

IRB Protocol
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Acetaminophen in Combination with N-Acetylcysteine vs. Placebo in the Treatment of Fever: A Double-Blind, Randomized Control Study

A. Study Purpose and Rationale

N-acetyl-p-aminophenol (APAP), also known as acetaminophen is a popular anti-pyretic and analgesic that is sold over-the-counter and in several preparations such as Tylenol and Percocet. APAP is remarkably safe but it well known that overdoses can cause dose-dependent fatal and nonfatal hepatic necrosis¹. Because of its widespread availability and underestimation of its toxicity, APAP accounts for more overdose and overdose deaths in the United States and United Kingdom than any other pharmaceutical agent^{2,3}.

According to the annual report of the American Association of Poison Control Center's National Poison Data System, there were 43,052 reported cases of APAP related overdoses and 352 resultant fatalities in 2006².

At therapeutic dosages, acetaminophen is primarily metabolized via Phase II metabolism in the liver to inactive sulfate and glucuronide metabolites which is excreted in the urine. A small but significant amount is metabolized by cytochrome P450 enzymes including CYP2E1 and CYP1A2 into N-acetyl-p-benzo-quinone imine (NAPQI), an alkylating metabolite that binds to hepatic and renal tubular cells and is responsible for APAP's toxic side effect^{4,5}. At therapeutic dosages of APAP, NAPQI is conjugated with glutathione and inactivated. However, at toxic doses, the sulfate and glucouronide pathways become saturated with shunting of the metabolism towards the cytochrome P450 enzymes and production of NAPQI. The resultant overproduction of NAPQI overwhelms the hepatic supply of glutathiones for detoxification eventually causing hepatotoxicity⁴.

N-acetylcysteine (NAC) is the antidote of choice for APAP toxicity. NAC is a glutathione precursor that both increases glutathione stores and combines directly with NAPQI to enhance sulfate conjugation^{6,7,8}. If given within 8 to 10 hours of APAP ingestion, NAC can prevent serious hepatotoxicity and death^{9,10,11,12}. One study of 2540 patients with APAP toxicity treated with NAC showed a 6.1% rate of severe hepatotoxicity when treated within 10 hours of APAP ingestion compared to a 25.4% rate when treated between 10 to 24 hours and a 58% rate with conservative management⁹. A review looking at four key studies evaluating NAC showed no deaths in 733 patients when treatment was initiated with NAC within 10 hours of ingestion as compared to 1.3% mortality among 1513 patients when treatment was delayed to 10 to 24 hours and 7% mortality among 85 patients managed conservatively¹². Thus early administration of NAC in APAP overdose appears to reduce the toxicity from the drug. Therefore, it may be beneficial to administer APAP in combination with N-acetylcysteine routinely to reduce rates of hepatotoxicity. Toxic doses of APAP are highly variable but a conservative estimate of 150mg/kg of APAP ingestion in 24 hours may be enough to cause toxicity¹³. The Food and Drug Administration recommends a 140mg/kg loading

dose of oral N-acetylcysteine as part of a 72-hour oral course in the setting of APAP overdose⁹. Therefore, it may be reasonable to combine APAP and N-acetylcysteine in a one-to-one fashion. In the case of an overdose of the combination, a treatment dose of NAC would be ingested along with the toxic dose of APAP.

A randomized control study comparing the hepatotoxicity rates of the APAP-NAC combination versus APAP-placebo combination would require intentional overdoses of the study drugs to induce hepatotoxicity and would clearly be ethically unacceptable in human subjects. This study proposes to take a small but important step in the evaluation of the proposed APAP-NAC combination. For this combination drug to be acceptable for routine use, it must be shown that the combination does not diminish the therapeutic effect of APAP in any way. Because NAC's main role is to reduce the accumulation of NAPQI, which is normally an inconsequential metabolite⁵, the concomitant administration of NAC should have no impact on the efficacy of APAP as an anti-pyretic and analgesic. Thus, we propose a single-center, non-inferiority randomized control study comparing the efficacy of the APAP-NAC combination as compared to APAP-placebo as an anti-pyretic agent.

B. Study Design and Statistical Analysis

Subjects will be recruited from the Columbia-Presbyterian Medical Center adult inpatient units in the event of a fever defined as a tympanic membrane temperature of 38.5°C. The study will include patients aged 18 to 75. Subjects will be excluded if they have a prior adverse reaction to acetaminophen or N-acetylcysteine. Subjects will be consented and randomized to one of two arms: the APAP-NAC group and APAP-placebo group. Within 15 minutes of the recorded fever, the subjects will be blinded and receive APAP 500mg/placebo or APAP 500mg/NAC 500mg, depending on the arm of the study to which they are assigned. The subjects will have their temperature measured again 2 hours after administration of the study drugs by a blinded clinician.

We will perform an unpaired T-test comparing the mean reduction of temperatures in the two arms of the study. In order to show a 0.2°C difference between the two mean reductions with a power of 80% and an α of 0.05, we will enroll a total of 250 patients. We expect a 1.0°C drop in temperature in the APAP-placebo group with a non-significant difference of less than 20% (0.8°C) in the APAP-NAC group. This reduction in temperature is consistent with prior APAP efficacy studies¹⁴. The sample size was obtained using a conservative standard deviation of 0.5°C with an effect size of 0.2°C. We calculate that the study will require approximately 100 subjects in each group with an additional 50 patients for potential withdrawals.

C. Study Procedure

The subjects' initial temperatures upon randomization will be recorded via a tympanic temperature monitor. The study drug (APAP/placebo vs. APAP/NAC) will be administered in a blinded fashion within 15 minutes of the initial temperature recording. The subjects will have their temperature remeasured in 2 hours by a blinded clinician.

Other attempts at temperature reduction during the interim, including use of NSAIDS, ASA or cooling blankets, will not be discouraged but will be noted. Side effects including anaphylactic reaction, rash, nausea, vomiting, diarrhea, abdominal pain, unpleasant taste, hypotension, cough, dyspnea, dysphoria, and mortality occurring 24 hours after the administration of the study drugs will be obtained. Basic characteristics of the patients will be collected including age, race, gender, co-morbid conditions, presence of known liver dysfunction in the past, reason for admission, duration of admission, and reason for fever.

D. Study Drugs

Acetaminophen is an approved anti-pyretic drug, and rare side effects include rash, anemia, blood dyscrasias, renal failure, liver failure, and hypersensitivity reaction¹⁵. N-acetylcysteine is an approved antidote for acetaminophen toxicity and side effects include anaphylactoid reaction with IV formulation (17%), angioedema (2-8%), vasodilation (1-6%), hypotension (1-4%), tachycardia (1-4%), syncope (1-3%), chest tightness (1%), flushing (1%), dysphoria (<1-2%), urticaria (2-7%), rash (1-5%), facial erythema (<1%), palmar erythema (<1%), pruritis (<1-3%), puritus with rash and vasodilation (2-9%), vomiting (<1-10%), nausea (1-10%), dyspepsia (<1%), gait disturbance (<1-2%), eye pain (<1-3%), ear pain (1%), bronchospasm (1-6%), cough (1-4%), dyspnea (<1-3%), pharyngitis (1%), rhinorrhea (1%), throat tightness (1%), and diaphoresis (<1%)¹⁶.

E. Medical Device

None

F. Study Questionnaires

None

G. Study Subjects

Subjects population will be all patients between the age of 18 and 65 admitted to the Columbia Presbyterian Medical Center inpatient unit with fever. Patients will need to be able to consent to the study. Subjects will be excluded if they have a absolute contraindication for acetaminophen or N-acetylcysteine, such as fulminant liver failure or prior adverse reactions to the drugs. Subjects will also be excluded if tympanic membrane temperature cannot be obtained.

H. Recruitment of Subjects

Potential study subjects will be identified among the patients admitted in the Columbia Presbyterian Medical Center inpatient unit (CPMC), including medicine and surgery patients on general as well as ICU floors. When a patient is identified to have a fever (38.5°C), they will be approached by our medical team and informed consent for the study will be obtained.

I. Confidentiality of Study Data

All study subjects will be coded and data collected will be stored in a secure location, accessible only to the investigators

J. Potential Conflict of Interest

None

K. Location of the Study

Columbia Presbyterian Medical Center inpatient medicine and surgery units, general as well as ICU floors.

L Potential Risks

Subjects may experience more side effects in the study arm with the administration of N-acetylcysteine. Furthermore, the acetaminophen and N-acetylcysteine combination may be an inferior anti-pyretic regimen as compared to the acetaminophen alone.

M. Potential Benefits

None

N. Alternative Therapies

None

O. Compensation to Subjects

None

P. Costs to Subjects

None

Q. References

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