Drug-Specific Risk of Severe QT Prolongation Following Acute Drug Overdose

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Background: Severe QT prolongation (SQTP) has been identified as a strong predictor of adverse cardiovascular events in acute drug overdose. Research Question: What are the drug-specific causes of SQTP in the setting of acute drug *overdose?*

Methods: This was a prospective cohort study at > 50 hospital sites across the USA using the ToxIC Registry between 2015 and 17. Inclusion criteria were adults (≥ 18 years) receiving medical toxicology consultation for acute (or acute-on-chronic) drug exposures. Cases lacking ECG, known cardiovascular medical history, or laboratory values were excluded. Medical toxicologists provided bedside consultation for each patient and independently reported the primary agent(s) responsible for drug toxicity, which was used for drug-specific QT analysis. The primary outcome was SQTP, which was defined using the previously validated cut point [1] of 500 ms. Drugs associated with SQTP were analyzed with chi-squared, odds ratios (OR) and 95% confidence inter- vals (CI). Assuming 10% drug class exposure and 10% baseline SQTP risk, we calculated the need to enroll 5138 patients to have 90% power to detect 50% increased risk.

Results: From 18,438 patients screened, 5588 met inclusion criteria (49.6% female, mean age 38.9, 66.2% Whites, 13.7% Blacks, 1.8% Asians, 18.3% other/unknown, 9.9% Hispanic) with SQTP occurring in 469 (8.4%). The drug classification with the highest number of SQTP drugs was antidepressants (*n* = 9). The top three drugs with the highest risk of SQTP were imipramine (OR 76.8, CI 4–1500), sotalol (OR 21.9, 4–120), and nortriptyline (OR 12.9, 4–39). Haloperidol (OR 4.2, CI 1.5–12), quetiapine (OR 3.4, 2.4–4.6), and risperidone (OR 2.3, CI 1.0–5.1) were the only three antipsychotics associated with SQTP. Aside from Class III antidysrhythmics, sodium channel blockers, and known potas- sium channel blockers, novel drugs associated with SQTP included cyclobenzaprine (OR 3.6, CI 1.8–7.1), trazodone (OR 2.9, CI 2.0–4.1), clonazepam (OR 1.87, CI 1.1–3.2), and oxycodone (OR 1.8, CI 1.0–3.1). Discussion: SQTP drugs notably did not include lithium, ondansetron, nor olanzapine. Implications for prescribing practices to prevent drug- induced QT prolongation require future study.

Conclusion: In this large US cohort, we have identified high risk drugs associated with SQTP, including novel associations with cyclobenzaprine, oxycodone, clonazepam, and trazodone.