PHARMACOTHERAPY

Validation and Clinical Utility of the hERG IC50:C_{max} Ratio to Determine the Risk of Drug-Induced Torsades de Pointes: A Meta-Analysis

David F. Lehmann,[1*] William D. Eggleston,[2,3] and Dongliang Wang[4]

[1]Department of Medicine, SUNY Upstate Medical University, Syracuse, New York; [2]Department of Emergency Medicine, SUNY Upstate Medical University, Syracuse, New York; [3]Department of Pharmacy Practice, Binghamton University School of Pharmacy and Pharmaceutical Sciences, Binghamton, New York; [4]Department of Public Health and Preventive Medicine, SUNY Upstate Medical University, Syracuse, New York

Background Use of the QT interval corrected for heart rate (QTc) on the electrocardiogram (ECG) to predict torsades de pointes (TdP) risk from culprit drugs is neither sensitive nor specific. The ratio of the half-maximum inhibitory concentration of the hERG channel (hERG IC50) to the peak serum concentration of unbound drug (C_{max}) is used during drug development to screen out chemical entities likely to cause TdP.

Purpose To validate the use of the hERG IC50:C_{max} ratio to predict TdP risk from a culprit drug by its correlation with TdP incidence.

Data Sources Medline (between 1966 and March 2017) was accessed for hERG IC50 and C_{max} values from the antihistamine, fluoroquinolone, and antipsychotic classes to identify cases of drug-induced TdP. Exposure to a culprit drug was estimated from annual revenues reported by the manufacturer.

Study Selection Inclusion criteria for TdP cases were provision of an ECG tracing that demonstrated QTc prolongation with TdP and normal serum values of potassium, calcium, and magnesium. Cases reported in patients with a prior rhythm disturbance and those involving a drug interaction were excluded.

Data Extraction and Synthesis The Meta-Analysis of Observational Studies in Epidemiology checklist was used for epidemiological data extraction by two authors.

Main Outcome and Measure Negligible risk drugs were defined by an hERG IC50:C_{max} ratio that correlated with less than a 5% chance of one TdP event for every 100 million exposures (relative risk [RR] 1.0).

Results The hERG IC50:C_{max} ratio correlated with TdP risk (0.312; 95% confidence interval 0.205–0.476, $p<0.0001$), a ratio of 80 (RR 1.0). The RR from olanzapine is on par with loratadine; ziprasidone is comparable with ciprofloxacin. Drugs with an RR greater than 50 include astemizole, risperidone, haloperidol, and thioridazine.

Conclusions The hERG IC50:C_{max} ratio was correlated with TdP incidence for culprit drugs. This validation provides support for the potential use of the hERG IC50:C_{max} ratio for clinical decision making in instances of drug selection where TdP risk is a concern.

Key Words drug induced, TdP risk, hERG IC50:C_{max}, meta-analysis, pharmacometrics.

(Pharmacotherapy 2018;38(3):341–348) doi: 10.1002/phar.2087

Polymorphic ventricular tachycardia, or torsades de pointes (TdP), is a life-threatening cardiac rhythm disturbance associated with a variety of drugs. Most drugs that cause TdP inhibit the alpha subunit of the inward-rectifier potassium channel (I_{Kr}) encoded by the human Ether-à-go-go-Related Gene (hERG) to produce a

Conflict of interest: The authors have declared no conflicts of interest for this article.

*Address for correspondence: David F. Lehmann, Department of Medicine, SUNY Upstate Medical University, 750 E. Adams Street, Syracuse, NY 13210; e-mail: lehmannd@upstate.edu.

prolongation of the QT interval on the surface electrocardiogram (ECG) before the development of TdP.[1] Among a variety of methods, an in vitro model that assesses the relationship between drug concentration and I_{Kr} receptor response inhibition was used during the drug development process to screen out chemical entities that may cause QT interval prolongation, thereby increasing the risk of TdP.[2] Specifically, a ratio of 30 for the relationship between the half-maximum inhibitory concentration of the hERG channel (hERG IC50) to the peak serum concentration of the drug unbound to plasma proteins (C_{max}) is used as a cutoff value.[3] Use of this ratio enables manufacturers to eliminate potentially wasteful expenditures for a new chemical entity. However, the utility of this ratio to predict the likelihood of a medication used in clinical medicine to cause TdP has not yet been evaluated systematically.

The QT interval corrected for heart rate (QTc) on the ECG is the current standard used to assess risk to help determine whether to prescribe a medication purported to be associated with TdP. However, use of this measure is neither sensitive nor specific for an individual drug as a predictor of risk.[4] An additional challenge is a lack of consensus with respect to the use of QT correction formulas, QT nomograms, and what specifically defines QTc prolongation when using surface ECGs in this manner. Databases used to assess TdP risk rely on voluntary reports that may not account for confounders and are prone to overreporting for certain culprit drugs that are prescribed in high volume. Furthermore, these databases do not assess risk based on incidence (TdP cases per time interval of exposure to the culprit drug). Rather, they compare the frequency of TdP reports from a culprit drug with overall reports of TdP events from all drugs in the culprit' therapeutic class. This type of analysis may easily mask a small, but present, TdP association secondary to the increase in background reporting.[5]

Given these considerations, by combining techniques in pharmacometrics and clinical epidemiology, the utility of an alternative approach was evaluated to assess TdP risk from selected drugs in three therapeutic classes: antihistamines, fluoroquinolones, and antipsychotics.

Methods

Drug Class Selection

Antihistamines were selected to define the extremes of cases associated with TdP as determined by their status on the U.S. market (e.g., astemizole [removed from U.S. market due to TdP] vs the over-the-counter status of loratadine, fexofenadine, and cetirizine).[6–15] Fluoroquinolones were selected due to their high volume of prescribing and the variable reports of TdP association with individual drugs.[16–27]Antipsychotics completed the data set due to persistent concern about their association with TdP and its impact on individual drug selection and dose escalation in clinical practice.[28–40]

Pharmacometric Data Selection

Pharmacodynamic Data

The half-maximum concentration required for a drug to inhibit the hERG channel (hERG IC50) was used as the standard comparator between drugs. Medline was accessed between 1966 and March 2017 to extract hERG IC50 data for individual drugs. Values derived from experiments were eligible if they tested recombinant hERG channels in whole mammalian cell lines incubated at 37°C and used conventional voltage patch clamp techniques, considered the current gold standard, in whole cells.[3] All units of measurement were converted to nanomoles per liter and used as the pharmacometric numerator for statistical analysis.

Pharmacokinetic Data

Peak plasma concentrations of unbound drug (C_{max}) were derived from the most commonly prescribed oral dose in adults with normal liver and kidney function, with preference given to values at steady state, accessed through standard references in pharmacology.[41] All units of measurement were converted to nanomoles per liter and used as the pharmacometric denominator for statistical analysis.

Epidemiological Data Selection

Eligibility Criteria for Cases of Torsades de Pointes

Medline (between 1966 and March 2017) was accessed to identify eligible cases of drug-induced TdP and used as the epidemiological numerator for statistical analysis.[6–40] Two authors (D.F.L. and W.E.) separately applied the same criteria to identify eligible cases. Inclusion criteria were the provision of an ECG tracing

that demonstrated QTc prolongation (greater than 450 msec) followed by documented TdP and normal serum values of potassium, calcium, and magnesium. Case patients exposed to an overdose of the culprit drug were eligible for inclusion. Case patients were excluded for a history of prior rhythm disturbances and exposure to drug(s) known either to interact with the culprit drug or reported to cause TdP from analysis.

Estimating Annual Exposure to Each Culprit Drug

The 12-month period closest to the year that encompassed most of the literature reports of TdP cases was used to estimate patient exposure. For drugs without reports of TdP, the 12-month period just before the loss of U.S. market exclusivity was used. These time periods were inclusive of literature reports involving overdoses of the culprit drug that did not result in TdP events. Very rough estimations of annual worldwide revenues reported by the pharmaceutical manufacturer holding U.S. patent protection for the culprit drug through a variety of open sources were accessed.[41–52] This dollar figure was then divided by the average wholesale price (AWP) per day for the most commonly used total oral daily dose of the culprit drug. The dividend was then multiplied by an estimate of the number of days per year that a patient would be expected to ingest the culprit drug. The assumptions used for this number was 365 days per year for antipsychotics, 10 days per year for fluoroquinolones, and based on an annual prevalence of seasonal allergic rhinitis, perennial rhinitis, and mixed rhinitis, 138 days per year for antihistamines. The calculations are summarized as follows:

$$\$\,\text{Revenues}/\$\,\text{AWP/day} \times \text{days/year exposed} = \text{annual patient-days}$$

Statistical Methods

The negative binomial regression model was used to evaluate the impact of the hERG IC50:C_{max} ratio over the TdP risk, under the assumption that logarithm of the TdP risk was linearly associated with the logarithm of the hERG IC50:C_{max} ratio, and at any specific level of the hERG IC50:C_{max} level the observed number of TdP followed the negative binomial distribution. To provide guidance for clinical practice, the negative binomial model was also used to determine the hERG IC50:C_{max} ratio associated with less than a 5% chance to have a risk of one TdP event for every 100 million exposures (in patient-days). Drugs with a hERG IC 50:C_{max} ratio at or above this value were designated as negligible TdP risk. The hERG IC50:C_{max} value was then used as a comparator for all drugs for the subsequent analysis. All statistical analyses were performed using SAS v.9.4 (IBM Inc., Armonk, NY, USA).

The prolongation of the QTc interval immediately before the development of TdP identifies a drug as the culprit. However, the baseline QTc does not accurately predict TdP risk of an individual exposure to a potentially culprit drug. Therefore, the exact length of the QTc interval was not included in the model.

Advanced age and female sex were reported to predispose to TdP but are significantly confounded and overwhelmed by the more important factors of cardiac comorbidity and electrolyte disturbances as predictors of risk.[53] For these reasons and due to the small number of case patients, age and sex were not included in the analysis.

Results

Table 1 provides the pharmacometric and epidemiological data used for the statistical analysis. Peak plasma concentrations (C_{max}) reflect steady state values of the free fraction (unbound) of drug. The hERG IC50 values are from the most recent in vitro studies using mammalian cell lines at physiologic temperature. The incidence numerator is composed of case reports of TdP without confounders. Patient-days (incidence denominator) reflects an estimate of exposure to the culprit drug that occurred during, or no greater than 1 year following, the bulk of TdP case reports for that drug.

Figure 1 correlates the log hERG IC50:C_{max} ratio with TdP risk per 100 million exposures in patient-days. The two parameters were strongly correlated: the relative risk (RR) associated with every doubling of the log hERG IC50:C_{max} ratio was 0.312 (95% confidence interval [CI] 0.205–0.476, $p<0.0001$). The negative binomial regression analysis also predicts that a drug with a hERG IC50:C_{max} ratio of 80 has less than a 5% chance to have one TdP case per 100 million exposures. Drugs designated as negligible TdP risk had a hERG IC50:C_{max} ratio greater than 80. Such negligible risk drugs include ciprofloxacin, ziprasidone,

Table 1. Pharmacometric and Epidemiological Parameters

Drug	hERG IC50, nmol	C_{max}, nmol	hERG IC50:C_{max}	Cases, n	Annual exposure, patient-days
Antihistamines					
Astemizole	0.34	7.8	0.044	11	46,107,584
Cetirizine	30,000	47.4	633	0	1,295,336,724
Loratadine	170	0.176	966	0	4,176,349,200
Fexofenadine	100,000	186	538	0	1,650,000,000
Fluoroquinolones					
Ciprofloxacin	966,000	10,000	97	1	205,000,000
Levofloxacin	915,000	12,000	76	1	92,000,000
Gatifloxacin	130,000	9000	14	2	11,000,000
Moxifloxacin	129,000	5900	22	4	40,000,000
Antipsychotics					
Thioridazine	93	43.7	2.1	8	18,615,000
Haloperidol	100	1.96	51	4	12,115,000
Olanzapine	6013	4.47	1345	0	440,000,000
Quetiapine	5765	136	42.4	0	406,100,000
Risperidone	167	40.4	4.13	1	355,385,000
Ziprasidone	169	1.64	103	0	93,077,000
Aripiprazole	1096	5.39	203	0	186,154,000
Clozapine	2500	83.4	30	0	33,846,100

C_{max} = maximum serum concentration; hERG IC50 = half-maximum inhibitory concentration of the hERG channel.

aripiprazole, fexofenadine, cetirizine, loratadine, and olanzapine.

Figure 2 shows the TdP risk from each drug relative to one with a risk of one TdP event per 100 million exposures (hERG IC50:C_{max} 80, RR 1.0). This analysis allows for an inter- and intra-therapeutic class assessment of TdP risk. For example, the RR of TdP from olanzapine (0.00874) is on par with loratadine (0.0152); and ziprasidone (0.654) with ciprofloxacin (0.729). Drugs with an RR greater than 50 include astemizole (59.3), risperidone (100), haloperidol (105), and thioridazine (441).

Discussion

A model that applied a pharmacometric tool used in the drug development process was strongly correlated with the incidence of TdP for individual culprit drugs. This validation supports the hERG IC50:C_{max} ratio as a template for further study to ultimately support its use in clinical decision making in instances of drug selection where TdP risk is a concern.

Our model may help assuage prescribing concerns by identifying drugs with a TdP risk considered negligible (to a statistical confidence of less than one event per 100 million exposures). The current clinical standard uses a biomarker, QTc, that poorly correlates with the ability of a drug to inhibit I_{Kr}.[4] As such, this tool cannot accurately predict TdP risk from an individual culprit drug. Conversely, because the mechanism of TdP from hERG channel inhibition is independent of therapeutic class, the hERG IC50:C_{max} ratio may enable a more accurate comparison of TdP risk between compounds than the surface ECG.

However, because it is based on published pharmacometric values, our model does provide the potential for an approximation TdP risk equivalence between selected antipsychotics and commonly prescribed antimicrobials, over-the-counter products, and a drug removed from the market (astemizole) due to concerns over TdP risk. Providers can then use the hERG IC50:C_{max} ratio in conjunction with parameters specific to a patient (concomitant medications, electrolyte values, etc.) to help determine TdP risk before prescribing a new medication.

Female sex and advanced age have correlated with a greater risk of TdP, but the latter is confounded by comorbidity.[53] Although prolongation of the QTc interval compared with baseline in the setting of culprit drug exposure and immediately before a TdP event confirms the diagnosis, QTc prolongation at baseline does not. Given these considerations, combined with the design of the meta-analysis that uses pharmacoepidemiological data to validate the hERG IC50:C_{max} ratio, these variables were not included in the current model. Indeed, this validation provides support to refine a pharmacometric approach using pharmacokinetic/pharmacodynamic modeling methods built around the plasma concentrations occurring at the time of marked QTc interval prolongation before a TdP event in the relevant cases

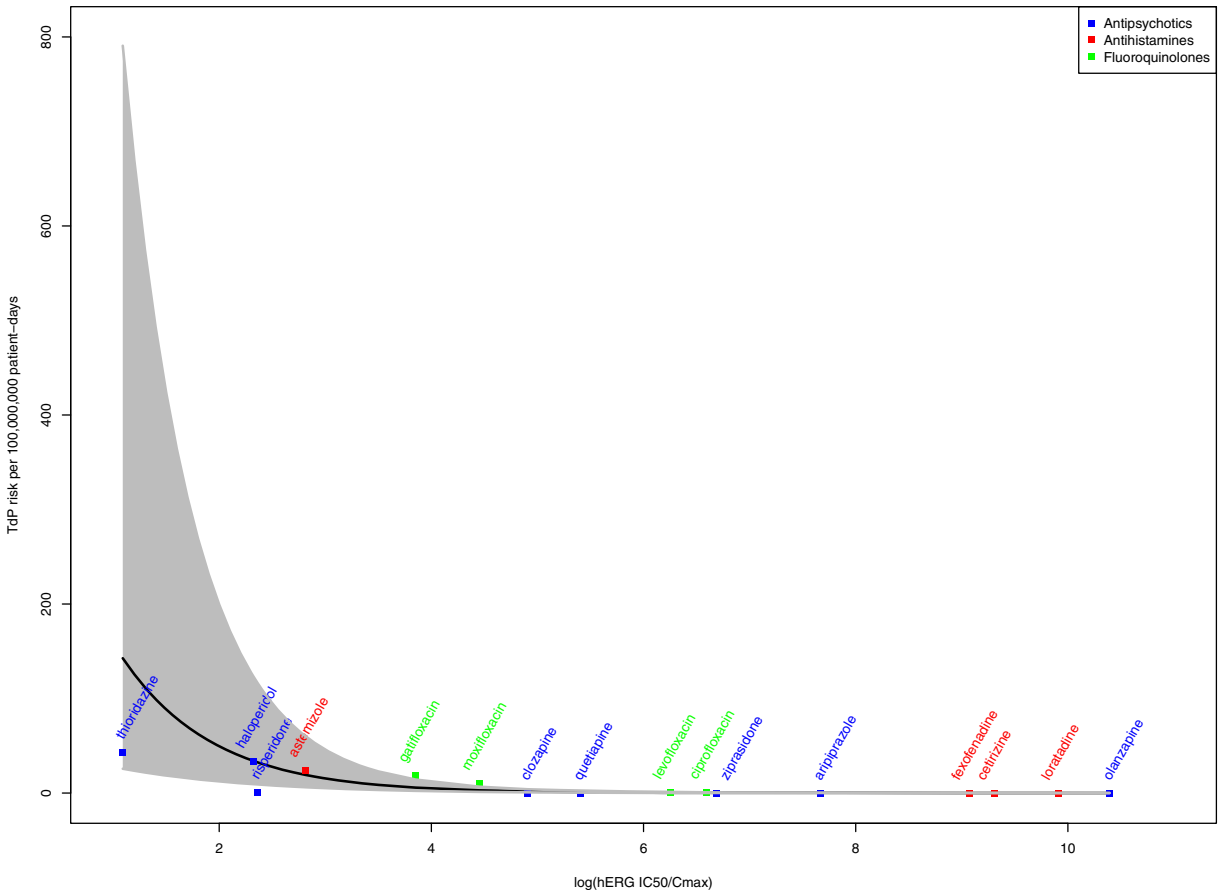

Figure 1. Association of torsades de pointes (TdP) risk with hERG IC50:C_{max} for specified drugs was evaluated by fitting a negative binomial regression model, as illustrated here, with the 95% confidence band (shaded area). Log (# TdP cases/patient-days) = −12.19–1.16* log2 (hERG IC50:C_{max}). The p value associated with the model is < 0.0001. C_{max} = maximum serum concentration; hERG IC50 = half-maximum inhibitory concentration of the hERG channel.

contained here while expanding the culprit drug data sets to include cisapride and terfenadine.

The addition of an interclass comparator with its specific TdP risk per 100 million patient exposures can be easily linked to an antipsychotic drug, when prescribed, and imported into a pharmacy database for use in patient care settings for drug interaction screening. For example, describing the similar RR of olanzapine to loratadine could allay concerns over TdP risk when prescribing olanzapine. Conversely, providing comparative risk data for astemizole (a drug removed from the U.S. market due to TdP risk) when risperidone or haloperidol is prescribed could alert clinicians to monitor more closely or select an alternative antipsychotic.

Limitations

Our model has several limitations. The hERG IC50:C_{max} ratio cannot be used to determine risk for drugs that cause TdP by an alternative mechanism to hERG channel inhibition, most notably tricyclic antidepressants. The method used to determine the incidence denominator for an individual compound (patient-days) should be considered preliminary. To maximize the internal validity of our model, particularly with regard to the ability for interclass risk comparisons, a strict criteria for case definition was applied. The inclusion of culprit drug overdose eligibility in both the numerator and denominator mitigates any confounding by dose. Indeed, given the greater frequency of literature reports of overdose without TdP for antipsychotics, as compared with selected antihistamines (e.g., astemizole), strengthens the model's validity.[54, 55]

Thus our model cannot estimate TdP risk in clinical settings that either dramatically increase the serum concentration or enhance the effect of a culprit drug on the hERG channel (e.g., culprit drug overdose, past cardiac history, drug

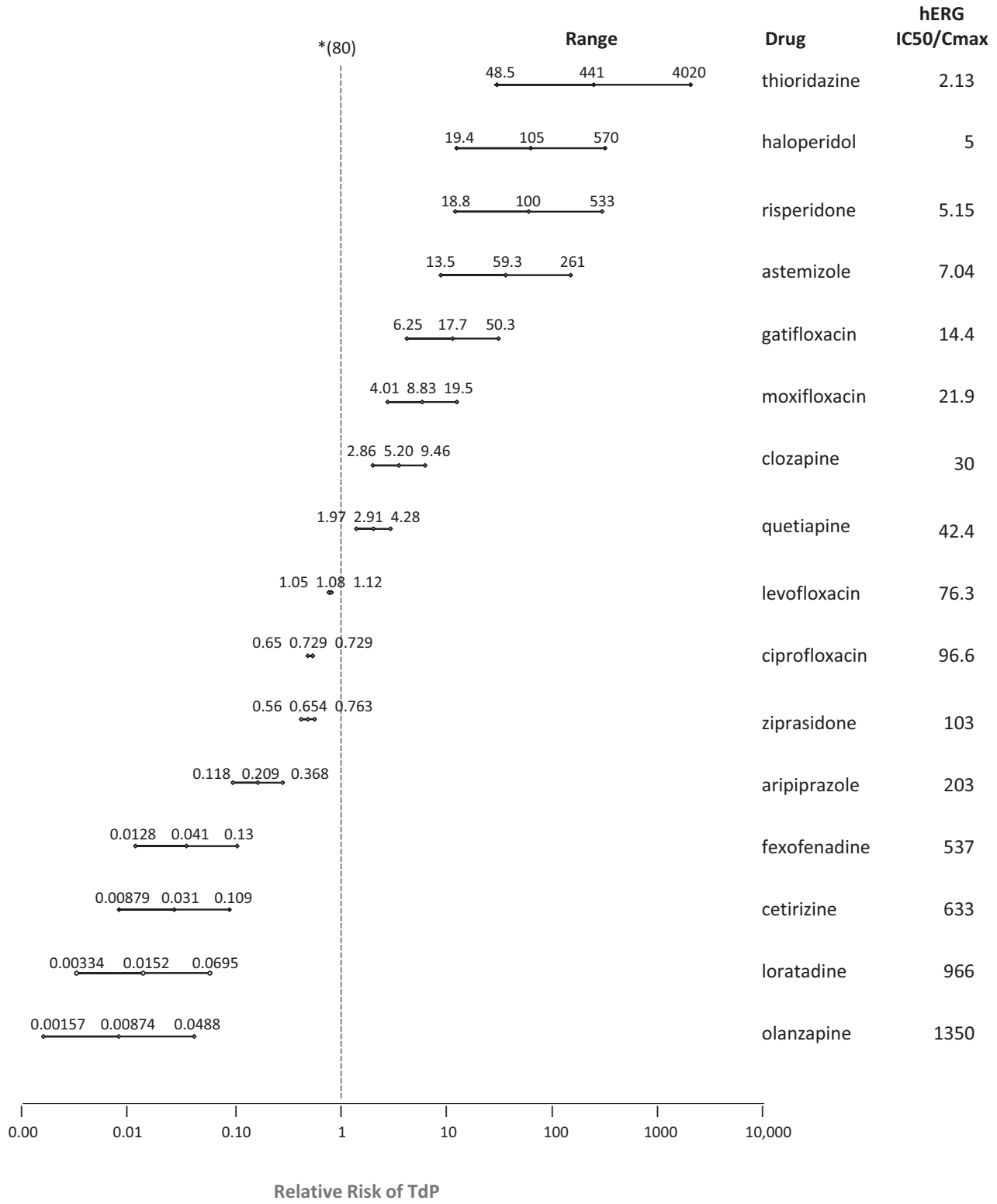

Figure 2. Relative torsades de pointes (TdP) risk. TdP risk of each drug studied compared with one with a TdP risk of 1:100,000,000 exposures in patient-days (relative risk 1.0, $p<0.05$). *(hERG IC50:C_{max}) for each drug. hERG IC50 = half-maximum inhibitory concentration of the hERG channel. C_{max} = maximum serum concentration.

interactions, electrolyte disturbances). Indeed, our model should serve to underscore the importance of accounting for and correcting such factors, where possible, before prescribing a potentially culprit drug, instead of relying solely on the surface ECG.

Conclusion

Drug-induced TdP is a rare but clinically important occurrence due to its life-threatening nature. The use of the hERG IC50:C_{max} ratio offers a new approach to provide greater clarity and better inform prescribing decisions for drugs that may be associated with TdP. We recognize our model is preliminary and welcome scrutiny to further validate and refine our approach.

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