MODELING OF DRUG- AND SYSTEM-RELATED CHANGES IN BODY TEMPERATURE: application to drug-induced hypothermia, long-lasting tolerance and diurnal variation

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INTRODUCTION AND AIM

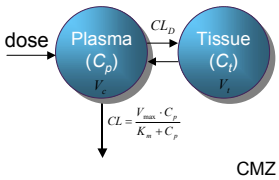
- The objective is to develop a pharmacokinetic-pharmacodynamic model for the characterization of clomethiazole (CMZ) -induced hypothermia(1) with components for complete tolerance development, diurnal variation in baseline and influence of handling.

METHODS AND EXPERIMENTAL DESIGN

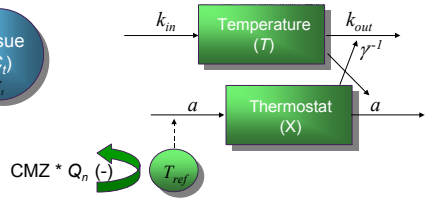
- CMZ-induced hypothermia and onset of tolerance was characterized using body temperature telemetry in male Sprague Dawley rats after subcutaneous (sc) bolus administration of 0, 15, 150, 300 and 600 µmol·kg^{-1} and 24-h continuous administration of 0, 20 and 40 µmol·kg^{-1}·h^{-1} using osmotic pumps.
- The duration of tolerance was studied by repeated injections of 300 µmol·kg^{-1} with intervals ranging from 3 to 32 days.
- Plasma exposure to CMZ was obtained in satellite groups of catheterized rats.

MODEL, MODELING STRATEGY AND ASSUMPTIONS

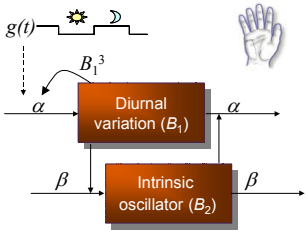
CMZ pharmacokinetics



Temperature regulation



Diurnal variation and handling



Tolerance

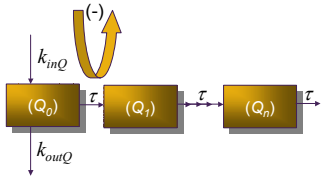


Figure 1. *Pharmacodynamic model for CMZ.*

- Diurnal variation in baseline is described by a novel feedback model with a squared-wave function for the external light schedule. Temporary increase in temperature due to handling is described by an empirical exponential function.
- CMZ has dual actions:

1. CMZ modulates body temperature via T_{ref} following an inhibitory S_{max} function (S_1).
2. CMZ removes an unknown modulator (Q_0) following a second S_{max} function (S_2), which is cascaded through a number of transit compartments(2) to Q_4.
   - Q_4 diminishes the effective stimulus (S_1) at T_{ref} resulting in a tolerance.
   - Q_0 has a turnover half-life of several days and the transit time (τ) of the cascaded stimulus is in the range of hours resulting in a fast but not direct onset and a long duration of tolerance.

- Set-point temperature model(3) is used because it showed to be more flexible than an indirect response model.
  - For reasons of parameter identification, the set-point model is reduced to three parameters: A, k_{in} and γ by rescaling temperature. Baseline was fitted before rescaling the data following: $T_{rescaled} = \frac{T_{obs} - T_{min}}{T_{baseline} - T_{min}}$ T_{min} is 31°C.

RESULTS: NON-LINEAR EXPOSURE TO CMZ

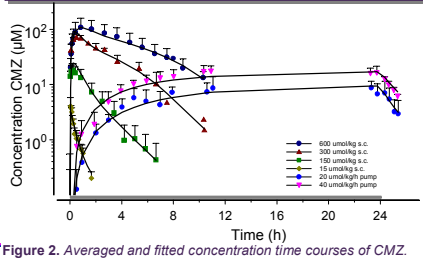


Figure 2. *Averaged and fitted concentration time courses of CMZ.*

Table 1. Pharmacokinetic parameter estimates

Parameter	Unit	Estimate	±	SE	i.i. (%)
V_{max}	µmol·min^{-1}·kg^{-1}	1.75	±	0.32	<1
K_m	µmol·L^{-1}	53.1	±	11.2	44
V_c	L·kg^{-1}	1.59	±	0.15	<1
V_t	L·kg^{-1}	2.57	±	0.45	46
CL_D	L·min^{-1}·kg^{-1}	0.09	±	0.02	79
K_a *	min^{-1}	1.37	±	0.18	69
F (sc)		1.03	±	0.16	27
F (pump)		1.10	±	0.17	27

- A two-compartment kinetic model incorporating Michaelis-Menten elimination(4) described the concentration-time courses of both s.c. injections and via constant osmotic pump delivery.

*K_a estimate for 15 µmol/kg dose. The K_a estimates for the 150, 300, 600 µmol/kg sc doses and 20, 40 µmol/kg/h pump doses were 10, 20, 40, 68 and 138 times smaller, respectively, due to decreased pH in injection solution.
i.i: inter-individual variability

RESULTS: DIURNAL VARIATION

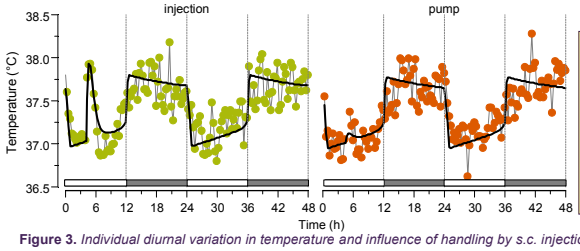


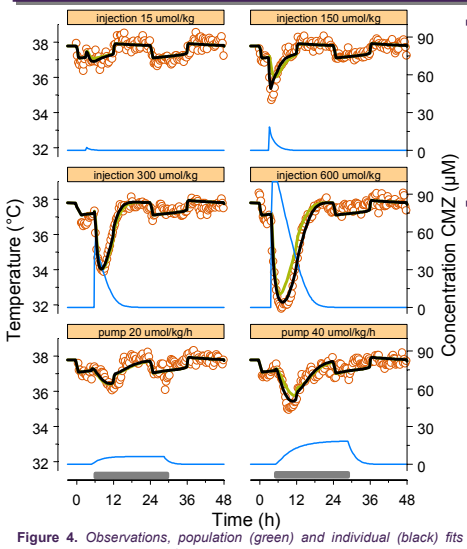
Table 2. Baseline parameter estimates

Parameter	Unit	Estimate	±	SE	i.i. (%)
α	min^{-1}	0.066	±	0.009	-
β	min^{-1}	0.002		fixed	-
T_{ref}	°C	37.4	±	0.18	<1
amp	-	0.034	±	0.003	-
g	-	0.010	±	0.003	-
k_{HD}	min^{-1}	0.029	±	0.004	-
$P_{(pump)}$	-	0.010	±	0.006	55
$P_{(injection)}$	-	0.035	±	0.008	67

Figure 3. *Individual diurnal variation in temperature and influence of handling by s.c. injection or osmotic pump implantation*

- The applied feedback model is a general model to describe asymmetric diurnal variations in baseline of various pharmacodynamic endpoints such as body temperature.
- Handling of animals resulted in a temporary increase of temperature

RESULTS: HYPOTHERMIA AND ONSET OF TOLERANCE



- Dose-dependent hypothermia after s.c. injection and constant administration could only be described when tolerance was induced with a delay of 365 min. This delay was estimated using 4 transit-comp.
- k_{outQ} was fixed at 0.022 days^{-1} (half life of ~32 days) in single dose analysis.

Table 3. Drug- and system-parameter estimates

Parameter	Unit	Estimate	±	SE	i.i. (%)
$S_{max,1}$	-	1		fixed	-
$SC_{50,1}$	µM	27	±	1	125
$SC_{50,2}$	µM	5.2	±	0.7	11
k_{in}	°C·min^{-1}	3.9	±	0.3	-
A	min^{-1}	0.017	±	0.0001	39
γ	-	0.7	±	0.01	38
k_{outQ}	day^{-1}	0.022		fixed	-
τ	min	91	±	1	8

Figure 4. *Observations, population (green) and individual (black) fits for 6 representative individuals. Gray bar represents implementation duration of osmotic pump. Blue line represents plasma concentration (right y-axis)*

RESULTS: DURATION OF TOLERANCE

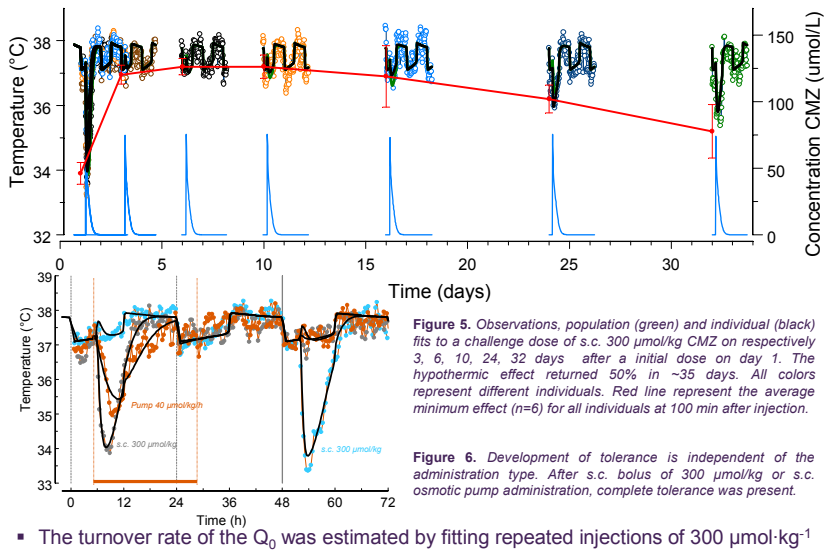


Figure 5. *Observations, population (green) and individual (black) fits to a challenge dose of s.c. 300 µmol/kg CMZ on respectively 3, 6, 10, 24, 32 days after a initial dose on day 1. The hypothermic effect returned 50% in ~35 days. All colors represent different individuals. Red line represent the average minimum effect (n=6) for all individuals at 100 min after injection.*

Figure 6. *Development of tolerance is independent of the administration type. After s.c. bolus of 300 µmol/kg or s.c. osmotic pump administration, complete tolerance was present.*

- The turnover rate of the Q_0 was estimated by fitting repeated injections of 300 µmol·kg^{-1} with intervals ranging from 3 to 32 days. Turnover rate constant was 0.015 ± 0.001 (10%) day^{-1}, yielding a half life of turnover of 46 days.

CONCLUSIONS AND PERSPECTIVES

- A novel feedback model was applied to asymmetric diurnal variation in temperature
- A tolerance model utilizing transit compartments described the onset and duration of tolerance. The half-life of return of response was estimated at 46 days.
- Drug induced hypothermia during continuous, acute or repeated administration was successfully described by the multi-component model
- The predictive properties of the model will be challenged by data with repeated injections at three occasions at 1, 15, and 32 days.

(1) Visser, et al., (2004) Rapid and Long-lasting Tolerance to Clomethiazole-induced Hypothermia in the Rat, submitted.
(2) Sun and Jusko, (1998) Transit compartments versus gamma distribution function to model signal transduction processes in pharmacodynamics. J.Pharm.Sci. 87, 732-737.
(3) Zuideveld et al., (2001) Setpoint with oscillatory behavior estimates 8-OH-DPAT's pharmacodynamics from its hypothermic effect. *Am.J.Physiol Regul.Integr.Comp Physiol* **281**:R2059-R2071.
(4) Gabrielsson and Weiner (2000). Pharmacokinetic and pharmacodynamic data analysis. Swedisch Pharmaceutical Press, Stockholm.