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DRUG-EXERCISE INTERACTIONS

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INTRODUCTION

The bulk of the studies performed to investigate the effects of drugs on exercise and of exercise on drug biotransformation have dealt with the antihypertensive class of medications. However, complicating the understanding of drug-exercise interactions are the confounding contributions of caffeine, salicylates, anabolic steroids, and alcohol consumed as ergogenic aids in normals and those with cardiovascular diseases. In patients with hypertensive and other forms of cardiovascular disease who exercise or who are undergoing cardiac rehabilitation, it is beneficial to allow activity without the adverse effects of extreme increases in pulse rate, blood pressure, catecholamines, and potassium. As a result, laboratories are seeking drugs that will allow a patient to exercise while keeping this expected rise in exercise parameters modest, protecting an oftentimes compromised and vulnerable myocardium.

In general, all the drugs consumed by patients with cardiovascular disease, with the exception of β–adrenergic blocking agents, permit a normal exercise response. This normal response acutely is an increase in systolic and no change or fall in diastolic blood pressure and an increase in heart rate, stroke index, and cardiac index. Following a conditioning program, the various regulatory responses result in the appropriate increases during physical activity but at a lower level.

The majority of the studies reported have investigated the effects of drugs

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during acute episodes of exercise. The literature contains short-term chronic studies but they are scant in number. Within the context of this paper, we will show some evidence for the long-term effect on patients receiving propranolol and performing dynamic physical activity, citing the training capability even when on a β–adrenergic blocking agent. Thus, when the majority of antihypertensives, calcium-channel blocking drugs, digitalis preparations, antiarrhythmic agents, and nitrates are prescribed, there is no embarrassment to the acute response during stress testing or beyond the initial exercise period, wherein training effects would be blunted.

Review material will be presented that relates the biochemical and physiologic responses to exercise in people taking ergogenic acids. The paper will also attempt to elucidate the effects of drugs on the hemodynamic and/or biochemical responses during stress testing and where possible refer to the long-term effects of training under the influence of such drugs taken for cardiovascular disease.

DRUGS USED IN CARDIOVASCULAR DISEASES AND THE EFFECT OF EXERCISE

Diuretics

The hemodynamics of diuretic effect have been studied by Lund-Johansen (1), who found that not all diuretics have similar actions during exercise. Thiazides bring about a drop in exercise blood pressure via a decrease in peripheral resistance and plasma volume. Thiazide-like diuretics, specifically chlorthalidone 100 mg daily, were shown to reduce blood pressure during exercise by decreasing cardiac output. However, at dosages of 200 mg per day, there was a paradoxical increase in diastolic blood pressure and heart rate (2), probably a reflection of marked volume contraction. Long-term thiazide dosing does not cause a drop in cardiac output. Although studies involving drug effects on exercise have included patients with heart failure who are taking furosemide, no studies dealing with this drug's direct effects on exercise parameters have been carried out. Additionally, as with any diuretic therapy, hypokalemia can become significant, resulting in moderate ST segment depression, cardiac irritability, and skeletal muscle fatigue.

During vigorous exercise serum potassium increases. The source is skeletal muscle. This can occur in the setting of diuretic-induced hypokalemia, and the response indicates that total body potassium is not depleted (3). However, to insure against potassium loss, patients on diuretics should receive potassium supplements.

Thus, diuretics result in a moderate decrease in the blood pressure response to exercise, and, with adequate potassium supplementation, should not invoke any drug-related risks during physical activity.

Central α Agonists

Many studies dealing with the central α-agonist antihypertensives have been recently performed. Both clonidine and α-methyldopa (methyldopa) decrease central and/or peripheral outflow of catecholamines. This results in reductions of plasma norepinephrine at rest and during exercise (4, 5). Although both of these drugs can blunt the sympathetic response during exercise, they have significantly different hemodynamic effects.

During bicycle ergometry in mild hypertensives, methyldopa may decrease the blood pressure and heart rate response (6). Total peripheral resistance and cardiac output may (7) or may not (8) decrease. On the contrary, work in our laboratory with normals taking methyldopa in multiple doses for one week demonstrated no decrease in heart rate at rest or at peak exercise, yet systolic pressure was reduced at these times after one week of treatment (9). Differences between this and clonidine's response may result from the peripheral effects of the false neurotransmitters of methyldopa.

Clonidine differs from methyldopa in that, in addition to reducing blood pressure and heart rate during exercise, it decreases both resting blood pressure and pulse rate (10, 11). The decrease in heart rate through central vagal stimulation results in a drop in cardiac output (12). This, however, is not considered a negative inotropic property, since after chronic use cardiac output is normalized.

In several studies (5, 9, 11), the exercise-associated changes seen in serum potassium, renin, and aldosterone have been observed in normal volunteers following single and multiple doses of clonidine and methyldopa. Increases in potassium during dynamic exercise in subjects taking clonidine or methyldopa were parallel to the response on placebo. With both α agonists, plasma renin concentration was suppressed at rest and the expected increase was blunted during exercise at maximum dosages. Plasma aldosterone apparently had no significant differences in value with the drugs when compared to placebo, increasing during exercise in all groups. No significant ST-T changes have been shown to occur during exercise using these drugs. The rise in diastolic blood pressure (DBP) induced by isometric activity, i.e. 50% handgrip, may be decreased with methyldopa or clonidine, especially if the resting DBP is reduced. However, the mean change is not different from rest to peak handgrip during placebo and with multiple doses of these drugs (Figures 1, 2; Tables 1, 2).

β *Blockers*

The hemodynamic changes during exercise have been intensively studied in association with β-blockade. Response mechanisms as they relate to isometric and dynamic activity lead to a reduction in cardiac output without any peripheral vascular effects. A reduction in myocardial contractility and heart rate are the

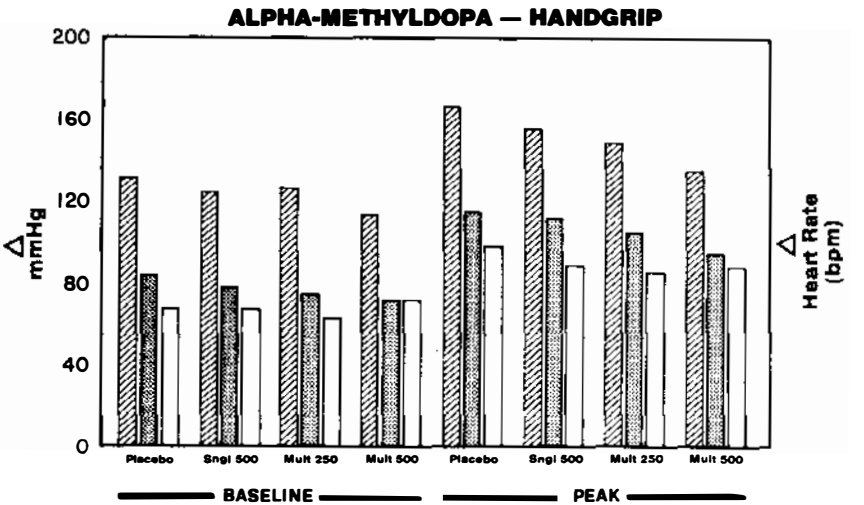

Figure 1 50% handgrip systolic and diastolic blood pressure and heart rate response under the influence of placebo, methyldopa 500 mg, methyldopa 250 mg bid for one week, and 500 mg bid for one week. Patients were studied at rest and at peak levels of activity. The change from baseline to peak is no different from placebo through maxiumum dosage. Resting diastolic pressure is apparent with the chronic dosing regimen and thus peak response is blunted.

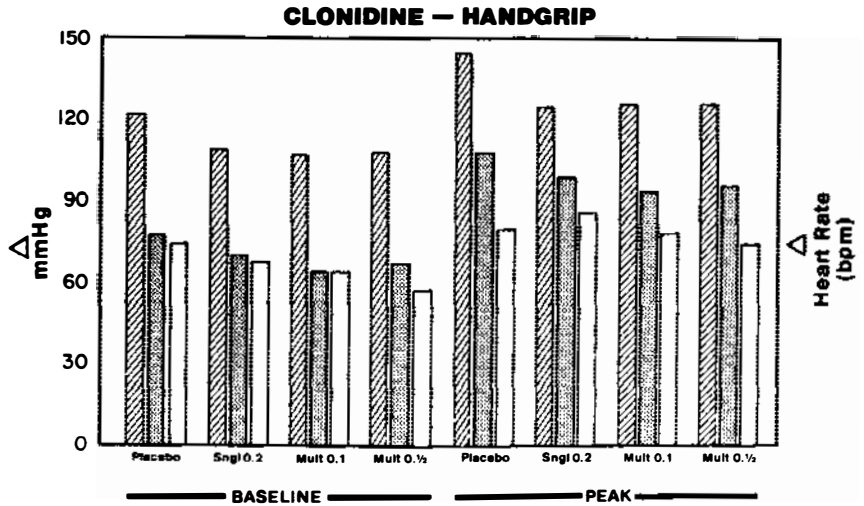

Figure 2 50% handgrip systolic and diastolic blood pressure and heart rate response under the influence of placebo, clonidine 0.2 mg single, 0.1 mg bid, and 0.1 mg AM and 0.2 mg PM each times one week. Patients were studied at rest and at peak levels of activity. The change from baseline to peak is no different from placebo through maximum dosage. Resting diastolic pressure is apparent with the chronic dosing regimen and thus peak response is blunted.

Table 1 Antihypertensives that do not blunt cardiovascular response during dynamic physical activity (bicycle ergometer or treadmill)

Clonidine
Diuretics
Guanabenz
Methyldopa
Nifedipine
Prazosin
Verapamil

Table 2 Antihypertensives that obtund the diastolic pressor response to static exercise (handgrip 50%)

Atenolol
Clonidine
Methyldopa
Prazosin
Propranolol

basis for these alterations. Both bring about a longer diastolic phase that allows for better coronary perfusion. This observation lends itself best to patients with coronary artery disease who undergo cardiac rehabilitation. Many of these subjects have increased dynamic exercise duration, less angina, and fewer incidents of ST depression (13). Indeed, it has been shown that up to a 31% improvement in exercise capacity as a direct result of training can occur in patients with ischemic heart disease on propranolol (14). It has been postulated that since cardiac output is reduced to a greater extent than is blood pressure, peripheral resistance must increase (15, 16). This results from the fact that α receptors are not blocked and can give rise to vasoconstriction with catecholamine release during exercise (15). However, this increased vascular resistance is thought to be obtunded by chronic β-blockade, leading to lower blood pressure (17, 18).

It has been demonstrated that in patients with ischemic heart disease receiving β–adrenergic blocking drugs (BABD), a training effect can be observed even though there is an obtundation of the normal cardiovascular response. This implies an increase in the duration of activity over a period of time as well as an increase in the workload being performed. Studies in our laboratory (19) have confirmed this data and have extended them into a consideration of whether the elderly are capable of achieving a similar training effect on and off the β–adrenergic blocking drugs. The data in Tables 3 and 4 show that

Table 3 Relationship between age and dynamic training[a]

	≤ 54 years		> 54 years	
	Pre-training	Post-training	Pre-training	Post-training
Total exercise duration (min)	11 ± 3	15 ± 4[b]	8 ± 2	13 ± 2[b]
Exercise workload (kpm)	678 ± 295	1163 ± 393[b]	386 ± 222	713 ± 179[b]

[a] Values are mean ± SD
[b] $p \leq .001$

Table 4 Relationship between β-adrenergic blocking drugs (BABD) and dynamic training[a]

	On BABD		No BABD	
	Pre-training	Post-training	Pre-training	Post-training
Total exercise duration (min)	9 ± 3	14 ± 4[b]	10 ± 3	14 ± 3[b]
Exercise workload (kpm)	474 ± 279	933 ± 337[b]	592 ± 313	1020 ± 375[b]

[a] Values are mean ± SD
[b] $p \leq .001$

regardless of age, i.e. greater or less than age 54, and regardless of β-blocker regimen, patients can have a training response. The factors of age and BABD considered independently demonstrated significant increases in the pre- and post-training values of exercise duration and workload. Training in this particular study totaled eight weeks, three times per week, 45 minutes per session, using treadmill, bicycle ergometer, arm ergometry, rowing machine, steps, wall pulleys, and light weights.

In regard to isometric and isotonic physical activity, propranolol and the cardioselective β-blockers atenolol and metroprolol have been studied in normal volunteers against placebo (5, 9, 20, 21). In a study comparing propranolol, metoprolol, and placebo in a graded treadmill exercise, it was shown that both heart rate and systolic blood pressure are reduced at maximum exercise (20). There were no significant changes in diastolic blood pressure, oxygen consumption, or anaerobic threshold (that point at which oxygen consumption fails to increase in proportion to minute ventilation) (20). According to Sklar et al (20), this indicates blood flow to the active muscles is unaltered.

Pharmacodynamically there may be some small differences between car-

dioselective and nonselective β–adrenergic blocking drugs (22). Following nine months' administration of chronic atenolol, metoprolol, pindolol, and sustained-release propranolol, researchers found that atenolol and metoprolol reduced exercise-induced increases in systolic blood pressure significantly whereas pindolol and propranolol did not. Cardioselective β blockers therefore appear to be more effective than nonselective agents in blunting the increase in systolic blood pressure with dynamic physical activity. On the other hand, there is marked interindividual variability of β blocking effects on heart rate and blood pressure during exercise (23). Normal volunteers given parenteral metroprolol or placebo in intraindividual cross-over design using bicycle ergometry showed comparable plasma levels of metoprolol after each intravenous dose, but the extended inhibition of exercise-induced tachycardia or increase in systolic blood pressure varied considerably among the subjects (23). There was never any correlation between the extended inhibition of heart rate and systolic blood pressure increase during exercise on β blockade. The extent of a β-blocking effect on these parameters is an individual constant in acute as well as in chronic conditions.

Studies in our laboratory (21) dealing with isometric exercises in which normal volunteers are dosed with atenolol and propranolol indicated that both resting and peak exercise diastolic blood pressures are reduced at maximum dosages when compared to placebo. This is due to a reduction in rest DBP and the ensuing lower pressor response to handgrip. The mean change from rest to peak is no different with placebo or with single or multiple doses of the drugs (Figures 3, 4). Although disputed by investigations indicating the failure of antihypertensives to attenuate blood pressure rises during isometric exercise (7, 10), the data (21) imply that persons with cardiovascular disease receiving antihypertensive therapy may be at decreased risk for pressor response when performing arm labor.

Similar results have been discovered in research with hypertensive patients on β-blocking drugs (4). In these subjects, both metoprolol and propranolol reduced heart rate and systolic blood pressure at rest and at peak exercise over placebo controls. Concurrently, similar decreases in heart rate and diastolic blood pressure at rest and at peak activity were seen when the patients used a 30% hand grip exercise. However, it was shown that in patients with borderline hypertensive heart failure as defined by radiologic criteria, i.e. cardiac enlargement, M-mode echocardiography, and ECG findings, metoprolol, with and without prazosin vasodilatory treatment, does not safely abolish dangerous increases in blood pressure during isometric activity (24–27).

The studies on the metabolic effects of β blockade during exercise have produced a number of provocative results. Propranolol in single and multiple doses has been reported to cause an increase in serum potassium significantly greater than placebo during dynamic exercise. However, it has more recently

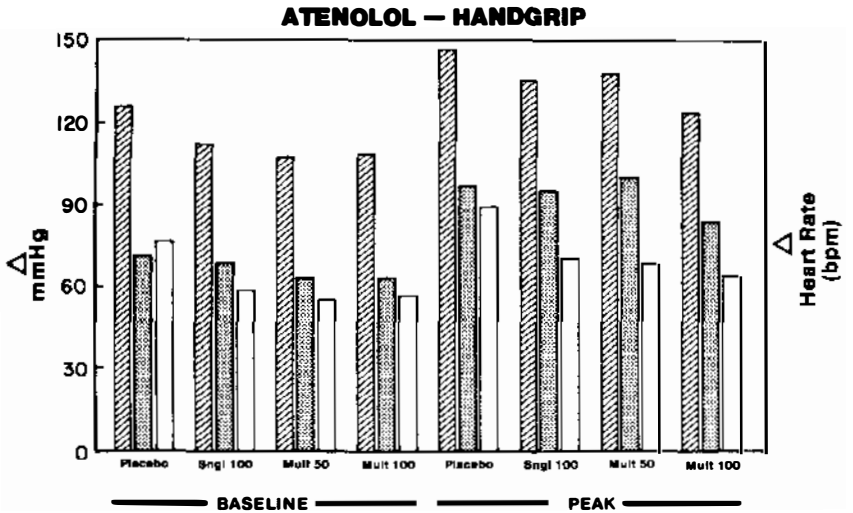

Figure 3 50% handgrip systolic and diastolic blood pressure and heart rate response under the influence of placebo, atenolol 100 mg single, 50 mg bid for one week, and 100 mg bid for one week. Patients were studied at rest and at peak levels of activity. The change from baseline to peak is no different from placebo through maximum dosage. Resting diastolic pressure is apparent with the chronic dosing regimen and thus peak response is blunted.

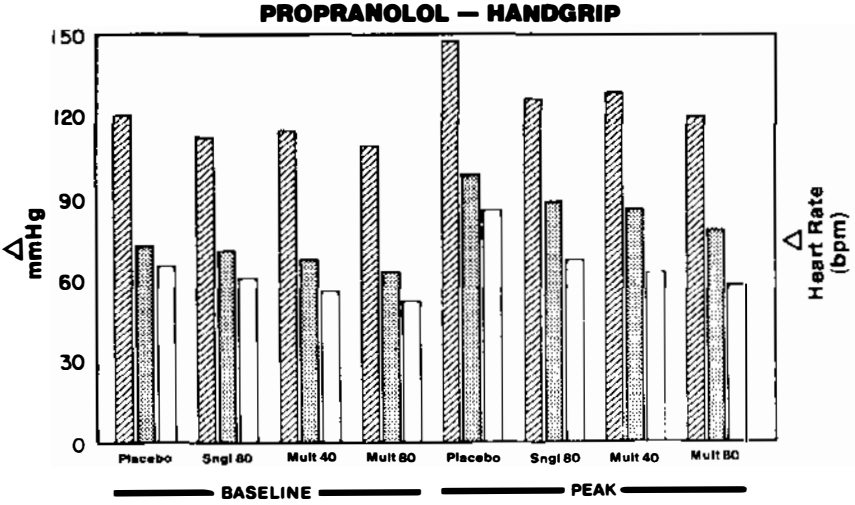

Figure 4 50% handgrip systolic and diastolic blood pressure and heart rate response under the influence of placebo, propranolol 80 mg single, 40 mg bid for one week, and 80 mg bid for one week. Patients were studied at rest and at peak levels of activity. The change from baseline to peak is no different from placebo through maxiumum dosage. Resting diastolic and pressure is apparent with the chronic dosing regimen and thus peak response is blunted.

been shown that this hyperkalemic effect may occur only upon initial treatment with the drug (5). In addition, Lowenthal et al (5) revealed that β blockade results in significantly decreased levels of renin at rest and at peak exercise. Despite this, when compared to placebo, no changes in plasma aldosterone values have been seen, most likely because of a lag time in the suppression of the renin-aldosterone axis or because of too low a dosage of propranolol (40 mg bid for one week). Unlike the central α agonists, propranolol and metoprolol either increase plasma norepinephrine (28) or give rise to expected normal increases in plasma values (5, 29) during physical activity. The latter observation has been attributed to the hypothesis that during light exercise vagal withdrawal occurs yet sympathetic activity does not increase until the heart rate rises beyond 30 beats per minute (30).

In order to determine the origin of β-receptor antagonist-induced exercise fatigue seen in normal, active individuals (in contrast to drug-induced exercise longevity in cardiac patients), Lundborg (29) undertook a study to examine specific metabolic effects of β blockade. After the disruption of neuromuscular transmission and decreased blood flow to working muscles were ruled out as causes of subject fatigue, investigators targeted exercise substrate limitation, i.e. glucose and nonesterified fatty acid availability. In fact, blood glucose, nonesterfied fatty acid, and glycerol levels were found to be significantly reduced during bicycle activity on propranolol and metoprolol. This was followed by more rapid rises in glucagon levels on the drugs and most likely results from decreased muscle glycogenolysis, a β–adrenoreceptor mediated process.

Conflicting metabolic studies involving β blockade during exercise include the finding that neither propranolol nor metoprolol decreases the ventilatory response to CO_2 during physical activity (30). This would be significant for the management of COPD patients, in whom these drugs will not worsen CO_2 retention at rest or during exercise. On the contrary, following 80 mg of propranolol given in single oral dosage to normal volunteers, the response to submaximal and maximal bicycle ergometry revealed a reduction in oxygen consumption at both submaximal and maximal efforts (31). These changes were not related to any difference in muscle fiber type distribution (32–34). It has been suggested that individuals with muscles made up of high proportions of slow twitch fibers and possessing a great capillary supply were most impeded by β-adrenergic blockade.

Similar results have been obtained at submaximal workloads of 50% and 70% wherein ventilation (VE), CO_2 (VCO_2), and O_2 uptake (VO_2) were measured. Propranolol effected an early reduction in all of these parameters at 50% and 70% maximum by five minutes (35). Ventilation was greater at five minutes owing to an increase in venous lactate, and the initial reductions in VO_2 and VCO_2 were related to reduction in cardiac output and muscle perfusion

induced by the propranolol. Since anaerobic metabolism is increased early during heavy exercise, the increase in ventilation could be explained on this basis. These results could not necessarily be extrapolated to individuals with impaired cardiac function (35).

Finally, another unrelated investigation pointed out that plasma levels of both propranolol and acebutolol increase significantly during exercise; this occurrence is possibly related to pH changes during physical activity (36) or possibly attributable to the decrease in hepatic blood flow during activity that would affect those drugs with a high hepatic-extraction ratio.

Vasodilators

The vasodilators, used adjunctively with other drugs in the treatment of hypertension, include hydralazine, minoxidil, and prazosin (more of an atypical α antagonist than a direct-acting vasodilator) for which a number of exercise-related investigations have been performed.

In normal volunteers, hydralazine acts to decrease arterial pressure with a resultant reflex tachycardia. This tends to increase cardiac output through an increase in sympathetic drive, which in a compromised heart may lead to myocardial ischemia, e.g. angina and/or infarction, in cardiac patients (37). However, the drug is useful as an afterload reducer in chronic heart failure (38). Prazosin, an atypical α blocker, similarly has been shown to decrease mean arterial blood pressure and total peripheral resistance at rest and at dynamic workloads (39). In contrast to hydralazine, during arm-cycle ergometry using single and multiple prazosin doses, there is no reflex increase in heart rate or pressor response greater than that seen when compared to placebo (40). During isometric activity, hydralazine neither improves skeletal muscle oxygen delivery during exercise in patients with heart failure (41) nor adequately attenuates isometric-induced increases in sympathetic activity (24, 42).

Prazosin therapy results in reduction in both baseline and peak exercise values of diastolic and systolic blood pressure during 50% hand-grip activity at single and multiple doses (42). Since upper-extremity activity confers a greater heart rate-blood pressure product than the type of work seen with lower extremity activity, the blood-pressure response to prazosin during graded arm ergometry exercise reveals that prazosin does significantly lower systolic blood pressure at rest and at peak exercise; however, no change in heart rate has been observed. There is a fall in diastolic blood pressure, as would be anticipated with any form of dynamic physical activity. This data is based on studies in normal volunteers and may not necessarily be extrapolated to draw conclusions of safety in patients with ischemic heart disease and/or heart failure.

As a result of the increasing use of vasodilators in cardiac patient management, a great deal of interest in the effects of these drugs during exercise of heart-failure subjects has arisen. While increasing cardiac output with reduc-

tion in afterload, hydralazine reduces both arterial and pulmonary wedge pressure and increases stroke volume at rest and to a lesser degree during bicycle exercise in patients with chronic heart failure (38). The reduced effect during physical activity is thought to reflect initial impaired pump function and may also give rise to the observation of unimproved exercise tolerance despite improved hemodynamic parameters with oral hydralazine. In addition, hydralazine does not increase compromised blood flow to peripheral musculature during hand-grip activity in patients with heart failure, indicating that its vasodilatory effect does not add to that of local metabolic effects (41), the significance of which may also limit improvement in exercise tolerance of these individuals treated with the drug. Prazosin has been tested in patients with borderline hypertensive heart failure (25), giving rise to the observation that the drug similarly improves hemodynamics (cardiac output) and obtunds the increases in diastolic blood pressure associated with isometric activity. Minoxidil, a most potent direct vasodilator, may improve exercise tolerance in patients with chronic heart failure due to its afterload-reducing properties.

Angiotensin–Converting Enzyme Inhibitors

Captopril is an angiotensin–converting enzyme inhibitor. Data on its effects on dynamic exercise vary among investigators. Although Pickering and coworkers (43) found no changes in blood pressure or heart rate during graded treadmill activity, other studies indicate a significant reduction in systolic and diastolic blood pressure during bicycle exercise (44), seen to be even more pronounced during physical activity than at rest (45). Similar decreases in blood pressure with dynamic activity have been seen with saralasin, an angiotensin II partial antagonist (46). The reduction in angiotensin II with captopril and saralasin, coupled with an unaltered blood-pressure response to exercise, indicates that angiotensin II is not a major determinant of blood-pressure regulation during exercise in hypertensive patients.

Manhem and colleagues (44) investigated the metabolic effects of captopril during dynamic exercise, measuring the drug's effect on catecholamines, renin activity, angiotensin II levels, and plasma aldosterone. After 4–5 days of high-dose captopril, both angiotensin II and plasma-aldosterone levels were reduced significantly at rest and during physical activity. Plasma-renin activity underwent increases over placebo at baseline and peak exercise, while concentration of norepinephrine and epinephrine remained unchanged.

Calcium Antagonists

The calcium antagonists verapamil and nifedipine have differing clinical usages, the former as an antiarrhythmic agent particularly in paroxysmal atrial tachycardia, the latter in treatment of angina and in post-MI and CABG management to prevent further ischemia and augment collateral myocardial

flow (47). However, both drugs are equally effective as antianginal agents and useful in post-MI and CABG management. The understanding of their effects on physical activity is important in terms of rehabilitating cardiac patients while on these drugs.

In normal, active volunteers, both nifedipine and verapamil have little effect on resting and treadmill or on systolic and diastolic blood pressure, although verapamil appears to have a slight obtunding effect on diastolic blood pressure increases during isometric exercise (48). In patients with chronic angina, however, studies have shown consistent improvement in patients on both verapamil (49) and nifedipine (50). The reductions in exercise-induced angina and ST-depression seen in these patients is thought to be due to a reduction in myocardial oxygen demand, and this is associated with a decrease in afterload with both drugs (50, 51). An enhancement of left ventricular diastolic filling seen with verapamil may also explain some of the beneficial effects with its usage in the angina syndrome. Although serum potassium levels were seen to rise in isometric activity with placebo in a recent study (48), no significant variance from this increase could be seen in either isometric or dynamic activity with these calcium antagonists. Thus, verapamil and nifedipine may be used during training programs with cardiac patients without risk of dangerous increases in blood pressure or serum potassium when compared to placebo.

Nitrates

In normal men, nitrates, represented by nitroglycerine and isosorbide dinitrate, have a number of hemodynamic effects, most attributable to their venodilatory actions. These include reduced mean arterial pressure, decreased cardiac filling and increased heart rate (52). During dynamic activity, these parameters balance out to produce an unchanged cardiac output as determined by exercise radionuclide angiography (53). More important, however, are changes resulting from the drug in patients with coronary artery disease and/or heart failure. It is well known that nitroglycerine is effective in controlling angina pectoris, and it follows that it also increases exercise duration limited by chest pain in most patients. These actions are thought to result from a decrease in preload that gives rise to a reduction in left ventricular end-diastolic pressure (LVEDP) (53). An earlier theory involving the redistribution of blood flow to ischemic myocardium is apparently less valid (54).

The long-acting nitrate isosorbide dinitrate is similar in its effects on exercise. In patients with congestive heart failure these changes are not seen during initial treatment, but improvement in cardiac output, oxygen consumption, and exercise duration occur after three months of treatment when compared to placebo (55). This is thought to be due possibly to a time-related enhancing of peripheral utilization of oxygen by the drug. Isosorbide dinitrate does not

improve vasodilation in exercising muscle of patients with congestive heart failure in short-term drug administration (41). With individual dosages of isosorbide dinitrate and compared to placebo, the mean exercise time of patients with angina due to coronary heart disease increases 54% at one hour following drug dosing, 36% at three hours, and 13% at five hours (56).

The acute administration of 20–50 mg of isosorbide dinitrate to 21 patients with the angina syndrome resulted in a significant reduction in resting systolic pressure from a half hour to five hours after drug dosing. It also produced a marked increase in heart rate within the same time frame after drug dosing. These changes were significant when compared to placebo. Other studies have demonstrated an increase in net exercise time of at least 25% at one hour after isosorbide dinitrate dosing, with similar results at three hours and at five hours (57). These results have been reproduced by others wherein an enhanced exercise tolerance has been demonstrated in patients with angina receiving large doses of oral isosorbide dinitrate. In patients undergoing exercise, nitrates will not bring about any worsening in ST-segment changes during physical activity (56). In fact, reduced ECG evidence of myocardial ischemia after exercise has been observed in patients with angina after they have received large doses of isosorbide dinitrate (58).

Digitalis

A great deal of research involving digitalis and exercise has been performed. In normal volunteers, digitalis causes a reduction in heart rate and cardiac output with no change in blood pressure (50). It has also been shown to produce ST-segment depression during exercise in persons with normal coronary vessels (13). In patients with congestive heart failure, digitalization brings about a reduction in ventricle size and oxygen consumption at baseline (60) and decreases left ventricular end diastolic pressure during exercise (61). Unfortunately, however, no changes in exercise tolerance have been noted in these patients (62). Arrhythmias associated with the drug can be provoked by exercise, especially with concurrent diuretic-induced potassium depletion (63). As a result, patients who take digitalis should be monitored carefully in any training program with regard to electrolyte values as well as for ectopy.

Antiarrhythmics

Studies by Gey and co-workers (64, 65) have shown that procainamide and quinidine exhibit no change in heart rate or oxygen uptake during dynamic exercise, yet a slight drop in systolic blood pressure may be observed. Exercise-induced arrhythmias were seen to decrease in number and to be of less severity in most patients in the study. Others have pointed out that both procainamide and quinidine can mask exercise-induced ST-segment depres-

sion-producing false negative stress tests (66, 67). Thus, in patients with demonstratable ectopy during physical activity not corrected by overdrive suppression, these drugs may be used effectively to reduce the risk of exercise-induced arrhythmias.

Conclusion

The graded treadmill or cycle ergometry exercise must be interpreted in the context of the drug regimen the patient is following. An appreciation of the hemodynamic and/or biochemical changes induced by drugs is critical for a logical critique of the performance of the patient during exercise and for the projected exercise prescription that the patient is being asked to follow. Drug therapy is clearly not a contraindication to acute or chronic exercise as long as the principles of basic exercise physiology in the unmedicated can be translated and understood in the medicated patient.

ERGOGENIC AIDS TO PERFORMANCE

In spite of physicians' efforts to provide rational and individualized therapy for patients and despite warnings to healthy participants in sports, the consumption of caffeine, salicylates, nonsteroidal antiinflammatory drugs (used to decrease colonic motility in runners), alcohol, anabolic steroids, and amphetamines to improve performance is rampant.

The following will amplify on the salient effects of a number of these drugs and their interaction during exercise.

Caffeine

Caffeine has long been considered an ergogenic aid and/or doping agent (68) that can elicit physiological changes to enhance work or athletic performance (69, 70, 72, 73). However, the ergogenic effects of caffeine and related methylxanthine compounds are often unclear and equivocal. The lack of a well-defined understanding of caffeine's influence on work or athletic performance enhancement may be due to caffeine-induced physiological responses that are influenced by dose (74, 75), differ between habitual and nonhabitual users (75–79), and elicit both direct and indirect effects.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM Caffeine and related methylxanthines have been documented to exert a stimulating action on the central nervous system (80, 81) because of the ability of these compounds to pass the blood-brain barrier (82). Caffeine increases locomotor activity (81), increases spontaneously firing units in the sensorimotor cortex (80), and may act directly on the medullary vasomotor and vagal centers (83).

Caffeine has been demonstrated to decrease the perception of drowsiness

while increasing the perception of alertness (76) and possibly to reduce the perception of fatigue during prolonged work (69, 71, 77). The exact mechanisms responsible for the decreased perception of fatigue during prolonged work after caffeine ingestion are unclear but possibly occur by reducing neuronal thresholds (84), by influencing central catecholamine receptors, and/or by a direct effect on the adrenal medulla (85).

Caffeine may exert its influence in part as an antagonist to adenosine receptors in the brain (86). Adenosine has depressant, anticonvulsant, and hypnotic properties in the central nervous system. Adenosine antagonism occurs at lower caffeine concentrations than are needed for peripheral actions (87). This observation suggests that caffeine increases arousal and thereby decreases the perception of fatigue by its antagonistic effect on adenosine receptors. Potentiation of adenosine-elicited inhibition in the central nervous system may occur through norepinephrine, which rises with caffeine administration, suggesting that caffeine alters some of the neural actions of this transmitter. Certainly, considerable research remains to elucidate the mechanism(s) of caffeine on the reduced perceptors of fatigue by the central nervous system during prolonged work.

EFFECTS ON SKELETAL MUSCLE Caffeine and related methylxanthines may potentiate the contractile activity of skeletal muscle by the following mechanism(s): (*a*) facilitation of neurotransmitter release and impulse transmission; (*b*) potentiation of twitch responses in both rested and fatigued muscle.

Caffeine and related methylxanthines have been reported to have an effect on neuromuscular impulse transmission (88). The enhancement of neuromuscular impulse transmission may be due to a prejunctional action via increased acetylcholine release (89). Expanding the work by Waldeck (84) to the myoneural junction, the possibility exists that caffeine increases neuronal excitability by reducing neuronal threshold.

Caffeine will rapidly distribute to skeletal muscle mass whether administered in vivo (90) or in vitro (91), and the physiological response to caffeine is proportional to its concentration (74). Enhanced in vitro muscle tension production has been observed when caffeine is added to normal Ringer's solution (92). Caffeine has been shown to induce shortening of the muscle resting length (91); the degree of shortening may be due in part to fiber types (91, 93). In these studies, high doses of caffeine result in "contractures" and loss of ability to respond to electrical stimulation with a twitch. Researchers have proposed that changes in muscle length are mediated by calcium release and independent of electrical activity at the sarcolemma (94). The phenomenon known as *escalation* (95) is related to caffeine-induced local release of calcium from the sarcoplasmic reticulum that in turn induces further release along the sarcoplasmic reticulum. However, this calcium release is not enough to induce a full

twitch. Caffeine's ability to induce a release of calcium suggests that caffeine may enhance muscle contraction, thereby reducing the state of fatigue in working muscle. Caffeine's enhancement of contractile state during times of muscle fatigue is suggested to be due in part to an increase in calcium permeability of the sarcolemma (96) and/or vesicles (97), a more rapid calcium release (98), and/or a decrease in calcium uptake (99) by the sarcoplasmic reticulum, and in part to an increase in cyclic AMP levels by the inhibition of phosphodiesterase (100) or mediated by all the forecited proposed mechanisms (101). Metabolically, the accumulation of glucose-6-phosphate may enhance contractility (102). The increase of glucose-6-phosphate is due to caffeine's stimulation of glycogenolysis (81, 103).

SUBSTRATE MOBILIZATION AND UTILIZATION Fuel availability, in particular muscle glycogen, is related to exhaustion during prolonged exercise in which glycogen is significantly degraded (104–106). Caffeine may exert a pronounced influence on substrate mobilization and utilization during prolonged work by stimulating adipocyte lipolysis (69, 77, 107) via the activation of lipase (108); by altering glucose homeostasis, inducing a hyperglycemic action (81); by activation of liver phosphorylase (109); and/or by affecting muscle triglyceride utilization (110–112) and fatty acid availability. Caffeine is proposed to alter these substrates via inhibition of phosphodiesterase, which alters the concentration of cyclic AMP (100) and/or increases plasma catecholamine levels (75, 85, 113).

The stimulation by caffeine of adipocyte lipolysis (via lipase) may be due to either direct inhibition of phosphodiesterase (114, 115), which increases the activity of cyclic AMP, or by an indirect effect of increased catecholamine. Catecholamines may activate adenyl cyclase, thereby increasing cyclic AMP activity (116). The indirect effect of catecholamine stimulation is probably the primary mechanism, since phosphodiesterase inhibition requires caffeine levels several-fold greater than levels required to stimulate catecholamine-induced lipolysis (69, 77, 107, 117). Exercise stress itself increases circulating catecholamines (116), which in the presence of caffeine should markedly stimulate lipolysis (115).

The profile and the time course of plasma free fatty–acid elevation are altered by caffeine dose (71, 75, 77, 118). However, the increased mobilization of adipose free–fatty acids would make more free fatty acids available to working muscle. Free fatty acid uptake by muscle increases with the duration of exercise and free fatty acid oxidation progressively increases with time (119, 120). Increased oxidation of free fatty acids for the same intensity of work would in turn suppress glycogen degradation, thereby "sparing" glycogen (69, 71, 120). The sparing of muscle glycogen would be due in part to the high rates of fatty

acid oxidation, which may inhibit the activities of phosphofructokinase and pyruvate dehydrogenase reactions (121–123).

The increased turnover of free fatty acids in man cannot account for all of the fat oxidized during prolonged work (112, 124, 125). Therefore, local triglyceride stores must be oxidized in working muscle (126). Caffeine influences muscle triglyceride utilization (77, 127). In his study, Crass estimated that endogenous triglyceride utilization increased by about 60% during 30 minutes of exercise. Theophylline, a methylxanthine, has also been demonstrated to stimulate endogenous utilization of triglycerides (110).

CAFFEINE AND EXERCISE PERFORMANCE Caffeine has been demonstrated to significantly improve work production in trained cyclists and cross-country skiers (71, 128). It is interesting to note that in the cycling study (71) perception of the intensity of the activity remained unchanged from the control conditions, even though oxygen consumption increased with the additional work. Another study from the same laboratory demonstrated that caffeine administration prolongs the time to voluntary exhaustion by about 12% when working at 80% of maximum oxygen consumption (69). In this study, the perceived exertion was lower with caffeine administration. These findings are supported by earlier investigations in which caffeine was reported to increase an individual's work output on a bicycle ergometer work time to exhaustion (73, 129). Enhancement of work performance only occurs during prolonged cycling ergometry work and not during short-term work episodes (129) (Table 5).

Caffeine administration has no apparent influence on work performance of short-duration exercise (129). Speed enhancement for a 100-yard swim was found to be unaffected by caffeine administration (130). Likewise, caffeine has been shown to have no effect on short-duration tasks such as work capacity on the Balke walking treadmill test (131), short-term cycling to exhaustion (132), and running to exhaustion on a treadmill (133). In cardiac patients, caffeine administration has resulted in no effect on isometric grip and cardiovascular parameters during a stress test (134).

Salicylates

Salicylates and similar nonnarcotic analgesic and antiinflammatory agents are often used by athletes, athletic trainers and team physicians for a variety of musculoskeletal disorders. The availability and the numerous therapeutic applications of salicylates and other nonnarcotic analgesic compounds make them one of the most commonly used groups of agents worldwide. Aspirin, the best known nonnarcotic analgesic, is commonly used therapeutically by athletes for its potent analgesic and antiinflammatory properties.

Table 5 Selected caffeine and exercise interactions

Amount of caffeine	Time after ingestion	Subjects	Exercise	Results	Reference
250 mg	90 min.	Untrained	100-yd. swim	No time difference	130
200 mg	?	Untrained	Balke test	No difference	131
390 mg	30 min.	Cardiac patients	3 min. isometric grip	No difference in dysrrhythmias	134
			25 min. arm and leg cycling	No difference in heart rate and blood pressure	134
330 mg	60 min.	Trained cyclist	80% VO_2 max. cycling to exhaustion	Increased work time, FFA, 19.5% glycerol, lipid oxidation. Decreased RQ. No difference. VO_2 max., HR, lactate, glucose	69
5 mg/kg	60 min.	Volunteers	70% VO_2 max. cycling	Increased FFA, 18% increase in TG utilization. Decreased glycogen utilization by 42%. No difference in caloric expenditure.	77
4 mg/kg	60 min.	Trained cross-country skiers	7 mile race; 3 mile race	Decreased time of race at high altitude. Decrease time for 7 mile race at low altitude.	128
250 mg twice	60 min.	Trained cyclist	Variable cycling for 2 hours	Increase total work by 7.4%, and VO_2 max. by 7.3%. Increased FFA by 31%. Increased total fat oxidation.	71

Intolerance to aspirin has been well documented. Commonly cited toxic manifestations include angioedema and rhinitis and bronchial asthma and gastrointestinal complications (135, 136). The severity of these disturbances may be age-dependent (137, 138). Disturbances of acid-base balance and respiratory alkalosis resulting from altered respiratory stimulation have been reported (125, 136, 139). Aspirin intoxication may result in a pronounced pyrogenic effect, which may be due to an uncoupling of oxidative phosphorylation, resulting in paradoxical hyperthermia (140–145).

Exercise increases the metabolic rate and thereby heat production. In hot environments, the physiological responses to exercise are dependent on the intensity of the exercise, the ambient temperature, and the humidity (146, 147). Exercise and aspirin (heat producers) and hot environments (diminish passive avenues of heat dissipation) may result in an increased susceptibility to heat injury.

Paradoxical Hyperthermia

Salicylates have been demonstrated to increase total energy and heat production in healthy resting canines (141, 148), rodents (138, 149), and man (140, 145). In the study by Wood & Reichert (148), heat production in canines increased by about 40% following salicylate administration. This increased heat production, coupled with increased oxygen consumption, has been observed by others (141). Locus of the increased energy production has been thought to be of skeletal muscle origin.

Paradoxical hyperthermia is of clinical importance since severe hyperthermia results when the rate of heat production exceeds the capacity of heat-dissipating mechanisms (150). An increase in total heat production is not the sole cause of hyperpyrexia, however. Severe hyperpyrexia cannot develop unless the normal heat-regulating mechanisms are impaired (151, 152). Passive means of heat loss are attenuated when blood is shunted to the skin (153, 154) to equilibrate the heat-production and heat-dissipation mechanisms. If the ambient temperature is greater than skin temperature, heat cannot be lost through convection and radiation, necessitating the activation of the sweating mechanism for evaporative heat loss (155). Salicylate's direct action of inducing sweating at rest may enhance heat loss, thereby maintaining a constant body temperature. However, during long-duration exercise the efficiency of sweating is important in thermoregulation. Inefficient sweating in hot environments may lead to dehydration and electrolyte and acid-base disturbances (156–158). We have demonstrated 62% and 69% increases in salicylate-induced sensitivity to sweating during exercise bouts for two hours at 25° C and 35° C respectively (150). These findings suggest that sweating occurs at lower rectal temperatures. In a case study (160), researchers suggested that therapeutic doses of aspirin may have resulted in severe heat disturbances during a 100-mile race.

Profuse sweating occurred and symptoms of heat illness, such as chills and loss of thirst, were observed.

In exercise studies where salicylates were administered, varying results have been observed (159, 161). In the study by Troup, oxygen consumption was significantly increased after salicylate administration during the neutral ambient environment. The subjects in this study exercised approximately four times longer than in the two aforementioned studies. Although Downey & Darling (162) did not find a difference in exercise oxygen consumption and rectal temperature, they did report an increase in rectal temperatures during recovery after salicylate administration.

Alcohol

Recently there has been a furor over the supposedly salutary effects of beer consumption for electrolyte replacement during long-distance races, especially marathons (42 km). In long-distance races, runners depend on free fatty acids and triglycerides for energy utilization during the exercise (see caffeine section above) (163–166). Alcohol will raise the levels of circulating fatty acids but will also inhibit the oxidation of this substrate (167, 168). Metabolizing the ethanol-oxidation system accounts for 20%–30% of alcohol metabolism without generating any energy source (167). Alcohol plus an accumulation of reduced NADH may prevent gluconeogenesis, thereby resulting in hypoglycemia (167). Work performed in our laboratory demonstrated a marked decrease in blood glucose after the consumption of 25 ml of ethanol (169). The ethanol was administered in grapefruit juice in two equal volumes of 12.5 ml at 10 minutes prior to and at 30 minutes of a one-hour treadmill run. Blood glucose decreased by 11% between 30 minutes and the termination of exercise, while blood glucose remained constant for the placebo treatment.

Assuming the steady consumption of an alcohol beverage prior to and during a race, the metabolic consequences of alcohol ingestion are impaired gluconeogenesis, hyperuricemia, an increase in free fatty acids, an increase in ketones, and an increase in lactate (167). The rate of liver and muscle glycogen degradation is of paramount importance during a marathon or long-duration race, since glycogen depletion is related to metabolic exhaustion (163–166). Endurance-trained athletes utilize lipids to a greater extent than carbohydrates for energy sources, and untrained athletes depend more on carbohydrate, in particular muscle glycogen, for substrate (163). The low free fatty acid utilization in untrained individuals is associated with high serum lactate concentrations. The fact that ethanol impairs liver gluconeogenesis and fatty acid oxidation should qualify this drug for exclusion during athletic performance.

As a result of training, the skeletal muscle of endurance-trained athletes responds to increased plasma concentrations of free fatty acids by increasing the activity of cytochrome *c* and the rate of lipid oxidation (170). The consump-

tion of alcohol is related to an increase in lactate, a depression of free fatty acid oxidation, and consequently hypertriglyceridemia (168, 169). Coincidentally, carbohydrate loading stimulates insulin release. Insulin inhibits lipolysis (163). Thus, the fashionable practice of carbohydrate loading coupled with alcohol consumption may result in poor lipid utilization even in the trained athlete.

Lactate accumulation secondary to alcohol will block uric acid secretion. In the state of volume contraction and renal hypoperfusion experienced by distance runners, uric acid retention with or without alcohol may be a consequence of muscle catabolism and may play a pathogenic role in rhabdomyolysis (171).

Exercise in hot, humid environments has been reported to be a significant cause of rhabdomyolysis and acute renal failure (171, 172). Exercise-induced rhabdomyolysis occurs in part as a result of potassium deficiency (173). Potassium deficiency diminishes potassium release and blunts the normal exercise-induced increase in skeletal muscle blood flow and produces necrosis of muscle cells. The necrosis may lead to increased hematin, a product toxic to renal tubular cells (174) and uric acid via released muscle purines (175). Uric acid competes with lactic acid for excretion. Blood lactate increases with the increasing intensity of exercise, which may be potentiated after alcohol consumption. This could in turn lead to dangerously high levels of uric acid in renal interstitial fluid, favoring uric acid precipitation and acute renal failure. Since beer consumption while racing is proposed to replenish electrolytes, one would expect higher levels of alcohol consumption in hot environments. The greater levels of alcohol consumption in hot environments may precipitate severe renal problems.

Alcohol is also a myocardial depressant. Impaired myocardial performance parameters, such as a decrease in stroke work with concomitant increase in LVEDP and in the left ventricular work and tension time index, have been reported after alcohol ingestion (176–178). Alcohol consumption has been demonstrated to increase skin blood flow and sweating (179, 180). Heart rate and cardiac output at rest and during submaximal exercise are reported to be higher after ingestion of alcohol, whereas the total arteriovenous oxygen difference and total peripheral resistance decrease. During maximal work, pulmonary ventilation is reduced but circulatory responses are not affected (181, 182).

Thus, alcohol does not have a salubrious and/or ergogenic effect beneficial during exercise.

Anabolic Steroids

The Press sisters from the Soviet Union were the first athletes in Olympic competition, at Melbourne in 1956, alleged to have been primed with androgenic agents. Twenty years later, in Montreal in 1976, the International Olympic Committee (IOC) inaugurated tests for anabolic steroids using urine

specimens submitted for specific radioimmunoassay (183, 184). The IOC began testing for doping drugs at the winter and summer Olympic games of 1968.

Androgens have been given to victims of starvation and to debilitated patients with chronic disease to help induce a state of positive nitrogen balance. The anabolic steroids are less virilizing drugs than pure testosterone and are used today by weight lifters, shot putters, discus throwers, wrestlers, and football players. The rationale for their use is that they enhance performance by increasing muscle mass, strength, and body weight, especially if consumed with a diet high in protein (185–188). Since many of the studies reaching this conclusion were poorly controlled, there is ample evidence that negates these contentions (189, 190). It has been demonstrated that no change occurs in body weight or strength with dianabol whether or not it is accompanied by high dietary protein (191). Casner (192) demonstrated that the increase in weight is due primarily to water retention (188). Carefully controlled studies in male albino rats (193) found no change in body weight or performance, but did find an increase in SGOT with high doses of nandrolone deconate.

Several factors may account for the conflicting data. Testosterone is the only androgen capable of enhancing muscle mass, strength, and body weight. The type and degree of response to synthetic anabolic steroids depend largely on the age of the subject. Increased muscle strength occurs to a greater extent when the drugs are administered before puberty or after the age of 50, as a result of decreased testosterone production in both instances. The dosage of the drug and the regularity with which it is administered also influence the results. The usual recommended dosage of methandrostenolone (methandienone, Dianabol®) is 10 mg per day for 6–12 weeks. Ill-advised athletes may enormously exceed this dosage by two or three times (194, 195). Is it any wonder that there is a conflict between subjective impressions of an increase in strength and the lack of confirmation by scientific evidence?

Body weight, total body potassium and nitrogen, muscle size, leg performance, and strength increased significantly in men taking methandinone but not during placebo (196). The increase in total body nitrogen implies that the weight gain is not only intracellular fluid. The increases in body potassium and nitrogen are too great in proportion to weight gain for this to be attributed to gain of normal muscle or other lean tissue. Thus, the appearance may be anabolic but the weight gain produced is not normal muscle.

The adverse effects of anabolic steroids should suffice to keep athletes from using them. Most notable among these adverse effects are the following: hepatic dysfunction, including cirrhosis of the liver and hepato-cellular carcinoma (seen in aplastic anemia); decreased libido, testicular atrophy; gynecomastia; salt and water retention; and hypertension. Anabolic steroids may also cause premature closure of the epiphyses (189, 197).

In women, anabolic agents may produce such signs of virilization as beard, increased body hair, male escutcheon, increased musculature, and receding hair line. Amenorrhea and sterility have also been noted. Therefore, anabolic steroids play no role in maintaining the health of the athlete and are of questionable benefit as aids to enhanced performance (195).

Amphetamines and Related Stimulants

It is well known that athletes consume amphetamines and related stimulants in large dosages, but their effects are controversial and dangerous (198, 199). Their original medical indication was for weight control, but they are no longer recommended for this purpose. They have been found more useful in the treatment of narcolepsy and hyperactivity in children. The customary dosage of benzadrine or dexadrine is 15 mg, but professional football players allegedly consume 150 mg of amphetamines per game (200). The short-term effects of the average dose (15 mg) include a decrease in appetite, a dramatic increase in alertness and confidence, an elevation in mood, an improvement in physical performance and concentration, and a decrease in the sense of fatigue; yet associated with these is a feeling of anxiousness or of generally being on a high.

On the other hand, the short-term effects of large amounts (150 mg) of amphetamines are profound overstimulation, acute paranoia, agitation, insomnia, fear, irritability, a sharp rise in blood pressure, fever, chest pain, headaches, chills, stomach distress, rhabdomyolysis due to a direct toxic effect of the amphetamine on the skeletal muscle, and, rarely, death. For those who depend on the long-term effects of chronic abuse, tolerance develops rapidly. Psychological dependence on and preoccupation with these drugs is customary. The user may suffer from paranoia, auditory and visual hallucinations, and formication. Withdrawal syndrome is very well appreciated. It would be senseless to belabor the issue that amphetamines are in fact deleterious to the athlete as well as to the nonathlete when improperly consumed.

Cocaine has an effect similar to amphetamines, but the subjective symptoms of the drug are more intensely felt. This may be due to the fact that the way in which cocaine is taken results in a more rapid onset of action and a shorter duration of effect for the average dosage. Short-term effects of large amounts of cocaine are similar to amphetamines; however, an initial tachycardia may become slow and weak and the tachypnea may become shallow and slow.

Conclusion

An example of the principles of clinical exercise physiology and pharmacology is demonstrated clinically wherein the relationships between diuretic-induced hypokalemia, water loss from diuretics and lack of heat acclimatization, alcohol, amphetamines, and salicylates can have adverse effects on skeletal muscle, resulting in rhabdomyolysis and renal failure.

We have attempted to review significant developments in the burgeoning area of exercise pharmacology. The incorporation of the precepts of clinical pharmacology and of exercise physiology are herein woven into a scenario of cardiovascular pharmacology and ergogenic aids to performance.

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