AMPS-QT

The AMPS Quarterly - Issue n.11 - 3Q2011 Editors: Fabio Badilini PhD, FACC and Martino Vaglio MS

AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

As the focus of the industry, and the FDA, seem to be steadily shifting more and more toward making a better use of holter-collected data in the context of pharmaceutical trials we received, and very proudly publish, a paper from one of the pioneers of the holter technology, Dr. Lawrence Z. Satin, MD, FACC. In 1968 Dr Satin in fact worked with Norman Holter (inventor of the Holter Monitor) in the NASA space program studying the effects of space travel on astronauts. At that time, newly devised Holter recorders weighed 50 pounds and were outfitted in astronauts' backpacks. From that innovative era until the present day, Dr. Satin's research teams have always remained at the leading edge of Holter technology application. Nowadays Dr. Satin is regarded as one of the United States leading research cardiologists with more than 40 years of distinguished experience, and we are positive our readers will greatly benefit from his contribution. As usual: enjoy!

A Noteworthy Contribution:

How a Leading Core Lab Enhances the Intent of ICH-E14 with Holter Bin.

By Lawrence Satin, MD, FACC, Chief Medical Officer, Cardiocore.

Readers of this newsletter are familiar with WinAtrec as presented in the very first issue of AMPS-QT by its developer Dr. Fabio Badilini and subsequently addressed by its most renowned proponent, Dr. Fabrice Extramiana, in issue number four. Our indebtedness is owed to both of them. In the last issue Dr. Badilini reports on the events of the June 17, 2011 CSRC webinar where the now venerable "White Paper on Methods to Assess QT/QTc in the Presence of Drug-induced Heart Rate Changes" was discussed and where I was one of many invited reviewers. Initially, I was somewhat dismayed by a statement in the initial draft that Holter bin was E14 non-compliant; allegedly, due to an intrinsic limitation of the software (WinAtrec) to provide a time-based synchronized assessment of the QT effect during the administration of drug and placebo. Perhaps this limitation existed in the minds of those without firsthand experience of using WinAtrec or without knowledge of user modifications that could readily lead to meaningful workarounds. The foremost tenet of E14 has always been to specifically evaluate the worst possible scenario, and in fact, WinAtrec can intrinsically provide that quality. Surely the issue of E14 compliancy could be raised with other methods discussed in the White Paper especially where daytime and nighttime values are merged to provide a so-called "normal" baseline. Rightly so, the reviewers of the webinar agreed to eliminate E14 non-compliancy from the Holter bin description. In The AMPS Quarterly, Issue number 10, 2Q 2011, Dr. Badilini goes on to describe most elegantly the new modification to WinAtrec software that will permit both rate- and time-related ECG signal averaging simultaneously to achieve ICH-E14 compliance.

What follows is a case study of how we successfully enhanced the original intent of ICH-E14 by applying WinAtrec to examine the worst possible scenario by comparing the QT interval on-drug to placebo at the identical heart rate during the hours of greatest drug concentration.

Over two years ago we were faced with a new compound that had a profound positive chronotropic effect, increasing the mean heart rate by 10-12 bpm. Not surprisingly, traditional QT correction formulas (Bazett and Fridericia) and the subject-specific correction (QTcI) resulted in a so-called "positive" thorough QT trial where six time points during peak concentration significantly breeched the double delta 10 ms 95% CI upper bound.

The new compound had a peak concentration spread over four hours between 2 and 6 hours post-dose. During this "selective time window" the nominal ECG time points extracted from Holter flashcards in triplicates occurred at 2.0, 2.5, 3.0, 3.5, 4.0, and 6.0 hours post-dose on Day -1 and on each treatment day. The baseline rate related (RR) bins were 20 ms in duration, containing a minimum of 10 beats, acquired on Day -1, and were time-matched to the identical selective time windows of the treatment days. First, the average of the QT intervals in the time-matched RR bins on-drug and those on placebo were compared to the same time-matched RR bins at baseline to yield the single-delta QT. Second, the same process was used to compare the baseline adjusted time-matched QT intervals from the same RR bins (same heart rate) on-drug to placebo, thereby deriving the double-delta value. Our "modification" of the traditional Holter bin method allowed a comparison of the QT intervals at identical heart rates for both the study drug and placebo. Where traditional QTc formulas attempt to *correct* for heart rate, Holter bin *controls* for heart rate by removing it as a confounding factor. The analysis resulted in a "negative" through QT trial with all the mean QT intervals at every nominal time point falling well below the 10 ms threshold of regulatory concern.

Critical to the success in establishing the validity of this process is the need to provide sufficient beats in a wide variety of rate bins that encompass heart rates achieved by the supratherapeutic dose of the study drug in both the baseline and placebo samples. This is, of course, true for all methods that analytically seek to assess QT/QTc in the presence of drug-induced heart rate changes. This was easily achieved by allowing normal activity during baseline acquisition and the naturally occurring autonomic effects during placebo administration at rest. We have seen heart rates accelerate to levels of 120 bpm during placebo treatment and have not had to engage artificial means to increase heart rate.

It should be pointed out that the same Holter bin process was applied to the active control (moxifloxacin) arm. The peak moxifloxacin concentration coincidentally appeared within the same four hour selective time window as did the study drug. As expected for any drug that intrinsically produces ion channel blockade within the cardiomyocytes, the QT prolongation induced by the fluoroquinolone antibiotic remained positive when compared to placebo despite acquiring the QT interval comparisons at the same heart rate.

There are perhaps a few final thoughts that should be intuitively considered when confronting a new compound that has a positive chronotropic effect. Drug-induced Torsade de Pointes is a rare, often self-correcting, but potentially life threatening arrhythmia heralded by a slowing of the heart rate, and not acceleration. Transient increases in QT interval duration due to a sudden increase in heart rate are often related to hysteresis since the adaptation of the QT interval to a change in heart rate is never instantaneous. If this physiologic event were inherently dangerous we would all have died in infancy. It is not the same phenomenon as ionic channel blockade. Finally, when considering drugs that have been shown to induce QT prolongation, one would be hard pressed to name a single one that increased heart rate.

Products News

Looking forward

In Q4 AMPS is planning to release:

- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- an update version of FAT-QT with new scoring metrics, synchronized with FDAEcg Suite v.2.
- a new version of TrialPerfect, with enhanced graphical interface and optimized ECG workflow.

- Enhancements to CalECGv3 algorithm, available in the next version:
  - Re-design for the detection of PR interval onset.
  - Re-design for the detection of QRS interval offset.
  - Optimization/tuning of QT interval measurements using more than 300.000 annotated ECGs from different studies and different core labs.
  - New design of Median beats generation algorithm, with user direct control/review on the QRS complexes involved.

- Additional future CalECGv3 enhancements in the works:
  - Additional intervals (e.g. QTpeak interval).
  - Additional amplitudes (e.g. Q, R and S waves).
  - New parameters related to re-polarization morphology based on Gaussian Mesa function data fit (Refer to the following paper for more details: The Time Course of New T-Wave ECG Descriptors Following Single- and Double-Dose Administration of Sotalol in Healthy Subjects, Extramiana F et al, Ann Noninvasive Electrocardiol 2010;15(1):26–35; Efficient Modeling of ECG Waves for Morphology Tracking; Dubois R et al; Computers in Cardiology 2009;36:313−316 and AMPS-QT 3Q2009).

- Synchronization with the latest versions of the FDAEcg Suite and FAT-QT algorithms.

AMPS Notebook

Fabio Badilini has been appointed chairman for next year 37th **ISCE conference** that will be held in Birmingham, AL from April 20 to April 24, 2012.
Fabio Badilini will be attending the **American Heart Association**, Scientific Session held from November 12th to 16th, 2011 in Orlando, Florida.

AMPS People

We continue our round of staff introductions with Gianfranco Toninelli.
Gianfranco is the youngest and most recent AMPS acquisition, as he joined the team in 2010 thanks to an internship for the development of an ECG plug-in.
Earlier this month Gianfranco has obtained his Bachelor degree in Engineering from the University of Brescia, discussing his thesis titled: "Implementation of a software component for the acquisition of Schiller-XML format".
All the while working at AMPS he is also continuing his studies in Engineering, towards the Master degree.
He is currently participating in the project for the development of a software tool for the analysis of the tachogram in dynamic conditions, in collaboration with the Milan Sacco Hospital and in the last few months he has been involved in the ECGScan project.