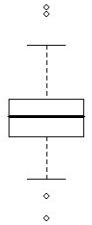
Washington DC – 2018-05-22



Issues with exposure-response analysis
How we can close the gap

Georg Ferber, Statistical Consultant

Statistik.Georg.Ferber@bluewin.ch

What gap?

Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-017-9558-5

REVIEW PAPER

Scientific white paper on concentration-QTc modeling

Christine Garnett[1] · Peter L. Bonate[2] · Qianyu Dang[4] · Georg Ferber[3] · Dalong Huang[4] · Jiang Liu[5] · Devan Mehrotra[6] · Steve Riley[7] · Philip Sager[8] · Christoffer Tornoe[9] · Yaning Wang[5]

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- **The white paper gives the basics and points to open issues**
  - In Table 1, it lists issues that go beyond what is discussed there.

Table 1 of the White Paper

Combination drugs or active metabolites

Cytotoxic oncology drugs

Drug-induced changes in heart rate

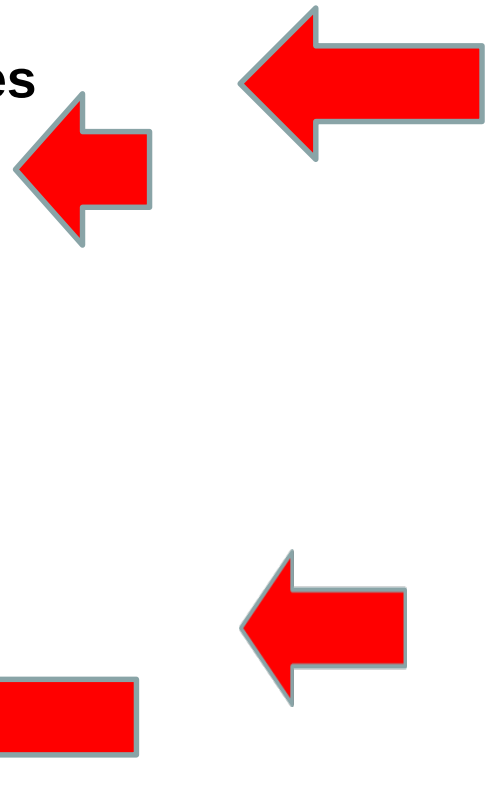
Extended Release products

PK/PD hysteresis

Non-HERG changes in QTc

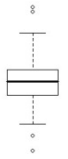
Drug interaction studies

Food effect studies



Combination drugs and metabolites
What table 1 says

- **Characterize the effect of each analyte (*i.e.*, individual drug parent and/or metabolite concentrations)**
- **Any interaction between analytes**
- **... should not be analyzed as a series of univariate analyses, but rather analyzed using separate slopes for each analyte and with corresponding interaction**
- **Combination drugs – include both monotherapies ...**



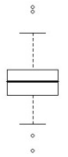
Combination, Interaction, Metabolites

They have in common that concentrations of more than one moiety are involved

But:

- **With metabolites we usually cannot control the relationship between them,**
- **while this is possible with combinations and drug interaction.**

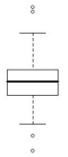
So let us start with the simple one – drug interaction and combination drugs



Drug interaction studies

Table 1 of the White Paper:

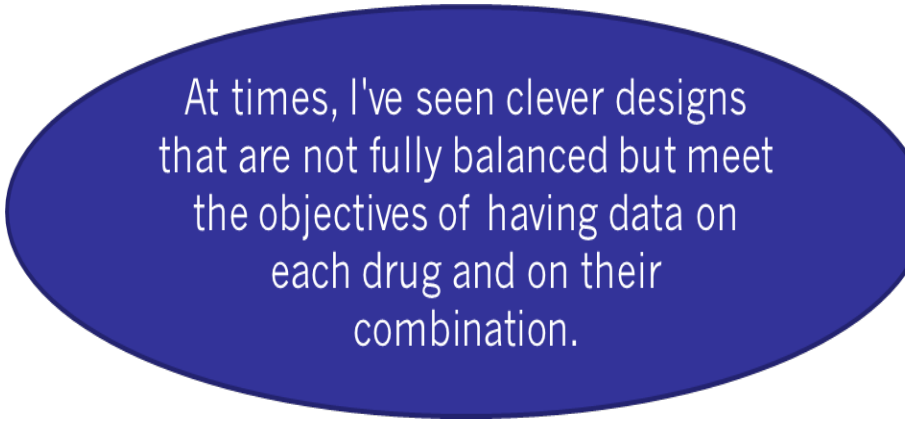
It is important to characterize the effect of the test drug and interacting drug as the interacting drug could prolong the QT interval (e.g., ketoconazole) similar to combination drugs described above.



Drug Interaction Studies and Combination Drugs

If used to assess QT effects, these should follow a factorial design, i.e. always include

- **each treatment as monotherapy**
- **the combination**
- **placebo.**



This will allow to fit a model with both moieties and an interaction term.

Predictions can be made at a wide range of combinations of the concentrations covered.

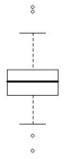
It is acknowledged that a factorial desing may, at times, be challenging.

Predictions – at what concentrations?

If we have one moiety only, we predict at geometric mean C_{max}.

If we have several moieties how to proceed?

- **Predict at combination of geometric mean C_{max} for each moiety**
  - Is rarely realistic.
  - May be overly pessimistic if both drugs prolong QTc,
  - but could also be optimistic in case of negative interactions.
- **For each moiety, determine individual T_{max} and predict at the mean of the concentrations seen at there.**
  - If PK differ strongly, occasional zero values would bring the geometric mean to zero. So I use the geometric mean for the moiety for which T_{max} was determined, and arithmetic means for all others.



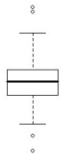
Metabolites

We have limited possibilites to vary the relationship between concentrations of the moieties.

- **This may be a problem, in particular if variants of metabolism must be expected in clinical practice**
  - slow metabilizers, metabolic inhibition, hepatic impairment

However:

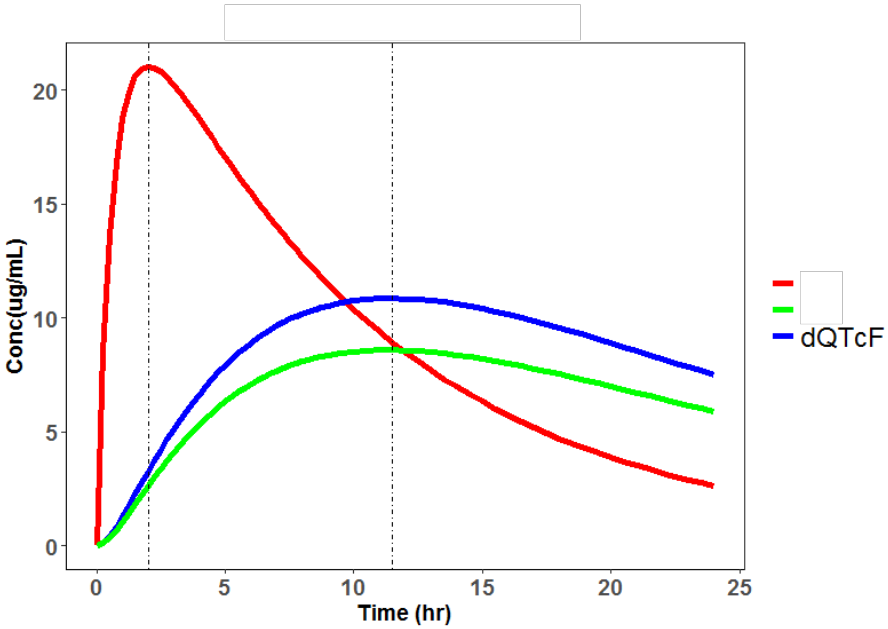
- **Active metabolites are not considered a special problem in a by timepoint analysis.**
- **We only need to know if there is prolongation of interest or not**
  - in concentration-QTc modelling, an active metabolite needs to be taken into account because it may be the reason for hysteresis between the parent compound PK and the QTc effect.



Ideal Situation

Effects of all moieties and even an interaction may be identified if

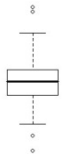
- **the PK profiles of parent and metabolite are sufficiently distinct**
  - need measurements around T_{max} of all moieties
- **there is a QT effect**



One way to fit a model

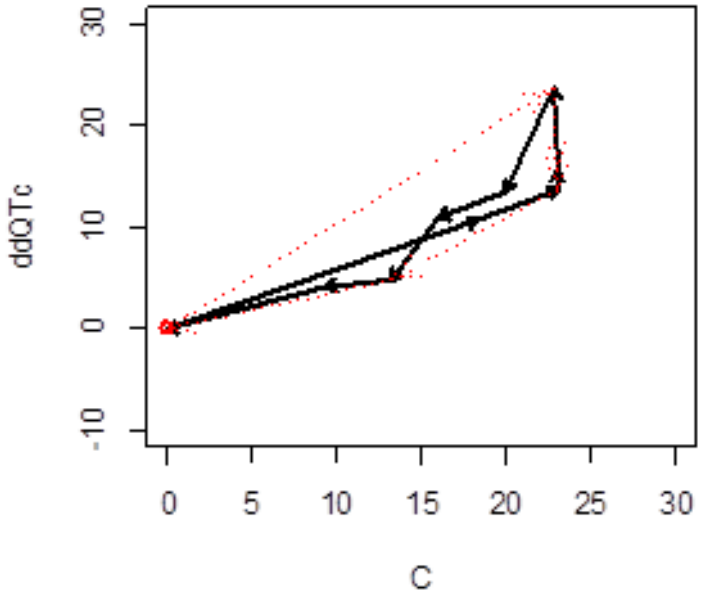
In such an ideal situation one may proceed as follows:

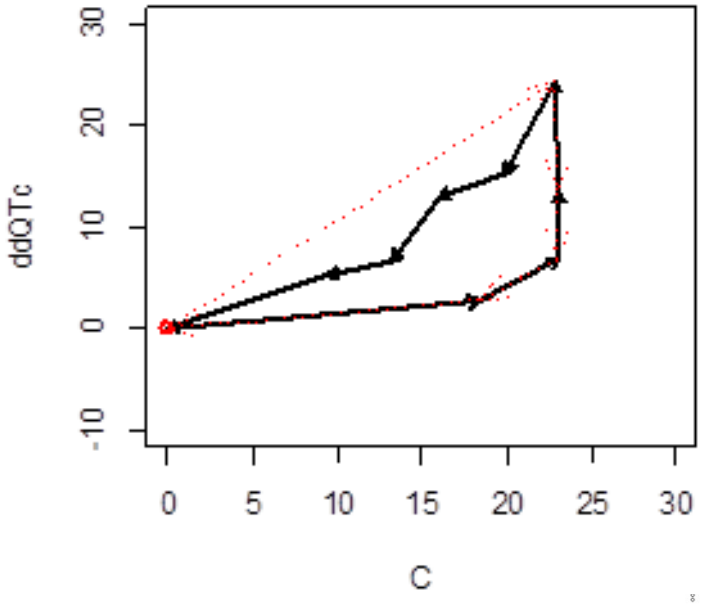
- **Fit a model including concentrations from all known metabolites**
  - Calculate AIC and t-value for treatment effect and slopes
- **Remove concentration with least significant slope from model**
  - Calculate AIC and t-value for treatment effect and slopes
- **Until only one moiety is left.**
- **For models with significant treatment effect progress to e-max models.**
- **Among models with non-significant treatment effect, select the one with lowest AIC as primary.**



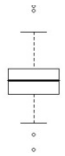
Use hysteresis loops

Another way to select an appropriate model is the use of hysteresis loops.



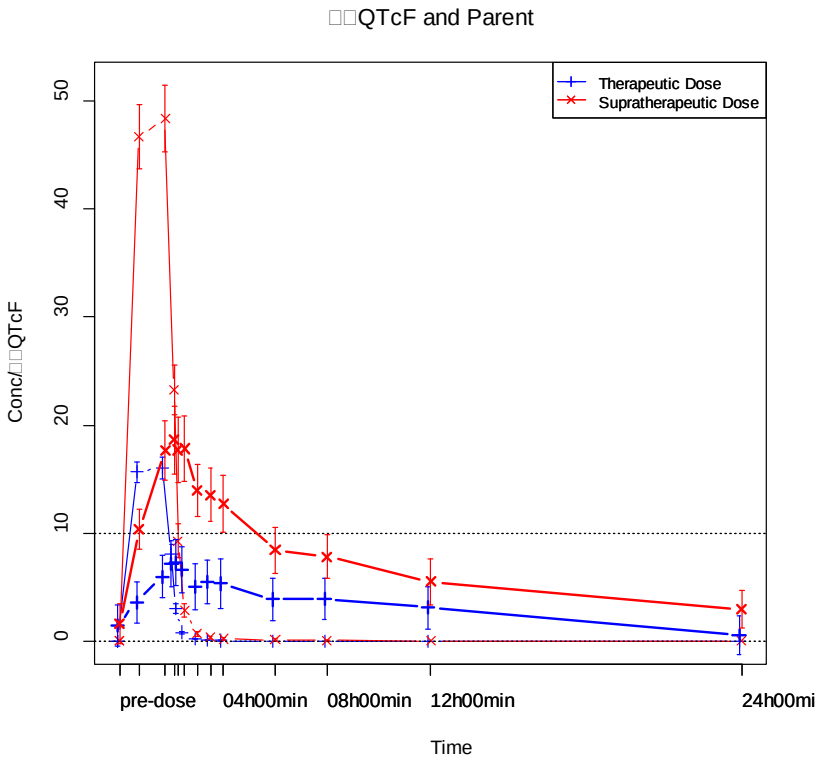


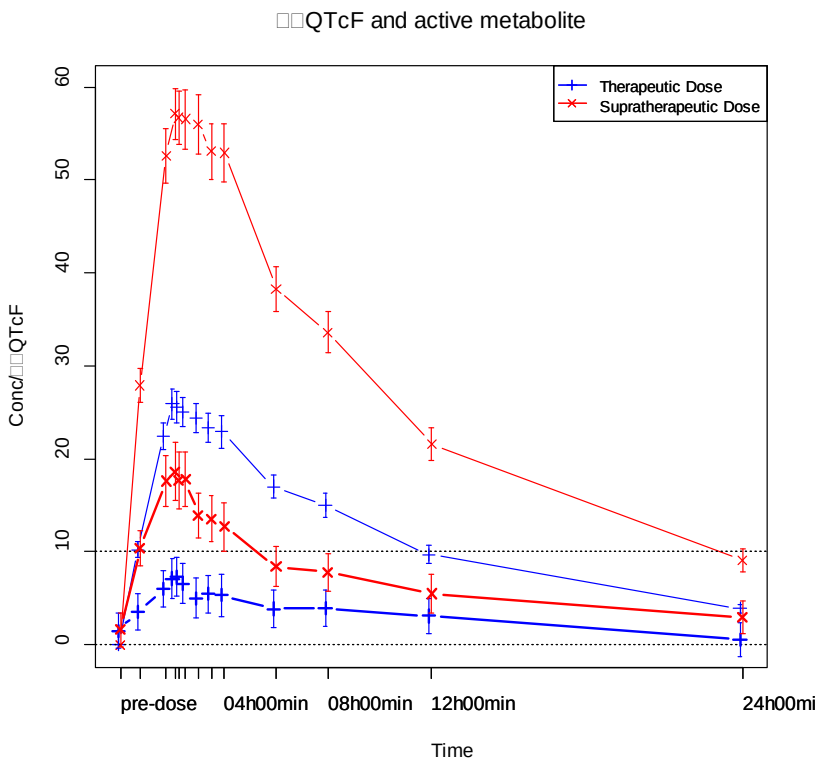
Simulated data

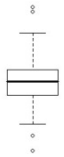


Example A

- **A prodrug with an active metabolite.**
- **An additional metabolite was measured.**



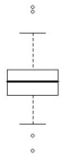




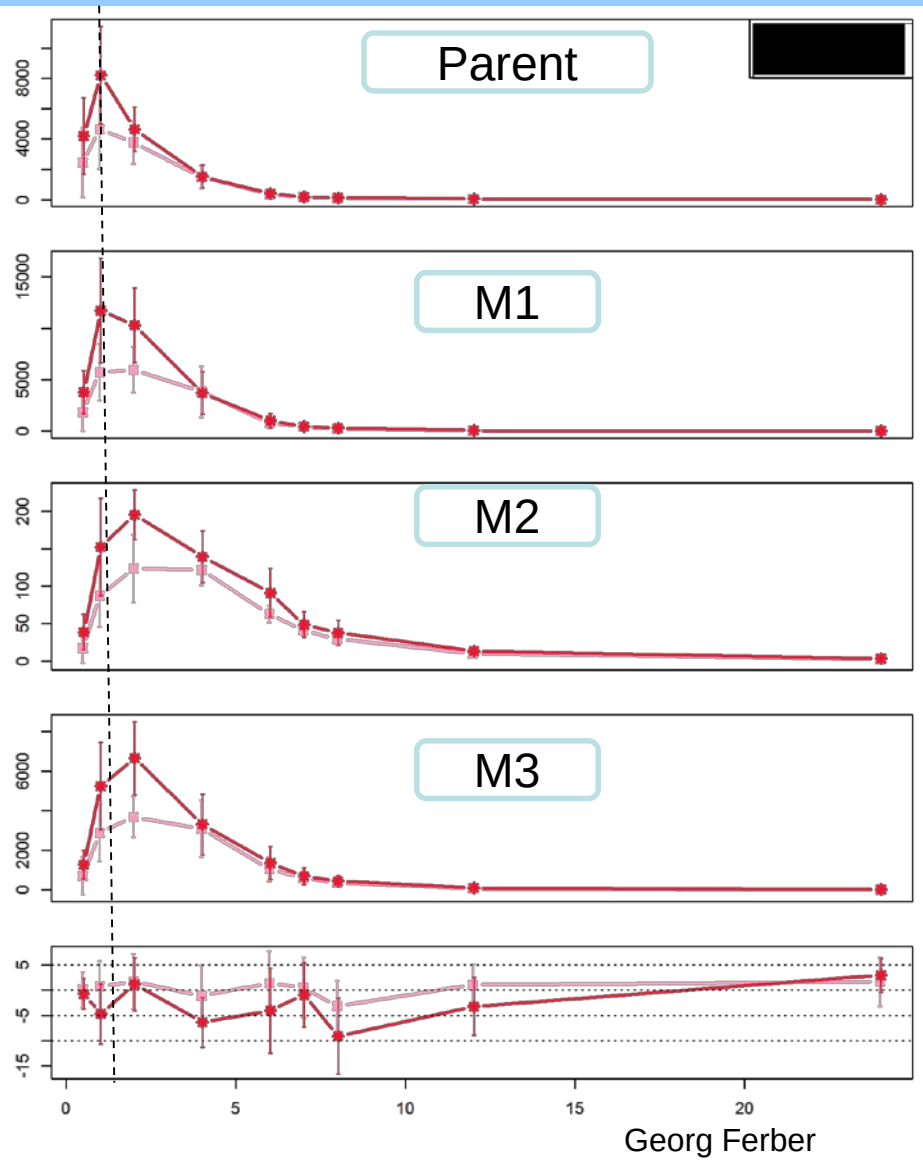
Example A – Model selection

Model	AIC	Residual error	t of treatment effect
All 3 moieties	12035.3	5.33	0.07
Prodrug and Active drug	12100.9	5.55	-0.24
Active drug only	12155.0	5.72	-0.06

The model with all three moieties was selected, but the simpler model with only the active drug also performed quite well.



Example B



Even if there was an effect on QTc, it would be difficult to decide which moiety was responsible.

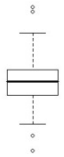
Example B – Model selection

Model	Status	AIC	t of treatment	Residual error
All	planned	3216.2	0.44	5.03
M1, M2, M3	planned	3204.7	0.45	5.05
M2, M3	primary	3196.6	0.44	5.15
M2	planned	3196.8	0.25	5.19
Parent only	ad hoc	3193.5	0.02	5.17

No clear preference for one model, if AIC is used.

None of the models considered predicted any relevant prolongation.

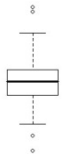
Don't forget: Our purpose is prediction, not an optimal model fit.



Proposed strategy

- **Prespecify a procedure on what models to look at:**
  - should include a model with all moieties
  - may use information derived from hysteresis loops
  - this strategy should also adress potential non-linearities, but this part needs to be executed only if an effect cannot be excluded.
  - Include a model with active drug or metabolite only
- **Predict any QTc-effect at relevant concentrations for all models.**
- **Only if predictions do not agree is a more detailed model discussion necessary.**

I am not sure that interactions need to be taken into account.



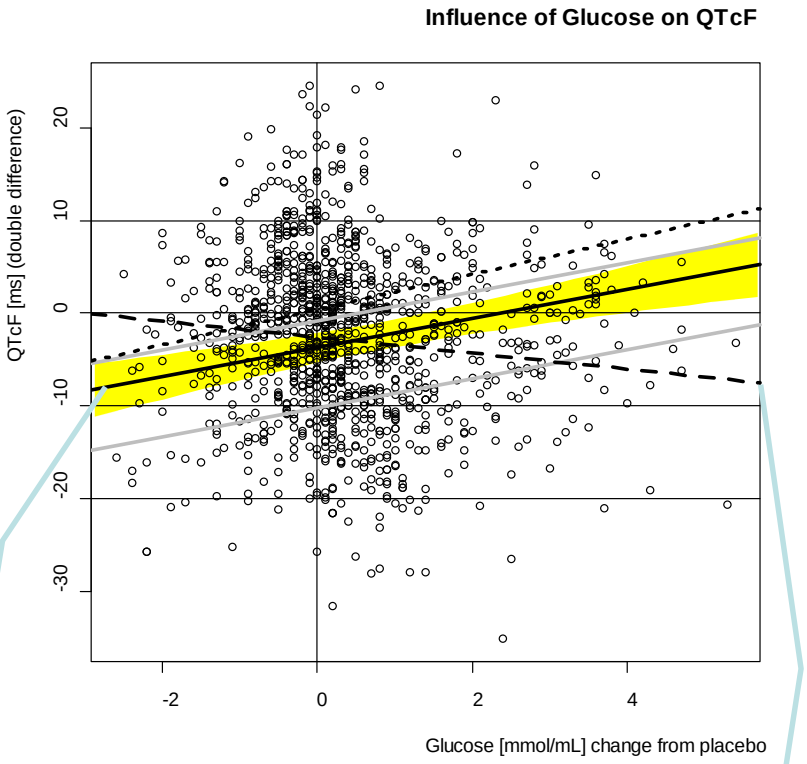
Food effect studies

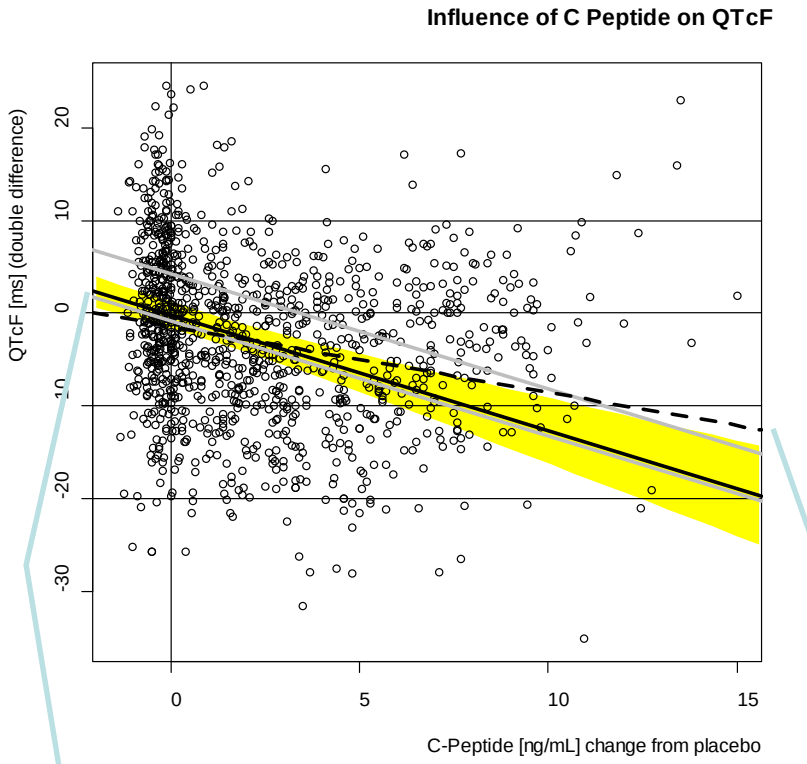
Table 1 of the White Paper:

Food affects the QT interval. Consideration should be given to standardize meals across periods, preferably at time points removed from T_{max}. Special care is needed for drugs that affect gastric emptying, glucose uptake or metabolism, since both glucose and C-peptide have been shown to influence QTc.

Taubel T, Lorch U, Ferber G, Singh J, Batchvarov VN, Savelieva I, Camm JA: Insulin at normal physiological levels does not prolong QTc interval in thorough QT studies performed in healthy volunteers. Brit. J of Clin Pharmacol 75 (2013): 392-403.

Basic relationships





Relationship corrected for C-Peptide

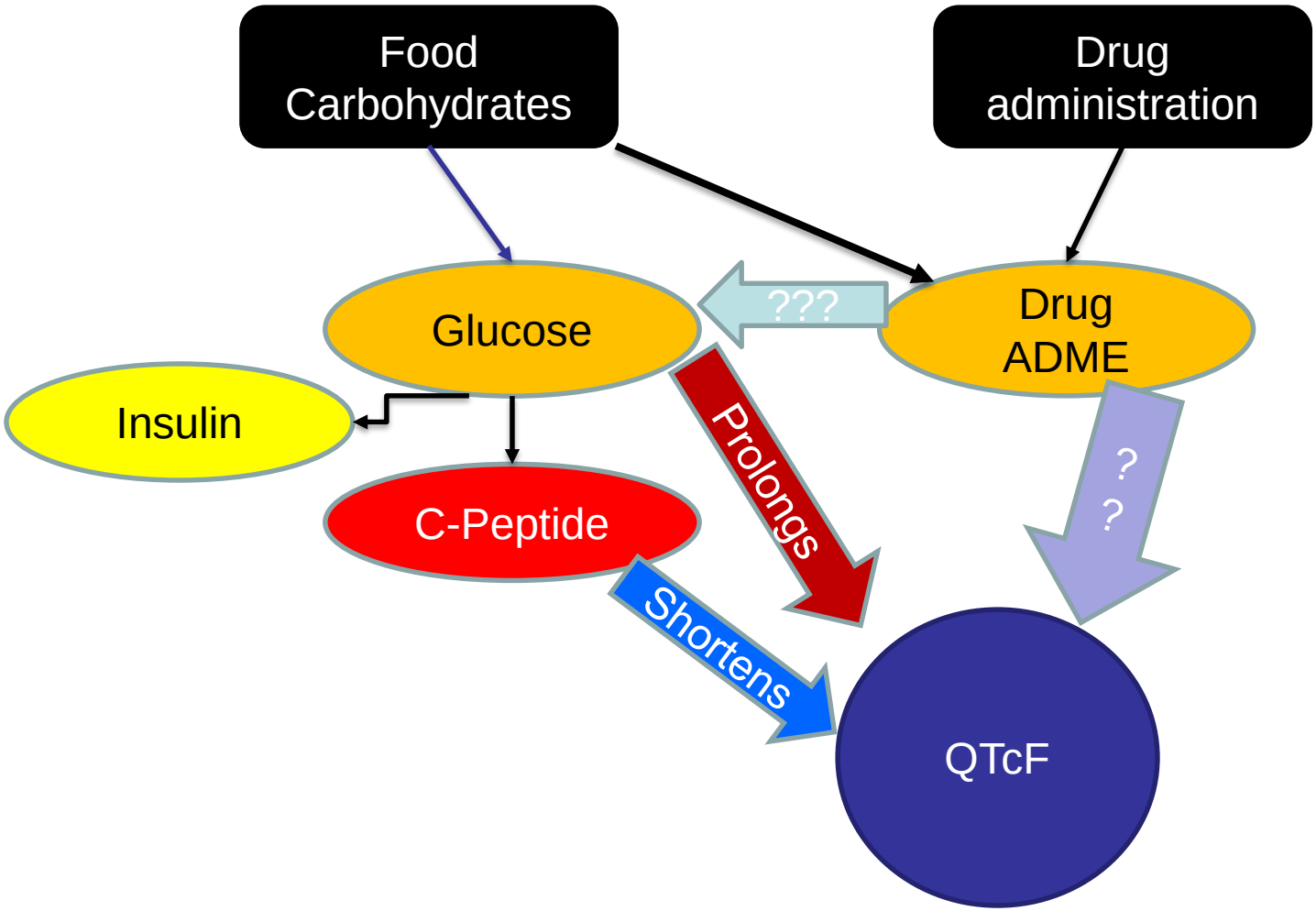
Uncorrected relationship

Relationship corrected for glucose

Uncorrected relationship

Crossover Study comparing fasting ("Placebo"), two types of Breakfast and an euglycemic clamp - Analysis based on difference to fasting condition.

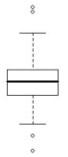
Relationships to consider



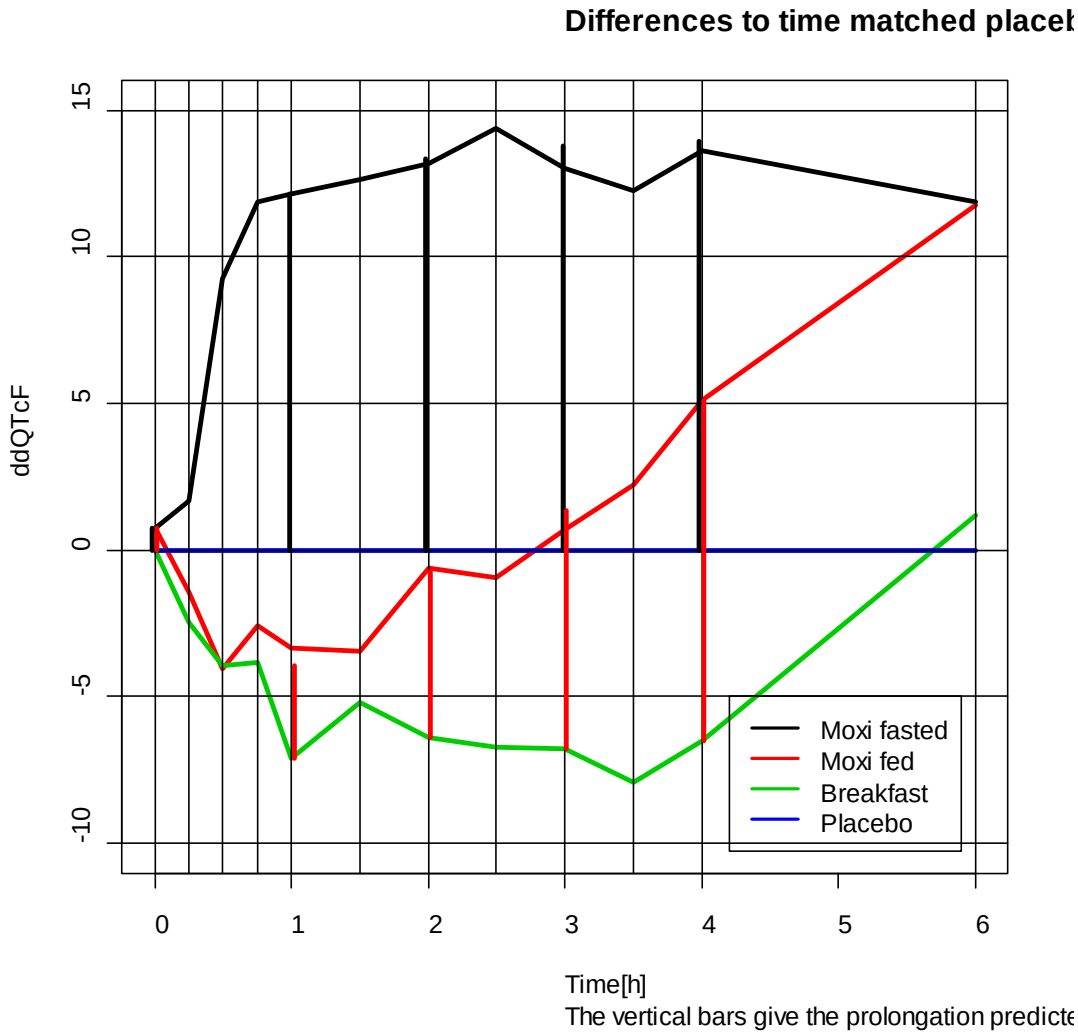
What does this mean?

General:

- **1 – 4 h after a meal, a shortening of QTcF will be seen. This will show up in the time effect of the C-QTc-model.**
- **As a consequence, timing and content of the meal need careful standardisation.**
- **If T_{max} of the drug in this time window, there is a risk of aliasing. A placebo arm is of high importance.**
- **If feeding differs between groups, separate time factors need to be used in the model.**
- **The slope under fed and fasted conditions should be the same, even if food affects PK of the drug.**



Moxifloxacin in fasted and fed state



The study also studied moxi in fasted and fed state.

- **The effects of breakfast and of moxi on QTc add,**
- **there is also an effect of food on the PK of moxi.**

If your drug affects glucose

Assume your drug inhibits glucose uptake in a concentration dependent way, but does not affect QTc.

Consider two studies:

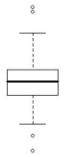
- **Drug is investigated in fasted state.**
  - ΔQTcF will not change much under placebo
  - ΔQTcF will not change much under drug

} Negative Study

- **Drug is given with food**
  - ΔQTcF will shorten under placebo by about 5 – 10 ms
  - drug inhibits glucose, so ΔQTcF will not change much under placebo

This happens for the C-effect analysis and for a by-timepoint analysis.

False positive study

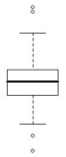


Cytotoxic oncology drugs

... many challenges and it is beyond the scope of this paper to detail them. Challenges that could impact a MAP are

1) *patients may be on multiple drugs in addition to the drug of interest and it is not possible to measure the drug concentration for every drug they are taking;*
2) *patients have wider between-patient variability than seen in healthy volunteer studies;*
3) *it may not be ethical to have a placebo and/or positive control groups; and*
4) *it may not be feasible to obtain exposures higher than the therapeutic exposures.*

In such cases, there is a reluctance to draw conclusions of a lack of an effect and the MAP should be designed to exclude mean effects as large as 20 ms.

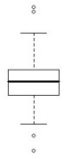


And if you still need to look at it?

Some points to think about:

- **Although placebo has been shown to be necessary to control the risk of a false negative study, concentration-response analysis may be the best way to separate unwanted variability from drug related one.**
  - A model without time as a factor may be used as senstivity analysis. However, keep in mind that this model will introduce bias.
  - Comparing the time effect estimates to the PK may also help to detect aliasing.

Ferber G, Sun Y, Darpo B, Garnett C, Liu J: Study Design Parameters Affecting Exposure Response Analysis of QT Data: Results From Simulation Studies. J Clin Pharmacol. 58 (2018), epub. ahead of print.



Some more considerations

- **Since SAD studies often start with very low doses, these may be used as surrogate for placebo.**
- **We model change from baseline. For a lower variability, restrict the data to the first day(s) of drug administration. The further apart baseline is, the higher the variability.**

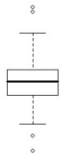


Table 1 of the White Paper

Combination drugs or active metabolites √

Cytotoxic oncology drugs √

Drug-induced changes in heart rate

See next presentation

Extended Release products

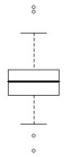
PK/PD hysteresis

I hope I can tell you more next time.

Non-HERG changes in QTc

Drug interaction studies √

Food effect studies √



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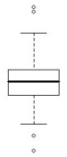
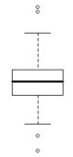
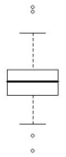


Backup



Combination Drugs or Active Metabolites

When modeling the QT effect of a combination drug or a drug with active metabolites, it is important to characterize the effect of each analyte (i.e., individual drug parent and/or metabolite concentrations), as well as any interaction between analytes. Careful design of the sampling time points is needed to ensure that C_{max} is captured for all analytes. Each analyte should not be analyzed as a series of univariate analyses, but rather analyzed using separate slopes for each analyte and with corresponding interaction. Careful interpretation is needed to understand the contribution of each analyte to the total effect. PD models may not necessarily be the same for both analytes, e.g., one analyte may be linear and the other nonlinear in nature. For combination drugs, the study design should consider including each drug administered alone and in combination at the highest safe dose.



Example C

OBE022 (ObsEva SA, Geneva) – parent drug - prodrug

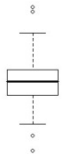
OBE002 (Active metabolite).

Models investigated: Individual moieties and joined model.

The drug did not show an effect on QTcF.

According to the criteria set out, the model using OBE002 only would be best.

Model	AIC	t treatment	Res. Error
Both	5579.9	-0.12	5.79
OBE002	5574.9	0.01	5.82
OBE022	5578.6	-0.22	5.85



Example D

Three moieties (A, B, C) with rather different time profile, some effect on QTcF.

- The model fit is very similar between models.
- Predictions differ somewhat.

Model	AIC	Res. Error	t of treament effect
ABC	3341.6	6.18	1.7
BC	3322.5	6.20	1.7
AC	3332.4	6.22	1.4
AB	3333.2	6.21	1.8
A	3324.9	6.22	1.6
B	3321.9	6.21	1.9
C	3321.3	6.23	1.6