Acetaminophen-induced anaphylaxis: a case report

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ABSTRACT

Acetaminophen is known to be generally safe, and the occurrence of anaphylaxis due to acetaminophen has been rarely reported. We report a case of acetaminophen-induced anaphylaxis in a healthy male subject who participated in a clinical trial on the pharmacokinetics of ibandronate. The subject had not experienced an allergic reaction to acetaminophen prior to this incident. The patient received 1300 mg oral acetaminophen at about 12 hours after receiving 150 mg ibandronate. After about 10 minutes, the subject developed whole-body urticaria and hypotension. The temporal association suggested that the anaphylaxis was due to acetaminophen and not ibandronate. Anaphylaxis could occur due to acetaminophen even in the absence of allergic reactions in the first dosing.

Keywords: Acetaminophen; Anaphylaxis; Drug Hypersensitivity

INTRODUCTION

Acetaminophen has long been widely used as a primary treatment for mild-to-moderate pain, as an adjunctive analgesic to opioids in moderate-to-severe pain management, and as an antipyresis. For adolescents and adults over 50 kg, oral acetaminophen can be administered up to 4,000 mg/day, 1,000 mg every 6 hours, or 650 mg every 4 hours [1]. Acetaminophen is considered to be quite safe, and cases of acetaminophen-induced anaphylaxis have been rarely reported [2-5].

With the recent development and active administration of vaccines against coronavirus disease 2019 around the world, the Center for Disease Control and Prevention advised that acetaminophen could be taken for fever caused by the vaccination [6]. Therefore, the use of acetaminophen is expected to sharpen and significantly increase. Accordingly, more attention should be paid to the potential risk of rare but serious adverse events of acetaminophen.

In this report, we present a case of anaphylaxis that appeared after taking acetaminophen as a pretreatment in a participant of a phase 1 clinical trial [7]. This clinical trial consisted of two periods, and ibandronate was once orally administered for each period. Fever and myalgia appeared in all 24 subjects after ibandronate administration in the first admission group. So, from the second admission group, acetaminophen was administered prophylactically to all subjects. This anaphylaxis case occurred in the second admission group.
CASE REPORT

A 22-year-old healthy male participated in a clinical trial comparing the pharmacokinetic characteristics of ibandronate (product name: BONVIVA Tab. 150 mg) when administered alone or with vitamin D3.

On the first day of dosing, the subject received one oral dose of ibandronate 150 mg tablet at 08:22. Tylenol ER (acetaminophen) 1,300 mg was orally administered once at 22:11 on the same day to prevent adverse events associated with ibandronate. Urticaria appeared on the face and body at 22:21, and a pheniramine tablet was orally administered. When the subject stood up at 22:40, his face became pale and a hypotensive shock occurred. The subject had no loss of consciousness but complained of nausea. He was immediately transferred to the emergency room and the vital sign (V/S) at 23:25 was 72/49 mmHg, 42 beats/min (systolic blood pressure [SBP]/diastolic blood pressure [DBP], heart rate [HR]). The subject was monitored with a 12-lead electrocardiogram and arterial blood gas analysis (ABGA). Macperan (metoclopramide) 10 mg was intravenously infused to manage nausea. After an 18-Gauge intravenous (IV) line was secured, a normal saline full drip was performed, and oxygen was supplied. As acetaminophen anaphylaxis was suspected, Methysol (methylprednisolone) 125 mg IV infusion was carried out. There was no loss of consciousness during the treatment, and there were no abnormalities in ABGA and serum electrolytes. Serum Na+/K+/Cl- were 140/4.1/102 mmol/L at pre-dose and 136/4.0/104 mmol/L at the emergency room. Ionized calcium was low at 1.10 mg/dL at the emergency room (normal range, 3.9–4.5). The results of ABGA at the emergency room were as follows: pH 7.420, pCO2 41.0 mmHg, pO2 127.0 mmHg, base excess 1.9 mmEq/L, bicarbonate 26.6 mmEq/L, and O2 saturation 99.0% under 2 L/min of oxygen via nasal prong.

On the next day at 06:30, the symptoms were improved and the V/S was 101/58 mmHg, 50 beats/min (SBP/DBP, HR). As the subject could walk without any help, oxygen inhalation was stopped and he was transferred from the emergency room to the clinical trial center. After close observation until 16:00, the disappearance of symptoms was confirmed and the subject was discharged. After the disappearance of symptoms, the serum Na+/K+/Cl- levels were 140/4.3/108 mmol/L.

One week later, the subject was diagnosed with an allergic reaction to Tylenol at the Department of Allergy and Clinical Immunology. Thereafter, the subject dropped out and completed without adverse events.

DISCUSSION

Hypotensive shock or anaphylaxis caused by acetaminophen is rare, but several reports have described cases of acetaminophen-induced anaphylaxis [2-5]. Considering the temporal relationship between drug administration and the adverse event, the subject’s anaphylaxis is likely due to acetaminophen and not ibandronate, as symptoms appeared at 12 hours after ibandronate administration and 10 minutes after acetaminophen administration. There are reports on the occurrence of hypersensitivity resulting from BONVIVA Tab. in the post-marketing setting. However, since these allergic reactions have been voluntarily reported in an unspecified population, it is difficult to determine their exact frequency or causal relationship with drug exposure [8]. Moreover, there is no available literature on ibandronate-induced anaphylaxis.
Acetaminophen exhibits analgesic and antipyretic effects, and works by inhibiting the cyclooxygenase pathway of the central nervous system [9,10]. The mechanism of acetaminophen-induced anaphylaxis is not yet clear, but it is thought that specific IgE or leukotriene may be involved [11]. In fact, only 18.8% of patients with acetaminophen hypersensitivity had a positive skin prick test [2,11]. Our present case was not allergic to nonsteroidal anti-inflammatory drugs and had no allergic reactions after a single oral dose of acetaminophen prior to this incident. The acetaminophen administered in this study became a type of drug rechallenge test. The mechanism of acetaminophen-induced anaphylaxis should be further examined in a targeted study.

Our present case showed decreased ionized calcium, which seems to have been caused by ibandronate considering that ibandronate lowers blood calcium levels [12,13]. The acetaminophen-induced anaphylaxis and decreased blood calcium levels in this subject were considered to be irrelevant. Decreases in the blood calcium levels are among the known adverse events of acetaminophen [14]; however, hypocalcemia does not directly lead to anaphylaxis and mild hypocalcemia is usually asymptomatic. Moderate-to-severe hypocalcemia is usually manifested by neuromuscular irritability, including paresthesia of peripheral extremities, muscle cramps, tetany, and seizures [15]. Therefore, it is difficult to conclude that anaphylaxis occurred due to the low ionized calcium level.

Even drugs that are already known to be safe may require close observation when administered to subjects in clinical trials.

REFERENCES

1. FDA. Acetaminophen label [Internet]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204767s000lbl.pdf. Updated 2015. Accessed May 6, 2021.
2. Bachmeyer C, Vermeulen C, Habki R, Blay F, Leynadier F. Acetaminophen (paracetamol)-induced anaphylactic shock. South Med J 2002;95:759-760. PUBMED | CROSSREF
3. Brown G. Acetaminophen-induced hypotension. Heart Lung 1996;25:137-140. PUBMED | CROSSREF
4. Rojas Perez-Esquerra P, Sánchez-Morillas L. Seven cases of anaphylaxis to paracetamol. Cureus 2013;5:e101.
5. Vidal C, Pérez-Carral C, González-Quintela A. Paracetamol (acetaminophen) hypersensitivity. Ann Allergy Asthma Immunol 1997;79:320-321. PUBMED | CROSSREF
6. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States [Internet]. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed May 6, 2021.
7. Choi HY, Kim MJ, Kim YH, Lee J, Lee T, et al. Pharmacokinetic characteristics of ibandronate and tolerability of DP-R206 (150 mg Ibandronate/24,000 IU Vitamin D3) compared to the ibandronate (150 mg) monotherapy in healthy adults. Transl Clin Pharmacol 2014;22:22-29. CROSSREF
8. FDA. BONVIVA Label [Internet]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021455s019lbl.pdf. Accessed May 6, 2021.
9. Bottig R.M. Mechanism of action of acetaminophen: is there a cyclooxygenase 3? Clin Infect Dis 2000;31 Suppl 5:S202-S210. PUBMED | CROSSREF
10. Anderson BJ. Paracetamol (acetaminophen): mechanisms of action. Paediatr Anaesth 2008;18:915-921. PUBMED | CROSSREF
11. Rutkowski K, Nasser SM, Ewan PW. Paracetamol hypersensitivity: clinical features, mechanism and role of specific IgE. Int Arch Allergy Immunol 2012;159:60-64. [PUBMED] [CROSSREF]

12. Pecherstorfer M, Ludwig H, Schlosser K, Buck S, Huss HJ, Body JJ. Administration of the bisphosphonate ibandronate (BM 21.0955) by intravenous bolus injection. J Bone Miner Res 1996;11:587-593. [PUBMED] [CROSSREF]

13. Pecherstorfer M, Herrmann Z, Body JJ, Manegold C, Degardin M, Clemens MR, et al. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. J Clin Oncol 1996;14:268-276. [PUBMED] [CROSSREF]

14. Gerriets V, Anderson J, Nappe TM. Acetaminophen. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK482369/.

15. Schafer AL, Shoback DM. Hypocalcemia: diagnosis and treatment. South Dartmouth (MA): MDText.com, Inc.; 2000.