EXPLORING THE HYPOTHESIS THAT AGE-RELATED DIFFERENCES IN THE RESPONSE TO TRIAZOLAM ARE DUE TO ALTERED PHARMACOKINETICS AND INCREASED SENSITIVITY TO THE DRUG IN THE ELDERLY.

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Background

Reasons for the enhanced central nervous system depressant effects of benzodiazepines in older patients compared with younger patients on similar doses remain poorly understood. In a study that examined the relationship between plasma drug concentrations in the young and elderly and response to triazolam as assessed by the digit-symbol substitution test (DSST), it was concluded that marginal differences in pharmacokinetics (PK) together with age-related differences in sensitivity (expressed as the concentration required to produce a 30% decrement in DSST performance i.e.EC_{30}) could account for the enhanced response in the elderly.[1] In this study, PBPK/PD modelling and brain unbound drug concentrations, which may be more relevant for the pharmacological action of triazolam, were used to explore this observation further .

Methods

PBPK Models

* Simcyp V14
* Sim-Healthy Volunteer population – young subjects: 20 – 36 years
* Sim-Geriatric NEC Population – elderly subjects: 65 – 75 years
* Simcyp model for Triazolam
* Full PBPK model
* First-order absorption model
* 0.25 mg triazolam orally
* Young : 10 trials with 10 subjects
  Elderly: 10 trials with 9 subjects each

PBPK/ PD Models

- Simple Emax model using plasma concentrations
- Young male subjects
  - Emax = -18[1] (CV% = 30)
  - Baseline = 100
  - EC_{50} = 0.007µM (parameter estimation)
- Elderly male subjects
  - Emax = -48[1] (CV% = 30)
  - Baseline = 100
  - EC_{50} = 0.005µM (parameter estimation)

Verification of Models

PBPK/ PD Models using unbound brain concentrations of triazolam

- Simple Emax model
- Young male subjects
  - Emax = -18[1] (CV% = 30)
  - Baseline = 100
  - EC_{50} = 0.0009µM (parameter estimation)
- Elderly male subjects
  - Emax = -48[1] (CV% = 30)
  - Baseline = 100
  - EC_{50} = 0.0006µM (parameter estimation)

Results

A favourable comparison between the predicted and observed[1] PK profiles for triazolam was seen following simulations with the PBPK models for young and elderly subjects (Figure 1). Similarly, the PBPK/PD models were also acceptable (Figure 2). Observed elderly to young AUC ratios for PK and PD were 1.8 and 3.8 respectively while corresponding predicted ratios were 1.4 and 3.3.

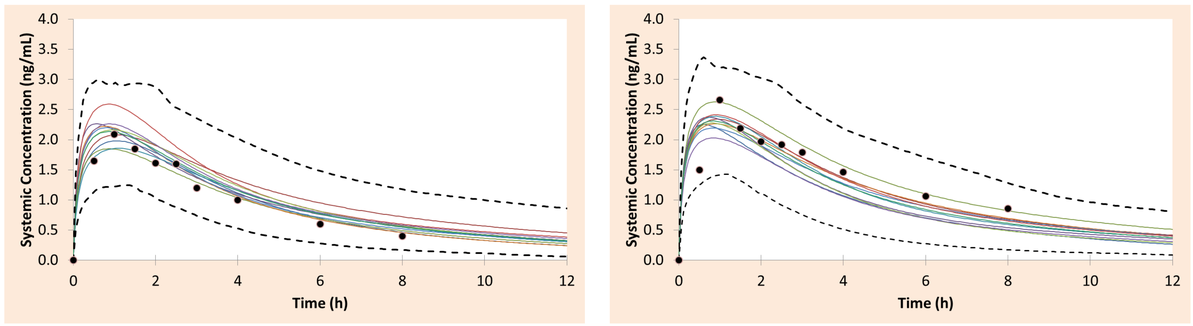

Figure 1: Comparison of predicted (solid line s = mean for each trial with dashed line showing 5% and 95% percentiles) and observed[1] (filled circles) plasma concentration-time profiles in the young (left) and elderly subjects .

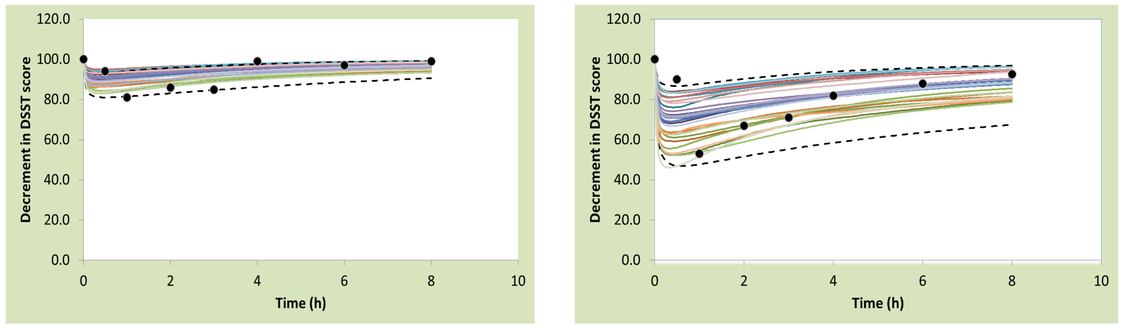

Figure 2: Comparison of predicted (solid line s = mean for each trial with dashed line showing 5% and 95% percentiles) and observed[1] (filled circles) response profiles in the young (left) and elderly subjects .

Predicted brain concentrations of triazolam are depicted in figure 3. The PK AUC ratio for elderly:young for brain concentrations was 1.5. The estimated EC_{50} for the PD model using brain drug concentrations in elderly and young subjects were 0.6nM and 0.9nM respectively and the resulting model recovered the clinical data acceptably (figure 4).

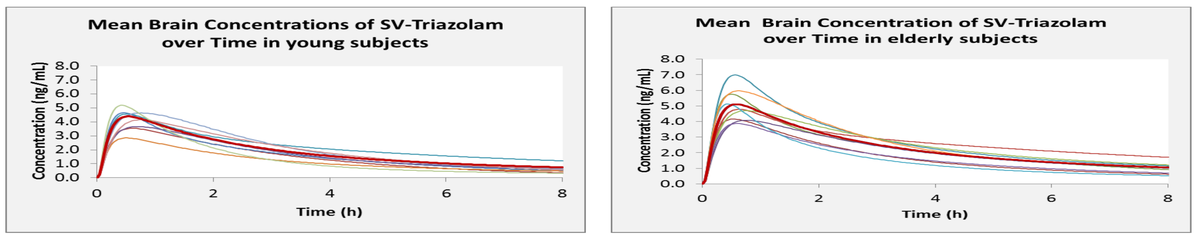

Figure 3: Predicted brain concentration-time profiles in young (left) and elderly subjects

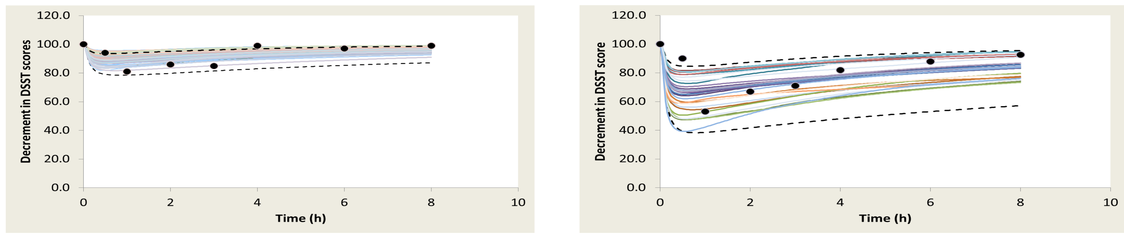

Figure 4: Predicted response-time profiles in young (left) and elderly subjects, using brain concentrations.

Conclusion

Simulations using the developed PBPK/PD models have recovered the marginal PK differences observed in young and elderly subjects and the significant differences in response. Differences in the EC_{50} values (indicative of sensitivity to the drug) between young and elderly were seen when plasma concentrations were used in the PBPK/PD model and these differences in the EC_{50} values were even greater when brain concentrations were used in the PBPK/PD model. These results support the hypothesis that small PK differences combined with age-related differences in sensitivity to the drug may account for the age-related differences in response.

Reference

1. Greenblatt et al. *CPT*, 2004, 76: 467-479