CHAPTER 13

PHARMACOKINETICS OF CREATINE

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Abstract: Research has demonstrated that creatine supplementation has some therapeutic benefit with respect to muscle function and more recently neurological function. Despite the growing body of literature on the pharmacologic effect of creatine, very little is known about the disposition of creatine after supraphysiologic doses. The movement of creatine throughout the body is governed by transport processes which impact the absorption of creatine from the intestine, clearance of creatine from the kidney, and access of creatine to target tissues. With repeated doses of creatine, it appears that the clearance of creatine decreases mainly due to the saturation of skeletal muscle stores. Insulin and insulin-stimulating foods appear to enhance muscle uptake of creatine but at the same time, high carbohydrate meals may slow the absorption of creatine from the intestine. Little is known about creatine disposition in special populations including the elderly and patients with neuromuscular disease. Knowledge of creatine disposition in these clinically relevant populations can help remove some of the guess work of dose selection during clinical trials

1. INTRODUCTION

Pharmacokinetics is the study of the behavior of a substance (e.g., drug) in an organism through quantifying the processes of absorption, distribution, metabolism and excretion. The fate of substances after their administration is important for the sole reason that it is the concentration of a substance at the site of action that drives physiologic, pharmacologic or toxicologic effects. Beyond basic knowledge about the time course of concentrations, pharmacokinetics can provide useful information for health-care professionals related to dose adjustments. Understanding pharmacokinetics allows clinicians to design dosing regimens to obtain desired drug concentrations, thus maximizing drug effectiveness while at the same time decreasing drug toxicity.

Though the positive physiologic effects of creatine supplementation have been well-studied, there is still much to learn regarding the pharmacokinetics of exogenous, supraphysiologic doses of creatine. Specifically, relatively little is

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known about the relationship between blood and tissue concentrations of creatine in intact organisms. Since creatine is known to have beneficial effects on tissues with high energy demands (e.g., skeletal muscle, nervous tissue, cardiac tissue), it is important to elucidate the pharmacokinetic profile of creatine at its sites of action. This information will give researchers new insights into how to optimize the use of creatine to treat specific diseases or unveil potential barriers of creatine as a therapeutic agent. In addition, further understanding of creatine pharmacokinetics will enable the design of optimal dosing regimens for varied patient populations.

2. ABSORPTION

Creatine can be obtained through an omnivorous diet. Because creatine is a nutrient, it is not surprising that the literature suggests creatine is absorbed from the gastrointestinal tract via a process similar to other nutrients (e.g., amino acids, glucose, vitamins). Transporters mediating creatine flux through the intestinal wall have been identified in rodents in the ileum (Peral *et al.*, 2005) and jejunum (Tosco *et al.*, 2004) and on the apical (Peral *et al.*, 2002; Tosco *et al.*, 2004) and basolateral membranes of enterocytes (Orsenigo *et al.*, 2005). Orsengio *et al.* (2005) also suggested possible paracellular movement of creatine by solvent drag as a mechanism of creatine absorption. However using the Caco-2 monolayer as a model of intestinal absorption, creatine showed poor apical to basolateral movement (Dash *et al.*, 2001), suggesting that the contribution of the paracellular route to the transcelluar route is minimal and that the Caco-2 cell may not express creatine transporters. One study modeled concentration-time data after oral doses of creatine and found that the model supported saturable absorption kinetics consistent with transport processes in the intestine (Persky *et al.*, 2003c). This study also seems to indicate potential two peaks in the concentration-time profile for a single dose of creatine (Figure 1); this

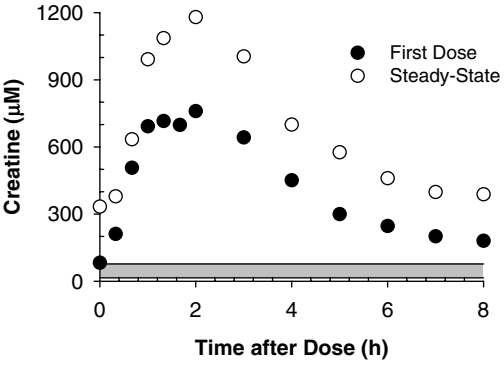

Figure 1. Concentration-time profile of creatine in the blood after administration of 5 g of creatine monohydrate to healthy volunteers. Closed circles represent single-dose concentrations. Open circles represent steady-state concentrations (5 g four times a day for 6 d). Grey box indicates the K_m of sarcolemmal creatine transporters (Snow and Murphy, 2001). Data taken from Persky *et al.* (2003c).

phenomenon has been be noted in another study (Green *et al.*, 1996b). Although the reason for the small double peak is unclear, it may suggest more than one absorptive process. Clearly, more research needs to be performed before the exact means of creatine absorption is determined, especially in humans as species differences may play a role in creatine disposition (Green *et al.*, 1996a; Kreider, 2003; Tarnopolsky *et al.*, 2003b).

Although it can be difficult to quantify absorption rate, the time to maximal concentration (t_{max}) and the maximal concentration, C_{max}, can be used as surrogate markers of absorption kinetics (Table 1). Although both t_{max} and C_{max} give some assessment of absorption processes, they are relatively inaccurate measures of absorption rate because they are secondary parameters dependent on other pharmacokinetic parameters (e.g., elimination rate, dose). Regardless of inaccuracies, these parameters can be used for relative comparisons as typically seen in bioequivalence studies.

2.1. Bioavailability

The absolute bioavailability (i.e., the fraction of dose absorbed from a non-intravenous route compared to an intravenous route) of supraphysiologic doses of creatine is unknown. There are four potential reasons why creatine bioavailability could be less than 100%. The first reason could be that creatine is susceptible to degradation in an acid environment with the highest rate of degradation at pH 3 (Cannan and Shore, 1928). Regardless, the combination of stomach pH (pH 1) and the relatively short time creatine might spend in the stomach means that very little of the oral dose of creatine should be lost. The second reason for less than 100% bioavailability could be that creatine is degraded by intestinal bacteria (Twort, and Mellanby, 1912). It has been noted that intestinal bacteria can degrade creatine and that creatine and its metabolite, creatinine, are lost in the feces (Wixom *et al.*, 1979).

Table 1. Pharmacokinetics after a single oral dose of creatine .

Dose (g)	t_{max}(hr)	C_{max}(μM)	Reference
2	0.5 to 2	180 to 390	Harris *et al.*, 2002
2.5	1	400	Schedel *et al.*, 1999
5	0.75 to 1.6	620 to 1300	Green *et al.*, 1996b; Harris *et al.*, 1992; Persky *et al.*, 2003c; Rawson *et al.*, 2002; Schedel *et al.*, 1999; Steenge *et al.*, 2000
10	2.25	1000	Schedel *et al.*, 1999
15	3	2100	Schedel *et al.*, 1999
20	3 to 4	2200	Schedel *et al.*, 1999

t_{max}: time to maximal concentration; C_{max}: maximal concentration.

The third reason could be that creatine may not be absorbed due to the kinetics of transport across the intestinal epithelia. If creatine absorption is limited to distinct anatomical locations along the intestine and absorption is a time consuming process, it is possible that flow down the intestinal tract pushes creatine past the transporters in the gastrointestinal tract. The efficiency of creatine absorption within the intestine then becomes a function of transit time through the intestine and the uptake clearance into enterocytes. The fourth reason for decreased bioavailability could be incomplete dissolution of creatine solid dosage forms (e.g., powder, tablet); only dissolved creatine will be absorbed, and thus if creatine does not enter solution it will not be absorbed.

Although there is no data to support the absolute bioavailability of creatine, it is most likely that lower doses of creatine (< 5 g) will have a larger bioavailability than higher doses (> 10 g) based on kinetics of a saturable process (i.e., Michaelis-Menten). Most studies that discuss the bioavailability of creatine base their discussion on urinary output of creatine. Although this is a fairly convenient measure of bioavailability, it is assuming 1) complete recovery of the creatine (and its degradation products) in the urine; 2) that there is no other loss of creatine within the system or all other loss is accounted for (i.e., mass balance) and 3) that endogenous creatine production and creatinine formation do not change. This mass balance approach to estimate bioavailability is at best a rough estimate because one or more of the three assumptions may be violated.

2.2. Impact of Dosage form on Absorption

Creatine may be consumed in several different forms beyond meat and fish. Creatine supplements sold over the counter are typically sold as solutions, powders, suspensions, capsules, or chewable tablets. One study compared the relative bioavailability of several of these dosage forms (Harris *et al.*, 2002). The authors found that ingesting 2 g of creatine, in different dosage forms, resulted in plasma peak concentration (C_{max}) where solution $>$ suspension $=$ lozenge $>$ meat. There was little difference in time to maximal concentration (t_{max}) across dosage forms but the shape of the concentration-time profile suggested possible differences in absorption kinetics. It is not surprising that the solution yielded the shortest t_{max} and highest C_{max} as a molecule is required to be in solution prior to absorption; the solid dosage forms (e.g., lozenge, meat) would require disintegration and dissolution while suspensions would require dissolution of the suspended particles. Since solutions eliminate these other steps (i.e., degradation and dissolution), they have a more rapid rate of absorption. The authors also compared the area under the concentration-time curve (AUC), which can be helpful in determining bioequivalence and systemic exposure. They concluded that creatine in solution and meat had similar AUC to one another, but that the AUC of creatine solution was significantly higher than a lozenge formulation or suspension. This finding suggests that the solution delivers more creatine than either the lozenge or suspension. Though this study suggests not all formulations of creatine are equivalent, AUC was calculated only for measured

Table 2. Potential barriers to creatine absorption from the intestine .

Barrier	Potential Impact on Blood Concentrations
Low pH of the stomach	✓
Dissolution of solid dosage forms	✓
Movement across apical and basolateral membranes of epithelial cells	✓✓✓✓
Intracellular degradation in epithelial cells	✓
Degradation by intestinal bacteria	✓

✓ = minimal to ✓✓✓✓✓ substantial

time points; in order to fully establish bioequivalence, the AUC would have to be extrapolated through infinity in order to fully define systemic exposure. Therefore it is difficult to say which formulation of creatine delivers the largest fraction of the administered dose.

2.3. Impact of Food on Absorption

Research suggests that ingesting carbohydrates, as simple sugars or as a carbohydrate/protein combination, enhances muscle uptake of creatine. These findings will be discussed later in the clearance section, but ingestion of sugars and protein can impact the absorption of creatine. Although relatively low concentrations of sugar show no negative effect on absorption ($< 4.5\%$), high sugar concentrations can slow absorption (Vist and Maughan, 1995). Studies examining the concomitant intake of sugars or sugar and protein with creatine have found slight increases in t_{max} by up to 40 min (Green *et al.*, 1996b; Steenge *et al.*, 2000). The use of carbohydrates might also impact possible gastrointestinal side effects if those carbohydrates draw water into the lumen or delay gastric emptying (e.g., high fructose fruit juices). It is still not fully clear if food impacts the oral bioavailability (i.e., fraction of the dose absorbed) or absorption kinetics of creatine and whether those changes significantly impact systemic concentrations to ultimately affect target tissue concentrations. Table 2 summarizes potential barriers of creatine absorption.

3. DISTRIBUTION

Creatine is distributed throughout the body in tissues such as the brain, eyes, cardiac muscle, testes, and kidneys (Walker, 1979; Wyss and Schulze, 2002). The primary site of creatine distribution is skeletal muscle, where greater than 95% of creatine is located (Walker, 1979). The volume of distribution of creatine approaches that of total body water (approximately 45 L) (Persky *et al.*, 2003a). Distribution of molecules throughout the body is, in part, determined by the binding affinity of plasma proteins. The binding of creatine to plasma protein in humans is insignificant, at less than 10% (Persky *et al.*, 2003b). Thus a large unbound fraction of creatine is

free to distribute into tissues and is available as substrate for the creatine transporter that allows creatine to access tissues. Table 3 summarizes potential barriers to creatine entry into the biophase of pharmacologic tissue targets.

Skeletal muscle is the most studied tissue with respect to creatine disposition. Interestingly, the ability of skeletal muscle to accumulate creatine is finite; that is, it is possible to saturate muscle stores of creatine (Harris *et al.*, 1992). One reason that skeletal muscle may become saturated with creatine is possible down-regulation of either creatine transporter number or function. To date there is little evidence to support either conclusion (Tarnopolsky *et al.*, 2003a). Further discussion of the creatine transporter and its regulation can be found in chapter 6 (Christie, 2007).

Brain has become an increasingly popular tissue with respect to creatine disposition in the investigation of neurological disease. To date there is little evidence that brain creatine accumulation is saturable like skeletal muscle accumulation. Several studies have examined brain concentrations in Huntington's patients. One study found that patients receiving creatine (8 g/d for 16 weeks) had a 7.5 to 13% increase in brain creatine depending on brain region (Hersch *et al.*, 2006). A second study found an ~8% increase in brain creatine after 6 months of 10 g/d creatine (Tabrizi *et al.*, 2003). However, a third study in this patient population found no increase in brain creatine when patients received 20 g/d for 5 d followed by 6 g/d for 8 to 10 weeks (Bender *et al.*, 2005). In athletes receiving 20 g/d for 5 days, creatine supplementation did not appear to change brain concentrations of creatine (Wilkinson *et al.*, 2006) compared to individuals given 20 g/d for 5–7 days followed by 2 g/d for 7 d. This latter supplementation protocol (i.e., 20 g/d for 5–7 d followed by 2 g/d for 7 d) resulted in a 8-9% increase in brain creatine and an ~4% increase in brain phosphocreatine (Lyoo *et al.*, 2003). Although creatine distributes into the brain, similar doses that raise muscle creatine >20% tend to only increase brain creatine by <10%. This difference between brain and muscle uptake of creatine may be a reflection of a lower intrinsic clearance (i.e., V_{max}/K_m) for creatine transport into the brain via the blood-brain barrier compared to muscle.

Table 3. Potential barriers to creatine uptake into the biophase (i.e., pharmacologic effect compartment) and pharmacologic effect .

Barrier	**Potential Impact on Biophase Concentrations and Pharmacologic Effect**
Transport across the plasma membrane	✓✓✓✓✓
Transport into the mitochondria	✓✓✓✓
Conversion to phosphocreatine	✓✓✓
Intracellular degradation	✓✓
Phosphate pool	✓✓

✓ = minimal to ✓✓✓✓✓ substantial

4. CLEARANCE

Clearance is defined as the volume of a reference fluid (usually blood) irreversibly removed of a compound (e.g., drug) per unit time. In healthy individuals, creatine is irreversibly removed from the blood by both skeletal muscle and kidney. Muscle is typically not thought of as a clearing organ for drugs but because creatine is trapped and utilized in skeletal muscle of healthy individuals, it can be thought of as a clearance process; this may not be the case in patients with muscle disease. Early studies have shown that patients with muscle disease have ineffective trapping of creatine, leading to creatine efflux back into circulation (Fitch *et al.*, 1968). Creatine is irreversibly trapped in muscle because its polar nature prevents passive efflux back into circulation. Within the muscle, creatine and phosphocreatine spontaneously degrade into creatinine with an approximate half-life of 40 days, at physiologic pH. It has been previously hypothesized that muscle clearance is around 17 L/h using the well-stirred model of organ clearance (Persky *et al.*, 2003a,c); similar values can be estimated using the parallel-tube model derived by Pang and Rowland (1977). This latter model might be more appropriate for skeletal muscle because of the anatomical structure of muscle relative to blood flow. Creatine clearance by muscle is probably affected by the same factors that may affect the creatine transporter, which include insulin, IGF-1, catecholamines, exercise, and intracellular creatine levels (see chapter 6; Christie, 2007). The effects of insulin on creatine uptake by skeletal muscle have been studied in humans both by direct administration of insulin (Steenge *et al.*, 1998) and by insulin-stimulating foods such as carbohydrates and certain proteins/amino acids (Green *et al.*, 1996a,b; Steenge *et al.*, 2000). It should be noted that fructose tends to have a lower insulin response than glucose (Tappy *et al.*, 1986; Truswell, 1992) and thus fruit juices, in theory, are not as recommended as glucose containing products for enhancing creatine uptake through insulin stimulation. In addition, the amount of muscle mass may affect creatine clearance (Persky *et al.*, 2003a). Larger muscle mass likely correlates to a greater number of transporters and more storage area for creatine, suggesting that when dosing creatine, it may be more appropriate to scale the dose to bodyweight, ideal bodyweight, or lean body mass.

Creatine is also eliminated from the body by the kidney. At first it was thought that creatine underwent renal clearance at rates equivalent to glomerular filtration rate (GFR) (Pitts, 1934). However, later evidence revealed that creatine is reabsorbed in the kidney. In addition, the presence of creatine transporter in the kidney further supports creatine reabsorption from urine (Wyss and Schulze, 2002), assuming that the creatine transporter is effluxing creatine from the renal tubule back into systemic circulation. Studies looking at renal clearance of creatine have shown varied values. Poortmans and co-workers (Poortmans *et al.*, 1997, 2005; Poortmans and Francaux, 1999) reported renal clearance of creatine under unsupplemented conditions of 0.3–0.8 L/h, much less than GFR ($\sim$ 7.0 L/h) which again supports the reabsorption of creatine in the kidney. Under conditions of supplementation, renal clearance of creatine increased to 9–22 L/h; values higher than GFR would imply secretion of creatine from the blood into the renal tubules. Vandenberghe

et al. (1997) reported creatine excretion rate under unsupplemented conditions of 0.038 g/day, compared to 3.6 g/day after supplementing with 5 g of creatine per day for 10 weeks. Unfortunately, steady-state blood levels were not assessed to calculate renal clearance in this study. Most studies estimate the renal clearance of creatine from 24 h urine collection but from a data analysis standpoint, smaller windows of urine collection and blood sampling would be needed for a more accurate estimate of renal clearance. Recommended collection windows should be less than a half-life of the compound. In any case, the evidence suggests that creatine is reabsorbed in the kidney which causes dose-dependent renal clearance, and it is possible that there is a secretory mechanism for creatine as well. As blood concentrations increase and more creatine is filtered, less reabsorption occurs and a greater percentage of creatine will be lost in the urine.

Few studies have estimated systemic clearance of creatine. After a single dose of creatine in healthy volunteers, the apparent oral clearance was 14 L/h which is close to the predicted contribution of skeletal muscle (Persky *et al.*, 2003c). At steady-state, however, clearance was estimated to decrease to around 7 L/h, which is close to the prediction of renal clearance (Persky *et al.*, 2003c). The non-stationary behavior, i.e., parameters governing creatine pharmacokinetics change over time, suggests that as skeletal muscle approaches its capacity to store creatine, the kidney and possibly other tissues are responsible for the removal of creatine from the blood. This decrease in clearance over time should translate to smaller doses over time. For example, during early doses (i.e., doses within the first one to three days) when clearance is high, doses of 10 to 15 g per day will give blood concentrations greater than the K_m for the creatine transporter. As the muscle becomes saturated and clearance decreases, it may be necessary to ingest 3 to 5 g of creatine a day to maintain similar blood concentrations. Figure 1 represents plasma concentrations of creatine after a single dose and after steady-state has been reached for a 5 g dose of creatine monohydrate in healthy volunteers.

As mentioned, both muscle and the kidney contribute to the systemic removal of creatine. Exactly how much the kidneys and muscle contribute to creatine clearance is probably dependent on dose and dose frequency (Persky *et al.*, 2003a). As a person continues to take creatine, muscle stores become saturated and clearance shifts from muscle uptake to primarily renal elimination.

5. INTRACELLULAR PHARMACOKINETICS

As stated earlier in the chapter, it is the concentration of drug at the site of action that drives pharmacologic response. For creatine, the main site of action is thought to be skeletal muscle and, more recently, the brain. Within the muscle cell, creatine may potentially exert its pharmacologic effects in the cytosol or mitochondria. Creatine's pharmacologic effects are mainly due to the formation of phosphocreatine. If not converted to phosphocreatine, it is unlikely that creatine supplementation would be of benefit. There are three rate-determining steps to intracellular kinetics: entry

into the cytosol through the membrane-bound creatine transporter, entry into the mitochondria perhaps via a creatine transporter, and the creatine kinase reaction.

Previous chapters have focused on the creatine transporter but some discussion on the pharmacokinetic implications is warranted. In humans, the K_m for plasma membrane transport is on the order of 20 to 100 μM. Under normal conditions plasma concentrations are 25 to 50 μM, which is in the range of the K_m of the transporter. The kinetics of the system keeps interstitial concentrations at approximately 40% of plasma concentrations (Persky *et al.*, 2003c). Once in the cell, creatine is taken up into mitochondria through a creatine transporter, although the evidence for this is limited (Speer *et al.*, 2004). Finally the creatine kinase reaction is at equilibrium under normal conditions with approximately two-thirds of cytosolic creatine being in the phosphorylated form (Meyer *et al.*, 1984). The kinetics of the intracellular system have been previously described [see (Meyer *et al.*, 1984; Wallimann *et al.*, 1992)] but these studies did not take into account possible saturable processes of creatine entry into the cell or into the mitochondria. Additionally, the model did not examine the impact of increased plasma creatine concentrations seen under supplementation conditions. The kinetics of the intracellular system may dictate which individuals or populations respond to creatine therapy.

6. CREATINE DISPOSITION IN SPECIAL POPULATIONS

Historically, creatine research has focused on improving exercise performance in young, healthy males and females. However, accruing evidence shows that creatine may have a therapeutic role for the elderly or in individuals with certain diseases – especially muscular or neurological-based disease. Despite the potential therapeutic effect, not much is known regarding creatine disposition in special populations.

Rawson *et al.* (2002) showed that after a 5 g dose of creatine in young and elderly men, there was no increase in intramuscular phosphocreatine levels in the geriatric group despite similar plasma exposure and urinary excretion. This may be due to lack of conversion of creatine to phosphocreatine in either the cytosol or mitochondria. It is also possible that there is large variability in creatine uptake in the elderly but this would potentially lead to differences both in blood concentrations (higher in elderly) and muscle concentrations (lower in elderly). On the other hand, Brose *et al.* (2003) found that phosphocreatine did increase in the elderly when resistance training was concomitant with creatine ingestion; however no plasma data was available. Exercise has been shown to increase mitochondrial and creatine kinase content (Menshikova *et al.*, 2006). Thus, in the absence of exercise, elderly muscle may not respond to creatine supplementation due to lower mitochondrial function or creatine kinase activity.

Beyond its proposed use in elderly individuals, creatine supplementation is also being investigated as a therapeutic option for certain diseases. The implications of disturbances in creatine metabolism have been previously reviewed (Wyss and Schulze, 2002) and are outlined elsewhere in this book. Focusing specifically on

the pharmacokinetic implications of creatine in disease, it has been previously shown that hypercreatinemia and creatinuria are present in patients with muscular dystrophy; in addition, these patients show lower muscle levels of creatine and phosphocreatine (Fitch *et al.*, 1968). Similarly, patients with heart failure and myopathies show diminished expression of the creatine transporter, CreaT1, as well as lower muscle concentrations of creatine and phosphocreatine (Neubauer *et al.*, 1999; Tarnopolsky *et al.*, 2001). Fitch *et al.* (1968) previously proposed that the deficits in creatine and phosphocreatine levels were caused by either ineffective trapping of creatine in muscle or by lack of uptake. Despite recent studies evaluating creatine supplementation in muscular dystrophy, ALS and other neurological diseases, no formal pharmacokinetic study has been conducted in these patient populations.

7. FUTURE DIRECTIONS

Pharmacokinetic research on creatine is important to elucidate the reasons and mechanisms for the differences between individuals and populations. As research focuses on clinical application it is important to understand the disposition of creatine so predictions can be made 1) with respect to optimizing dosing regimens to obtain therapeutic tissue concentrations and 2) on the impact of disease on those tissue concentrations. While studies have looked at regulation of creatine turnover under normal conditions, it is necessary to investigate the systemic regulation of creatine turnover when supraphysiologic doses are administered. Studies using labeled creatine can be useful in this area to differentiate endogenous from exogenous creatine. Understanding the impact of tissue and blood concentrations on the uptake of creatine into target tissues (e.g., muscle, brain) *in vivo* in humans would lead to insight on how best to dose creatine to achieve optimal therapeutic effects.

8. SUMMARY

Creatine is absorbed from the gastrointestinal tract. Regardless of dosage form, creatine exhibits rapid absorption ($t_{max} < 2$ h); however, consuming very high doses of creatine results in a prolonged t_{max}. Ingestion of high amounts of carbohydrates appears to delay the time to peak concentration but, at the same time, decreases C_{max}. The absolute bioavailability is unknown for creatine but the fraction of creatine absorbed may be dictated by the creatine transporter kinetics. Although creatine is found in several metabolically active tissues, skeletal muscle is the major site of accumulation. Movement of creatine into tissue is governed by a transport process and regulation of this transport process is not fully elucidated to date. Removal of creatine from systemic circulation is governed by irreversible uptake into skeletal muscle and filtration by the kidney. Clearance of creatine appears to be non-stationary with clearance decreasing with repeated dosing. There is very little data differentiating the disposition of supraphysiologic doses of creatine between healthy

adults and patient or special populations (e.g., the elderly). The disposition of creatine may differ in these clinically relevant populations due to changes in total body water, renal function and skeletal muscle function.

9. RECOMMENDATIONS

Based on clearance of creatine during the initial days of supplementation, ingestion of 5 g three times a day (15 g/d) will maintain concentrations well above the K_m for the plasma membrane transporter throughout the day. After two days of the loading phase, muscle stores will approach saturation, resulting in an increased fraction of the dose being lost in the urine. Thus, after a short loading phase, doses can be reduced to 3 to 5 g/d to compensate for the reduction in clearance of creatine and to compensate for the loss of creatine via creatinine formation which is on average 2 g/d. Loading doses of creatine are probably best taken with glucose-based foods to maximize muscle uptake; maintenance doses may not require the carbohydrate/insulin stimulating component. For the elderly, physical activity might be an important parameter in increasing creatine uptake into muscle as exercise will improve the mitochondrial function within muscle. For patients requiring increased brain concentrations, doses of 5 to 10 grams for extended periods of time (e.g, >10 weeks) after an initial loading phase (e.g., 5 g three times a day for 2 to 5 days) might be necessary to attain the increase in brain creatine; despite this extended period of dosing, brain concentrations may only increase by 10%. There is little data to evaluate whether brain uptake of creatine changes with repeated dosing nor if higher doses are more effective; however, higher doses for extended periods of time may increase the risk of adverse events.

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