Annals of Clinical Case Reports

Case Report
Published: 08 Sep, 2021

A Case Report on Phenazopyridine-Induced Hemolytic Anemia

Randolph E Regal and Nicole Farah*

Department of Pharmacy, University of Michigan, USA

Abstract

This is the case of a 68 year old woman with a hematologist-confirmed case of phenazopyridine-induced hemolytic anemia. She had been using the drug for seven months at a dose of 800 mg daily for a chronic interstitial cystitis. Although an attempt was made to taper the medication to discontinuation, severe urinary pain impeded this process, and the patient could only accept a reduction in dose to 600 mg daily. Nonetheless, the hemoglobin improved from 9.1 g/dl to 10.4 g/dl after just one month on the lower dose. Several months later, while still taking 600 mg daily, the hemoglobin continued to improve to11.9 g/dl.

Introduction

Phenazopyridine hydrochloride (DPP) is a urinary analgesic used to treat patients experiencing pain, burning, urgency, or frequency caused by lower urinary tract mucosa irritation. These maladies may be due to infection, trauma, surgery, endoscopic procedures, imaging studies, or catheters [1]. PPD is able to ease patients' discomfort by providing a local anesthetic effect on the urinary tract mucosa. However, the precise mode of action of DPP is unknown.

DPP is found in a medication called AZO®, and is sold over the counter in many states. The recommended dose for adults is 200 mg three times a day after meals for a maximum of 2 days in patients with normal renal function. While there is no definitive dose adjustment for renal impairment, drug labeling states that "the dose must be lowered in those with impaired renal function [1]".

DPP (2-6-Diamino-3-Phenylazo Pyridine) is hepatically metabolized via hydroxylation to produce 2,3,6-triaminopyridine, or aniline [2]. It is also excreted unchanged, as shown in Figure 1. The ease with which DPP can be acquired as an OTC product sets the table for patients suffering complications from longer term use of this drug. It has been reported that chronic use can cause hemolytic anemia in the elderly [3], those with G6PD mutations [4], those with mild renal failure [4], and others [5,6]. This case report will demonstrate yet another example of chronic DPP use leading to hemolytic anemia.

Case Presentation

A 68-year-old woman with history of type 2 diabetes, hypertension, hyperlipidemia, hypothyroidism, osteoporosis, obstructive sleep apnea, previous pulmonary emboli, migraines, and interstitial cystitis was experiencing onset of shortness of breath, nausea, decreased appetite, dizziness and diarrhea over several weeks. In July of that year, her primary care provider found that she had a progressing case of anemia of unknown etiology.

The patient then contacted a pharmacist for a medication consult on August 16th, 2020. The pharmacist perused her medications, labs, and problem lists. Based on her labs from early August, as well as her history of recently beginning daily high dose DPP, the pharmacist suspected she might be experiencing DPP-induced hemolytic anemia. The patient reported she had been taking two 100 mg DPP tablets four times daily since January 2020. Clinically relevant labs included: Hgb of 8.7 g/dl, an MCV of 110 fL, haptoglobin of <10 mg/dl, LDH 383 U/L, a reticulocyte count of 295 (11%), and normal iron labs. The pharmacist recommended that she be referred to a hematologist for a complete work-up and diagnosis. At the behest of the pharmacist, she attempted to gradually taper off the DPP. However, this process was stalled because of the exacerbation of urinary pain at the lower doses.

By 9.1.20, the patient had managed to reduce the dose of DPP to 200 mg TID and had her first

OPEN ACCESS

Correspondence:
Randolph E Regal, Department of Pharmacy, University of Michigan, Victor Vaughan House, 1111 E Catherine Street, Ann Arbor, MI 48109-2054, USA, Tel: +1-734-647-4717; E-mail: reregal@umich.edu

Received Date: *13 Aug 2021*
Accepted Date: *25 Aug 2021*
Published Date: *08 Sep 2021*

Citation:
Regal RE, Farah N. A Case Report on Phenazopyridine-Induced Hemolytic Anemia. Ann Clin Case Rep. 2021; 6: 1988.

ISSN: 2474-1655

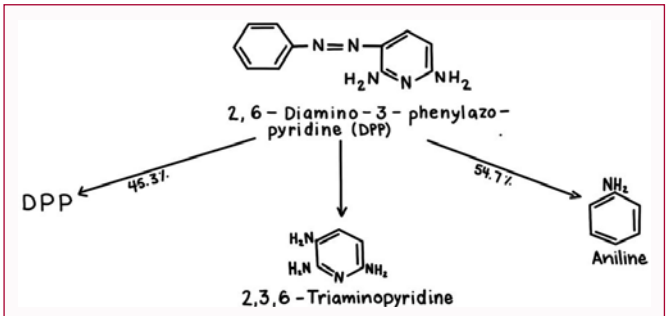

Figure 1: Metabolic pathway of phenazopyridine [2].

hematology visit. Her lab results at that visit yielded a Hgb 9.1 g/dl MCV of 108 fL, haptoglobin <10, mg/dl and LDH 267 U/L, all which suggested hemolytic anemia. Due to negative Direct Anti-globulin Tests (DAT) also done at that time, hematology felt they had ruled out autoimmune hemolytic anemia. As a result, the suspicion of DPP- induced anemia was strengthened. On 9.10.20, a decrease in the DPP dose from 200 mg TID to 200 mg BID was attempted. However, it was not successful, and 200 mg TID dose was resumed. During this time, she also visited a urologist in an attempt to find other remedies toward relieving her interstitial cystitis- related pain.

At the time of her second hematology appointment on 9.29.20, she was still taking DPP 200 mg TID. However, at the slightly lower dose, the patient's labs showed some improvement. Her Hgb was increased from 9.1 to 10.4 g/dL, MCV decreased from 108 fL to 103 fL, haptoglobin increased from <10 mg/dl to 23 mg/dl, LDH dropped slightly from 267 U/L to 256 U/L. As a result, the hematologist concluded that there was no emergent need to completely taper her off the medication. Therefore, the patient wished to continue on DPP 200 mg TID. On 10.30.20, hydroxyzine was attempted to treat her bladder spasms, but resulted in no appreciable effect.

Finally, at a follow-up visit on 6.2.2021, the patient was still on both DPP 200 mg TID and Levsin 0.125 mg Q4-6h as needed for pain. Results showed an Hgb increase to 11.9 g/dL, an MCV decrease to 92.7 fL, and all other lab results in normal ranges. The hematologists chose to not repeat haptoglobin or LDH levels. These results appeared to demonstrate a direct correlation between the DPP dose and the degree of drug- induced hemolytic anemia.

Discussion

Because of the mechanism involved in the adverse effect, DPP-

Table 1: Chronology of events and laboratory values.

Date	Description of Visit and Phenazopyridine Dose	Hgb g/dL	MCV fL	Haptoglobin Mg/dl	LDH U/L	Other labs
August 6, 2020	PCP visit On 800 mg daily since January, 2020	8.7	110	<10	383	Retic 11%
September 1, 2020	Hematology Initial Visit On 600 mg daily since mid-August	9.1	108	<10	267	DAT neg
September 29, 2020	Hematology Visit #2 Still on 600 mg daily	10.4	103	23	256	
June 2, 2021	Hematology Visit #3 Still on 600 mg daily	11.9	92.7	Not done	Not done	

Table 2: Summaries of case reports of phenazopyridine-induced hemolytic anemia.

Reference	Dose	Duration before manifestation of HA	Labs	Duration for labs to normalize once drug was stopped
Phenazopyridine-induced hemolytic anemia Noonan HM, Kimbrell M, Ben Johnson W, Reuler JB. Phenazopyridine-induced hemolytic anemia. Urology. 1983;21(6):623-4.	Phenazopyridine 400 mg TID Phenazopyridine 100 mg BID for five months, with the abrupt increase to 400 mg TID three weeks prior to admission	Five months of 100mg bid, three weeks of 400mg bid. Increasing shortness of breath and anginal-type chest pain of several weeks' duration.	-Hg 9.6 gm -Hematocrit 28 -Reticulocyte 5.6% -WBC 8,300 -Platelet 262,000 -Serum lactic dehydrogenase 449 IUiL (100-230); -Bilirubin 2.1 mg/dl (0.1-1.0). -SCr 1.3 mg,ldl (O.i-1.4)	n/a
Phenazopyridine Induced Hemolytic Anemia in a Patient with G6PD Deficiency Tishler M. Phenazopyridine-induced hemolytic anemia in a patient with g6pd deficiency. Acta Haematologica. 1983;70(3):208-9.	300 mg daily	Four days	-Hb 8.6g/dL -G6PD deficiency -Hct 0.28 -Haptoglobin 0.5g/dL -Reticulocyte 5%	Pt received 2 units of RBC's, Hb rose to 11.7 g/dL and after a few days the serum haptoglobin level became normal again.
Acquired Methemoglobinemia and Hemolytic Anemia after Usual Doses of Phenazopyridine Jeffery WH, Zelicoff AP, Hardy WR. Acquired methemoglobinemia and hemolytic Anemia after usual doses of Phenazopyridine. Drug Intelligence & Clinical Pharmacy. 1982;16(2):157-9.	Case 1: 200mg TID	10 days	-Hematocrit 34.7% -Reticulocyte 11.1% -MCHC 32% -Hemoglobin 9.3 g/dL	
	Case 2: 200mg TID for 3 days 200mg BID after start of SMX/TMP	6 days Oct 13: Initiated Oct 16: Dose reduction Oct 19: malaise, muscle aches, SOB Oct 20: blue discoloration of lips, tongue, extremities	Cyanosis of the tongue, lips, hands, and feet, slight left and right CVA tenderness, and no edema or clubbing of the extremities. -methemoglobin level of 34.9% of total hemoglobin -hemoglobin 8.7 g/dL -hematocrit 27.6%, -MCHC 31.7% -BUN 11 mg/dL -creatinine 0.8 mg/dL -bilirubin 1.2 mg/dL total -0.3 mg/dL direct	3 days later: -Methemoglobin 23.3% -Reticulocyte 15.2% 17 days later: -hematocrit 36.7% -Methemoglobin 4.6%

Phenazopyridine-Induced Hemolytic Anemia in Advanced Kidney Disease Chang L-C, Kuo C-W, Chau T, Lin S-H. Phenazopyridine-induced hemolytic anemia in advanced kidney disease. Journal of the American Geriatrics Society. 2014;62(12):2464-6.	100 mg TID for 10 days	10 days	-hemoglobin, 6 g/dL -LDH; 354	After phenazopyridine and blood transfusions were stopped, his hemoglobin level remained stable at approximately 9 g/dL, without fragmented red blood cells on the blood smear. Serum creatinine concentration remained at approximately 4.9 mg/dL over the following 3 months.

induced hemolytic anemia is thought to be dose-related. As previously mentioned, the drug is hepatically metabolized *via* hydroxylation to form aniline and its congeners (Figure 1). Of course, the higher the dose, the higher the concentrations of these oxidizing metabolites. At some critical individual-specific "threshold" level, the oxidizing effect of the aniline derivatives exceeds the endogenous reducing capacity of the enzymes within the host's RBC's. This then results in the net increased catabolism of hemoglobin and the clinical manifestation of hemolytic anemia [3].

In this case, the anemia was quite significant on 800 mg a day of DPP. The hemoglobin fell below 9 g/dl; and, the patient possessed symptoms of systemic hypoxia. Meanwhile, over a period of a few months, reducing the DPP dose 600 mg a day yielded an improvement in the hemoglobin to 11.9 g/dl with some commensurate improvements in other labs and exercise tolerance. The findings of a low haptoglobin and elevated LDH in this case were other classic characteristics of hemolytic anemia, and these normalized as early as late September (Table 1). Initially, it was hoped that the drug could be stopped altogether, but the continuance of urinary symptoms precluded the patient from doing this. This case shows that, in patients who do symptomatically require longer term daily use of DPP, a small reduction in dose could possibly reduce the magnitude of a drug-induced hemolytic anemia.

There have been several published reports of hemolytic anemia from the use of DPP in the literature (Table 2). Previous cases have shown an association of hemolytic anemia with chronic use of this drug in the elderly population, those with renal impairment, and those with G6PD mutations [3-6]. The patient in this case was 68 years old with multiple comorbidities, but she had normal renal function. A G6PD test was not done. The hematologists confirmed the pharmacist's suspicion through their clinical experience and the use of serial labs such as the hemoglobin, haptoglobin, LDH, and elevations in MCV levels. What made this particular case so unique was the stark difference in the magnitude of the anemia seen between the 800 mg and 600 mg daily doses.

Although DPP is not labeled for long term use, there are patients who can find no other modality for controlling bladder pain. All patients on long term DPP should be monitored for hemolytic anemia, especially if on higher doses. However, if hemolytic anemia does occur, a complete discontinuation of the medication may not be necessary.

References

1. Actavis Totowa LLC. Pyridium® (Phenazopyridine HCl Tablets, USP). Rockaway, NJ: Warner Chilcott (US), Inc. 2007.
2. Johnson WJ, Chartrand A. The metabolism and excretion of phenazopyridine hydrochloride in animals and man. Toxicol Appl Pharmacol. 1976;37(2):371-6.
3. Noonan HM, Kimbrell M, Ben Johnson W, Reuler JB. Phenazopyridine-induced hemolytic anemia. Urology. 1983;21(6):623-4.
4. Tishler M, Abramov A. Phenazopyridine-induced hemolytic anemia in a patient with g6pd deficiency. Acta Haematol. 1983;70(3):208-9.
5. Jeffery WH, Zelicoff AP, Hardy WR. Acquired methemoglobinemia and hemolytic Anemia after usual doses of Phenazopyridine. Drug Intell Clin Pharm. 1982;16(2):157-9.
6. Chang LC, Kuo C-W, Chau T, Lin SH. Phenazopyridine-induced hemolytic anemia in advanced kidney disease. J Am Geriatr Soc. 2014;62(12):2464-6.