Drug Saf - Case Rep (2018) 5:6
https://doi.org/10.1007/s40800-018-0075-2

CASE REPORT

Severe Secondary Polycythemia in a Female-to-Male Transgender Patient While Using Lifelong Hormonal Therapy: A Patient's Perspective

Ellen G. T. Ederveen[1] · Florence P. A. M. van Hunsel[1] · Marielle J. Wondergem[2] · Eugène P. van Puijenbroek[1,3]

Published online: 2 February 2018

Abstract After a registered drug is available on the market and used in everyday circumstances, hitherto unknown adverse drug reactions (ADRs) may occur. Furthermore, the patient can experience a previously unknown course of a known ADR. Voluntary reports by patients play an important role in gaining knowledge about ADRs in daily practice. The Netherlands Pharmacovigilance Centre Lareb received a report from a 55-year-old female-to-male transgender patient who experiences secondary polycythemia while using lifelong testosterone therapy. The onset age of the symptoms was 38 years. The symptoms appeared gradually and after approximately 1 year it was clear that the patient's hemoglobin and hematocrit had started to increase. A Naranjo assessment score of 6 was obtained, indicating a probable relationship between the patient's polycythemia and use of the suspect drug. Polycythemia is a known ADR in testosterone treatment, but little attention has been paid to the possible severity and complications of these symptoms as well as the impact on the patient's well-being.

Key Points

Patients play an important role in voluntary adverse drug reaction (ADR) reporting systems in gaining knowledge about ADRs in daily practice.

Transgender patients need lifelong hormonal therapy, which can lead to ADRs with a large impact on the their quality of life.

Polycythemia is a common adverse drug reaction during testosterone treatment, which can lead to severe complications.

Background

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [1]. Voluntary reporting systems play an important role in gaining knowledge about a drug's safety in real-world conditions. Voluntary reports can be seen as (clinical) concerns about a drug and the suspected reaction [2]. Next to healthcare professionals, patients play an important role in reporting adverse drug reactions (ADRs) [3]. Patients have various motives for reporting that can often be characterized as altruistic or personal [4]. Usually, there are multiple reasons for reporting. In The Netherlands, maintenance of the voluntary reporting system is carried out by the Pharmacovigilance Centre Lareb. Recently, Lareb

✉ Ellen G. T. Ederveen
e.ederveen@lareb.nl

[1] Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, The Netherlands

[2] Department of Hematology, VU University Medical Center Amsterdam, Amsterdam, The Netherlands

[3] PharmacoTherapy, -Epidemiology and -Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands

received a report concerning the development of secondary polycythemia while using testosterone therapy in a female-to-male (FTM) transgender patient. The patient with this ADR had an altruistic motivation for reporting it: transgender people use lifelong hormonal therapy, and therefore ADRs may have a strong impact on patients' well-being, and the patient wished to raise awareness of this. In this case report we describe, from a patient's perspective, one consequence of this lifelong hormonal therapy and the importance of patient reports.

Case Presentation

In April 2016, the Netherlands Pharmacovigilance Centre Lareb received a report of a 55-year-old FTM transgender patient who developed secondary polycythemia. He explained that 18 years ago he started with testosterone injections of 250 mg once every 2 weeks. As desired, this resulted in cessation of menstruation, voice deepening, increase of muscle volume, and hair growth according to the male pattern. After a year, the dosage was reduced to 250 mg once every 3 weeks, but unfortunately this dosage appeared to be insufficient. Over the years, he used various testosterone preparations (e.g., testosterone gel, testosterone injections of 100 mg weekly and injections of 1000 mg once every 12 weeks).

Approximately a year after start of the testosterone therapy, the patient's hemoglobin and hematocrit values started to increase. A few years later, his hemoglobin value slightly exceeded 11 mmol/L (reference range 8.5–11.0 mmol/L). Another 4 years later, his hemoglobin value was 11.5 mmol/L and hematocrit was 53% (reference range 40–50%). Besides the elevated hemoglobin and hematocrit, the erythrocytes were microcytic and had an abnormal morphology. The Janus kinase 2 (*JAK2*) mutation was negative (both exon 12 and 14), and therefore his hematologist considered primary polycythemia (polycythemia vera) to be highly unlikely.

Approximately 13 years after the start of hormonal therapy, the patient started treatment with an anticoagulant, acetylsalicylic acid in a dosage of 80 mg daily, and phlebotomy for the polycythemia. The patient's hemoglobin value at that point was 11.7 mmol/L and the hematocrit value was 53%. However, this therapy caused a decreased iron count, fatigue, and sensitivity to developing furuncles. Regarding the latter, iron is essential for normal functioning of the immune system—the susceptibility to infection is increased by iron deficiency [5, 6].

Approximately 5 months after initiation of the anticoagulant and phlebotomy, the patient's hemoglobin value decreased to 8.1 mmol/L and the hematocrit value decreased to 43%. The patient continued the testosterone therapy, anticoagulant, and phlebotomy. Except for a few abnormal values, the hemoglobin and hematocrit values have been within the normal range since then. The patient is now in an acceptable equilibrium with less frequent phlebotomy treatments and he uses a small amount of iron supplementation if his iron becomes too low for his well-being.

The patient reported this ADR at the Netherlands Pharmacovigilance Centre Lareb to raise awareness of the possible severity and impact of this ADR. The causality of the report was determined with a Naranjo assessment. Since polycythemia is a known adverse event, other possible causes were excluded, and the symptoms appeared after start of the testosterone, a Naranjo score of 6 was obtained. This Naranjo score indicates a probable relationship between the patient's polycythemia and the use of testosterone.

Polycythemia is a known common ADR of testosterone therapy but is usually mild in nature [7, 8]. It is important that patients who are planning to start hormonal therapy are aware of this possible ADR.

Discussion

In the case report presented here, the patient used several formulations of testosterone over time. Unfortunately, since the patient changed hematologist, details about which formulation corresponds to what blood values are lacking. In addition, since the patient started the anticoagulant and phlebotomy around the same time, it was unknown which treatment contributed the most to the decreased hemoglobin and hematocrit values. This also applies to the reduced iron count, fatigue, and sensitivity to furuncles, which appeared after the start of both the anticoagulant and phlebotomy.

'Transgender' is an umbrella term to describe individuals who differ from the cultural norm in gender expression or gender role behavior [9]. Exact numbers of patients diagnosed with gender dysphoria are lacking. The estimated numbers are dependent on the terminology used and the population studied, and vary broadly. However, available studies show that the number of patients presenting to clinics is increasing but that the number that undergo an actual transition to the opposite sex is considerably smaller [9].

The aim of the transition is to change the mental and physical state to that of the opposite sex. In addition to psychotherapy and sex reassignment surgery, the treatment consists of hormone replacement therapy [10]. For FTM transgender patients this requires lifelong testosterone administration. This therapy aims to induce the desired virilization and cessation of menstruation.

However, testosterone use can also lead to ADRs such as acne, increased aggressiveness, and weight gain. The label of testosterone injections mentions increased hematocrit, hemoglobin, and red blood cells and polycythemia as a common ADR [11]. In secondary polycythemia, plasma circulating factors such as erythropoietin or testosterone stimulate erythropoiesis [12, 13]. Polycythemia may occur in more than 20% of men receiving testosterone hormonal replacement therapy. An increase in hemoglobin of 5–7% during testosterone treatment has been described [13]. As of 4 July 2017, VigiBase®, the WHO international database of suspected ADRs, had 14 reports of polycythemia vera versus 218 of polycythemia related to testosterone treatment [14].

The most common long-term complications of primary polycythemia are thrombosis and malignancies [13, 15]. There is no conclusive evidence that secondary polycythemia caused by testosterone replacement therapy is associated with the same risks [16], although high blood viscosity might increase the risk of thrombotic events [16, 17]. It is unclear above what hematocrit level this risk appears [17]. Furthermore, there is no conclusive evidence that testosterone can be thrombogenic, with or without causing erythrocytosis. It seems that starting testosterone treatment, as investigated in men with age-related hypogonadism, increases the risk of thrombosis slightly, and that this risk declines after the first 6 months [18].

Conclusion

To minimize the risk of polycythemia-induced complications, patients are often treated in the same manner as for primary polycythemia, with phlebotomy and an antiplatelet drug [15]. The best approach to treating the symptoms would be to withdraw the hormonal therapy [19]; however, withdrawal of testosterone therapy is not an option for most FTM transgender patients. Before the start of hormonal therapy it is important that patients are well-informed about the possible ADRs, including polycythemia, since it may have a large impact on their quality of life. Furthermore, a blood count prior to the start of the therapy and monitoring the complete blood count during long-term hormonal therapy are essential [11]. In order to gain more knowledge and to raise awareness about this ADR, it is important that patients and healthcare professionals who treat transgender patients report possible ADRs to their national pharmacovigilance centers. To conclude, we add a quote that shows the patient's perspective on this ADR:

"I believe that it is almost impossible to have a functioning drug without this having an effect on other parts of the body. If I would have known this adverse drug reaction before start of the therapy, I would still choose to start this therapy. Solely I would be more regardful of changes in my blood values."

Funding No financial support was received for the conduct of this study or preparation of this manuscript.

Compliance with Ethical Standards

Conflict of interest Ellen Ederveen, Florence van Hunsel, Marielle Wondergem and Eugene van Puijenbroek declare that they have no conflicts of interest.

Informed consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent may be requested for review from the corresponding author.

References

1. World Health Organization (version date: 2017). 2017. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed 10 July 2017.
2. Edwards IR. Spontaneous reporting—of what? Clinical concerns about drugs. Br J Clin Pharmacol. 1999;48(2):138–41. https://doi.org/10.1046/j.1365-2125.1999.00000.x.
3. van Hunsel F, Härmark L, Pal S, Olsson S, van Grootheest K. Experiences with adverse drug reaction reporting by patients: an 11-country survey. Drug Saf. 2012;35(1):45–60. https://doi.org/10.2165/11594320-000000000-00000.
4. van Hunsel FP, ten Berge EA, Borgsteede SD, van Grootheest K. What motivates patients to report an adverse drug reaction? Ann Pharmacother. 2010;44(5):936–7. https://doi.org/10.1345/aph.1M632.
5. de Pontual L. Iron and susceptibility to infections. Arch Pediatr. 2017;24(5S):5S14–7. https://doi.org/10.1016/S0929-693X(17)24004-4.
6. Weijmer MC, Neering H, Welten C. Preliminary report: furunculosis and hypoferraemia. Lancet. 1990;336(8713):464–6.
7. Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. Arch Sex Behav. 1998;27:475–92.
8. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997;82(6):1661–7. https://doi.org/10.1210/jcem.82.6.3988.
9. Forcier M, Olson-Kennedy J. Overview of gender development and clinical presentation of gender nonconformity in children and adolescents (version: 18 Oct 2016). 2016. https://www.uptodate.com/contents/gender-development-and-clinical-presentation-of-gender-nonconformity-in-children-and-adolescents. Accessed 8 Feb 2017.

10. Nakamura A, Watanabe M, Sugimoto M, Sako T, Mahmood S, Kaku H, et al. Dose-response analysis of testosterone replacement therapy in patients with female to male gender identity disorder. Endocr J. 2013;60(3):275–81.
11. Dutch SmPC Nebido® 1000 mg/4 ml, oplossing voor injectie. (version date: 8 Jul 2009). 2009. http://db.cbg-meb.nl/IB-teksten/h30794.pdf. Accessed 8 Feb 2017.
12. Prchal JT. Molecular pathogenesis of congenital polycythemic disorders and polycythemia vera (version date: 8 Aug 2016). 2016. https://www.uptodate.com/contents/molecular-pathogenesis-of-congenital-polycythemic-disorders-and-polycythemia-vera. Accessed 15 Feb 2017.
13. Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. Indian J Urol. 2014;30(1):2–7. https://doi.org/10.4103/0970-1591.124197.
14. WHO Global Individual Case Safety Reports database (VigiBase®) (version date: 2 Jul 2017). 2017. https://vigilyze.who-umc.org/. Accessed 4 Jul 2017.
15. Tefferi A. Prognosis and treatment of polycythemia vera (version date: 11 Jul 2016). 2016. https://www.uptodate.com/contents/prognosis-and-treatment-of-polycythemia-vera. Accessed 15 Feb 2017.
16. Jones SD Jr, Dukovac T, Sangkum P, Yafi FA, Hellstrom WJ. Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. Sex Med Rev. 2015;3(2):101–12. https://doi.org/10.1002/smrj.43.
17. McMullin MF, Bareford D, Campbell P, Green AR, Harrison C, Hunt B, et al. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol. 2005;130(2):174–95. https://doi.org/10.1111/j.1365-2141.2005.05535.x.
18. Martinez C, Suissa S, Rietbrock S, Katholing A, Freedman B, Cohen AT, et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. BMJ. 2016;355:i5968. https://doi.org/10.1136/bmj.i5968.
19. Tefferi A. Diagnostic approach to the patient with polycythemia. (version date: 4 Nov 2016). 2016. https://www.uptodate.com/contents/diagnostic-approach-to-the-patient-with-polycythemia. Accessed 8 Feb 2017.