

Piperidine and Piperazine Substructures are a Common Feature of Drugs Labeled for QT Prolongation



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Introduction

- QT Prolongation (QTP) is used as a surrogate for drug-induced Torsade de Pointes (TdP), a serious and usually fatal ventricular arrhythmia.
- QTP occurs across many different drug classes.
- Because TdP tends to be a rare event, it is difficult to confirm without EKG monitoring
- Identifying possible toxicophores associated with QTP could be useful in strengthening safety signals and identifying the need for additional studies.

Hypotheses

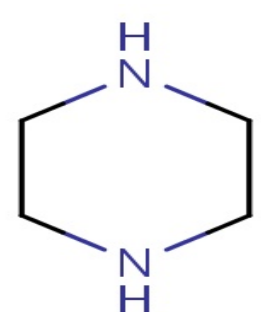
- Structural analyses and similarity searches may identify drugs that warrant additional QTP analyses
- Specifically an analysis of an association of piperidines and piperazines for QTP was done

Methods

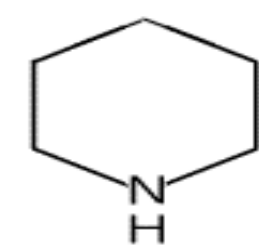
- FDA drug products were searched using natural language processing to identify drugs with QTP in the Warnings and Precautions sections. (Performed August 2013)
- The structural nitrogen containing features of these drugs were reviewed
- A chemical substructure search was performed to identify launched or withdrawn drugs that shared these common structural features (Performed August 2014)

Structures

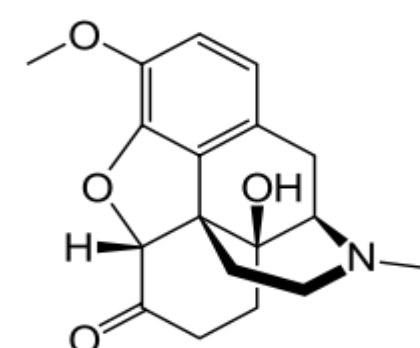
Piperazine



Piperidine



Oxycodone:
N-ring in proximity to aromatic ring



Results

Table 1. Drugs labeled for QTP in Box

| Drug | Piperidine/Piperazine | Other Nitrogen Containing Structures |
|------------------|-----------------------|---|
| Arsenic Trioxide | | |
| Droperidol | Piperidine | Benzimidazole |
| Ibutilide | | Tertiary Amine/Methanesulfonamide |
| Itraconazole | Piperazine | Triazole/Triazolone |
| Ketoconazole | Piperazine | Imidazole |
| Nilotinib | | Imidazole/Pyridine/Pyrimidine/Benzamide |
| Vandetanib | Piperidine | Quinazoline |

Table 2. Drugs labeled for QTP in Warnings and Precautions

| Drug | Piperidine/Piperazine | Other Nitrogen Containing Structures |
|---------------------|-----------------------|--------------------------------------|
| Amiodarone | | Tertiary Amine |
| Azithromycin | | Tertiary Amine in Lactone Ring |
| Bisacodyl | | Pyridine |
| Ciprofloxacin | Piperazine | Quinoline |
| Citalopram | | Tertiary Amine/Carbonitrile |
| Clarithromycin | | Tertiary Amine to 6-member O |
| Clozapine | Piperazine | Diazepine |
| Cyclophosphamide | | Tertiary Amine /Phosphoamine |
| Dasatinib | Piperazine | Thiazole/Pyrimidine |
| Dofetilide | | Tertiary Amine/Methanesulfonamides |
| Dolasetron | | Indole/Azatricyclo |
| Erythromycin | | Tertiary Amine to 6-member O |
| Ezogabine | | Secondary amine/Primary amine |
| Famotidine | | Thiazole/Sulfonamide |
| Fluconazole | | Triazole X 2 |
| Fluoxetine | | Secondary Amine |
| Gemifloxacin | | Pyrrolidine/Naphthyridine |
| Granisetron | | Indazole/Azabicyclo |
| Haloperidol | Piperidine | |
| Iloperidone | Piperidine | Benzisoxazole |
| Levofloxacin | Piperazine | Benzoaxazine |
| Lopinavir/Ritonavir | | Thiazole and Diazinane |
| Methodone | | Tertiary Amine |
| Nabilone | | |
| Ofloxacin | Piperazine | |
| Ondansetron | | Imidazole/Carbazole |
| Paroxetine | Piperidine | |
| Pimozide | Piperidine | Benzimidazole |
| Posaconazole | Piperazine | Triazole |
| Propafenone | | Secondary Amine |
| Quinine Sulfate | Piperidine | |
| Ranolazine | Piperazine | |
| Romidepsin | | Azabicyclo |
| Sevoflurane | | |
| Solifenacin | | Quinoline/Azabicyclo |
| Sorafenib | | Carbamoyl |
| Sotalol | | Secondary Amine/Sulfonamide |
| Sunitinib | | Tertiary Amine |
| Tacrolimus | Piperidine | |
| Tolterodine | | Tertiary Amine |
| Vandetanib | Piperidine | |
| Vardenafil | Piperazine | Azabicyclo |
| Vemurafenib | | Pyrrolopyridine |
| Voriconazole | | Triazole/Pyrimidine |
| Ziprasidone | Piperazine | |

Piperidine Containing Opioids

- Alfentanil, Carfentanil, Fentanyl, Remifentanyl
- Codeine, Dihydrocodeine, Oxycodone, Hydrocodone, Oxymorphone, Hydromorphone
- Loperamide, Meperidine, Morphine, Levorphanol, Butorphanol, Pentazocine, Buprenorphine, Nalbuphine, Piritramide

Piperazine Containing Antidepressants/Antipsychotics

- Labeled QTP:** Clozapine, Quetiapine, Aripiprazole, Ziprazodone,
- Labeled QT Changes:** Perphenazine, Prochlorperazine, Trifluoperazine, **Lurasidone**
- Unlabeled:** Nefazodone, Mirtazapine, Trazodone, Amoxapine, Olanzapine, Eszopiclone, **Vilazodone, Vortioxetine**
- Launched/Development:** Exoperidone, Opipramol, Isofloxythepin, Tiotixene, Blonanserin, Flupentixol, Tandospirone, Perospirone, Clotiapine, Azaperone
- Bold = Thorough QT (TQT) done**

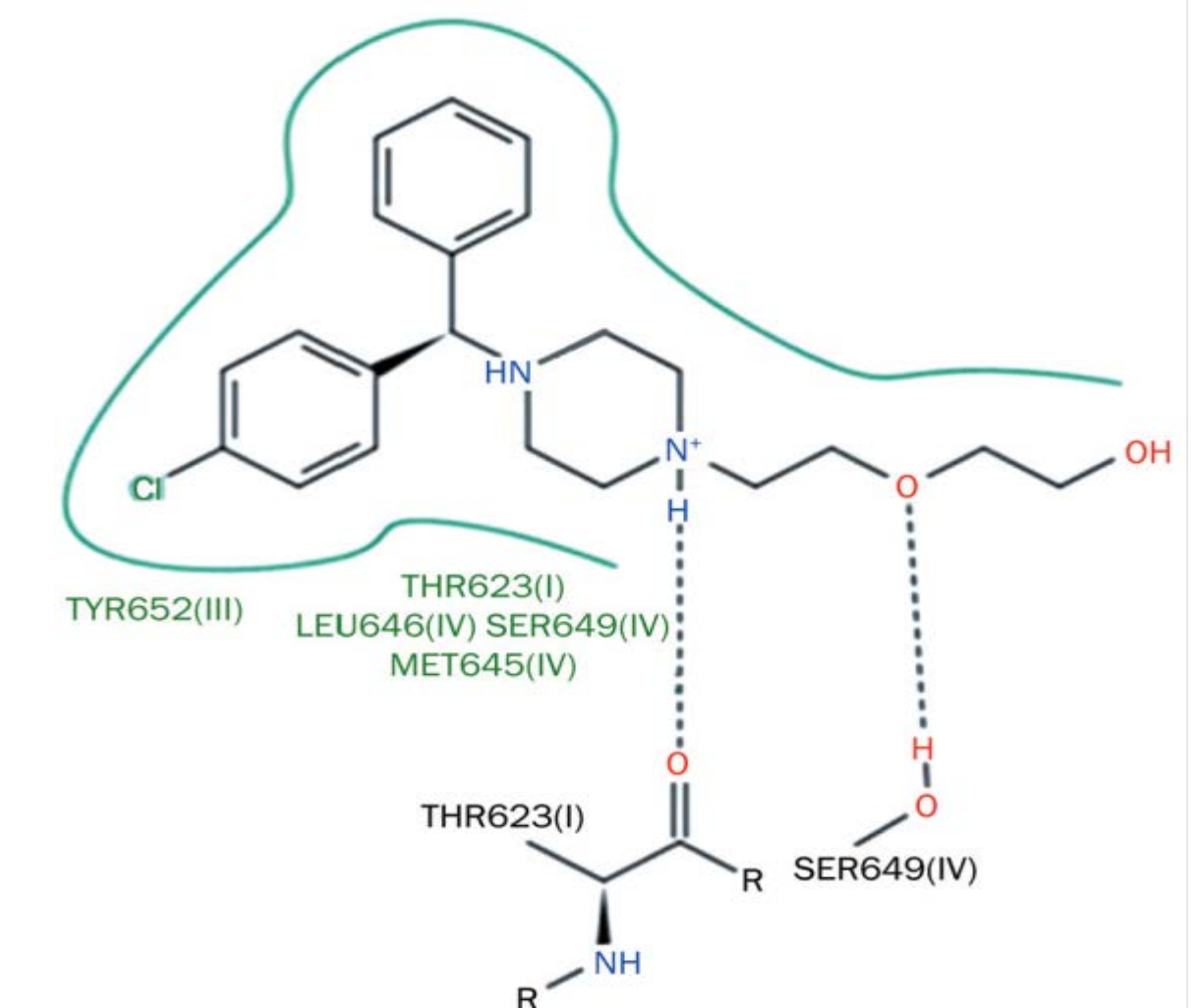
A preliminary review of the FAERS databases revealed reports of QTP or TdP for several of the unlabeled opioids and antipsychotics identified in the search.

Discussion

- Validated structural alerts are in use at the FDA for predicting carcinogenicity, mutagenicity, and hepatotoxicity and hERG inhibition.
- Literature notes structural co-occurrence of nitrogen substructure and aromatic ring (Figure)
- Many QTP and TdP FAERS case reports are confounded by the presence of multiple QTP drugs taken in combination or overdose making it difficult to identify the primary drug.
- QTP drugs may act synergistically.
- The piperidine and piperazine substructures are commonly found in drugs associated with QTP.
- Older opioids and antipsychotics may have unrecognized QTP liabilities or may contribute in drug-drug interactions that result in QTP/TdP.
- Some drugs identified in this search may carry a low risk for QTP in the population, but may carry risk in susceptible populations such as those with LQT, overdose and drug combinations.

Piperazine Drug Binding HERG

From Lee et al



Conclusions

- A substructure analysis of approved drugs labeled for QTP/TdP noted the prevalence of nitrogenous ring and tertiary amine based structures including piperidines and piperazines
- Identifying possible toxicophores associated with QTP could be useful in strengthening safety signals and identifying older drugs and the need for additional studies.
- Substructure and similarity searches may identify drugs that warrant additional evaluation for various adverse events and further inform medicinal chemistry.

Bibliography

- Lee BH et al. Effects of the histamine H1 receptor antagonist hydroxyzine on hERG K+ channels and cardiac action potential duration. *Acta Pharmacologica Sinica* 2011;32:1128-1137

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