Potential metabolic consequences of statins in sepsis*

David A. Brealey, MB, BS, PhD, MRCP, FRCA; Mervyn Singer, MB, BS, MD, FRCP; Marius Terblanche, FRCA, EDIC, Dip(Epi)

Objective: Statins may be important for the prevention and management of sepsis; however, through their impact on ubiquinone synthesis, they may impair mitochondrial and organ function in the septic patient. Here we provide a narrative review of the function and roles of ubiquinone in cellular metabolism, the interactions with statins, and the potential consequences in the critically ill.

Data Source: Literature search using the PubMed database. Search terms included statins, mitochondria, ubiquinone, and sepsis.

Conclusion: Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and act by decreasing mevalonate levels, a precursor for cholesterol synthesis. However, mevalonate is also a precursor for ubiquinone, an integral component of the mitochondrial respiratory chain and an important antioxidant. Plasma ubiquinone is inversely related to statin levels, and impaired statin metabolism or excretion can decrease ubiquinone levels markedly. This is potentially important as critical illness markedly impairs statin metabolism. As mitochondrial dysfunction may be a major contributor to sepsis-induced organ failure, it is plausible that low ubiquinone levels may exacerbate mitochondrial and organ dysfunction. Furthermore, although the clinical relevance of low ubiquinone levels is currently unknown in the critically ill, this is often cited as a possible cause of the myopathy and rhabdomyolysis associated with statin use. (Crit Care Med 2011; 39: 000–000)

Key Words: sepsis; statins; ubiquinone; mitochondria; antioxidant; organ dysfunction

Severe sepsis is a syndrome characterized by a systemic inflammatory response to infection resulting in acute organ dysfunction and a high mortality rate. Despite considerable efforts, only one immunomodulatory therapy (drotrecogin α) has been shown to reduce mortality (1, 2), although even this agent is under renewed scrutiny. More recently, a number of retrospective and prospective cohort studies have indicated that statins may have a role in the prevention and/or treatment of this complex condition. Patients receiving statins were less likely to develop subsequent sepsis and had a reduced incidence of intensive care unit admission and decreased mortality (3–6). Prospective, randomized studies are ongoing. However, the mechanisms through which statins exert possible protection remains uncertain; altered cell signaling with resultant immunomodulatory and antiinflammatory effects (7) may play a role.

While precise pathophysiological mechanisms underlying sepsis-induced multiple organ failure also remain unclear, compelling data suggest mitochondrial failure as an important etiology (8). This raises potential concerns for statin therapy as, through their effects on ubiquinone synthesis, they may impair mitochondrial function still further, negating any benefit or potentially causing harm. Ubiquinone is a powerful antioxidant and an integral component of the mitochondrial respiratory chain. The impairment of ubiquinone synthesis is frequently cited as a cause of the well-described muscle complications of statin therapy observed in the nonacute outpatient population. The effect of statins in the critically ill, who frequently experience alterations in drug metabolism and disposition, is uncertain and can easily be camouflaged within the general milieu of their poor health. While we, in general, share the enthusiasm for statins as a putative adjunctive therapy in sepsis, it is worth highlighting the potential downsides and complications that may ensue.

In this article, we provide a narrative review of the literature and explore potential mechanisms of interplay between statins and ubiquinone metabolism. We briefly outline muscle complications associated with statin therapy, describe the role of ubiquinone on mitochondrial function, the effects of ubiquinone insufficiency, and effects of statin therapy on plasma ubiquinone levels, and review the limited literature relating to ubiquinone in sepsis.

STATINS

Statins are heavily prescribed drugs with proven benefits in cardiovascular disease. However, their benefits appear to go beyond that of simple lipid lowering. Immunomodulatory actions include effects on cell signaling with consequent changes at the transcriptional level, including repressed major histocompatibility complex II and nuclear factor κB expression, induction of heme oxygenase, and direct alteration of leukocyte–endothelial cell interactions (7, 9–12). Since statins do not target individual inflammatory mediators but possibly reduce the overall magnitude of the systemic response, this effect could prove an important distinguishing feature, modulating the host response to a septic insult. These and other findings form the basis for the use of statins in dilated cardiomyopathy (13), breast...
cancer (14), subarachnoid hemorrhage (15), and, in critical care, acute lung injury (16) and sepsis (5, 17).

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting step in mevalonate synthesis. Mevalonate is a precursor for cholesterol, ubiquinone, and diacil (Fig. 1). While statins putatively decrease all three, the affinity of squalene synthetase (cholesterol) for farnesyl pyrophosphate (Fig. 1) is less than that of either cis-prenyl transferase (dolichol) or trans-prenyl transferase (ubiquinone) (18). This, in theory, suggests that cholesterol synthesis can be preferentially inhibited by statins. Hepatocytes are the main site of action of statins, at least with respect to their lipid-lowering, HMG CoA reductase inhibitory effect. The inhibition of HMG CoA reductase with subsequent decreases in mevalonate and nonsterol isoprenoids may, in part, explain their antiinflammatory effect (7, 11). Geranylgeranyl pyrophosphate and farnesyl pyrophosphate are intermediate metabolites of mevalonate that play an important role in posttranslational modification of proteins and are implicated in the inflammatory response to infection (11, 12).

That statins reduce cholesterol levels is undisputed. Its effect on ubiquinone, and the clinical significance of this, is less clear but is often cited as a possible mechanism for statin-induced myopathy. Muscle symptoms range from weakness and fatigue to pain and, very rarely, rhabdomyolysis. The frequency of myopathy in the general population treated with statins is approximately 11%, with 4% having symptoms severe enough to limit activity (reviewed by Harper and Jacobson [19]). Although classically associated with a raised creatine kinase, this may be normal in approximately 20% of patients (20, 21). Biopsies have been reported as being normal, demonstrating vacuolated fibers, T-tubule disruption, and, occasionally, necrosis (21, 22). Histologic changes can occur even in those with normal creatine kinase levels (21). Higher statin levels are associated with a higher frequency and severity of this side effect (20, 23). Certain pharmacokinetic properties may increase the potential for these side effects (reviewed by Igel et al [24]). Compared to the hydrophilic statins (e.g., pravastatin), the lipophilic statins (cerivastatin, simvastatin, lovastatin) are less hepatoselective and have an increased propensity for extrahepatic interactions and side effects. This, coupled with a high bioavailability, may explain why cerivastatin (now withdrawn) had a relatively high frequency of myopathy and rhabdomyolysis. With the exception of pravastatin, most statins are highly protein bound, raising the possibility that the hypoalbuminemia associated with sepsis may elevate the concentration of free (active) drug. This risk is further heightened by impaired metabolism related to organ dysfunction and/or drug interactions.

Simvastatin, lovastatin, atorvastatin, and fluvastatin are metabolized by the cytochrome P450 system. Impairment of this cytochrome system by disease processes such as sepsis and trauma (25) or drugs (e.g., amiodarone, erythromycin, itraconazole, and ritonavir) could markedly increase plasma statin concentrations. A review of 338 cases of statin-induced myopathy demonstrated patients were more likely to have renal disease, alcoholism, recent trauma, and diabetes and be receiving other drugs with potential to interact with statins (20). Concomitant fibrate usage was particularly linked to myopathy. The SLCO1B1 gene encodes the liver enzyme organic anion-transporting polypeptide IB1 that is responsible for hepatic transportation of statins. Certain alleles of this gene predispose the patient to higher plasma levels of simvastatin and a greater frequency of myopathy (26, 27). Similarly, inhibitors of organic anion-transporting polypeptide IB1 can increase statin levels markedly. The protease inhibitor lopinavir, a potent inhibitor of organic anion-transporting polypeptide IB1 (28), markedly elevated rosuvastatin levels in healthy volunteers and patients with human immunodeficiency virus when used in combination with ritonavir (29, 30). Similarly, a single dose of rifampicin can elevate atorvastatin levels through the same interaction (31).

The relevance of these factors to intensive care was demonstrated when critically ill patients were given a single dose of atorvastatin (20 mg) (32). The patients exhibited markedly raised peak plasma concentrations (approximately 18 times those of healthy volunteers) and a significantly raised area under the curve, particularly in those who were septic. This was even more marked in those receiving drugs that could inhibit atorvastatin metabolism. Drage and colleagues administered 40 mg of simvastatin to 27 critically ill patients, demonstrating higher plasma levels of both simvastatin and its active metabolite, simvastatin acid, compared to values obtained from healthy volunteers (33). Such raised levels are more likely to expose the critically ill patient to the risk of myopathy as well as other organ dysfunctions, including cardiac. A proposed pathway of impaired statin metabolism, ubiquinone depletin, and mitochondrial impairment is depicted in Figure 2.

**UBIQUINONE SYNTHESIS AND FUNCTION**

Ubiquinone (2,3-dimethoxy-5-methyl-6-polyisoprene para-benzoquinone), also known as coenzyme Q10, is a lipophilic, nonsterol isoprenoid found in virtually all
cell membranes. It is in particularly high concentration within the heart and liver (34). Most ubiquinone is synthesized within the cell, with a small proportion being obtained from the diet. It is synthesized from tyrosine and mevalonate and requires numerous steps. Synthesis takes place within the endoplasmic reticulum and Golgi body and requires the presence of vitamins B2, B9, B12, and C and the cofactors tetrahydrobipterin, nicotinamide, and pantothenic acid (18). The rate-limiting step within the pathway is known to be at HMG CoA reductase.

Ubiquinone is thought to have a number of important physiologic roles.

1) Energy Transduction. Contained within the inner mitochondrial membrane, ubiquinone is freely diffusible and is a vital component within the mitochondrial respiratory chain (Fig. 3). Mitochondrial ubiquinone exists in large molar excess compared to the other components of the respiratory chain. However, experimental evidence suggests that ubiquinone may become rate-limiting for reduced nicotinamide adenine dinucleotide oxidation if levels are to fall or its Michaelis constant is to increase, as can happen with aging (35).

As part of the respiratory chain, ubiquinone receives electrons from complex I (reduced nicotinamide adenine dinucleotide ubiquinone oxidoreductase) and complex II (succinate dehydrogenase). It also receives electrons transferred from fatty acid and amino acid catabolism by flavoprotein-ubiquinone oxidoreductase (electron transfer flavoprotein-ubiquinone oxidoreductase) and from glycerol-3-phosphate dehydrogenase, which provides a means of electron transfer from cytoplasmic reduced nicotinamide adenine dinucleotide directly to the respiratory chain. The transfer of electrons results in the reduction of ubiquinone to ubiquinol. The transfer of electrons from ubiquinol to complex III is complicated and is generally referred to as the Q cycle.

2) Antioxidant/Oxidant. Depending on intracellular conditions, ubiquinone may demonstrate either antioxidant or pro-oxidant activity. It is found in cell membranes in concentrations far in excess of that of tocopherol. Being mainly in the reduced form (aided by several reductase enzymes), it has the ability to act as an effective antioxidant (36). In conditions where levels of other antioxidants are decreased, Navarro et al (37) demonstrated a compensatory increase in ubiquinone levels and its associated reductase enzymes within rat liver.

Low-density lipoprotein and deoxyribonucleic acid were rendered more resistant to oxidation in volunteers given oral ubiquinone supplementation (38, 39), while topical application of ubiquinone reduced the level of oxidation in the epidermis (40). Ubiquinone also maintained thiol levels and reduced deoxyribonucleic acid damage in human keratinocytes exposed to ultraviolet A (40).

Under certain conditions, ubiquinone may have a pro-oxidant role. The semiquinone radical produced during the Q cycle in the inner mitochondrial membrane has long been considered one of the major superoxide generators. Under proinflammatory conditions, nitric oxide is capable of oxidizing ubiquinone, with subsequent production of superoxide and peroxynitrite.

In mitochondria isolated from endotoxic rats, ubiquinone content was directly related to hydrogen peroxide production (34). Other studies however show that addition of ubiquinone can halt the propagation of radical reactions (41) and improve markers of oxidation in animal models of sepsis (42, 43). These findings suggest that the ratio of nitric oxide to ubiquinone is important in terms of whether it is a pro-oxidant or antioxidant.
3) Cell Signaling. The single electron reduction of ubiquinone to a semiquinone radical can result in the production of superoxide and hydrogen peroxide. These, in turn, activate nuclear factor κB, a transcription factor capable of up-regulating proinflammatory genes. The application of ubiquinone to the human colon carcinoma 2 cell line resulted in the increased expression of over 690 genes (44). Of the genes identified, the majority were involved in cell signaling, intermediary metabolism, and transport. Muscle biopsies obtained from elderly patients receiving ubiquinone supplements demonstrated altered expression in 115 genes compared to matched controls (45).

UBIQUINONE DEFICIENCY AND DISEASE

Numerous studies have investigated ubiquinone deficiency, either primary or secondary, as a possible pathogenic mechanism in various disease states. Primary ubiquinone deficiency is rare and usually inherited in an autosomal recessive fashion (46). It produces a variable spectrum of disease that presents in childhood as encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, Leigh’s syndrome (growth retardation, ataxia, and deafness), or an isolated myopathy. This phenotypical variation suggests a number of possible molecular defects, as yet unknown.

Ubiquinone deficiency is also considered important in other neurodegenerative conditions such as Parkinson’s disease, Friedreich’s ataxia, and Huntington’s chorea (47). Case reports suggest that oral ubiquinone supplementation improves symptoms and biochemistry in patients with Leigh’s syndrome (growth retardation, ataxia, and deafness), or an isolated myopathy. This phenotypical variation suggests a number of possible molecular defects, as yet unknown.

There is an increasing body of evidence implicating ubiquinone deficiency in the pathogenesis of heart failure. Plasma ubiquinone levels independently predicted mortality in a prospective study of 236 patients with heart failure (52). Folkers et al (13) also demonstrated decreasing plasma and myocardial right ventricle ubiquinone levels in patients with increasing heart failure severity. An analysis of ubiquinone levels in a large trial examining rosuvastatin in heart failure found that low levels of plasma ubiquinone were associated with adverse outcomes; however, in itself, it was not an independent predictor of morbidity or mortality (53). In a small, double-blind, double-crossover study (54), patients with stable New York Heart Association class III/IV heart failure received 100 mg of oral ubiquinone daily or placebo for 12 wks and then a further 12 wks in the other arm following crossover. Ubiquinone treatment resulted in significant rises in plasma concentration and improved stroke volume/ejection fraction that slowly declined when the group rotated back to placebo. A total of 18 of the 19 patients enrolled reported clinical improvement, mainly with respect to functional activity. In a further crossover study of patients with heart failure, ubiquinone supplementation improved cardiac output and reduced end-systolic volume in response to exercise when compared to placebo (55). A daily dose of 100 mg of oral ubiquinone can increase the myocardial ubiquinone concentration by 20% to 80% (13). A systematic review of ubiquinone in heart failure concluded that supplementation was associated with significant (albeit small) improvements in cardiac function (56).

In a prospective study of 14 asymptomatic patients commenced on atorvastatin, ten had an asymptomatic fall in left ventricular diastolic function (57). Daily supplementation with 300 mg of ubiquinone resulted in at least partial resolution of these echocardiographic findings. Others have reported similar improvements in cardiac function in patients treated with statins who received ubiquinone supplementation (58).

Although none of these studies prove direct causation between low ubiquinone levels and disease, the fact that oral supplementation appears to increase plasma and tissue levels, often with an associated improvement in symptoms and biochemical and imaging features, does suggest that ubiquinone deficiency may be pathogenic.

Numerous studies have demonstrated lowering in plasma/serum ubiquinone levels in those treated with statins (reviewed by Hargreaves et al [18]). This can, in part, be explained by the lowering of ubiquinone carriers, in particular low-density lipoprotein. Plasma/serum levels are reflective of both dietary intake (accounting for approximately 25%) and hepatic synthesis and thus may not be representative of tissue levels that depend upon de novo synthesis (59).

In 20 hyperlipidemic patients treated with simvastatin (median dose 20 mg, range 10–80 mg), there were falls in both plasma ubiquinone and in the ubiquinone/low-density lipoprotein cholesterol ratio (60). This fall appeared to be in excess of that explained by reduced cholesterol levels alone. Similarly, patients treated with 80 mg of atorvastatin showed significant falls in plasma ubiquinone levels compared to the baseline; this could not be accounted for purely by a fall in circulating lipoproteins (61). Folkers et al (58) demonstrated falls in plasma ubiquinone in cardiac failure patients treated with lovastatin that could be ameliorated by oral supplementation. In a single volunteer, they demonstrated that plasma ubiquinone levels fell on commencement of lovastatin and that this was associated with a decrease in cardiac index. Both were restored with oral ubiquinone supplementation. In a prospective study, De Pinieux et al (62) examined 80 hypercholesterolemic patients, 40 of whom were treated with a statin (simvastatin, pravastatin, or fluvastatin) and 20 with fibrates (gemfibrozil, fenofibrate, or ciprofibrate), while 20 acted as controls. A further 20 volunteers acted as healthy controls. They found significantly lower serum ubiquinone/low-density lipoprotein ratios in the statin-treated group compared to the normal controls and a raised blood lactate/pyruvate ratio. They inferred this to be an indicator of mitochondrial dysfunction but were unable to show any direct correlation with serum ubiquinone levels.

Other studies have shown significant (27% to 40%) falls in plasma ubiquinone following pravastatin (63), atorvastatin and lovastatin (64), and simvastatin and pravastatin (65). Twenty-four patients receiving escalating doses of either lovastatin or pravastatin demonstrated a dose-dependent decrease in serum ubiquinone and an increase in the high-density lipoprotein/ubiquinone ratio (66). Although small (20 mg) doses of simvastatin resulted in a 25% fall in plasma ubiquinone levels (67, 68), there was no associated decrease nor correlation with either muscle ubiquinone or muscle adenosine triphosphate levels. This suggests that low-dose simvastatin isunlikely to affect muscle cellular metabolism. Furthermore, serum ubiquinone and total cholesterol levels paralleled each other during a statin treatment break, suggesting the fall in serum ubiquinone was purely a reflection of a
lower concentration of ubiquinone carriers. However, when the same group gave 48 hypercholesterolemic patients larger daily doses (simvastatin 80 mg, atorvastatin 40 mg, or placebo), they found that the muscle ubiquinone concentration had fallen by 30% in those taking simvastatin but not in those given atorvastatin or placebo (69). The difference between the two statins may reflect their different pharmacokinetic properties.

A case report of lovastatin (20 mg twice daily)-induced rhabdomyolysis demonstrated mitochondrial disruption on electron microscopy (70). The authors speculated this may have been due to inadequate ubiquinone synthesis. Duncan et al (23) demonstrated significantly lower muscle ubiquinone levels and impaired mitochondrial respiratory chain complex IV activity in two patients presenting with simvastatin (40 mg daily)-induced myopathy. Importantly, all three of the above patients were also receiving drugs that could interact with statin metabolism, including gemfibrozil, cyclosporine, and itraconazole. Muscle biopsies obtained from patients with presumed statin-induced myopathy demonstrated a modest decrease in ubiquinone (22) and alterations in mitochondrial morphology (71).

Animal models also support the concept that statins may impair mitochondrial function. In rats given cerivastatin, there was a decrease in muscle mass, mainly due to degeneration of type 2, fast twitch fibers. In nondegenerative cells, there were signs of distended mitochondria with disrupted cristae and cleared matrices (72). The authors suggested this damage may be severe enough to impair oxidative phosphorylation. Others have demonstrated that statins can cause mitochondrial depolarization and calcium efflux in type 2 muscle fibers (71, 73). Cerivastatin also caused apoptosis in human and rat myotubes, in a time-dependent manner, which could be prevented by the addition of mevalonate (74).

Trials investigating ubiquinone supplementation to alleviate statin-induced myopathy have had mixed results. Despite oral supplementation of 100 mg of ubiquinone daily resulting in a 40% decrease in the pain associated with statin-induced myopathy (75), other studies reported no benefit (76, 77).

Some have also speculated that the action of statins on ubiquinone synthesis is the reason why recent large trials of statins in heart failure have been equivocal (78, 79).

**UBIQUINONE AND SEPSIS**

Although there are numerous papers describing low antioxidant levels and impaired mitochondrial function in human sepsis (80–82), there are no data describing ubiquinone levels in septic patients. Several animal models have examined this question. Large doses of ubiquinone in an endotoxic rat model prevented lipid peroxidation, reduced nitrite/nitrate levels, and enhanced the reduced glutathione concentration in the brain (83). In another rat model, the use of Mito-Q, a molecule designed to deliver ubiquinol to the mitochondrial membrane, resulted in fewer organ dysfunctions and higher mitochondrial membrane potentials (84).

In a dog model of *Escherichia coli* sepsis, pretreatment with ubiquinone did not alter leukotriene, thromboxane, or tumor necrosis factor α levels but did significantly reduce the hemodynamic compromise and lipid peroxidation activity associated with the septic insult (42). Injection of ubiquinone into the rostral ventrolateral medulla of rats reduced mortality and hemodynamic compromise when they were then exposed to lipopolysaccharide (43). Ubiquinone supplementation also decreased levels of superoxide production in the rostral ventrolateral medulla compared to controls.

Future work investigating changes in plasma ubiquinone concentration need to be interpreted in conjunction with changes in its major carriers, the low- and high-density lipoproteins, both of which are depressed by sepsis and proinflammatory cytokines (85, 86). The reason for this depression is unknown, although potential mechanisms include binding and neutralizing lipopolysaccharide, impaired maturation, enhanced clearance (85), enhanced endothelial lipase activity, loss of apolipoprotein A1, or a dilutional effect. A direct effect of inflammation on HMG CoA reductase or its regulators, leptin and adiponectin, monophosphate-activated protein kinase, could also depress both cholesterol and ubiquinone levels. However, there is currently little evidence to support such a statement. Animal models have also implicated ubiquinone in the treatment of numerous other disease processes. Ubiquinone supplementation reduced mitochondrial deoxyribonucleic acid damage and restored antioxidant levels in rabbits fed an atherogenic diet (87). Ubiquinone markedly improved renal function in a mouse model of interstitial nephritis (88) and also ameliorated some of the oxidant effects in a hepatic ischemia/reperfusion model (89).

**CONCLUSION**

The antiinflammatory effects of statins may be protective in sepsis, either as prophylaxis or possibly in its very early management. However, as the disease progresses and multorgan dysfunction becomes established, its side effects may potentially outweigh the benefits. Severe side effects, myopathy in particular, although relatively rare in the general population, are dose-dependent and could be thus predicted to increase in the critically ill, particularly as the metabolism and excretion of these drugs may be impaired by renal or liver dysfunction and by the common concurrent use of drugs with cytochrome P450 and organic anion-transporting polypeptide 1B1 inhibiting effects. The cause for the myopathy has yet to be firmly elucidated; however, the possible inhibition of ubiquinone synthesis has been heavily implicated. Ubiquinone is an integral part of the mitochondrial respiratory chain and the cell’s antioxidant system. Its deficit is implicated in the pathogenesis of heart failure. How ubiquinone plasma or tissue levels change in human sepsis, with or without statins, is as yet known; however, it may be possible to offset any changes with supplementation. Inadvertently impairing ubiquinone synthesis in a condition that already has a high frequency of myopathy, cardiac instability, mitochondrial dysfunction, and depressed antioxidant levels (80) is arguably counterproductive. Only further research will appraise these statements; investigators studying statins in established critical illness need to evaluate the possibility of ubiquinone depletion, through either direct measurement or monitoring for side effects, e.g., myopathy and deterioration in cardiac function. Until then, we advise a cautious approach.

**REFERENCES**

3. Hackam DG, Mamdani M, Li P, et al: Statins and sepsis in patients with cardiovascular...
19. Harper CR, Jacobson TA: The broad spec-


miol Drug Saf* 2010; 19:223–231


athy and skeletal muscle damage. *CMAJ* 2009; 181:E11–E18

22. Lamperti C, Naini AB, Lucchini V, et al: Muscle coenzyme Q10 level in statin-related myo-


23. Duncan AJ, Hargreaves IP, Damian MS, et al: Decreased ubiquinone availability and im-

paired mitochondrial cytochrome oxidase activ-

ity associated with statin treatment. *Toxi-

col Metho Methods* 2009; 19:44–50

24. Igel M, Sudhop T, von Bergmann K: Metabo-

lism and drug interactions of 3-hydroxy-3-

methylglutaryl coenzyme A-reduce inhibitors 


27. SEARCH Collaborative Group, Link E, Parish 

S, et al: SLCO1B1 variants and statin-

therapy in patients with severe sepsis. *Int J 


tion of HIV protease inhibitors with 


ritonavir and rosvastatin in healthy volun-


30. van der Lee M, Sankatsing R, Schippers E, et al: Pharmacokinetics and pharmacody-

amics of combined use of lovastatin/ritonavir 

and rosvastatin in HIV-infected patients. *Antivir 

Ther* 2007; 12:1127–1132


OATP1B transporter inhibition on the phar-

macokinetics of atorvastatin in healthy vol-


preliminary study of atorvastatin plasma 

concentrations in critically ill patients with 


Plasma simvastatin concentrations in criti-


34. Lisdero CL, Carreras MC, Meulemans A, et al: The mitochondrial interplay of ubiquinol and 

nitric oxide in endotoxemia. *Methods Enzy-

mol* 2004; 382:67–81

35. Lenaz G, Parenti Castelli G, Fato, et al: Co-

enzyme Q deficiency in mitochondria: Ki-

netic saturation versus physical saturation. 


36. Crane PL: Biochemical functions of coen-


min E and selenium deficiency induces expres-

sion of the ubiquinone-depending anti-

oxidant system at the plasma membrane. 

*FASEB J* 1998; 12:1665–1673

38. Thomas SR, Neuzil J, Stocker R: Cosupple-

mentation with coenzyme Q prevents the 

prooxidant effect of alpha-tocopherol and in-

creases the resistance of LDL to transition 

metal-dependent oxidation initiation. *Arte-


and blood cells: Defense against oxidative 


41. Schipper P, Riobó N, Carreras MC, et al: Coen-


43. Chuang YC, Chan JY, Chang AY, et al: Neu-

roprotective effects of coenzyme Q10 at ros-

tral ventrolateral medulla against fatigue 

during experimental endotoxemia in the rat. 

*Shock* 2003; 19:427–432

44. Gronberg DA, Kindermann B, Althammer 

M, et al: Coenzyme Q10 effects expression of 

genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. *Int J 


plications for protection of mitochondria against nitrosative damage. *Biochem J* 2000; 

349:445–453

46. Quinzii CM, Hirano M, DiMauro S: CoQ10 


49. Panos EC, Koutsogianni E, Kollros I, et al: 

Coenzyme Q10 and alteration in the expression of 

Nrf2-dependent genes in cancer cells. *Biofactors* 2009; 35:116–124

50. Galpern WR, Cudkowicz ME: Coenzyme Q 

deficiency diseases in adults. *J Neurol Sci* 2006; 244:151–160


53. Chuang YC, Chan JY, Chang AY, et al: Neuro-


54. Groneberg DA, Kindermann B, Althammer 

M, et al: Coenzyme Q10 effects expression of 

genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. *Int J 


lications for protection of mitochondria against nitrosative damage. *Biochem J* 2000; 

349:445–453


CoQ10 deficiencies. *Biosci* 2008; 32: 113–118


58. Van Maldergem L, Triefels F, DiMauro S, et al: Coenzyme Q-responsive Leigh’s encephalo-


59. Gironi M, Lamperti C, Nemmi R, et al: Late-

onset cerebellar ataxia with hypogonadism and muscle coenzyme Q10 deficiency. *Neu-

rology* 2004; 62:818–820


