The Effects of Exercise on the Pharmacokinetics of Drugs

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Abstract According to the limited information available, exercise has no substantial effect on the absorption of orally given drugs. However, it appears to enhance absorption from intramuscular, subcutaneous, transdermal and inhalation sites. The effects of exercise on drug distribution are complex. Exercise increases muscular blood flow resulting, for example, in the increased binding of digoxin in working skeletal muscle. On the other hand, exercise may sequester some drugs such as propranolol in muscle and reduce the availability of the drug for elimination. In addition, exercise decreases the clearance of highly extracted drugs and increases their plasma concentration. It may also increase the clearance of drugs by increasing biliary excretion. Since exercise reduces renal blood flow, the plasma concentrations of those drugs which are primarily eliminated by the kidneys may increase. In conclusion, if maintaining the plasma concentration of a drug at a certain level is important, consideration should be given to alternative drugs if the patient is on intermittent or irregular exercise.

INTRODUCTION

Today there is great emphasis on personal health. More people are involved in exercising to control weight, induce a feeling of well being and improve their health conditions. Even more elderly individuals who are taking medications are exercising to improve their health and quality of life.

Pharmacokinetics describes the relationship between the absorption, distribution, metabolism, and excretion of a drug and its effects and duration of action. Exercise alters a number of physiological parameters including changes in cardiac output, blood flow to active skeletal muscles, skin, digestive system, kidney, liver, and other organs, which consequently may alter the pharmacokinetics of a drug. The number of studies evaluating the effect of exercise on the pharmacokinetics of drugs is limited. There are more data about the effect of drugs on the improved ability of the person to do exercise than data on the effect of exercise on the pharmacokinetics of drugs. However, pharmacokinetic studies are needed to determine exactly how physical exercise can affect the pharmacokinetics of various drugs. Additionally, it is important to know how exercise, by affecting the absorption and disposition of drugs, can alter their clinical effects.

This article reviews the effect of exercise on pharmacokinetics and discusses the possible effects of exercise on the absorption, distribution, metabolism and excretion of drugs.

ABSORPTION

Depending how a drug is administered, exercise may have different effects on drug absorption. Changes in the absorption of orally administered drugs by exercise seem to be of minor clinical significance. Absorption from intramuscular, subcutaneous and transdermal application sites may be increased by exercise, possibly causing harmful consequences, e.g., diabetics treated with insulin (1). Physical exercise seems to have the greatest potential to affect the absorption and distribution of drugs that are administered by subcutaneous, intramuscular or transdermal routes.

Oral absorption

Physical exercise influences several physiological functions which may affect drug absorption from the GI tract. Exercise redistributes cardiac output away from the splanchnic region, most likely due to increased sympathetic nervous activity (2). Changes in nervous activity, in circulating hormones, peptides and metabolic end products lead to changes in GI motility, blood flow, absorption and secretion.

The effect of exercise on pH, gastric emptying, intestinal motility, and intestinal blood flow depends on the intensity, duration and type of exercise. The effect of exercise on these physiological parameters also depends on the physiochemical characteristics of the drug.

Gastrointestinal pH

During exercise, lactic acid is produced which can decrease the pH of blood and muscle. Rowing for 30 min decreases the pH of both gastric mucosa (from 7.25 to 6.79) and arterial blood (from 7.42 to 7.29) significantly ($p<0.05$) (3). This change in pH may alter drug ionization and polarity. Drug absorption may be increased or decreased depending on the nature of the drug molecule and its pKa.

Gastric emptying and gastrointestinal motility

Gastric emptying regulates the rate of drug delivery to the absorption site (the small intestine for most drugs). Increased intragastric pressure, generated by contractions of the proximal region of the stomach is believed to be the primary mechanism for gastric emptying (4). Contractile activity within the stomach is controlled through the vagal system and/or the release of various gut hormones. There are many factors that control gastric emptying during exercise. Increased sympathetic tone and the release of catecholamines are responsible for the inhibition of gastric emptying with vigorous exercise (5-6). Adrenergic nerves are known to decrease the tone of the proximal stomach and diminish antral peristalsis. However, gastric emptying during exercise depends on the exercise conditions. While there is controversy about the effect of low levels of exercise on gastric emptying, there is fairly uniform agreement that high levels of exercise, usually characterized as above 75% maximum oxygen consumption, cause delayed gastric emptying (5-9).

After strenuous exercise, gastric contraction frequency in the antral areas is significantly reduced when compared to studies without exercise (10). Significant changes in contractile activity and configuration of the gastroduodenal junction with strenuous exercise are due to the cessation of contraction of the gastric antrum, pyloric closure, tubular narrowing of the distal gastric antrum, and cessation of flow from the antrum to the duodenum. These changes probably explain the decrease in gastric emptying that occurs with strenuous exercise (10). However, these changes are reversible and the normal patterns of contraction, flow, and configuration resume after a period of rest and normalization of the heart rate (10). Exercise was found to have no significant effect on gastric emptying in trained runners. Obviously, there is adaptation of gastric emptying to exercise due to training (11). The reduction of splanchnic blood flow during exercise could compromise plasma fluid uptake in the intestine, resulting in excess intestinal fluid volume, thereby causing a reduction in gastric emptying during exercise (7). Endogenous opioids such as β-endorphins are released from the pituitary after moderate levels of exercise and β-endorphins delay gastric emptying by decreasing the gastric contraction rate (12). However, it should be noted that increases in plasma β-endorphins are generally reported to occur after, and not during, exercise (13-14).

The intestinal absorption of drugs during exercise has not been evaluated. In general, it is known that exercise reduces the intestinal transit time. This effect is important for those drugs which are primarily absorbed from the intestine. For example, it has been found that a 6-week aerobic running program reduced the intestinal transit time significantly (22.8%) (15).

Exercise lasting more than 1 h significantly delays gastric emptying and increases the frequency and amplitude of contractions in the duodenum (16). Parasympathetic innervation of the gastrointestinal tract causes an increase in intestinal motility. While a single acute exercise reduces parasympathetic innervation to the GI tract, it is possible that chronic exercise increases parasympathetic innervation to the gut. The increase in GI tract motility causes a decrease in intestinal transit time (15). Accelerated transit through the small intestine during mild exercise has been documented (17). Mouth to cecum transit is significantly accelerated during mild exercise.

Another factor that may affect GI transit time is secretion of the thyroid hormone, thyroxin. Secretion of this hormone is known to be increased during early stages of training. This may be partially responsible for the decreased intestinal transit time (15).

With respect to the effect of exercise on the colon, it is known that during exercise there is an increase in sympathetic innervation which inhibits activity in the gastrointestinal tract thereby reducing segmentation of the colon. This reduced segmentation in conjunction with the up and down bouncing motion associated, for example, with jogging could conceivably cause the contents of the colon to

be moved into the rectum and provide a stimulus for defecation (15). Many athletes report the urge to defecate after exercise (18) and exercise is commonly recommended as therapy for constipation in sedentary adults. However, defecation is a colonic function and little is known about the effects of exercise on the large bowel. The urge to defecate seems to be more related to changes in gut motility and tone, as well as GI secretions (19).

It is generally accepted that light exercise accelerates liquid emptying, while vigorous exercise delays solid emptying and has little effect upon liquid emptying until near exhaustion (20).

Splanchnic blood flow

Many drugs (e.g., aniline, aminopyrine, antipyrine and salicylic acid) taken orally are absorbed through the intestine via the splanchnic blood supply. Exercise redistributes blood flow away from the GI tract (21-22) towards the active muscles and lungs and results in a reduction in splanchnic-hepatic blood flow (23, 21). Reduction in splanchnic blood flow is related to the relative intensity of the exercise (21). Splanchnic blood flow is reduced by approximately 50% at an exercise intensity of 70% of the maximum oxygen uptake. Blood flow to the gut is reduced up to 80% during intensive exercise (24). However, exercise may reduce the absorption rate of drugs showing a flow rate-limited absorption from the GI tract (lipophilic drugs). On the other hand, exercise may theoretically increase the absorption rate of those drugs for which diffusion is the rate-limiting step (25), since there is more chance to absorb the drug.

In summary, there is only limited data about the effects of exercise on the absorption of orally-administered drugs. For example, during a basketball game the rate of absorption of tetracycline, doxycycline and sulphamethizol was enhanced when compared to absorption of the drug in volunteers at rest (26).

Furthermore, during moderate physical exercise, the mean concentration-time curve of quinidine was lower than without exercise. However, there was no statistically significant difference in cumulative AUC. For sodium salicylate, although there was a rapid increase in the plasma concentration during exercise, the difference in plasma concentration-time curves was not significant between exercise and rest. The plasma concentration-time curves for sulphadimidine also were similar at rest and during exercise (27). Intermittent moderate exercise, between 20 and 70 min after administration of midazolam (15 mg) caused a reduction in its rate of absorption, as evidenced by decreased C_{max}, Ka and increased T_{max} in comparison to the control. For ephedrine (50 mg), which was given to the same volunteers following the same procedures, exercise did not influence absorption. Midazolam is highly metabolized by the liver and ephedrine is mainly excreted unchanged in urine (28). Therefore, a decrease in splanchnic-hepatic blood flow during exercise, associated with higher first-pass metabolism, caused a slower absorption of midazolam. However, the contribution of delayed gastric emptying during exercise could not be excluded. At submaximal exercise intensities adequate training leads to a less dramatic decrease of GI blood flow (19).

It is evident from these studies that it is difficult to conclude any general statement regarding the effect of exercise on the absorption of drugs after oral administration. Further studies should emphasize establishing more uniformity in experimental conditions, as well as in the type of drug being administered.

Subcutaneous and intramuscular absorption

Both neural and endocrine systems participate in the control of blood flow to various organs. Exercise places great demands on the circulation. At rest, in humans, skeletal muscle receives between 15% and 20% of the cardiac output, while during maximal exercise, this percentage reaches values of 80% to 90% (29). Active human muscle has a high-flow capacity that exceeds the capacity of the heart to maintain adequate blood flow to muscle. Exercise increases cardiac output and coronary blood flow, which rise linearly with increases in heart rate. While exercise increases the blood flow to active tissues, in nonexercising organs, the blood flow decreases to about 20% to 40% of the resting values as a result of competing vasoconstrictor and vasodilator drives (30). Therefore, drug absorption from sites in actively exercising tissue may be increased during exercise, while absorption from inactive tissues may be reduced during exercise.

The absorption of insulin, for example, is increased after its subcutaneous injection into thigh muscle during moderate and intensive leg exercise (31-32). Plasma insulin concentrations are increased by 12% (32) to 25% (31) or unchanged (33) during leg exercise. Increased absorption

of insulin occurs when the drug is injected into the active leg (32-33).

Moderate exercise (40% $VO2_{max}$), immediately prior to and following the intramuscular administration of atropine alters the pharmcokinetics of the drug. The absorption rate constant (Ka) was significantly increased (98%) following exercise, demonstrating that the combination of exercise both prior to and following drug administration increases the relative rate of drug absorption into the systemic circulation (34). The volume of distribution was reported to be significantly decreased (34). This decrease might be due to decreased splanchnic circulation as opposed to a change in muscle perfusion rates. Increased cardiac output and tissue perfusion rates, elevated by exercise, would return to normal within 15-20 min following the cessation of exercise. Atropine is a high clearance, flow dependent drug. Exercise both prior to and or immediately following drug administration has the capacity to modify the pharmacokinetics of atropine by concomitant changes in muscle and hepatic blood flow. These changes are greatest when exercise both precedes and follows administration of the drug (34).

Transdermal absorption

Some studies have shown that changes in skin temperature and skin blood flow alter the absorption of transdermally administered drugs. In general, there are several factors which may affect transdermal (percutaneous) absorption during exercise. These factors are skin temperature, the hydration state of the skin and skin blood flow (35). Exercise initially increases skin temperature (36), but due to sweating a subsequent decrease is often seen at higher work rates (37-38). Higher skin temperature during exercise may enhance the kinetic energy of drugs as well as increase skin blood flow, which may increase the transdermal absorption rate of drugs. Moreover, sweating increases skin hydration and therefore increases the transdermal absorption of drugs with diffusion rate-limited absorption (25).

For example, changes in skin temperature and skin blood flow have been found to have a major effect on nitroglycerin patch treatment. Increased skin blood flow increases plasma nitroglycerin concentrations two- to three-fold in subjects using a nitroglycerin patch (39). Increased temperature can significantly influence the subcutaneous circulation and, through vasodilation, can increase the uptake of nitroglycerin, possibly from a subcutaneous reservoir (40-41).

Sweating occurs after exercise and reduces skin temperature. During the recovery period, vasodilation is present favoring the loss of heat produced in the muscles during exercise. Persistent vasodilation could thus explain the discrepancy between lowered skin temperature and the relatively high nitroglycerin concentration.

The increased transdermal uptake of nitroglycerin during physical exercise may be beneficial to the exercising angina patient, however, the diminished diastolic pressure observed in hot surroundings may impair coronary blood flow and thus be harmful (40).

Exercise induces a similar increase in plasma nicotine concentrations in subjects treated with a nicotine patch (42).

Inhaled absorption

The absorption of inhaled drugs from the lung to the systemic circulation depends on the physiochemical properties of the drug and the physiologic properties of the lung surface area available for exchange, permeability of the absorption barrier and blood flow. Inhalation of terbutaline just prior to a bout of ergometeric cycling caused an increase in the rate of appearance of the drug in plasma (t_{max} from 53±8 to 26±7 min) and an increase in peak plasma concentrations of this drug (C_{max} from 11.4±3.7 to 17.3±7.1 nmol/L) (43). This effect was attributed to a concomitant increase in the pulmonary blood flow and increased movement of drug across the alveolar membranes due to opening of the epithelial cell tight junctions and hence increased permeability. However, the duration of protection against exercise-induced asthma by inhaled terbutaline is significantly shorter than the observed bronchodilatory effects (44). Therefore, it is recommended to increase the frequency of drug administration rather than increase the dose in order to prevent or ameliorate the development of exercise-induced asthma (43). According to this data, blood levels and the area under the curve (AUC) during exercise were greater than those at rest, without any change in the elimination phase. In contrast to higher bioavailability of the drug, the expected effect was shortened, most likely due to lower sensitivity in the effect profile.

DRUG DISTRIBUTION

Although, there is about a 10 to 15% decrease in plasma volume during exercise due to a redistribution of body fluids from the intravascular to extravascular space, it is worthy to mention that a reduction in plasma volume will change only the volume of those drugs which have a low volume of distribution. Therefore, the volume of plasma (V_P) and volume of tissue (V_T) may each contribute significantly to drugs with low volume of distribution values. On the other hand, highly distributed drugs have a much higher V_T compared to V_P. Therefore, changes in the V_P would not cause a significant change, because of the negligible contribution.

The effect of exercise on the distribution of the β-adrenoceptor blocking agents propranolol and atenolol, and the calcium antagonist verapamil, during exercise has been studied (45). In this study, exercise led to a reduction in the volume of distribution of propranolol during prolonged exercise (25 min) at 70% maximal aerobic power (W_{max}), which was not clearly demonstrable during 10 min of exercise at 50% $W_{max.}$ The volume of distribution of verapamil was reduced during 10 min of exercise at 50% W_{max}. No change in the volume of distribution of atenolol during exercise was observed. Therefore, it was concluded that changes in the volumes of distribution of propranolol and verapamil during exercise may contribute to preventing an increase in the half life of these drugs in patients performing physical exercise (45).

The change in the volume of distribution of propranolol, which is a highly distributed drug, is not due to protein binding, although the binding of weakly basic drugs to acidic phospholipids is pH dependent and decreases with decreasing pH (46). The plasma protein binding of propranolol is not changed during exercise (47).

The three mechanisms which most likely explain the change in the volume of distribution of propranolol and mainly the volume of tissue (V_T) during exercise are: 'washout' from less perfused sites, passive movements in response to pH gradients, or release from adrenergic or other tissues following membrane depolarization (47).

Usually, total plasma protein levels increase by 13% with exercise at 50% of each subject's predetermined peak heart rate reserve (48). Exercise was found to increase digoxin binding in working skeletal muscle with a concomitant decrease in the serum digoxin concentration (49). Intermittent submaximal bicycle exercise performed during and after a single injection of digoxin in healthy volunteers increased the digoxin concentration in the thigh muscle by a factor of three, with a 25% increase in the calculated apparent volume of distribution, compared to an injection followed by supine rest (50). Moderate exercise after the intake of a maintenance digoxin dose decreased the serum digoxin concentration and renal excretion of digoxin during the study period. When healthy subjects were allowed to rest 1.5 h in the supine position after termination of the study period, the serum digoxin concentrations increased and were then significantly higher than after rest during the study period (51).

RENAL EXCRETION

The elimination of a drug through the kidneys is a result of glomerular filtration, tubular reabsorption and tubular secretion. Protein binding, polarity and the state of ionization of the drug, as well as renal blood flow, may change renal function. Therefore, drugs which are primarily eliminated by the kidneys are going to be affected by altering renal functions.

The elevation of renal sympathetic nerve activity induced by exhaustive exercise may result in a reduction of renal blood flow (RBF) and changes in renal function. The elevation of renal sympathetic nerve activity may be manifested as increased plasma catecholamine and angiotensin II levels following exhaustive exercise (52). The increase in angiotensin II concentration is a result of an increase in renin release from the kidney, which in turn is mediated by renal sympathetic nerve activity (53). Exhaustive exercise reduced RBF by 53.4% compared to the pre-exercise values, and returned to 82.5% and 78.9% of the pre-exercise values at 30 and 60 min into the recovery period, respectively (52). The changes in RBF from immediately after exercise to 30 min after exercise are accompanied by reductions in creatinine clearance and/or urine volume. The reduction in creatinine clearance and urine volume might be due to the reduction of RBF (52).

A common drug, which is eliminated 99% as metabolites and 1% as unchanged by the kidneys is caffeine. During 75 min of cycling at a regular, steady speed which required 50% of the individual's maximal aerobic power ($VO2_{max}$), the reduction of caffeine elimination was much greater in cyclist women than in cyclist men (five-fold and two-fold,

respectively). In addition, in women there was a very large decrease in urinary volume, whereas this was reduced much less in men. This explains, in part, the difference observed: it is known that caffeine elimination depends on urinary flow (54).

Atenolol is a hydrophilic beta-adrenoceptor antagonist, which is excreted more than 90% unchanged in urine. The effect of physical exercise on plasma concentrations of R- and S-atenolol in ten patients receiving oral long-term treatment with racemic atenolol revealed a 1.74-fold increase in the plasma concentration of S-atenolol during exercise, whereas that of the R- enantiomer remained unaffected (64).

In another study, the effect of exercise on sulfadimidine and procainamide showed an increase in the serum concentration of these drugs (68). Procainamide is an antiarithmic drug, which is excreted unchanged, 45-65% in urine, and 45-65% is eliminated by the liver. Also, sulfamidine is mainly excreted by glomerular filtration into urine, Therefore, these increases probably are due to decreased renal clearance, since there was no marked changes in the acetylation rate or in the protein binding of the drugs.

The intensity of exercise is known to influence renal functions. Strenuous exercise changes both the renal glomerular and tubular functions (55-56) and may induce renal dysfunction. Short-term supermaximal exercise (130% maximal oxygen uptake) has been found to induce an increase in glomerular membrane permeability (57).

The effect of running different distances (100, 400, 800, 1500, 3000 m) on the renal function has been studied (58). Mean plasma lactate concentrations increased after the 100 m (from 1.17±0.12 at rest to 7.97±0.5 mmol/L), showed higher values for the 400 m (from 1.06±0.08 at rest to 12.74±0.53 mmol/L) and 800 m events (major anaerobic characteristics) (from 1.25±0.06 at rest to 11.32±0.05 mmol/L) and declined for the longer runs when the aerobic component became more prominent (from 1.19±0.09 at rest to 10.36±0.74 mmol/L for the 1500 m and 1.25±0.08 at rest to 9.83±0.43 mmol/L for the 3000 m runs). The glomerular filtration rate, as estimated by creatinine, was not influenced by the short runs but showed major decreases of 32% and 44% for the longer runs of 1500 m and 3000 m, respectively. The glomerular membrane permeability, assessed by albumin clearance was greatly increased by all events especially by 400 m and 800 m runs (average: 44-fold above the resting values). Also, the tubular reabsorption process, as indicated by the clearance of proteins of low molecular mass (beta 2-microglobulin and retinol-binding protein), was increased in all events, especially the 400 and 800-m run (average: 100-fold over the resting levels). The 100 m run had a moderate influence on the glomerulus with minimal changes in tubular cells.

Excess protein in urine was related to lactate concentrations measured at the end of exercise, which relates the anaerobic glycolytic component (lactate) and running speed to kidney function (protein excretion and clearance). The presence of protein in urine may be due to greater filtration of macromolecules through the glomerulus, as well as saturation of the tubular reabsorption process. Indeed, at rest, about 95% of filtered protein is reabsorbed by the proximal tubular cells and catabolized to amino acids (59).

It appears that short-term intense exercise is essentially characterized by a change in glomerular membrane permeability with only a minor effect on the tubular cell reabsorption process (58).

Acute renal failure has been reported four times in a patient after strenuous exercise (60). Renal hypouricemia was due to the defective proximal tubular reabsorption of uric acid at a pre-secretory site. Also, acute tubular necrosis and a decrease in creatinine clearance were found. Acute renal failure is prevented by the administration of allopurinol, which inhibits increased uric acid production after exhausting exercise (61).

Besides the physiological changes of renal function during exercise, little is known about renal drug elimination. Additional research is needed to determine the extent of the decrease in renal drug clearance and subsequent alterations in the clinical response to a specific drug due to physical exercise.

HEPATIC ELIMINATION

Exercise increases cardiac output, but diverts blood flow away from the liver and could decrease the hepatic clearance of drugs. According to the degree of the hepatic extraction ratio, drugs may be classified as high, intermediate and low extracted drugs. In general, a highly-cleared drug is efficiently removed by the liver, and its elimination is blood flow dependent, whereas for a low-cleared drug,

enzymatic and biliary excretion are determining factors. The pharmacokinetics of highly extracted drugs are more likely to be affected by exercise than the pharmacokinetics of drugs with a low extraction ratio (E), which are less likely to be influenced by changing blood flow during exercise.

Moderate to strenuous exercise reduces liver blood flow about 60% (21) and induces a diminished elimination of high-clearance drugs (62). However, some studies have failed to discern any dramatic reduction in hepatic clearance even with highly-extracted drugs, such as verapamil and propranolol.

Propranolol is highly extracted by the liver and its clearance may be more dependent on hepatic blood flow than on changes in enzymatic capacity. The effect of submaximal exercise on the pharmacokinetics of low dose propranolol (1 mg) after IV administration to healthy human subjects, showed that the mean value for each of the pharmacokinetics parameters (A, B, α, β, AUC, vd, and total body clearance) for the sedentary study was not statistically different from the exercise study, although most subjects had an increase in AUC and markedly decreased clearance (29). It may be primarily due to high inter-subject variability and partially to low blood levels (0.5-10 ng/ml), which was near the lower limit of sensitivity for the assay.

In another study, the effect of 16-weeks of aerobic exercise on the pharmacokinetics of a single oral dose of propranolol (80 mg) in young and elderly healthy volunteers showed neither changes in the kinetic parameters for propranolol nor unexpected pharmacodynamic changes (blood pressure or heart rate). It seems that long-term exercise can occur without evidence of enzyme induction, enzyme activity, or significant changes in liver blood flow estimated by idiocyanine green (ICG) (63).

Exercise also caused a 2.29-fold increase in the mean plasma concentration of R-propranolol and a 2.09-fold increase in S-propranolol in patients receiving oral long-term racemic propranolol. After 15 minutes of recovery, the mean plasma concentrations of both R-propranolol and S-propranolol did not differ from those obtained at rest before the onset of exercise. Mean plasma concentrations of S-propranolol were significantly higher (20%) than those of R-propranolol at rest. During exercise there was an increase in the plasma concentrations of both R-propranolol (129%) and S-propranolol (109%) (65).

Saruplase (urokinase-type plasminogen activator (u-PA) antigen) is a thrombolytic drug and is primarily eliminated by the liver. The plasma level of thrombolytic drugs in the body is very important. High concentrations of thrombolytic drugs could cause an increased risk of bleeding and low concentrations could possibly result in insufficient thrombolysis. During a continuous infusion of saruplase and ICG, exercise increased the total plasma concentration of u-PA antigen significantly from 263±67 ng/ml at the baseline to 393±113 ng/ml (an increase of 130 ng/ml compared to baseline). The plasma level of ICG, as a marker of hepatic blood flow, increased from 1.0±0.3 μg/ml at baseline to 2.3±0.6 μg/ml after exercise (66). Therefore, the decrease in liver blood flow during exercise may be associated with increased plasma levels of total u-PA antigen (66). Saruplase is a highly-cleared drug (its clearance during exercise is 935ml/min), therefore, the elimination of saruplase was influenced by liver blood flow (66). Similar responses are expected in patients with acute myocardial infarction where impaired liver blood flow caused by cardiogenic shock may result in higher plasma u-PA concentrations.

ICG is entirely cleared by the liver, and its hepatic extraction after an IV bolus injection has been shown to average 0.7 in normal subjects. It was suggested that hepatic plasma flow is the major factor in the clearance of drugs like ICG, which are rapidly removed by the liver. Another study showed that prolonged submaximal exercise caused a decrease in the clearance of ICG (67) but caused no change in the pharmacokinetics of verapamil.

At rest, cardiac output is 5-7 L/min, and 20% of this output circulates to muscle. However, skeletal muscle arterioles dilate with an increase in the percent of cardiac output distributed to muscle during exercise. With exercise, cardiac output increases up to 25 to 30 L/min and 90% of it is distributed to muscle. This represents an approximately 25-fold increase in skeletal muscle blood flow during exercise (29). Such a change in regional blood flow could act to sequester propranolol in the adipose tissues or skin. During recovery, when arterioles close and circulation to an organ system is reduced, propranolol may not re-enter the circulatory system. Sequestration of propranolol in tissue compartments could result in a decrease in its clearance (29). The process of sequestration of propranolol may also occur in muscle because of the increased blood flow. Increased blood flow to skeletal muscle during exercise could result in a higher degree of extraction of the drug

from the vasculature into tissues. The diminished blood flow to muscle after exercise could result in the sequestration of propranolol.

There is a reported 29% increase in testosterone levels during exercise, which is associated with a 28% decrease in testosterone clearance. It has been suggested that, since testosterone production was not altered, decreased hepatic clearance is largely responsible for the increase in testosterone levels during exercise (48).

BILIARY EXCRETION

Although there is not sufficient data about the effect of exercise on biliary excretion, evidence suggests that the biliary excretion of some drugs may be modified by exercise. Chronic voluntary activity produces a change in liver function that causes increased production of bile acids in exercising animals (69). Chronic exercise elevates bile acid transport by increasing the number of organic anion/bile acid transporters (70). The increase of these transporters can increase the clearance of drugs such as acetaminophen (71).

Acetaminophen is an organic anion and its hepatobiliary disposition changes with chronic voluntary exercise. Biliary excretion of acetaminophen and its sulfate conjugate was found to be increased in exercised animals until 90 min after injection (330 μmol/kg acetaminophen). Biliary excretion of the glucuronide conjugate, however, was increased only for the first 30 min postdose. Sedentary animals exhibited higher biliary excretion rates of both the sulfate and glucuronide conjugates at 150 min after dosing. There were no significant differences in the urinary concentrations of acetaminophen, its glucuronide, and sulfate conjugates in exercised vs. sedentary rats (71). Total clearance and biliary clearance were significantly increased in the exercised animals vs. the sedentary animals. The steady state volumes of distribution and the elimination half-lives were not different in the two groups (71). Therefore, the increased clearance of acetaminophen may be due to elevated bile acid secretion and an increased number of organic anion /bile acid transporters (71) which can not be compensated for by decreased hepatic blood flow.

In the same study, serum digoxin and bile flow rate did not differ over the experimental period between the exercised and sedentary groups. Digoxin is a neutral organic molecule that is removed from the body by exercised rats at the same rate as by sedentary rats. Less than 10% of the drug is metabolized. None of the pharmacokinetic parameters for digoxin were affected by chronic exercise (71). The biliary clearance and half-life of another neutral compound, ouabain, were also found to be unchanged in rats after 6 weeks of voluntary exercise (70). These results suggest, therefore, that only the hepatobiliary disposition of the organic anion, acetaminophen, changed with chronic voluntary exercise. Exercise apparently had little effect on the hepatobiliary transport of the neutral organic chemicals (digoxin and ouabain).

CONCLUSION

Exercise may influence the rate and extent of absorption, distribution, metabolism, and excretion of drugs by changing some of the physiological factors. The effect of exercise on the absorption of drugs depends on the route of administration. In addition, its effect on drug distribution mainly depends on the extent of drug distribution. However, other factors also may be involved in the drug distribution during exercise which make the relationship more complicated. Exercise may decrease clearance of highly extracted drugs which may consequently lead to increased plasma concentrations. On the other hand, exercise may increase total body clearance of some other drugs (e.g., the anionic drug acetaminophen) by increasing their biliary excretion leading to decreased plasma concentrations. The plasma concentrations of drugs primarily eliminated by the kidneys increase due to decreased renal excretion during exercise.

Additional research is needed to better understand the relationship between exercise and the pharmacokinetics of drugs in order to individualize the therapy for patients on chronic drug administration who exercise.

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