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Effervescent N-Acetylcysteine Tablets versus Oral Solution N-Acetylcysteine in Fasting Healthy Adults: An Open-Label, Randomized, Single-Dose, Crossover, Relative Bioavailability Study

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ABSTRACT

Background: Oral solution N-acetylcysteine (NAC) is an antidote for acetaminophen overdose, but its unpleasant taste and aroma can impede delivery even after the coadministration of antiemetic medications. Flavored effervescent NAC tablets dissolved in water might be a more palatable formulation than oral solution NAC diluted with soft drink.

Objectives: To evaluate the relative bioavailability of these 2 formulations and assess subjective preferences between them.

Methods: Thirty healthy adult volunteers (mean [SD] = 35.2 [9.14] years) were enrolled in this open-label, randomized, single-dose, crossover study, with a 7-day washout period. Volunteers were randomized to receive 11 g effervescent test formulation or the reference product under fasting conditions, after which 19 serial blood samples were collected over 48 hours. Total plasma NAC concentrations were evaluated by LC-MS, and pharmacokinetic parameters were calculated. The 2 formulations were considered bioequivalent if the 90% CIs of log-transformed ratios of pharmacokinetic parameters were within the predetermined bioequivalence range (80%–125%) established by the US Food and Drug Administration. Within 15 minutes of dosing, subjects were also asked to rank formulation attributes on a 5-point hedonic scale, with mean group differences analyzed by Wilcoxon signed rank test. Safety-profile assessment included treatment-emergent adverse events, physical examination, chemistry, and hematology parameters.

Results: The concentration-versus-time profiles were similar for the 2 formulations, with mean C_{max} of 26.5 μg/mL for effervescent NAC tablets and 28.4 μg/mL for oral solution NAC. The 90% CIs for the pharmacokinetic parameters met the criteria for concluding bioequivalence, and subjects preferred effervescent NAC tablets in terms of taste ($P = 0.0247$), flavor ($P = 0.0082$), texture ($P = 0.009$), and overall likeability ($P = 0.0012$), but there was no difference for smell ($P = 0.0533$). All treatment-emergent adverse events were mild, with no differences between the treatment groups.

Conclusions: Data from this study of a single dose of 11 g oral NAC demonstrated that effervescent NAC tablets and oral solution NAC met the regulatory criteria for bioequivalence in fasting healthy adult subjects. Effervescent NAC tablets appear to be a more palatable alternative for treatment of acetaminophen overdose. ClinicalTrials.gov identifier: NCT02723669. (*Curr Ther Res Clin Exp*. 2016; 83C:1–7) © 2016 Elsevier HS Journals, Inc.

Introduction

In the United States, acetaminophen is the medicine that is most commonly associated with overdose and the leading cause of overdose-related hepatotoxicity leading to acute liver failure.[1] Approximately half of overdose-related deaths are due to products containing acetaminophen in combination with other drugs.

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According to the 2015 report of the American Association of Poison Control Centers,[2] overuse of either acetaminophen alone or in combinations with other drugs accounted for the highest percentage of fatalities (16.9%) associated with single-substance exposures alone (10.70%) and in combinations (6.23%). In a 2011 epidemiology study,[3] acetaminophen-associated overdoses were responsible for an average of 78,414 annual emergency department visits and an average of 33,520 annual hospitalizations.

Oral solution N-acetylcysteine (NAC) was approved by the Food and Drug Administration (FDA) for treatment of acetaminophen overdose in 1978. Single large doses or repeated subtherapeutic doses of acetaminophen can deplete hepatic glutathione, which detoxifies N-acetyl-p-benzoquinone imine, a metabolite of acetaminophen that is extremely toxic to the liver. NAC prevents hepatic injury primarily by restoring hepatic glutathione.[1] The FDA-approved treatment protocol for use of oral NAC as an acetaminophen-overdose antidote requires a loading dose followed by 17 additional doses over 72 hours. Shortened courses of oral NAC ($\leq$48 hours), guided by laboratory parameters for patient-tailored discontinuation of treatment, have also been studied and are sometimes used.[4,5] Intravenous (IV) NAC was approved by the FDA for treatment of acetaminophen overdose in 2004. The FDA-approved treatment protocol for use of IV NAC requires a loading dose followed by 2 additional doses over 21 hours. Both oral solution NAC and IV NAC are highly effective in preventing hepatotoxicity from acetaminophen overdose, with comparable efficacy.[6,7] In the United States, institutional preference for either oral solution NAC or IV NAC for treatment of acetaminophen overdose depends on such factors as manpower and utilization costs associated with delivery of these different formulations.[7]

Because of its sulfur moiety, NAC has a putrid rotten-egg smell and taste, which can cause patients to experience nausea and vomiting and become intolerant of therapy. For patients receiving oral solution NAC, vomiting can be sufficient to impede medication delivery. Gastrointestinal adverse events occur not only with oral NAC solution, which is commonly diluted with diet caffeine-free soft drink to mask the smell and taste, but with IV NAC as well. These symptoms are often treated with antiemetic agents. In a retrospective, 503-patient multicenter comparison of the safety of oral versus IV NAC for treatment of acetaminophen overdose, the rate of nausea and vomiting was higher with oral NAC than with IV NAC (23% vs 9%), but the same percentage of patients in each group required antiemetic medication (25.5% vs 26.5%).[8]

Flavored effervescent tablets are a novel formulation of NAC intended for oral treatment of acetaminophen overdose. When effervescent NAC tablets are dissolved in water, the flavored taste and smell of the solution might be preferred to the combination of oral solution NAC diluted with diet caffeine-free soft drink. Our purpose was to compare the pharmacokinetic (PK) parameters and relative bioavailability of effervescent NAC tablets and oral solution NAC given as a single 11-g dose under fasting conditions to healthy adult subjects. This study was conducted in accordance with FDA regulatory criteria for assuming bioequivalence of orally administered drugs.[9] A secondary objective of this study was to assess subject preferences for attributes of effervescent NAC tablets compared with those of oral solution NAC.

Materials and Methods

Study design and subjects

To evaluate the relative bioavailability of effervescent NAC tablets versus oral solution NAC, we performed an open-label crossover study in 30 male and female subjects with a body mass index $<$ 30 and who were between the ages of 18 and 50 years. Conducted at a single research center, which recruited and paid volunteers to participate, the study consisted of a screening period, 2 crossover dosing periods (Period 1 and Period 2), with the actual dosing separated by a 7-day washout period, and a follow-up telephone call (Figure 1). Because of the obvious differences between the effervescent formulation and the standard solution, subjects and investigators were aware of treatment assignment.

The study was approved by the local institutional review board and was conducted in accordance with the principles in the World Medical Association Declaration of Helsinki. The ClinicalTrials.gov registration number for this trial was NCT02723669.

After providing informed consent, subjects underwent baseline testing, which included medical history, clinical examination, laboratory tests, and 12-lead ECG within the 30 days before starting the study. Inclusion required being a nonsmoker and a negative ß-human chorionic gonadotropin test in reproduction-capable women. Subjects were not allowed prescription or over-the-counter drugs (including vitamins and natural supplements) throughout the study duration.

On study Day 0, a basic metabolic profile with liver-function tests, complete blood count, and urinalysis were administered. Subjects were then provided a standard meal and fasted overnight for at least 10 hours. Subjects then underwent randomization using a balanced block randomization schedule, generated before the start of dosing, to ensure alternating NAC formulations for the crossover investigation.

Subjects received the first assigned formulation on Day 1 (Period 1), with samples for PK analysis collected predose and at scheduled postdose time points through 48 hours. Subjects completed a formulation-attribute survey within 15 minutes after completing dosing activities. Period 1 ended when subjects were discharged on Day 3. They then were readmitted on Day 7 for the beginning of Period 2. The crossover washout was 7 days—from the administration of the first dose on Day 1 to the administration of the assigned crossover NAC formulation on Day 8, again under

<table>
<tr><th>SCREENING</th><th>ADMISSION</th><th colspan="3">PERIOD 1</th><th>WASHOUT</th><th colspan="4">PERIOD 2</th><th>FOLLOW-UP</th></tr>
<tr><td>Days –30 to –1</td><td>Day 0</td><td>Day 1</td><td>Day 2</td><td>Day 3</td><td>Days 2 to 8</td><td>Day 7</td><td>Day 8</td><td>Day 9</td><td>Day 10</td><td>Day 12</td></tr>
<tr><td>Randomization</td><td>Check-in
Physical exam
Chemistry
CBC
Lab test</td><td>First formulation administered
Product-attribute survey</td><td></td><td>Discharge</td><td>Period between dosing</td><td>Second admission</td><td>Alternative formulation administered
Product-attribute survey</td><td></td><td>Discharge</td><td>Phone contact</td></tr>
<tr><td></td><td></td><td colspan="3">PK sampling through 48 hours</td><td></td><td></td><td colspan="3">PK sampling through 48 hours</td><td></td></tr>
</table>

Figure 1. Study design of the open-label, randomized-sequence, single-dose, crossover, relative bioavailability and attribute-preference study of effervescent N-acetylcysteine (NAC) tablets and oral solution NAC in fasting healthy adult subjects.