Paper 278-25

Linear and Non-linear modeling of a dose-response curve using SAS®

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ABSTRACT

In clinical trials response variables are measured at different times and doses. This paper explores methods to determine the dose that optimizes the response based on multiple responses and doses. Linear dose-response modeling can be performed using repeated measures analysis (using PROC MIXED) for change in response (Y) using dose (X) as a continuous explanatory variable with time, dose, and time-by-dose interaction as fixed effects. The error structure to model the correlation between the repeated measures needs to be determined e.g. using the Akaike information criteria. To compare the responses at each dose, additional analyses using dose as a classification variable can be performed and pairwise comparisons can be obtained. Non-linear dose response modeling can be performed using continuous dose, X (using PROC NLIN) with the following model: Percent change in Y= $b_0 + (X^{\gamma} . b_1)/(X^{\gamma} + b_2^{\gamma}) +$ error, where b_0 is the response at dose = 0, b_1 is the optimum % change in Y compared to dose = 0 and b_2 is the dose at 50% of b_1. A fixed value of γ can be chosen based on minimum residual sum of squares. Predicted values are calculated and plotted against the observed % change in Y for all doses. Additionally PROC CAPABILITY can be used to determine the best fitted distribution of Y among the exponential family and plotted for different doses. These methods were applied to analyze the pooled data from two clinical trials. Various determination of the "optimal dose" was considered.

INTRODUCTION

Two trials, which were designed with identical entry criteria and dose levels, were pooled where four doses of an experimental drug were administered on n patients. Two responses Y1 and Y2 were measured over ten visits. Dose X has four levels (0, which will be referred to as placebo, a, 2a and 5a). The higher the value of Y1 and lower the value of Y2, the better the experimental drug is compared to placebo. Baseline visit is defined as last of visit 1 (screening visit) or visit 2 (randomization visit). Endpoint is defined as the final visit (last available visit carried forward for the discontinued patients).

METHODS

REPEATED MEASURES ANALYSIS

A repeated measures analysis (Searle et al. 1992) was performed (using the PROC MIXED procedure in SAS® Version 6.09 [SAS Institute 1996]) for change in Y1 and Y2 using a continuous dose as an explanatory variable. Change rather than percentage change was used because the assumption of normality was better satisfied. In this model, trial, visit, dose, visit-by-trial interaction, and trial-by-dose interaction were included as fixed effects. A term for investigator-within-trial was initially included in the model, but was not significant for both the variables. Therefore, this interaction term was subsequently deleted from the model. No significant trial-by-dose interactions were detected at the 0.10 level for the two response variables. Therefore, this effect was removed from the model and the analyses were repeated to test for a common dose effect at the 0.05 level. Different error structures were tested and the one, which resulted in the minimum Akaike criteria, was used. A compound symmetry error structure was chosen to model the correlation between the repeated measures. To compare the three doses of X, an additional analysis using dose as a classification variable was performed. To display the results of the repeated measures analysis, the model-specific least-squares means for each response were plotted against each level of X.

NON-LINEAR E-MAX MODELING

A non-linear model using a continuous dose (0, a, 2a, 5a) as an explanatory variable on the % change from baseline to endpoint in Y1 was fitted using PROC NLIN in SAS® version 6.09. The model was as follows:
% Change in Y1 = $b_0 + (\text{dose}^{\gamma} . b_1)/(\text{dose}^{\gamma} + b_2^{\gamma}) +$ error
where b_0 is the intercept or the placebo response, b_1 is the maximum % change in the response compared to placebo and b_2 is the dose at 50% of the maximum % change in the response compared to placebo. γ was linearly dependent on the other parameters, so a fixed value of γ between 0.5 and 3 was chosen based on minimum residual sum of squares.

DENSITY PLOTS AND ANALYSIS

The distributions of the percentage change in Y2 from baseline to endpoint in subjects treated with the three doses compared with placebo were estimated using PROC CAPABILITY in SAS® version 6.09. The density of Y2 was approximated by a lognormal distribution and the goodness of fit was measured by Pearson's χ^2. The distributions for the four doses were plotted to compare the effect of dose on Y2.

RESULTS

RESULTS OF REPEATED MEASURES ANALYSIS

The change in Y1 and Y2 increased significantly with

increasing dose (p=0.019, p<0.001 respectively). As can be calculated from the data in Table 1, an increase of amount "a" in dose resulted in a $4.0 \times 10^{-5} \times a$ increase in Y1. For Y2, an increase in amount "a" dose resulted in a $0.0015 \times a$ decrease in Y2.

TABLE 1. SLOPE ESTIMATES FOR CHANGE IN RESPONSE

Variable	Slope Estimate	Standard Error	p-Value
Y1	4.0×10^{-5}	2.0×10^{-5}	0.019
Y2	-1.5×10^{-3}	4.0×10^{-4}	<0.001

The least squares means from the linear dose-response model using dose as a *continuous variable* was plotted against the three doses of X as presented in Figures 1 and 2.

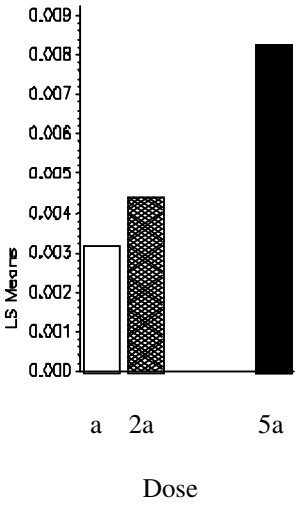

FIGURE 1. LEAST SQUARES MEANS FOR MEAN CHANGE IN Y1 BY DOSE

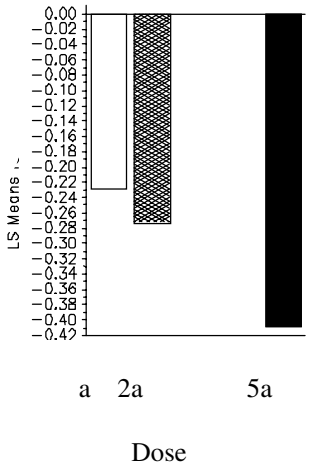

FIGURE 2. LEAST SQUARES MEANS FOR MEAN CHANGE IN Y2 BY DOSE

Additional pairwise comparisons, using dose as a classification variable, were performed for Y1. The results showed no significant difference between the dose levels 2a and 5a. However, the response in the dose level "a" was statistically significantly lower than that in either the 2a or the 5a dose levels (p=0.035, p=0.007, respectively).

TABLE 2. LSMEANS FOR Y1 USING DOSE AS A NOMINAL VARIABLE

OBS	LEVEL	LSMEAN	SE	DDF	T	P_T
1	DOSE a	0.00167725	0.00156826	740	1.07	0.2852
2	DOSE 2a	0.00638116	0.00158249	740	4.03	0.0001
3	DOSE 5a	0.00773347	0.00161737	740	4.78	0.0001

TABLE 3. MULTIPLE COMPARISON USING DOSE AS A NOMINAL VARIABLE

OBS	PARM	EST	SE	DDF	T	P_T
1	a vs. 2a	-0.00470391	0.00222471	740	-2.11	0.0348
2	a vs. 5a	-0.00605622	0.00225020	740	-2.69	0.0073
3	2a vs. 5a	-0.00135231	0.00226009	740	-0.60	0.5498
4	a vs. rest	0.01076013	0.00386231	740	2.79	0.0055
5	5a vs. rest	-0.00740853	0.00392345	740	-1.89	0.0594

RESULTS OF E-MAX MODELING

The value of $\gamma = 1.6$ yielded a minimum SSE for the non-linear model using a continuous dose (0, a, 2a, 5a) as an explanatory variable on the % change from baseline to endpoint in

Y1. The parameter estimates, their asymptotic standard error and confidence limits are presented in Table 4.

TABLE 4. NON LINEAR RESULTS FOR Y1

Parameter	estimate	asymptotic standard error	lower confidence limit	upper confidence limit
b_0	-1.206	0.256	-1.708	-0.704
b_1	2.782	0.369	2.058	3.506
b_2	21.803	7.695	6.701	36.904

The predicted values using the parameter estimates were calculated at doses from 0 to 5a at an interval of 5 (see Figure 3). In addition, the observed % change in Y1 was plotted for the available four doses. The predictor equation was:

Predicted % Change in Y1 = $\hat{b}_0$ + (dose$^{1.6}$. $\hat{b}_1$)/(dose$^{1.6}$ + $\hat{b}_2{}^{1.6}$)

where $\hat{b}_0$, $\hat{b}_1$ and $\hat{b}_2$ are the parameter estimates from the fitted model.

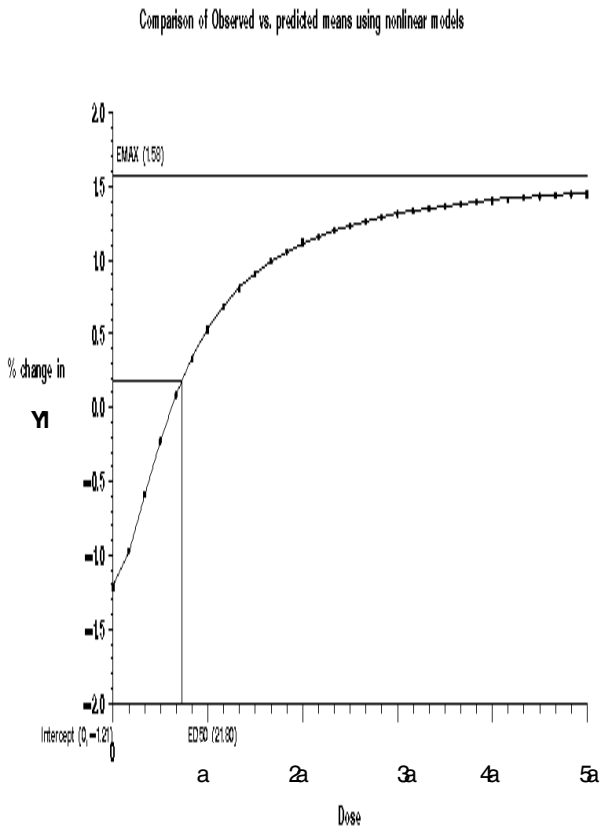

FIGURE 3. OBSERVED VS. PREDICTED MEANS USING NON-LINEAR MODELING

RESULTS OF DENSITY PLOTS AND ANALYSIS

All the non-zero levels of dose shifted the entire distribution representing the corresponding dose group to the left relative to baseline and placebo for Y2 whereas the distribution representing the placebo group shifted to the right compared with baseline. Figure 4 illustrates the globally favorable response of subjects to the experimental doses for Y2.

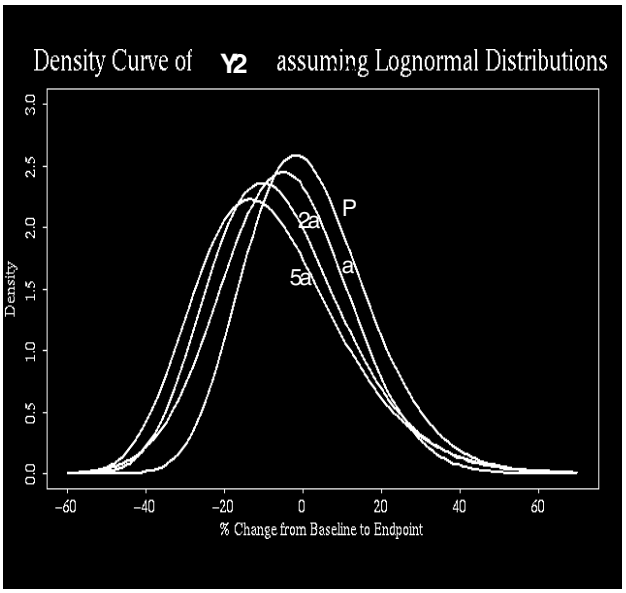

FIGURE 4. %CHANGE FROM BASELINE TO ENDPOINT FOR Y2 BY DIFFERENT DOSES

CONCLUSION

Repeated measures analysis on the pooled data from two trials demonstrated that increasing doses of the experimental drug were associated with a trend toward greater response in Y1 and Y2. Additionally, pairwise comparisons of the three experimental dose levels for Y1 demonstrated that dose “a” was less efficacious than either dose 2a or 5a with no visible clinical difference between the doses 2a and 5a.

Non linear modeling on the pooled data demonstrated that increasing doses of the experimental drug were associated with a trend toward greater response in Y1. The estimate of the ED-50 being 21.8, the minimum effective dose has to be chosen close to twice the ED-50 to obtain 100% of the maximum % change in the response compared to placebo.

Also, the graphical presentations of the density functions demonstrate that compared with placebo, the experimental drug has a globally favorable effect on Y2.

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