Trends-in-Medicine

January 2003
By Lynne Peterson

SUMMARY

The proposed Concept Document on QT is likely to morph into a formal guidance document very quickly – and with only minor changes. ♦ The FDA views any drug with a mean QT prolongation of >20 ms as having a problem – unless proven otherwise. ♦ The FDA is uncertain whether it is appropriate and safe to lower the dose of a proposed new drug to keep a QT effect to a minimum. ♦ When the rules are finalized, the FDA likely will require a QT comparator arm – something like Bayer's Avelox (moxifloxacin) -- in ***every*** Phase I trial for ***every*** new drug. ♦ The FDA is not ready to accept the theory that the area under the curve in QT prolongation (the area of transmural dispersion of repolarization) can predict the likelihood of a QT prolongation leading to Torsade de pointes.

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THE CLINICAL EVALUATION OF QT INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS

January 13-14, 2003
Rockville, Maryland

The Drug Information Agency (DIAI), in collaboration with the FDA, Health Canada and the North American Society for Pacing and Electrophysiology (NASPE) sponsored this workshop on QT prolongation. Every major pharmaceutical and biotech company was represented at the meeting, which surprised organizers with standing room only attendance. While this meeting was billed as a workshop to formulate policy, most pharma officials questioned agreed that it was more a forum for the FDA to outline the new rules it plans to impose. FDA officials appeared willing only to make very minor modifications to the plan, but one official indicated there will be more discussion and maybe even another workshop before the final guidelines go into effect.

The European Regulatory authorities also will be considering the guidelines, and a French regulator said he believes that the EU, Canada and the U.S. will come to agreement on final rules. However, he noted that, if there is no agreement, the FDA is likely to impose the rules it has drawn up, which would mean that pharmas would have different rules in the U.S. and Europe, making international trials much more difficult to conduct.

DETAILS

QT prolongation is only a surrogate marker for Torsade de pointes (TdP). TdP is very rare, but one speaker estimated that it occurs in 1% of the population in five years, and a pharma official said the risk in Sweden was found to be 4 per 100,000 people per month.

- An FDA official said, "The low range is sort of set by moxifloxacin (Bayer's Avelox). You could maybe have a trial not sufficient to detect <5 ms, but when you get to 10 ms, then you start getting into the range of cisapride (Johnson & Johnson's Propulsid) and others where the databases are more ambiguous, and you need to make the case clinically that there is no concern with missing it."
- A cardiologist commented, "The vast majority of QT prolongation is not associated with TdP, but the vast majority of TdP is associated with QT prolongation."
- Another FDA official said, "There is good evidence that the size of effect relates to the risk of TdP, but there ***could*** be other properties that mitigate or enhance the risk."

- Asked how the agency would view a drug with a QT increase of 11 ms which had a placebo increase of 7 ms, the official said, "We will subtract and say the drug had a 4 ms effect."

DEFINITIONS

The concept paper defines the FDA's current level of concern with QT prolongation, though FDA officials clarified that they are concerned with the effect of the drug when it is there – not at hour 24 if it is gone then. One official explained, "You don't want the 24-hour average, you want the largest effect the drug will have." Another official said, "You have to find out where the largest effect is, and that is not necessarily Cmax. If you are measuring throughout the day, you will get some idea whether it is related to a metabolite, to Cmax or whatever. You want the most extreme value." According to the Concept Paper:

- **<5 ms:** So far, there has been no TdP shown with this degree of prolongation, and FDA officials said they don't think drugs with <5 ms of prolongation have caused TdP. One commented, "<5 ms is probably not a worry."
- **5-10 ms:** There is no clear risk. Based on approval of moxifloxacin, FDA officials said they don't think there is much risk in drugs with this degree of QT prolongation, but "it is something worth labeling and something to think about."
- **10-20 ms:** There is uncertainty about drugs with this degree of QT prolongation. An FDA official said, "There is a rising concern, with the size of the change important."
- **>20 ms:** There is a "substantially" increased likelihood of these drugs being pro-arrhythmic. An official said, "This is serious…If the mean QT prolongation is >20 ms, we think there is a problem. Most anti-arrhythmic drugs with a problem are in this category, so a drug with that characteristic is probably in trouble unless it is arsenic trioxide and treats leukemia."

This prompted the following exchange:

- *FDA official:* "You feel confident enough that if dispersion is not increased, a drug is okay?"
- *Researcher:* "Not completely confident but it suggests that if a company comes to you and says let us study a drug, I might want them to pursue it, especially if the drug has potential benefit."
- *FDA:* "It may be the first 100,000 patient trial."

NEW RULES

Two of the key new rules in the Concept Paper are:

(1) careful analysis of metabolites, and

(2) a requirement for a separate QT comparator arm in ***every*** Phase I trial of ***every*** new drug. Pharma officials questioned all agreed that this almost certainly will be a requirement in the final guidelines. Several said they had expected to be able to persuade FDA officials not to impose this rule, but they all agreed that it appears the FDA has made up its mind on this issue and was rejecting pharma arguments about the cost and logistics burdens the rule would create.

NEW THEORY

The other important issue discussed at this workshop was a **dispersion theory** that might help researchers and regulators tell whether a QT prolongation is likely to led to TdP. **This theory is sort of an area-under-the-curve way of measuring dispersion.** Dr. Charles Antzelevitch, a professor of pharmacology and Executive Director of Research at the Masonic Medical Research Laboratory in Utica, New York, who was representing NASPE, said, "It is not necessarily QT prolongation but the spatial dispersion of repolarization that attends QT that is the principle problem. Drugs that increase Transmural Dispersion of Repolarization (TDR) are linked to TdP and those that don't increase TDR are not linked to TdP…There is a failure of correlating QT with the incidence of TdP…We find what works…is using the area under the peak, so the area under the second part of the T-wave provides a fairly good index of the spatial dispersion across the wall."

The following exchanges are illustrative:

FDA official: "Is this a way of discovering a new class of drugs that might be a problem or clearing drugs that appear to have a problem?"

Dr. *Antzelevitch:* "Our experience is that drugs that tend to increase the dispersion are the ones that … increase the area."

FDA: "Are there drugs with a 20-25 ms increase in QT that would not increase dispersion and are therefore not a problem?

Dr. Antzelevitch: "We've not seen that as yet. We have seen drugs that prolong QT but actually reduce the area."

A researcher said that, using this dispersion (or area under the curve) theory, some drugs with a QT prolongation more than 20 ms might be able to be approved. He explained, "Actually, I think you will see a drug -- if not several -- that increases QT >20 ms but does not affect depolarization…and I suggest there are two things you want to look at to see if a drug safe despite this: (1) the restitution characteristics – cycle length, QT interval slope. If that is unchanged, it is more likely this is a

safe drug. (2) whether there is a good measure of dispersion and that is absolutely unchanged."
This led to another interesting exchange with an FDA official.

FDA: "You feel confident enough that if dispersion is not increased, a drug is okay?"
Researcher: "Not completely confident but it suggests that if a company comes to you and says let us study a drug, I might want them to pursue it, especially if the drug has potential benefit."

FDA: "It may be the first 100,000 patient trial."

An FDA official who was interviewed during a break in the meeting indicated that this area-under-the-curve theory is interesting but will not be adopted by the FDA any time soon.

QT Background and Lessons from History

FDA concern with QT and TdP began in the 1970s, but accelerated recently. Dr. Robert Temple – Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs) – said, "In recent years. TdP has been the most common single cause of (drug) withdrawals – four of them." A Health Canada official said, "TdP and sudden cardiac death with non-anti-arrhythmic QT prolonging drugs are usually quite rare, may not be observed during the clinical trial program and are often detected only thru post-marketing adverse event reporting."

Among the drugs cited as having serious QT problems were:

- **Prenylamine**
- **Lidoflazine** (Organon), which the FDA rejected because of QT prolongation.
- **Bepridil** (Johnson & Johnson's Vascor), a CCB that prolongs QT >30 ms) and caused TdP in about 1% of people taking it. Dr. Temple said, "It was approved as a last resort treatment for angina only after an unequivocal showing that it was effective in diltiazem failures. It was labeled that it causes TdP, and we know it continues to cause it."
- **Terfenidine** (Hoescht's Seldane), which was withdrawn from the U.S. market in 1998. This is the drug that really put QT on the FDA map. Terfenidine is metabolized by the 3A4 pathway, and only becomes a QT problem when its metabolism is inhibited.
- **Astemizole** (Johnson & Johnson's Hismanal), which was withdrawn from the U.S. market in 1999. Dr. Temple said, "Astemizole – which was marketed at 10 mg OD – has a long half-life and could have been developed as a loading dose with 2-3 mg/day maintenance which is ***very*** far from the torsadigenic dose."

The key lessons speakers said could and should be learned from these early drugs are:

1. QT can be a problem with any drug, not only cardiovascular drugs
2. You must know both the parent drug and the metabolites as well as the effects of the metabolic inhibition to assess the risk. FDA officials indicated they want to see metabolites and metabolic interactions evaluated in a Phase I QT assessment. Dr. Douglas Throckmorton, Director of the FDA's Division of Cardio-Renal Drug Products, CDER said, "That means your knowledge of metabolism for a given compound has to be adequate for you to design that in Phase I."
3. The ability to modify physician prescribing behavior under the current systems is imperfect.

Risk vs. Benefit: A speaker said, "This is easy in concept but not necessarily in practice." Among the things that need to be weighed are:

a. Size of the risk, which requites interpreting QT effect, which is a surrogate marker.

b. Overall benefit of the drug (any unique effect, the need for alternatives, the properties of alternatives, etc.). An FDA official said, "The best case is a drug with a unique, important benefit in all or some defined population (for example refractory acute promyelocytic leukemia or angina unresponsive to diltiazem)…(and) A new product can't be worse than anything else already available…For lesser QT effects, we would also consider the number of treatments needed, whether it is an antibiotic or an antipsychotic, etc."

c. Ability to manage risk
   - Labeling. An FDA official said approval of a QT prolonging drug still depends on its benefits because label warnings are not fully successful.
   - Prevention of interactions.
   - Limited distribution.
   - Identify safe dose.

An FDA official cited these examples of risk vs. benefit:

1. **moxifloxacin** – "This is a quinolone of no special effectiveness with an increase in QT/QTc of about 6 ms (somewhat greater at a higher but unneeded dose)…It has been pretty well studied. It was approved because there is a low theoretical risk and no apparent arrhythmias in 4,000 patients."
2. **terfenidine** – "There is a risk in people receiving 3A4 inhibitors. Publicity reduced concomitancy by about 90% but there were still cases. It was withdrawn when another non-sedating antihistamine came on the market."

3. **ziprasidone** (Pfizer's Geodon) – "There was no documented superiority (to other approved anti-psychotics), but it has a different ADR spectrum and a well-studied QT effect of 10-12 ms with no increase in patients on ketoconazole. It was approved because there was a low-to-no theoretical risk, no interaction effect and a strong perception of a need for a variety of antipsychotics. It was labeled with a dark print warning. It is not second line, but the indication section says to consider the QT effect when making a decision to use it."
4. **dofetilide/sotalol** – "These have a large QT effect (>20 ms), with cases of TdP. They are indicated only for 'highly symptomatic' patients who feel very bad when they are fibrillating. We are now learning that control of rhythm may not be as important as we thought. But…there were outcome studies for both drugs. There is box warning for both, and dofetilide has controlled distribution to hospitals and prescribers, which may have driven people to sotalol instead."

PHASE I CONTROL ARM

The following dialog demonstrates the FDA's attitude on the subject of positive Phase I controls:

A doctor asked the audience: "Who has even done a Phase one study with positive controls?"

Audience response: Only a few hands went up.

Pharma official: "Are we saying every NME has to have a positive Phase I comparator study?"

FDA;s Dr.Throckmorton: "That's what we are asking."

Pharma official: "That's an enormous burden".

FDA's Dr. Temple: "Every time we look at a database on QT, we get substantial differences in effect. How do you know if there is no control if this is a study that can detect something?"

Pharma official: "That's what this meeting is about…There will be a large discussion on how to do it right.:

FDA's Dr. Temple: "That is a different question…We don't know why some studies showed a QT effect and others didn't. You don't know that any more than you know why half of antidepressant trials can't tell the drug from placebo even though everyone is trying very hard…What is such a big deal about adding another group. I expect positive control to show an expected difference from placebo…That is only a 20%-25% increase in the Phase I trial size."

Pharma official: "In a crossover trial that is a big increase. You are easily doubling the cost of Phase I."

FDA's Dr. Throckmorton: "Think of how we measure hematocrit or hemoglobin. This is, roughly speaking, analogous to that except there is no negative control. It seems that the problem is less that it is a bad idea but that it is burdensome." Later, Dr. Throckmorton said, "A well-done Phase 1 study allows for less intensive evaluations and fewer ECGs in the large, pivotal trials, so the reward for doing (a Phase I QT control) is relaxation in later trials."

FDA's Dr. Temple: "I don't understand what is so burdensome about adding one arm."

The drug most often mentioned at the workshop for use as a positive control in Phase I was Bayer's Avelox (moxifloxacin). A cardiologist said, "Using moxifloxacin as a control is a perfectly rational approach because of its small QT effect and our good experience with it." Dr. Temple said, "You can pretty much say there is uncertainty with moxifloxacin that hasn't turned out to be a problem."

OTHER AREAS OF FDA CONCERN

Dr. Temple cited what he called "four great questions":

1. Are there drugs with a small mean effect but a large effect on a subset of patients?
2. Is the apparent lack of TdP with small QT effects (<10 ms) real or just a matter of a lower but not-zero risk that is hard to detect in an uncontrolled setting?
3. Are the effects and risks of QT prolonging drugs additive, super-additive (synergistic), or independent?
4. Is all QT/QTc prolongation equal?

Other major areas in which FDA officials had questions and were looking for comment were:

How should the size and effect of QT prolongation be measured? Workshop participants generally agreed that:

- Quality control is badly needed in ECG measurements.
- 12-lead measurements should be encouraged.
- The current technology has limitations, and a precision of 4 ms - 5 ms may not be achievable. A pharma official said, "It is very difficult to standardize readings. It is very artsy fartsy stuff."
- The FDA will not accept Holter monitoring yet. Some workshop participants urged the agency to reconsider this, but it seems unlikely that the FDA will reverse its position until the technology advances further. Dr. Temple said, "The document says not yet because we haven't accepted that yet, but as soon as the data is submitted we will reconsider this. A number of people have said this is around the corner, and that would be fine."
- Measurements can be affected by: changes in posture, changing leads, using different brands of machine, food intake, time of day, etc.

A CRO official had an idea FDA officials seemed to like. He suggested, "One of the points of this conference should be to make an ECG more like routine lab tests (to which the audience applauded). Let's get reference standards for labs. If a pharma wants to do study with a new lab or group, then it should participate in a reference study with a known agent and repeated longitudinal testing for ongoing QA (quality assurance), and that probably should be managed by an industry consortium (of vendors and pharmas)….I have sympathy having seen the ECGs (the FDA has) to look at…There is nothing in the Concept Paper) about minimal standards for ECG machines."

How should "susceptibles" be assessed?

The paper calls for assessment in Phase II/III of a range of people including those potentially susceptible, such as those with electrolyte abnormalities, women, CHF patients, phenotypic poor metabolizers, patients with prolonged QT at baseline. Dr. Temple said, "We should at least think about including some of these…There is a strong urging in the plan to work up any patient who has a large effect and see what explains that, including genotyping and assessment of the risk factors and specific study of them. The paper does ***not*** specifically call for deliberate study of long-QT genotypes with normal QT or for concomitant use with known QT prolongers [e.g., Pfizer's Geodon (ziprasidone), Bayer's Avelox (moxifloxacin), etc)."

Could a small change in QT hide a large effect in some patients?

That is, could even a small effect be a problem for susceptible patients? Dr. Temple repeatedly asked this question. He said, "There is a need for more data. And the risk needs to be related to QT effect size and patient characteristics. We know women are more susceptible to drugs. If you keep the dose low so the QT effect is small, does that avoid risk or does it always have a problem at lower doses? We don't know for sure. There were no cases of TdP with uninhibited terfenidine. So if a drug has a dose response range, are you comfortable with a dose at the low end of the range? You probably are, but that needs further looking at."

What happens when more than one drug with a QT issue is taken by a patient?

Right now, the FDA warns in the label against using two QT prolonging drugs together, but FDA officials are not sure that this is necessary, and they would like to see research that proves this one way or another.

What can be learned from data on approved drugs?

Dr. Temple repeatedly commented that it is important to find out as much as possible about drugs already on the market to see if they are pro-arrhythmic or not. "We need better analysis of historical data. There is a wealth of data, some of it locked in labs, that could shed light on the QT issue," he emphasized.

When should studies be required or encouraged in high risk populations?

An expert suggested, "(These studies) should only be required when something suggests QT prolongation, and then look at special groups." A pharma official wondered, "You get an answer a lot faster if you expose patients at higher risk than lower risk, so why not expose patients at higher risk earlier in the development process?" A Merck official said, "Typically sponsors try to get an adequate safety data base in patients who have the target disease but are otherwise healthy before they are comfortable trying the drug in a sicker population…You don't expose high risk patients to a drug you don't know enough about...There may be an opportunity to find patients within what we thought was a well population." A Pfizer official said, "Frankly, in some cases you want labeling restrictions so susceptible patients don't get the drug." A researcher said, "I've never seen a well-evaluated drug in normals…where (the QT) effect was only identified in high risk patients. Therefore, with a proper, intensive Phase I trial, you will have the answer about which kind of high risk populations are worth looking at in Phase II/III subsets where they sneak in and have concomitant meds, rather than designing independent trials in these groups."

Should you exclude patients from Phase III trials who have a high QT at baseline?

The FDA's Dr. Temple wondered, "Should we be urging studies of this – careful studies, obviously?…And there is another issue" We know boxed warnings and advice not to do something are frequently not followed…We do it because we are all happier when we do a label like that, but there is a piece of me that says we should know (the effect). Like Geodon and moxifloxacin, which say don't give with any other drug that prolongs QT – maybe that is good advice and maybe not. Should we be urging people to find out?" A doctor responded, "The assumption is that QT effects are additive. There is no evidence to say that, but none to say it isn't. We should be able to settle this easily in the lab (in animals or cell lines). Does sotalol + moxifloxacin result in less prolongation of sotalol."

Which QT interval matters (e.g., group mean of values at a particular time or mean maximum recorded value)?

Dr. Temple said, "There seems to be general agreement that mean maximum recorded value is best…The document suggests taking the average."

How much EP workup should be done before a drug is taken into the clinic?

An FDA official said, "You might push the dose differently in Phase I if you knew there was problem. A common failing in my view is that people do not have this information."

IMPLICATIONS FOR DRUG DEVELOPMENT

Some of the implications of the Concept Paper for drug development, if it is adopted as written, are:

- QT interval prolongation – with or without documented arrhythmias – may be the basis for non-approval of a drug.
- Failure to perform an adequate clinical assessment of QT prolongation potential may be justification to delay or deny marketing authorization.
- In clinical trials ***all*** drugs should have ECG evaluation and a thorough Phase I work-up, including a study of doses above the therapeutic level.
- The use of a QT positive control arm will be required in *all* Phase I trials of ***all*** new drugs.
- Anti-arrhythmic drugs with QT prolongation "almost always needs to have outcome data to show a favorable risk/benefit relation."
- If QT prolongation is a class effect, comparison with concurrent active controls from the same therapeutic class should be performed.
- Baseline QT should be a mean of at least three readings over 2-3 days.
- QT interval prolongation – with or without documented arrhythmias – may be the basis for non-approval of a drug.
- Failure to perform an adequate clinical assessment of QT prolongation potential may be justification to delay or deny marketing authorization.
- When a pharma is making a go/no go on a screened compound, an FDA official urged companies to "try to keep the desired pharmacologic effect without the QT effect...Other things being equal, develop the drug without QT prolongation."
- For QT prolonging drugs, consider the:
  - Benefits in patients refractory to or intolerant of available therapies.
  - Availability of therapeutic alternatives that lack QT prolonging effects.
  - Morbidity/mortality associated with an untreated disease/condition.
  - Magnitude of QT prolongation effect.
  - Magnitude of the efficacy effect.
  - Dose/response because it may be possible to avoid a QT-prolonging dose.
  - Developing the drug as BID, TID or controlled release.
- If there is a QT prolongation by the parent compound, try to find a metabolite that is not metabolized by the 3A4 pathway.