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
  - $E_{max} = -18^1$ (CV% = 30)
  - Baseline = 100
  - $EC_{50} = 0.007 \mu M$ (parameter estimation)
- Elderly male subjects
  - $E_{max} = -48^1$ (CV% = 30)
  - Baseline = 100
  - $EC_{50} = 0.005 \mu M$ (parameter estimation)

Verification of Models

PBPK/ PD Models using unbound brain concentrations of triazolam
- Simple Emax model
- Young male subjects
  - $E_{max} = -18^1$ (CV% = 30)
  - Baseline = 100
  - $EC_{50} = 0.0009 \mu M$ (parameter estimation)
- Elderly male subjects
  - $E_{max} = -48^1$ (CV% = 30)
  - Baseline = 100
  - $EC_{50} = 0.0006 \mu M$ (parameter estimation)

Results

A favourable comparison between the predicted and observed1 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.

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).

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