REGULAR ARTICLE

Voriconazole-induced QTc prolongation in a paediatric population

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ABSTRACT

Aim: To evaluate Corrected QT (QTc) interval prolongation (QTcP) in paediatric patients treated with voriconazole (VRC) and identify its associated risk factors in this setting.

Methods: Clinical, VRC-related and QTc interval data were collected retrospectively from the electronic medical records of VRC-treated paediatric patients attending a large tertiary medical centre in 2011–2016 who underwent electrocardiography before and during therapy. Paired comparison of QTc intervals before and during VRC treatment was performed, adjusted for concurrent medications, electrolyte disturbances and co-morbidities.

Results: Fifty-five patients (mean age 10.1 ± 5.4 years) met the inclusion criteria; 34 had an oncologic or hemato-oncologic diagnosis. Mean QTc interval was 402.8 ± 27.9 msec before VRC treatment and 440.0 ± 45.3 msec on treatment ($p < 0.001$). During treatment, 38 patients (61.8%) had QTcP ≥30 msec and 17 (30.9%), QTc ≥60 msec; 10 patients (18.2%) had QTc ≥500 msec of whom one acquired torsades de pointes. On multivariate analysis, older age ($p = 0.025$), lower potassium level ($p = 0.025$) and longer baseline QTc (0.032) were associated QTcP ≥60 msec, but not daily or cumulative dose of VRC.

Conclusion: This study demonstrated a high rate of clinically significant QTcP in VRC-treated children. Proper QTc monitoring, together with laboratory monitoring and electrolyte imbalance correction, is important to prevent cardiac arrhythmias in this patient population.

INTRODUCTION

Owing to pharmacokinetic and pharmacodynamic differences among neonates, children and adults, medications should be evaluated for efficacy and safety for each age group. The need for drug development programs that include paediatric studies (when paediatric use is anticipated) was partially addressed by the US Pediatric Research Equity Act (1) which requires companies to assess new drugs/biologics in children. In addition, the Best Pharmaceuticals for Children Act (2) provides a financial incentive to companies to voluntarily conduct paediatric studies. Nevertheless, in most cases, paediatric practitioners are left with the choice of not administering potentially beneficial medications to children because they have not been evaluated and approved for paediatric use or treating children on the basis of adult studies with medications for which there is limited or no paediatric experience. The latter option is further complicated when drugs proven to be beneficial for children carry a risk of potentially life-threatening events that have been investigated only in adults.

Voriconazole (VRC) is an extended-spectrum triazole antifungal that was approved by the US Federal Drug Administration and the European Medicines Agency in 2002 and is increasingly being used in paediatric patients (3–6). The most concerning adverse event associated with

Abbreviations

ECG, Electrocardiogram; QTc, Corrected QT; QTcP, QTc interval prolongation; TdP, Torsades de pointes; VRC, Voriconazole.

Key notes

- The most concerning adverse event associated with voriconazole treatment is corrected QT (QTc) prolongation which can lead to life-threatening cardiac arrhythmias.
- This study demonstrates a high rate of clinically significant QTc interval prolongation (QTcP) in voriconazole-treated children.
- Proper QTc monitoring, together with laboratory monitoring and electrolyte imbalance correction, is important to prevent cardiac arrhythmias in this patient population.

VRC is QTc prolongation (QTcP) which can lead to torsades de pointes (TdP), ventricular fibrillation and sudden death (7–9). Most of the data on VRC-induced QTcP and TdP are derived from adult studies. Only three case reports have linked QTcP events to VRC treatment in children (10,11). The FDA Adverse Event Reporting System database for pharmacovigilance contains only five reports of VRC-induced QTcP and four reports of VRC-induced TdP in children (age <18 years) (12).

We recently investigated rates of VRC-induced QTcP in adult patients with hemato-oncologic diseases (13). Prompted by the reported differences between children and adults in both VRC pharmacokinetics/pharmacodymaics and the cardiac conduction system, in the present study we sought to evaluate QTc interval changes in paediatric patients treated with VRC and to identify potential risk factors associated with significant QTc changes in this setting.

PATIENTS AND METHODS
Design
A retrospective study was conducted at a large paediatric tertiary medical centre assessing intra-patient changes in QTc interval from before (baseline) to during VRC treatment. The study was approved by the institutional review board.

Cohort definition and data extraction
The protocol of Schneider Children's Medical Center of Israel requires electrocardiogram (ECG) monitoring of all patients treated with VRC regardless of other risk factors. For the present study, we reviewed the medical records of all VRC-treated patients hospitalised in our centre between January 2011 and May 2016 for whom a documented baseline ECG (within four months prior to VRC initiation) and a second ECG while on VRC treatment (at least 48 hours after treatment initiation) were available. For each patient, we recorded age and sex, co-morbidities (malignancies, bone marrow transplantation, etc.), laboratory variables (serum creatinine, sodium, potassium, magnesium and calcium) and medications administered prior to and during VRC treatment (loop diuretics, thiazides, potassium-sparing diuretics, β blockers, calcium channel blockers, antiarrhythmics, proton pump inhibitors, anti-platelet aggregation medications, anticoagulants, glucocorticoids, immunosuppressants such as cyclosporine, cyclophosphamide, tacrolimus, and azathioprine, antimicrobials such as β-lactams, β-lactamase inhibitors, cephalosporins, macrolides, fluoroquinolones, metronidazole and vancomycin, in addition to acyclovir, ganciclovir, antipsychotics and selective serotonin reuptake inhibitors.) VRC-related variables included the initial and maximal daily dose as well as treatment duration. We also recorded cytotoxic treatments administered during VRC treatment, within five days preceding the second ECG. The follow-up period was defined as the number of days from initiation of treatment to the second ECG.

Outcome measures
QTc interval was calculated manually for each ECG using the Bazett formula, $QTc = QT/RR^{0.5}$, which reflects common practice in paediatric patients. Three thresholds were selected to define QTcP based on the guidelines of the International Conference on Harmonisation (14): absolute QTc ≥500 msec; QTc interval prolongation ≥30 msec from baseline; QTc interval prolongation ≥60 msec from baseline. When several ECG recordings before or during VRC treatment were available for one patient, we used the longest QTc interval for analysis.

Data analysis
Patient characteristics are presented as mean ± standard deviation (SD) for continuous variables and proportions for ordinal variables. QTc intervals prior to and during VRC therapy were compared using paired *t*-test. Univariate analysis was employed to determine the association between different variables and prolonged QTc, defined either as an absolute QTc interval of ≥500 msec on VRC therapy or QTcP of ≥60 msec from baseline. Multiple linear regression analysis was used to determine the relative effect of patient-related and VRC-related variables on QTcP ≥60 msec. All analyses were two-tailed, and a p value of <0.05 was considered significant. Statistical analyses were generated using SPSS software, version 21 (IBM®, SPSS® Inc., Chicago, IL).

RESULTS
Study cohort
Of 151 children who were treated with VRC at Schneider Children's Medical Center of Israel during the study period, 96 were excluded from the study because of missing ECG recordings before or during VRC therapy. The remaining 55 children comprised the study cohort. There were 29 female patients (52.8%) and 26 male patients of mean age 10.1 ± 1.4 years at VRC initiation. Thirty-four (61.8%) had an oncologic or hemato-oncologic diagnosis.

VRC-related variables
The mean daily dose of VRC was 12 ± 6.7 mg/kg, and the mean maximal daily dose was 13.4 mg/kg/day (95% CI 11.6–15.2). During VRC treatment, the mean estimated glomerular filtration rate was 155.8 ± 60.2 mL/min. The median duration of follow-up was 55 days (range 2–191).

QTc-related variables
The mean QTc interval was 402.8 ± 27.9 msec before VRC initiation and 440.0 ± 45.3 msec during VRC treatment (p < 0.001). QTcP ≥30 msec was recorded in eight patients (61.8%), and QTcP ≥60 msec was recorded in 17 patients (30.9%). There was no difference in mean VRC initial daily dose/kg and maximal daily dose/kg between patients with QTcP ≥60 msec and QTcP <60 msec (p = 0.33 and 0.21, respectively; Table 1). An absolute QTc value of ≥500 msec was documented in 10 children

(18.2%), all of whom had QTcP ≥60 msec (range 70–130 msec). None of these 10 patients had an abnormal baseline QTc interval, and only one patient had a baseline QTc of ≥450 msec (460 msec). There was no difference in mean VRC initial and maximal daily dose/kg between patients with QTc ≥500 msec and QTc <500 msec (p = 0.33 and 0.54, respectively; Table 1).

TdP developed in one 14-year-old girl on the third day of VRC treatment. Her baseline QTc of 420 msec was prolonged to 520 msec on the day of the TdP event, and she was transferred to the paediatric intensive care unit. Successful defibrillation led to her full recovery. There were no cases of death due to arrhythmia in any of the children during the study period.

Use of other QTc-producing medications

Concomitant use of other QTc-prolonging medications according to the Arizona Center for Education and Research on Therapeutics classification before and during VRC treatment was recorded in 30 patients (54%). The median number of QTc-prolonging drugs in both the QTc <500 msec and QTc ≥500 msec groups was 1 (IQR 0–1.25 and 0–1, respectively).

There were no significant differences in the number of QTc-prolonging medications during VRC treatment between patients with QTcP ≥60 msec and QTcP <60 msec, (64.7% vs. 50.0%, p = 0.31) nor between patients with QTc ≥500 msec and QTc <500 msec (51.1% vs. 70%, p = 0.29). Of note, only four children were treated with cytotoxic drugs (cytarabine, mitoxantrone, vincristine, idarubicin and tretinoin) within five days preceding the second ECG.

Risk factors of significant QTc change

On univariate analysis, low potassium concentrations were associated with QTcP ≥60 msec (p = 0.007). Mean serum calcium and magnesium levels did not differ between patients with QTcP ≥60 msec or QTcP <60 msec (Table 1). Multivariate linear regression with delta QTc (from before to during VRC treatment) as a continuous variable demonstrated a significant association with QTcP of older age (p = 0.025), lower potassium level (p = 0.025) and longer baseline QTc (p = 0.032). Multivariate logistic regression analysis demonstrated that older age and lower potassium level were significantly associated with QTc ≥500 msec (p = 0.05 and 0.03, respectively). VRC daily dose, co-morbidities or concurrent medications had no significant effect.

DISCUSSION

Drug-induced QT prolongation predisposes patients to life-threatening arrhythmias such as TdP (9). As for many other drugs commonly used in paediatric patients, VRC safety data in children are mainly extrapolated from adult studies. This is the first study assessing the prevalence and clinical characteristics of prolonged QTc in children treated with VRC. We found a QTcP of ≥60 msec in 17/54 children (30.9%) in our cohort, and QTc reached ≥500 msec in 10 of them (8.2%), including one child with TdP. These findings are in line with the 43% rate of QTcP ≥30 msec and the 28% rate of QTcP ≥60 msec reported in our recent study of VRC-treated adult patients (13).

As described in previous studies, QTc ≥500 msec is the threshold above which the risk of TdP grows exponentially, thus is the most important risk factor for life-threatening TdP

Table 1 Univariate analysis of patient characteristics by QTc interval change during VRC treatment

Variable	QTcP <60 msec	QTcP ≥60 msec	p value	QTc <500 msec	QTc ≥500 msec	p value
Demographics						
Female/total	21/38 (55.3)	8/17 (47.1)	0.57	24/45 (53.3)	5/10 (50)	0.84
Age (years)	9.2 ± 5.4	11.9 ± 5.1	0.33	9.2 ± 5.5	13.9 ± 2.7	0.1
Arrhythmogenic drugs						
Antibiotics*	18 (47.4)	10 (58.8)	0.43	22 (48.9)	7 (70)	0.52
Antipsychotics/SSRIs†	4 (10.5)	4 (23.5)	0.2	5 (11.1)	3 (30)	0.12
Tacrolimus	2 (5.3)	2 (11.8)	0.39	4 (8.9)	0 (0)	0.32
Laboratory analysis						
Serum potassium (mmol/L)	4.16 ± 0.5	3.76 ± 0.6	0.007	4.14 ± 0.6	3.57 ± 0.4	0.007
Serum magnesium	1.88 ± 0.3	1.87 ± 0.2	1	1.87 ± 0.2	1.87 ± 0.1	1.0
Serum calcium (mg/dL)	8.94 ± 0.6	8.71 ± 0.6	0.17	8.93 ± 0.5	8.58 ± 0.6	0.17
eGFR (mL/min)	159 ± 62	146 ± 55	0.64	156 ± 65	153 ± 29	0.61
VRC-related						
Initial daily dose (mg/day)	12.7 ± 7.3	10.55 ± 5.0	0.33	12.7 ± 7.1	9.3 ± 3.4	0.33
Maximal daily dose (mg/day)	14.2 ± 7.5	11.6 ± 5.0	0.21	14.1 ± 7.2	10.2 ± 4.1	0.54
Baseline QTc ≥450 msec	1 (2.6)	1 (5.9)	0.55	1 (2.2)	1 (10)	0.33

eGFR = Estimated glomerular filtration rate; QTcP = QTc interval prolongation; SSRIs = Selective serotonin reuptake inhibitors; VRC = Voriconazole.
Values are presented as n (%) or mean ± SD.
*Antibiotics included only quinolones and co-trimetoxazole, agents known to prolong QTc independent of electrolyte imbalance. Agents used by less than 2% of the study population were not included.
†Other medications known to increase QTc interval independent of electrolyte imbalance used by 2% or more of the study population.

(15–17). To the best of our knowledge, our study is the first to describe the rate of QTcP in a cohort of voriconazle-treated paediatric patients demonstrates strikingly high rate of QTc ≥500 in comparison with the rate of this adverse event in previous reports (8,13). This finding highlights the importance of routine ECG monitoring prior to initiation and during VRC treatment. Moreover, it presents a clinical dilemma with respect to the optimal approach in attempt to balance benefits versus risks of VRC treatment in these patients. Our local practice in these cases is to perform risk assessment including correction of electrolyte abnormalities, a comprehensive review of the patients' medication list, withdrawal of unnecessary QTc-prolonging agents and if possible – switch VRC treatment to another antifungal agent.

There were no differences in VRC-related variables (daily dose and length of treatment) between patients with QTcP ≥60 msec and QTcP <60 msec or between patients with QTc ≥500 msec and QTc <500 msec. Furthermore, on multivariate analysis, QTc ≥500 msec was associated only with low serum potassium level and older age; QTcP ≥60 msec was also associated with longer baseline QTc.

According to the Arizona Center for Education and Research on Therapeutics, most antifungal azole agents including VRC are categorised as posing a conditional risk of QTcP triggered by electrolyte disturbances, increased dose, a drug–drug interaction or decreased metabolism (2). VRC is a broad-spectrum agent indicated mainly for invasive fungal diseases affecting immune-compromised patients with a complicated disease course who are often on multiple drug therapies. Indeed, 54% of the patients in our cohort were being treated concurrently with other QTc-prolonging medications (among others). Thus, VRC should be investigated in the context of polypharmacy.

In the present cohort, 38% of the children did not have an oncologic disease, and there was no difference in the rate of QTcP ≥60 msec between the oncology and non-oncology patients (30% and 33%, respectively). Nevertheless, 9 of the 10 children with QTc ≥500 msec during therapy had an underlying malignancy. This finding may be explained by the complex clinical course of oncologic diseases and treatments which predispose patients to various complications such as chemotherapy-induced diarrhoea and electrolyte imbalances. Indeed, low potassium levels in our cohort were associated both with QTcP ≥60 msec and QTc ≥500 msec. It is noteworthy that only one of the nine oncology patients with QTc ≥500 msec received cytotoxic therapy (high-dose cytarabine) within five days preceding the second ECG (demonstrating the prolonged QTc).

Another important finding of this study is the low rate of adequate ECG monitoring in the VRC-treated children. In about two-thirds of cases, there was no documentation of ECG monitoring before or during VRC therapy in the electronic medical records. The need to adhere to routine monitoring in children under polytherapy including VRC is emphasised by the high rate of QTcP in our cohort.

Our study has several limitations:

Given its retrospective design, we defined a four-month period prior to VRC initiation as the period which reflects the patient's baseline ECG. While this relatively long period may allow intra-patient variability in QTc, we acknowledge that it may not be the ideal baseline value. However, in order to minimise this variability we accounted for concurrent drug treatments, relevant electrolytes concentrations and renal function.

The pharmacokinetic profile of VRC carries large inter- and intra-individual variability, and routine therapeutic drug monitoring is now the standard of care as it has proved to improve efficacy and minimise toxicity. Owing to technical considerations, we could not collect data on VRC blood concentrations. The relatively small sample size might partially account for the lack of a statistically significant effect of VRC-related factors on QTcP.

CONCLUSION

This study demonstrates that QTcP is a clinically significant, relatively common and often overlooked adverse effect of VRC treatment in the paediatric population and could lead to life-threatening arrhythmias. We found that the main risk factors for QTcP were low baseline potassium level and older age. Proper ECG monitoring, in addition to laboratory monitoring and aggressive correction of electrolyte imbalances (most specifically hypokalemia), is an important safety measure in this setting.

FUNDING

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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