anaerobic power, and aerobic power.

Short-term efficacy of verapamil was studied by De Ponti et al. It was found that in subjects with stable angina, verapamil extended the time of work performed before the onset of angina, and delayed the onset of S-T depression (12). Similar results were found by Subramanian et al when studying the long-term efficacy of verapamil in subjects
with stable angina (52). This study showed no significant change in maximal heart rate or blood pressure during exercise while treated with verapamil.

Atterhog et al and De Ponti et al have found similar responses to exercise in subjects with stable angina when treated with nifedipine as when treated with verapamil (3, 12). Atterhog et al studied nifedipine administered sublingually and exercise response. Work time and load on the bicycle ergometer were increased with nifedipine (3). Heart rate was increased and systolic blood pressure decreased at rest and during exercise following administration of nifedipine. De Ponti et al administered nifedipine orally, and observed the same effects of increased heart rate, decreased systolic blood pressure, and increased exercise tolerance (12).

Diltiazem's effects on exercise tolerance in subjects with stable angina are similar to those of verapamil and nifedipine. Treatment with diltiazem will also increase worktime and load prior to the onset of angina. It will also prolong the time to occurrence of S-T depression. Studies by Hossack et al and others have shown the following results with administration of diltiazem. Along with an increased working capacity and delayed S-T depression response, changes during exercise included: a decrease in heart rate at submaximal levels but no change in this
parameter at maximum effort, a decrease in diastolic blood pressure and no change in systolic blood pressure at all work levels, a decrease in rate-pressure product at submaximal work, and no change in this parameter at maximal work. End-exercise S-T depression was not reduced, however the workloads at which it occurred were greater (27, 28, 29, 51). These studies were all symptom-limited tests performed on the treadmill, without direct measurement of oxygen consumption.

Summary

The three calcium antagonists considered here all appear to have their mechanism of action at the muscle cell membrane. Verapamil and diltiazem appear to slow the influx of Ca++ through the calcium channels when the membrane is in the depolarized or repolarizing state (46), while nifedipine appears to block the calcium channels while the membrane is either depolarized, repolarizing, or at rest (46). There is evidence, however, that there may be intracellular sites of action for these drugs as well (7, 56).

Currently used for their vasodilatory effects in the treatment of various forms of angina pectoris (2, 50), other uses range from treating supraventricular arrhythmias (48) to preserving the myocardium during cardio-pulmonary by-pass surgery (9, 24, 35).
Verapamil, nifedipine and diltiazem show similar effects on exercise tolerance in subjects with stable angina. They prolong work time and enable the subject to work at greater loads. None of these agents effected maximum heart rate, however nifedipine increased and diltiazem decreased heart rate at submaximal workloads. All the agents lowered diastolic blood pressure, while nifedipine also lowered systolic blood pressure. All these agents delayed the occurrence of S-T segment depression in the electrocardiogram taken during exercise (3, 12, 27, 28, 29, 51).
The purpose of this study was to determine what effect, if any, a group of calcium antagonists would exhibit on skeletal muscle function, anaerobic power and aerobic power. The investigation followed a protocol of, treatment with a drug followed by testing of performance variables involving Cybex II equipment, the Fitron stationary bicycle and a motorized treadmill.

The Subjects

The subjects for this study were all volunteers recruited by the investigator. Each subject was not engaged in a regular training regime of any nature prior to or during this investigation. Each subject received a medical exam by a physician prior to participating in this investigation. This exam included a resting electrocardiogram.

Approval was given by the Human Subjects Review Committee of The Ohio State University to conduct this investigation, and each subject gave written consent to participate.
The subjects were eight males, ages 19 to 26 years. The physical characteristics of individuals and mean values for the group are presented in Table 1.

Table 1
Subjects Profile

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Mean: 23.1 70.9 179.1 15.2 150.4 28.7
S.D.: 2.75 1.46 25.05 7.73 10.04 18.66

Conditions of Testing
All physiological testing was conducted at The Ohio State University Laboratory of Work Physiology.

Research Design
A post-test only, double blind design was used, incorporating a placebo, with each subject acting as his own control.
Methods

Each subject received eight different treatments. These included two doses of verapamil, two doses of nifedipine, two doses of diltiazem and two placebo treatments. Treatments with verapamil were 80mg, every eight hours and 120mg, every eight hours (21, 32, 53, 59). Treatments with nifedipine were 10mg, every eight hours and 20mg, every eight hours (21, 53, 59). Treatments with diltiazem were 90mg, every eight hours and 120mg, every eight hours (54, 60). Treatments were administered in random order and in a double blind manner.

Physiological parameters measured following each treatment included; 1) strength of the muscles which extend and flex the knee 2) endurance of the muscles which extend and flex the knee 3) anaerobic power, 4) aerobic power. Skeletal muscle strength and endurance were measured by performing isokinetic knee extension/flexion using the Cybex II dynamometer. Anaerobic power was measured by a sustained 45 second maximal effort on the Fitron stationary bicycle. Aerobic power was measured by performing a graded exercise test on the treadmill.
Procedures

Each subject was given an oral low dose and an oral high dose treatment of verapamil, nifedipine, and diltiazem. In addition, each subject received 2 placebo treatments, also given orally, making a total of eight treatments received by each subject. The drugs and placebo were packaged in opaque capsules to avoid identification by the subjects and the administrator.

The treatment protocol was as follows: both the low dose and high dose treatments of the same drug were given over a continuous eight day period. Days 1 - 4, the low dose was given and the subjects tested on days 3 and 4. Days 5 - 8, the high dose was given and the subjects tested on days 7 and 8. The subjects then had 6 days off all treatment to allow for washout of the drug. This low dose/test/high dose/test/6 day washout schedule was followed for the administration of verapamil, nifedipine, diltiazem, and the placebo. It was necessary to have 2 placebo treatments in order to insure the double-blind administration of all treatments.

Doses of verapamil were: LOW - 80mg 3 times/day (every 8 hrs.), HIGH - 120mg 3 times/day (every 8 hrs.) (21, 32, 53, 59). Doses of nifedipine were: LOW - 10mg 3 times/day (every 8 hrs.), HIGH - 20mg 3 times/day (every 8 hrs.) (21,
Doses of diltiazem were: LOW - 90mg 3 times/day (every 8 hrs.), HIGH - 120mg 3 times/day (every 8 hrs.) (54, 59).

During treatment, each subject reported to the testing lab once a day to receive his appropriate dose for the following day. The treatments were administered in a double-blind manner, and the order in which each subject received either verapamil, nifedipine, diltiazem or the placebo was decided by random selection.

Each test following treatment was conducted over a two day period. On the third day of each treatment, skeletal muscle strength and endurance, and anaerobic power were measured. First, right knee extension/flexion strength (expressed in foot-pounds of torque produced) was determined at three separate speeds on the Cybex II isokinetic dynamometer. Four maximal effort repetitions of knee extension and flexion were performed at each of the following speeds, in the following order; 60°/sec., 180°/sec., and 300°/sec (27). Work performed was recorded by the Cybex dual channel strip chart recorder and work integrator, with a damping setting of "2". Peak torque was taken as the highest single repetition of the four maximal effort repetitions. Each subject received 30 seconds rest upon completion of the four maximal repetitions, prior to beginning the warm-up at the next testing speed.
Second, right knee extension/flexion endurance was measured on the Cybex II isokinetic dynamometer. This test was performed two minutes following the 300°/sec. strength test. Each subject performed continuous maximal effort repetitions of knee extension and flexion until he was no longer able to generate a minimum of 50% of the peak torque generated on extension within the first four repetitions of the test. This test was performed at a speed of 180°/sec (27).

Third, anaerobic power was measured five minutes following the muscle endurance test. The anaerobic power test consisted of a 45 second, maximum sustained effort on the Fitron stationary bicycle, pedaling at a rate of 150 revolutions per minute. Total work was recorded by the Cybex dual channel strip chart recorder and work integrator, with a damping setting of "2".

On the fourth day of each treatment, aerobic power (maximal oxygen consumption) was measured. A graded exercise test was performed on the treadmill following the standard Bruce protocol (6). Each subject's heart rate and blood pressure were monitored at rest immediately prior to exercise, at the end of each stage (every 3 minutes) throughout the exercise bout, and during recovery. Heart rate was monitored by direct wire of lead CR₅ to the Erich Jaeger metabolic cart. Blood pressure was monitored
by auscultation using a sphygomanometer and stethoscope.

Maximal oxygen consumption \( (V\text{O}_2 \text{ max}) \) values
were obtained by open circuit spirometry using the Erich
Jaeger Ergo-Pneumotest metabolic cart, with a Rudolph head
support assembly and a Rudolph value #2600.

**Statistical Methods**

The data was treated statistically with a One Way
Analysis of Variance. An alpha level of 0.05 was selected
for all measured variables.
CHAPTER IV

RESULTS

In order to determine any statistical difference between treatments, the data obtained for each of the 11 variables measured in this investigation was treated with a one-way analysis of variance at the .05 level of significance. The ANOVA tables for these 11 variables can be found in the appendix.

Right Knee Extension 60°/sec.

There were no statistical differences between treatments (P<.05) in the mean torque produced by the subjects at this speed. Mean values ranged from 146.5±10.3 to 162.3±9.8 ft-lbs of torque produced. (see figure 1).

Right Knee Flexion 60°/sec.

There were no statistical differences between treatments (P<.05) in the mean torque produced by the subjects at this speed. Mean values ranged from 95.4±5.5 to 103.4±4.5 ft-lbs of torque produced. (see figure 2).
Figure 1

Cybex: Right Knee Extension Performed
at 60°/sec.

<table>
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<th>Mean Torque Produced (ft-lbs)</th>
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</thead>
<tbody>
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<td>110</td>
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<td>100</td>
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</table>

Brackets represent mean ± SEM
Mean Range = 146.5 - 162.3

\[ V_L = \text{Verapamil, 80mg, 3 times per day} \]
\[ V_H = \text{Verapamil, 120mg, 3 times per day} \]
\[ N_L = \text{Nifedipine, 10mg, 3 times per day} \]
\[ N_H = \text{Nifedipine, 20mg, 3 times per day} \]
\[ D_L = \text{Diltiazem, 90mg, 3 times per day} \]
\[ D_H = \text{Diltiazem, 120mg, 3 times per day} \]
\[ P_1 = \text{First placebo treatment} \]
\[ P_2 = \text{Second placebo treatment} \]
Figure 2

Cybex: Right Knee Flexion Performed
at 60°/sec.

Mean Torque Produced (ft-lbs)

Brackets represent mean ± SEM
Mean Range = 95.4 - 103.4

\(V_L\) = Verapamil, 80mg, 3 times per day
\(V_H\) = Verapamil, 120mg, 3 times per day
\(N_L\) = Nifedipine, 10mg, 3 times per day
\(N_H\) = Nifedipine, 20mg, 3 times per day
\(D_L\) = Diltiazem, 90mg, 3 times per day
\(D_H\) = Diltiazem, 120mg, 3 times per day
\(P_1\) = First placebo treatment
\(P_2\) = Second placebo treatment
Right Knee Extension 180°/sec.

There were no statistical differences between treatments (P<05) in the mean torque produced by the subjects at this speed. Mean values ranged from 113.9±4.6 to 120.5±7.4 ft-lbs of torque produced. (see figure 3).

Right Knee Flexion 180°/sec.

There were no statistical differences between treatments (P<05) in the mean torque produced by the subjects at this speed. Mean values ranged from 75.3±4.0 to 78.1±3.8 ft-lbs of torque produced. (see figure 4).

Right Knee Extension 300°/sec.

There were no statistical differences between treatments (P<0.05) in the mean torque produced by the subjects at this speed. Mean values ranged from 87.3±4.1 to 91.9±3.5 ft-lbs of torque produced. (see figure 5).

Right Knee Flexion 300°/sec.

There were no statistical differences between treatments (P<0.05) in the mean torque produced by the subjects at this speed. Mean values ranged from 59.4±4.6 to 64.9±2.8 ft-lbs of torque produced. (see figure 6).
Cybex: Right Knee Extension Performed at 180°/sec.

Figure 3

Mean Torque Produced (ft-lbs)

Brackets represent mean ± SEM
Mean Range = 113.9 - 120.5

$V_L$ = Verapamil, 80mg, 3 times per day
$V_H$ = Verapamil, 120mg, 3 times per day
$N_L$ = Nifedipine, 10mg, 3 times per day
$N_H$ = Nifedipine, 20mg, 3 times per day
$D_L$ = Diltiazem, 90mg, 3 times per day
$D_H$ = Diltiazem, 120mg, 3 times per day
$P_1$ = First placebo treatment
$P_2$ = Second placebo treatment
Figure 4

Cybex: Right Knee Flexion Performed at 180°/sec.

Brackets represent mean ± SEM
Mean Range = 75.3 - 78.1

$V_L$ = Verapamil, 80mg, 3 times per day
$V_H$ = Verapamil, 120mg, 3 times per day
$N_L$ = Nifedipine, 10mg, 3 times per day
$N_H$ = Nifedipine, 20mg, 3 times per day
$D_L$ = Diltiazem, 90mg, 3 times per day
$D_H$ = Diltiazem, 120mg, 3 times per day
$P_1$ = First placebo treatment
$P_2$ = Second placebo treatment
Figure 5

Cybex: Right Knee Extension Performed
at 300°/sec.

Brackets represent mean ± SEM
Mean Range = 87.3 - 91.9

\[V_L = \text{Verapamil, 80mg, 3 times per day}\]
\[V_{H} = \text{Verapamil, 120mg, 3 times per day}\]
\[N_{L} = \text{Nifedipine, 10mg, 3 times per day}\]
\[N_{H} = \text{Nifedipine, 20mg, 3 times per day}\]
\[D_{L} = \text{Diltiazem, 90mg, 3 times per day}\]
\[D_{H} = \text{Diltiazem, 120mg, 3 times per day}\]
\[P_{1} = \text{First placebo treatment}\]
\[P_{2} = \text{Second placebo treatment}\]
Figure 6

Cybex: Right Knee Flexion Performed at 300°/sec.

Brackets represent mean ± SEM
Mean Range = 59.4 - 64.9

$V_L$ = Verapamil, 80mg, 3 times per day
$V_H$ = Verapamil, 120mg, 3 times per day
$N_L$ = Nifedipine, 10mg, 3 times per day
$N_H$ = Nifedipine, 20mg, 3 times per day
$D_L$ = Diltiazem, 90mg, 3 times per day
$D_H$ = Diltiazem, 120mg, 3 times per day
$P_1$ = First placebo treatment
$P_2$ = Second placebo treatment
Right Knee Extension/Flexion Endurance 180°/sec.

There were no statistical differences between treatments (P<.05) in the mean number of repetitions performed to reach fatigue by the subjects. Mean values ranged from 27.8±1.4 to 30.5±3.3 repetitions to fatigue (see figure 7). Fatigue was defined as the inability to generate a minimum of 50 percent of the peak extension torque generated within the first four repetitions of this test.

Anaerobic Power

There were no statistical differences between treatments (P<.05) in the mean amount of work performed by the subjects in a 45 second work bout on the fitron stationary bicycle. Mean values ranged from 20.4±2.6 to 22.3±2.8 kilogram meters per kilogram of body weight per minute (see figure 8). Pedal speed was set at 150 revolutions per minute, and subjects maintained a maximal effort over the entire 45 second time period.

Maximal Oxygen Consumption

There were no statistical differences between treatments (P<.05) in mean oxygen consumption of the subjects. Mean values ranged from 47.8±3.2 to 50.9±3.5 milliliters per kilogram of body weight per minute (see figure 9).
Cybex: Right Knee Extension/Flexion Endurance
Performed at 180°/sec.

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<th>Dosage</th>
<th>Frequency</th>
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<td>$V_H$</td>
<td>Verapamil, 120mg</td>
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<td>$N_L$</td>
<td>Nifedipine, 10mg</td>
<td>3 times per day</td>
</tr>
<tr>
<td>$N_H$</td>
<td>Nifedipine, 20mg</td>
<td>3 times per day</td>
</tr>
<tr>
<td>$D_L$</td>
<td>Diltiazem, 90mg</td>
<td>3 times per day</td>
</tr>
<tr>
<td>$D_H$</td>
<td>Diltiazem, 120mg</td>
<td>3 times per day</td>
</tr>
<tr>
<td>$P_1$</td>
<td>Placebo treatment</td>
<td></td>
</tr>
<tr>
<td>$P_2$</td>
<td>Placebo treatment</td>
<td></td>
</tr>
</tbody>
</table>

Brackets represent mean ± SEM
Mean Range = 27.8 - 30.5
Figure 8

Fitron Anaerobic Power Test

45 seconds at 150 rpms

Mean Work Performed (kgm/kg/min)

<p>| | | | | | | |</p>
<table>
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</table>

Brackets represent mean ± SEM
Mean Range = 20.4 - 22.3

\[ V_L = \text{Verapamil, 80mg, 3 times per day} \]
\[ V_H = \text{Verapamil, 120mg, 3 times per day} \]
\[ N_L^H = \text{Nifedipine, 10mg, 3 times per day} \]
\[ N_H^L = \text{Nifedipine, 20mg, 3 times per day} \]
\[ D_L^H = \text{Diltiazem, 90mg, 3 times per day} \]
\[ D_H^L = \text{Diltiazem, 120mg, 3 times per day} \]
\[ P_1 = \text{First placebo treatment} \]
\[ P_2 = \text{Second placebo treatment} \]
Maximal Oxygen Consumption

Brackets represent mean ± SEM
Mean Range = 47.8 - 50.9

\( V_L \) = Verapamil, 80mg, 3 times per day
\( V_H \) = Verapamil, 120mg, 3 times per day
\( N_L \) = Nifedipine, 10mg, 3 times per day
\( N_H \) = Nifedipine, 20mg, 3 times per day
\( D_L \) = Diltiazem, 90mg, 3 times per day
\( D_H \) = Diltiazem, 120mg, 3 times per day
\( P_1 \) = First placebo treatment
\( P_2 \) = Second placebo treatment
Time on Treadmill

There were no statistical differences between treatments ($P < .05$) in the mean time on the treadmill to exhaustion by the subjects. Mean values ranged from 11.8±0.6 to 12.5±0.7 minutes (see figure 10).

Maximal Heart Rate

There were no statistical differences between treatments ($P < .05$) in mean maximal heart rate of the subjects. Mean values ranged from 177±4 to 193±6 beats per minute (see figure 11).
Figure 10

Time on Treadmill to Exhaustion

Brackets represent mean ± SEM
Mean Range = 11.8 - 12.5

\[ V_L \] = Verapamil, 80mg, 3 times per day
\[ V_H \] = Verapamil, 120mg, 3 times per day
\[ N_L \] = Nifedipine, 10mg, 3 times per day
\[ N_H \] = Nifedipine, 20mg, 3 times per day
\[ D_L \] = Diltiazem, 90mg, 3 times per day
\[ D_H \] = Diltiazem, 120mg, 3 times per day
\[ P_1 \] = First placebo treatment
\[ P_2 \] = Second placebo treatment
Maximal Heart Rate

Brackets represent mean ± SEM
Mean Range = 177 - 193

$V_L$ = Verapamil, 80mg, 3 times per day
$V_H$ = Verapamil, 120mg, 3 times per day
$N_L^H$ = Nifedipine, 10mg, 3 times per day
$N_H^H$ = Nifedipine, 20mg, 3 times per day
$D_L^H$ = Diltiazem, 90mg, 3 times per day
$D_H^H$ = Diltiazem, 120mg, 3 times per day
$P_1^H$ = First placebo treatment
$P_2^H$ = Second placebo treatment
This investigation failed to show any statistical difference ($P < .05$) in any of the performance parameters measured, between any of the treatments administered.

Past research involving calcium antagonist agents and dealing with human subject models, has confined itself to central and peripheral changes in the cardiovascular system caused by the effect these agents produce on cardiac and smooth muscle tissue. In vitro studies have shown these compounds to have effect on skeletal muscle fibers, but nothing has been done in human models to assess the possible implications of these findings. Therefore, this investigation was undertaken to determine if three calcium antagonists; verapamil, nifedipine and diltiazem, have any in vivo effect on skeletal muscle function in humans by measuring four different performance parameters in which skeletal muscle function plays a key role. These parameters were; isolated muscle group strength, isolated muscle group endurance, anaerobic power, and aerobic power.

Strength was tested using the Cybex II dynamometer, involving the muscle groups which extend and flex the lower leg at the knee joint. These large muscle groups are well representative of the skeletal muscle tissue in the body, and were also involved in the testing done on the other performance parameters. Strength was tested at three different
speeds through the range of motion to determine a possible effect on the force-velocity relationship of muscle contraction. In normal muscle, contraction at higher velocity will produce less force (see figure 2). This relationship was unaffected by any of the treatments in this investigation.

Figure 12

Force-Velocity Relationship
In Muscle Contraction

FORCE
(ft-lbs)

0

VELOCITY
(degrees/sec)

0
Isolated muscle endurance was also measured using the Cybex II dynamometer, and involved the same muscle groups as the strength test. Fatigue was defined as the point at which the subject was unable to produce an amount of torque on extension, equal to at least 50% of the highest torque produced on extension in the first four repetitions of the test (30). This test was performed at a speed of 180 degrees per second (30), and endurance was expressed in total number of repetitions performed until the defined point of fatigue was reached.

A true test of anaerobic power has yet to be developed. Tests which are familiar throughout the literature, fail to test for the full capacity of the anaerobic energy systems. Most are of insufficient duration to take the anaerobic systems to the limit of energy production. With this in mind, the test used in this investigation was developed. It was designed to last for a sufficient length of time (45 seconds) to more completely push anaerobic metabolism to it's upper limit of energy production, and to take advantage of the Fitron stationary bicycle's progressive resistance function and recording ability of the Cybex strip chart recorder. With this equipment, it was possible to obtain a printed curve, the area under which was representative of the work accomplished during the work bout. The absolute work (kgm's) for the 45 second bout has been converted and expressed here in relative terms (kgm/kg/min.). The treatments in this investigation exhibited no effect on the subjects' anaerobic work capacity as measured by this test.
Measurement of aerobic power was accomplished through the use of a graded exercise test, to exhaustion, on the treadmill, utilizing the standard Bruce protocol (6). This protocol is used widely throughout the literature and can be used to test a wide population of people. The treatments in this investigation exhibited no effect on the subjects' aerobic work capacity as measured with this protocol.

The results of this investigation show no difference between any of the treatments in any of the variables measured. With no previous studies in the literature involved with measurement of these variables, it leaves little with which to compare these results. What can be done, however, is point out possible reasons, within the limits of this study, that none of the treatments showed any effect.

It is known that the agents used as treatments in this investigation show a high affinity binding to skeletal muscle tissue (19, 31, 46). In vitro studies have shown these agents potentiate twitch, tetanus, and contractures in skeletal muscle fibers (13, 20, 58). These facts, plus the exhibited side effect of these agents of muscle cramps, would lead one to believe that these compounds may effect in vivo function of skeletal muscle (i.e. strength and endurance of contraction). The doses used in this study were representative of the normal range used clinically, and allowed for a more than ample concentration of the agents to effectively "block" the calcium channels in skeletal muscle (31). Therefore, assuming that the influx of extracellular calcium was effectively blocked, the results of this study
indicate that extracellular Ca++ is of little importance to skeletal muscle contraction.

Subject adherance to the dose regime can not be stated with absolute certainty. For practical administration purposes, the drugs were given to the subjects in single day doses, trusting them to ingest the capsules every eight hours as prescribed. Subjects were instructed to inform the investigator if a dose was missed. No missed doses were reported.

The maintenance of a consistant level of physical activity by the subjects throughout the treatment period was assumed. Subjects were requested to neither increase nor decrease any type of physical training in which they may have been involved, and if such changes were made, to report them to the investigator. No such changes in activity levels were reported by any subject.

Repetition of maximal effort by each subject on each test parameter can not be documented with absolute certainty. Attempts to ensure maximal effort on each test for each treatment included testing the subject at the same time of day for the different sessions, and similar encouragement from the investigator during each testing session.

The reliability of the equipment used for testing, and therefore the results obtained, can never be absolute. Controls used in this investigation for reliability were, frequent calibration of all equipment used and administration of each testing session by the same individual.
The results, showing no significant effect of verapamil, nifedipine, or diltiazem on any of the performance variables measured, indicate the nonparticipation of extracellular calcium in excitation-contraction coupling of skeletal muscle. They indicate further that any physical work limits imposed on individuals by use of these agents are not due to any inhibition of skeletal muscle function.
CHAPTER VI

SUMMARY AND CONCLUSIONS

Effects of calcium antagonist agents on cardiac and vascular smooth muscle have been well documented (5, 14, 15, 17, 25). Recently, effects of these agents on skeletal muscle (in vitro) have been shown as well (13, 20, 58). No information is presently available concerning the effect of these drugs on skeletal muscle in human subjects. This study endeavored to determine two things. First, do three calcium antagonists, verapamil, nifedipine, and diltiazem have any effect on skeletal muscle strength, skeletal muscle endurance, anaerobic power, and aerobic power? Second, if any of these drugs do show effect on any of these parameters, is the effect dose related?

Eight healthy male subjects were recruited to receive two doses of each of the aforementioned drugs plus 2 placebo treatments. Treatments of verapamil were 80mg, 3 times daily and 120mg, 3 times daily. Treatments of nifedipine were 10mg, 3 times daily and 20 mg, 3 times daily. Treatments of diltiazem were 90 mg, 3 times daily and 120mg, 3 times daily. The 2 placebo treatments were also given in a 3 times per day regime. Treatments were administered in random order and in a double blind manner.

Each treatment was followed by performance tests which consisted of: 1) Right knee extension and flexion strength, measured with the
Cybex II isokinetic dynamometer, 2) Right knee extension/flexion endurance, measured with the Cybex II isokinetic dynamometer, 3) Anaerobic power, measured with the Fitron Stationary bicycle, 4) Aerobic power, measured with a maximal treadmill graded exercise test.

Results showed no difference (P<.05) between any of the treatments and the subjects' mean performances on all of the test parameters.

Conclusions

Within the limitations of this study, the following conclusions were derived:

1. Verapamil, Nifedipine, and diltiazem, when given in currently recommended doses, do not effect skeletal muscle strength in normal adult males.

2. Verapamil, Nifedipine, and diltiazem, when given in currently recommended doses, do not effect skeletal muscle endurance in normal adult males.

3. Verapamil, Nifedipine, and diltiazem, when given in currently recommended doses, do not effect anaerobic power in normal adult males.

4. Verapamil, Nifedipine, and diltiazem, when given in currently recommended doses, do not effect aerobic power in normal adult males.
5. These findings support the theory of this group of calcium antagonists having effects specific to cardiac and smooth muscle in humans.

**Recommendations**

Possibilities for further investigation include:

1. An aerobic training study to determine the effect of these agents on the training response as it relates to changes in stroke volume, cardiac output, and $d_p d_t$ max.
### Analysis of Variance for Right Leg Extension 60°/sec.

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### Analysis of Variance for Right Leg Flexion 60°/sec.

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### Analysis of Variance for Right Leg Flexion 180°/sec.

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Analysis of Variance for
Right Leg Extension 300°/sec.

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Analysis of Variance for
Right Leg Flexion 300°/sec.

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### Analysis of Variance for Right Leg Extension/Flexion Endurance 180°/sec

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### Analysis of Variance for Relative Anaerobic Power

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### Analysis of Variance for Maximal Oxygen Consumption

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### Analysis of Variance for Time on Treadmill

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## Analysis of Variance for Maximal Heart Rate

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47. Singh B: An overview of slow channel blocking drugs: Pharmacological basis for therapeutic applications. Cardiology. 69: Suppl. 1, 2-25, 1982


