CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20545

STATISTICAL REVIEW(S)

DF

AUG 23 1995

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-545
Applicant: Parke-Davis Pharmaceutical Research
Drug Name: Procanbid (extended release procainamide HCl) Tablets
Indication: Ventricular arrhythmia
Document Reviewed: Volume 1.1, 1.29, 1.31, 1.32, 1.33, 1.34
SAS datasets on a diskette

This review was completed after discussion with the medical reviewer, Dr. Gerald Bunker.

1. INTRODUCTION

This review pertains to a single multicenter clinical study that was conducted to compare the effects of BID and QID formulations of procainamide hydrochloride on suppressing ventricular premature depolarizations. This clinical study was conducted under two protocols, 610-43 and 610-44. The two protocols were identical except for inclusion of PK/PD analyses in protocol 610-43.

2. STUDY OVERVIEW

According to the study protocol, the primary objective of this 14-center clinical trial was to demonstrate the pharmacological equivalence of market formulation Procan SR administered QID and a new formulation of procainamide administered BID.

All patients screened for the study must currently be receiving procainamide SR/QID therapy at a dose not greater than 4000 mg/day and must be taken off drug when entering the baseline period. Following withdrawal of procainamide during a 1-week washout period, ninety-nine patients who had frequent ventricular premature depolarizations (VPDs) were randomly assigned to 1000, 2000, 4000 mg/day procainamide, or placebo and BID or QID form in the first week of double-blind cross-over phase. In the second week, the patients were crossed over for treatment with the other formulation. This randomization provided eight treatment groups. *There was no washout period between the crossover periods.*

The primary activity variable is the percent reduction in VPD (measured by 48-hour monitor recordings) from baseline at the end of the one-week treatment.

Sample size

The sponsor expected that the mean percent reduction in VPDs for the Procan SR/QID treated patients will be 50% over the three dose levels. According to the protocol, the total number of patients required to detect a difference of 30% between the mean percent reduction in VPDs in the procainamide SR/BID formulation-treated patients and the Procan SR/QID-treated patients, over the three dose levels, with 95% power at the 0.05 significance level, two-tailed, is 100 evaluable, or 25 patients per each of the three active treatment groups and 25 patients in the placebo group, assuming that the standard deviation of percent reduction in VPDs for within patients is 25%. The sample size calculation is also based on the assumption that there is no carryover effect or treatment by period interaction of any kind.

Statistical method

Statistical methods to be used for analysis were only described very briefly in the protocol. It was stated that the four treatment groups and the two formulations will be compared based on the percent reduction in VPDs using the analysis of variance in which dose group, formulation, period, and center will be included in the model. The NDA report includes Appendix C.1. (finalized on October 18, 1993) that describes in great detail the statistical methods the sponsor used. The methods involved two main models. First, by eliminating nonsignificant interactions terms (except dose by formulation term) from an ANOVA model matched with the study design, the resulting model consisted of protocol, dose, sequence, patient(protocol dose sequence), period, formulation, and dose*formulation. Second, an ancillary analysis using a cell means model for the between patient factors was done. A TREATMENT variable was created using the 16 possible combinations of protocol (2 levels), sequence (2 levels), and dose (4 levels). The model then consisted of treatment, patient(treatment), period, formulation, and dose*formulation. In either model, the MSE associated with

patient(protocol dose sequence) was used as the denominator in the tests of significant differences among linear combinations of the cell means. Contrasts among periods, formulations, and the levels of the dose by formulation interaction were tested with the residual MSE from the first model. Carryover effect was not investigated.

Patient cohort for analysis

A total of 99 patients were randomized to double-blind treatment. One patient was randomly assigned to 1000 mg BID form but did not receive study medication. Among the 98 patients who received study medication, 4 withdrew from the study due to adverse events (one in placebo QID form, 1 in 2000 mg BID form, 2 in 4000 mg BID form). Therefore, 94 patients completed the study and received both QID and BID forms.

The primary analysis only included the patients who had at least 24 hours of evaluable Holter monitoring recordings at screening, at the end of the first period, and at the end of the second period. There were 78 patients who met this criteria. Patient 3 from Site 5 in protocol 610-43 was dropped from the final analysis because a low baseline value yielded extremely inflated percentage changes from baseline for both the QID and BID formulations. Consequently, a total of 77 patients were included in the main analysis, referred to as the primary activity analysis. The intent-to-treat analysis included all patients who had any evaluable Holter monitoring data at screening, at the end of the first period, or at the end of the second period. There were 98 patients who were included in the intent-to-treat analysis.

Demographics and baseline characteristics

Most patients were white men (83%) and the median age for all patients was 67. The dosage groups appeared to be well-balanced for each patient characteristic; so did the formulation sequences (BID-QID, QID-BID); see Tables 1a and 1b.

Concurrent medications

Patients maintained essentially the same concurrent medications throughout the study regardless of the dosing regimen of procainamide administered. The most commonly prescribed cardiovascular medications were digoxin, aspirin, and lasix.

Efficacy results

Among the 98 patients who received the double-blind treatment, 8 (16%) patients in the BID-QID formulation sequence and 12 (24%) patients in the QID-BID formulation sequence missed the primary activity data (that is, had < 24 hours of 48-hour Holter monitoring at baseline or at either visit during double-blind); see Table 2. The distribution of patients who missed the activity data across the formulation and dose is given in Table 3. These two tables appear to suggest a possible trend of more patients missing activity data with the BID formulation.

Patient 3 of Center 5 (protocol 610-43) who received 1000 mg/day procainamide, was eliminated from the primary analysis since his VPD response (percent change from baseline) was considered an outlier both statistically and clinically. The VPD response to BID form for this patient was +934% and his response to QID form was +343%. These VPD reponses, particularly to BID form, accounted for 50% of the variation in the primary analysis. With the exclusion of this patient, the number of patients actually included in the primary abalysis was 77. Patient characteristics of the 77 patients were similar to those 99 patients randomized to the study.

As per the sponsor's analysis, the sequence, period, and dose by formulation effects were not significant in the analysis of variance. The least square mean (generated from the analysis of variance) percent change from baseline in VPDs for the 77 patients is summarized in Table 4a. A significant linear dose-response relationship was noted for combined forms (see the column 'Total' of Table 4a). All BID form dosages of 2000 mg/day and 4000 mg/day and combined formulation dosages of these two doses demonstrated significant VPD percent decreases compared to placebo and a significant linear dose-response relationship was observed. The 95% confidence interval for the mean absolute

percent change difference between formulations is (-21.2%, 5.7%) which falls within the range (-30%, 30%) that defined formulation equivalence for this study.

A secondary analysis was performed that included all patients with Holter data, with the exception of the so-called outlier patient. The results of this secondary analysis showed that the reduction in VPDs observed in 2000 mg/day QID form and combined active dosages of QID form was now significantly greater than placebo (Table 4b). An all-patient analysis including the outlier patient showed significantly greater VPD suppression with the highest dosage (4000 mg/day) only and no combined formulation dosages were found significantly greater than placebo in VPD suppression (Table 4c).

All the analyses indicated a significant linear trend in dose response with BID regimen ($p < 0.003$), but not with QID regimen ($p = 0.16$).

The sponsor reported that there were no apparent differences in VPD percent change based on age (< 65 and 65+ years), gender, or race.

3. REVIEWER'S EVALUATION AND COMMENTS

Issue of equivalence

The primary objective of the study is to show equivalence of the BID formulation and the marketed QID formulation. The sponsor expected that the mean percent reduction in VPDs for the QID formulation will be 50% over the three dose levels, but the data showed a 29% reduction with 95% confidence interval (9%, 48%) in the primary analysis. The specified range for formulation equivalence was (-30%, 30%); that is, the BID formulation with a mean percent reduction of 20% to 80% can be called equivalent to the QID formulation with a 50% reduction. If the true mean reduction in VPDs for the QID formulation is close to 29% estimated from the data, then the BID formulation having no effect (i.e., 0% reduction) can be declared equivalent to the QID formulation. Thus, there is a question as to whether this equivalence range (-30%, 30%) is acceptable.

To show equivalence of the two formulations, the firm used the criterion that the 95% confidence interval of the difference between the two formulations by pooling the three dose groups falls in the range of (-30%, 30%). This criterion of equivalence has another problem of interpretation. To elucidate the potential problem, suppose hypothetically that BID formulation minus QID formulation is -15% with 95% C.I. (-40%, 10%) at a low dose, 0% with 95% C.I. (-25%, 25%) at a middle dose, and 15% with 95% C.I. (-10%, 40%) at a high dose, assuming that the dose groups are of equal sample size. By pooling the three dose groups, the resulting difference is 0% with 95% C.I. (-14%, 14%) which will lead one to conclude equivalence of the two formulations. However, the two formulations are clearly not equivalent at the low dose and at the high dose, since the 95% C.I. is not contained in the range (-30%, 30%). Therefore, in my view, the equivalence should be studied at individual dose levels, not at the pooled dose.

Issue of carryover effect

There was no washout period between the crossover periods. The sponsor's analysis does not assess the potential carryover effect.

To assess the carryover effect, the mean reduction of VPDs and its standard error are presented in Tables 5a and 5b. As shown in the two tables, the difference (BID minus QID) in VPDs for 4000 mg/day appeared to differ between the two study sequences ($p=0.097$ in primary activity analysis and $p=0.070$ in intent-to-treat analysis); this indicates a potential carryover effect or inconsistency of the difference between BID and QID when the two formulations are studied in different order of the crossover periods. There were large numerical deviations in the difference of (BID minus QID) between the study sequences for placebo in both primary activity analysis and intent-to-treat analysis and for 2000 mg/day in the intent-to-treat analysis; the large deviations are not statistically significant (this could be due to the fact that test of carryover effect usually has low power). However, there was no consistent pattern for such an inconsistency across the doses. For placebo and the 1000 mg/day dose, the difference of BID minus QID was smaller in sequence 2 than sequence 1; for the 2000 mg/day and 4000 mg/day doses, the

difference was larger (Table 5a). Thus, it is difficult to explain such an inconsistency. To be on the conservative side, one can use only the first period data to assess the efficacy of the 4000 mg/day dose.

Interpretation of analysis results

1. Efficacy

Based on the first period data, both the primary activity analysis and the intent-to-treat analysis gave a 39% reduction from baseline in VPDs for the 4000 mg/day BID. Only the primary activity analysis showed that this reduction is significantly greater than that of the placebo (Tables 5a and 5b); the size of the deviation in the placebo effect between the primary activity analysis and the intent-to-treat analysis seemed to be the reason for not achieving statistical significance in the intent-to-treat analysis. The estimated effect size is approximately 28% to 37% for the 4000 mg/day BID (relative to placebo). The 4000 mg/day QID is not significantly different from placebo; the estimated effect size is 50%. The QID data had a much larger variability. By pooling both period data, the sponsor's analysis estimated an effect size of about 70% to 74% for the 4000 mg/day BID and about 30% to 34% for the 4000 mg/day QID (Tables 4a-4c). The effect size estimates for the 4000 mg/day BID and QID differ greatly between the first period analysis and the two periods analysis.

For the 2000 mg/day dose, both the first period analysis and two period analysis gave a similar estimate of the effect size for BID and for QID relative to placebo (60% for BID and 36% for QID). The 2000 mg/day BID had a significantly greater reduction in VPDs than placebo; the QID did not.

For the 1000 mg/day dose, there appeared to be no serious inconsistency in the difference of BID minus QID between the two study sequences. Based on the first period data, only the primary activity analysis seemed to indicate a significantly greater reduction in VPDs with BID formulation; the intent-to-treat analysis did not show significance. Nor did the sponsor's analysis. The QID formulation was not significantly different from placebo.

2. Equivalence

As said above, the equivalence should be studied at individual dose levels, not at the pooled dose. In addition, there seems to be a problem with the definition of equivalence range (-30%, 30%) based on the absolute difference in VPDs between BID and QID formulations (see the explanation in the subsection of 'Issue of equivalence' on page 5).

Assuming that the definition of equivalence is acceptable, by pooling both periods the primary activity analysis suggested an equivalence of BID and QID at 1000 mg/day and 2000 mg/day doses (Table 4a). The intent-to-treat analysis without the outlier (patient 43-5-3) also suggested an equivalence of the two formulations at the 1000 mg/day dose (Table 4b). Based on the first period data, no 95% confidence interval falls within the range of (-30%, 30%); equivalence is not conclusive; see Tables 6a and 6b.

3. Subgroup analysis

The sample size for female, black patients or the patients less than 65 years old was very small (ranging from 0 to 6). The descriptive statistics for these subgroups are of little value and hence are not presented in this review.

4. CONCLUSION

The 2000 mg/day BID of procainamide yielded a significantly greater reduction in VPDs than placebo. None of the three doses administered QID are significantly different from placebo.

As explained above, the equivalence of BID and QID should be studied at individual dose levels, not at the pooled dose. In addition, there seems to be a problem with the definition of equivalence range (-30%, 30%) based on the absolute difference in VPDs. The equivalence of the BID and QID formulations is, in my view, inconclusive.

/S/

H.M. James Hung, Ph.D.
Mathematical Statistician

This review consists of 9 pages of text and 11 tables.

Concur: Dr. Chi /S/ for C. Chi 08/23/95

for Dr. Dubey /S/ 8/23/95

cc: Orig. NDA
✓ HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Bunker
HFD-110/Mrs. Diana Willard/Mrs. Natalia Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Hung

Jhung/594-5436/SERB/procain.wpd/07-24-95

Table 1a. Baseline characteristics by dosage group

Characteristics	Combined BID and QID Forms (mg/day)			
	Placebo N=25	1000 N=24	2000 N=28	4000 N=22
Gender, N (%)				
Female	3 (12)	4 (17)	6 (21)	4 (18)
Male	22 (88)	20 (83)	22 (79)	18 (82)
Race, N (%)				
White	21 (84)	20 (83)	26 (93)	20 (91)
Black	3 (12)	3 (13)	1 (4)	1 (5)
Other	1 (4)	1 (4)	1 (4)	1 (5)
Age, yr				
Median	67	68.5	66	68
Range	31-93	51-80	38-83	56-77
Age group, N (%)				
< 65 years	8 (32)	8 (33)	13 (46)	6 (27)
65 + years	17 (68)	16 (67)	15 (54)	16 (73)
Number of VPDs/hr				
Median	137	180	159	156
Range	24-1461	23-1010	20-2886	23-1445

APPEARS THIS WAY
ON ORIGINAL

Table 1b. Baseline characteristics by dosage group

Characteristics	BID-QID N=50	QID-BID N=49
Gender, N (%)		
Female	10 (20)	7 (14)
Male	40 (80)	42 (86)
Race, N (%)		
White	44 (88)	43 (88)
Black	4 (8)	4 (8)
Other	2 (4)	2 (4)
Age, yr		
Mean		
Median	67.5	67
Range	38-90	31-93
Age group, N (%)		
< 65 years	18 (36)	17 (35)
65 + years	32 (64)	32 (65)
Number of VPDs/hr		
Mean		
Median	183	165
Range	23-2886	20-1445

APPEARS THIS WAY
ON ORIGINAL

Table 2. Number (%) of patients missing primary activity data (< 24 hours of 48-hour Holter data) by formulation sequence

	BID-QID N=49	QID-BID N=49
Baseline	1 (2)	2 (4)
Double-blind phase Week 1 Week 2	 7 (14) 4 (8)	 4 (8) 7 (14)
Any	8 (16)	12 (24)

Table 3. Number (%) of patients missing primary activity data (< 24 hours of 48-hour Holter data) by formulation

Dosage group	Baseline N=98	BID N=98	QID N=98	Any N=98
Placebo	0 (0)	7 (7)	1 (1)	7 (7)
1000 mg/day	1 (1)	0 (0)	2 (2)	3 (3)
2000 mg/day	2 (2)	4 (4)	3 (3)	7 (7)
4000 mg/day	0 (0)	3 (3)	1 (1)	3 (3)

Table 4a. Mean* percent change from baseline in VPDs (primary activity analysis)

Dosage group	BID N=77	QID N=77	Total N=77	Mean diff. BID-QID	95% CI for mean difference
Placebo	20.4	0.6	10.5	NA	NA
1000 mg/day	-14.7	-19.7	-17.2	5.0	(-18.4, 28.5)
2000 mg/day	-40.5+	-35.8	-38.2+	-4.7	(-27.2, 17.8)
4000 mg/day	-53.4+	-29.9	-41.6+	-23.5	(-46.9, -0.02)
All doses	-36.2+	-28.5	-32.5+	-7.7	(-21.2, 5.7)#

Table 4b. Mean* percent change from baseline in VPDs (intent-to-treat analysis without the outier, pat. 43-5-3)

Dosage group	BID N=97	QID N=97	Total N=97	Mean diff. BID-QID	95% CI for mean difference
Placebo	16.4	0.4	8.4	NA	NA
1000 mg/day	-17.5	-21.6	-19.5	4.1	(-19.8, 28.0)
2000 mg/day	-33.7+	-43.5+	-38.6+	9.8	(-11.4, 31.0)
4000 mg/day	-53.2+	-34.2	-43.7+	-19.1	(-43.0, 4.9)
All doses	-34.8+	-33.1+	-34.0+	-1.7	(-15.0, 11.6)#

Table 4c. Mean* percent change from baseline in VPDs (all patient analysis)

Dosage group	BID N=98	QID N=98	Total N=98	Mean diff. BID-QID	95% CI for mean difference
Placebo	16.7	0.1	8.4	NA	NA
1000 mg/day	38.4	8.3	23.4	30.1	(-3.8, 64.0)
2000 mg/day	-34.0	-43.3	-38.6	9.3	(-21.4, 40.1)
4000 mg/day	-53.5+	-33.9	-43.7	-19.6	(-54.4, 15.1)
All doses	-16.4	-23.0	-19.7	-6.6	(-12.6, 25.8)#

NA: Not applicable * least squares means generated from ANOVA

+ significantly greater reduction in VPDs compared with placebo by ANOVA, $p < 0.05$

Within the range (-30%, 30%) that defined formulation equivalence

Table 5a. Mean percent change in VPDs (Primary activity analysis) by sequence

	Sequence 1				Sequence 2				Diff in BID-QID P-value
	N	QID	BID	BID-QID	N	BID	QID	BID-QID	
Placebo	11	13.7 (25.2)	40.0 (36.0)	26.3 (24.7)	7	-1.8 (8.2)	-10.2 (19.3)	8.4 (18.0)	.49
1000 mg/day	9	4.9 (43.8)	14.5 (43.6)	9.6 (16.5)	10	-34.7* (10.6)	-35.8 (11.3)	-1.1 (10.5)	.58
2000 mg/day	8	-20.9 (25.7)	-29.2 (19.9)	-8.3 (22.3)	13	-61.2** (6.7)	-59.4 (9.4)	-1.8 (5.2)	.78
4000 mg/day	9	-37.1 (18.6)	-77.8 (10.4)	-40.7 (16.6)	10	-38.6* (15.8)	-30.8 (21.5)	-7.8 (10.8)	.097

Comparison between dose and placebo: * $p < 0.05$ ** $p < 0.0001$
Number in the parenthesis is standard error.
Sequence 1: QID (period 1), BID (period 2)
Sequence 2: BID (period 1), QID (period 2)

Table 5b. Mean percent change in VPDs (Intent-to-treat* analysis) by sequence

	Sequence 1				Sequence 2				Diff in BID-QID P-value
	N	QID	BID	BID-QID	N	BID	QID	BID-QID	
Placebo	13	13.0 (21.3)	45.3 (31.6)	32.2 (21.9)	10	-11.9 (15.0)	-13.6 (17.0)	1.7 (14.5)	.25
1000 mg/day	12	-3.8 (33.6)	3.6 (32.9)	7.4 (14.7)	10	-34.7 (10.6)	-35.8 (11.3)	1.1 (10.5)	.73
2000 mg/day	11	-30.8 (19.3)	-4.9 (29.7)	26.0 (31.3)	14	-61.9++ (6.2)	-60.1 (8.8)	-1.8 (4.8)	.38
4000 mg/day	9	-37.1 (18.6)	-77.8 (10.4)	-40.7 (16.6)	11	-39.5 (14.3)	-33.9 (19.7)	-5.6 (10.0)	.070

Comparison between dose and placebo: ++ $p < 0.01$
Number in the parenthesis is standard error.
* missing values deleted
Sequence 1: QID (period 1), BID (period 2)
Sequence 2: BID (period 1), QID (period 2)

Table 6a. 95% confidence interval for (BID minus QID) based on first period data (primry activity analysis)

	QID n mean	BID n mean	BID-QID	95% CI+++
Placebo	11 13.7	7 -1.8	NA	NA
1000 mg/day	9 4.9	10 -34.7	-39.6	(-128.0, 48.8)
2000 mg/day	8 -20.9	13 -61.2	-40.3	(-92.4, 11.8)
4000 mg/day	9 -37.1	10 -38.6	-1.5	(-49.3, 46.3)

+++ based on normal approximation

Table 6b. 95% confidence interval for (BID minus QID) based on first period data (intent-to-treat analysis***)

	QID n mean	BID n mean	BID-QID	95% CI+++
Placebo	13 13.0	10 -11.9	NA	NA
1000 mg/day	12 -3.8	10 -34.7	-30.9	(-100.9, 39.1)
2000 mg/day	11 -30.8	14 -61.9	-31.1	(-70.9, 8.7)
4000 mg/day	9 -37.1	11 -39.5	-2.4	(-48.5, 43.7)

*** missing values deleted

+++ based on normal approximation