Combining PK and PD data; it was 20 years ago today….

(apologies to Sgt. Pepper)

Janet R Wade, PhD

09 Feb 2019
The influence of 20 years

Some things change a lot.....

Others not so much.....
Combining PK and PD data - Setting the scene

- Twenty years ago there were already many publications about population PK/PD analyses, but no research had been done on the best way to combine PK and PD data.
- Analysing PK and PD simultaneously was considered to be the gold standard, avoiding that potential PK model misspecification would inflate PD parameter standard error estimates (SEs), but could be computationally difficult.
- Sequential PK/PD analysis was computationally simpler but estimation error in the PK is ignored and so PD parameter SEs may be underestimated.
Combining PK and PD data – Results presented at PAGANZ 1999 (and PAGE 1999)

• A body of simulation work was presented which had looked at 4 different approaches for combining PK and PD data.
  1. Simultaneous PK/PD analysis.
  2. Fit PK data. Fix individual PK parameters. Fit PD data.
  3. Fit PK data. Fix population PK parameters. Fit PD data.
  4. Fit PK data. Fix population PK parameters (but retain the PK data in the analysis data file). Fit PD data.

• The simulation results of 20 years ago found that approaches 1 and 4 performed equally well, and approach 2 performed least well.

• The work was not published but the results were confirmed by Zhang, Beal & Sheiner who published in 2003 (JPKPD, Vol 30, p387).
Combining PK and PD data – Results presented at PAGANZ 1999 (and PAGE 1999)

• The work presented in 1999 was performed for the situation where the PK response was assumed to drive the PD response.
  • PD is independent of the PK.

• The effect of PD model misspecification on PK parameter estimation was also explored for simultaneous PK/PD analyses.
  • Using the FOCE algorithm protected against the effect of PD model misspecification. This was not the case for the FO algorithm.
Combining PK and PD data – Model misspecification

• Zhang et al (JPKPD, 2003, Vol 30, p405) also looked at the effect of PK model misspecification on PD parameter estimation.
  • More frequent PK data than PD observations.
  • Simultaneous fitting protected against the effect of PK model misspecification on PD parameter estimation.
  • Found a different result for influence of PD model misspecification; simultaneous and sequential approaches performed similarly.
  • Analysis of a real data example found that the PK fitted with the simultaneous method can be quite sensitive to PD model misspecification.
    • Do both simultaneous and sequential fits and compare the PK fits. If they differ appreciably, this is a diagnostic indicating PD model misspecification.
The influence of 20 years

1999

New Zealand prime ministers, then and now.

2019
Moving forward 10 years

• David Lunn in 2009 (JPKPD, Vol 36, p19-38) proposed;
  • A simultaneous PK/PD approach implies equal confidence for both the PK and PD models.
  • A sequential approach where individual PK parameters are fixed implies total confidence in the PK model.
  • Sequential approaches where population PK parameters are fixed (with or without the retention of the PK data) lies between these two extremes.
  • The quantity (and quality) of the PK and PD data is also relevant.
Moving forward to 2014


• The tutorial first referred back to the Zhang 2003 paper when addressing how to combine PK and PD data.

• The case where PK is dependent on PD often necessitates simultaneous fitting of the data.
  • The PK of many biological agents depends on the PD response.
  • In such situations, it may be reasonable to first include the PD assessment as a covariate to allow preliminary evaluation of the PK data, followed by simultaneous model development.
The influence of 20 years

Two Slices of Pizza

Twenty years ago
500 calories

Today
850 calories
Considerations for combining PK and PD data – where are we now?

- Sequential versus simultaneous fitting;
  - What is the question to be answered?
  - Which data (PK or PD) is most reliable?
  - What is the relative quantity of PK and PD data amounts?
- Is the PD response delayed, and if so, by how long?
  - Can impact choice of PK variable that drives PD response.
- PD data may not just comprise PD response but can also include the disease state being treated.
  - Does the disease state itself influence the PK?
  - If there is no feedback of disease state on PK, then there is still a choice about using a simultaneous or sequential approach.
  - If disease state does affect PK, then a simultaneous approach is needed and which includes the mechanism by which disease influences the PK.
Example – Disease influence - Pembrolizumab

  • Pembrolizumab – 200 mg or 2 to 10 mg/kg every 3 weeks
• Found an unusual pattern of improved survival in subjects with higher exposure within each dose level which is incongruent with the similarity in overall survival across the 5-fold dose/exposure range.
  • Suggests a confounding of PK and overall survival independent of direct pharmacologic effects on patient outcome.
Example – Disease influence – Pembrolizumab (cont)

- Work is no doubt still ongoing here. The authors currently conclude;
  - Given that the confounded association of longitudinal disease burden and PK has been observed across a class of oncology therapies, caution is warranted in interpreting apparent exposure-response relationships, especially in the context of oncology trials evaluating a single dose-level of biologic/mAb.

- The influence of sequential or simultaneous approaches is probably not interpretable until the mechanism behind the confounded association of longitudinal disease burden and PK has been elucidated. Incorrect definition of this mechanism will lead to incorrect results regardless of sequential or simultaneous approach.
The influence of 20 years

The best time to plant a tree was 20 years ago.
The second best time is now.
– Chinese Proverb
Example – Disease influence - Malaria

• The pharmacokinetic (PK) properties of antimalarial drugs are often altered in patients with malaria compared with healthy subjects. The PK properties therefore change as the patient recovers (Newton et al, AAC, 2000, Vol 44(4), p972).

• Modelling such PK/PD data could be done;
  • Empirically. A maturation function for the PK can be included that is independent of the PD data. Such an approach could be done simultaneously or sequentially.
  • Mechanistically. The disease state feeds back to drive the change in the PK, which drives the disease status, in a circular fashion. Such an approach to defining the PK/PD relationship would have to analyse the PK and PD data simultaneously.
Discussion points

• What is the goal of the analysis?
  • Model and modelling process (simultaneous, sequential) should be fit for purpose.

• Relative quantity and quality of the PK and PD data should also contribute to the decision whether simultaneous or sequential modelling approach is to be selected.

• Does PK drive PD or is the system more complex?
  • More complex models could have parameter identifiability issues. Parameter identifiability may manifest differently for the simultaneous or sequential modelling approaches.
  • Complex systems (such as pembrolizumab) may need mechanistic models that will need to be analysed simultaneously.