Variability in Human Drug Response
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Effects of exercise on human drug response

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ABSTRACT

Increased physical activity is currently advised to many patients with a variety of diseases for therapeutic reasons, but also for reasons of general well being and health. Therefore, many patients on drug therapy are nowadays involved in regular exercise. In view of these large number it is surprising that relatively little is known about the interaction between exercise and the response to drug treatment in these active patients. On theoretical grounds both acute exercise and exercise training may be expected to influence the response to drugs by their effect on parameters involved in the pharmacokinetics of these drugs. The acute effects of exercise include changes in haemodynamics, enzyme activities, pH, plasma protein concentration, temperature and gastrointestinal function. Therefore, absorption, distribution and clearance may all be affected by acute exercise. In addition, exercise training may lead to more permanent adaptations that also pertain to the resting situation. The effects of exercise will vary among drugs, because of differences in physicochemical properties. Clinically relevant interactions between drugs and exercise are most likely in those drugs with a steep dose-response curve, a narrow therapeutic range, the need for continuous therapeutic efficacy and a short half-life.

Key words: pharmacokinetics, exercise, training, drug response, human, interaction.

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INTRODUCTION

Interindividual variability in human drug response can result from pharmacokinetic as well as pharmacokinetic variability between individuals. For a long time it has been assumed that most of the variation in human drug response was due to interindividual pharmacokinetic differences. More recently it has become evident that pharmacodynamic variability, i.e. the variability in the relationship between pharmacological effect intensity and drug concentration,

may also be substantial and reproducible in humans, and often more pronounced than pharmacokinetic variability [1].
Exercise is one of the factors that may affect human drug response. On theoretical grounds both acute exercise and exercise training may be expected to influence the response to drugs by their effect on parameters involved in the pharmacokinetics of these drugs. Moreover, factors that may account for pharmacodynamic variability, such as receptor density and affinity, the concentration of endogenous ligands, postreceptor transduction processes, homeostatic responses and transport processes [1], may also be affected by exercise.

Increased physical activity and regular exercise are currently advised to many patients with a variety of diseases for therapeutic reasons, but also for reasons of general well-being and health. Therefore, many patients on drug therapy are nowadays involved in regular exercise. In view of these large numbers it is surprising that relatively little is known about the interaction between exercise and the response to drug treatment in these active patients.

ACUTE EXERCISE AND PHARMACOKINETICS

On theoretical grounds both acute exercise and exercise training may be expected to influence the response to drugs by their effect on parameters involved in the pharmacokinetics of these drugs. The acute effects of exercise include changes in haemodynamics, enzyme activities, pH, plasma protein concentration, temperature and gastrointestinal function. Therefore, absorption, distribution and clearance may all be affected by acute exercise. In addition, exercise training may lead to more permanent adaptations that also pertain to the resting situation. The effects of exercise will vary among drugs, because of differences in physicochemical properties.

In 1990 and 1991 the interaction between exercise and the pharmacokinetics of drugs has been extensively reviewed [2,3,4]. The reviews concluded that only few studies had really investigated the effects of exercise on pharmacokinetics and that more studies were needed to complete the picture. One review [2] stressed that although there are indications that acute exercise and exercise training may affect the pharmacokinetics of certain drugs, there is hardly any evidence for clinically relevant effects. Either because the drug showing an interaction would not be used in combination with exercise, or because the demonstrated effects were clinically insignificant. A notable exception is the effect of exercise on the absorption of insulin from subcutaneous or intramuscular injection sites, which is associated with increased plasma insulin concentration and reduced plasma glucose levels [5,6]. It was concluded that clinically relevant interactions between drugs and exercise are most likely in those drugs with a steep dose-response curve, a narrow therapeutic range, the need for continuous therapeutic efficacy and a short half-life. The literature on the interaction between exercise and pharmacokinetics since 1990 has been reviewed for this paper, in order to see whether any advances have been made and whether these conclusions are still valid.

Exercise and absorption

In 1990 it was concluded that exercise, if anything, was likely to reduce the gastrointestinal absorption of drugs, although there were no experimental data to support this [2,3]. In 1992 a study was published by Strömberg *et al* [7] investigating the effects of 50 minute aerobic treadmill exercise on the pharmacokinetics of orally administered midazolam

and ephedrine. The absorption coefficient (K_a) of midazolam was significantly reduced by exercise (from 0.10±0.06 to 0.04±0.03 L/min), the K_a of ephedrine was also lowered (from 0.031±0.015 to 0.024±0.011 L/min), but this difference was not statistically significant. The T_{max}, time to reach peak plasma concentration, was increased by exercise in both drugs, although differences did not reach statistical significance. Both the decreased K_a and T_{max} are suggestive for a reduced rate of absorption with exercise.

In contrast to the effects on gastrointestinal absorption, the effect of exercise on subcutaneous and intramuscular absorption is relatively well studied, although the studies mainly concern the effect of exercise on insulin absorption. In the 70ties and 80ties it was shown that exercise increases the absorption of insulin from active tissues and this effect was due probably due to the massageing effect of muscle contractions rather than to changes in local blood flow [5,6,2]. An additional study showed that environmental temperature also affects insulin absorption. Although there was no synergism between exercise and environmental temperature, the most rapid absorption of insulin and the lowest plasma glucose concentrations were found during exercise at high environmental temperatures [8]. It was concluded that to avoid hypoglycemia after exercise at warm temperatures appropriate adjustments in diet and insulin dose should be made [8]. When comparing the effects of exercise on the absorption of insulin from subcutaneous and intramuscular injection sites in the thigh, it was shown that exercise affects absorption from intramuscular sites much stronger than from subcutaneous sites: the peak plasma free immunoreactive insulin (IRI) was 39 mU/L higher, the area under the IRI curve was 80% greater and the decrease in plasma glucose was 2mM greater after intramuscular than after subcutaneous injection [9]. It was concluded that the risk of accidental intramuscular injection of insulin should be minimised by injection into a skinfold or by use of shorter needles [9].

In most studies of transdermal drug administration, total drug absorption and plasma drug concentration have increased during heat exposure. This phenomenon appears to be mediated by acceleration of skin blood flow. Other contributing factors may be changes in the physicochemical properties of transdermal patches, sweating and increased humidity of the skin. At temperatures above 30°C 1.5 to 2.5-fold increases in plasma concentrations have been found [10]. Exercise also enhances skin blood flow, at least at relatively low exercise intensities, sweating and skin humidity and may therefore have similar effects on transdermal absorption as heat exposure [2]. Since the 80ties no further studies addressing the effect of exercise on transdermal absorption have been published.

Exercise and distribution

In the 1990/1991 reviews it was shown that the volume of distribution of drugs may increase or decrease during exercise, depending on the physicochemical properties of the drug (high or low plasma protein and tissue binding) and pH and blood flow changes during exercise [2,3]. Strömberg *et al* [7] demonstrated an increase in the apparent volume of distribution of midazolam after oral administration. It remains unclear whether this reduction is due to a reduced absorption/availability of midazolam or to an actual change in the volume of distribution. The apparent volume of distribution of ephedrine, on the other hand, did not change by exercise [7]. A study in horses showed that the steady-state volume of distribution of cortisol was significantly increased during a 56-km endurance exercise [11]. In contrast, the distribution volume of caffeine was found to be significantly reduced during exercise [12].

In rats acute exercise increased the rate of decarbamylation of physostigmine in red blood cells, brain and heart, but decreased it in diaphragm and skeletal muscle. Therefore, acute exercise reduced the central anticholinesterase efficacy of physostigmine treatment. The investigators suggest that the differences between the various tissues may be due to tissue-specific blood flow changes during exercise [13].

Exercise and clearance

Most studies reviewed in 1990/1991 [2,3,4] were unable to demonstrate an effect of exercise on the pharmacokinetics of drugs with a low hepatic extraction ratio. The only exception being a study on theophylline, where a 25% increase in clearance was found over an 8-hour period including 2 hours of exercise [14]. This finding had not been replicated or supported by additional studies. A study on the effect of exercise on the elimination of caffeine, a low extraction drug metabolised by liver enzymes, showed an unchanged clearance, assuming a 100% bioavailability after oral administration [12]. A recent review on the effects of environmental temperature on the elimination of low clearance drugs indicates that there is not much evidence for an acute effect of an increase in temperature on hepatic drug metabolism [10]. This suggests that it is also unlikely that the temperature elevation associated with exercise affects the clearance of low extraction drugs.

In contrast to low extraction drugs, the clearance of high extraction drugs by the liver is generally assumed to be reduced by exercise, due to the reduction of liver blood flow [2,3,4]. Nevertheless, significant reductions of clearance by exercise are often not found [2,3,15,16].

Renal elimination of drugs depends on filtration, secretion, reabsorption and urine flow, which may all be affected by exercise. In general the clearance of drugs by the kidneys is was found to be reduced during exercise [2]. Gillies *et al* [17] showed that the urinary content of pseudoephedrine measured over 6 hours, with or without a 40-km time trial on a cycle ergometer, did not differ, although the urinary pseudoephedrine concentration was increased on the exercise day. However, plasma pseudoephedrine concentration was increased during exercise, suggesting that renal clearance may actually have been reduced. On the other hand Strömberg *et al* [7] found that the apparent clearance of ephedrine, a drug largely excreted unchanged in the urine, was unchanged by exercise. Plasma ephedrine concentration and apparent volume of distribution were also unaffected. However, since the effect of exercise on the availability of ephedrine after oral administration is unknown, these results are difficult to interpret.

Clearance by extrarenal and extrahepatic mechanisms can also change during exercise, as shown by Lassourd *et al* [18] for the clearance of intravenously administered ^{3}H-cortisol in horses. The large increase of plasma cortisol clearance could not be explained by changes in clearance of classical organs such as liver, kidney and lungs. It was suggested that the muscles might have been responsible for the increased clearance of cortisol, in association with the increase in muscle blood flow during exercise.

In conclusion, since 1990 only a limited number of additional studies on the effects of acute exercise on pharmacokinetics of drugs has been published. These new data in general support the conclusions of previous reviews [2,3,4].

EXERCISE TRAINING AND PHARMACOKINETICS

In 1980 Frenkl and coworkers [19] introduced the concept of the 'trained liver'. They demonstrated that athletes had a higher antipyrine elimination rate than non-athletes. Antipyrine is metabolised extensively by the cytochrome P450 liver enzymes. It shows negligible protein binding and its elimination is not limited by liver blood flow. Other cross-sectional studies have confirmed these results [20,21]. The only longitudinal training study performed in humans showed that the hepatic clearance of aminopyrine and antipyrine increased by 13% and 12% respectively with training [22]. The increase in hepatic metabolism was correlated with the increase in VO_2max.

Furthermore, a small number of longitudinal training studies has been performed in rats. Frenkl *et al* [23] showed that liver P450 content and antipyrine elimination was increased after swimming training in Wistar rats. In contrast, running training for 8 weeks inhibited the microsomal metabolism of p-nitroanisole and aniline, whereas the metabolism of ethoxyresorufin was not significantly affected in Fisher-344 rats. This suggests that the various P450 isozymes have different sensitivities towards exercise training. The total P450 content was reduced 30% in exercised rats [24]. An additional finding in this study was that the hepatotoxic action of CCl_4 was completely prevented in rats after exercise training. CCl_4 is reduced to a trichloromethyl radical by the same P450 isozyme that is involved in aniline metabolism [24]. When exercise training by swimming and running were compared, running training was shown to reduce the hepatic microsomal P450 content and activity, whilst swimming training tended to increase P450 content and aniline metabolism [25]. It was suggested that it was the exposure to water rather than the exercise training that resulted in these changes in swimming rats [25]. A study which investigated the effects of running training on the clearance of ethanol at rest in Sprague-Dawley rats showed an increase in ethanol clearance. Since the in vitro alcohol dehydrogenase activity was not affected by training, other metabolic pathways, for instance stimulation of the hepatic cytochrome P450-dependent mixed-function oxidase system, may have been responsible for this increased ethanol clearance [26].

Only one study has looked at the effects of exercise training on renal drug metabolism. Piatowski *et al* [27] showed that running training increased the renal phase I drug metabolism without affecting phase II processes.

In conclusion, although in humans cross-sectional studies and a single longitudinal study all seem to indicate that exercise training increases the capacity of the liver for drug metabolism, the results from training studies in rats are equivocal. Clearly more studies are needed in this area to be able to fully understand the effect of exercise training on the pharmacokinetics of drugs.

EXERCISE AND PHARMACODYNAMICS

Pharmacodynamic variability can be defined as interindividual variability in the plasma concentration-effect relationship. Factors that may account for pharmacodynamic variability, such as receptor density and affinity, the concentration of endogenous ligands, postreceptor transduction processes, homeostatic responses and transport processes [1], may all be affected by exercise. However, no information on the effect of acute or chronic exercise on parameters

of pharmacodynamic variability, such as the coefficient of variation of the EC_{50}, is available. Nevertheless, there are indications of pharmacodynamic interactions with exercise and some examples will be presented.

A 15 min treadmill running exercise at moderate intensity has been shown to increase the behavioral sensitivity to the carbamate cholinesterase inhibitor physostigmine in untrained and trained rats [28]. Exercise training reduced the behavioral sensitivity to carbamates due to an exercise bout, when the animals had been resting for at least 72 hours after the last exercise bout [28]. This suppressing effect of exercise training was also shown for other centrally acting drugs such as midazolam, scopolamine and benactyzine [29]. Whether this effect of acute exercise was due to the exercise *per se* or to the stress associated with exercise is not known. However, stress induced by forced swimming has been shown to disrupt the blood brain barrier for physostigmine and pyridostigmine in mice, resulting in CNS-mediated side effects [30]. Exercise training may decrease the stress of an acute exercise bout and thus partly prevent the central effects induced by acute exercise.

The response to β-adrenoceptor agonist stimulation before and after acute exercise has been compared in two studies. In one study the responsiveness of heart rate, diastolic blood pressure and lower extremity blood flow to the β-adrenoceptor agonist isoprenaline was found to be unchanged between 20 and 60 minutes after 1 hour exercise at low or high intensity [31]. In contrast, the systolic blood pressure response to isoprenaline was blunted after high intensity exercise which may be a manifestation of reduced cardioinotropic sensitivity. In the other study the dose of isoprenaline needed to increase heart rate by 25 beats/min was increased at 15 minutes after prolonged (95 min) exercise. The increase in dose was closely correlated with the reduction of the ejection fraction , suggesting reduced chronotropic sensitivity. Circulating lymphocyte β-adrenoceptor density and affinity and adenylate cyclase levels were unchanged after exercise [32]. Therefore, certain but not all β-adrenoceptor mediated responses may be blunted after acute exercise, but the mechanism remains to be elucidated.

Studies in rats suggest that exercise training may affect β-adrenoceptor densities, adenylate cyclase activity and G-protein content. However, the effects appear to vary among tissues and the data are far from consistent. For instance skeletal muscle β-adrenoceptor density has been found increased [33], unchanged [34], and reduced [35] after exercise training in the rat.

Cross-sectional and longitudinal studies indicate that endurance exercise training increases in vitro lipolytic responsiveness to catecholamines of adipocytes in humans. Since the density of receptors does not appear to change with training, the increased responsiveness appears to be a post-receptor adaptation, probably at the level of hormone-sensitive lipase [36]. β-Receptor density also does not change with training in human skeletal muscle [37]. In addition the heart rate and calf blood flow response to the b-adrenoceptor agonist isoprenaline did not change with training [31].

Exercise has been shown to improve the decreased response to a flicker fusion test after midazolam. The flicker fusion test is a sensitive test for measuring the sedative effects of psychotropic drugs. However, it could not be ascertained whether this effect was solely due to the pharmacokinetic changes or to the general alerting effect of exercise [7].

These examples show that it is likely that acute and chronic exercise influence drug response by pharmacodynamic mechanisms, although pharmacokinetic influences in some cases have not been fully excluded.

In summary, acute and chronic exercise may influence drug response by pharmacokinetic as well as pharmacodynamic mechanisms. Exercise and training status should therefore be considered in studies on human drug response. On the other hand, few clinically relevant effects of exercise or exercise training on drug response have been described up till now.

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Discussion: Effects of exercise on human drug response

M. Lader:
There are some natural disease states which are essentially mimicking some of the effects of exercise, such as generalised anxiety disorder. Forearm blood flow in these patients, even at rest, is something like five to tenfold over the normal resting levels, so it is quite a dynamic circulation. You will need a higher dose of a sedative drug, a barbiturate or a benzodiazepine, in order to reach a sort of sedation end-point.

M. van Baak:
I do not think that you can characterise the human dynamic state that you reach by exercise training as a hyperkinetic state at rest, because usually the system is depressed a little bit in well-trained people. This activated system only appears during the exercise, although this period is so short compared with the half-life of drugs. It is hard to study the effect of drugs during exercise itself, because exercise has such a profound effect on its own that it is very difficult to find out what is the effect of exercise and what is the drug response.

M.M. Reidenberg:
Is it your judgement that few clinically relevant effects have been identified because there are few or because we are missing them?

M. van Baak:
I think there must be big pharmacodynamic effects because the exercise-trained individual really is very different, metabolically and hemodynamically, from an untrained individual. But, on the other hand, there are not many patients on drug therapy that will be that well trained. I think the reason that this area has not attracted much attention may be because people are just not triggered to it, but also that the effects that have been shown until now are really not clinically important.

N. Benowitz:
Acute effects of exercise on transdermal drug absorption have been shown, at least for nicotine. When temperature of the skin goes up and blood flow goes up, you can anticipate a faster absorption. In some situations, maybe clonidine or other drugs, that could matter.

M. van Baak:
It has been shown that plasma concentrations of nitroglycerin after transdermal administration are very much increased during and after the exercise. If you compare for instance to sauna, the increases are even higher. There have been no clinical effects measured in these studies, so it is hard to extrapolate any data on resulting drug effects.

A.J.J. Wood:
We have previously seen frailty as an index of extreme aging and now some data in which the elderly are trained. There are studies looking at the effects of training in the elderly on cardiovascular and osteoporosis indices. Perhaps it may be a relevant link to the training, because presumably we could make some of the elderly less frail if we trained them better.

There have been attempts to do that in some studies. Does Mark Kinirons want to comment on that?

M. Kinirons:

Mary Tinetti in Connecticut has published consistent data showing that multidisciplinary exercise programmes can improve cardiovascular responsiveness in those kind of frail elderly who fall (Tinetti M *et al.*, N Engl J Med, 1994), and that training can reduce the risk of falling. It is possible to predict that would also change their sensitivity to drugs that impair balance.