Use of Concentration-effect Modelling for Cardiac Safety ECG Assessments

Concentration-effect modelling (CEM) is a method of data evaluation which is also commonly referred to as pharmacokinetic-pharmacodynamic (PK-PD) modelling or exposure-response (ER) modelling. It uses time-matched pairs of a PK measurement (usually plasma concentration of a compound or its metabolite) and some type of “pharmacodynamic” outcome. The purpose is to determine if there is a relationship between the concentration of whatever drug is being evaluated and the specific effect of interest.

As discussed in the first article in this series, assessments of a drug’s effects on cardiac repolarisation have historically been performed using a by-timepoint evaluation of changes from baseline of the QTc interval, as described in the 2005 ICH E14 Guideline. A mixed effects model and the Intersection Union Test are used. Since each timepoint after dosing is analysed independently, this approach has the limitation of requiring large numbers of participants in order to have adequate power. Historically, thorough QT/QTc (TQT) studies have required 40-50 participants for a crossover trial, and from 200-260 participants for a parallel design trial. To improve precision, they have generally been performed in healthy volunteers rather than patients with the disease targeted by the new compound. However, many new drugs (including the majority of new oncologic agents) cannot be administered to healthy volunteers in sufficiently high doses, and for such new drugs an alternative to the QT has been necessary. In such cases where a standard QT has not been feasible, alternative study designs have been used, and have often relied upon CEM rather than a by-timepoint analysis: CEM uses all of the data for all participants in a single analysis, and therefore generally requires much smaller numbers of participants than a by-timepoint analysis.

In late 2015, the ICH E14 Questions & Answers document was revised again [ICH E14 Q&A (R3)] to allow the use of CEM as an alternative to a by-timepoint analysis. This potentially allows for the use of ECG and PK data collected in Phase I ascending dose studies to replace the data which was previously collected in a standard TQT study, but without requiring a large, dedicated cardiac safety trial. CEM data may potentially allow a full characterisation of the ECG effects of a new drug (we are interested in any effects on heart rate and the PR and QRS intervals, not just QTc: see Nada and colleagues). In some cases, Phase I trials may not be sufficient to collect all of the data required to fully assess the ECG effects of a new drug, but may provide enough data to reduce the size and scope of additional ECG evaluations.

Data Collection for Performing CEM of Cardiac Safety Parameters

To perform CEM to adequately characterise the ECG effects of a new drug, one must plan to collect PK specimens at enough timepoints to fully explore the PK of the parent drug and all active metabolites. In practice, the PK collection schedules which have become standard in current ascending dose Phase I studies are usually adequate for this purpose, even though the timepoints will differ for different drugs.

The ECG timepoints that are required will be the same as the PK timepoints. Again, they should cover the entire PK spectrum of the parent compound and metabolites, including the rise in concentration, Tmax, decline in concentration, and timepoints out to at least 24 hours (to allow detection of delayed effects on repolarisation due to alterations of ion channel trafficking). ECGs should be collected in triplicate (to reduce variability) and should always be collected before the PK samples. In nearly all cases it is best to collect ECGs with a continuous 12-lead ECG recording system (12-lead Holter recorder or 12-lead telemetry system) as this will reduce the inconvenience for the site personnel and participants, as well as potentially allowing the later collection of ECGs at additional unplanned timepoints if necessary. ECGs may be analysed immediately or at a later date, but the same robust analysis by a centralised ECG core lab as required for a TQT should be utilised.

The decision as to whether to utilise data from single- or multiple-ascending dose trials should be made based on the PK of the parent compound and metabolite(s). Similarly, the decision as to whether to use a time-matched baseline (requiring collection of a full set of ECGs on the day prior to dosing) or a time-averaged baseline (3-5 triplicates collected in the 60-90 minutes prior to dosing), and the decision as to which QT correction method to utilise, will be made based on the profile of the individual compound being evaluated.

The use of CEM endpoints reduces the number of participants required for a full characterisation of the ECG effects of a new compound, but adequate power is still necessary. Current estimates based on previous trials as well as modelling approaches suggest that 3-4 cohorts of participants receiving dosages spanning the therapeutic to supratherapeutic exposure range should be adequate for a thorough evaluation of a drug’s electrocardiographic effects. Standard cohort sizes of 8-12 are usually adequate, with 2-3 individuals per cohort receiving placebo. Note that having additional participants who receive low doses of medication which yield low or unmeasurable plasma concentrations will not
add to the trial’s power. One typically would like to have at least 200 triplicate ECG-PK pairs (the mean value of the measurements from each triplicate are used) in order to have a good model fit.

**Assay Sensitivity and Supratherapeutic Exposure**

In a standard TQT study, one attempts to test a supratherapeutic dose of the investigational agent in order to allow regulators to answer the clinical question, “What will the drug do if a patient has a much larger than average exposure?” as may happen if a patient has a drug-drug interaction, or develops renal or hepatic impairment. Regulators have avoided making blanket guidance as to a specific required multiple of the mean therapeutic exposure, as the potential risk of a “supratherapeutic” exposure varies greatly from compound to compound. When feasible, we have generally tried to achieve a 3-5-fold multiple of the mean therapeutic Cmax with the “supratherapeutic” dose in a TQT, though drug tolerability may be an issue leading to use of a lower “supratherapeutic dose”. However, in standard TQTs we have always used a positive control (usually oral moxifloxacin) to demonstrate assay sensitivity, regardless of how high a multiple of the drug’s therapeutic exposure has been reached.

In contrast, the issues of “supratherapeutic dose” and whether demonstration of assay sensitivity will be required for ascending dose CEM endpoint trials are less clear. ICH E14 Q&A R3 indicates that if a “sufficiently high multiple of the clinically relevant exposure” is achieved, then a separate positive control would not be necessary. However, the “sufficiently high multiple” remains undefined. Regulators have indicated that whether the ECG effects of a new drug are studied with ascending dose studies and CEM, or a standard TQT study with by-timepoint analysis, a supratherapeutic exposure is still desirable (when feasible) in order to answer the questions about a “worst case” scenario where a patient has a much higher than average exposure. In order to avoid the requirement for a positive control to demonstrate assay sensitivity, the required “sufficiently high multiple of the clinically relevant exposure” will generally be higher than the “supratherapeutic exposure” used in a standard TQT study. In a TQT study, the supratherapeutic exposure is required to inform the clinical “worst case” scenario; in an ascending dose study using CEM, the supratherapeutic exposure must also be high enough to eliminate any concerns about a false negative result due to trial conduct, ECG or PK measurements, or statistical methods. How much higher? That will likely depend on the specifics of the compound, but some regulators have suggested that a 5-7-fold multiple of the clinically relevant exposure would likely be adequate to avoid the need for demonstration of assay sensitivity.

At the current time, the only well-characterised method for demonstrating assay sensitivity in an assessment of a drug’s effects on the ECG has been the use of a positive control, which has usually been moxifloxacin. There are several possible ways to incorporate a moxifloxacin positive control in a Phase I ascending dose study, though this scenario has met with little enthusiasm within the clinical pharmacology community. Current Phase I studies are already becoming increasingly complex, and the addition of a positive control would further complicate, lengthen, and increase the cost of early-phase investigations. Fortunately, the FDA and other regulatory groups are currently exploring alternative, non-pharmacologic methods of assessing assay sensitivity (e.g., testing for circadian or food effect variations in QTc, effects of orthostatic manoeuvres, or statistical analyses), which may in the future reduce or eliminate the need for positive controls in ECG trials.

**Concentration Effect Modelling - Statistical Methods**

There are many possible statistical methods for performing CEM in cardiac studies. It is strongly recommended that the method to be used should be stated prospectively in a statistical analysis plan, in order to avoid any appearance of having chosen a method post-hoc in order to achieve a specific result. Several publications by members of the FDA Cardiovascular and Renal Drug Products review division have provided very helpful insights into appropriate models to be used. Models should be used for all ECG intervals being assessed (usually heart rate, PR, QRS, and QTc), and tests for hysteresis and linearity should be included. The statistical team performing these complex analyses should be experienced in performing CEM on ECG data.

**Limitations of the New Paradigm**

Although the use of CEM endpoints in early-phase trials is simple in concept, there are a number of uncertainties and complexities which make the actual design and interpretation of these data difficult.

- Ascending dose trials will need to be performed to the exacting standards of a TQT if we wish to have the adequate precision to replace the dedicated ECG trial. This applies both to the conduct of the trial and the analysis of the ECG data and the statistical work.
- The design of an adequate trial may be very difficult at the time that a first-in-human study is planned, as the PK of the parent drug, presence of human specific metabolites, tolerability, clinical dosage, and potential effects on ion channel trafficking are as yet unknown. One must make one’s best guess based on non-clinical data during the design of the cardiac safety portion of the trial, and the assumptions used may turn out to have been faulty.
- It may be difficult to put the data collected in early-phase trials into clinical context until later-phase trials have clarified the clinical usage of the medication and the true “worst case” scenarios which are possible. It may not be possible to determine if an adequate range of exposures has been tested until later in development, leaving open the possibility that additional assessments may still be required.
- CEM is a powerful tool, but it does have limitations.
Careful ER modelling of a parent compound will not help detect the repolarisation effects of a long-acting metabolite, and may miss delayed repolarisation effects due to ion channel trafficking.

- Concerns remain about further increasing the cost and complexity of early-phase trials.

**Conclusion**

ICH E14 Q&A (R3) provide exciting new options for drug developers by allowing the use of CEM, and thus potentially ascending dose ECG data, for the assessment of the electrocardiographic effects of a new drug. The use of this strategy will require careful trial design, including centralised collection and evaluation of ECG data, and careful statistical analysis by an experienced statistical team. Though methodologic questions remain concerning the determination of an adequate supratherapeutic exposure and the use of a positive control, the use of CEM for cardiac safety data in early-phase trials is a valuable addition which promises to increase the speed and reduce the overall cost of drug development.

**References**


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