Nonlinear mixed effects models applied to cumulative concentration-response curves

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Résumé en anglais

Objectives
In experimental pharmacology, drug effect studies currently establish and analyse cumulative concentration–response curves (CCRC) under repeated measurements designs. Usually the CCRC parameters are estimated using the Hill's function in a nonlinear regression for independent data. The two-way analysis of variance is generally used to identify a statistical difference between the responses for two treatments but that analysis does not take into account the nonlinearity of the model and the heteroscedasticity (uneven distribution) of the data. We presently tested the possibility of finding a statistical solution for the nonlinear response in repeated measurements data using the nonlinear mixed effects (nlme) models.

Methods
Experimental data sets, originating from studies on β-adrenoceptor-induced relaxation in rat thoracic aorta ring, were analysed using the nlme methods.

Key findings
Comparison with classical methods showed the superiority of the nlme models approach. For each pharmacological parameter (E_m, n, pD_2), a point estimate, a standard error and a confidence interval are returned by the nlme procedures respecting the assumption of independency and normality of the residuals.

Conclusions
Using the method presently described, it is now possible to detect significant differences for each pharmacological parameter estimated in different situations, even for designs with small samples size (i.e. at least six complete curves).

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