Medical Mycology Case Reports 4 (2014) 23–25

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Voriconazole associated torsades de pointes in two adult patients with haematological malignancies

Jeremy D. Brown [a,*], Lyn-li Lim [a], Sonia Koning [b]

[a] Eastern Health, Department of Infectious Diseases, Nelson Rd., Box Hill, Victoria 3128, Australia
[b] Eastern Health, Department of Pharmacy, Nelson Rd., Box Hill, Victoria 3128, Australia

ARTICLE INFO

Article history:
Received 25 February 2014
Accepted 2 March 2014

Keywords:
Voriconazole
Arrhythmia
Torsades de pointes
QTc

ABSTRACT

Voriconazole can prolong the QT interval contributing to life-threatening cardiac arrhythmia. Torsades de pointes is an uncommon but serious complication of voriconazole use which may be under-recognised. We present torsades de pointes in two patients with underlying haematological malignancy being treated for invasive fungal infection with voriconazole. Patients receiving voriconazole should be screened and monitored for evidence of QT prolongation, and if prolongation detected, consideration given to alternative treatments or more intensive cardiac monitoring.

© 2014 The Authors. International Society for Human and Animal Mycology Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Torsades de pointes (TdP) is a rare, potentially fatal cardiac arrhythmia that is associated with both prolongation and dispersion of the corrected QT (QTc) interval of any cause [1]. The causes of prolonged QTc are protean and include genetic susceptibility, many drugs, electrolyte disturbances, underlying cardiac abnormality and an increased predisposition if female [2]. Voriconazole, approved by the FDA in 2002, is the preferred treatment for invasive aspergillosis, where it confers a survival advantage and has increased tolerability over other antifungal drugs such as amphotericin-based formulations [3,4]. A recognised side-effect of voriconazole is its inhibition of the rapid potassium rectifier channel (I_{Kr}) in the cardiac myocyte that can lead to a pathologically prolonged QTc [5]. In congenital long QT syndrome, a QTc of greater than 500 ms is associated with a higher risk for TdP, with a 7–9% increase in risk for every 10 ms prolongation over this level [6].

Since 2004, there have only been a handful of published reports of voriconazole-induced TdP, three in the adult population and three in the paediatric population, with the first dating back to 2004 [7–12]. Our experience of two adult presentations with voriconazole-associated TdP in one centre adds to the literature for this uncommonly reported event.

2. Cases

2.1. Case 1

A 59 year old Chinese man was admitted (day 0) to commence treatment for natural killer (NK) cell lymphoma: his chemotherapeutic regimen was cyclophosphamide, doxorubicin, etoposide, vincristine and methylprednisolone. He was previously well, with no family history of syncope or sudden cardiac death. A gated cardiac blood pool scan prior to chemotherapy showed a normal left ventricular ejection fraction. An electrocardiograph (ECG) taken six days prior to commencing chemotherapy showed a prolonged QTc interval of 520 ms ($N = < 470$ ms). On day 1, he suffered respiratory distress requiring intensive care support and commenced piperacillin/tazobactam and vancomycin as empirical treatment for hospital-acquired pneumonia. A high-resolution computer tomogram (CT) of the thorax three days prior had not shown any evidence of infection.

Over the following week the patient's respiratory function improved; however, he developed melena requiring multiple blood transfusions and was commenced on total parenteral nutrition (TPN).

On the ninth day of admission to the intensive care unit (day 10), the patient became suddenly unresponsive. His cardiac rhythm at the time of arrest was TdP (Fig. 1) that degenerated into ventricular fibrillation (VF). The patient was successfully resuscitated with cardiopulmonary massage, adrenaline and external defibrillation. His medications at the time of his arrest included voriconazole 200 mg IV twice a day, piperacillin/tazobactam 4.5 g intravenously (IV) twice a day, vancomycin 1 g IV daily, trimethoprim–sulfamethoxazole 180 mg/400 mg three times orally per week, frusemide 60 mg IV four times

* Corresponding author. Present address: Centre for Infectious Diseases and Microbiology, Westmead Hospital, Darcy Rd., Sydney, NSW 2148, Australia. Tel.: +61 2 9845 6065; fax: +61 2 9893 8659.
E-mail address: jeremy.brown@health.nsw.gov.au (J.D. Brown).

http://dx.doi.org/10.1016/j.mmcr.2014.03.001
2211-7539/© 2014 The Authors. International Society for Human and Animal Mycology Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

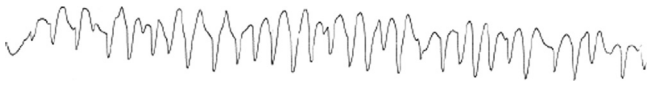

Fig. 1. Torsades de pointes in patient 1.

Table 1
Biochemistry and haemotology of patients 1 and 2.

	Patient 1	Patient 2	Normal
Potassium	3.8	3.5	3.5–5.0 mmol/L
Magnesium	1.00	0.64	0.65–1.05 mmol/L
Corrected calcium	2.23	2.39	2.10–2.60 mmol/L
Creatinine	430	67	40–90 mmol/L (F) 50–110 mmol/L (M)
Gamma glutamyl-transpeptidasse	257	548	10–71 IU/L
Haemoglobin	77	99	120–150 g/L (F) 130–170 L (M)

a day, prednisolone 7.5 mg orally daily, pantoprazole 40 mg IV daily, filgrastim 300 μg subcutaneous daily and tranexamic acid 500 mg orally daily. His relevant blood test results at the time of arrest are shown in Table 1. An ECG performed soon after recovery from cardiac arrest showed a prolonged QTc interval of 579 ms ($N = < 450$ ms).

Voriconazole was ceased and not replaced with another antifungal, and electrolyte disturbances were corrected. There were no further episodes of TdP. With respect to antifungal prophylaxis, non-azole based treatment was used without incident.

2.2. Case 2

A 54 year old woman with relapsed diffuse large B-cell lymphoma with cerebral involvement, treated with intrathecal methotrexate, cytarabine and hydrocortisone, was admitted with febrile neutropaenia (day 0). On day 23 she collapsed and was found to be in ventricular fibrillation. Two episodes of TdP were documented on the following day in the intensive care unit, and the collapse is assumed to represent an episode of TdP that degenerated into VF. The patient had a pre-treatment QTc interval of 405 ms ($N \leq 480$ ms) but had no ECG recorded in the time before her arrest. A post-arrest ECG showed a significantly prolonged QTc of 533 ms. Her antifungal therapy was switched to liposomal amphotericin and a convalescent ECG showed a normalised QTc of 423 ms. The patient made a full recovery from this episode.

At the time of her arrest, the patient's medications included voriconazole 200 mg IV twice daily and caspofungin 50 mg IV daily, for presumed hepatic fungal abscess. She was also prescribed prednisolone 15 mg orally daily and metoclopramide 10 mg orally or intravenously three times a day. She was receiving TPN, had recurrent episodes of hypokalaemia and hypomagnesaemia and had biochemical evidence of hepatic impairment (see Table 1).

3. Discussion

Voriconazole is a synthetic second generation triazole and an effective drug for invasive mycoses, including aspergillosis, that has supplanted amphotericin-based formulations in the management of these life-threatening infections of the immunosuppressed [3,4]. Ketoconazole, an imidazole released in the 1980s, was first associated with TdP in 1990 [13]. The first generation triazoles (itraconazole and fluconazole) were approved for use in the 1990s and several cases of TdP have been reported since, both in combination with other QT interval prolonging agents and without [14]. A 5-year evaluation of the US FDA Adverse Event Reporting System database retrieved 75 cases of triazole antifungals associated with TdP [15], where fluconazole was the most commonly reported agent ($n=47$), followed by voriconazole ($n=17$), itraconazole ($n=8$) and posaconazole ($n=3$), however, many of these cases involved other concomitant QT interval prolonging drugs or were duplicated reports.

Voriconazole was first identified in 2004 as the likely cause of TdP in a paediatric patient [7]. Since then, there have been five further reports (three in adults) of voriconazole contributing to TdP, with no deaths [7–12]. In all cases, including both described here, patients had additional risk factors for TdP.

Risk factors in prolonged QTc are additive and frequently cluster in cases of TdP [14,17] and strongly suggest the need for careful monitoring with baseline and post-treatment ECGs when instituting voriconazole therapy in patients with haematological malignancy. Half of the previously reported cases of voriconazole-related TdP, and both cases presented herein, involved recent chemotherapy for haematological malignancy. Anthracycline-based chemotherapy, in particular, is recognised to both prolong the QT and cause QT dispersion [8]. Furthermore, patients undergoing chemotherapy have an increased risk of receiving other QT interval-prolonging agents such as anti-emetics including $5HT_3$ antagonists or haloperidol, selective serotonin re-uptake inhibitors, other antimicrobials and diuretics [16]. These patients are also at increased risk for the pro-arrythmic electrolyte disturbances due to drugs, altered oral intake, vomiting and diarrhoea. Typically, at the time of our first patient's episode of TdP, multiple risk factors for QTc prolongation, and therefore TdP were identified including voriconazole, baseline QT prolongation that may represent a genetic tendency, TPN, multi-organ failure and electrolyte imbalance.

Patients' concomitant medications should also be carefully reviewed with respect to the mode of drug delivery. Intravenous route of administration of QTc prolonging drugs is hypothesised to predispose to TdP through multiple mechanisms, including a higher peak concentration and a more rapid rise to peak concentration [6]. Of previously published case reports of TdP attributed partially to voriconazole, two-thirds were receiving the drug intravenously [7–12].

It has also been hypothesised that metabolism of voriconazole by the cytochrome P450 pathway isoenzyme CYP2C19 (as well as CYP2C9 and CYP3A4) is subject to significant inter-individual efficacy variation, with 15–20% of people of Asian extraction displaying a poor-metaboliser phenotype that can lead to increased drug levels, and therefore increased risk of dose-dependent side-effects, such as QTC prolongation [18].

Monitoring of voriconazole levels to guide therapy has been variably shown to reduce the commonly encountered non-cardiac adverse effects of voriconazole [15,19,20] but has not been proven to reduce the less common cardiac adverse reactions; however, I_{Kr} channel inhibition is a dose-dependent effect [2]. In both our cases, re-challenge of voriconazole was not conducted due to risk of further TdP. Currently, there are no consensus recommendations about re-initiation of voriconazole or other azole antifungals in patients who have developed cardiac adverse reactions. In the previously described cases, voriconazole therapy was re-introduced in four of the reported six TdP cases with two cases of persistent QTc prolongation [7,10], one case without incident [8] and one case resulting in repeat TdP [12].

4. Conclusion

TdP engendered by QTc prolongation is thought to be a rare complication of voriconazole therapy. However, two cases at our centre has raised our awareness of this potentially life-threatening condition and highlighted the need for a careful arrhythmia risk-assessment of patients commencing voriconazole therapy. The dearth of published case reports raises the possibility that this condition is under-recognised. In patients prescribed voriconazole,

baseline ECG screening should be performed and a review of the patient's concomitant medications and mode of delivery of other drugs that potentially affect QTc. Ongoing intensive monitoring of the QTc interval should be performed in patients that are identified to be at increased risk of prolonged QTc and TdP due to underlying genetic tendency, potential cytochrome polymorphisms, recurrent electrolyte disturbance or drug interactions. Monitoring of serum voriconazole levels has not been clearly demonstrated to reduce the cardiac side-effects of voriconazole.

Conflict of interest statement

All authors declare there are no conflicts of interest.

References

[1] Cubeddu LX. Iatrogenic QT abnormalities and fatal arrhythmias: mechanisms and clinical significance. Curr Cardiol Rev 2009;5:166–76.
[2] Tamargo J. Drug-induced Torsade de pointes: from molecular biology to bedside. Jpn J Pharmacol 2000;83:1–19.
[3] Herbrecht R, Denning DW, Patterson TF, Bennett JE, Oestmann JW, Kern WV, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–15.
[4] Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. Pediatr Infect Dis J 2002;21:240–8.
[5] Owens CR, Nolin TD. Antimicrobial-associated QT interval prolongation. Clin Infect Dis 2006;43:1603–11.
[6] Drew BJ, Ackerman MJ, Funk M, Gibler B, Kligfield P, Philippides GJ, et al. Prevention of torsades de pointed in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010;121:1047–60.
[7] Alkan Y, Haefeli WE, Burhenne J, Stein J, Yaniv I, Shalit I. Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration dependent adverse effect. Clin Infect Dis 2004;39:e49–52.
[8] Philips JA, Marty FM, Stone RM, Koplan BA, Katz JT, Baden LR. Torsades de pointes associated with voriconazole use. Transpl Infect Dis 2007;9:33–6.
[9] Eiden C, Peyriere H, Tichitt R, Cociglio M, Amedro P, Blayac J, et al. Inherited long QT syndrome revealed by antifungals drug-drug interaction. J Clin Pharm Ther 2007;31:321–4.
[10] Prosser JM, Mills A, Rhim ES, Perrone J. Torsade de pointes caused by polypharmacy and substance abuse in a patient with human immunodeficiency virus. Int J Emerg Med 2008;1:217–20.
[11] Aypar E, Kendirli T, Tutar E, Çiftçi E, Ince E, Ileri T, et al. Voriconazole-induced QT interval prolongation and torsades de pointes. Pediatr Int 2011;53:761–3.
[12] Elbey MA, Cil H, Onturk E, Islamoglu Y. QTc prolongation and torsades de pointes ventricular tachycardia in a small dose voriconazole therapy. Eur Rev Med Pharm Sci 2012;16:100–2.
[13] Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. J Am Med Assoc 1990;264:2788–90.
[14] Justo D, Zeltser D. Torsades de Pointes induced by systemic antifungal agents: lessons from a retrospective analysis of published case reports. Mycoses 2006;49:463–70.
[15] Poluzzi E, Raschi E, Motola, Moretti U, De Ponti F. Antimicrobials and the Risk of Torsades de Pointes. Drug Saf 2010;33(4):303–14.
[16] Becker TK, Yeung SJ. Drug-induced QT interval prolongation in cancer patients. Oncol Rev 2010;4:223–32.
[17] Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine (Baltimore) 2003;82(4):282–90.
[18] Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. Drugs 2007;67(2):269–98.
[19] Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 2008;46:201–11.
[20] Park WB, Kim N, Kim K, Lee SH, Nam W, Yoon SH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomised controlled trial. Clin Infect Dis 2012;55:1080–7.