Case Report

Propafenone-associated Gross Hematuria: A Case Report and Review of the Literature

Shuqing Chen, MS[1]; Wenhui Ding, MD[2]; Jing Ye, MS[2]; Zining Wang, PhD[1]; Xia Zhao, MS[1]; and Yimin Cui, MD, PhD[1]

[1]*Department of Pharmacy, Base for Clinical Trial, Peking University First Hospital, Beijing, China; and* [2]*Department of Cardiology, Peking University First Hospital, Beijing, China*

ABSTRACT

Purpose: Propafenone hydrochloride has been widely used for the treatment of supraventricular and ventricular arrhythmias. We present a case report of an 81-year-old patient with propafenone-associated gross hematuria.

Methods: The Naranjo Adverse Drug Reaction Probability Scale was used to assess causality. We also performed a literature search to find publications that report propafenone-associated gross hematuria.

Findings: The Naranjo scale generated a score of 6, suggesting a probable association between gross hematuria and propafenone therapy. Thirteen publications that reported an association between gross hematuria and propafenone administration were found.

Implications: A probable association exists between gross hematuria and propafenone. (*Clin Ther.* 2019;41:1614–1620) © 2019 Elsevier Inc. All rights reserved.

Key words: antiarrhythmic medication, gross hematuria, paroxysmal atrial fibrillation, propafenone.

INTRODUCTION

Propafenone hydrochloride is a Vaughan Williams class 1c antiarrhythmic medication that also exhibits β-adrenergic and fast sodium channel blockade.[1,2] Propafenone hydrochloride has been widely used for the treatment of supraventricular and ventricular arrhythmias since the 1980s, when it was approved in Europe and the United States.

Propafenone can be nearly completely absorbed after oral administration and exhibits extensive saturable presystemic biotransformation (first-pass effect). It can be metabolized through 2 different patterns based on genetics. For >90% of patients, propafenone can rapidly and extensively metabolize into 2 active metabolites: 5-hydroxypropafenone (formed by CYP2D6) and *N*-dipropylpropafenone (formed by both CYP3A4 and CYP1A2). The other 10% of patients, also called slow metabolizers, have a decreased ability to form 5-hydroxypropafenone, resulting in delayed metabolism and a change in half-time from 2 to 10 h to 10–32 h.[3] Therefore, patients with reduced CYP2D6 activity (CYP2D6*10) can have a significantly higher plasma concentration of propafenone.

There are some commonly (>5%) reported adverse reactions during clinical trials and the propafenone hydrochloride postmarketing period, such as unusual taste, nausea and/or vomiting, dizziness, constipation, headache, fatigue, first-degree atrioventricular block, and intraventricular conduction delay.[3–5] However, there are also some new and rare adverse reactions observed, such as sinoatrial block, cardiotoxicity, temporary amnesia, and acute neutropenia.[6–9] In this article, we report a case of suspected propafenone-associated gross hematuria, along with a thorough review of the literature. Literature searches of relevant English-language articles were conducted through PubMed and Embase, whereas searches for relevant Chinese-language articles were conducted through the China National Knowledge Infrastructure (Wanfang Data Co Ltd, Beijing, China), both searches spanning 30 years (1988–2018). Written informed consent for scientific publication of personal medical data was obtained from the patient whose case is presented in this report.

Accepted for publication May 6, 2019
https://doi.org/10.1016/j.clinthera.2019.05.002
0149-2918/$ - see front matter

Case Description

An 81-year-old Han man presented to the clinic on June 6, 2018, with gross hematuria. He had an extensive medical history, including paroxysmal atrial fibrillation (AFib) with long intervals, hypertension, cerebral infarction, dyslipidemia, osteoporosis, and benign prostate hyperplasia. He was 1.80 m tall and weighed 60 kg. He denied any history of smoking or drinking. Urine examination revealed the following: positive urinary protein test result; highly positive urinary occult blood test result; white blood cell count, 54.4/μL; and red blood cell count, 15,059.9/μL (microscopy full visual field). Blood testing revealed the following: serum creatinine, 126 μmol/L; glucose, 6.30 μmol/L; potassium, 4.03 μmol/L; and brain natriuretic peptide, 172 pg/mL.

The patient's home medication until this visit included propafenone 150 mg 3 times daily, dabigatran 110 mg twice daily, atorvastatin 20 mg/d, calcium gluconate 1 tablet (500 mg calcium) twice daily, calcitriol 0.25 μg/d, bisoprolol 5 mg/d, spironolactone 20 mg/d, and furosemide 20 mg as needed. All these medications were used regularly for at least 1 year, except for propafenone, which was added 1 week before this visit. ECG examination revealed that episodes of AFib had stopped and normal sinus rhythm was returning. The physician suggested taking propafenone for another week and withdrawing it if the AFib did not recur. The symptom of gross hematuria continued during the 1 week of taking propafenone and stopped after propafenone was withdrawn; no other treatment was conducted.

This was not the first time that the patient had had gross hematuria after taking propafenone. A previous episode occurred once in November 2017, when he was newly diagnosed with paroxysmal AFib. The physician adjusted the previous prescription by stopping bisoprolol hemifumarate and nicorandil treatment while adding propafenone 150 mg 3 times daily and trimetazidine hydrochloride for home medication.

One week after his prescription was changed, the patient found that his urine color had changed discontinuously. He then went to the nephrology department for evaluation. Routine urine examination revealed the following: positive urinary protein test result; highly positive urinary occult blood test result; white blood cell count, 17.8/μL; and red blood cell count, 5184.5/μL (microscopy full visual field). Blood testing revealed the following: red blood cell count, 3.86×10^9/L; hemoglobin, 126 g/L; and platelet count, 108×10^9/L. Type B ultrasonic examination of both kidneys, ureter, and bladder revealed no significant pathologic changes. The urologist suggested that this symptom was probably induced by medication. However, propafenone was primarily ruled out as the cause of gross hematuria because there is no such adverse reaction listed in propafenone's pharmaceutical profile. Because the AFib did not recur for 2 weeks, propafenone was withdrawn by the physician. The gross hematuria symptoms stopped shortly after. The patient did not go back to the clinic until he suspected that the gross hematuria might be caused by propafenone.

Literature Review

Because gross hematuria has not been listed as a determinate adverse drug reaction (ADR) in propafenone's pharmaceutical profile, we performed a literature review to find out whether other patients had experienced the same symptom. Literature searches of relevant English-language articles were conducted through PubMed and Embase, whereas searches for relevant Chinese-language articles were conducted through China National Knowledge Infrastructure (Wanfang Data Co Ltd), both searches spanning 30 years (1988–2018). Finally, 13 articles (with a total of 20 cases) reporting propafenone-associated hematuria were found.[10–22] The characteristics of these cases are listed in Table I. These 20 cases had many similarities.

First, all articles reported that ADRs occurred in Chinese patients; no similar ADRs were reported in patients of other ethnicities. Moreover, ADR symptoms had several similarities. The most common symptom was gross hematuria, along with nausea, sweat, headache, or dysphoria. Nearly all patients had positive urinary occult blood test results and urinary protein test results. Finally, gross hematuria happened shortly after administration of propafenone and stopped soon after drug withdrawal.

In most cases, patients did not take anticoagulant drugs and antiplatelet drugs simultaneously. However, in the case presented by Wang et al,[15] the patient was taking aspirin 75 mg once daily for 15

Table I. Description of 13 reports for propafenone-induced hematuria.

Report	Age, y	Sex	Injection Dosage, mg	ADR Symptoms	U-OB	U-P	Time to ADR Onset	Intervention	Time to Recover
Zeng et al,[10] 1991	62	M	350*	Nausea, sweat, cardiopalmus increased bilirubin, gross hematuria	+++	NA	3 h	Drug withdraw	5 d
	62	F	210	Gross hematuria, nausea, headache	++	++	3.5 h	Drug withdrawal, cardiac glycosides, diuretics	5 h
Li et al,[11] 1994	60	M	210	Gross hematuria	+++	+	2 h	Drug withdrawal, promethazine hydrochloride, fluid infusion	3 d
Yang et al,[12] 1994	34	M	140†	Gross hematuria	+++	++	30 min	Drug withdrawal/fluid infusion	3 h
Liang et al,[13] 2000	66	M	140	Gross hematuria	++	++	1 h	Drug withdrawal, fluid infusion, urine alkalization, dexamethasone	2 d
Yan et al,[14] 2000	56	M	210	Gross hematuria	+++	+++	30 min	Drug withdrawal	1 d
Wang et al,[15] 2001	66	M	150*	Gross hematuria	+++	+++	4 h	Drug withdrawal	1 d
Yang et al,[16] 2003	59	M	210†	Dysphoria, sweat, gross hematuria	+++	+	2 h	Drug withdrawal, promethazine hydrochloride	2 da
Xu et al,[17] 2003	45	M	210*,†	Gross hematuria	+++	NA	12 h	Drug withdrawal	1 d
Liu et al,[18] 2006	76	M	105	Gross hematuria	++	+	1 h	Drug withdrawal, fluid infusion	12 h
Chen et al,[19] 2006	47	F	140	Gross hematuria	+++	NA	50 min	Drug withdrawal	2 d
	57	M	105	Gross hematuria	+++	NA	1 h	Drug withdrawal	1 d
	70	M	315	Gross hematuria	+++	NA	12 h	Drug withdrawal	2 d
	85	F	280	Gross hematuria	+++	NA	2.5 h	Drug withdrawal	2 d
Qu et al,[20] 2008	16	M	215	Dysphoria, sweat, gross hematuria	+++	++	1 h	Drug withdrawal, fluid infusion	3 d
	45	F	35	Gross hematuria	+++	NA	2 h	Drug withdrawal	NA
Yang et al,[21] 2011	27	F	70	Gross hematuria	NA	NA	40 min	Drug withdrawal	2 d
	70	M	210	Gross hematuria	NA	NA	60 min		2 d

Table I. (*Continued*)

Report	Age, y	Sex	Injection Dosage, mg	ADR Symptoms	U-OB	U-P	Time to ADR Onset	Intervention	Time to Recover
								Drug withdrawal, fluid infusion	
Tang et al,[22] 2012	34	F	105	Gross hematuria	+++	++	40 min	Drug withdrawal	1 d
	49	M	140	Gross hematuria	+++	+	1 h	Drug withdrawal	1 d

ADR = adverse drug reaction; NA = not available.
* ADR symptoms recur after propafenone readministration.
† Oral administration of 150 mg BID.

days until the ADR onset. For another case presented by Liu et al,[18] the patient has been subcutaneously injecting low-molecular-weight heparin 5000 IU q12h for a few days before using propafenone, and it was withdrawn right after the hematuria started. Both presenters ruled out the possibility that hematuria was caused by antithrombotic drugs based on the lack of temporal correlation, but they did not discuss the potential influence of drug—drug interaction.

DISCUSSION

We report the case of an 81-year-old man who presented with gross hematuria. Apart from his regular medications, propafenone was added 1 week before this visit. Because normal sinus rhythm was returning to normal, the physician suggested taking propafenone for another week and withdrawing it if the AFib did not recur. The symptom of gross hematuria continued during the 1 week of taking propafenone and stopped after propafenone was withdrawn.

Hematuria is the presence of red blood cells in the urine. If there are enough red blood cells, the urine can become bright red, pink, or cola colored, which is called gross hematuria. There are several possible causes of hematuria, such as urinary tract infection, kidney stone, tumors in the kidney or bladder, and drugs. In this present case, organs of the urinary system did not have significant pathologic changes on ultrasonic examination. In addition, there was an obvious temporal correlation of propafenone administration with hematuria. The count of red blood cells increased significantly during the 2 times propafenone was used and returned to normal after it was withdrawn. The association between hematuria and propafenone according to Naranjo Adverse Drug Reaction Probability Scale has a score of 6 (Table II).[23] Therefore, this ADR has a probable association with administration of propafenone.

The mechanism of propafenone-associated hematuria is still unclear. Zeng et al[10] suggested that propafenone-induced hematuria is likely to be a symptom of drug-induced autoimmune hemolytic anemia (DIIHA). DIIHA can be diagnosed when there is laboratory evidence of hemolysis, the patient has a positive direct antiglobulin test (DAT) result, and clinical evaluation has excluded an alternative cause. According to the characteristics of previous reports, many researchers suggested DIIHA as the

Table II. Naranjo Adverse Drug Reaction Probability Scale scores of the patients.

Question	Answer	Score
Are there previous conclusive reports on this reaction?	No	0
Did the adverse event occur after the suspected drug was administered?	Yes	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes	+1
Did the adverse reaction reappear when the drug was readministered?	Yes	+2
Are there alternative causes (other than the drug) that could have on their own caused the reaction?	Yes	−1
Did the reaction reappear when a placebo was given?	Do not know	0
Was the drug detected in the blood (or other fluids) in concentrations know to be toxic?	Do not know	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Do not know	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes	+1
Was the adverse event confirmed by any objective evidence?	Yes	+1
Total score		6

main cause of this adverse reaction. However, none of them have conducted other laboratory examinations to confirm this diagnosis.

Although there is no clear warning about propafenone-induced hematuria, some related information has been published by the European Medicines Agency in their Summary of Product Characteristics.[24] this summary lists hypersensitivity of the immune system as a rare ADR (cannot be estimated from the available data), which may theoretically cause anaphylaxis and vasculitis. Moreover, symptoms such as leukopenia and lupus-like syndrome also have a close connection with vasculitis. Mild drug-induced vasculitis of the urogenital system can cause hematuria. In addition, this symptom can be quickly recovered after the drug is withdrawn. Because in our case the patient did not undergo a biopsy, we cannot rule out the possibility of vasculitis.

Because propafenone is mainly metabolized by CYP2D6, CYP1A2, and CYP3A4, its plasma level may increase with the concomitant administration of CYP2D6, CYP1A2, and CYP3A4 inhibitors. In addition, drug−drug interactions can also occur when propafenone is coadministrated with digoxin, warfarin, orlistat, β-antagonists, lidocaine, P-glycoprotein, or ABCB1 inhibitors. In our case, the patient took only propafenone orally; thus, the cause of hematuria might be different from that in previously reported cases. In this patient's long-term prescription, bisoprolol and dabigatran are administered the entire time that propafenone is administered. Clinical trial data have proven that coadministration of β-antagonists and propafenone can increase only the plasma concentration of β-antagonists. The pharmacokinetic properties of propafenone were not affected. Dabigatran is an anticoagulant drug that may cause bleeding. In this case, administration of dabigatran did not have time dependence on the occurrence of gross hematuria. However, we cannot rule out the possibility of a drug−drug interaction. It is known that the serum concentration of active metabolites of dabigatran etexilate may be increased by P-glycoprotein/ABCB1 inhibitors.[25] Propafenone and its major metabolites, 5-hydroxy propafenone and *N*-desalkyl propafenone, are all P-glycoprotein inhibitors. We can assume that the concomitant administration of propafenone and dabigatran may cause a higher anticoagulation effect.

Other reasons may potentially relate to the patient's gross hematuria after administration of propafenone. According to the literature review, only Chinese patients have been observed to have propafenone-related hematuria. It is reasonable to suggest that the

probability of this ADR may be related to pharmacogenomic properties. Other causes, such as age, dosage, and administration, may also increase the risk for propafenone-induced gross hematuria.

Propafenone is a widely used medication for arrhythmia; many of the drugs are for geriatric use or administered concomitantly with P-glycoprotein inhibitors. It is important to be cautious with these patients when rare ADRs occur and to stop the administration of the medicine immediately.

CONCLUSION

Propafenone-induced gross hematuria is a rare ADR that has been observed only in Chinese patients. The mechanism of this ADR is still unclear; however, DIIHA, vasculitis, drug–drug interaction, pharmacogenetic properties, drug dosage, and administration might be causes. Additional studies need to be conducted to determine the exact mechanism for this ADR to provide better protection for patients.

FUNDING SOURCES

This study was supported by grant 81573504 from the National Natural Science Foundation of the People's Republic of China, grant 7171012 from the Beijing Municipal Natural Science Foundation, grants 2017ZX09304028 and 2017ZX09101001 from the National Science and Technology Major Projects for Major New Drugs Innovation and Development of China, and grant 2018SF081 from the Scientific Research Seed Fund of Peking University First Hospital.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

All authors read and approved the final manuscript. All authors contributed equally to the design and construction of the manuscript.

REFERENCES

1. Couto N, Ferreira M, Reis E. Neutropenia and cutaneous lesions secondary to propafenone. *Eur J Dermatol*. 2009;19:365–367.
2. Funckbrentano C, Kroemer HK, Lee JT, et al. *Propafenone N Engl J Med*. 1990;322:518–525.
3. Highlights of prescribing information PYTHMOL. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019151s015lbl.pdf. Accessed 28 Jan 2019.
4. Podrid PJ, Cytryrr R, Luwn B. Propafenone: noninvasive evaluation of therapy. *Am J Cardiol*. 1984;54:530–601.
5. Ravid S, Podrid PJ, Novrit B. Safety of long term propafenone therapy Fur cardiac arrhythmia: expedience with 774 patients. *J Electrophysiol*. 1987;1:580–590.
6. Wożakowska Kapłon B, Stępień Walek A. Propafenone overdose: cardiac arrest and full recovery. *Cardiol J*. 2010;17:619–622.
7. Ovaska H, Ludman A, Spencer EP, et al. Propafenone poisoning—a case report with plasma propafenone concentrations. *J Med Toxicol*. 2010;6:37–40.
8. Jones RJ, Brace SR, Vander Tuin EL. Probable propafenone-induced transient global amnesia. *Ann Pharmacother*. 1995;29:586–590.
9. Couto N, Ferreira M, Reis E. Neutropenia and cutaneous lesions secondary to propafenone. *Eur J Dermatol*. 2009;19:365–367.
10. Zeng ZQ, Zhu L. Hemolytic reaction resulting from propafenone administration [in Chinese]. *Chin J Intern Med*. 1991;30:217.
11. Li HJ. One case with hemoglobinuria caused by intravenous injection of propafenone [in Chinese]. *Chin Circ J*. 1994;9:467.
12. Yang JX, Shen YM, Di WH, et al. One case with hemoglobinuria caused by intravenous injection of rytmonorm [in Chinese]. *[chinese J Hematol*. 1995;16:217.
13. Liang XL, Shao ZY. One case with hemolysis caused by intravenous injection of propafenone [in Chinese]. *Chin J Pharmacoepidemiol*. 2000;9:17.
14. Yan JL, Tang BX. One case of propafenone induced hemoglobinuria [in Chinese]. *Chin J Clin Pharm*. 2000;9:254.
15. Wang B, Li GR. One case of rytmonorm induced hemoglobinuria [in Chinese]. *Chin Commun Doctors*. 2001;17, 43–43.
16. Yang RZ, Liu MY. One case with hemolysis caused by intravenous injection of rytonorm [in Chinese]. *Shandong Med J*. 2003;43:19.
17. Xu L, Wang Q. Hematuria following high-dose propafenone therapy. *Adverse Drug React J*. 2003;5:259–260.
18. Liu HQ, Xue Z, Liang F. Arrhythmia treatment of prapafenone causing gross hematuria: a case report [in Chinese]. *Clin Focus*. 2007;22, 356–356.
19. Chen ML, He MQ. Hematuria caused by intravenous injection of propafenone: 4 case reports [in Chinese]. *Chin J Med Guide*. 2006;8:441–442.

20. Qu YL. Two cases of rytmonorm induced hemoglobinuria [in Chinese]. *Mod Health (Med Innovation Res)*. 2008;5:127.
21. Yang TF, Wang SX. Two cases of rytmonorm induced gross hematuria [in Chinese]. *Chin Med Mod Distance Educ China*. 2011;9:100.
22. Tang JH, Li L. Analysis of intravenous injection of propafenone caused hematuria from 20 cases [in Chinese]. *Chin J Mod Drug Appl*. 2012;6:91–92.
23. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.
24. https://www.medicines.org.uk/emc/product/1733/smpc. Accessed April 26, 2019.
25. Bachmakov I, Rekersbrink S, Hofmann U, Eichelbaum M, Fromm MF. Characterisation of (R/S)-propafenone and its metabolites as substrates and inhibitors of P-glycoprotein. *Naunyn-schmiedeberg's Arch Pharm*. 2005;371:195–201.

Address correspondence to: Cui Yimin, PhD, MD, Department of Pharmacy, Peking University First Hospital, No. 6, Dahongluochang Street, Xicheng District, Beijing, 100034, China. E-mail: bdyyyljd@126.com