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The effects of high physical activity on pharmacokinetic drug interactions

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Introduction: With the development of new drugs, it is common practice for drug manufacturers to measure their pharmacokinetic parameters. This testing involves the discovery of the absorption, distribution, metabolic, excretory and toxicological properties of drugs. The testing is usually done in non-stressful conditions at rest, however, this does not necessarily tell the entire picture as there is increasing knowledge about the effects that high levels of physical activity can have on the pharmacokinetics of some medications.
Areas covered: This review discusses the alterations that physical activity can have on the absorption, distribution, metabolism and elimination parameters of commonly used medications, and clinical outcomes data are reported when known, demonstrating that an interaction exists between exercise and certain medications. This drug–exercise pharmacokinetic interaction alters the performance of medications especially under conditions where exercise is performed for a long period of time. Particular medications that may be affected are those with a narrow therapeutic dosing range, such as digoxin, theophylline and warfarin. Other important medications include insulin and those administered via a transdermal patch drug delivery system. For this review, a literature search was performed between 1966 and 2010.
Expert opinion: Patients and healthcare providers should be aware that exercise can adversely affect the way some medications are intended to work. Patients taking certain medications should be closely monitored when performing high amounts of physical activity.

Keywords: drug–exercise interaction, exercise, pharmacokinetic, physical activity

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1. Introduction

It has been shown that more than 80% of the United States adult population takes at least one prescription medication, non-prescription medication, herbal product, vitamin or mineral supplement during any given week [1]. Most healthcare professionals are aware that certain medications cannot be taken together due to adverse drug–drug interactions. Drug interactions can also exist between prescription or non-prescription drugs and herbal supplements and even between medications and some foods. It is less well known, however, that drug–exercise interactions also exist.

As new drugs are being developed, it is a standard of practice for manufactures to measure and test the pharmacokinetic parameters of the product. This involves establishing the absorption, distribution, metabolism and elimination properties so that the outcomes of the drug can be predictable. Most often, these parameters are established and tested under resting, non-stressful conditions. Suspected drug–drug, drug–food and drug–herb interactions are often tested to ensure drug safety and establish patient education information. It is uncommon for

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Article highlights.

- Several physiological changes take place as a result of exercise such as a redistribution of blood flow, increases in skin temperature and hydration, loss of water in the plasma, and others that can alter the pharmacokinetics of some medications.
- The absorption of subcutaneously injected insulin can be increased if the injections is in a location of the body which is about to be involved in exercise (e.g., thigh injection prior to cycling exercise).
- The absorption of drugs that are administered via transdermal patch, especially nitroglycerin and nicotine, are increased while exercising as a result of increased subcutaneous blood flow and skin hydration.
- The distribution of digoxin is altered during exercise as digoxin has been shown to bind to actively working muscles, thus decreasing serum digoxin levels.
- Warfarin has shown to have an inverse relationship of increased physical activity levels over time with decreased International Normalized Ratio (INR) which is thought to be a result of increased warfarin binding to serum albumin, thereby decreasing free warfarin concentrations.
- Theophylline half-life has shown to increase and clearance decrease as a result of a single bout of physical activity.

This box summarizes key points contained in the article.

drug manufacturers to test for potential drug–exercise interactions. As a result, little is known about drug–exercise interactions or its clinical significance.

There are two ways to address the interactions that are believed to exist between physical activity and drug therapy. Drug–exercise interactions can be examined from the perspective of the effects that medications have on the ability to perform physical activity. The other is to examine the effect that physical activity has to the ability of the drug to work as it is designed.

The former drug–exercise interaction is often referred as a pharmacodynamic interaction. The beta-blocker class of drugs is often used to illustrate this drug–exercise pharmacodynamic interaction [2-7]. Beta-blockers are a class of cardiovascular medication that can be used to treat a variety of cardiovascular-related issues such as hypertension, arrhythmias, post-myocardial infarction and others. Some of the clinical pharmacological effects of beta-blockers include decreased cardiac output, decreased cardiac automaticity, decreased cardiac conduction velocity and negative chronotropic and inotropic effects [6,7]. Each of these can adversely affect an individual's ability to perform physical activity. This and other drug–exercise pharmacodynamic interactions are commonly known and have been documented for years [2-7].

On the other hand, exercise can affect the absorption, distribution, metabolism and elimination of some medications. These are referred to as drug–exercise pharmacokinetic interactions. The purpose of this manuscript is to review the current literature available on drug–exercise pharmacokinetic interactions, discuss the clinical relevance for healthcare professionals and suggest future areas of research that are needed to better understand this topic.

2. Physiological adaptations with exercise that affect drug pharmacology

Transitioning the body from a state of rest to that of physically active requires several physiological changes. These physiological changes are at the root of drug–exercise pharmacokinetic interactions. **Table 1** lists some of the physiological changes that induce pharmacokinetic parameters to change from what are expected during resting conditions.

One of the most influential physiological factors that may change drug pharmacokinetics is that of blood flow alterations that occur during and immediately following a bout of exercise [8]. During rest or exercise, the body circulates ~ 5 L of blood [8]. The distribution of the blood, however, changes as a result of increasing physical activity intensity. During exercise, blood is shunted away from organs (except the heart) towards the working muscles to meet the increased oxygen demand and towards subcutaneous tissue to help control body temperature [9,10]. **Table 2** shows the redistribution of blood flow that occurs during physical activity.

For most medications, their intended effects are dependent upon blood flow distribution through important organs such as the liver and kidneys. The redistribution of blood flow during exercise can alter the medications' intended effects by changing one or more pharmacokinetic parameters. At rest, the liver receives the greatest amount of the 5 L of blood (27%), followed closely by the kidneys (22%) [8]. This drops to 1% each with maximum intensity exercise. Drug pharmacokinetic parameters that are based on resting blood flow quantities will not be the same when an individual is exercising, especially at a high intensity.

Blood flow changes that may affect the pharmacokinetics of some drugs will theoretically have the greatest effects during and immediately following the individual sessions of exercise [11]. For these reasons, prolonged bouts of physical activity may have a more significant effect on drug pharmacokinetics than short-term bouts of activity. It is important to note that the redistribution of blood during exercise is similar in both trained and untrained subjects [8]. Studies illustrating this drug–exercise interaction will be presented later in this manuscript.

Not all drugs, however, are highly dependent on blood flow. The pharmacokinetics of some medications can be altered by changes in metabolic rate. Therefore, individuals progressing from an untrained to a trained condition may alter the pharmacokinetics of some drugs. There is much less information available to support this theory, but will be discussed in more detail later.

Table 1. Physiological changes with physical activity that affect drug pharmacokinetics [8-10].

Redistribution of blood flow
Increase in skin temperature
Increase in skin hydration
Increase in cardiac output
Decrease bowel transit time
Loss of water from plasma into tissues
Increase metabolic enzyme activity
Increase respiratory rate
Increase tidal volume

Table 2. Blood distribution during physical activity and rest (%) [9,10].

	Muscle	Liver	Kidney	Skin	Heart	Other
Rest	20	27	22	6	4	21
Exercise						
Light	47	12	10	15	4	12
Moderate	71	3	3	12	4	7
Maximum	88	1	1	2	4	4

3. Drug absorption and physical activity

The absorption of medications into the body can occur at several sites depending on the route drug administration. For example, medications that are taken orally are absorbed through the gastrointestinal tract, injectable medications are absorbed through the subcutaneous or muscular tissue, inhaled drugs through the lungs and others are absorbed through the skin via transdermal patch. As shown in **Tables 1** and **2**, a bout of physical activity will alter blood flow distribution but will also alter airflow through the lungs as well as skin temperature and skin hydration.

Much of the information that exists for drug–exercise pharmacokinetic interactions with regard to drug absorption is with subcutaneous insulin injection and with those medications that are delivered via transdermal patch. Specific studies and case reports on these will be presented below. No information currently exists on effects of exercise on commonly used inhaled medications.

3.1 Insulin absorption with physical activity

Several studies have been published on the effect of physical activity on insulin absorption [12-21]. During exercise, blood flow generally shifts towards the working muscles to aid in exercise performance. As shown in **Table 2**, blood flow is also shifted towards the skin, especially during light-to-moderate intensity activity. It is thought that the absorption of medications administered via subcutaneous injection will be altered during exercise due to the increased blood flow to the area as well as the messaging effect of the exercising muscle [14].

A study published in 1978 was designed to test the hypothesis that increased subcutaneous blood flow will alter the absorption of subcutaneously injected medication [14]. Eleven participants with type 1 diabetes mellitus between the ages of 20 and 29 were enrolled in the study. The study was designed to examine the disappearance of fast-acting and intermediate-acting insulin that was injected into various sites on the body just prior to performing a leg exercise routine [14]. The injection sites consisted of the upper arm, abdomen and leg (thigh). The exercise regimen consisted of four consecutive periods of cycling separated by 5 min of rest at an intensity of up to 100 Watts for men (n = 9) and 75 Watts for women (n = 2). Blood samples were taken every 15 min during the first hour and then every 30 – 60 min for the following 5 h [14].

The results showed that the disappearance of insulin when injected into the leg occurred at a rate that was 135% greater during the first 10 min of exercise compared with rest ($p < 0.05$) [14]. During the entire 1 h exercise period, insulin absorption occurred at rate that was 50% greater compared with rest ($p < 0.025$). During the recovery period, however, insulin absorption was not significantly different from rest ($p > 0.05$). In addition, the results showed a mean decline in blood glucose levels that was greater after injecting insulin into the leg (164 mg/100 ml), arm (103 mg/100 ml, $p < 0.01$) and abdomen (55 mg/100 dl, $p < 0.001$) [14]. Additional studies supported the results of this original publication [13,15-19].

By contrast, there have been a few studies that have not shown exercise to have an effect on insulin absorption [12,20,21]. In 2005, a study on 13 type 1 diabetes patients between the age 18 and 45 years were administered insulin glargine subcutaneously into the thigh on the evening (21:00) before the study day on two occasions 1 week apart [12]. The participants were randomly assigned to 30 min of cycling at an intensity of 65% of their maximum oxygen uptake (VO_2 peak) on one of the two study days. The results showed no significant insulin glargine decay between the two study days ($p = 0.548$) [12].

3.2 Transdermal patch absorption with physical activity

Evidence exists to show that drug absorption via transdermal patch drug delivery system may be altered with increased physical activity. Although the quantity of information in this area is still limited, there are enough research and case reports published to conclude that increases in the blood flow to the skin, as well as increases in skin temperature and hydration can alter the absorption of medications that are delivered through a transdermal patch. A summary of these studies and case reports is provided below.

The two most common medications that are formulated to be delivered via transdermal patch are nitroglycerin and nicotine. Because of this, much of the information known about transdermal patch interactions with exercise comes from these two medications. The first study on this topic was published

in 1986 with nitroglycerin [22]. Twelve healthy volunteers applied a 10-mg nitroglycerin as a transdermal patch for a 6-h time period for three consecutive days. One of the 3 days was a control day, another was an exercise day consisting of riding a bicycle ergometer and the third day was sitting in a sauna for 20 min. Plasma nitroglycerin concentrations increase from 1.0 nmol/l at baseline to 1.5 nmol/l at rest, 3.1 nmol/l with exercise ($p < 0.001$) and 7.3 nmol/l while in the sauna ($p < 0.001$). The authors concluded that exercise increased the subcutaneous circulation of blood, which in turn increased nitroglycerin transport from the transdermal patch [22].

Since this first study, three others have been published showing similar results [23-25]. One study showed that six healthy male volunteers had increased plasma nitroglycerin concentrations significantly more when exercising for 60 min with a 10-mg nitroglycerin patch compared with resting and wearing a 10-mg nitroglycerin patch ($p < 0.05$) [23]. Another study found that exercising for just 20 min at 50% maximum workload was enough to significantly increase plasma nitroglycerin levels beyond that observed while resting ($p < 0.01$) [24]. In this particular study, peak nitroglycerin levels occur 5 min after the exercise session was stopped, confirming the theory that drug–exercise pharmacokinetic interactions can occur during both the active exercise session and the recovery period.

The most recent study on transdermal nitroglycerin and exercise was published in 1991 and looked at the effects of nitroglycerin concentrations during exercise comparing a 10-mg patch worn for 24 h versus 2 h [25]. Study participants exercised for 20 min at a load adjusted to give a heart rate of 110 – 120 beats per minute. The results showed a significant increase in plasma nitroglycerin levels when exercising after wearing the patch for 2 h (56%, $p < 0.001$) as well as after 24 h (19%, $p < 0.05$). Additionally, the researchers found that when the patch was removed and then exercise was performed for 20 min, significantly increased plasma nitroglycerin concentrations was still observed (30%, $p < 0.05$). Each of the exercise–nitroglycerin patch studies concluded that increased subcutaneous blood flow as a result of exercise causes significant increases in the blood levels of the drug compared with resting conditions. Additionally, these increased blood levels occur even during the exercise recovery period and during conditions when the patch was just removed and followed by a bout of exercise.

Two studies and three case reports have been published demonstrating the effects of exercise on nicotine drug absorption while using a transdermal patch for drug delivery [26-28]. In one study, healthy subjects were administered with a 14-mg nicotine patch on a control and an exercise day. After 11 h of patch application, plasma nicotine concentrations were measured before and after a 20-min exercise session (bicycle ergometer) and after 20 min of rest. The results showed that plasma nicotine concentrations were significantly greater following a bout of exercise compared with that observed under resting conditions ($p = 0.015$), and that these changes were believed to be due to increased blood flow to the skin while exercising [27].

A more recent study, published in 2005, was designed to see if differences in transdermal patch designs affected nicotine absorption alternations that occur while exercising [28]. The study compared a reservoir system transdermal patch versus a matrix system transdermal patch. The reservoir system has a semi-permeable layer design to control the release of the medication and is thought to be less prone to variations in skin temperature. The matrix system does not have a semi-permeable layer and is thought to be influenced by skin temperature, humidity and blood flow. Ten male smokers were enrolled in the study and randomly received a 21 mg/day dose patch of either the matrix or reservoir system at rest and with exercise. The exercise session consisted of 30 min of cycling at 50 – 150 Watts performed 8 h post-nicotine patch placement. Study results demonstrated that both transdermal patch systems increased nicotine blood levels compared with rest but no significant difference existed between the two patch systems [28].

Case studies on this topic report three separate individuals who experienced untoward side effects after being appropriately dosed with a nicotine patch and then performed exercise. In each of the cases, the individuals reported symptoms of nicotine toxicity such as nausea, vomiting, palpitations and insomnia following exercising for the first time while wearing a nicotine patch. The individuals were regular exercisers and the side effects in each case were thought to be due to the combination of exercise and the nicotine patch [26].

3.3 Gastrointestinal absorption

Although much of the information on drug–exercise pharmacokinetic interactions exists with subcutaneous injection (insulin) and transdermal patch administration, there is some evidence that gastrointestinal absorption alterations of oral medications exist with exercise. Two studies relating to the physiological changes in the gastrointestinal tract during exercise have, at least theoretically, suggested a potential drug–exercise pharmacokinetic interaction. One study demonstrated that exercise slows gastric emptying when the intensity of the exercise reaches 70% of the maximum oxygen uptake [29]. Theoretically, oral medications may have slowed absorption in the gastrointestinal tract. Another study demonstrated that bowel transit time decreases as a result of a 6-week training program [30]. Decreases in bowel transit time as a result of higher fitness levels may not allow adequate time for absorption because the drugs would move through the gastrointestinal tract at a faster rate. This may also theoretically indicate that drug absorption in the gastrointestinal tract may be decreased for oral medications as a result of exercise.

Specific studies in this area are limited, however, a few exist that may indicate orally administered medication absorption is altered with exercise. One study tested propranolol 80 mg in 10 healthy subjects cycling for 20 min at 50% maximum capacity [31]. The results of the study showed a decreased

plasma half-life and a decreased area under the concentration–time curve which the authors thought was partially due to reduced intestinal absorption during the exercise period [31].

These results, however, are conflicting when compared with that of two other studies which showed increased intestinal absorption as a result of exercise. In one of these studies, doxycycline 200 mg was administered 15 min after the beginning of an exercise period [32]. The type of exercise in this study consisted of playing basketball for 50 min every hour for four consecutive hours while maintaining a heart rate of 130 – 140 beats per minute [32]. Another study showed that the intestinal and gastroduodenal permeability of aspirin increased when the drug was administered immediately prior to a 60-min bout of treadmill running compared with a placebo [33].

Although the results of these studies are conflicting, the rate of absorption of medications through the gastrointestinal tract may, in part, be affected by the duration and intensity of the activity. The studies demonstrating an increase in gastrointestinal absorption involved an exercise period that was at least 60 min long and was of more vigorous activity. By contrast, the study which showed decreased drug absorption while exercising involved an exercise period that was only 20 min in duration at 50% maximum capacity during a non-weight bearing activity.

4. Drug distribution and physical activity

The distribution of medications to the site of action is dependent upon variables that affect the delivery of the drug to the intended site (tissue), the passage of drug through the tissue membrane, and the binding of the drug to plasma proteins, among others [34]. Exercise may affect one or more of the steps involved in drug distribution. It has already been discussed above that the blood flow redistribution occurs during exercise. The redistribution of blood to active muscles may limit the drugs ability to reach its intended site and/or not allow a drug to be cleared from the site of action. This will be discussed in greater detail below with digoxin.

Exercise has also been shown to alter drug binding to plasma proteins and tissues. Studies have shown that plasma protein concentrations increase during exercise due to a loss of water from the plasma into the tissues [35,36]. This increased plasma protein concentration is due to increased osmolality in the active tissues and increased hydrostatic pressure and fluid loss in the form of sweat. This may alter drug distribution, especially for those drugs highly dependent on protein binding [35].

4.1 Digoxin

Digoxin is used for the treatment of supraventricular arrhythmias such as atrial fibrillation and atrial flutter and is considered one of the drugs of choice in treating chronic heart failure (CHF) [37]. Digoxin is considered to have a narrow therapeutic range where toxicity symptoms can be significant. Because of this, it is important to be able to adequately predict digoxin pharmacokinetics. Several studies relating exercise and digoxin pharmacokinetics have been published [38-42].

In a study designed to determine if increased muscle activation increases skeletal muscle digoxin binding, 10 healthy men between the ages of 21 and 34 years participated in a 3-week study [38]. After 2 weeks' intake of oral digoxin (0.5 mg/day), the first of the two exercise tests was performed 24 h after the latest dose. The second exercise test was completed 2 – 7 days later. The exercise test consisted of cycling at an intensity of 80 – 200 Watts to achieve a heart rate of 140 beats per minute for 60 min [38]. Digoxin levels were measured in both the blood and skeletal muscle via muscle biopsy of the quadriceps femoris at five time points during the exercise period and at six time points during the 60-min recovery period [38].

The results showed that during exercise serum digoxin level significantly decreased ($p < 0.001$), while the skeletal muscle concentration of digoxin significantly increased ($p < 0.01$) when compared with levels measured during rest periods [38]. This indicates that during exercise, digoxin binds to actively working muscles. Digoxin concentrations returned to pre-exercise levels within 60 min following exercise. Other similar studies measuring digoxin–skeletal muscle binding during a single bout exercise session were conducted and reported similar findings [39-42].

It should be noted that one study has been conducted looking at the effects of digoxin pharmacokinetic changes that result from a long-term training program [43]. Eighteen healthy subjects, 12 older (average 68.5 years) and 6 younger (average 30.3 years), completed 16 weeks of treadmill or stairclimber activity consisting of three 1-h bouts per week at 75 – 85% of maximum capacity. Prior to and after the 16-week program, a single oral dose of digoxin 3200 μg was administered to the participants followed by 15 venous blood samples. At the completion of the study, aerobic capacity increased significantly in the older subjects (16%, $p = 0.0002$), but not in the younger subjects (3%, $p = 0.41$). The pharmacokinetic variables measured during the study included time of onset of drug effect, time of maximum digoxin concentration and elimination half-life. No significant differences were found in the pharmacokinetic variables of digoxin between the exercise and control groups ($p > 0.05$). Likewise, no differences were found between the younger and older groups ($p > 0.05$) [43].

4.2 Warfarin

Anticoagulation with warfarin is a necessary and effective therapy to prevent thromboembolism in many cardiovascular disease states. Like digoxin, warfarin has a narrow therapeutic range and several factors may influence the therapeutic level of warfarin. These factors can include concomitant drugs and food intake and possibly physical activity.

No data have been published looking specifically at warfarin pharmacokinetic interactions with exercise. A small study, however, was conducted on three patients with cardiovascular disease stabilized on warfarin that show an inverse relationship with increased physical activity and decreased International Normalized Ratio (INR) [44]. The patients involved in the study were prescribed warfarin for either aortic valve replacement, stroke or coronary artery bypass graft surgery and in each case the patient's INR was stable prior to increasing physical activity. Measurements of physical activity level were conducted with the use of a pedometer and all other variables that may affect INR were controlled during the study period [44].

The first patient, a 72-year-old male, increased his average number of steps per day from 5000 to 12,570 during which he experienced a decrease in INR from 2.3 to 1.6 [44]. The second patient, a 29-year-old female, increased her steps per day from 4000 to 8000 and experienced an INR drop from 2.2 to 1.75 as a result of the increase in physical activity. The third patient, a 70-year-old male, increased his activity from 3400 to 11,460 steps per day and likewise had a drop in INR from 1.8 to 1.4 as a result of the increase in physical activity [44]. Neither a timeframe of these changes nor a statistical analysis of these patients was reported.

Seven additional warfarin stabilized patients were enrolled into this same study but were not controlled for extraneous factors when increasing exercise and measuring INR changes. Physical activity was increased with the use of a pedometer similar to the three previous study patients. These 10 patients were then statistically analyzed. The results of these 10 patients showed that a change in the number of steps from 3885 ± 1375 (mean + SD) to 9259 ± 2379 was associated with a significant change in INR from 2.07 ± 0.35 to 1.7 ± 0.44 ($p < 0.05$) [44].

Although pharmacokinetic data were not specifically collected during this study, the researchers hypothesized that the observed physical activity–INR inverse relationship could be due to physical activity's effect on serum albumin. Increased physical activity may increase the amount of warfarin linked to serum albumin, which then may decrease free warfarin concentrations resulting in a decreased INR [44]. Further research is needed to prove this theory and confirm the results.

4.3 Beta-blocker medications

Several studies have been conducted with individual beta-blockers medications that measure plasma concentration changes that may result from a single bout of increased physical activity [45-57]. Specifically, bisoprolol, propranolol and atenolol have demonstrated increased plasma concentrations during exercise [45-49]. By contrast, plasma concentrations of carvedilol and nebivolol have been shown not to increase during exercise, indicating that changes to plasma concentrations during exercise are not a beta-blocker class effect [45,56,57]. In each of these studies, the exercise time periods were short, lasting only a maximum of 20 min.

5. Drug metabolism and physical activity

Drug metabolism can occur in many different organs, however, the liver is the principal organ responsible for drug metabolism in the body [34]. Drug metabolism is a complex process involving the conversion of a drug into another substance. Several factors, including blood flow and metabolic enzyme activity, can influence this process [34]. As discussed above, physical activity can have an effect on blood flow redistribution and may also affect metabolic enzyme activity. Depending on its physical and chemical properties, each drug is taken up and extracted by the liver to different degrees [34]. Knowing the affinity of drugs for extraction by the liver can be important information when trying to predict various influences on drug metabolism and can vary from high extraction to low extraction [34,58].

5.1 High hepatic extraction

Drugs with a high hepatic extraction have a metabolism that is significantly dependent upon blood flow through the liver and tend to be less available to the systemic circulation [34]. Changes in hepatic blood flow can dramatically alter the metabolism of high extraction drugs [34]. Thus, as expected, the shift in blood flow away from the liver during exercise has been shown to alter the clearance of high extraction drugs [59]. The clearance changes of these drugs due to exercise only occurs during the exercise session or during the time of blood flow alteration. Examples of drugs with a high hepatic extraction that have been studied with regard to drug–exercise pharmacokinetic interactions are propranolol and verapamil.

Studies specifically looking at the pharmacokinetic effects of propranolol due to exercise have shown significant changes during short bouts of activity [47,60,61]. Study participants receiving propranolol at dosage ranges from 80 to 320 mg and simultaneously performing submaximal exercise between 12 and 35 min showed statistically significant changes in plasma half-life (decreased), area under the concentration–time curve (decreased) and clearance (decreased) when compared with resting conditions [47,60,61]. Interestingly, however, a 16 week continuous training program did not show statistically significant changes in the propranolol pharmacokinetic parameters of maximal concentration, time to maximum concentration, terminal half-life, area under the concentration–time curve, protein binding, intrinsic clearance, bioavailability, clearance or volume of distribution [62]. Therefore, it appears that single bouts of exercise with propranolol may affect pharmacokinetic parameters but increased fitness levels may not.

A single study has been conducted with verapamil with regard to the effects exercise may have on its pharmacokinetic parameters [63]. In this study, participants rode a bicycle ergometer for 20 min at 50% of their maximum capacity, then rested for 30 min, and repeated this for 7 h after receiving verapamil 80 mg [63]. In contrast to the propranolol study, a single bout of exercise did not produce significant changes

with regard to the parameters of total clearance, volume of distribution or plasma half-life.

5.2 Low hepatic extraction

Drugs with a low hepatic extraction (< 20%) have a hepatic clearance that is almost completely independent of hepatic blood flow and tend to be more available to the systemic circulation [34,58]. Examples of drugs with a low hepatic extraction that have been involved in drug–exercise pharmacokinetic interaction studies are digoxin, warfarin, theophylline, insulin and carvedilol. Metabolism of these drugs is dependent upon metabolic enzyme activity and the unbound fraction of the drug present in the plasma [58]. As a result, blood flow changes in the liver during single bouts of exercise may not, theoretically, show an effect on the metabolism of low extraction drugs [38,58].

Drugs with a low hepatic extraction, however, may have metabolism affected by physical conditioning. It has been shown that improved physical fitness levels stimulate liver oxidative metabolism [64]. In one study, antipyrine, a very low hepatic extraction drug, was shown to have a significantly higher clearance (0.44 and 0.35 ml/min/kg) and lower half-life (11.6 and 15.2 h) in trained versus untrained subjects, respectively ($p < 0.05$) [64]. Therefore, it is conceivable that metabolism and pharmacokinetics of low hepatic extraction drugs could change in patients progressing from an untrained to a trained condition. In addition to the previous discussion on warfarin–albumin binding, this may partially explain why warfarin INR decreases with increased physical activity over time. There is however, very little clinical evidence to support these theories.

5.3 Theophylline

Theophylline is a bronchodilator used to treat asthma, chronic bronchitis and emphysema [65]. Like warfarin and digoxin discussed earlier, theophylline has a narrow therapeutic range and extra care must be taken when dosing theophylline because the increased potential for toxic effects [37]. Theophylline has a low hepatic extraction ratio. Because of this, blood flow redistribution resulting from single bouts of physical activity should theoretically not alter the drugs pharmacokinetic parameters, but rather, may be effected by greater enzymatic activity that comes with an increased fitness level. Unfortunately, long-term continuous training studies on theophylline have not been conducted to test this hypothesis. However, one single bout of exercise study has been conducted with theophylline [66].

Six healthy volunteers consumed 200 mg/m^2 of theophylline and then were examined under four exercise and room temperature conditions: at rest at 22°C, with exercise at 30% VO_2 max at 22°C, with exercise at 50% VO_2 max at 22°C, and with exercise at 30% VO_2 max at 40°C [66]. The exercise period consisted of cycling for a 2-h time period. The results showed that significant prolongations ($p < 0.05$) in the half-life of theophylline and reductions in body clearance were observed during exercise sessions to 30% of VO_2 max both at 22°C and 40°C, as well as during exercise at 50% VO_2 max at 22°C for up to 4 h post-exercise [66]. Because theophylline has a low-hepatic extraction ratio, the clearance of the drug should be determined independent of the blood flow through the liver. This study, however, showed that theophylline half-life was prolonged and clearance was decreased during and for 4 h post-exercise. This is similar to what would be expected of a drug with a high-hepatic extraction ratio and are inconsistent with what was expected. The authors of this study conclude that more research with exercise and theophylline needs to be conducted in order to find out the reasons for the pharmacokinetic responses of theophylline [66].

6. Drug elimination and physical activity

Elimination of drug from the circulation can occur through the urine, bile, sweat, expired air, breast milk or seminal fluid [34]. The primary elimination routes for most drugs are through the urine and bile [34]. Renal elimination is the net effect of glomerular filtration, tubular secretion and tubular reabsorption [34]. The rate of glomerular filtration is dependent on the amount of blood flow into the kidneys. As shown in **Table 2**, exercise decreases renal blood flow in an intensity-dependent manner.

Glomerular filtration rates have been shown to decrease by as much as 30% during physical activity [35]. The greater the exercise intensity, the lesser the renal blood flow, and therefore the lower the glomerular filtration rate [35]. In one study, exhaustive exercise reduced renal blood flow by 53% compared with pre-exercised renal blood flow [67]. During the post-exercise recovery period, renal blood flow returned to nearly 80% of pre-exercised value at 30 and 60 min. Reductions in creatinine clearance and urine volume also accompanied renal blood flow changes immediately following and at 30 min post-exercise [67].

The elimination pharmacokinetics of drugs that are most likely affected by exercise are those that are primarily eliminated unchanged in the urine or whose elimination is dependent on renal function [68]. Atenolol is one such drug that is eliminated 90%+ unchanged in the urine and has been studied for its drug–exercise pharmacokinetic potential. Plasma concentrations of atenolol during exercise showed a 1.7 time increase compared with pre-exercise conditions [49]. Likewise, procainamide and sulfadimadine are also eliminated unchanged in the urine and demonstrated increased plasma concentrations resulting from exercise [69]. Additionally, doxycycline elimination was significantly lower during 50 min/h for four consecutive hours of playing basketball compared with rest ($p < 0.05$) [32].

7. Conclusion

As medication use continues to increase in addition to increased emphasis on physical activity to manage chronic

conditions, the potential for adverse drug–exercise pharmacokinetic interactions may continue to increase. The current level of research in this area is limited, but several studies have been conducted that warrant advising patients to be cautious when exercising and taking certain medications. The information that is currently known about exercising while taking the medications theophylline, digoxin and warfarin, as well as insulin injections into actively working muscles, and transdermal patch drug administration should warrant healthcare providers to educate patients about the potential interactions. Although little clinical information resulting from the pharmacokinetic changes is available, patients on these medications should be closely managed and educated on the signs and symptoms of drug toxicity. In addition, longer duration activities may affect drug pharmacokinetics more so than shorter duration activities. Further research is needed to more fully understand the scope of drug–exercise pharmacokinetic interactions as well as their clinical significance.

8. Expert opinion

With regard to the total body of evidence available in the literature, it is clear that physical activity can and does have an interaction with some medications and vice versa. Exercise–pharmacodynamic interactions that effect exercise performance are more easily understood and measured. Exercise–pharmacokinetic interactions that effect medication performance is not as well understood largely due to the impracticality of obtaining data. Research in this area has been conducted since the 1960s yet most healthcare providers are unaware that such interactions exist. Perhaps the reason for this is the fact that little clinical data can be tied to even the pharmacokinetic parameter changes that prove to be statistically significant. With the information that is available to date, the practical emphasis of drug–exercise pharmacokinetic interactions should be focused on three areas: insulin injection site and timing relative to a bout of physical activity, medications that have a narrow therapeutic range and medications that are administered via transdermal patch drug delivery system, especially when coupled with activities that are of long duration.

Although conflicting reports have been published with regard to insulin absorption and exercise, the majority of the literature shows that insulin is absorbed faster if it is subcutaneously injected into an area of the body that is about to experience increased blood flow with exercise. In addition, there is clinical evidence to show that blood glucose levels are less consistent when injecting insulin into the thigh compared with the abdomen or shoulder prior to riding a bicycle. It would be good practice for healthcare providers to inform all patients with diabetes about this drug–exercise interaction to increase awareness and prevent adverse events. Patients should be advised to administer insulin injections into the shoulder or abdomen if lower body and/or weight bearing physical activity are planned.

Digoxin, theophylline and warfarin are all considered to have a narrow therapeutic dosing range. Blood levels outside the therapeutic range for these medications can have serious consequences when they are both toxic and sub-therapeutic. Monitoring the pharmacokinetic and clinical variables of these medications in a person who is physically active may be particularly important. In addition, it would behoove the healthcare professional to educate the patient about the signs and symptoms of drug toxicity with these medications should an adverse reaction develop as a result of increased physical activity. For warfarin, more frequent INR measurements should be warranted for individuals who are involved in a training program.

Simple patient counseling can also be conducted with patients who are using a transdermal patch drug delivery system as this type of drug administration may become more popular in the future due to its convenience. Special attention should be paid to a small but distinct group of individuals who may be at a particularly high risk for drug absorption changes resulting from exercise. This group would be individuals who participate in long duration sporting events such as marathon running, ultra-marathon running or other event in which exercise lasts for long periods of time. These individuals participate in both long lasting events and long lasting training sessions which may make them particularly vulnerable to changes in skin temperature, hydration and blood flow, and increased drug absorption for long periods of time. Enhanced patient education regarding these potential interactions and proper transdermal patch use can help prevent adverse drug reactions resulting from increased drug toxicity.

Future research needed in this area largely centers on expanding the number of study participants and including those who have a chronic medical condition in addition to measuring clinical outcomes that occur due to the drug–exercise interactions. The studies that have been published up to this point have involved very few participants (usually around 10) and are generally healthy individuals. In addition, very few studies have been published that have looked at the pharmacokinetic changes that occur as a result of a participant becoming more fit through a long-term training program. It is helpful to know how pharmacokinetic parameters can change with a single bout of exercise, but it may be even more helpful to know if changes occur as a result of a daily walking program, for example. Managing chronic conditions such as hypertension, dyslipidemia and diabetes through increased exercise in addition to drug therapy is a recommendation from each of these condition's treatment guidelines. Knowing more information about drug–exercise pharmacokinetic interactions may lead to improved patient safety as well as improved clinical outcomes.

Declaration of interest

TL Lenz has declared that he has no conflict of interest and has received no payment in the preparation of this manuscript.

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