




Food can serve as a non-pharmacological control in thorough cardiac safety studies

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Proposal



- Food can be used as a non pharmacological marker to confirm assay sensitivity in
 - Oncology TQT studies
 - Paediatric TQT studies
 - early phase studies such as MAD studies for hypothesis generation
- A “food day” can easily be added into almost any type of clinical trial

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3

Table of Contents




- Presentation of our research results
 - Study Design
 - Assay Sensitivity
 - Results
- Discussion of results
 - Limitations and opportunities
- Conclusions

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4

Study Design (1)



Periods 1-4: Four way cross over study in N=60
 Period 1-4 consisting of an ECG baseline day followed by a treatment day
 12-lead standard resting bed-side ECG: pre-dose, half-hourly for 4 hours post dose
 Single doses in fasting condition with a 10 day washout period


Period 5: *Parallel group extension* study to assess multiple doses and food effects after 14 days of BD dosing

Period 1	Period 2	Period 3	Period 4	Period 5
<ul style="list-style-type: none"> • TD • SD • Mox • Placebo 	<ul style="list-style-type: none"> • Placebo • TD • SD • Mox 	<ul style="list-style-type: none"> • Mox • Placebo • TD • SD 	<ul style="list-style-type: none"> • SD • Mox • Placebo • TD 	<ul style="list-style-type: none"> • SD • Placebo

TD = Therapeutic Dose; SD = Supra-therapeutic dose;
 Moxi = 400mg oral dose of Moxifloxacin (Avelox)

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Study Design (2)




Period 5:
Extension study in the remaining volunteers (N=55) to assess multiple doses and food effects. For the two baseline days subjects were *randomised for sequence* of food/fasting Pre-dose (baseline) ECG were taken before breakfast
 Breakfast was consumed -30 to -20 minutes before a dose of placebo at time "0"

Period 5 (exploratory extension)		
<p>Day -2</p> <p><input type="checkbox"/> Baseline</p> <ul style="list-style-type: none"> • Food • Fasting 	<p>Day -1</p> <p><input type="checkbox"/> Baseline</p> <ul style="list-style-type: none"> • Fasting • Food 	Other assessment days

♦ Data from the two baseline days (Day-2 and Day-1) was used in a secondary analysis to assess the effects of food on Heart rate, PR, QT and QTcX

6


Subject Demographics



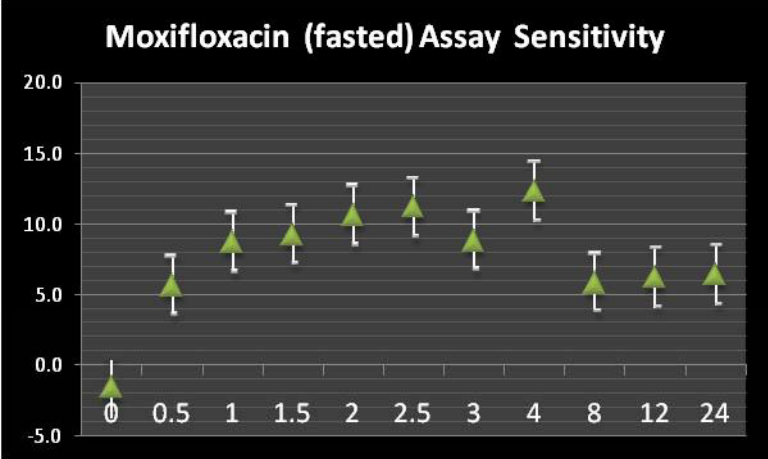
	Mean ± SD
Age (years)	28.6 ± 5.3
Sex	31 males 24 females
Weight (kg)	65.84 ± 9.74
BMI (kg/m ²)	22.29 ± 1.95

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7

Confirmation of Assay Sensitivity



Moxifloxacin (fasted) Assay Sensitivity



Time (h)	Mean Sensitivity
0	-1.0
0.5	5.5
1	8.5
1.5	9.0
2	10.5
2.5	11.0
3	8.5
4	13.0
8	6.0
12	6.5
24	6.5

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ECG and Data Analysis

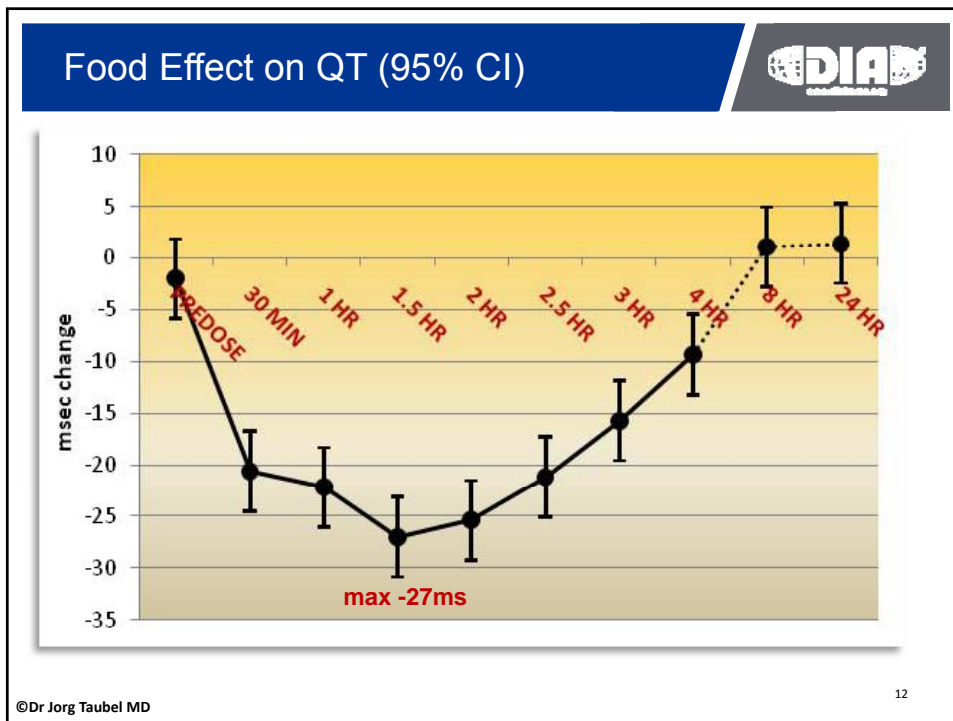
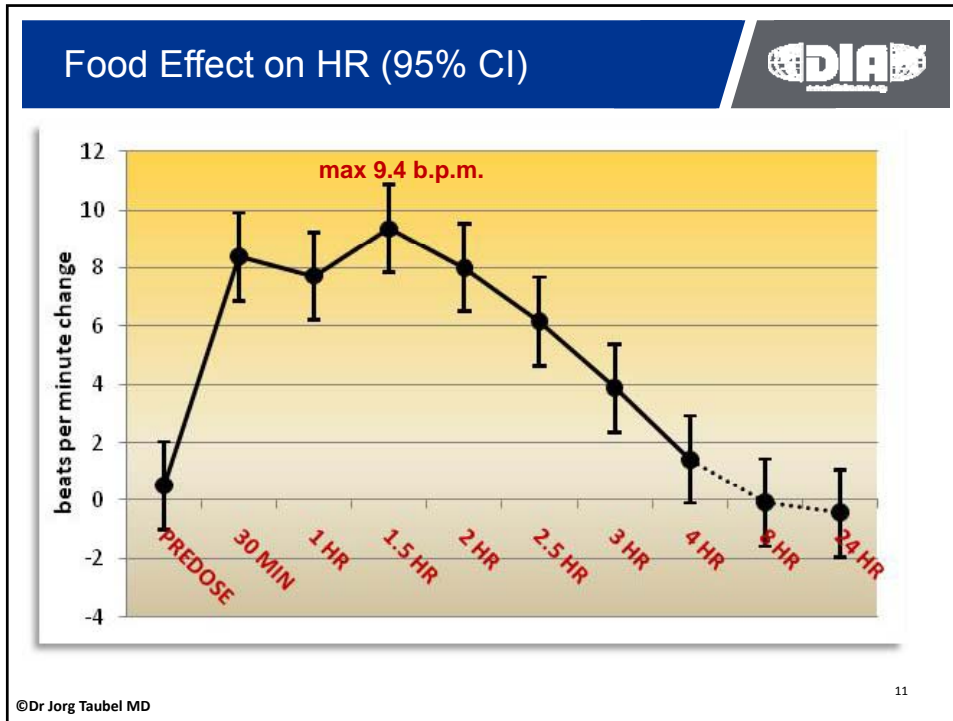
- ECG were analysed automatically using SL-12
- All beats from all leads were manually over-read by a cardiologist highly experienced in QT analysis (manual adjudication)
- Individual heart rate corrections were calculated (QTcIp, QTcIi)
- Intervals were extracted and QTcX calculated
- The food effect is calculated as time-matched $\Delta QTcF = (QTcF_{fed} - QTcF_{fasted})$

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Meal Composition (09.068)

Breakfast	Serving	Calories	Proteins		Carbohydrates		Fat		Fibre	
		(kcal)	(g)	kcal	(g)	kcal	(g)	kcal	(g)	kcal
Breakfast										
Cereal, Kellogg's Cornflakes	30g	111.9	2.1	8.4	25.2	100.8	0.3	2.7	0.9	0.0
Milk	150ml	72.5	5	20.0	7.5	30.0	2.5	22.5	0	0.0
Sugar	10g	40.0	0	0.0	10	40.0	0	0.0	0	0.0
Wholemeal hoagie (roll)	79g	178.1	8.6	34.4	27.6	110.4	3.7	33.3	5.5	0.0
Jam	20g	50.0	0	0.0	12.5	50.0	0	0.0	0.2	0.0
Butter	10g	72.9	0	0.0	0	0.0	8.1	72.9	0	0.0
Apple Juice	200ml	91.3	0.3	1.2	22.3	89.2	0.1	0.9	0.1	0.0
Total		617	16.0	64	105.1	420	14.7	132	6.7	0
			10%		68%		21%		0%	

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Food Effect on QTcF (95% CI)



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13


HR and Inverse QT Change



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14


HR and Inverse QT and QTcIp Change



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15

Food Effect on QTcB (95% CI)



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16

Autonomic Changes



- **QTc prolongation** due to (some examples):
 - Sleep (vagal effect) ¹
 - Brain damage/death (impaired autonomic control) ^{2,3,4}
 - Atropine (removing vagal control) ⁵
 - Diabetes (neuropathy impairing vagal control) ⁶
 - Gender (differences in autonomic balance?) ⁷
 - Food ⁸
 - Fasting (hypoglycaemia) ^{9,10}

¹ Browne K et al. Am J Cardiol 1982;50:1099–103 ⁹ Petrov DB, Texas Heart Institute Journal, 30; 234 References on request 1; 86-87; 2003
⁵ Annala et al. Br J of Anaesthesia 71(5):736 ¹⁰ Ireland et al Physiol. Meas. 21 (2000) 295–303.
^{6,7,8} References on request

Autonomic Changes




- **QTc shortening** has only been reported as congenital disorder and as a drug effect

Shah R, Bjerregaard P, Gussak I. Drug-induced QT interval shortening: an emerging component in integrated assessment of cardiac safety of drugs. *Journal of Electocardiolog.* 2010;43:386-9

Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, Lorch U, Taubel J. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. *Br J Clin Pharmacol.* 2008;26:396-404

Harada T, Naseem A, Ardeleanu M, Arezina R, Lorch U, Taubel J and Camm AJ *SKY0402 (bupivacaine) does not prolong QTc interval in a thorough QT/QTc study in healthy volunteers* *Jpn J Clin Pharmacol Ther* 40/suppl 2009




We found the following effects:

0<2 hours after food	2-4 hours after food
<ul style="list-style-type: none"> › HR increases immediately max effect at 1:30hr (9bpm) › QT shortens immediately max effect at 1:30hr (-27ms) › QTcIp shortens reaching significance at 1:30hr (-3ms) 	<ul style="list-style-type: none"> › HR decreases steadily returning to baseline at 4hr › QT prolongs steadily but disproportionally remaining shortened at 4hr (-10ms) › QTcIp shortens further until 3:00hr (-6ms)

Note: breakfast starts at -0:30hr and finishes at -0:10 relative to dosing at 0:00

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Effects of food on HR in literature:

0<2 hours after food	2-4 hours after food
<ul style="list-style-type: none"> › HR increases max effect at 1:30hr after food (+12bpm) Widerlöv et al. › HR increases max effect at 1:30hr after food (+10bpm) Scott et al. › HR increases max effect at 0:40hr after starting euglycemic clamp +5 bpm) Gastaldelli et al. 	<ul style="list-style-type: none"> › HR increases sustained for >3 hours returning to baseline after 4-5 hours Widerloev et al.

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1999

DIAD
Dietary Intake Assessment Database

E. Widerlöv · K.-G. Jostell · L. Claesson
B. Odland · M. Keisu · U. Freyschuss

Influence of food intake on electrocardiograms of healthy male volunteers

N=12 Heart rate

food at 1.5 h vs. fasting **+12 b.p.m**

food at 5.5 h vs. fasting

Plus a reduction in the area under the T-wave

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2002

DIAD
Dietary Intake Assessment Database

Carbohydrate ingestion, with transient endogenous insulinaemia, produces both sympathetic activation and vasodilatation in normal humans

Eleanor M. SCOTT^{*}, John P. GREENWOOD[†], Giovanni VACCA[†], John B. STOKER[†], Stephen G. GILBEY^{*} and David A. S. G. MARY[†]

N=15

G **I**

Figure 3 Changes in HR and BP following ingestion of a carbohydrate meal in 15 healthy subjects
Data are expressed as means ± S.E.M. Significance of changes relative to baseline (ANOVA): *P < 0.05, †P < 0.01, ‡P < 0.001.

Figure 1 Changes in blood glucose and serum insulin following ingestion of a carbohydrate meal in 15 healthy subjects
Data are expressed as means ± S.E.M. Significance of changes relative to baseline (ANOVA): ‡P < 0.001.

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Effects of food on QTc in literature:

0-2 hours after food

- › QTcB prolongation of +3.5ms 0:15 to 1:00hr after food (end of experiment); **Nagy et al.**
- › QTcF shortening after food in a TQT study of max -11ms at 1:30 after a meal, associated with HR increase; **Bloomfield et al.**

2-4 hours after food

- › QTcF shortening after food sustained for more than 3 hours ; **Bloomfield et al.**

Note: breakfast starts at -0:30hr and finishes at -0:10 relative to dosing at 0:00

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1997

QTc Interval (Cardiac Repolarization): Lengthening After Meals

David Nagy,* Ronald DeMeersman,† Dympna Gallagher,* Angelo Pietrobelli,* Adrienne S. Zion,† Deborah Daly,* Steven B. Heymsfield*

N=10
 consumed a 500 kcal formula meal (Sustacal; Mead-Johnson Nutritional Group, Evansville, IN) over 5 minutes that provided 28.8%, 18.4%, and 52.8% of energy as fat, protein, and carbohydrate, respectively. Subjects rested quietly for a

+3.5 ms
QTcB

HR increase +10 b.p.m.
QT shortening -30 ms
 (approximates)

Time (min)	Meal Group (ms)	Water Group (ms)
0	0.37	0.37
15	0.39	0.35
30	0.38	0.35
45	0.37	0.35
60	0.36	0.35

Figure 1: QTc interval vs. time after formula meal or water ingestion. Results are expressed as group mean ± SE for each time. Corresponding p values are summarized in Table 2.

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24

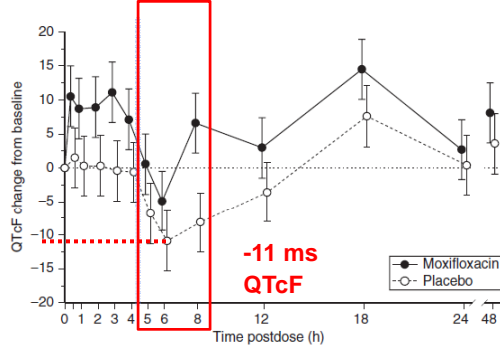
2008



The Effect of Moxifloxacin on QTc and Implications for the Design of Thorough QT Studies

DM Bloomfield¹, JT Kost², K Ghosh³, D Hreniuk¹, LA Hickey³, MJ Guitierrez⁴, K Gottesdiener¹ and JA Wagner¹

Figure 4 illustrates the change in QTc from baseline (PDB) brought about by treatment. Moxifloxacin appears to be associated with a ~10 ms increase in QTc CFB, which becomes evident from the first measurement at 30 min and persists over the first 4 h after the dose. In contrast, the mean change in QTc interval associated with placebo over this same 4-h period remained close to zero. Interestingly, there is a transient decrease in the change in QTc from baseline at 5 and 6 h after the dose, similar in both the moxifloxacin and placebo treatment groups. This drop in QTc was associated with small but consistent increases in heart rate that occurred following the meal (which was given to all subjects 4 h after the dose). A secondary increase in QTc appears after 6 h, persisting through 24 h.



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25

HR data of a TQT study in fed condition (unpubl.)



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26

DIAD
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Effects of food on **Insulin and Glucose** in literature:

0>2 hours after food

- › **Glucose** max increase 0:40 after food
- Insulin** max increase at 1:20 after food;
- Scott et al.**
- › **HR increases +5b.p.m.** max effect at 0:40hr after starting euglycemic clamp decreasing during infusion
- Gastaldelli et al.**

2-4 hours after food

- › No published data

Note: breakfast starts at -0:30hr and finishes at -0:10 relative to dosing at 0:00

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DIAD
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2000

Insulin prolongs the QTc interval in humans in a euglycemic clamp¹
N=35

Fasting plasma glucose, mM	5.1 ± 0.1	4.2–6.0
Fasting plasma insulin, pmol/l	91 ± 5	52–195
Steady-state plasma glucose, mM	5.0 ± 0.1	4.2–6.0
Steady-state plasma insulin, pmol/l	652 ± 28	357–1,087
M value, $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg FFM}^{-1}$	40 ± 2	15–61

+5 b.p.m

+10 ms

Fig. 1. Time course of heart rate (top), QT interval (middle), and QTc (bottom) during resting conditions and during 100 min of euglycemic hyperinsulinemia in 35 nondiabetic subjects. ■, Means ± SE. bpm, Beats/min.

¹ Gastaldelli A et al. Am J of Physiol Regulatory Integrative Comp Physiol 279: R2022-5 (2000)

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Limitations of this Study



- This is the first study published in literature using state of the art ECG assessments and HR correction formulae to quantify
 - the extent of shortening of QTc due to food
 - The duration of effect
- The mechanisms leading to QTc shortening after food are complex and not fully understood
- The test-meal thus requires standardisation
 - The magnitude of effect may vary with different types of food (higher or lower carbohydrate content)

Limitations of this Study (2)



- The effect is a QTc shortening not a prolongation
 - However we are interested in the magnitude of change more than direction
- The effect is not due to ion channel blockade
 - However, this is also true for other “positive” QT studies e.g. beta-mimetics

Opportunities



- The effect can be demonstrated in small study populations (robust)
- It has occurred in numerous published studies (reproducible)
 - It is consistent with regard
 - to time course of HR changes
 - QTc changes when applying the appropriate HR correction formula
- Therefore is suitable as a positive control to assess assay sensitivity

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- Dr Ulrike Lorch
- Clinical team at Richmond Pharmacology
- Dr Georg Ferber

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