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Review Paper

Prolongation of the QT Interval and Psychotropic Drugs: Current Issues

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Abstract

The example of QT prolongation measurement and monitoring in relation to psychotropic drugs is critically examined because the proposed value of measuring it is being promoted through various channels, including via pharmaceutical companies' PIs/SPCs. There are subtle and complex questions about measurement of the QT interval, and the reliability and specificity of predictions made therefrom, that are not addressed by such sources. This commentary illustrates that much of the monitoring advice and instruction content, which is in 'MIMS' and the 'Physicians' Desk Reference' etc., is of little or no clinical value. These sources contain biased, superficial and poor science. Yet they purport to advise and instruct doctors to monitor various clinical and laboratory variables at great cost of time and money and often with little or no evidence of benefit. The simplest approach is to avoid drugs causing QT prolongation unless there is a good reason to do otherwise. Following recommendations about QT monitoring, if that is considered appropriate, involves considerable time and expense if it is to be done properly and scientifically.

Key words: QTc prolongation, psychotropic drugs, torsades de pointes, sudden cardiac death, channelopathies, HERG-K+ channels

Introduction

Increasing attention is being paid to the deceptively easily measurable quantity of QT interval prolongation, and its uncertain relationship to dangerous cardiac arrhythmias and possible **sudden cardiac death SCD (fatal cardiac arrhythmia FTA)**. Recommendations are being promulgated concerning precautions and monitoring of many drugs: however, the basis on which these are founded is uncertain, and the benefit and cost of taking such action is unproven. The science and evidence behind such ideas deserves careful examination because there are important medical practice and cost issues involved.

The **'Product Information Sheets' (PIs),** also referred to as **'Summary of Product Characteristics' (SmPC, or just SPC),** which are prominent vehicles making these recommendations, are written by drug companies, and are not peer-reviewed, and are provided to regulatory agencies (and published in book, and now electronic form e.g.

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'MIMS' and 'Physicians' Desk Reference') in order to satisfy *legal* requirements for gaining regulatory approval for their drug.

Further discussion of these complex issues is contained in the supplementary information online

http://www.psychotropical.com/qt-predictive-value

Inadequacies of Advice on QT Prolongation

There are wide-ranging inadequacies of the general advice given in SPCs/PIs (see below). The topical question of QT prolongation is examined in detail because for many psychotropic drugs (about 25%) monitoring of the QT interval is suggested or 'mandated' (wording varies in different countries), but with dubious justification and little consideration of the usefulness and cost of doing that. For instance, in the SPCs/PIs reviewed recently Warnier et al. found: 'in almost half of the drugs [there was] no clear message on QT prolongation' (1).

There are complex questions to be addressed if QT prolongation is going to be considered a recommended or necessary step with a significant number of newer generation psychotropic drugs. The degree of risk is currently unclear, both with therapeutic doses and over-doses. The usefulness of monitoring, how best to go about it, and how to assess its cost are questions that research has barely started to address.

If the degree of risk related to **Torsades des pointes TdP** and the occurrence of **FTA/SCD** is deemed sufficiently frequent to require action, then the obvious approach will be to simply not use any of the drugs which cause QT prolongation, unless there is a compelling reason to do so.

Since, generally speaking, there is little or no evidence that one drug is significantly therapeutically superior to others there seems to be a strong case for not using such drugs at all. Such a simple course of action would save much time, trouble and expense. Considerably more epidemiological data needs to be gathered before such questions can be answered definitively, and this is likely to take many years, so this problem will be with us for a while.

The QT Interval and its Prolongation

It is illustrative to consider the QT prolongation issue because it is a good example of the clinical problems that result from a combination of incomplete knowledge and the uncritical application of science to clinical medicine. Drug companies and the FDA (and other similar agencies) are unsure because they do not really know what the risks are, nor what best to do. They tend to (indeed may be obliged to) play safe because there is insufficient information. Therefore they issue a 'Black Box' warning which may then be misconstrued and may elicit inappropriate and

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unintended reactions from doctors, other health professionals and auditing authorities etc. This shows why one should not accept uncritically what the PIs recommend, nor how others interpret them.

Further comment on these and similar peripheral but pertinent matters is contained in the supplementary information online

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Many research papers in the QT field report measurements of the QT interval that are less useful than they might be because they use the less accurate, but easy, automated measurements from standard electro-cardiograms (2-4). Therefore, from just this one inaccuracy, much of the data being considered are made imprecise from the outset.

QT Prolongation is only a surrogate marker for FCA/SCD. Surrogate markers are notoriously quixotic. They are nonetheless popular because they are quick and easy.

Issues of Science and Measurement

There are a series of issues concerning science and measurement, as well as logical reasoning, that are pertinent.

1) Measurement. The QT interval, as measured in common clinical practice and research, is taken from the computerised ECG which gives a significantly inaccurate estimation of the real QT interval (e.g. (4)). Even medical toxicologists use the computerised ECG output half of the time (5), and half also use the unsatisfactory Bazett's QT rate correction. Only a small minority used the benchmark QT normogram (6).

2) Rate correction. The corrected QT interval (QTc) which is intended to correct for its length as the heart rate varies, usually uses the Bazett formula which is inaccurate and not commensurate with current best practice. Bazett's formula is only useful for a narrow range of heart rates and significantly over-corrects for fast heart rates and under-corrects for slow heart rates (6).

3) Reference QT values. Population averaged QT values are less appropriate for individuals because an individual's QT intervals are stable (i.e. there is low intra-individual variation), but inter-individual values in a population vary much more (7). It is therefore the change from an individuals baseline value which is the more reliable indicator, not deviation from a population average. Relatively few studies have assessed changes from baseline values, those that have not are of diminished predictive validity.

4) Cutoff values. There are very few data from which good predictions about TdP or FCA can be made based on particular cut-off values. There is no consensus definition of 'clinically significant' prolongation of QTc interval, 450 ms or an increase from baseline of 30 ms are commonly used minimal values: NB the ICH document (2014) now

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states 'Bazett's corrections is no longer warranted' (8). Different centers adopt different values, ranging between 440 and 500 ms. An upper 95% confidence limit of the average 24-hour QTc interval was 440 msec in men and 460 msec in women in one study.

5) The relationship between drug induced QT prolongation and TdP and FCA is not reliably established. In case reports at least one other established risk factor for QTc prolongation was present in over 90 % of cases. Hasnain and Vieweg's conclusion was 'There is little evidence that drug-associated QTc interval prolongation by itself is sufficient to predict TdP. (9)'. An assessment of drugs that affect QT prolongation is maintained at www.CredibleMeds.org.

6) The relationship between QT prolongation and the risk of TdP* is different for different drugs. In other words, some drugs cause QT prolongation but not TdP and other drugs cause TdP with less significant prolongation. E.g. amiodarone and most tricyclic anti-depressants cause QT prolongation but not TdP (10, 11).

*Note: TdP is spelled in various ways in both French and English texts, but it is plural, so torsades de**s** pointe**s** is preferable (12).

7) TdP itself is not necessarily a good predictor of the occurrence of potential or FCA. Other factors seem to be significant or even dominant determinants of the occurrence of arrhythmias (ironically, ones which are sometimes not recognized or considered). E.g. alpha-1 adrenergic antagonism (13), channelopathies (14, 15), various other drugs (e.g. sotalol), obesity, electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), cardiac ischaemia, cardiomyopathies, hypothyroidism and hypoglycaemia (3). Also age, female gender and even time of day influence QT length.

8). The hydrophobic central cavity of the HERG-K+ channels, allows a large number of structurally unrelated drugs to bind and cause direct channel inhibition (16). There are in fact about 10 separate K^+ channels expressed in various parts of heart muscle which have slightly different properties, three drive ventricular repolarization, with some redundancy (17, 18). It may be that functional impairment of more than one of them is required before fatal arrhythmias are likely to occur. Genetic abnormalities of several of these channels have been linked to various syndromes, e.g. Brugada and long QT (19).

QT Prolongation: What Predictive Value?

Reliable data concerning which drugs really do cause an increase in **fatal cardiac arrhythmias (FCA)** are sparse, and since this is the key question, substantial predictive uncertainty remains (11, 20, 21). It will be some time before the complexities of the situation can be untangled because (as a hypothetical scenario) some drugs may cause FCA even at

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therapeutic doses, but only if a particular genetic abnormality is present (or another drug), but not cause FCA in over-dose in the normal population, whereas others may be the reverse i.e. cause no problems at therapeutic doses but FCA in overdose. A Gordian knot to be untangled: who will rule Asia?

Just as is the case in my area of expertise, serotonin toxicity, one of the crucial elements required to clarify the picture is good systematically collected data on human toxicology, as has been pointed out in the past (22). The tremendous value of such an endeavour has been highlighted in a recent paper summarizing more than 25 years-worth of prospectively gathered data from the Hunter Area Toxicology Service (HATS) in Australia (23). This group have gathered data which have been valuable in assessing the issue of QT prolongation and FCA (many key papers referenced herein emanate from the HATS group). The HATS data have also been the most valuable single source of information for my research on ST. We all owe the HATS group members, past and present, a considerable debt of gratitude for what must have required a great deal of hard work.

So I would like to publically thank all who have been members of the HATS team over the years who surely are justifiably proud of their collective achievements.

Note: key reference, The Hasnain and Vieweg paper has a wealth of information and references (9). Likewise (17).

General Inadequacies of Advice in PIs

There are wide-ranging inadequacies of advice in PIs. At least five major aspects of poor PI content have been adversely commented on recently: QT prolongation, drug-drug interactions, dose adjustment in renal impairment, management of over-doses, pregnancy and breastfeeding (24).

Further background and details about various aspects of general PI information usefulness and reliability are discussed in the supplementary online material

http://www.psychotropical.com/qt-predictive-value

Product Information Sheets: Background and Context

NB further discussion on this issue is contained in the supplementary online material above.

In brief: the compendium made up of 'Product Information Sheets' provided by drug companies to regulatory agencies (e.g. MIMS and 'Physicians' Desk Reference') is a source of information about drugs that, apparently, is frequently used both by doctors and other healthcare professionals (25). However, anecdotal information suggests there is

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great regional variation in its utilization and that specialists and more experienced doctors regard it as of little value and rarely use it. It would appear to have more prominence in 'commercial' software packages for practice management and clinical records which are used more in private practice. In the UK most doctors (appropriately) prefer the BNF which is independent and is compiled by practicing doctors and pharmacists.

The unhelpful recommendations and instructions in PIs are a matter of some consequence since these compendiums may contain extensive suggestions and 'requirements' (the word 'mandatory' is used) for the monitoring of drug side effects and adverse interactions before and during treatment. These, especially black box warnings, are being written about, taken notice of and acted on, at least by some, e.g. Moore describes how authorities in California have threatened to remove re-imbursements or accreditation from hospitals where continued use of droperidol occurs (26). The unease and even fear that some doctors experience in relation to not adhering to such guidelines and mandates is real and has a negative influence on medical practice.

Suggestions and requirements for monitoring in the PIs include tests that often need to be done by other specialists and repeated on a number of occasions. It is obvious that the costs will be considerable and will also mount rapidly. It is hardly surprising that doctors, apparently, take little notice of QT monitoring recommendations (27).

PIs have little to do with optimal clinical management (they are not written by practicing clinicians) and are influenced by medico-legal considerations, presumably intended to protect the producer from liability.

Overview

A recent paper evaluating the general effectiveness of SmPCs (28) concluded 'Current content and presentation of SmPCs [PIs], while meeting regulatory approval standards, contribute little to the safe and effective use of medication in practice.', which is hardly surprising considering they are really regulatory/legal texts, not clinical texts.

This poor advice contained in PIs is a frequent, time-consuming and expensive problem, and doctors generally will be well advised to seek alternative sources of truly independent clinically orientated information and advice. In some countries' PIs an ECG is *required* for 25% of listed antipsychotics (29, 30).

The only rational comment that can be made about this absurd situation is that if such burdensome monitoring measures are required then the drug is automatically disqualified from being usable in general clinical practice and would only be considered in rare special circumstances where there is no alternative.

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Conclusion

QT interval prolongation has a complex and uncertain relationship to TdP and SCD/FCA. QT interval measurement is not a simple, reliable or cost-free procedure. The recommendations being promulgated (often partisan) concerning monitoring have uncertain costs or benefits. There are important medical practice cost issues involved. If monitoring recommendations were to be adopted and taken seriously (which is obviously not happening) then it seems there is only one way to avoid the issue: do not use such drugs. Unless there is a compelling reason to do otherwise it may be wisest to choose one of the many available drugs that are not implicated as causing QT interval prolongation, TdP or SCD.

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