Modelling Ordered Categorical Allergic Rhinitis Scores in an Environmental Exposure Unit Study

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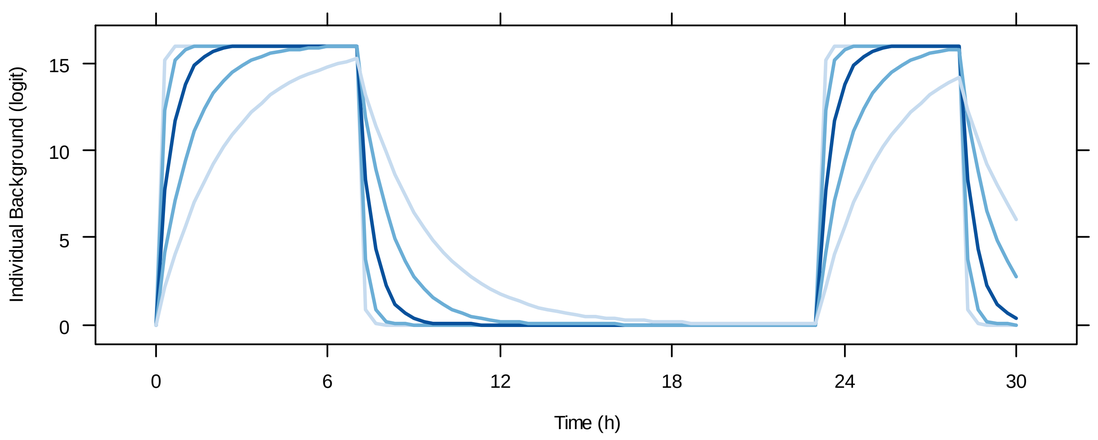
Introduction

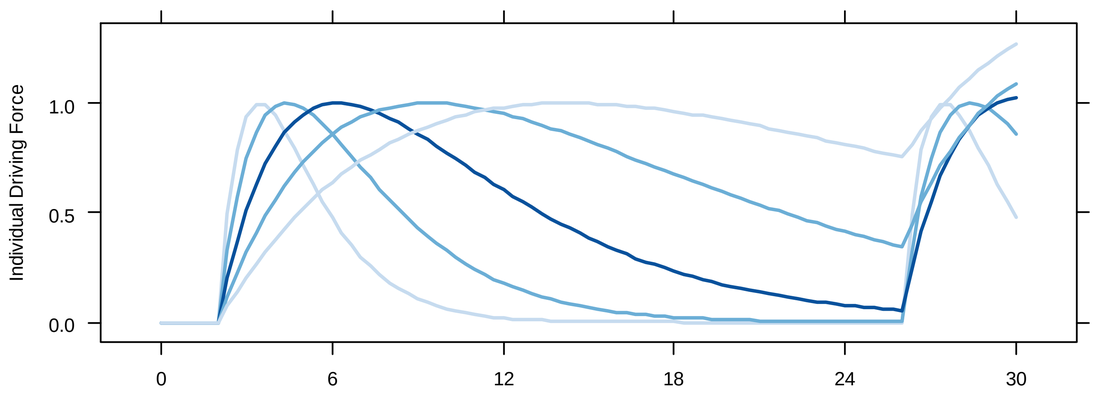
An Environmental Exposure Unit (EEU) study was performed in allergic rhinitis patients to determine the effects of placebo (n=90), fexofenadine (n=225) and cetirizine (n=225) on self-assessed rhinoconjunctivitis symptoms. Patients were exposed to ragweed pollen and treated on two consecutive days. Day 1 consisted of seven hours of ragweed pollen exposure where treatment was started two hours after initiating allergen exposure and Day 2 consisted of six hours of ragweed pollen exposure where treatment was started three hours after initiating allergen exposure.

Methods

Model development was performed using non-linear mixed effects modelling with a proportional odds model. A novel modelling approach was invented describing both the increase in score due to allergen exposure:



where Background describes the score on logit scale over time without the influence of treatment, and the subsequent decrease in score due to treatment. The treatment profile for both active and placebo treatments (called the Driving Force, scaled between zero and one for the first dose) was described using K-PD-type methodology[1]:



where the driving force defines the shape of the profile while the individual magnitude of effect is quantified using an EDF50-parameter that relates the scaled driving force, for all three treatments, with 50% of the maximum effect. Parameters were estimated using the SAEM algorithm in both Monolix and NONMEM VII. Novel graphics were developed to generate visual predictive checks for time profiles of ordered categorical data.

Results

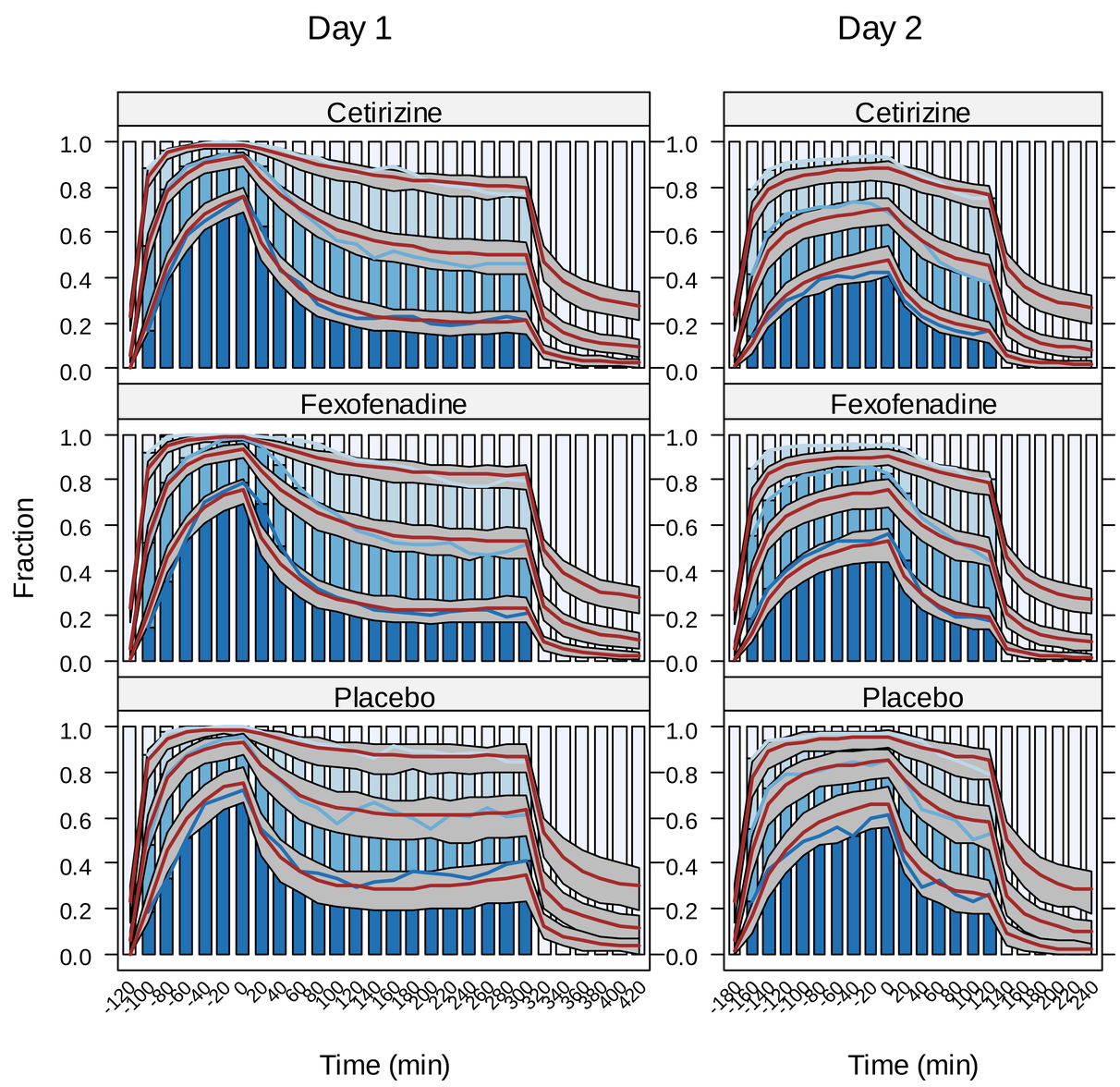
Results are illustrated using the rhinorrhea (runny nose) score. Sensitivity to treatment was quantified using the EDF50-parameter and duration of action over both days of treatment was quantified using a half-life.

Parameter	Estimate (95% CI)	IIV (%)
$T_{1/2ka}$ (Allergen half-life, min)	19.3 (17.0 / 21.6)	111
EDF_{50} placebo	1.23 (1.02 / 1.45)	91
EDF_{50} factor change to ceterizine	0.659 (0.542/0.802)	
EDF_{50} factor change to fexofenadine	0.736 (0.604/0.895)	
$T_{1/2kdf}$ (DF half-life, min) placebo	145 (114 / 176)	75
$T_{1/2kdf}$ (DF half-life, min) ceterizine	257 (231 / 284)	
$T_{1/2kdf}$ (DF half-life, min) fexofenadine	218 (197 / 240)	
dsm	16.6 (15.8 / 17.5)	
B3	-12.1 (-12.9 / -11.4)	449
B2	3.52 (3.35 / 3.70)	40
B1	3.93 (3.70 / 4.16)	42

Administration of fexofenadine was associated with a 26.4% significantly lower EDF50 population value and an even higher decrease of 34.1% was estimated for ceterizine. Ceterizine and fexofenadine also had a much longer driving force half life than placebo (257 and 218 minutes compared to 145 min for placebo) resulting in a longer duration of action extending into day 2. The typical allergen half-life ($T_{1/2ka}$) was estimated to be 19.3 min, which is the time it takes for 50% of the allergen effect to appear.

NONMEM was incapable of converging to acceptable parameter estimates using the provided initial estimates. Implementation of the same model in Monolix showed it to be far less critical in the choice of initial estimates than NONMEM and resulted in convergence to adequate parameter estimates. Re-running the model with NONMEM using the final Monolix estimates provided identical results for Monolix and NONMEM.

Various predictive checks illustrated the adequacy of the model both for predicting derived statistics, such as average score 2-5 hours post-treatment and time to onset of effect (not shown) and for predicting symptom-score time profiles:



These stacked histograms provide the observed rhinorrhea (runny nose) score distribution in the population (actual bars) with superimposed VPC results. Blue lines are observed fractions, red lines are median simulated fractions and gray areas contain 95% of simulated fractions.

Conclusions

Excellent descriptions were obtained of individual score profiles both for the five scores on the 0-3 point scale and the Total Symptom Severity Complex (TSSC), an aggregated score on the 0-12 point scale. Implementation of a proportional odds model enabled a more accurate description of the specific ordered categorical nature of the data with model predictions corresponding to the observed data range. The underlying K-PD model allowed both a description of the treatment profile in the absence of concentration measurements and an adequate description of the placebo treatment effect. The current model-based approach will allow newly developed drugs to be more easily quantified and compared with existing drugs, facilitating across treatment comparison and quantification of both effect-time profiles and derived parameters.

Reference

[1] Jacqmin P, Snoeck E, van Schaick EA, Gieschke R, Pillai P, Steimer JL and Girard P. Modelling Response Time Profiles in the Absence of Drug Concentrations: Definition and Performance Evaluation of the K–PD Model. J Pharmacokinet Pharmacodyn, 34(1), 2007, 57-85.