*Cardiology in the Young*

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# The effect of antipsychotic medications on QTc and delirium in paediatric cardiac patients with ICU delirium

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## Original Article

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## Abstract

*Objective:* Children with prolonged hospital admissions for CHD often develop delirium. Antipsychotic medications (APMs) have been used to treat delirium but are known to prolong the QTc duration. There is concern for prolongation of the QTc interval in cardiac patients who may be more vulnerable to electrocardiogram (ECG) changes and may have postoperative QTc prolongation already. The goal of this study was to determine the effect of APM on QTc duration in postoperative paediatric cardiac patients and determine the effect of quetiapine and risperidone in treating delirium and QTc prolongation. *Design:* Retrospective study, July 1, 2017–May 31, 2022. *Setting:* Tertiary children's hospital. *Patients:* Included were patients admitted to the paediatric cardiac ICU at Children's Healthcare of Atlanta. *Interventions:* None. *Measurements and Main Results:* ECGs, delirium scores, and drug information were collected. Delirium was defined as Cornell Assessment of Pediatric Delirium (CAPD) score >9. Mixed effect models were performed to evaluate the effect of surgery on QTc change and the effect of antipsychotics on QTc and CAPD changes. There were 139 children, 55% male and 67% surgical admissions. Median age was 5.9 months. Mean QTc increased after cardiac surgery by 18 ms ($p = 0.014$, 95% CI 3.65–32.4). There was no significant change in QTc after antipsychotic administration ($p = 0.064$). The mean CAPD score decreased (12.5–7.2; $p < 0.001$). Quetiapine had the most improvement in delirium, and risperidone had the least improvement (77.8%, $n = 14$; 37.8%, $n = 34$, respectively; $p = 0.002$). *Conclusions:* The QTc interval did not have a statistically significant change after the administration of antipsychotics, while there was improvement in the CAPD score. APMs may be administered safely without significant prolongation of the QTc and are an effective treatment for delirium.

Delirium is acute cerebral dysfunction resulting in fluctuating cognitive function, behaviour, and awareness.[1–4] Risk factors for delirium include a prolonged stay in the ICU, prolonged duration of mechanical ventilation, and increased sedative medication doses.[3–5] Approximately 25% of children admitted to paediatric ICU and 50% of postoperative cardiac surgery patients have delirium.[4,6,7] Studies have shown that patients with delirium have worse outcomes after cardiac surgery with increased morbidity and mortality.[6] The Cornell Assessment of Pediatric Delirium (CAPD) scoring system is used to screen delirium in critically ill children and validated in all paediatric ages for both verbal and non-verbal children.[8]

The treatment of delirium often includes the unapproved use of Food and Drug Administration-approved drugs, also known as "off-label" use. After initial non-pharmacologic interventions to treat delirium, antipsychotic medications (APMs) such as risperidone and quetiapine are commonly used. Previous paediatric studies have suggested these medications are safe for use with low rates of adverse effects.[9–11] The documented adverse effects of these medications include the risk of QTc prolongation which can precipitate Torsade de pointe and ventricular tachycardia.[10] The objective of this study was to determine the effect of APM on QTc duration in children with CHD and the effect of APMs on CAPD scores.

## Methods

### Data sources and patient population

This is a retrospective single-centre study performed at the paediatric cardiac ICU (CICU) at Children's Healthcare of Atlanta (CHOA), a large paediatric tertiary cardiac referral centre in the Southeast United States for children with CHD. This study was approved by the CHOA

Institutional Review Board (IRB # STUDY00000519) with a waiver of informed consent. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Included in this study were any patients, 0–21 years old, admitted between July 1, 2017, and May 31, 2022, to the CICU for either a medical or surgical admission and received APMs during their hospitalisation. Excluded were patients already receiving APMs prior to admission, patients receiving antiarrhythmic medications while on APMs during their hospitalisation, or patients receiving medications known to cause QTc prolongation.[12]

Electrocardiograms (ECGs) were collected prior to surgery, immediately after surgery, prior to APMs, and after the end of treatment with APMs. For surgical patients, ECGs obtained post-operatively served as their baseline ECG prior to antipsychotics. Clinically significant prolonged QTc was defined as a QTc > 480 ms for both males and females and calculated with the Bazett method retrospectively.[13,14]

The CAPD score was used to screen for delirium by nursing staff every 12 hours and is used as part of the treatment protocol in the CICU as part of the standard of care. Delirium was defined as CAPD score >9. If a patient is noted to have a score >9, staff evaluated the patient for common causes of delirium and promoted environmental measures. If the score continued >9 at the next reassessment and no medication withdrawal was noted, patients were then administered risperidone or quetiapine. Medication choice was made according to the preference of the attending physician and dosed per the practice guideline (Supplemental Table 1). To evaluate the effectiveness of APM on CAPD, baseline CAPD was defined as the CAPD score 24 hours before the initiation of APM and compared to the last CAPD recorded when APMs were discontinued or at day 7, whichever came first.

To summarise patient demographic distribution, descriptive statistics were reported using median, mean, and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. Wilcoxon sum rank test, Chi-square test, and Fisher's exact test were used to compare differences between types of APMs taken. To assess the effect of surgery and APMs on QTc change and/or CAPD score change, mixed effect models were performed to account for patient variability. A $p < 0.05$ was considered statistically significant. Analyses were performed using R and RStudio software (4.3.1).

## Results

There were 139 patients that met inclusion criteria, 76 (55%) male and 54 (47%) female. There were 93 (67%) surgical and 46 (33%) medical admissions. Median age was 5.8 months old (IQR 1.6–93.7). Of the 139 total patients, 115 received risperidone and 24 received quetiapine. The median time to start APMs was 14 days (6–41 days), duration on quetiapine was 2 days (1–4 days), and risperidone was 5 days (2–19 days). There were no arrhythmias associated with the use of APMs among the study population (Table 1).

Pre-operatively, the mean QTc was 437 ms (IQR 426–449 ms). Post-operatively, the mean QTc was 455 ms (IQR 446–465 ms) with a mean difference of 18 ms (4–32 ms), $p = 0.014$. Overall, the mean QTc prior to the initiation of APM but after surgery was 449 ms (443–456 ms). The mean difference was −9 ms (−19–0 ms), $p = 0.064$. When analysing by medication, patients receiving risperidone had a mean QTc of 447 ms (440–455 ms) at baseline and a mean QTc of 437 ms (428–447 ms), a mean difference of −10 ms (−21–2 ms), $p = 0.095$. Among the patients receiving quetiapine, the mean QTc was 458 ms (443–473 ms) prior to starting medications and 447 ms (431–463 ms) at the end of treatment, a mean difference of −11 ms (−32–10 ms), $p = 0.314$. Over time, there was no statistically significant change in QTc by medication (Table 2).

Overall, there were 108 patients with recorded CAPD scores among the 139 who received APMs. At the initiation of APM, the overall mean baseline CAPD score was 12.5 (11.6–13.5). At the time of APM discontinuation, mean CAPD was 7.2 (6.3–8.1), a mean difference of -5.4 (−6.4 to −4.4, $p < 0.001$) (Table 3). By medication, among patients receiving risperidone, the mean CAPD was 12.6 (11.7–13.6), and at the time of discontinuation of risperidone, the mean CAPD was 7.9 (7.0–8.9), a mean difference of −4.7 (−5.8 to −3.7, $p < 0.001$). Among the patients receiving quetiapine, the mean CAPD prior to initiation was 12 (9.8–14.3) and 3.6 (1.5–5.7) at discontinuation, a mean difference of −8.4 (−10.8 to −6, $p < 0.001$) (Fig. 1a). Over time, CAPD decreased after initiating APM with a faster decrease with quetiapine (risperidone slope = −0.03, 95% CI −0.04 to −0.03, $p < 0.001$) (quetiapine slope = −0.06, 95% CI −0.08 to −0.05, $p < 0.001$) (Fig. 1b). When adjusted for patient age, among patients receiving risperidone, CAPD decreased 4.7 points ($p < 0.001$), and among patients receiving quetiapine, CAPD decreased 8.5 points ($p < 0.001$). The changes of CAPD interval from baseline to the end of treatment were significantly different between medications after controlling for age ($p = 0.005$) (Table 4).

Overall, 74 (69%) patients had resolved delirium, 32 (30%) remained with delirium, and 2 (2%) patients with worse delirium scores. By medication, more patients resolved delirium with quetiapine than risperidone (n = 18, 100% vs n = 56, 62%, $p = 0.002$). When adjusting for age, there was no statistically significant difference in resolved delirium and medication ($p = 0.082$) (Table 3). There were no incidences of arrhythmia, Torsade de point, or ventricular tachycardia on interim ECGs, and no patient stopped APMs due to concerns for prolonged QTc.

## Discussion

This study demonstrates that the use of APMs for the treatment of delirium in patients with CHD did not significantly prolong the QTc interval, and there were no arrhythmias among the study population while receiving APMs. APMs were associated with the reduction of CAPD scores, with a faster reduction in patients receiving quetiapine, even after adjusting for age. It was noted that among patients admitted for surgery, the QTc was prolonged post-operatively compared to their pre-operative baseline, before the initiation of APMs.

Prolongation of the QTc interval may be due to the inhibition of delayed potassium rectifier channel (Ikr) which is responsible for repolarisation of ventricular myocytes.[15,16] Animal models of APMs on the gene coding for Ikr has been used in drug development and has demonstrated that antipsychotics, at therapeutic levels, may prolong the QTc interval. In vivo studies have shown that the use of APMs was safe with low rates of adverse effects with an increased risk of QTc prolongation.[11,17] APMs have been shown to increase the risk of sudden death among adults.[18] However, serious adverse effects such as arrhythmias and QTc prolongation have not been reported in children administered risperidone or quetiapine for the treatment of ICU delirium.[9] Similar to our study, risperidone has been shown to be administered safely without any effect on QTc in the acute treatment of paediatric patients.[19] A similar study investigating the use of APMs in treating paediatric ICU delirium found risperidone and quetiapine

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**Table 1.** Patient demographics by medication, N = 139

| Characteristic | Overall, N = 139[1] | Risperidone, N = 115[1] | Quetiapine, N = 24[1] | P value[2] |
|---|---|---|---|---|
| **Age at admission (months)** | 5.8 (1.6, 93.7) | 4.0 (0.5, 15.0) | 174.6 (137.7, 196.7) | <**0.001** |
| **Gender** | | | | 0.209 |
| Female | 63 (45%) | 55 (48%) | 8 (33%) | |
| Male | 76 (55%) | 60 (52%) | 16 (67%) | |
| **Ethnicity** | | | | >0.999 |
| Hispanic/Latino | 10 (7.2%) | 9 (7.8%) | 1 (4.2%) | |
| Not Hispanic/Latino | 129 (93%) | 106 (92%) | 23 (96%) | |
| **Race** | | | | 0.601 |
| White | 67 (48%) | 53 (46%) | 14 (58%) | |
| Black | 54 (39%) | 46 (40%) | 8 (33%) | |
| Other | 18 (13%) | 16 (14%) | 2 (8.3%) | |
| **Admission type** | | | | 0.145 |
| Medical | 46 (33%) | 35 (30%) | 11 (46%) | |
| Surgical | 93 (67%) | 80 (70%) | 13 (54%) | |

[1]Median (IQR); n (%).
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

**Table 2.** QTc interval change

| | LS-mean (95% CI) | LS-mean difference (95% CI) | P value |
|---|---|---|---|
| Prior to surgery | 437.42 (426.20–448.63) | Ref | |
| After surgery | 455.44 (446.01–464.88) | 18.03 (3.65–32.40) | **0.014** |
| Baseline | 449 (443–456) | Ref | 0.064 |
| End of treatment | 440 (432–448) | −9 (−19–0) | |

| | Baseline LS-means (95% CI) | End of treatment LS-means (95% CI) | LS-means post or prior difference (95% CI) | P value |
|---|---|---|---|---|
| Risperidone | 447 (440–455) | 437 (428–447) | −10 (−21–2) | 0.095 |
| Quetiapine | 458 (443–473) | 447 (431–463) | −11 (−32–10) | 0.314 |

**Table 3.** Change in CAPD score, n = 108

| | LS-means (95% CI) | LS-mean difference (95% CI) | P value |
|---|---|---|---|
| CAPD at baseline | 12.5 (11.6–13.5) | Ref | <**0.001** |
| CAPD at the end of treatment | 7.2 (6.3–8.1) | −5.4 (−6.4 to −4.4) | |

| | At baseline LS-means (95% CI) | At the end of treatment LS-means (95% CI) | LS-means post or prior difference (95% CI) | P value |
|---|---|---|---|---|
| Risperidone | 12.6 (11.7–13.6) | 7.9 (7–8.9) | −4.7 (−5.8 to −3.7) | <**0.001** |
| Quetiapine | 12 (9.8–14.3) | 3.6 (1.5–5.7) | −8.4 (−10.8 to −6) | <**0.001** |
| **Controlling for age** | | | | |
| | At baseline LS-means (95% CI) | At the end of treatment LS-means (95% CI) | LS-means post or prior difference (95% CI) | P value |
| Risperidone | 13 (12–14) | 8.2 (7.3–9.2) | −4.7 (−5.8 to −3.7) | <**0.001** |
| Quetiapine | 14.4 (11.2–17.6) | 5.9 (2.8–9) | −8.5 (−10.8 to −6.1) | <**0.001** |

*CAPD interval between baseline and the end of treatment was significantly different by medication (p = 0.006).
**The changes of CAPD interval from baseline to the end of treatment were significantly different between medications after controlling for age (p = 0.005).

to be among the safest antipsychotics administered without significant effects on QTc prolongation.[20] There is some suggestion that dangerous drug-induced QTc prolongation may occur when it co-exists with other risk factors such as heart failure, genetic predisposition, electrolyte imbalance, or organ injury.[21] It is possible that in our population, patients may not

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**Table 4.** Change in delirium, N = 108

| | Overall, n = 108 | Risperidone, n = 90 | Quetiapine, n = 18 | P value* |
|---|---|---|---|---|
| **Resolved (%)** | 74 (69%) | 56 (62%) | 18 (100%) | **0.003** |
| **Continued delirium (%)** | 32 (30%) | 32 (36%) | 0 (0.0%) | |
| **Worse (%)** | 2 (2%) | 2 (2%) | 0 (0.0%) | |
| **Predicted probability for change in delirium, controlling for age, N = 108** | | | | |
| | Risperidone (95% CI) | | Quetiapine (95% CI) | P value⁺ |
| **Change in Delirium** | | | | 0.214 |
| **Resolved (%)** | 89% (76%–96%) | | 11% (4%–24%) | |
| **Continued delirium (%)** | 98% (69%–100%) | | 2% (0%–31%) | |
| **Worse (%)** | 65% (8%–98%) | | 35% (2%–92 %) | |

CAPD = cornell assessment of paediatric delirium.
*Fisher's exact test, ⁺Logistic regression.

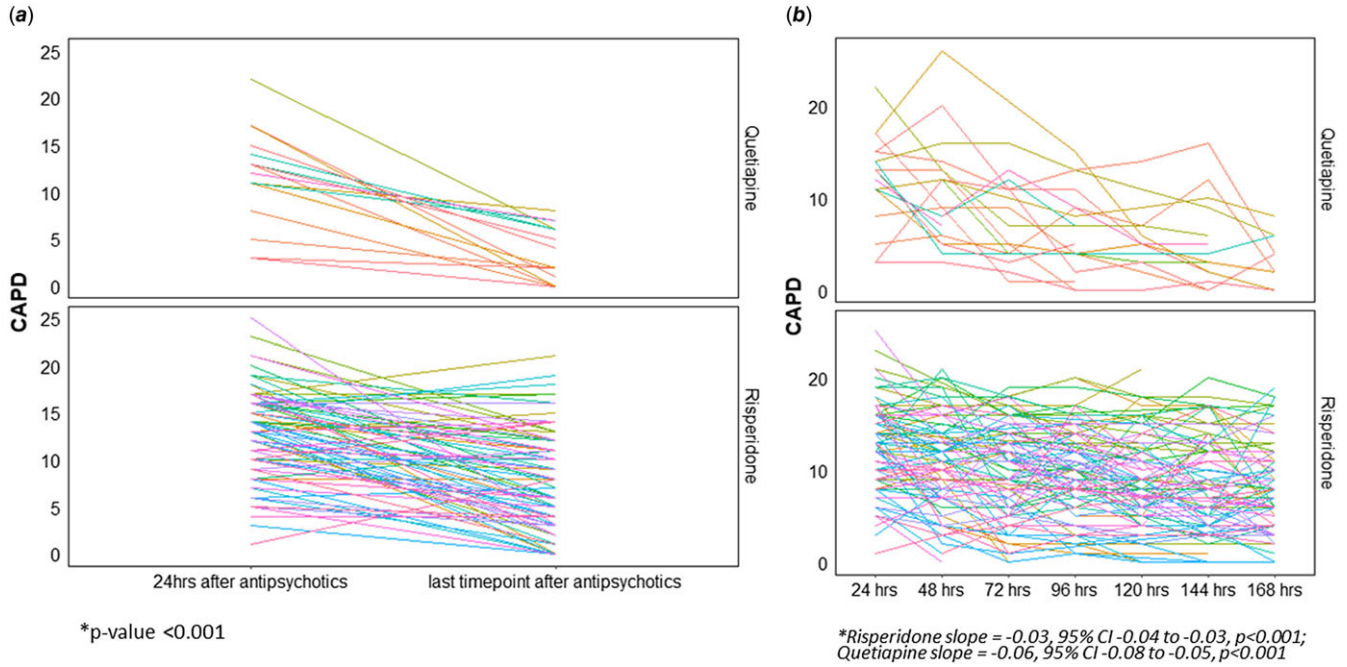


**Figure 1.** ***a***. Change in CAPD by antipsychotic medication. ***b***. Decrease in CAPD by medication over time.

have amassed drug levels to induce prolonged QTc or have been closely monitored for electrolyte disturbances while admitted to the CICU.

Our study showed reduction in CAPD scores with administration of APMs and patients receiving quetiapine having a faster improvement compared to risperidone. While our centre uses atypical APMs risperidone or quetiapine, others commonly use typical APMs such as haloperidol or the atypical APM olanzapine.[22] In two placebo-controlled trials of quetiapine for the treatment of delirium in the adult population, the use of quetiapine resulted in faster delirium resolution.[23,24] It has been proposed via animal studies that the neuroprotective effects of atypical APM for the treatment of delirium are due to improved cellular glucose uptake and make cells more resistant to stress and increase levels of nerve growth factor and brain-derived neurotrophic factor.[25] Our centre created a protocol to address variation in treatment and assist in screening of delirium and made an institutional decision to use risperidone or quetiapine to minimise extrapyramidal symptoms and reduce variation. This has improved the standardisation of medication dosing and limited the use to one of two APMs to improve cost and increase familiarity with the medications.

A secondary aim of our study was to evaluate the influence of cardiac surgery on the QTc interval in this patient population. Similar to our findings, Punn and colleagues demonstrated an association between paediatric cardiac surgery with cardiopulmonary bypass and lengthening of the QTc interval. They showed that longer cross-clamp times may have been a risk factor and that QTc prolongation was a transient phenomenon for most patients.[26] While the mechanism of QTc interval prolongation remains unclear, theories include myocardial ischaemia contributing to altered repolarisation.[26,27]

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### Limitations

Our study was a single-centre, retrospective analysis of APM and QTc prolongation and therefore might be limited in generalisability and scope and limited by the nature of retrospective studies. Although our study showed that more patients receiving quetiapine recovered and had a faster recovery, we are unable to definitively affirm that quetiapine is superior in the treatment of delirium without a randomised control trial. Additionally, we found APMs were safe to use in the CICU setting but are unable to determine the overall safety in lower acuity or unmonitored settings.

## Conclusion

QTc interval was not significantly prolonged with the use of either atypical APM. Secondarily, post-surgical patients did have a significantly prolonged QTc from their pre-operative baseline; however, this was prior to the initiation of APMs. There were no adverse events or arrhythmias associated with the use of APM. Both risperidone and quetiapine were effective in treating ICU delirium as measured by CAPD scores with some indication that quetiapine may be more beneficial. While additional studies are needed to validate the efficacy and safety of APMs in the treatment of paediatric delirium in patients with CHD, it appears safe and effective.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124025162.

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**Competing interests.** None.

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