Detecting pharmacodynamic drug-drug interactions

a pharmacometric success story

Biostatistics and Programming

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Introduction

For many diseases, the co-administation of multiple compounds is standard practice to treat patients, e.g., HIV, epilepsy,...

Caution: Co-administration of 2 compounds could potentially alter the underlying exposure (Pharmacokinetic interaction) and/or the effects (Pharmacodynamic interaction) of the individual compounds.

Nonclinical setting: To detect potential interactions and their potential therapeutic impact.

Typically, the Bliss and Loewe models are used to detect synergy in in-vitro tests. We have an in-vivo setting and will focus on a PK-PD approach.

Outline

1. Introduction
2. Case study
3. Methodology
4. Model fit
5. Conclusion

Case Study

To study the co-administration of a novel molecule with an existing, marketed treatment.

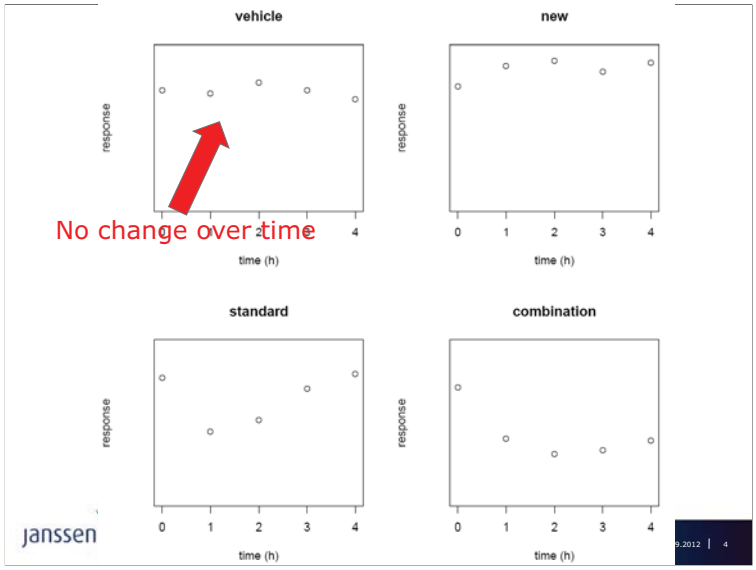
To maximize the chances for success, extreme high doses were used to detect the interaction.

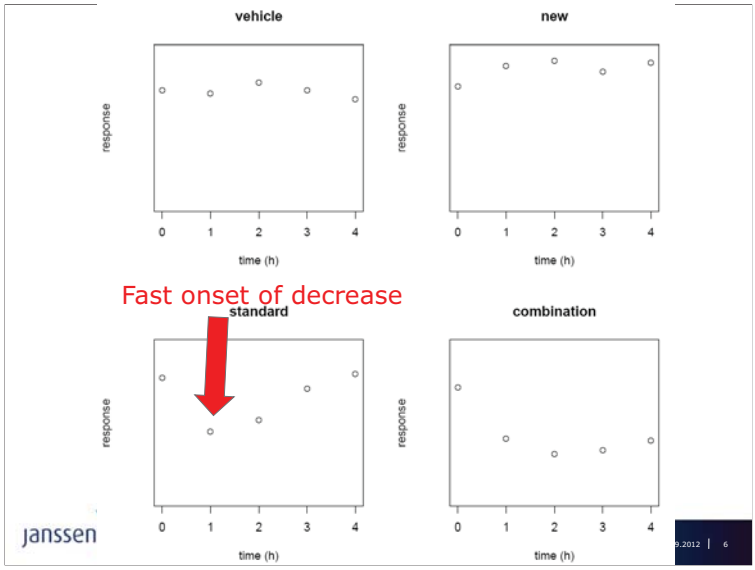
5 rats/group (vehicle, standard, new, combination).

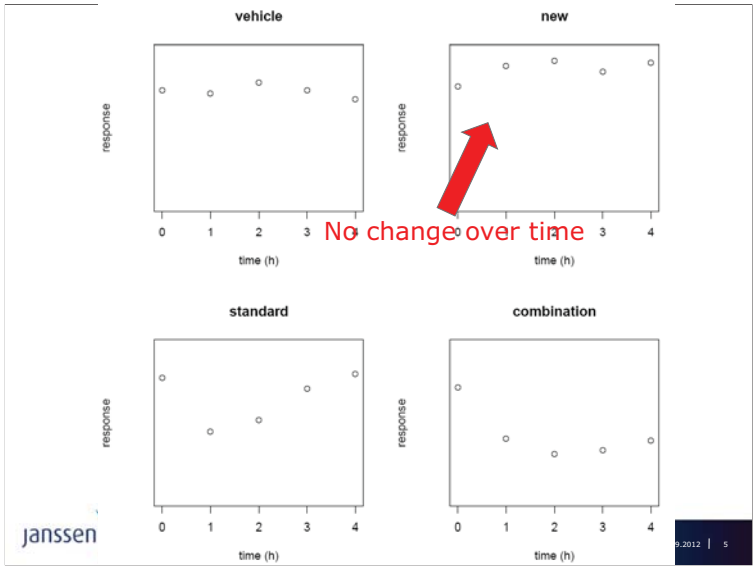
The continuous response (side effect) was assessed 5 times during the study.

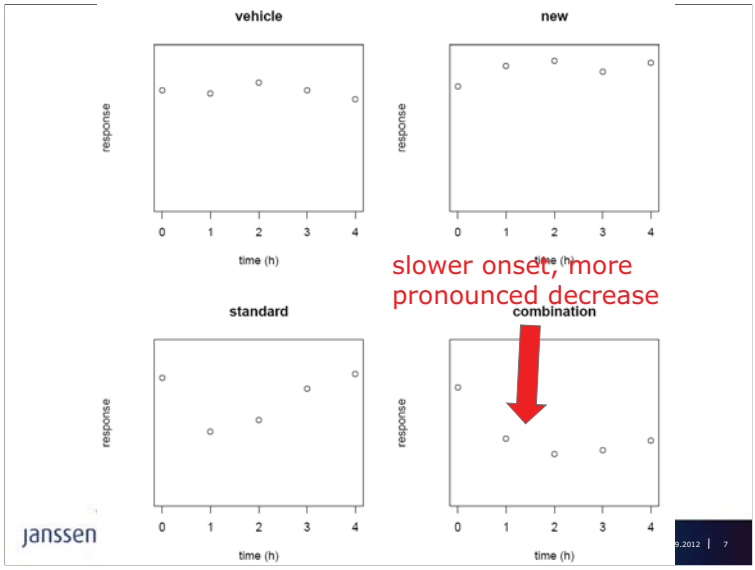
No differences observed in PK.

The next slide represents a typical animal for each group.


vehicle
new
standard
combination
response
time (h)
No change over time
janssen


vehicle
new
standard
combination
response
time (h)
Fast onset of decrease
janssen


vehicle
new
standard
combination
response
time (h)
No change over time
janssen


vehicle
new
standard
combination
response
time (h)
slower onset, more pronounced decrease
janssen

Methodology

A meta-analysis is performed by combining the data with the historical dose-response data for the standard compound.

The response is modeled with a turnover model:

$$\frac{dR_{ijk}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{v_{ij}}}{EC_{50_k} + C_{v_{ij}}}\right) - k_{out}R_{ijk}$$

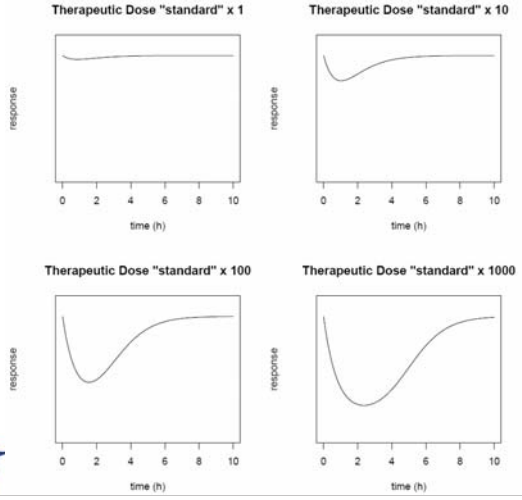
where we assume that a virtual conc-time profile of the old compound drives the effect

$$c_{ij}(t) = \frac{Dk_a}{V_f(k_a - k_e)}\left(\exp(-k_e t) - \exp(-k_a t)\right)$$

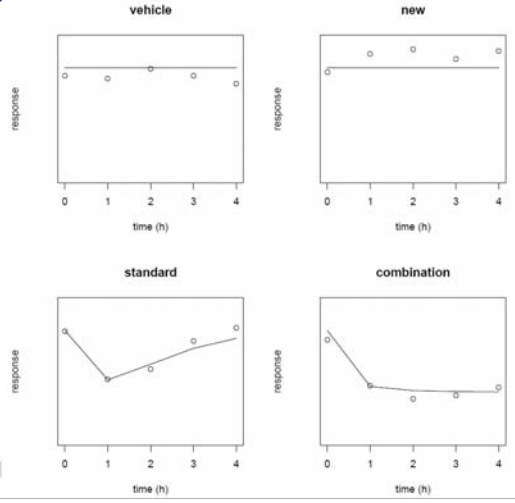
Assumptions:

- V_f=1 (normalization factor); k_a=exp(5) because confounding with k_{out}
- Combinatory treatment is assumed to affect only EC_{50}: the EC_{50} of the standard compound is modified in the presence of the new compound

How does such a model look like?



Model prediction: a shift in potency in this study?



Model prediction: indications of an unforeseen interaction at high doses

Intermediate summary:

- No PK interaction
- synergetic-like behaviour at high doses
- but very promising compound at lower doses

Only a thorough understanding of the dose response of both compounds could save the project, hence 5 more studies are initiated at a variety of doses (low, intermediate, high).

Question: does the shift in EC_{50} depend on the dose of only the new compound, or of both compounds?

Methodology

How to implement to combination treatment in EC_{50}?

Additive effect:

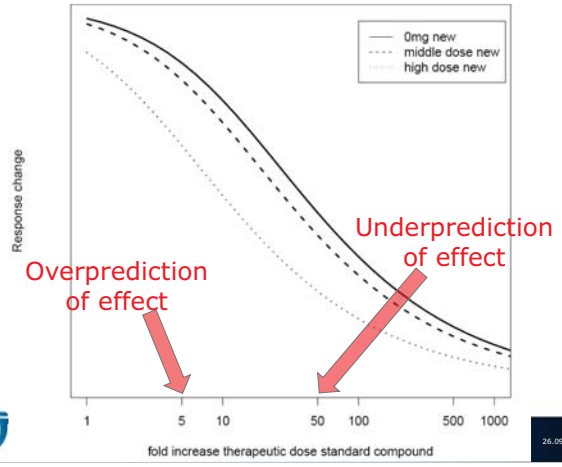
$EC_{50} = 1 + (\exp(\beta D_{new}) - 1)\ 1_{new}$

Multiplicative effect:

$EC_{50} = 1 + (\exp(\beta D_{new} D_{stand}) - 1)\ 1_{new}$

Note: EC_{50} for "standard" only is confounded with the virtual plasma concentration time profile. It is therefore not estimated explicitly. The impact of "new" (and combination) is estimated.

Maximum effect as a function of dose of the standard compound: Additive model



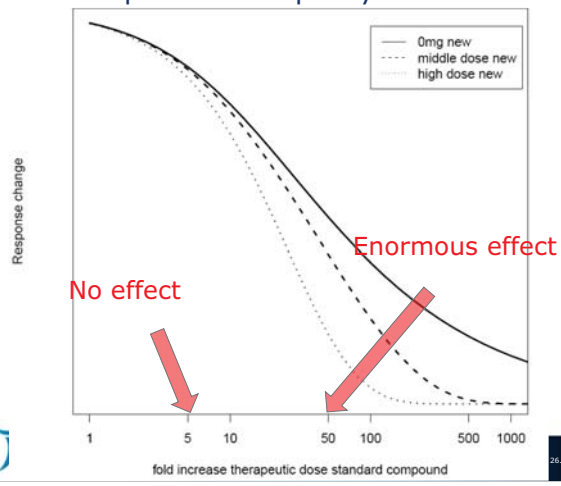
Results: Multiplicity model

Likelihood difference is 124.905, hence multiplicity model is far more likely to explain the data: The PD interaction depends on both doses.

Parameter interpretation:

- A dose and time dependent change is estimated with the model, with a maximum attainable (asymptotic) decrease of exp(-1.97)/(1+exp(-1.97))=12%.
- Dose-dependent change in virtual potency is a factor exp(-0.0147 D_{new} D_{stand})

Maximum effect as a function of dose of standard compound: Multiplicity model



Conclusion

The outcome from study 1 was confirmed using study 2-6, confirming the PD interaction and finetunes the estimates.

Assumptions:

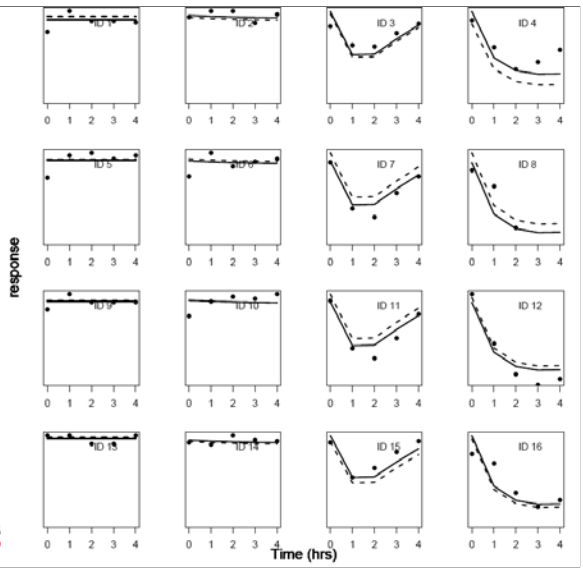
- Meta-analysis of 7 studies (including one historical dataset)
- Dose range of both compounds was tested
- Virtual PK model drives the effects, assuming absence of PK interaction (confirmed in PK interaction study).
- PD interaction impacts only the potency; also other aspects of the dose response might be affected

A marked dose-dependent "synergy-like" behaviour was observed between both compounds

Although initially not expected, the interaction turns out to be predictable, and no effects are observed at the anticipated therapeutic dose range.

Combining biology with statistical modeling leads to improved drug development.

Back up



References

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- Jacqmin, P., Snoeck, E., van Schaick, E., Gieschke, R., Pillai, P., Steimer, J.-L., and Girard, P. (2007). Modelling Response Time Profiles in the Absence of Drug Concentrations: Definition and Performance Evaluation of the KPD Model. Journal of Pharmacokinetics and Pharmacodynamics, 34, 57-85.
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Back up