

# NRCT clinical study in to acetaminophen-induced liver injury

## Abstract

Acetaminophen (APAP) (N-acetyl-p-aminophenol) is a chemical compound used mostly in paracetamol medication to release pain and reduce fever. In June 2009, the Foods and Drugs Administration (FDA) advisory committee warned about the risk of overdose of APAP because of its side effects including drug-induced liver injury. Furthermore, the FDA started multicenter non-interventional case-control studies to collect data about biomarkers of APAP toxicity in children and adolescents. As part of the FDA, the National Center for Toxicological Research (NCTR) oversees the implementation of APAP clinical studies in collaboration with other health institutes (hospitals, universities, and clinical centers) across the United States. These clinical trials aim to produce enough data to establish a list of biomarkers linked to acetaminophen toxicity, which can be matched with specific adduct proteins; this information could then be used to analyze and predict future risks in children receiving acetaminophen.

**Keywords:** acetaminophen, paracetamol, drug-induced liver injury, non-toxic, biomarkers, the food and drugs administration, clinical trial, kidney failure, bleeding disorders, coma, genomics, metabolomics, proteomics, technologies, integrated biologic, toxic

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**Abbreviations:** APAP, acetaminophen; NCTR, the national center for toxicological research; FDA, food and drugs administration

## Introduction

Acetaminophen (APAP) (N-acetyl-p-aminophenol) is used to treat moderate to severe pain and release fever, usually in a mixture with other active ingredients in acetaminophen-based medicine.<sup>1</sup> However, APAP overdose leads to serious liver damage. Since 2009, the FDA has started a health campaign against the overdose and abuse of APAP to protect public health. Studies of drug-induced liver injury due to overdose of APAP have revealed the presence of biomarkers in patients' blood, such as the expression of specific mRNA.<sup>2</sup> Therefore, the FDA has begun a clinical trial in the younger population to collect data about these markers to assess the risk of this mechanism of APAP-induced liver injury in young people. This paper exposes the rationale and the design of an ongoing multicenter NCTR study to analyze biomarkers for drug-induced liver injury in children and adolescents who were excessively exposed to APAP.

## Rationale behind the study

Usually, patients take APAP medications orally which enter the blood stream by the GI tract, then are metabolized primarily in the liver to release toxic and non-toxic byproducts.<sup>3</sup> APAP overdose leads to drug-induced liver injury, the symptoms of which after 12 to 24 hours are nausea and vomiting, due to a considerable acid buildup in the blood leading to kidney failure, bleeding disorders, and possibly coma.<sup>1,4</sup>

Studies have shown that between 1998 and 2003, acetaminophen was one of the leading causes of death related to acute liver failure in the United States, with statistics showing that 47.78% of acetaminophen-related cases (131 of 275) resulted from its overdose.<sup>5</sup> Furthermore, preclinical and clinical studies showed significant differences in the build-up of MicroRNAs in the blood of APAP-

overdosed cases compared to controls in clinical trials. It was hypothesized that genomic medicine analysis could help in the early detection of biomarkers linked to APAP-related liver injury to prevent further liver damage in patients who have overdosed on paracetamol.<sup>6</sup> Therefore, the FDA has begun clinical research to collect enough data about these biomarkers to assess the risk of APAP-induced liver injury in the young and adult population.

## Multicenter FDA clinical trials on acetaminophen biomarkers

FDA clinical trials on drug-induced liver injury analyze the biomarkers for acetaminophen toxicity in children, adolescents by analyzing an acetaminophen (APAP) protein adduct, and markers in blood samples of patients and controls. The data collected from these studies will be used to detect the next generation of biomarkers due to acetaminophen toxicity and their specific protein adducts to assess future risks of an overdose of APAP in children.<sup>7</sup>

## The study design

The Arkansas Children's Hospital Research Institute is one of the host sites for these clinical trials in collaboration with the National Institute of Health and NCTR.<sup>6</sup> Their objective is the study of newly identified mechanisms for biomarkers of adverse responses to acetaminophen. The study is an observational prospective case-control study, meaning that the study will compare the blood samples of people who are receiving normal doses of APAP, people who are hospitalized due to APAP overdose, and people who have not been exposed to acetaminophen within 14 days.<sup>6</sup> The inclusion criteria of participants are: children between 1 and 18 years old who are hospitalized and receiving a standard dose of APAP; children with no APAP use in the past 14 days; and children hospitalized with an acute overdose of APAP estimated to have been within a two hour timeframe.<sup>6</sup> Children who have a history of liver disease or dysfunction were excluded from

the study. The study started on October 28, 2009, and was updated in November 2012, and is still recruiting participants; on the website, it is recorded as “No Result Posted” meaning that the results of the study are not yet available.<sup>2</sup>

## Conclusion

The outcome of this clinical project will hopefully be a listing of biomarkers and their protein adducts for APAP induced liver injury that may help to understand the biologic mechanism of the process by which this injury occurs. This trial illustrates the current trend in disease treatment, which is to translate findings of molecular-based studies into clinical practices.<sup>6</sup> This model study may provide enough data to address health problems associated with APAP drug overdose and treatment methodologies that can be applied in a variety of drug overdose situations. This study underlines the NCTR’s missions and objectives, which are to promote the regulation of medical products for safe and effective drug use through an applied and integrated biologic research system strategy using genomics, metabolomics, and proteomics technologies.<sup>3</sup>

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## Conflict of interest

The author declares no conflict of interest.

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