CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18118

STATISTICAL REVIEW(S)

AUG 7 1979

STATISTICAL REVIEW AND EVALUATION

July 31, 1979

NDA #: 18-118

Applicant: Burroughs Wellcome Co.

Name of Drug: Lanoxicaps Capsules

Documents Reviewed: Lanoxicaps Capsules Statistical Reports dated May 8, 1979 (desk copy)

Requestor: Nora Chiang, Ph.D., HFD-522

I. Introduction

The Division of Biometrics was asked to review Attachment B of the volume received: Statistical Analysis of Lanoxicaps Multi-Center Bioavailability Study. The submission reviewed is a revision of a report prepared on August 13, 1976.

The bioavailability of three sizes of capsules containing digoxin solution (Lanoxicaps) was compared to an oral digoxin solution, digoxin tablets, and an intravenous solution of digoxin. The primary questions raised by Dr. Chiang concerned the sponsor's method of pooling the data and the sponsor's technique of "zeroing out" the baseline measurements.

II. Sponsor's analysis

The study protocol called for 6 subjects each for 3 investigators, with each subject receiving 5 treatments at .40 mg doses according to a balanced incomplete block changeover design. Although the investigators did not follow the random allocation lists sent to them, the sponsor comments that the deviations did not severely hamper the statistical analysis using the SAS computer program.

Three variables - total urinary excretion, area under the blood level curve (AUC) and peak blood values (Cmax) were analyzed by a linear model taking into account differences among the centers, among the periods within the centers, and the interaction of formulations with centers (to determine the validity of using a pooled data set). For the variables AUC and Cmax the hour 0 baseline values were subtracted before analysis; the sponsor states that "baseline levels were considered 'noise' and zeroed out." Residuals from the model were used to check for outliers and skewness.

When nonsignificant interaction between centers and formulations was found ($p > .05$), the interaction sum of squares was pooled with the error term and contrasts of interest were tested. The interaction was insignificant for each variable (p-values of .64, .09, .56).

For each variable analyzed the formulation means in order from highest to lowest are always I.V., Lanoxicaps, oral solution, and tablets, with Lanoxicaps always statistically higher than tablets and oral solution ($p < .01$) and with at least borderline significance when compared with I.V., (p-values of .08, .01, .01).

III. Reviewer's Comments

The original submission analyzed AUC and Cmax by using the baseline value as a covariate in an analysis of covariance as opposed to the present method of "zeroing out" the baseline. Each method has assumptions which must be considered, but the fact that similar conclusions are reached by either method gives additional credence to the conclusions.

The sponsor's technique for pooling of data is reasonable; results from individual centers appear in agreement with the overall results from the pooled data. For example, all centers showed significantly higher values for capsules than tablets at the 5% level.

It is unclear why the sponsor combined the interaction sum of squares with the error term after testing for interaction. This does not, however, affect the results of the analyses.

The sponsor does not mention the fact that simultaneous tests are being made for the comparisons of interest, which may lead to an overall error rate larger than the nominal 5% rate chosen for each comparison. This problem may be solved here by making individual comparisons at a lower significance level. If only these 5 comparisons are of interest, we may make each at the 1% level, leading to an overall error rate of at most 5%. We may then safely state that the comparisons made in the study are significant at the 5% level. It may be noted that all significant comparisons at the 5% level from the pooled data had p-values of .0004 or lower.

IV. Conclusions

The sponsor's conclusion that Lanoxicaps formulation is statistically higher than tablets and oral solution with respect to each of the 3 variables (total urinary excretion, AUC, Cmax) analyzed is acceptable. In addition, the data shows Lanoxicaps values for these 3 variables to be below the corresponding values for I.V. administration.

S. Edward Nevius

S. Edward Nevius, Ph.D.
Mathematical Statistician

cc:
Orig. NDA 18-118
✓HFD-522
HFD-522/Dr. Chiang
HFD-232/Dr. Dubey
HFD-232/Dr. Nevius
Chron.
SENevius/kah/7/31/79

Concur: Dr. Pledger gP 7/31/79

WR7
for Dr. Dubey 7/31/79