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REVIEW ARTICLE

Role of acetaminophen in reducing the risk of kidney injury from Rhabdomyolysis: Narrative Review

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Abstract

Background: Rhabdomyolysis is a clinical syndrome that results in releasing myoglobin content from damaged muscle cells into circulation and often causes acute kidney injury (1). Different mechanisms are considered to be responsible in rhabdomyolysis and renal failure. However, free radical generation is the most important mechanism resulting in kidney injury. Thus, the effect of various antioxidants has been investigated. Acetaminophen, with antioxidant ability in therapeutic dose, has shown a considerable protective effect on kidney after muscle injury. The investigations have shown that acetaminophen enhances renal function, decreases renal damage and reduces oxidant injury. The aim of this review was to summarize proven evidences for etiology to renal injury and abilities of acetaminophen in reducing it.
Methods: Articles published from 2010 to 2017 in PubMed and Google Scholar were covered in this review. The articles investigating the role of free radical in renal injury following Rhabdomylosis were searched using the keywords Rhabdomyolysis, kidney and oxidative stress. The keywords used to find articles regarding antioxidant ability of acetaminophen were antioxidant and acetaminophen.
Conclusions: With assessment of evidences form antioxidant capacity of acetaminophen and mechanism of renal failure in Rhabdomyolysis, this drug can be useful for prevention and treatment of kidney injury especially following rhabdomyolysis.

Keywords: Acetaminophen; Kidney Injury; Rhabdomyolysis

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INTRODUCTION

According to American reports, the global prevalence of rhabdomyolysis is estimated to be 26,000 cases annually and acute kidney injury happens in 4% to 33% of them. As the incidence of kidney damage in this patient is not exactly known and with regard to lack of valid reporting system, the number of AKI is underestimated and its prevalence is probably higher (2).

Rhabdomyolysis is determined by damage to skeletal muscle, which can occur in different conditions, such as intense physical exercise and severe trauma (2, 3). Myoglobin as a result of damaged muscles would be released into the blood stream and filter in the glomeruli of the kidney. Accumulation of myoglobin and heme causes damage to the kidney via different mechanisms. One of the confirmed etiologies to renal injury is associated with reactive oxygen species (ROS) production (2-7). When myoglobins enters to tubular cells, ferrous (Fe 2+) state of iron in myoglobin oxidizes to ferric (Fe 3+) form and consequently leads to hydroxyl radical production. Additionally, the inversion of ferric (Fe 3+) to ferrly (Fe 4+) myoglobin causes more radical species (2, 8, 9).

Lipid peroxidation induced by free radicals can cause malondialdehyde and F2-isoprostanes production which are detectable in the urine of rhabdomyolysis cases (2). F2-isoprostanes stimulate vasoconstriction and expression of pro-inflammatory cytokines (MCP-1) and intercellular adhesion factors such as VCAM-1. Furthermore, ferryl myoglobin in urine is a potent scavenger of nitric oxide, which is associated with vasoconstriction, endothelial dysfunction and platelet aggregation in kidney (2). Thus, the detection of useful and practical antioxidant, which could decrease or prevent events following rhabdomyolysis, seams to be necessary.

METHODS

Published articles from 2010 to 2017 in PubMed and Google Scholar were covered in this review. The keywords used to find articles regarding antioxidant ability of acetaminophen were antioxidant and acetaminophen. The research was divided into two steps: first, all articles that

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included data regarding the role of free radical in renal injury following Rhabdomyolysis were searched with the keywords of Rhabdomyolysis, Kidney and oxidative stress. The second set of articles about the antioxidant ability of acetaminophen was found with the keywords of antioxidant and acetaminophen**.**

Acetaminophen and antioxidant ability

Acetaminophen (APAP), as either a single agent or an active ingredient in many products, is one of the most highly used drugs. One of the reasons for acetaminophen toxicity is that it is often available in the home and overdose and contaminated use with other drugs is possible, and the legalization of sales in some countries has reduced its toxicity (10, 11). Although this drug can cause oxidative stress and induce liver and kidney damage in overdose, it has documented beneficial effects in some circumstances, such as coronary syndrome, high blood glucose levels, and AKI (12, 13). According to recent studies, these effects may be contributed to the antioxidant capacity of acetaminophen due to phenolic ring in its structure (12). Based on either electron or hydrogen atom transfer in the process of antioxidant activity, acetaminophen with hydrogen phenolic atom and potent source of electron has the perfect property for antioxidant nature (14).

One of the therapeutic aspects of acetaminophen is the inhibition of prostaglandin synthesis, which leads to fever and pain control. As Prostaglandin H (PGHS) is related to lipid peroxidation it reduction by acetaminophen causes the restriction of oxidative stress (9). An animal study has indicated that ROS production in multiple tissue types, for example, skeletal muscle and over aging, can be effectively reduced by acetaminophen (12). The efficacy of acetaminophen is higher than many other phenolic antioxidants, such as butylated hydroxytoluene (BHT), which are widely used. For example, acetaminophen at concentrations of 2–10 μmol showed more scavenging effect on reactive oxygen in cell-free systems in contrast to BHT. Acetaminophen can inhibit globin radicals and hemoprotein-induced lipid peroxidation by its ability to reduce ferrly heme to its ferric state (12).

In therapeutic range for humans, acetaminophen can reduce the active state of Mb and subsequently prevent oxidation of arachidonic acid induced by Mb in combination with H2O2, within an in vitro study. However, other known antioxidants such as ascorbic acid (vitamin C) and Trolox with IC50 4-fold and 7-fold higher than acetaminophen respectively were less effective (9). In a mouse model of atherosclerosis, dose-dependent reduction of epoxyalcohol-aldehyde-cardiolipins formed as a product of cardiolipins oxidation in isolated liver mitochondria treated with pro-apoptotic protein t-Bid was observed after acetaminophen incubation as a peroxidase inhibitor (15). APAP, also named as a pleiotropic inhibitor of peroxidase-catalyzed lipid peroxidation, can inhibit cytochrome-c from induction of free fatty acid oxidation as equal as prevention of cardiolipin oxidation in isolated mitochondria (16). In human, lipid peroxidation following coronary reperfusion in myocardial ischemia because of cardiac surgery leads to kidney injuries such as AKI (17). APAP could decrease the biomarkers of oxidative stress like isofurans, and myocardial injuries followed by reperfusion without affecting AKT in children and adults with cardiopulmonary bypass (CPB). Isofuran is a marker of lipid peroxidation and is increased during hemolysis (18, 19). APAP also has a renoprotective effect on obese rat model of metabolic syndrome (20). Treatment with acetaminophen was provided for 6 months in obese Zucker rats with glomerulosclerosis attenuates proteinuria, glomerulosclerosis, podocyte injury, and inflammation. Acetaminophen exerted this renoprotective effect by reducing p38MAPK hyperphosphorylation and renal oxidative stress (20).

Among patients with diagnosis of sepsis, it was evident that acetaminophen decreased oxidative stress induced by cell-free hemoglobin, and risk of death was independently lower in these patients. Cell-free hemoglobin induced in sepsis causes oxidative stress and it is associated with a higher risk of death (21, 22). Acetaminophen could improve renal function in this condition.

In a rat model of adenine-induced renal failure, acetaminophen with antioxidant activity could improve the survival rate. Acetaminophen attenuated the progression of renal failure and significantly recovered concentration of glutathione, which demonstrates the efficacy of this drug in treatingchronic kidney disease (CKD) patients (1).

The neuroprotective effect of APAP against lipopolysaccharide (LPS)induced cognitive impairment and inflammatory and oxidative stress was confirmed by an in vivo study. APAP with antioxidant and anti inflammatory properties could prevent intrinsic apoptosis by inhibition of the involved factors like inflammatory cytokines and mitochondrial permeability transition (MPT) pore and increasing of antioxidant enzyme such as superoxide dismutase (SOD) (23).

Exposure of HepG2 cells to high concentration of APAP was cytotoxic, however, low doses of this drug could increase transcriptional regulators of mitochondrial biogenesis and so the amounts of mitochondrial DNA, proteins and capacity of antioxidants including glutathione and MnSOD were significantly up regulated (24).

Acetaminophen and kidney failure in Rhabdomyolysis

Investigations showed that acetaminophen could not affect the muscle damage induced by rhabdomyolysis because of the similar detectable amount of myoglobin deposits in the urine of the treated and untreated animal. However, this drug by reducing the redox cycling of the heme group of myoglobin can attenuate and/or prevent this injury (2, 9). As mentioned previously, kidney damage attenuation and renal function improvement during treatment with acetaminophen in rhabdomyolysis are the result of APAP ability in decreasing the production of reactive oxygen species (12).

Intense vasospasm in the kidney of a rat model of rhabdomyolysis was reduced by acetaminophen which works through blocking of lipid peroxidation and finally prevents renal failure (14). In APAP treated animal, the amount of F2-isoprostanes and ferrly myoglobin, an indicator of lipid peroxidation, plasma creatinine and one of indicators of

renal failure are significantly attenuated (2, 8, 9, 25). Accordingly, acetaminophen can be effective for prophylaxis and kidney failure during rhabdomyolysis.

Cross-linking between heme and protein in Mb (Mb-X) which is found in the urine of patients with rhabdomyolysisis is a more cytotoxic form of Mb. In vitro study showed the prevention of Mb-X formation after APAP treatment within the range known as the therapeutic range in human (9). In the absence of APAP, 21% of the heme converted to Mb-X at 19–26 min buturinary levels of Mb-X was reduced almost by 75% compared to untreated rats after APAP administration. By inhibition of PGHS, acetaminophen can reduce protoporphyrin radical caption and production of tyrosyl radical, as well as lipid peroxidation following rhabdomyolysis in vitro study (9, 26).

In a rat model of rhabdomyolysis treated with APAP, appearance of kidneys was different in comparison with untreated rats. Treatment with APAP caused a decrease in discoloration of the kidneys and only a slightly mottled color was observed (9, 25). Furthermore, the amount of structural renal damages such as loss of proximal tubular brush border decreased following APAP therapy (9). Rhabdomyolysis and renal vasoconstriction following that are known causes of acute renal failure (ARF). Acetaminophen in glycerol-induced rhabdomyolysis of the female rat did not affect vascular responses, BUN levels or creatinine clearance, but it showed a protective effect on kidney histology (27). In clinical condition, acetaminophen administration in addition to intravenous hydration in a woman with rhabdomyolysis prevented renal failure and the patient was finally discharged without any electrolyte abnormalities (28).

CONCLUSION

According to recent researches, acetaminophen is able to induce antioxidant system and protect the body from oxidative stress in addition to possessing the phenolic ring and ability to scavenge free radicals in low dose. As one of the reasons for renal damage in rhabdomyolysis is oxidative stress, this drug probably could affect prevention and treatment of renal failure. In this review, we summarized the known antioxidant effects of acetaminophen against rhabdomyolysis studied during recent years, however, understanding of the detailed molecular mechanisms requires further investigation.

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