Why write a book about PK/PD modeling?

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(RETIRED!)

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Outline

- Why we chose to do it in 1994
- If we/I were to do it now
- Tales from the trenches (Part 1)
- General conclusions

Why write the book in 1994?

- Because we wanted to understand the existing methods, and the best way to understand something is to teach it or to write about it
- Because we were young(er), and incredibly naive
- To foster better collaboration among statisticians, pharmacometricians, and clinical pharmacologists

Why write the book in 1994?

- Because there was/is a genuine need for sound methods for analyzing population PK/PD data, as the following example establishes beyond doubt

- Corollary: the better the general understanding of existing methods, their advantages and limitations, the more hope for their intelligent use

Motivating Example

- Apologies for self-plagiarism
- The following example, involving a Phase II trial of a potential IIbIIIa antagonist to inhibit coagulation, has already been presented in several fora (including PAGE 2000 in Salamanca), but has never been written up formally
- I take the liberty of re-presenting it here, because it is a kind of canonical motivating example
- (also, I'm retired, so ……)

IIbIIIa inhibitors

- It is well known that aspirin has a protective effect against coronary events such as M.I. or stroke
- Aspirin blocks one pathway by which platelets aggregate
- IIbIIIa is a particular glycoprotein found on the surface of platelets which facilitates their aggregation (“platelet velcro”)
- This suggests that a drug which binds to IIbIIIa may have a clinical effect, mediated through blockage of platelet aggreagation
- Reopro, an injectable monoclonal antiibody, is one therapy with this method of action
- Search for a “super-aspirin”, oral agent in this class

Phase II trial design

- Novel, small-molecule, IIbIIIa antagonist, under study for possible chronic administration
- Patient population: recent acute coronary event
- 28-day treatment period
- Initial randomization to one of four dose groups, targeted to span a range of inhibition of platelet aggregation
- Ability to add/delete dose groups, based on aggregation results for first 7 subjects in each group
- Once-a-day dosing groups dropped from consideration early on – more twice-daily dose groups added as study progressed

Phase II trial design (continued)

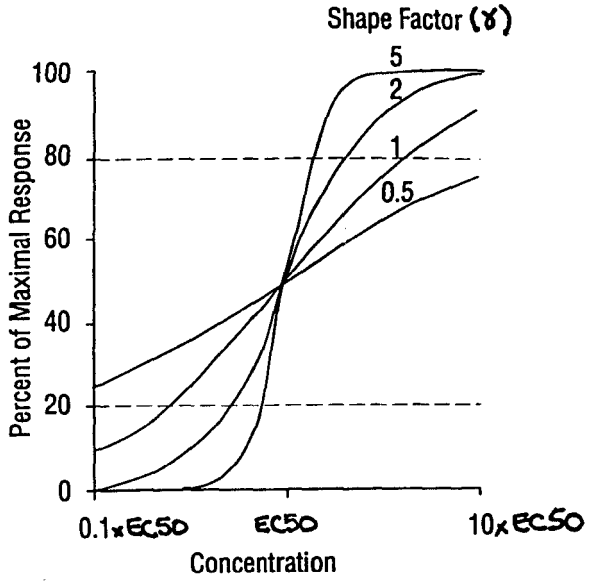
- Intensive PK/PD evaluations on day 1 and day 28 (6 to 9 timepoints each day)
- PK: serial measurements of free and total drug concentration
- PD: serial measurements of ADP-induced platelet aggregation at timepoints roughly concurrent with PK sampling (expressed as % inhibition relative to the subject's baseline)
- About 100 patients in this PK/PD portion – subsequently ~ 250 subjects added to selected dose groups to augment safety data
- Main safety variable : incidence of bleeding events
- For brevity, today I will focus on PD results

Pharmacodynamic analysis - objectives

- Characterise the concentration-response relationship
- Identify dose groups achieving inhibition of platelet aggregation in the target range (20% to 80%) with an acceptable safety profile
- Quantify variability in pharmacodynamic behavior
- Identify subject characteristics which are predictive for differences in PD response

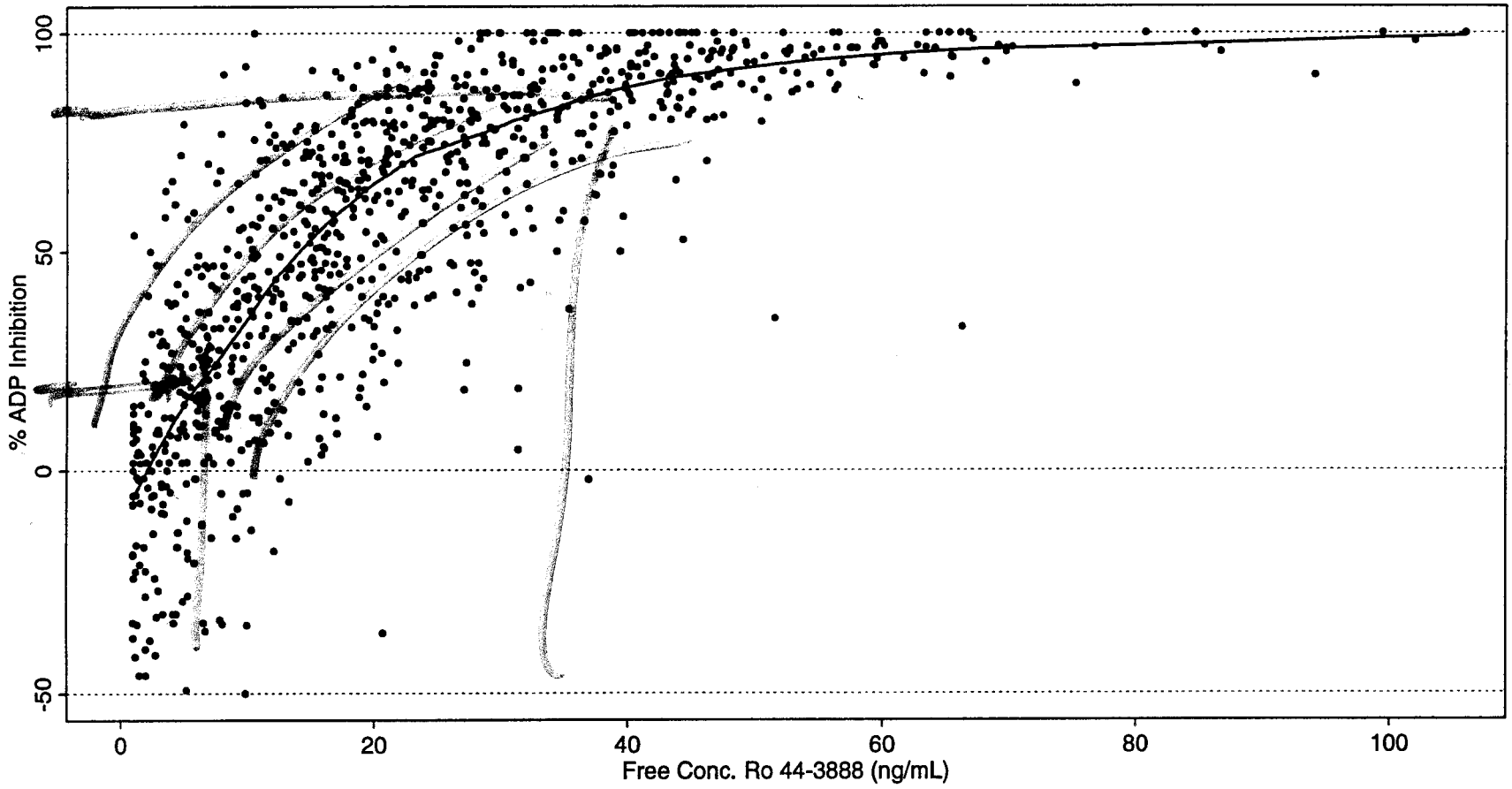
Pharmacodynamic analysis – results (ctd.)

- These data provide a textbook illustration of the need to account appropriately for the repeated measures character of the data when fitting the PD model
- Naïve fitting approaches, which fail to accommodate both the within-subject and between-subject variability, give misleading parameter estimates, underestimating the “slope” parameter in particular
- Fitting techniques based on an underlying (nonlinear) mixed model, which do accommodate both levels of variability, provide better parameter estimates and a better fit overall
- Estimated Hill coefficient is close to 2, indicating a very steep concentration-response curve


Shape Factor (γ)
5
2
1
0.5
100
80
60
40
20
0
Percent of Maximal Response
0.1×EC50
EC50
10×EC50
Concentration

Pharmacodynamic analysis – results (ctd.)

- High degree of variability across subjects in the estimated EC50 values
- **The combined plot of inhibition versus concentration has very high potential to mislead if subject ID is suppressed**
- Why? Because the overall visual impression of the combined data plot is that of a more gradual dependence of inhibition on dose than is actually the case
- Inspecting the individual-subject profiles reveals a series of extremely steep response curves, anchored at different EC50 values for different subjects
- The same concentration which induces complete inhibition in one subject may not be enough to generate any response at all in a more resistant subject

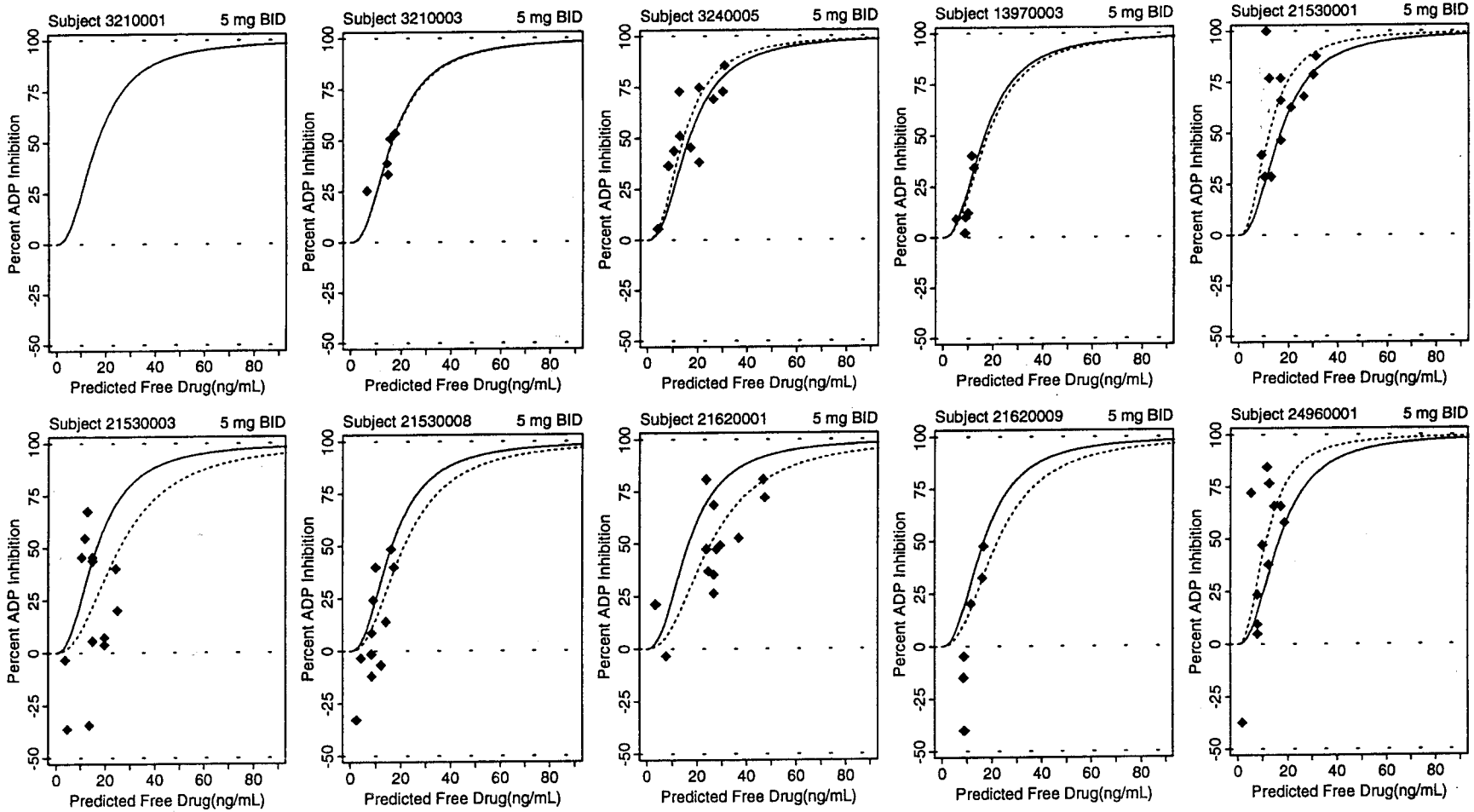


Source: Biostatistics(jdr) Pgm(/oral/IIbIIIa/w0684g/final/biostat/gpki.s)

Individual Concentration-Effect Curves

% ADP Inhibition vs Predicted Free Drug

Sigmoidal Emax Model with Subject-Specific EC50: Emin=0,Emax=100,Hill=2.3,aveEC50=16.6



Pharmacodynamic analysis - results

- The high inter-subject variability in EC50 values is not good news
- No identifiable subject covariates which accounted for the apparent differences in responsiveness – candidate variables such as clinical status, platelet count, receptor density, concomitant medication usage were not predictive
- The single variable which appeared to contribute most to inter-subject variation in EC50's was – study site
- Depressingly, this more likely reflects differences in assay conduct across sites than genuine differences among subjects in their responsiveness to the drug

If we were to write the book today

- Obviously, there would be a blog, documenting the meta-activity around the writing of the book

- What might some of those blog entries look like? (cue special flashback effects)
- Let’s take a look, shall we?
- Come with me, on a voyage into the past …

Journal Entry : Day 2 (January 2nd, 1994)

This is gonna be so great. We're both so psyched about this. And our plan is foolproof! 12 chapters in 12 months! What could be simpler?

We're gonna bring this baby in to land before Christmas, with time to spare!

Go us!!!!

Journal Entry : Day 32
(February 1st, 1994)

Wow, that was probably the most brutal month of my life.

Still, one chapter down, eleven to go!

Still on track for a Christmas delivery

Journal Entry : Day 90
(March 31st, 1994)

Oh dear God. This is bad. This is really, really bad.

M was just here for 5 days. None of our programs will even compile.

We have one lousy chapter, and a bunch of text fragments.

WHAT HAVE WE GOTTEN OURSELVES INTO?

Journal Entry : Day 190
(July 10th, 1994)

Boston, Saturday evening, midnight.

TODAY WAS, QUITE SIMPLY, THE WORST DAY OF MY LIFE EVER.

I CAN’T EVEN WRITE ABOUT IT HERE.

THAT PICNIC! THE HORROR!

Journal Entry : Day 3XX
(November XX, 1994)

Boston, early morning.

I don’t even know what day it is any more.

I’m soooo hungry.

I think Marie hates me.

I know that damned cat hates me …..

« Demon kitty » (spawn of Satan)

Journal Entry : Day 3XX
(November XX, 1994)

Boston, Saturday afternoon.

I don’t even know what day it is any more.

But at least the Bayesian chapter is done.

90 minutes later : “damn! I think Butch (Tsiatis) may actually have supernatural powers”.

What changed? What did we learn?

Goal #1 attained: yes, our understanding of the methods deepened.

Goal #2: to build a bridge between statisticians and pharmacometricians?

Maybe we helped a little. Though sometimes it seems (personal opinion):

“Plus ça change, plus c’est la même chose ?”

What did I learn?

My hatred for hypothesis testing only became deeper.

The older I get, the more Bayesian I become.

For about ten years, one is (more or less) happy to be identified as “the population PK/PD guy”.

But at some point, enough is enough.

Thanks and Acknowledgements

Major thanks are due to Marie, who is infinitely smarter than I, and who put up with me (more or less patiently) throughout the process. The fact that we remain the best of friends is terrific and amazing.

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