Comparison and selection of dosing regimens by discretization, optimizing efficacy and evaluating exposure demonstrated for KAE609 (Cipargamin)

Thomas Bouillon (1), P. Timothy Pollak (2) [pollak@ucalgary.ca]

(1) Academic Affiliation: Department of Anesthesia, University of Berne, CH, (2) Department of Medicine and Cardiac Sciences, University of Calgary, CA

BACKGROUND

- Dosing regimen finding by discretization was formally proposed by D'Argenio in 1994 [1], but simulation of "plausible" regimens and picking an "OK" one is still prevalent vs. optimization based on a predefined target.
- We demonstrate an approach to evaluate different dosing regimens by optimizing for target attainment in virtual individuals. The practicable dosing regimen with the lowest **cumulative dose for target attainment (CDTA)** "wins". Cmax is also displayed.
- The investigated scenario focuses on comparison of single vs. multiple dose regimens.
- KAE609/cipargamin, an antimalarial, for which population PKPD models (efficacy) in healthy volunteers infected with malaria [2] and patients [3] exist is used as test case.

OBJECTIVES

- To suggest a change in dose finding (Simulation of target att.-> Estimation of opt. Dose).
- To demonstrate that "single dose radical cure" regimens can come with a steep price.
- To demonstrate that optimal dose finding can be performed efficiently (minor effort).

METHODS

- **Source Population:** Based on the published PKPD models of KAE609 ([2,3], supplements essential), 1000 virtual patients for each parameter set were drawn from the parameter distributions (no truncation, EC50 of [3] set to 354 mcg/L (plausibility).
- **Dosing Regimens:** Single Dose (comparator), Multiple Dose: q12h3d, q24h3d, q24h5d
- **Efficacy criterion:** Maximal parasite reduction ratio (PRRmax) of 5*10^11), assumed to be curative in severe adult malaria (10^5 parasites/µL blood, blood volume 5 L).
- **Dataset** for estimation of individual doses: Unit dose, **AMT of 1 at t=0**. Efficacy criterion as dependent variable at t=28d, 11.7 in log10 units. Individual PKPD parameters **except** "**F**" as regressors. Different **dosing regimens** were introduced via **II (0,12,24 [h])** and **ADDL (0,2,4 [-])**, i.e., each virtual individual had **one dosing and one observation record (**you could also define a time course of effect (multiple "target points")**)**.
- **Estimation:** With AMT=1, individual PKPD parameters as regressors and residual error fixed to 0.001, the **EBEs of "F" yield the optimal individual doses for target attainment** of the respective regimen. Note that F can take any positive value here.
- **Check:** Desired vs. achieved PRRmax (**DV vs. IPRED**).
- **Individual cumulative doses for target achievement (CDTA)** were calculated (**F*(ADDL+1)**).
- The **distribution of CDTA ratios and respective Cmax ratios vs. SD** were compared between regimens and parameter sets using empirical cumulative distribution plots.
- The results were summarized in language accessible to non-modelers.

All operations were done in R using the public version of IQdesktop [4] with Monolix [5] as "estimation engine".

RESULTS

- Model predictions wrt. PRRmax of KAE609 were first tested by simulation. While the parameter set of [2] yielded plausible (and published) results (SD95mg->PRRmax=9), this was not the case for the parameter set of [3] (EC50 approximately 50 times lower than that of [2], SD0.1mg->PRRmax=10). We assumed a unit error. Dose as a covariate on Emax(?) was also not considered, Emax was fixed to 0.59 (=for 30 mg dose) (Table 1).

Table 1. Pharmacokinetic and dynamic parameter estimates used in simulations (F set to 1).

Parameters	TV McCarthy [2]	BSV [2]	TV Hien [3]	BSV [3]
CL [L/h]	5.5	0.325 (SD)	1.72	0.19 (SD)
V1 [L]	64.4	0.23 (SD)	40.6	-
Corr (V1,CL) [-]	0.76			
Q [L/h]	12.9	0.1 (SD)	NA	NA
V2 [L]	107	0.1 (SD)	NA	NA
ka [1/h]	0.92	0.1 (SD)	1.65	1.78 (SD)
MeanTransitTime [h]	NA	NA	0.87	0.65 (SD)
nTransitComp [-]	NA	NA	3	-
kgrowth [1/h]	0.048*	0.024 (SD)	0.048	-
Emax [1/h]	0.23	0.2 (SD)	0.59#	0.62 (SD)
EC50 [mcg/L]@	15.1	0.2 (SD)	354@	-
Hill	5	-	1	-
kact [1/h]	NA	NA	0.099	0.42 (SD)
FrctSensPar	NA	NA	0.99	0.82 (SD)

Standard nomenclature not explained. kgrowth: spontaneous growth rate of parasite; Emax: maximal "kill rate" of drug; kact: rate of transfer from non-sensitive to drug sensitive state; FrctSensParasite: Initial Fraction of parasite sensitive to drug; CAVE: *value used by [2] in simulations, calculated was 0.07; #adjusted from 0.56, @ 0.354 ng/mL -> 0.354mg/L (plausibility). Initial parasite load irrelevant for calculation of PRR. BSV: Log normal dist.

- Consequences for dosing regimen selection (all regimens achieve the efficacy criterion of PRRmax=11.7 log10 units): See ecdf's (pick your own quantiles and fractions ☺).

Figure 1. Empirical cumulative densities [2]

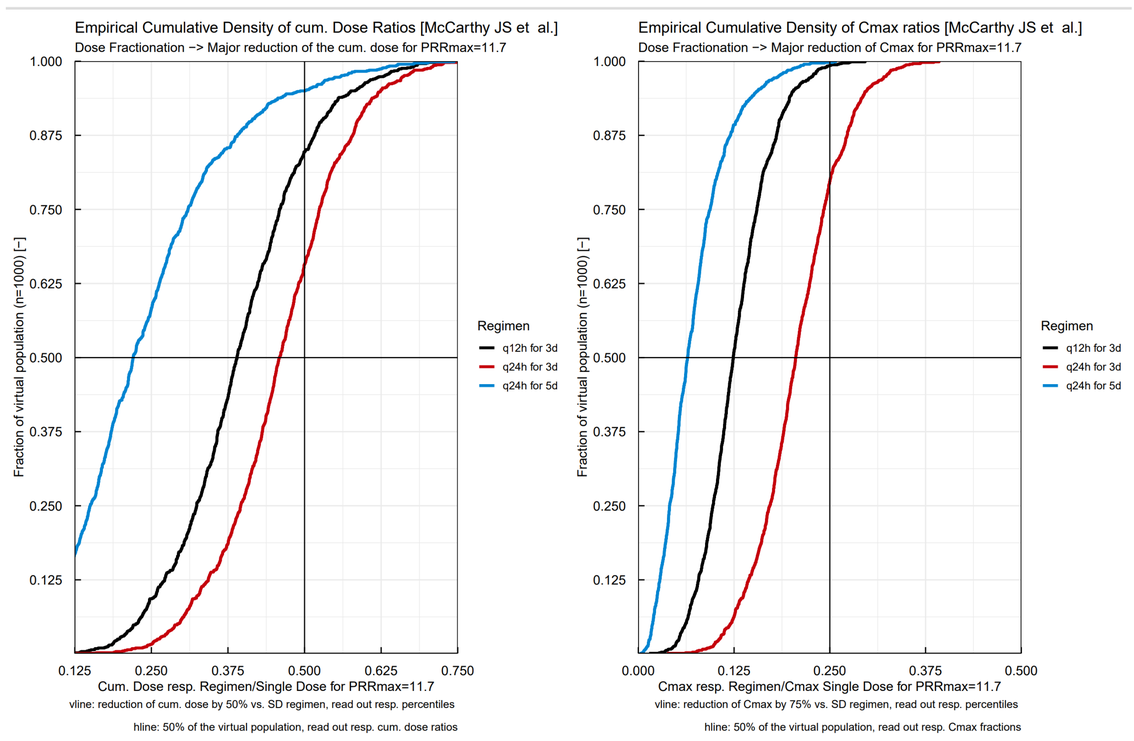
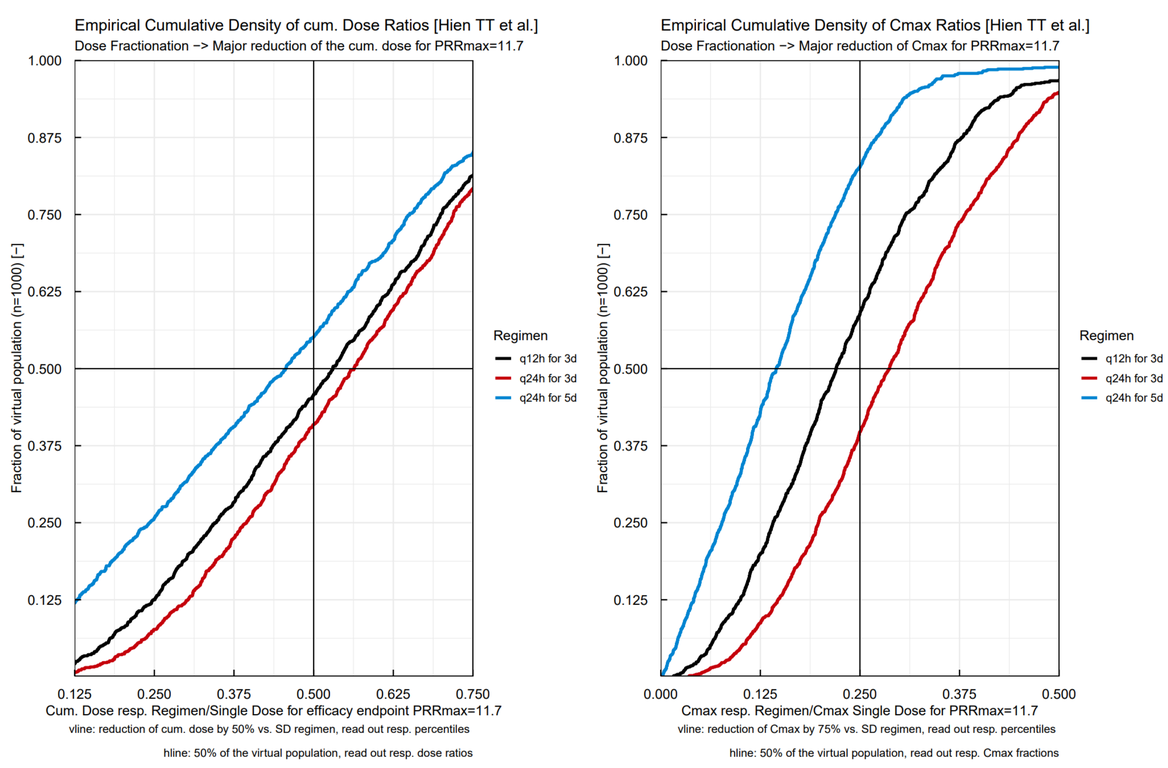


Figure 2. Empirical cumulative densities [3]



- Based on the parameter constellations, we could call **KAE609 [2]** a drug with **"time dependent" killing**, **KAE609 [3]**, a drug with **"concentration dependent" killing**.
- Regardless of the parameter set, equally effective multiple dose regimens were shown to be far superior to the single dose regimen (less cumulative exposure and Cmax). **On average, switching to a 3d regimen saves half the amount to be administered (cost, less potential for adverse effects) while not foregoing efficacy.**
- The effect is even more pronounced for Cmax, where a four-fold decrease is observed.
- The predictions nicely show the increasing differentiation between the parameterizations for the 5d regimens (massive reduction of exposure for "time dependent", moderate reduction of exposure for "concentration dependent" killing (compare "vertically").
- **The approach can be highly automatized (workflow) and customized.**

CONCLUSIONS

- An easily implementable approach to estimate optimal doses for target attainment in a population with standard software was "reinforced" and presented to the community.
- The usefulness was demonstrated by comparing dosing regimens wrt. target attainment (conditio sine qua non) and exposure needed (the lower, the better).
- The "exposure penalty" of single dose vs. practical multiple dose regimens has been highlighted for KAE609, an antimalarial in development since approx. 2012.
- The "optimize for target" approach in dose finding should be investigated further by colleagues with formal math training, e.g. Bachmann F et al. (oral pres. C20, Thur) ☺ .

References:
[1] D'Argenio DZ, Rodman JH. Controlling the systemic exposure of anticancer drugs: The Dose Regimen Design Problem (p 363-378). In: Pharmacodynamics and Drug Development: Perspectives in Clinical Pharmacology. 1994. ISBN 0-471-95052-1
[2] McCarthy JS et al., AAC 65(2021): p 1-11 (+ suppl.)[3] Hien TT et al., AAC 61(2017): p 1-10 (+ suppl.) [4] IQdesktop. A Qualified Virtual Modeling & Simulation Environment Supporting Efficient Model Informed Drug Development. iqdesktop.intiquan.com. [5] Lixoft/SimulationsPlus