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CASE REPORT

# Serious adverse events during clinical trial for pharmacokinetic interaction between telmisartan and chlorthalidone in healthy Korean subjects: A case report

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Telmisartan is an angiotensin II receptor antagonist and chlorthalidone is a thiazide-like diuretics. In this study, we report serious adverse events (SAEs) during clinical trial for pharmacokinetic interaction between telmisartan and chlorthalidone in healthy Korean subjects. Two separate, randomized, multiple-dose, two-period, one-sequence studies were conducted at Kyungpook National University Hospital. In part A, 43 volunteers received telmisartan for 7 days, and then chlorthalidone for 14 days (days 8-21). Telmisartan was co-administered during day 15-21 to evaluate the effects of chlorthalidone on the pharmacokinetics of telmisartan at steady state. A healthy 36-year-old male in part A was referred to the emergency room due to severe nausea and vomiting developed about 3 h after administration of chlorthalidone on day 9. Hypokalemia and QT prolongation were observed during his initial laboratory examination and electrocardiogram (ECG) monitoring in the emergency unit. Nausea and vomiting improved after conservative management with hospitalization for 9 days. We consider that the episodes of excessive nausea and vomiting resulted in hypokalemic state which was potentiated by chlorthalidone. And the hypokalemic state caused the lengthening of the QT interval on ECG.

Telmisartan is an angiotensin II receptor-subtype 1 (AT1) antagonist and chlorthalidone is a thiazide-like diuretics.[1,2] Several controlled clinical trials have demonstrated that combination of telmisartan with a low-dose thiazide showed superior effect on lowering BP than either telmisartan or thiazide alone.[1] In this study, clinical trial was performed to ascertain whether the co-administration of telmisartan and chlorthalidone would influence on the pharmacokinetic properties of either drug in healthy Korean male subjects.

Two separate, randomized, multiple-dose, two-period, one-sequence studies were conducted. In part A, we evaluated the effects of chlorthalidone on the pharmacokinetics of telmisartan at steady state. A total of 43 volunteers received 80 mg of telmisartan orally for 7 days, and then chlorthalidone 25 mg orally for 14 days (days 8-21). The 80 mg of telmisartan was co-administered during days 15-21. In part B, we investigated the effects of telmisartan on the pharmacokinetics of chlorthalidone at steady state. A total of 14 volunteers received oral chlorthalidone 25 mg for 13 days, followed by co-administration with 80 mg of telmisartan for 7 days. In this study, Micardis® (telmisartan 80 mg) and Hygroton® tablets (chlorthalidone 25 mg) were used as investigational products, provided by the sponsor, HanAll BioPharma Co., Ltd. (Seoul, Republic of Korea). All volunteers who received drugs were monitored for safety. Vital signs (blood pressure, pulse rate and body temperature), physical examinations, 12-lead ECG, hematology, biochemistry, urinalysis, and self-reporting of participants were included in the safety assessment. All tests were undertaken at baseline and planned times according to the protocol.

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) standards, and all related laws. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (Daegu, Republic of Korea) before the study began. All volunteers received a full explanation regarding the study and submitted a written informed consent before screening tests for eligibility in the study.

In total, seven subjects (part A: 6, part B: 1) were withdrawn due to SAEs (n=1) or withdrew voluntarily (n=6) from the study. Generally, the treatments were well-tolerated in all subjects, except for the one subject assigned to the part A, who was withdrawn due to the severe nausea and vomiting occurred during the second treatment period.

A 36-year-old male subject without any specific past medical history reported that severe nausea and vomiting had developed about 3 h after administration of chlorthalidone on day 9. The subject was referred to the emergency room of Kyungpook National University Hospital due to aggravation of nausea and vomiting on day 10 and was immediately dropped from the trial. Hypokalemia (arterial blood level of 3.2 mmol/L) and QT prolongation (corrected QT interval of 503 ms) were observed during his initial laboratory examination and ECG monitoring in the emergency unit (Table 1). Such SAEs were reported to Korean Food and Drug Administration and IRB.

His initial arterial blood gas and electrolyte study results were: pH 7.404, $PaCO_2$ 38.5 mmHg, $PaO_2$ 57.3 mmHg, $HCO_3$ 24.3 mmol/L, sodium 137 mmol/L, potassium 3.2 mmol/L (arterial blood normal range: 3.8–5.0 mmol/L) and chloride 105.4 mmol/L. Serum creatinine and blood urea nitrogen were 0.96 mg/dL and 18.5 mg/dL respectively. Although his initial vital signs were within normal range, he experienced orthostatic syncope on the 1$^{st}$ day of admission.

He did not complain any other gastrointestinal symptoms such as abdominal pain or diarrhea related with gastroenteritis. CNS diseases such as Meniere's disease were ruled out because the patient did not complain CNS symptoms including vertigo and tinnitus.

To evaluate the possibility of cardiovascular disease, 2D echocardiography was conducted, but no significant abnormal finding was detected. No abnormality in his vital signs was identified, including systolic and diastolic blood pressure and body temperature and oxygen saturation, with the exception of the unstable heart rate. Intermittent QT prolongation findings returned to normal range after 48 h from admission to the emergency room after conservative treatment in the emergency intensive care unit. Bile reflux gastritis and reflux esophagitis were identified by esophago-gastro-duodenoscopy which was undertaken to investigate abnormal gastrointestinal problems. Initially, severe nausea was not ameliorated despite several medications including metoclopramide and ondansetron. Symptoms were improved only after conservative management underhospitalization for 9 days. The SAEs resolved without any sequelae after discharge from the hospital. At a follow-up visit, both ECG and gastric emptying time scan results were not remarkable.

With the ever-increasing number of pharmaceutical products, the incidence of gastrointestinal adverse events such as nausea, vomiting, abdominal pain, diarrhea, and constipation have also increased.[3] Generally, they are mild in intensity and self-limiting without serious complications.[3] The major role of vomiting is to eliminate toxic substances to the outside of the body and while it is considered a defense mechanism, much is still unknown.[4,5] The mechanism of action of emesis involves gastrointestinal receptors and/or central mechanisms mediated by chemoreceptors in the area postrema.[4,5] At present, there is no evidence for clinical or biochemical signs of gastrointestinal or other organ injury due to drug-induced nausea. Thus, it is known that drug-induced nausea and vomiting may be mediated mainly by central pathways.[5]

Nausea and vomiting triggered by xenobiotics are mediated by their direct circulation or via the secretion of diverse neurotransmitters. The key neurotransmitters involved in the pathophysiology of nausea and vomiting are dopamine, histamine, acetylcholine, and GABA.[5] Neurokinin-1 (NK1) and 5-hydroxytryptamine 3 (5-HT3) receptors are also involved in the emesis response.[6] Especially, several studies have suggested a role of substance P and its receptor, the NK1 receptor, in the emesis pathway.[6] In this study, 5-HT3 antagonists and dopaminergic D2 receptor blocker were administered to control the profound nausea; however, these agents did not ameliorate the symptom. In this case, a pathway involving NK1 receptor blocker, that was not used in this case, is considered to be possible mechanism; further research is necessary to assess this. To our knowledge, there is no previous report of an association between angiotensin receptor blockers or diuretics and severe emesis. As there has been few researches on drug-induced nausea

**Table 1.** Changes in the levels of corrected QT interval and potassium level of SAE case

| Period | Screening period | ER admission | | | Follow up period |
|---|---|---|---|---|---|
| Day | | Day 1 | Day 2 | Day 3 | |
| Corrected QT interval (ms) | 454 | 503 | 522 | 465 | 425 |
| Potassium (mmol/L) | 4.3 (serum) | 3.2 (arterial blood) | 3.1 (serum) | 3.4 (serum) | 4.3 (serum) |

other than in cancer chemotherapy, identification of the precise mechanism of severe nausea like in this case was not possible.

An acquired long QT interval results chiefly from drug therapy or electrolyte imbalance, especially hypokalemia induced by thiazide diuretics.[7-9] Biochemical adverse effects, such has hypokalemia in connection with thiazide diuretics, tend to be more frequent with long-acting drugs such as chlorthalidone, especially when high doses are administered.[10] Hypokalemic conditions can also be induced by severe emesis that can result in substantial loss of bodily fluid and gastric juice. Loss of gastric acid causes metabolic alkalosis with elevated plasma bicarbonate concentrations. Hypovolemia caused by emesis results in aldosterone secretion. These effects then aggravate urinary potassium loss and then in the hypokalemic state that may provoke the lengthening of the QT interval.[7,11]

Exposure to specific medications may also lead to marked QT interval prolongation, which is termed drug-induced long QT syndrome.[9] Abnormal electrolytes influence the QT interval indirectly, but some drugs prolong it directly.[7] The most common are anti-dysrhythmics, such as amiodarone, sotalol, dofetilide, and quinidine.[12,13] Also, QT prolongation has also been reported after the use of some antihistamines, antibiotics, and antipsychotics.[13,14] However, to our knowledge, it has not been reported previously that angiotensin receptor blockers and diuretics lead to prolonged QT intervals directly.

Another possible explanation may be associated with pharmacogenetic factors. Individuals who have a mutation or polymorphism in causal genes of long QT syndrome have a subclinical condition until they are exposed to a particular agent or environment.[7,9,13] To date, 13 genes responsible for congenital long QT syndrome have been identified.[9]. Of these, mutations in KCNQ1 (LQT1) and KCNH2 (LQT2, HERG) are the most frequent.[9,13] In particular, inhibition of the HERG channel is involved in the mechanism of increased cardiac action potential length and thus the lengthening of the QT interval.[13]

We consider that the episodes of excessive nausea and vomiting resulted in hypokalemic state which was potentiated by the administration of chlorthalidone. And the hypokalemic state caused the lengthening of the QT interval on ECG. Additional research including a pharmacogenomic analysis is needed to identify the mechanism underlying the findings of this study.

## References

1. Maillard MP, Burnier M. Is the fixed-dose combination of telmisartan and hydrochlorothiazide a good approach to treat hypertension? Vasc Health Risk Manag 2007;3:265-278.
2. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 2003;43:4-9.
3. Leong RW, Chan FK. Drug-induced side effects affecting the gastrointestinal tract. Expert Opin Drug Saf 2006;5:585-592.
4. Naylor RJ, Inall FC. The physiology and pharmacology of postoperative nausea and vomiting. Anesthesia 1994;49 Supple:2-5.
5. Kretzing S, Abraham G, Seiwert B, Ungemach FR, Krügel U, Teichert J, et al. In vivo assessment of antiemetic drugs and mechanism of lycorine-induced nausea and emesis. Arch Toxicol 2011;85:1565-1573. doi: 10.1007/s00204-011-0719-9.
6. Yamada T, Tanaka N, Yokoi K, Ishikawa N, Seya T, Horiba K, et al. Substance P and anticancer drug-induced emesis. Gan To Kagaku Ryoho 2007;34:903-906.
7. Digby G, MacHaalany J, Malik P, Methot M, Simpson CS, Redfearn D, et al. Multifactorial QT interval prolongation. Cardiol J 2010;17:184-188.
8. Marinella MA, Burdette SD. Visual diagnosis in emergency medicine. Hypokalemia-induced QT interval prolongation. J Emerg Med 2000;19:375-376.
9. Kannankeril PJ, Norris KJ, Carter S, Roden DM. Factors affecting the degree of QT prolongation with drug challenge in a large cohort of normal volunteers. Heart Rhythm 2011;8:1530-1534. doi: 10.1016/j.hrthm.2011.03.042.
10. Sica DA, Carter B, Cushman W. Thiazide and loop diuretics. J Clin Hypertens 2011;13:639-643. doi: 10.1111/j.1751-7176.2011.00512.x.
11. Cheungpasitporn W, Suksaranjit P, Chanprasert S. Pathophysiology of vomiting-induced hypokalemia and diagnostic approach. Am J Emerg Med 2012;30:384. doi: 10.1016/j.ajem.2011.10.005.
12. Taira CA, Opezzo JAW, Mayer MA, Höcht C. Cardiovascular drugs inducing QT prolongations: facts and evidence. Curr Drug Saf 2010;5:65-72
13. Ayad RF, Assar MD, Simpson L, Garner JB, Schussler JM. Causes and management of drug-induced long QT syndrome. Proc (Bayl Univ Med Cent) 2010;23:250-255.
14. Johnson JA, Cavallari LH, Beitelshees AL, Lewis JP, Shuldiner AR, Roden DM. Pharmacogenomics: application to the management of cardiovascular disease. Clin Pharmacol Ther 2011;90:519-531. doi: 10.1038/clpt.2011.179.