

Possible Doxazosin-Induced Leukopenia

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INTRODUCTION

Doxazosin is a selective long-acting α_1 -adrenergic antagonist. It is indicated for the treatment of benign prostatic hyperplasia and stage I and II (mild to moderate) essential hypertension.¹ A MEDLINE search revealed no previous reports of leukopenia associated with the use of doxazosin.

CASE REPORT

A 66-year-old man with end-stage renal disease secondary to acute tubular necrosis had been undergoing hemodialysis for 2 years. He then underwent renal transplantation, but the kidney was rejected. Upon discharge from hospital after the transplant procedure, all immunosuppressants, with the exception of prednisone, were discontinued. Four months later, nephrectomy of the transplanted kidney was performed, and doxazosin (2 mg once daily at bedtime) was started (upon discharge) for treatment of hypertension, which developed after the nephrectomy. Complete blood cell count had been monitored weekly while the patient was undergoing hemodialysis. Mean leukocyte count (\pm standard deviation) was $(4.6 \pm 1.8) \times 10^9/L$ (range $2.8 \times 10^9/L$ to $8.6 \times 10^9/L$; normal range $4.0 \times 10^9/L$ to $10.0 \times 10^9/L$), mean neutrophil count was $(4.9 \pm 2.3) \times 10^9/L$ (range $3.0 \times 10^9/L$ to $7.8 \times 10^9/L$; normal range $2.0 \times 10^9/L$ to $7.5 \times 10^9/L$), and mean platelet count was $(178.6 \pm 53.1) \times 10^9/L$ (range $113 \times 10^9/L$ to $271 \times 10^9/L$, normal range $150 \times 10^9/L$ to $400 \times 10^9/L$) over the 4 months after the transplant.

In addition to the renal transplant procedure and subsequent organ rejection and nephrectomy, the patient's medical history was significant for alcohol abuse 30 years previously, a seizure 5 years previously, chronic obstructive pulmonary disease, hypothyroidism and peripheral vascular disease. His other medications included Replavite multivitamin preparation once daily, calcitriol 0.75 μ g once daily, calcium carbonate 2250 mg 3 times daily with meals, enteric-coated acetylsalicylic

acid 81 mg once daily, prednisone 7.5 mg every other day, omeprazole 20 mg once daily, ipratropium 40 μ g inhaled twice daily, erythropoietin 8000 units IV 3 times weekly, iron dextran 100 mg IV once monthly, and salbutamol 200 μ g inhaled 4 times daily when needed. Except for the doxazosin, he had been receiving all medications on a long-term basis.

The patient's leukocyte count had been stable over the 4 months before initiation of doxazosin (mean $4.6 \times 10^9/L$). One week after the patient started the doxazosin therapy, the count had declined to $3.1 \times 10^9/L$. It continued to decline over the next month to reach $1.8 \times 10^9/L$, at which time the doxazosin was discontinued (31 days after initiation). The patient's platelet count also decreased after initiation of doxazosin, and transient decreases in platelet count continued even after withdrawal of doxazosin.

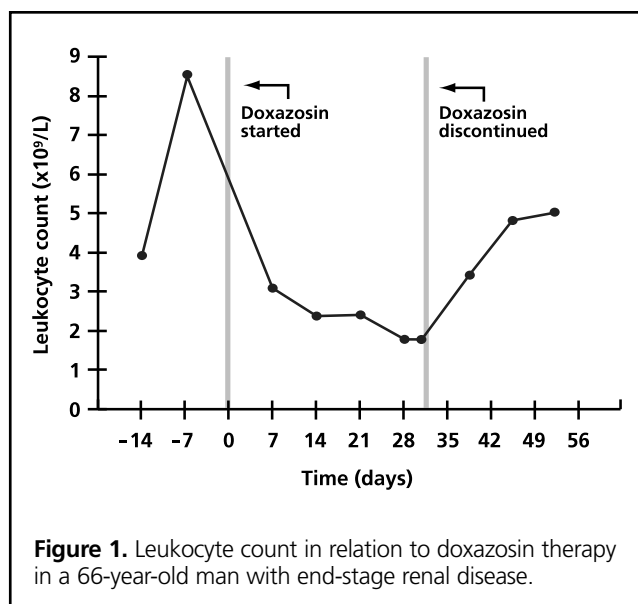
One week after discontinuation of doxazosin, the patient's leukocyte count had risen to $3.4 \times 10^9/L$; by day 14 after discontinuation, the count had normalized at $4.8 \times 10^9/L$ and it remained normal over the following month. No other medications, including over-the-counter medications, had been started in the 4 months preceding the episode of leukopenia, and the patient reported no changes in his diet during that time.

DISCUSSION

Doxazosin was considered the most likely cause of this patient's leukopenia. The development of leukopenia seemed temporally related to the initiation of doxazosin, and the subsequent response to discontinuation of the medication was prompt.

The likelihood of this patient's leukopenia being induced by doxazosin was considered "possible", given a score of 4 on the adverse drug reaction probability scale of Narano and others.² Before initiating doxazosin, the patient's leukocyte and platelet counts were normal and stable. The leukocyte and platelet counts dropped after the initiation of doxazosin, which led to leukopenia and a measurable decrease in platelets.





This patient had normocytic, normochromic anemia due to his chronic renal disease. He was receiving treatment for this anemia (in the form of iron dextran and erythropoietin), and his leukopenia was thought to be unrelated to these drugs. The poor response to erythropoietin was thought to be secondary to chronic kidney rejection, and the response improved after nephrectomy. None of the patient's long-term medications have been associated with leukopenia. Doxazosin does not undergo cytochrome P450 metabolism, so it is unlikely that a drug–drug interaction caused this toxic effect. Other potential causes were not evident, although alcohol abuse has been associated with a decrease in polymorphonuclear neutrophils.³ The patient denied any current alcohol use, and his alkaline phosphatase and gamma glutamyl transferase levels were normal. Unrecognized chronic low-grade inflammatory processes can lead to macrophage activation and chronic antigenic stimulation, resulting in enhanced neutrophil extravasation, osteopenia and reduced neutrophil production.³ However, this process usually results in mild chronic neutropenia and leukopenia of insidious onset, whereas in this case the leukopenia had a rapid onset and resolved quickly upon discontinuation of the medication.

According to the product monograph,¹ doxazosin has been associated with a decrease in mean leukocyte and neutrophil counts (by 2.4% and 1%, respectively)

relative to placebo ($n = 747$ patients). In a database of 2400 patients,⁴ there were 4 suspected cases of drug-induced neutropenia. In benign prostatic hyperplasia, the incidence of clinically significant abnormalities of leukocyte count was 0.4% with doxazosin. In postmarketing experience, rare cases of leukopenia and thrombocytopenia have been reported.¹ A transient decrease in leukocyte count was reported in 1 of 20 patients receiving prazosin 1 mg 3 times daily for a period of 6 weeks, but whether this was related to the drug is unclear.⁴ No other drugs in this class have been associated with leukopenia.

The mechanism for this side effect is unknown, but it may involve direct toxic effects to the marrow, as well as an immune mechanism. Noncytotoxic drug-induced leukopenia usually occurs within 3 months of initiation of the causative drug and resolves within 2 to 7 days after drug withdrawal.⁵

Given the temporal relationship, the improvement on withdrawal of the suspected agent, and lack of other potential causes, it appears that doxazosin was associated with the decreased leukocyte count. Clinicians should be aware of this potential adverse effect.

References

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