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Review Article

Acetaminophen (Paracetamol): a Magic Bullet

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Abstract

Acetaminophen (Paracetamol) has been used in Western medicine for more than one hundred years. By all measures, when taken as directed it is both efficacious and safe. The analgesic's recently-discovered properties go well beyond reducing fever and pain. There is mounting evidence that it is cardioprotective, neuroprotective, mitoprotective and generally cytoprotective. Much of this evidence has been collected in experimental animal studies. Now there is a growing need to replicate and extend these findings to the clinical and medical human arenas.

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INTRODUCTION

In this article I hope to disclose and promote some of the 'magic bullet' virtues of acetaminophen (paracetamol). These virtues extend far beyond the drug's ability to lower fever and reduce pain. The benefits of taking acetaminophen, as needed, can be gained at relatively low cost, with maximum confidence in efficacy and safety, and without the approval of a health-care provider other than the reader. For the cynic, the risk of acetaminophen-induced hepatotoxicity occurs only in those who try harming themselves or others by taking 'industrial strength truckloads' of the drug. The doses I describe here and in other publications do not cause hepatotoxicity [1-3].

We have been investigating the general cytoprotective actions of acetaminophen for more than twenty years. These experiments have been conducted in my experimental cardiovascular research laboratory (animals and humans) and nonchalantly on me. The first such experiments were initiated in 1999 (the past century), and continue to this day (2021, a new century). They have been focused on the heart [4-10], the brain [11,12], skeletal muscle [13], and musculoskeletal joints (unpublished observations).

BRIEF HISTORY OF ACETAMINOPHEN

Perhaps the best source of summary information about acetaminophen (paracetamol in Europe and elsewhere) was written by Laurie Prescott twenty years ago in his superb book, Paracetamol (acetaminophen): A Critical Bibliographic Review [14]. I had the great pleasure of meeting Professor Prescott a number of years ago on Queen Elizabeth's yacht near Scotland. We were attending a 3-4 day conference in Edinburgh on recent advances with acetaminophen. According to Professor Prescott the drug's discovery took the following path.

Paracetamol was a product of Germany's chemical industry in the late eighteen hundreds. At the time the only agents available to lower fever were quinine and salicylates. When new products like acetanilide, acetophenetidin, acetylsalicylic acid and antipyrine became available they were eagerly accepted by the medical community [14]. Two physicians, Cahn and Hepp, were treating intestinal worms in patients with naphthalene [15-17]. A newly-hired pharmacist accidentally substituted naphthalene with acetanilide. Gastrointestinal problems did not improve, but some patients had reduced temperatures and seemed to be in less discomfort. When Cahn and Hepp discovered the mistake they began a systematic study of the analgesic/antipyretic properties of acetanilide. Their original publications did not mention the accidental discovery [15-17].

CARDIOPROTECTION AND ACETAMINOPHEN

Our own encounter with the general cytoprotective properties of acetaminophen began more than twenty years ago. McNeil Consumer Healthcare, a Johnson & Johnson company near Philadelphia in the U.S., announced a grant competition in late 1998. The announcement said McNeil would consider funding any project that might discover new actions for acetaminophen. We did a hasty literature review and discovered there were few peer-reviewed, published reports of the potential cardiovascular effects of acetaminophen.

Being cardiovascular physiologists, we proposed to investigate the coronary circulatory actions of acetaminophen, followed by the general cardiovascular effects of the drug. McNeil liked our ideas and funded us for two years to collect preliminary evidence that acetaminophen possessed coronary vascular actions. We completed those initial experiments in 1999-2001 and reported that acetaminophen lacked either direct or indirect coronary vascular effects. Those experiments were performed in isolated, perfused, Langendorff guinea pig hearts, an experimental preparation we were thoroughly experienced with [4,18,19].

We subsequently proposed to McNeil to investigate potential cardioprotective properties of acetaminophen and they continued

our funding for another three years. In those experiments we treated guinea pigs chronically (added acetaminophen to their drinking water) and acutely and found consistent and prominent cardioprotection during global, low-flow, myocardial ischemia and reperfusion experiments [4-8]. After our experiments in guinea pig hearts were completed and published, we proposed to investigate acetaminophen's influences *in vivo* on local myocardial infarction (another three year project funded by McNeil). These experiments were performed in anesthetized, instrumented, dogs. We found that not only did acetaminophen reduce the size of a myocardial infarction [9], but that it had important antiarrhythmic properties as well [20].

Thus, after several years, and for the first time in its 125 plus year history of clinical/medical use, we began reporting important cardiovascular actions of the analgesic [1-10]. Those experiments stimulated work in other labs and clinics around the world, and that work continues to this day [21-23]. Equally importantly, our work on acetaminophen-mediated mechanisms of action in cardioprotection has stimulated continuing interest elsewhere [24-26].

MECHANISMS OF CARDIOPROTECTION BY ACETAMINOPHEN

Acetaminophen is a monophenol. Most phenols have antioxidant properties. The more phenolic the molecule the greater the antioxidant actions (i.e. polyphenols are better antioxidants than monophenols, etc) [27-29]. Thus, we proposed that acetaminophen would provide antioxidant inhibition during ischemia/reperfusion and other forms of cardiac injury. We focused on the oxidants: hydroxyl radical ($^{\bullet}OH$), peroxynitrite ($ONOO^{-}$), superoxide anion (O_2), and hydrogen peroxide (H_2O_2). In each case we found that the production of these potent, molecular/cellular/tissue-damaging molecules was impaired by pretreating the tissues with acetaminophen [30-36].

Cardiac functional and structural proteins play important roles in both diastolic and systolic phases of the cardiac cycle. For example, the Troponin complex (Troponin C, Troponin I, Troponin T) plays physiological roles in the healthy heart and is useful in diagnosing myocardial infarction [31]. Matrix metalloproteases (MMP), are known to damage the Troponin complex and to disrupt its physiological functions [31]. We hypothesized that acetaminophen's cardioprotective properties might involve blockade of MMP production/actions [31]. We found that MMP-2 was indeed inhibited by acetaminophen and believe this contributes to the cardioprotective properties of the phenol [31].

Later, we examined electronmicrographs of the ischemia/reperfused guinea pig heart in the absence and presence of acetaminophen. We found that cardiac striations and mitochondria appeared healthier in the presence of acetaminophen. Indeed, when subjecting tissue samples to FACS cell sorting procedures we found greater numbers of healthy cells and fewer cases of apoptosis in the presence of acetaminophen than in its absence. This encouraged us to dig deeper mechanistically and we began scrutininzing the 'mitoprotective effects' we had observed.

One of the important proteins that maintains mitochondrial acid/base homeostasis is the mitochondrial permeability transition protein (MPTP), [also the mitochondrial permeability transmembrane pore, (MPTP)] [32]. We investigated this protein during ischemia/reperfusion injury in the absence and presence of acetaminophen and found it to be more stable with acetaminophen (less apoptosis and less mitochondrial damage) [32].

CEREBROPROTECTION AND ACETAMINOPHEN

After finding so many salutary cardiovascular actions of acetaminophen, it seemed only natural to extend our investigation to other organs and tissues. First among these was the brain. We used the anesthetized rat and occluded both carotid arteries simultaneously while causing systemic hypotension (hemorrhage via both femoral arteries to a mean systemic arterial pressure near 50 mmHg). After sixty minutes of this procedure, the shed blood was returned to the rats and they were reperfused for an additional 120 minutes. This experiment was performed in the absence and presence of acetaminophen (15 mg/kg i.v. pre-occlusion).

After completion of reperfusion, rats were sacrificed, brains extracted, and areas of infarction plus areas at risk of infarction were stained, sectioned and quantified. In all cases the sizes of the cerebral infarctions and accompanying areas at risk were significantly reduced in the presence of acetaminophen. Moreover, evidence of cerebral apoptosis was significantly reduced by acetaminophen (e.g. reductions in cytosolic cytochrome C, reductions in expression of caspase-9, maintenance of mitochondrial morphology and membrane potentials, reductions in osteopontin) [33-36].

The above CNS results with acetaminophen are corroborated by the findings of Tripathy and Grammas [37]. They found evidence that acetaminophen inhibits neuronal inflammation and protects neurons from oxidative stress. Their experiments were performed *in vitro* in cultured neurons harvested from the cerebral cortex of 18-day old fetal rats.

STRIATED SKELETAL MUSCLE AND ACETAMINOPHEN

Since acetaminophen seems to be so efficacious in cardiac striated muscle, we hypothesized that it might have similar salutary actions in striated skeletal muscle. Although the two tissues have important similarities, they also have marked and significant physiological differences [38]. Our experiments with striated skeletal muscle, thus far, are still preliminary.

In these experiments we used either the extensor digitorum from the digits of mice (unpublished observations) or the gastrocnemius from the hindlimbs of frogs [13]. In both cases we compared strength and force of contraction of muscle in the absence and presence of acetaminophen. We then exercised the muscles to fatigue with and without acetaminophen and compared the outcomes. Whether mammalian or amphibian, all muscles treated with acetaminophen outperformed those treated with acetaminophen-vehicle (unpublished observations, 13).

In additional unpublished, preliminary experiments the author has made observations on himself (muscle function with and without acetaminophen). Thus far these are simply

subjective and require support from more well-designed, objective experiments using larger sample sizes. Still, exercises performed using legs, upper/lower arms, shoulders, and backs eight to twelve hours after a 500-1000 mg dose of acetaminophen (6-12 mg/kg, oral) are performed more easily with less discomfort and pain than when performed in the absence of acetaminophen. These doses are similar to those we used in dogs studying myocardial infarction and arrhythmias (15 mg/kg i.v.) [9,20], which are similar to those used in pediatric cardiothoracic surgery (21-23, i.e. about 15 mg/kg i.v.).

SUMMARY AND CONCLUSIONS

Acetaminophen is a safe and efficacious analgesic (when taken according to printed instructions). It has been used in western medicine for nearly 125 years. Our work and that of others demonstrates that there are non-analgesic properties of this compound that are probably as important as its analgesic properties. However, other than cardioprotection and cerebroprotection in animals, these properties are still waiting to be discovered (e.g. acetaminophen and skeletal muscle function).

Among the virtues of this 'magic bullet' are: its antiarrhythmic actions, cardioprotective actions, cerebroprotective actions, cost, efficacy, mitochondrial protective actions, nonprescription availability, and safety. When taken as directed, we are unaware of toxic side effects (including hepatotoxicity). According to packaging instructions, most manufacturers report that one can safely take up to 4000 mg/24-hour period without worry or harm. We have used 500-1000 mg or less in our experiments (i.e. among the lowest doses recommended by the manufacturers).

We wonder what other salutary effects might be seen with higher but still safe doses. For example, could aging patients and wounded veterans who live with near-constant pain benefit from high-dose acetaminophen vs opiate-containing drugs that are powerfully-addicting and destructive? Much more work is needed to answer this and related questions.

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