UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

April 2, 2021 Vol. 1, No. 5

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Antiemetic Adverse Drug Reactions: Focus on QTc Prolongation

Background:

Antiemetics fall under several drug classes including: phenothiazines, antihistamines, anticholinergics, benzamides, serotonin antagonists, cannabinoids, benzodiazepines, prokinetics, corticosteroids, butyrophenones, and NK-1 receptor antagonists. Given their different mechanisms of action they target unique etiologies of nausea. We commonly recommend antiemetics in palliative care to improve quality of life for our patients.

Importance:

Most antiemetics, albeit different mechanisms of action, seem to carry *some* risk of QTc prolongation. Clinically significant QTc prolongation has been described as absolute QTc $\geq$ 500 msec, and as QTc $\geq$ 25% from baseline, or change of QTc $\geq$ 60 msec given individual variability.[1] It is important to note that the degree of QTc prolongation is only a modest predictor of the risk of Torsades de Pointes and sudden cardiac death. Still, it is important for palliative care clinicians be aware of this risk of commonly prescribed medications in our practice and other known QTc prolongation risk factors.

Known QTc prolongation risk factors:

- Age $\geq$ 65
- Female
- *Electrolyte imbalances: hypokalemia, hypomagnesemia, hypocalcemia*
  - This risk factor is heightened for those with ongoing emesis (hypoK+)
- Impaired hepatic and/or renal function
- Cardiovascular Disease (CHF, AFib, MI)
- Medications
  - Methadone, Tyrosine Kinase Inhibitors (Crizotinib, Sunitinib, Vemurafenib, Sorafenib, Imatinib), SSRIs, Fluoroquinolones, Amiodarone, Antipsychotics, Antiemetics
  - Drug interactions: inhibition of cytochrome P450 enzyme and subsequent increase in medication plasma levels
    - Antifungals, Macrolide antibiotics, ritonavir, verapamil, St. Johns Wart

The Literature:

J Clin Anesth. 2014 Nov;26(7):511-6.

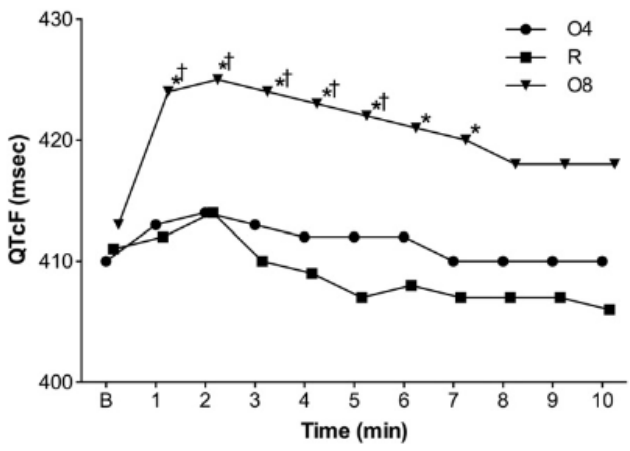
Effects of Prophylactic Ramosetron and Ondansetron on Corrected QT Interval during General Anesthesia

Methods: Prospective, RCT

- 3 groups: ondansetron 4mg IV, ondansetron 8mg IV, ramosetron 0.3mg IV

Results:

- Table below depicts QTc interval after administration of all medications; ondansetron 8mg IV had the highest QTc interval increase



Conclusion:

- QTc prolonging effects seem to be influenced by dose and route of administration

Ann Emerg Med. 2014 Jun;64(1):19-25.

Ondansetron and the risk of Cardiac Arrhythmias: A Systematic Review and Postmarketing Analysis

Methods: Systematic Review

Results:

- No reported arrhythmias that developed after a single oral ondansetron dose
- Adult cases associating ondansetron administration (any dose, frequency, or route) to the development of an arrhythmia
  - 49 adult cases:
    - Literature (n=17)
      - 88% of adult patients had concomitant risk factors such as significant PMH or other known QTc-prolonging medications
      - 70% involved IV administration of ondansetron
    - ADR Registries (n=32)
      - 91% received concomitant other known QTc-prolonging medications
      - 60% involved IV administration of ondansetron

Conclusion:

- Ondansetron may contribute to QTc prolongation when administered intravenously to higher risk patients on other medications known to prolong QTc

CLINICAL PEARL:

Recommend using lowest effective dose of antiemetic possible, and avoid co-administering with other QTc-prolonging medications, factoring in other comorbidities/risk factors.

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The Literature Continued:

AANA J. 2020 Aug;88(4):312-318.

Evidence-based Antiemetic Decision Tool for management of postoperative nausea and vomiting in patients at high risk of QT prolongation and Patients receiving Neurotransmitter-Modulating Medications

Pharmacotherapy Review

Antiemetics (or class)	Risk of QTc Prolongation
Ondansetron^	*** (IV > PO)
Haloperidol+	*** (IV > PO)
Promethazine	*
Prochlorperazine	*
Metoclopramide	*
Fosaprepitant	-
Palonosetron	-
Benzodiazepines	-
Cannabidiols	-
Corticosteroids	-
Anticholinergics	-
Antihistamines	-

^: Ondansetron 4mg IV x1 has been found to increase QTc by 16.2msec[2]

+: will get into antipsychotics in a separate The Tablet edition; highlighting haloperidol here

Bottom Line:

- There is little data to suggest that promethazine, prochlorperazine, and metoclopramide increase QTc as low dose monotherapy, however when given with other QTc prolonging meds, can contribute to QTc prolongation.
- For agents that have QTc prolonging effects, most of the risk is associated with higher doses, and quick IV push administration suggesting a dose dependent/concentration dependent effect
- It is important to be mindful of other QTc prolonging risk factors, as it is unlikely that a single antiemetic agent would produce life-threatening arrhythmia
- For those patients with multiple QTc prolonging risk factors and other QTc-prolonging medications it may make sense to dive into our classes of medications that do NOT prolong QTc, such as steroids, benzos, cannabinoids

References:

1. *Ann Noninvasiv Electrocardiol.*2020;25:e12699.
2. AM J Health-Syst Pharm. 2018;75:276-82.

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