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Acetaminophen

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Abbreviations

PAR	Acetaminophen
ESR	Electron Spin Resonance
NAPQI	*N*-actyl p-benzoquinone imine

Table of Contents

Abstract

Acetaminophen is one of the most used non-steroidal anti-inflammatory drug with potent antipyretic and analgesic actions. Acetaminophen have both oxidant properties and antioxidant properties. Its toxicity is due to its ability to form free radicals. In this short review these oxidant and antioxidant properties will be discussed.

Introduction

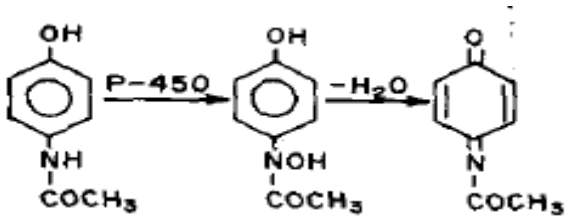
Acetaminophen (PAR), known as Paracetamol® in the United Kingdom and Tylenol® in the united states was introduced to medicine in 1893 [1, 2]. Acetaminophen is a non-steroidal anti-inflammatory drug with potent antipyretic and analgesic actions but with very weak anti-inflammatory activity [3]. A large number of metabolites are produced from acetaminophen in biological systems; some of them can form covalent bonds with cellular molecules, and other can form free radicals and superoxide. Formation of these reactive free radicals and their metabolites are though to contribute to the toxicity, mutagenicity, and potential carcinogenicity of acetaminophen [4].

Acetaminophen is mainly metabolized by cytochrome P 450to form an electrophilic metabolite, *N*-actyl p-benzoquinone imine, which inactivated by conjugation with glutathione. At high doses, the detoxification pathway becomes saturated, and the intermediate metabolite accumulates, and this cases the drug toxicity [5-8].

Free radical biology of acetaminophen

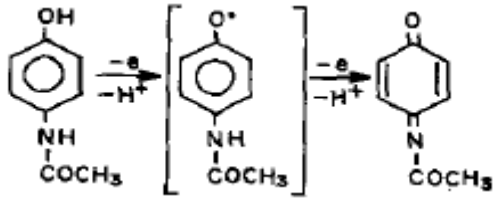
The radical

As mentioned above the toxicity of acetaminophen is mainly from the formation of *N*-actyl p-benzoquinone imine (NAPQI), where the metabolic activation occur through the *N*-oxidation of acetaminophen to *N*-hydroxyacetaminophen, followed by dehydration to arylating *N*-acetyl-p-benzoquinone imine, equation 1 [9].



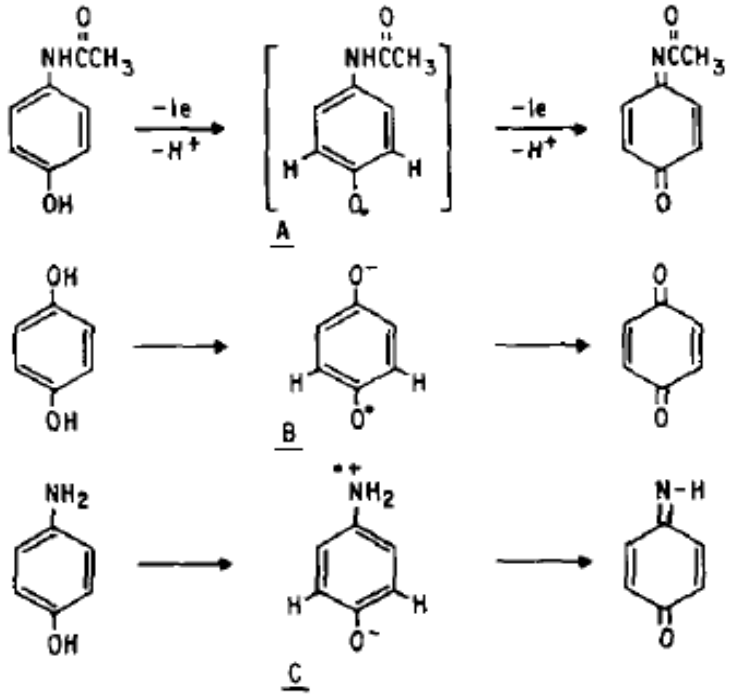
(1)

Many studies proposed that *N*-hydroxyacetaminophen is not formed as intermediate, instead it undergoes one or two electron oxidation to quinine imine reactive species, where different mechanisms and enzymes may be involved including cytochrome P-450 oxidase and prostaglandin hydroperoxidase, Equation 2 [10-14].



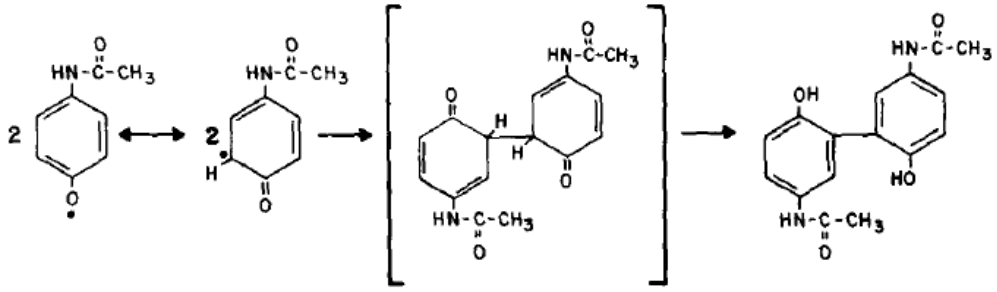
(2)

Equation 3 show these one and two electron oxidation rection where in the one electron reaction transient free radical intermediates are formed, such benzoaemiquinone (B) and aminophenol (C).



(3)

After acetaminophen radicals formation, it undergo a radical coupling reaction usually on the 3` and 5` positions, equation 4 [15] .



(4)

Phenoxyl free radical formation was also observed by West, et al, using ESR. A three line ESR spectrum with ratios 1:2:1 and the signal has a characteristic g value of 2.0043 ± 0.0002 that can be assigned to an oxygen centered phenoxyl free radical figure 1 [16].

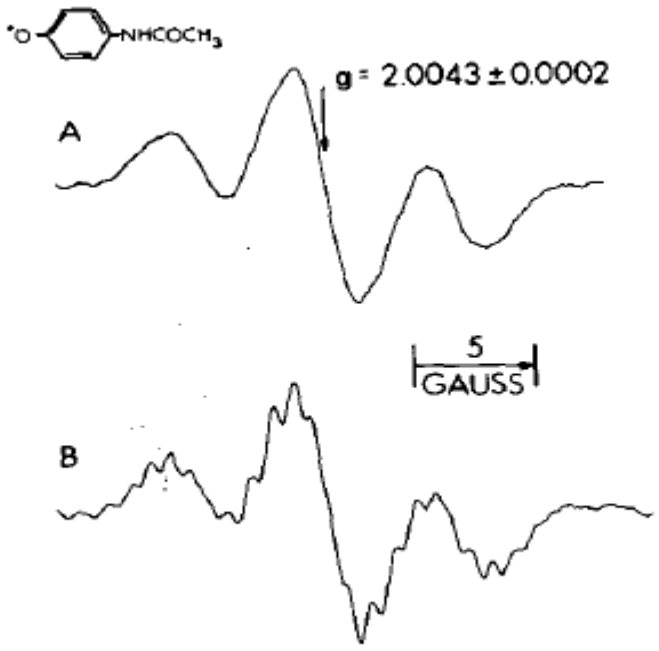


Figure 1 ESR fast-flow spectra of the acetaminophen free radical produced in the presence of horseradish peroxidase and hydrogen peroxide. Adapted from [16].

Toxicity

At normal doses of PAR, only atrace amount of the reactive intermediate NAPQI is formed, and in the presence of reduced glutathione (GSH) NAPQI can either be reduced back to PAR or covalently linked to GSH to form PAR-SG without playing significant effects [17]. Under toxic conditions GSH is depleted more extensively and can no longer compensate for a massive production of NAPQI, and this depletion, specially the mitochondrial GSH is correlated with the drug toxicity [18].

NAPQI can oxidize the cysteine thiols in GSH leading to GSSG and in protein giving rise to protein disulfides and GSH mixed disulfides. Oxidation of GSH by NAPQI occurs via *ipso*-attack of GSH on the C1 carbon [19].

Lipid peroxidation (LPO) has been regarded to be important initiation event in the toxicity mechanism of PAR . Reactive oxygen species (ROS) such hydrogen peroxide and superoxide anions, are required for the initiation of LPO by NAPQI, as NAPQI is expected to incapable of initiating a hydrogen abstraction from lipids. However, reduction of NAPQI, which can occur in the presence of flavoproteins, followed by reoxidation by oxygen could rise to superoxide anions with a consequent formation ROS and LPO, even NAPQI bound to proteins was suggested to be liable to one electron reduction [20].

Acetaminophen as an antioxidant

Although the toxic effects of PAR through its ability to form free radicals, it also considered as antioxidant. On proposal of its antioxidant abilities, is the fact its role in protein oxidation may not be a significant toxic reactions, but it may well be that protein thiol oxidation and glutathiolation are protective mechanisms after exposure to high doses of PAR [21].

In more direct antioxidant effect of PAR, Merrill, *et al.* showed that, during ischemia and reperfusion, acetaminophen attenuated the release of hydroxyl radicals and peroxynitrite. They examined that by testing the ability of acetaminophen to attenuate the burst of hydroxyl radicals released by the postischemic, reperfused guinea pig myocardium.They used 2,5-dihydroxybenzoic acid (2,5-DHBA) as a trap for hydroxyl radicals, and found that acetaminophen significantly attenuated the perfusate concentration of this marker between 2 – 10 min of reperfusion . The results with hydroxyl radical and acetaminophen were corroborated with peroxynitrite and acetaminophen under similar conditions of ischemia/reperfusion in the perfused guinea pig heart, figure 2 and 4, [22].

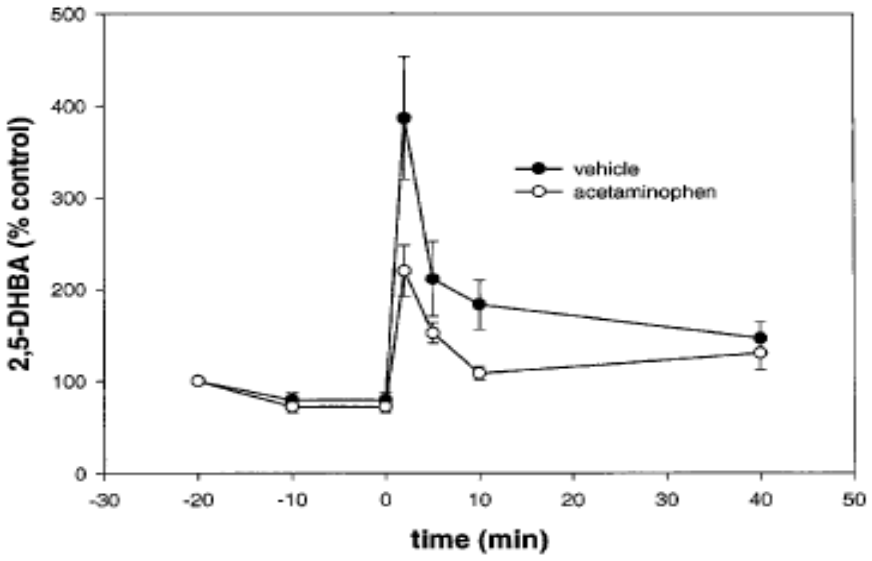


Figure 2 Influence of acetaminophen (0.35 mmol/l) on the production of hydroxyl radicals in the first few minutes of reperfusion following a 20 min period of low-flow, global myocardial ischemia in the isolated, perfused guinea pig heart. Adapted from [22].

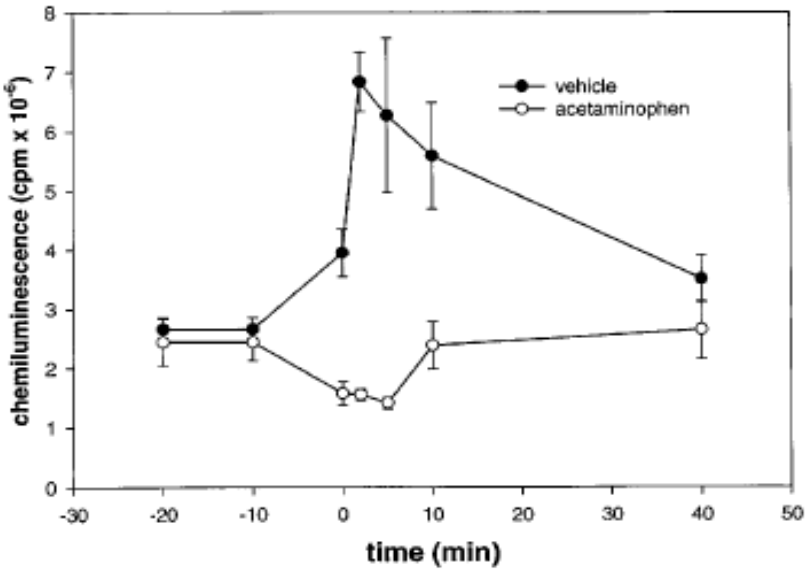


Figure 3 Influence of acetaminophen (0.35 mmol/l) on the luminescence produced by peroxynitrite when it oxidizes luminol in the presence of the nitric oxide generator, SIN-1. Adapted from [22].

Dinis T and coworker also showed that PAR act as inhibitor of membrane lipid peroxidation and as peroxyl radical scavengers [23]. As mentioned above PAR can act as antioxidant to peroxynitrite, Van Dyke K, and others , showed that PAR dramatically inhibit peroxynitrite formation, figure 4, [24].

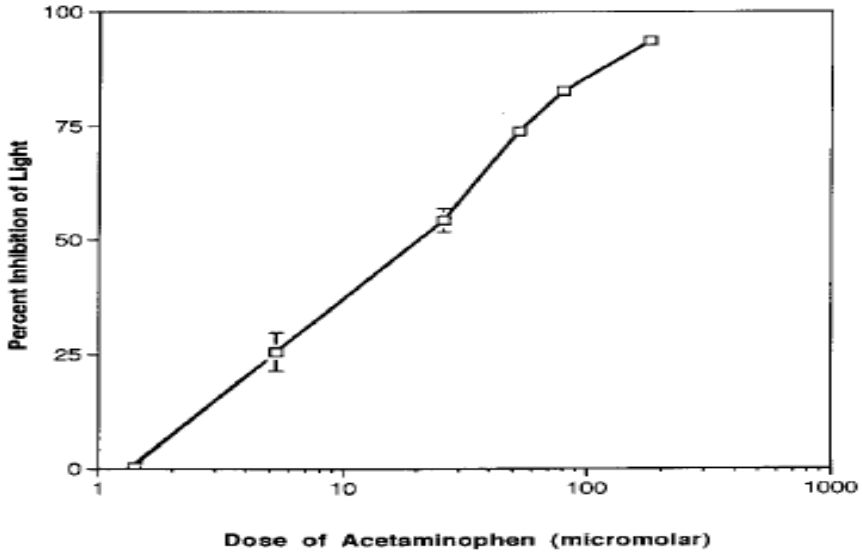


Figure 4 Acetominophen inhibitory dose-response curve of peroxynitrite-activated luminal chemiluminescence. Adapted from [24].

Summary

Acetaminophen is one of the most used non-prescription drug in the market. At high doses and prolonged use it has been to be a major hepatic toxin due to its ability to form free radicals and deplete the glutathione stores of the cell which have very damaging effects. On the other hand, acetaminophen considered as antioxidant because of its cardio protective abilities and ability to protect from membrane lipid oxidation by scavenging peroxyl radicals and peroxynitrite.

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