CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20545

MEDICAL REVIEW(S)

PF

(5)

JUL - 7 1995

Medical Review of NDA

NDA #: 20-545

DRUG: EXTENDED RELEASE PROCAINAMIDE HCl (PROCANBID)

SPONSOR: PARKE-DAVIS

PROPOSED INDICATION: TWICE-DAILY USE IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS

RELATED NDAS: ANDA 86-065, 87-510, 88-489

RELATED INDS: [ ]

PHARMACOLOGIC TYPE: CLASS 1A ANTIARRHYTHMIC AGENT

DOSAGE: 500 and 1000 mg

DATE OF NDA SUBMISSION: 21 December 94

Reviewer: Gerald E. Bunker MD, PhD

Review last revised: 3 July 1995

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III. HISTORY AND BACKGROUND OF THE APPLICATION

1. History

This New Drug Application deals with a new preparation of a drug historically established in cardiology for forty-five years.

Procainamide hydrochloride, a quinidine-like class IA antiarrhythmic, was derived from the local anaesthetic procaine by replacement of an amide for an ester linkage.

Mautz observed in 1939 that procaine elevated the stimulation threshold of ventricular muscle in the frog. Procaine administered iv to anesthetized human subjects suppresses ventricular arrhythmias but without general anaesthesia causes unacceptable CNS stimulation.

Procaine's rapid hydrolysis suggested that its antiarrhythmic action might be directed through one of its metabolites. Derivatives were screened by measuring their ability to protect against ventricular tachycardia produced by epinephrine in anesthetized dogs.

Diethylaminoethanol was shown to have antiarrhythmic activity less than the parent compound but with much reduced toxicity, unlike the other derivatives studied.

Therefore the search was on to develop a stable related compound that would have an enhanced antiarrhythmic effect without toxicity.

W.A. Lott, an E.R. Squibb and Sons staff chemist, suggested and synthesized procainamide which in 1950 came into use as an antiarrhythmic alternative to its classmate quinidine.[1]

Procainamide's place for chronic treatment -- suppression or prophylaxis of ventricular and atrial arrhythmias -- was limited by (1) the fact that a small but inevitable number of patients develop a lupus erythematosus syndrome and (2) the short half-life of the immediate release oral preparation (2.5 - 5 hours) requiring

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[1]Mark, LC et al, The Physiological Disposition and Cardiac Effects of Procaine Amide, J Pharmacol Exp Ther 1951;102:5.

nominal q 3 h dosing --making compliance difficult for the elderly patients who are the usual candidates for antiarrythmics.

Thus to expand oral procainamide's outpatient use pari passu with improvements in pharmaceutical engineering (and doubtless with the expiration of Squibb's patent) several manufacturers developed nominal qid extended release preparations, including Procan SR by current sponsor approved on the basis of bioequivalency studies by the Division of Generic Drugs in 1980.

Qid is more convenient than q 3 h but still irksome. The next step was to develop and test a bid preparation. But by this time (1987) the climate of drug approval, understanding of pharmacodynamics, and ideas about the risk-benefit ratio of anti-arrythmics had changed.

Despite the development of serum procainamide assays, effective dose has to be sought clinically. Because of the lack of direct correlation between serum levels and clinical effect, also because of genetic and physiologic differences in metabolism, dose and interval need to be tailored to the individual. There is some irony to the commercial drive to develop established interval preparations for a drug that should not be given at a fixed interval; the name Procanbid has been **approved** for what should in theory be only approximately a bid preparation.

2. Background of the Application

In the wake of FDA rejection of several petitions requesting approval of sustained release procainamide on the basis of bioavailability studies, PARKE-Davis requested a meeting with the Cardiorenal Division to clarify what would be required for approval of their proposed bid procainamide.

During the first meeting, 3 December 1987, Division recommended a single clinical trial of parallel titrated design comparing the proposed new formulation with an approved procainamide formulation and placebo across a wide dose range.

FDA Office of Drug Evaluation Director Robert Temple himself outlined in 1982 the problems which arise with a two-arm active medicine trial in the absence of placebo.

1. It is more difficult to prove statistically that two results are the same than that they are different. If both treatments yield the same effect, there is no test to establish that a statistically significant similarity exists...

2. Since the investigator does not wish to observe a difference between treatments, there is no incentive to conduct the trial well. In fact the more poorly it is conducted, the more likely that the data will be the same with both medicines...

3. There is no accepted statistical means of demonstrating either medicine worked if there is no statistically significant difference between them in results obtained. If both medicines are approximately equal in the effect they elicit, it does not prove that either medicine is truly efficacious.[2]

Furthermore, in the case of procainamide there is so little understanding of the relationship between dose, serum levels, and effect that it is impossible to specify what serum levels of two preparations would be close enough to be deemed "bioequivalent."

For these reasons - statistical principles relating to the comparison of two drugs and specific properties of procainamide - FDA officials advised the sponsors that the bid preparation should demonstrate ectopic suppression demonstrated by Holter monitor throughout the proposed dosing interval comparable to that achieved by an existing preparation (by preference the original immediate release preparation) and better than placebo.

An increase in adverse effects in the bid as opposed to the qid preparation would not be accepted as the price for the increased length of action.

A year and a half later the sponsors requested a further meeting to discuss a clinical study along the lines discussed previously. The sponsor submitted the following schematic

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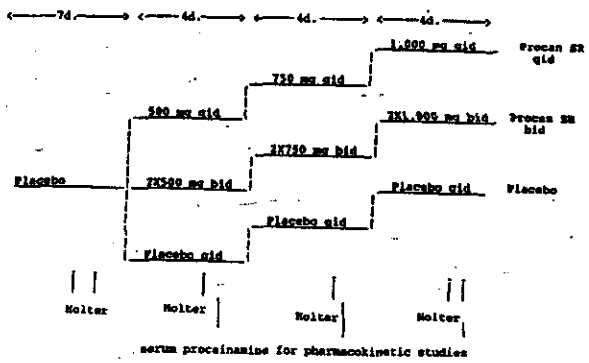
[2] Spilker, Bert, **Guide to Clinical Trials**, New York, 1991; p.721.

illustrating their plan at this point (15 June 1989.)[3]



This trial envisioned enrolling sixty patients in each treatment arm and thirty-two in the placebo arm. It was judged adequate to demonstrate efficacy vs. placebo with 95% power at the 0.05 level.

The Division promised scrutiny of monitoring hour by hour to establish suppression over entire dosing interval. Neither decreased efficacy at the end of the dosing period nor increase side effects at the beginning would be accepted as the price for bid dosing.

Sponsors asked whether enrolled patients must suffer from symptomatic ventricular ectopy (according to the contemporaneous labeling change) or could they also accept patients with asymptomatic ventricular arrhythmias. Division's advice was "not to hold out for symptoms."[4]

On 6 July 1990 the sponsor met again with the Cardiorenal Division. Sponsor now understood Division's approval of inclusion of asymptomatic patients but misunderstood Division's requests with respect to Holter monitoring -- 48 hours after the first dose and 72 hours commencing the last day of dosing.

Not long after (24 Oct 1990) sponsor filed IND [ ] and

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[3]NDA 20-545,1.1,attachment 3.

[4]NDA 20-545, 1.1, attachment 3.

proceeded straightaway with the clinical trial (protocols 610-43 and 44) since Division deputy director waived the 30-day waiting period as requested.

However the protocols were of a design quite unlike that discussed with the Division during the previous years. Instead of a parallel design - three (bid, qid, placebo) arms x 60 patients each subjected to increasing doses of the same preparation - it was a crossover design. The arms were now defined by dose: placebo, 1000 mg, 2000 mg, 4000 mg per day. The comparison between preparations was now to be by crossover with no washout period. The patients taking qid would switch to bid and vice versa.

Because of the possibility of carryover antiarrhythmic effect it is only in the pre-crossover period that the treatment arms are completely comparable. This design weakness (to be more fully discussed later) brings into question the adequacy of the trial.

The Division's safety meeting held 30 Nov 1990 did not discuss the design change -- which did not affect safety -- but did decide "the proposed study protocol is acceptable and the study may proceed."

Division Medical Officer Sughok K. Chun expressed concern at this point that a longer acting procainamide might lead to increased hematologic sequelae especially relating to leukocyte formation. To follow through on this concern the sponsor was requested to prepare an epidemiological analysis to evaluate previous frequency of such events.

At a later date (3 June 1991) Division questioned the statistical power of the protocol to sufficiently demonstrate VPD suppression. In response to protocol amendment #1 received 29 May 1991 Dr. Chun expressed by phone her view that "calculated sample size and power considerations with respect to primary objective and hypothesis probably is incorrect."[5] Details of amendment and criticism will be discussed below.

IV. NON-CONCERNS AND CONCERNS ABOUT APPROVING PROCAINAMIDE BID NOW

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[5] IND 2.1: Medical Officer's Review, 29 June 1991.

1. Non-concerns as Stated by the Division

A. Toxicology and Human Safety

Procainamide has been used clinically in humans for more than 40 years. For this reason this application does not require animal or human toxicology studies.

B. Testing on Asymptomatic Subjects

Suppression of nonsymptomatic ventricular premature depolarizations (VPD) in patients proven responsive to and tolerant of procainamide is taken as a surrogate marker for efficacy in a population with life-threatening arrhythmias, that is, in the population for which the drug is currently approved.

C. The Future Clinical Place of Procainamide and Other Antiarrythmics

Recent epidemiology (**CAST**, etc.) deprecates the value of arrhythmia suppression in the absence of severe symptoms. The sponsor clearly recognizes this in conservative labeling indicating proposed use only in life-threatening arrhythmias.[6]

Thus, although bid procainamide would be far less used in the current environment than if it had appeared forty years ago, there is no intent to question that the parent drug has a place in the pharmacopeia.

2. Concerns

A. The Trial Design

There are three objectives that should be met in order to demonstrate equivalence in suppressing VPD's over the entire dosing range:

(1) the active control (procainamide qid) should distinguish itself

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[6]"PROCANBID tablets are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia that in the judgement of the physician, are life-threatening. Because of the proarrythmic effects of procainamide, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular depolarizations should be avoided."

from placebo (If not, equivalence is unconvincing).

(2) procainamide bid also should be better than placebo and

(3) the study should be of sufficient power to show a difference between the approved and the new preparations if a difference exists.

The real question is whether the crossover design has adequate power to permit these demonstrations.

B. The Dose Range

But logically prior to consideration of adequacy of design the adequacy of the dosing range must be considered. The protocol used doses of 1000/2000/4000 mg daily. As stated above, dosing needs to be empiric; serum levels are not reliable guidelines of efficacy. Nonetheless the sponsor recommends (in the Procan SR PDR monograph) an initial total daily oral dose for younger patients with normal renal function 50 mg / kg; i.e. 3500 mg/day. A study contemporaneous with the approval of Procan SR began with doses of 3500 mg and increased to 7500 mg as required.[7] Mean maximal and minimal concentrations of procainamide and NAPA were 10.4/12.0 and 6.8/8.7 micrograms/ml respectively.

As illustrated by the following graph of percent patients responding to procainamide vs. plasma procainamide in mg/ml,[8] the therapeutic window, that is the plasma concentration in which maximal efficacy and minimal side effects can be achieved is 4 - 8 mg/ml. The therapeutic index -- the separation of the therapeutic and toxic concentration-effect curves or the toxic dose divided by the therapeutic dose -- is approximately 3.

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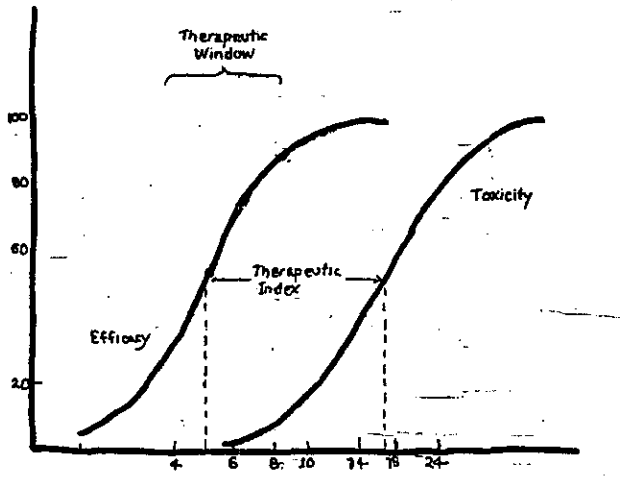
[7] EGV Giardina et al, Efficacy, Plasma Concentrations and Adverse Effects of a New Sustained Release Procainamide Preparation, AJ Card, November 1980; 46.855-862.

[8] redrawn from Wyngaarden, JB et al, ed, Cecil Textbook of Medicine, 19th edition, Saunders 1992, p.87.



"Therapeutic" plasma range of procainamide traditionally has been regarded as 4 to 10 micrograms / minute with 10-15 micrograms / minute required for some arrhythmias.[9] Inspection of the graph "Procainamide Concentration vs Time" in section IX, "Pharmacokinetic Outcomes" reveals that only the 4000 mg daily dose achieved plasma concentrations in the "therapeutic" range. Doses below 2000 mg / day turned out not to beat placebo in suppressing VPD's; in fact statistically appear to increase VPDs.

It is clear therefore that many of the trial patients were given sub-therapeutic doses and hence give information of little value. Ten patients were given 4000 mg/day prior to crossover, nine post-crossover for a maximum of nineteen treated with a dose in the therapeutic window.

Although a low arguably sub-therapeutic dose range may minimize adverse drug effects, it also makes it more difficult to demonstrate dose related efficacy. The FDA advised the sponsor in a letter dated 14 August 1991 summarizing the 6 July meeting that they must "study all useful dosages."[10] This was not done.

V. CHEMISTRY

Procainamide Hydrochloride is formally named Benzamide,4-amino-N-{(2-diethylamino)ethyl}-,monohydrochloride or p-Amino-N-{2-(diethylamino)ethyl}benzamide monochloride.

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[9] Anderson, JL, Conventional and Sustained-Release Procainamide: Update on Pharmacology, Clinical Pharmacology 1985, 7:5.618-40.

[10] IND

The molecular formula of procainamide hydrochloride is $C_{13}H_{21}N_3O.HCl$. The molecular weight of the anhydrous monochloride is 271.79 and of the anhydrous free base 235.33. See the chemist's review for a detailed discussion of chemistry.

VI. CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

See the Biopharmacological review for detailed discussions of clinical pharmacokinetics. Here are a few considerations:

Absorption of oral procainamide appears to be a first order process taking place at all levels of the small intestine; the rate of absorption varies among individuals.

The most important clinical consequences of procainamide metabolism are (1) the formation of the active metabolite N-acetyl procainamide (NAPA), (2) the bimodal genetic distribution of fast and slow acetylators in the population, and (3) changes in metabolism with changes in body function and concurrent medication.

NAPA itself has significant anti-arrhythmic activity with a half-life of approximately seven hours in normal volunteers. It has been investigated for possible use as an antiarrhythmic because it seems less prone to cause the lupus syndrome than the parent drug. NAPA is cleared to a greater extent by the kidneys than the parent compound (85% vs. 50%) so it accumulates faster with decline in renal function.

About half the population of the United States - black and white - acetylate procainamide and other drugs - isoniazid, sulfamethazine, dapsone, sulfapyridine - quickly; the other 50% are slow acetylators.

With respect to this trial it was decided not to stratify by

acetylator type but to depend on random selection to randomize for that characteristic.

Metabolism and serum levels are also affected by glomerular filtration rate, and in congestive heart failure, liver disease, obesity and by concurrent therapy with such drugs as amiodarone, cimetidine, and trimethaprim.

Eleven studies were conducted in healthy volunteers to:

(1) assess the pharmacokinetics of procainamide tablets bid vs. qid tablets and the effect of food on absorption[11]

(2) assess the dose-proportionality of the bid tablets -- leading to the rejection of the 750 mg bid preparation and

(3) assess the bioequivalence of the bid formulations prepared for the clinical trial, "clinical study tablets," with those

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[11]610-35 12 volunteers; bioavailability of bid compared with Procan SR qid; effect of food on bioavailability of bid. single -dose, non-blind, 3-period crossover; bioavailability of 1000 mg bid tablets equivalent to 1000 mg Procan SR. Negligible effect of high-fat meal on bid absorption.

610-38 identical to above comparing bioavailability of 500 mg bid vs. Procan SR 500 mg.

610-39 18 volunteers; 1000 mg bid vs. Procan SR 500 mg. Bid showed similar absorption, and increased release time.

610-40 identical to above comparing 500 mg bid vs. Procan SR 500 mg.

prepared for eventual sale, "market image tablets."[12]

Brief comment on biopharmacokinetic findings of the clinical trial appear following discussion of its design.

VII. DESIGN OF THE CONTROLLED TRIAL (PROTOCOLS 610-43 AND 610-44)

SUMMARY: The protocols comprise a single multi-center trial evaluating VPD suppression, bioequivalence, and safety.

Fourteen centers in Florida, Illinois, Kansas, Michigan, Minnesota, Ohio, and Virginia participated. The first patient entered the two-week double-blind crossover on 6 December 1990 and the last patient finished 30 December 1992.

All the centers participated in the double-blind, placebo-controlled, dose-response, formulation crossover pitting the new bid preparation against the approved qid Procan SR and against placebo.

The primary objective was to demonstrate equivalent suppression of ventricular premature depolarizations with an equivalent side-effect profile. Secondary objective was to evaluate procainamide and NAPA pharmacokinetics as a function of dose and formulation and to characterize the relationship between plasma concentration and VPD suppression. Six of the fourteen

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[12]610-47 24 volunteers: 500 mg bid clinical trial formulation compared to 500 mg market-image bid; Bioequivalence.

610-49 24 volunteers; dose proportionality of market-image bid; comparison of absorption kinetics with Pronestyl; 750 mg bid releases drug faster than 500 mg, 1000 mg bid.

610-51 24 volunteers; demonstrating equivalent bioavailability of 1000-mg clinical study bid vs. 1000 mg market-image bid.

610-52 23 volunteers; dose-proportionality of market-image 500 mg, 750 mg, 1000 mg bid; drug release was faster and greater from 750 mg.

610-53 24 volunteers; 500 mg market image bid vs. clinical study 500 mg bid; extent of absorption similar but C max of market image slightly higher; absorption of clinical study tablets slower than expected due to altered manufacturing conditions.

610-54 24 volunteers; dose proportionality and bioequivalence of market-image 500 mg bid vs 1000 mg bid

centers participated in this bioequivalence study which is described in Protocol 610-43.

Protocol 610-44, identical to 610-43, but without bioequivalence studies, applied to the remaining eight centers. In other respects the two protocols make up a single study with pooled data.

Statistical analysis shows that there was no significant treatment x center interaction.

After completion of the two-week double-blind crossover, these same patients (including those treated with placebo) were invited to use the new preparation for one year to evaluate safety and adverse events - Protocol 610-43X (with respect to the six centers which had studied bioequivalence) and Protocol 610-44X (with respect to those which had not).

PROTOCOL:

The original protocol is dated 26 July 1990. It was amended three times: 2 October 1990, 10 May 1991, 14 October 1991.

The following description is that of the protocol as amended unless otherwise noted.

Since the patients for the "open-label" extension safety trial flowed out of the double-blinded crossover, they had already been screened for the same enrolment and exclusion criteria and thus all the specifications enumerated below applied in equal measure.

▸ **Enrollment criteria**:

To enter the first week, procainamide washout leading up to receiving active drug (or placebo), each patient had to be

(a) 21 years or older

(b) if female, post-menopausal or proven non-pregnant

(c) currently responding to and tolerating procainamide SR

therapy for the indication of frequent VPD[13] and

(d) total dose of procainamide SR 4000 mg or less.

▸ **Qualifying criteria:**

In order to enter the double-blind period the patients must:

(a) demonstrate at least 30 VPD per hour[14] on a 48 -hour Holter recording

(b) of these, at least 40 hours must be evaluable.

▸ **Exclusion criteria:**

So far as was possible all entrants were stable and not likely to become emergent. Specifically the following were grounds for exclusion:

1. documented history of life-threatening ventricular arrhythmias[15] or syncope of cardiac origin

2. history of acute myocardial infarction, coronary angioplasty or open heart surgery within the previous three months

3. NYHA Class III or IV heart failure

4. pacemaker dependence or internal defibrillator affecting evaluation of Holter records[16]

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[13]This was amended to allow inclusion of patients with previously untreated VPDs. They were briefly treated with procainamide to prove that their arrhythmia was responsive.

[14](revised to 20 VPD/hour.)

[15](hemodynamically unstable ventricular tachycardia or sustained ventricular tachycardia or fibrillation requiring cardioversion.)

[16] Later amendment admitted non-pacemaker-dependent patients.

5. Patients with known accessory bypass tracts

6. Patients with 2nd degree (Type II Mobitz) or 3rd degree AV block, QTc > 550 msec, or symptomatic bradycardia

7. Systolic blood pressure <90 mm Hg or uncontrolled hypertension defined by a systolic blood pressure >170 mm Hg or a diastolic blood pressure >110 mm Hg

8. Unstable angina

9. Significant hepatic disease (AST or ALT 2X upper limit of normal)

10. Significant renal disease (BUN 2X upper limit of normal or creatinine > 2 mg/dL)

11. any condition which could result in significantly altered absorption, distribution, accumulation, or excretion of procainamide

12. previous treatment with amiodarone

13. treatment with barbiturates within 4 weeks prior to entry into study

14. current or recent illicit drug use/alcohol abuse

15. current or recent treatment with any investigational drugs

▸ **Concurrent medication**

Patients continued their current medications with the exception of alternative antiarrythmics. The antihypertensives verapamil and sotalol which have antiarrhythmic action were excluded.

▸ **Treatment regimen**:

On study day 1 after history, examination, clinical

laboratory and EKG, eligible patients began a week unblinded "wash-out" off procainamide. From day 5 to 7 they were Holtered for 48 hours to establish VPD level.

Eventually ninety-nine patients randomized to eight groups began the active treatment stage, day 8.

There were eight groups as follows:

1. qid placebo crossed-over to bid placebo,
2. bid placebo crossed-over to qid placebo,
3. 1000 mg total daily dose of procainamide: qid preparation crossed-over to bid,
4. bid preparation crossed over to qid,
5. 2000 mg total daily dose of procainamide: qid preparation crossed-over to bid,
6. bid preparation crossed-over to qid
7. 4000 mg total daily dose of procainamide: qid preparation crossed-over to bid, and
8. bid preparation crossed over to qid.[17]

The medications were compounded and dispensed so that neither investigator nor patient could determine whether active or placebo was being given, whether the dosing was bid or qid or what dosage level was being dispensed.

All tablets were coated grey. A large placebo tablet (designated PL in the table below) mimicked the 1000 mg preparation, a small placebo tablet (designated PS) the lower doses.

The bid-qid blind was maintained by giving all patients bottles labelled "A" and "B" from which they were to draw medication consecutively.[18]

Thus regimens for the four crossover pairs were as follows:

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[17]NDA 20-545; 1.24:125,127.

[18]IND

Placebo crossover (1 and 2 above):

Large qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets from bottle B bid.

	Bottle A	Bottle B	vs. Bottle A	Bottle B.
6 am	PL	PL	PS	PL PL
12 noon	PL		PS	
6 pm	PL	PL	PS	PL PL
12 midnight	PL		PS	

1000 mg total daily dose crossover (3 and 4 above):

Large qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets from bottle B bid.

	Bottle A	Bottle B	vs. Bottle A	Bottle B
6 am	PL	500bid	250SR	PL PL
12 noon	PL		250SR	
6 pm	PL	500bid	250SR	PL PL
12 midnight	PL		250 SR	

2000 mg total daily dose pair (5 and 6 above):

Small qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets from bottle B bid.

	Bottle A	Bottle B	vs. Bottle A	Bottle B
6 am	PS	1000bid	500SR	PL PL
12 noon	PS		500SR	
6 pm	PS	1000bid	500SR	PL PL
12 midnight	PS		500SR	

4000 mg total daily dose crossover:

Large qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets bid from bottle B

	Bottle A	Bottle B	vs. Bottle A	Bottle B
6 am	1000SR	PL	PS	1000bid 1000bid
12 noon	1000SR		PS	
6 pm	1000SR	PL	PS	1000bid 1000bid
12 midnight	1000SR		PS	

It is only the 2000 mg total daily dose bid sequence which breaks total symmetry. Placebo, dose and interval are well blinded.

Holter monitoring was performed for the first 24 hours

beginning 30 minutes before the first procainamide dose and again for 48 hours from day 12 to 14 at the end of the first cycle.

At the end of this 48 hour Holter, the bid and the qid groups received their first dose of the alternative "crossed-over" preparations, day 14. No "washout" procainamide-free interval was provided and no Holter was performed during the initial phase of the second cycle.

On day 19, the sixth day of the second cycle, 48 hour Holter monitoring commenced. Medication ceased with the second dose on day 20, the seventh day of the second cycle, so this Holter overlapped the withdrawal from medication. A further 24 hour Holter was carried out from day 21 to day 22, off procainamide.

▸ **Demographics and Treatment Group Comparability**:

The protocol's patient population was not diverse. The requirement of ventricular ectopy makes it not surprising that the mean age was 67 years. Little gender or racial diversity was achieved: eighty-three percent were white men.

Recruiting in fact became more difficult in the course of the study as concerns about the safety of antiarrythmics increased. This necessitated the protocol amendments already mentioned.

APPEARS THIS WAY
ON ORIGINAL

Study 610-43/44: Characteristics of Patients Randomized to Treatment

Characteristics	Combined BID and QID Forms (mg/day)								Formulation Sequence			
	Placebo N = 25		1000 N = 26		2000 N = 28		4000 N = 22		BID→QID N = 50		QID→BID N = 49	
Gender, N (%)												
Women	3	(12)	4	(77)	6	(21)	4	(18)	10	(20)	7	(14)
Men	22	(88)	20	(83)	22	(79)	18	(82)	40	(80)	42	(86)
Race, N (%)												
White	21	(84)	20	(83)	26	(93)	20	(91)	44	(88)	43	(88)
Black	3	(12)	3	(13)	1	(4)	1	(5)	4	(8)	4	(8)
Other	1	(4)	1	(4)	1	(4)	1	(5)	2	(4)	2	(4)
Age, yr												
Median	67		68.5		66		68		67.5		67	
Min, Max	31, 93		51, 80		38, 83		56, 77		38, 80		31, 93	
Distribution by Age, N (%)												
<65 years	8	(32)	8	(33)	13	(46)	6	(27)	18	(36)	17	(35)
≥65 years	17	(68)	16	(67)	15	(54)	16	(73)	32	(64)	32	(65)
Number of VPDs/hr												
Median	127		180		199		156		183		165	
Min, Max	24, 1461		23, 1010		20, 2886		25, 1445		23, 2886		20, 1445	

VPD = Ventricular premature depolarization.

As shown in the table above[19], the various dosage groups seem to be well balanced with respect to gender, race, age, and VPD rate. It is true that very few women or blacks were included.

▸ How Much of a Difference in VPD Reduction Would Constitute a Disproof of Equivalence?

Statistical analysis begins with the null hypothesis that there is no difference between the evaluated populations. In this case the objective is to prove rather than disprove equivalence; that with respect to VPD suppression procainamide bid is equivalent to the approved formulation. To be convincing, the study must have enough power to detect a difference if it exists.

The final draft of the original protocol (26 July 1990) stated

> It is expected that the mean reduction in VPDs for the Procan SR/QID treated patients will be 50% over the three dose levels. The total number of patients required to detect a difference of 30% between the

[19]NDA 20-545;1.24.25.

> 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, two-tailed, is 100 evaluable, or 25 patients per each of the three active treatment groups and 25 patients in the placebo group. This calculated sample size is based on the assumption that the standard deviation of percent reduction in VPDs for within patient groups is 25%. [20]

▸How much VPD suppression to distinguish active treatment from placebo?

In order to validate an equivalence study, to demonstrate that acceptance of the null hypotheses is not due simply to wide variance, the active treatments must stand out against placebo. Once again the degree of difference it is desired to detect between the treated and untreated groups affects the power of the study, number of patients required, to detect it. Protocol amendment of 2 October 1990 reads

> It is expected that the mean percentage reduction in VPDs for the high dose of procainamide bid will be **70%**. The mean response of the placebo group is expected to be 10%. The total number of patients required to detect the difference between the high dose of procainamide BID and placebo with 95% power at the 0.05 level, two-tailed, is 88 evaluable or 22 patients per treatment group. This calculated sample size is based on the assumption that the standard deviation of percent reduction in VPDs for between patients is 25%. Twenty- two patients per group will also provide information about the similarity of the two formulations (relative difference between formulations within 30% by confidence interval analysis).[21]

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[20]NDA 20-545; 1.24:95.

[21]NDA 20-545;1.24:104.

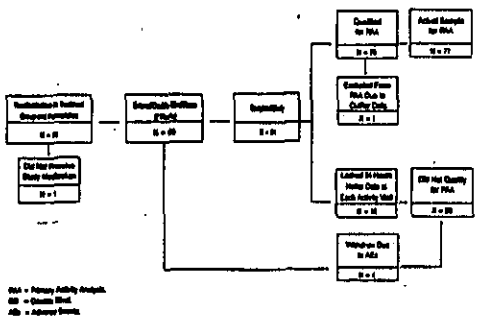
As previously mentioned, division medical officer Sughok K. Chun in her IND review of this amendment dated 3 June 1991 took exception. She felt that sponsor was underestimating placebo response and therefore underestimating patient numbers required to achieve statistical significance:

> Sponsor calculated the sample size with expectation that the mean percent reduction in VPDs at high dose of procainamide BID will be 70%. The mean response in the placebo group is expected to be 10%. However, the placebo response in VPD reduction is around 30% (20-40%) in various antiarrhythmic studies that calculated sample size and power considerations with respect to the primary objective. Hypothesis testing is probably incorrect.[22]

VIII. WHAT DATA ARE USABLE?

(1) How many patients qualify for evaluation?

The original parallel trial design envisaged 270 patients necessary to achieve adequate statistical power; the crossover design first envisaged 100 patients. This was, contrary to Division advice, revised down to eighty-eight. In the end the data from only 77 patients was judged evaluable. The scheme below illustrates the process.[23]



[22]IND N(PI)004/5/29/91.

[23]NDA 20-545;1.24:34.

(2) How good is the Holter data?

As may be seen above, 16 patients were excluded from analysis for failure to have 24 hour Holter data at baseline or at either double-blind visit. But sponsor had been advised in writing on 14 August 1991 of the need for 48 hours after the first dose and 48 hours after the last dose plus 48 additional hours to observe return of VPDs (total 72 hours), so what was provided was substantially short of what was deemed requisite by the Agency.[24]

It is uncertain from the protocol how rigid was the timing of the Holters in relation to the protocol dosing schedule. According to the protocol, "To allow flexibility in scheduling patient appointments ... the start of Holter ECG recordings ... may be scheduled 1 day earlier or later than the day shown in the flowchart."[25]

So there is some doubt about the quantity and timing precision of the Holter data.

(3) Is the Post-crossover Data Evaluable?

When sponsors presented their IND they substituted for the parallel trial earlier discussed a crossover design with no provision for washout; in other words, used the first of the two designs illustrated below.[26]

---

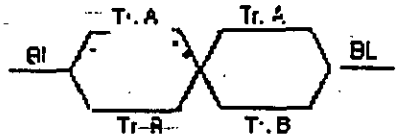
[24] IND 2.1, 14 August 1991.

[25] NDA 20-545;1.24:84.

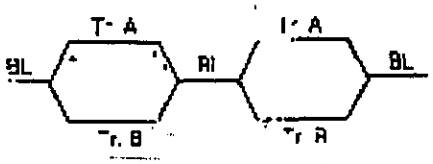
[26] Spilker, Bert, Guide to Clinical Trials, New York, 1991, p.33.

The possibility that data in the post-crossover phase may be contaminated by what has happened in the pre-crossover phase is a well-known weakness of the crossover design.

1. SINGLE CROSSOVER WITH NO INTERVENING BASELINE
(i.e., No Medicine -free Interval)



2. SINGLE CROSSOVER WITH INTERVENING BASELINE



There are two mechanisms for post-crossover contamination. The first is biopharmacological. Antiarrythmics in particular may continue a therapeutic effect for a time even as serum levels decline after cession of treatment. The second is statistical. "Period x treatment interaction" may indicate a carryover effect, confounding analysis despite biological implausibility.

What should be done at this point to evaluate this application for approval? One authority says, "the only acceptable option ... is to view the first part of the clinical trial as a parallel design and to compare the data of the two groups."

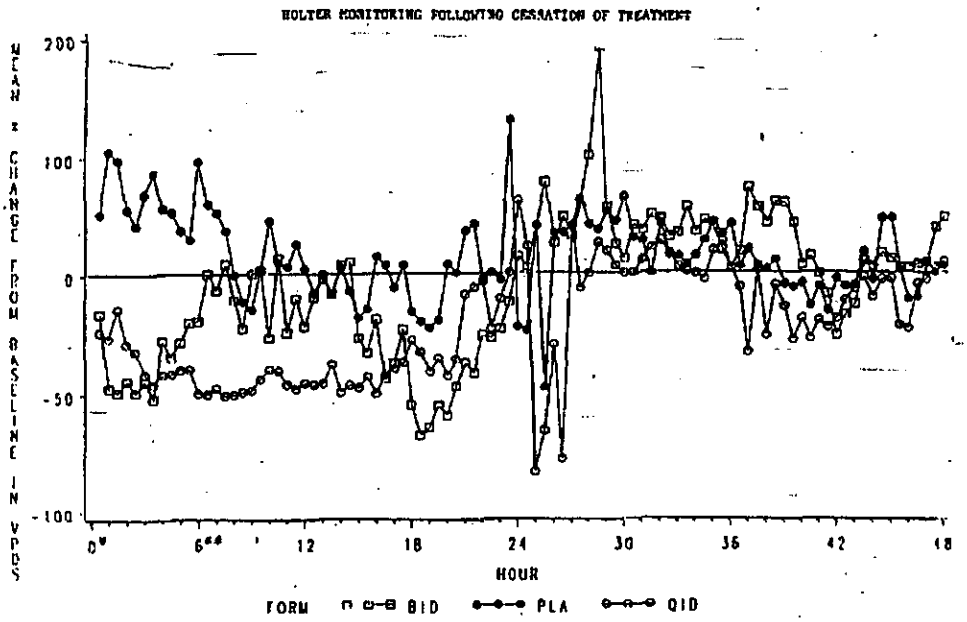
"This approach," he continues, "is invariably unsatisfactory because fewer patients were originally enrolled in each treatment group than would have been enrolled if the clinical trial were initially designed as a parallel trial." [27]

If the VPD suppression outcomes need to be recomputed using pre-crossover data the evaluable patients will be reduced to ten on 4000 mg, thirteen on 2000 mg, ten on 1000 mg, daily doses

[27] Spiker, Bert, Guide to Clinical Trails, New York, 1992, p. 32.

of procainamide bid. These may be compared to similar numbers receiving procainamide qid and seventeen receiving placebo. [28] Only ten patients received a therapeutic (4000 mg/day) dose pre-crossover.

A strong argument in favor of accepting the post-crossover data is that Holter recording performed after the second active treatment week, that is, on completion of the study, VPDs of patients on active treatment (squares and empty circles) reached the level of the placebo patients (solid circles) within 24 hours. [29]



* PATIENTS TOOK THE LAST BID DOSE
** PATIENTS TOOK THE LAST QID DOSE

Since the Holter data for the post-crossover period was taken at the end, it can be argued that in fact pre-crossover drug effect contamination may have been small. This argument does not address the "period x treatment" interaction" objection.

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[28]NDA 20-545;1.24.246.

[29]NDA 1.24:239.

VIII. VPD SUPPRESSION OUTCOMES

Computations on patients accepted by the sponsor for primary activity analysis were done as follows:

To be included in the primary analysis, a subject had to have at least 24 hours Holter at screening (48 hours, on day 5 to 7 per protocol), 24 hours at the end of the first period (48 hours on day 12 to 14 per protocol) and 24 hours at the end of the second period (48 hours on day 19 to 21 per protocol).

Note that the 24 hour post-second-period 24 hour "washout" Holter is not required. Note also that Holters may be one day early or one day late from protocol time.

Seventy-eight patients met the above criteria; one patient was removed as a statistical outlier -- because his VPD were extremely increased on both preparations -- leaving Holter data from 77 patients.

1. Percent Change in Baseline vs. Placebo

The main efficacy measure analyzed was percent change from baseline in mean VPD per hour. This was calculated for each monitoring period as follows:

$$\%\_change = 100 * (VPD-Baseline)/Baseline$$

where VPD = VPD/hr and Baseline = VPD/hr during baseline Holter.

Negative values represent decrease in VPD, the desired result of treatment.[30]

PERCENT CHANGE IN VPDs BY PREPARATION AND DOSE[31]

---

[30]NDA 20-545 1.24:36.

[31]prepared from data presented in NDA 20-545;1.24:241 and 246.

Placebo	No. of PATIENTS 18 (7 B TO Q, 11 Q to B)	BID 20.35 (-13.85, 54.54)	QID 0.58 (-33.61,34.77)
1000 mg/day	19 (10 B to Q, 9 Q to B)	-14.66 (-48.35,19.03)	-19.68 (-53.37,14.00)
2000 mg/day	21 (13 B to Q, 8 Q to B)	-40.52* (-74.87,-6.18)	-35.81 (-70.15,-1.46)
4000 mg/day	19 (10 B to Q, 9 Q to B	-59.39* (-86.65,-20.12)	-29.91 (-63.18,3.35)

*indicates that the mean is significantly different than the corresponding mean in the placebo group.

Inspection of the above table[32] reveals the goal of 70% VPD suppression at the 4000 mg daily dose of the bid preparation is not reached. Nonetheless the 95% confidence limits for the 2000 mg and 4000 mg doses are negative, suggesting statistically significant suppression as compared to placebo.

The lower confidence levels of placebo ranged between -13.85 and -33.61. The Division had noted that the placebo effect as seen in current studies was 20% - 40%.

Whether statistical review will support and find significant sponsor's interpretation of nearly 60% reduction remains to be seen.

The fact that the bid preparation at 1000 mg and the qid preparation at all doses fail to achieve statistical significance in VPD suppression is, I believe, due to failure of the protocol to provide an adequate therapeutic dose range. The VPD suppression efficacy of the approved preparation is not in question.

2. Comparison of VPD Suppression between Preparations

[32] NDA 20-545;1.24:247.

The difference between the qid and bid preparations with respect to VPD reduction was calculated by

D =(bid % change) - (qid % change).

Therefore positive D favors qid and negative D favors bid. This data is presented in the following table.[33]

FORMULATION DIFFERENCES AND ASSOCIATED CONFIDENCE INTERVALS FOR PERCENT CHANGE IN VPDa

INTENT-TO-TREAT ANALYSIS

Dose Group	Difference (BID-QID) 95% Confidence Int.
1000 mg/day	30.10 (- 3.81, 64.02)
2000 mg/day	9.33 (-21.42, 40.09)
4000 mg/day	-19.64 (-54.35, 15.06)
All Active Doses	- 6.60 (-12.55, 25.75)

In this case the objective is to prove lack of difference, that is, the closer the mean is to zero, the stronger the study hypothesis. The study design had asserted that equivalence with respect to VPD suppression would be established if the 95% confidence interval for the absolute difference between the bid and qid formulations fell within +30% and -30%. The recorded confidence interval (+25.55% to -12.55%) more than meets this preset standard. In fact the data seems to support greater equivalent dose efficacy of the bid preparation.

Once again, the weight of this computations awaits statistical review.

This information is presented graphically.[34]

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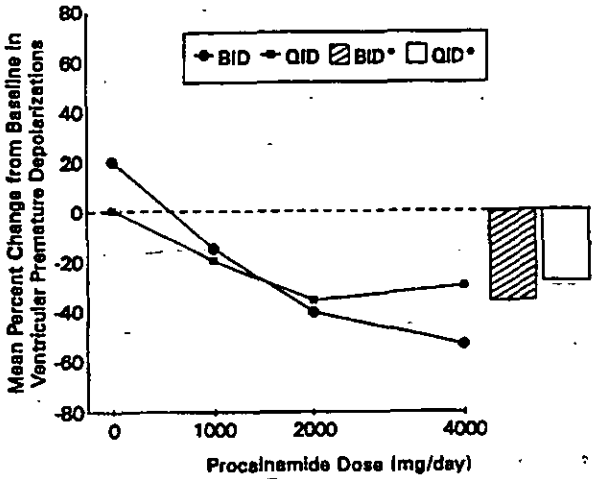
[33]compiled from tables contained in NDA 20-545;1.24:246 and 247.

[34]IND 2.1, 14 August 1991.



IX. PHARMACOKINETIC OUTCOMES

Pharmacokinetic (serum level) studies were conducted on only 43 of the 77 patients who were analyzed for VPD reduction. These were trial patients at six of the fourteen centers. These studies are specified in Protocol 610-43.

These studies

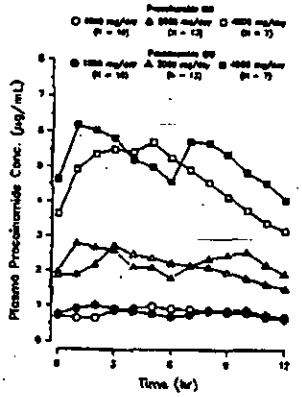
(1) evaluating procainamide and N-acetylprocainamide pharmacokinetics as a function of dose and formulation and

(2) characterizing by pharmacokinetic/pharmacodynamic methods f the relationship between plasma concentration and pharmacologic effect

contained in NDA 20-545, volumes 1.13 and 1.14 respectively are interestingly reviewed by Olof Borga, PhD., biopharmacologist.

A. Procainamide Concentration vs. Time by Preparation and Dose[35]

[35]NDA 20-545;1.1:100.



Mean Plasma Procainamide Concentration-Time Profiles at Steady State Following Administration of Procainamide BID Tablets q12h or Procainamide QID Tablets q6h at Each Dose Level. Data from Visits 5 and 7 were pooled to calculate mean values by formulation (Protocol 610-43)

Sponsor submits the data from which after elaborate statistical analysis the above graph is drawn in appendix D, volume 1.13. Their own conclusion is that "Minimum plasma concentrations following administration of procainamide BID tablets every 12 hours are slightly lower than those for administration of Procan SR tablets every 6 hours."[36]

The argument is made however that the overall pharmacokinetics are equivalent.

> Despite the fact that the study design and patient population were suboptimal for bioavailability comparisons across formulations, 90% confidence intervals for ratios of dose-normalized mean Cmax and mean AUC values were within or virtually within an 80% to 125% interval indicative of bioequivalence of the two treatments. When data from all dose groups were combined, procainamide BID tablets were bioequivalent to QID tablets with respect to maximal observed concentration and extent of absorption.

[36]NDA 20-545;1.13:17.

The difference between the qid and bid preparations with respect to VPD reduction was calculated by

D =(bid % change) - (qid % change).

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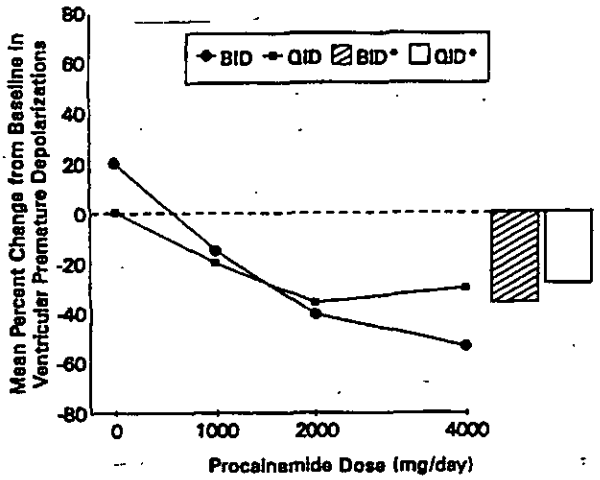

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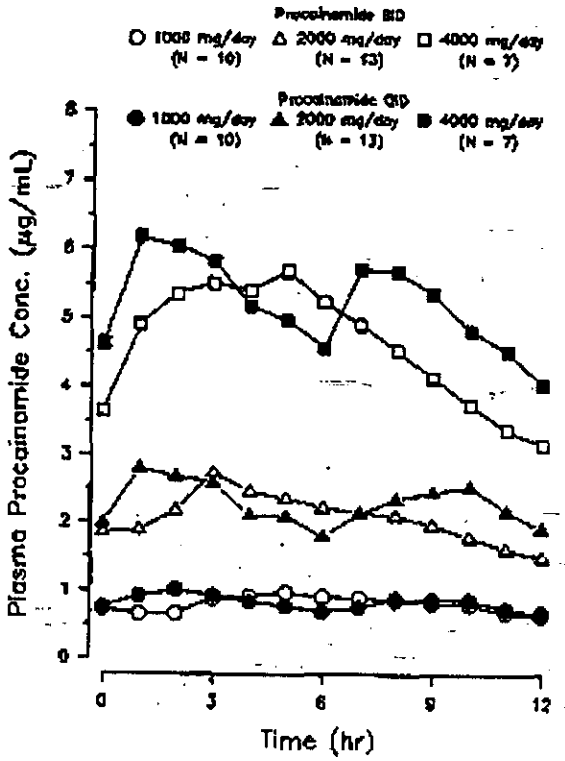

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According to FDA standards however, bioequivalence means that the outer 95% confidence limit (not the mean) of the tested drug be within 20% of the mean of the standard.

B. Relationship Between VPD Rate and Plasma Concentration of Procainamide and NAPA[38]

The sponsor submits the following graphic depictions of the serum concentrations of procainamide and NAPA vs. VPD rate in

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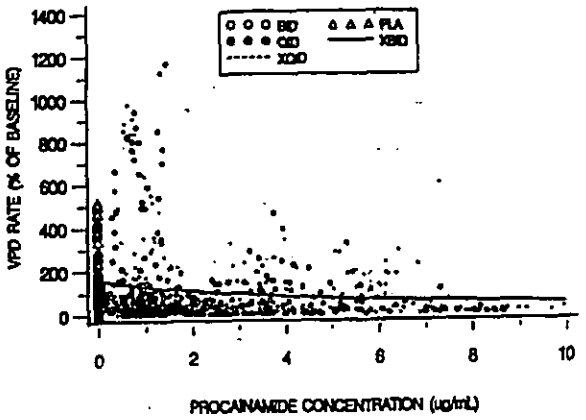
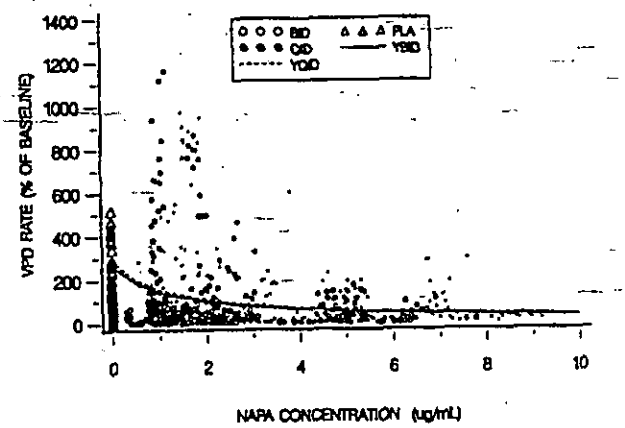
[37]NDA 20-545;1.1:99.

[38]NDA 20-545;1.1:130.

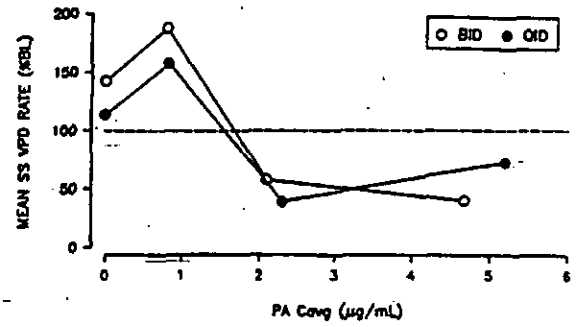


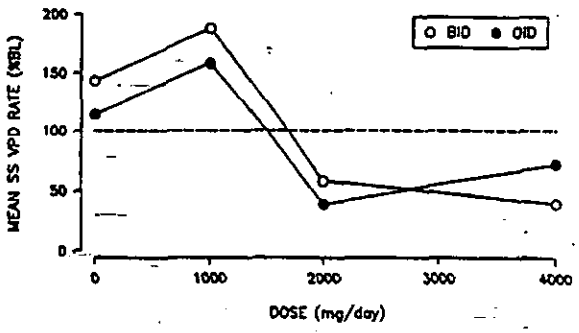


an effort to demonstrate dose-response.

Efforts to model this data to achieve a concentration-response relationship have been unsuccessful. One serious difficulty in constructing a consistent statistical model is that the mean VPD rate graphed vs dose actually shows the VPD rate increased above placebo at the 1000 mg dose in the 43-patient

sample who were assayed pharmacologically.[39] This is not true in the overall analysis of 77 patients which showed 19.68% (-53.57, 14.00) reduction at the 1000 mg dose. The only tentative finding is a decrease in clinical effect with increasing age.





Steady-state VPD Rate vs. Mean Procainamide Concentration and Dose

Dr. Borga therefore feels that because the plasma concentration-time profiles of the two preparation are "far from identical" the sponsors' claim of equivalence with respect to VPD suppression[40] is not accurate. He believes that the failure to establish concentration-effect relationship is due to "(1) a large intra- and inter-subject variability of the effect at a particular concentration and (2) a weak response to the drug." The anomalous finding of VPD increase at the 1000 mg dose appears to be due to an unfortunate population sample and a subtherapeutic dose.

X. REVIEW OF CLINICAL OUTCOMES

[39] prepared by Dr. Borga from sponsor's data.

[40] NDA 20-545; 1.1: 131.

The new preparation came short of its stated goal for demonstrating suppression of VPDs although at least accepting post-crossover patients, it is significantly more active than placebo.

In the clinical trial a new drug (procainamide bid) was pitted against active control (procainamide qid) and placebo.

The questions to which the trial should have provided affirmative answers leading to an affirmative answer to the application are:

(1) Is the active control (Procan SR) better than placebo in this trial?
(2) Is procainamide bid better than placebo?
(3) Is the study powerful enough to tell a difference if one exists?

The approved drug is ipso facto better than placebo but may not have been so demonstrated under the conditions of this trial. The dose range was far lower than that used for previous trials leading to approval. The anomalous increase of VPD's in a subset at the 1000 mg dose is partially explained by being subtherapeutic..

The answer to the second question is that data as analyzed does show bid superiority to placebo. But if data is discarded, will it still be possible to make the same demonstration?

The third question - does the study have enough power to show a difference? - awaits further analysis.

XI. SAFETY OUTCOMES

The sponsor provides (1) elaborate documentation of laboratory parameters and complaints during the two-week crossover period and more significantly, reports (2) one-year follow up of a subset of these same patients maintained on the study medication.

In response to Division's request, sponsor also prepared (3) an epidemiologic survey of procainamide-related bone marrow suppression.

1. The Two Week Crossover Period

In evaluating the safety data from the crossover study period one should keep in mind the particulars of the study:

(a) patients were already proven tolerant to procainamide

(b) patients were selected for stability and absence of risks

(c) the short time involved.

Assuming therefore that this new preparation of a drug widely used for forty years was not grossly toxic, drug-related significant untoward events were not very probable.

64 patients reported a total of 154 adverse events.[41]

The most frequent complaints were asthenia, dizziness, chest pain, palpitation, and dyspnea. Chest pain occurred more frequently in the procainamide group than placebo, arrhythmia and palpitations evenly distributed across dosage groups and formulations. There were no malignant arrhythmias.

Not mentioned above are two patients with proarrythmias -- one patient increased his VPD rate 4 times on Procan SR and 10 times on Procanbid; another increased his VPD 4-fold on Procan SR.

Three patients on active drug were beset by serious adverse events during the two week trial.[42]

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[41] NDA 20-545; 1.24:46.

[42] NDA 20-545;1.24:5; 53.

1. A 72 year old man with CHF, angina, ventricular ectopy, suffered a non-Q-wave myocardial infarction after two days of qid procainamide 2000 mg qd. He continued procainamide and made a good recovery and completed the study.

2. A 74 year old man receiving bid procainamide 4000 mg total daily dose was hospitalized for two days after 6 days of treatment for recurrent chest pain. He was withdrawn from the study after 13 days of treatment. His angina continued after withdrawal of procainamide which he had tolerated for several years.

3. A 68 year old man with CHF secondary to cardiomyopathy was hospitalized due to worsening of his condition after less than a day on procainamide bid 2000 mg/day. He was diuresed, released, and completed the study.

The sponsor's judgement that none of these events were related to study medication seems justified.

▸ **Summary**

There was no serious or unexpected toxicity related to procainamide bid in the two-week blinded study.

2. The One Year Open-Label Continuation Safety Trial (Protocols 610-43x, 610-44x)

Patients completing the double blind crossover trial were given the option to continue on the new preparation for one year to assess safety and side effects.

Sixty-eight patients entered this phase; twenty withdrew from the study, nine for adverse events, eleven for other reasons. One patient died, leaving 47 patients who completed the year's therapy.

Since this study was a continuation of the blinded trial, it had the same inclusion and exclusion criteria, and roughly the same demographic profile: most of the patients were white men over 65.

Twenty-five percent of the participants had been treated with placebo during the trial; hence all participants received 24 hour Holter monitoring two weeks into the study.

Monitoring was focussed on development of (1) hematological and immunological abnormalities, especially antinuclear antibody titer (2) proarrythmias and (3) adverse symptoms.

Baseline laboratory values were taken to be those at the beginning of the double-blind clinical trial.

Although one patient received procainamide bid 1500 mg daily, the remainder received 1000 mg daily (864 patient days), 2000 mg daily (11,625 patient-days), 3000 mg daily (5900 patient days) or 4000 mg daily (3073 patient-days).[43]

Thirteen (20%) had possibly clinically important deviations from baseline in hemoglobin, hematocrit, platelets and eosinophils. All but one occurred during 2000 and 3000 mg bid therapy and most during the first six months of open-label therapy. One of these withdrew from the study due to gastrointestinal hemorrhage thought probably drug related.

One patient died, a 68 year old man with congestive heart failure, frequent VPD, and hypertension after hospital admission following excessive salt intake and non-compliance with his medicines. The exacerbation of CHF and subsequent death was judged not due to study medication.

Three (5%) had clinically important antinuclear antibody (ANA) rise. Clinically important was defined as (a) 4-fold increase in titer relative to base value if screening titer was <1:40 and (2) a 2-fold change if screening = or >1:40. Thus eight patients who converted to ANA positivity <1:20 during the study were not included.

- **Summary:**

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[43]NDA 20-545;1.28:16.

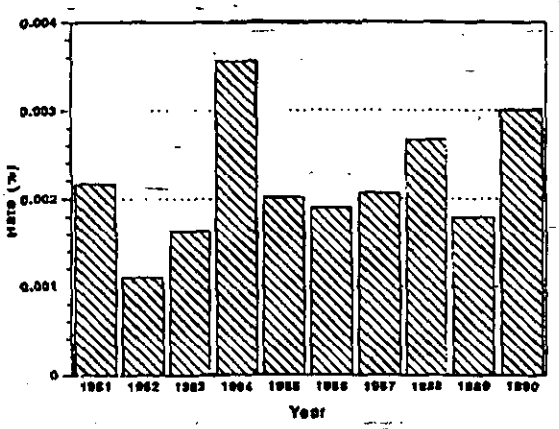
The safety experience of procainamide bid over the one year open-label trial presented no surprises.

3. Procainamide-associated Blood Dyscrasias

At Division request the sponsor performed an epidemiological study from 1981 to 1990 of procainamide-associated blood dyscrasias indicative of bone marrow suppression --agranulocytosis, granulocytosis, neutropenia, pancytopenia, aplastic anemia.

The three hundred cases identified represent approximately 0.0022% of new prescriptions written; the annual rates ranged from 0.0011% to 0.0036%[44].

The higher rate in 1984 was associated with a study population largely post-thoracotomy and hence with an incidence of bypass and transfusion complications such as thrombocytopenia, and CMV infection. It is further suggested that many cases may be caused by concomitant medications: 71% were receiving such, and of these 81% known to cause bone marrow suppression[45].



Annual Rate of Reported Cases of Procan SR-Associated Blood Dyscrasias

It was assumed that the reporting rate was greatly less than the incidence; assuming one in one hundred reported, sponsor suggests that a fairer incidence might be 0.22% of prescriptions written.

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[44]NDA 20-545;1.23.10.

[45]NDA 20-545;1.23.12.

▸ **Summary:**

This may have not been a very useful study because of an uncertain population in the denominator; prescriptions written differ from new prescriptions differ from patients or patient years. Nonetheless results suggest that procainamide administration rarely causes bone marrow suppression.

XI. Conclusions

Twenty-five years ago a plausible new preparation for an established drug would have, like sponsor's qid preparation, have been approved on the basis of serum assays.

A changed regulatory climate and new knowledge about antiarrythmics led the Division from 1987 on to request clinical trial data to support claims of satisfactory procainamide activity and side effect profile.

The sponsor and the Division reached agreement on an appropriate parallel trial design.

There should have been a straight-forward run to completion and approval.

The sponsor's change to a crossover design weakens the data. Because of the possible residual effect following crossover, fully half of rhythm data is suspect.

Even the patient numbers that sponsor brings forward for primary analysis may not give the study sufficient power.

Furthermore the study was crippled in its effort to show efficacy because much of its dosing range was sub-therapeutic.

The overall shape of the data suggests the sponsor's contention that what their bid preparation performs with the efficacy and side-effect profile inherent to the drug.

XII. —RECOMMENDATIONS

From a clinical point of view, if one accepts that oral procainamide still has a useful place in medical practice (by definition "life-threatening" arrhythmias cry out for treatment), then the increased ease of compliance with a bid preparation make its approval in the public interest. The clinical trial establishes efficacy (although much less well than a parallel design with adequate dosing could have done); both clinical and pharmacological investigations establish safety. I therefore recommend approval.

/S/ 6 July 1995

Gerald E. Bunker, MD, PhD Date
Medical Officer

cc: HFD-110 division file, CSO (HFD-110), R. Fenichel (HFD-110) , G.Bunker (HFD-110), O. Borga (Room 5036).

APR 12 1995

Medical Review of NDA

NDA #: 20-545

DRUG: EXTENDED RELEASE PROCAINAMIDE HCl (PROCANBID)

SPONSOR: PARKE-DAVIS

PROPOSED INDICATION: TWICE-DAILY USE IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS

RELATED NDAS: ANDA 86-065, 87-510, 88-489

RELATED INDS: [ ]

PHARMACOLOGIC TYPE: CLASS 1A ANTIARRHYTHMIC AGENT

DOSAGE: 500 and 1000 mg

DATE OF NDA SUBMISSION: 21 December 94

Reviewer: Gerald E. Bunker MD, PhD
Review last revised: 10 April 1995

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1. Two Week Crossover Period

2. One Year Open-label Extension: Protocols 610-43x and 610-44x

3. Epidemiological Study of Bone Marrow Toxicity

XI. CONCLUSIONS

XII. RECOMMENDATIONS

III. HISTORY AND BACKGROUND OF THE APPLICATION

1. History

This New Drug Application deals with a new preparation of a drug historically established in cardiology for forty-five years.

Procainamide hydrochloride, a quinidine-like class IA antiarrhythmic, was derived from the local anaesthetic procaine by replacement of an amide for an ester linkage.

Mautz observed in 1939 that procaine elevated the stimulation threshold of ventricular muscle in the frog. Procaine administered iv to anesthetized human subjects suppresses ventricular arrhythmias but without general anaesthesia causes unacceptable CNS stimulation.

Procaine's rapid hydrolysis suggested that its antiarrhythmic action might be directed through one of its metabolites. Derivatives were screened by measuring their ability to protect against ventricular tachycardia produced by epinephrine in anesthetized dogs.

Diethylaminoethanol was shown to have antiarrhythmic activity less than the parent compound but with much reduced toxicity, unlike the other derivatives studied.

Therefore the search was on to develop a stable related compound that would have an enhanced antiarrhythmic effect without toxicity.

W.A. Lott, an E.R. Squibb and Sons staff chemist, suggested and synthesized procainamide which in 1950 came into use as an antiarrhythmic alternative to its classmate quinidine.[1]

Procainamide's place for chronic treatment -- suppression or prophylaxis of ventricular and atrial arrhythmias -- was limited by (1) the fact that a small but inevitable number of patients develop a lupus erythematosus syndrome and (2) the short half-life of the immediate release oral preparation (2.5 - 5 hours) requiring

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[1]Mark, LC et al, The Physiological Disposition and Cardiac Effects of Procaine Amide, J Pharmacol Exp Ther 1951;102:5.

nominal q 3 h dosing --making compliance difficult for the elderly patients who are the usual candidates for antiarrythmics.

Thus to-expand oral procainamide's outpatient use pari passu with improvements in pharmaceutical engineering (and doubtless with the expiration of Squibb's patent) several manufacturers developed nominal qid extended release preparations, including Procan SR by current sponsor approved on the basis of bioequivalency studies by the Division of Generic Drugs in 1980.

Qid is more convenient than q 3 h but still irksome. The next step was to develop and test a bid preparation. But by this time (1987) the climate of drug approval, understanding of pharmacodynamics, and ideas about the risk-benefit ratio of anti-arrythmics had changed.

Despite the development of serum procainamide assays, effective dose has to be sought clinically. Because of the lack of direct correlation between serum levels and clinical effect, also because of genetic and physiologic differences in metabolism, dose and interval need to be tailored to the individual. There is some irony to the commercial drive to develop established interval preparations for a drug that should not be given at a fixed interval; the name Procanbid has been **approved** for what should in theory be only approximately a bid preparation.

2. Background of the Application

In the wake of FDA rejection of several petitions requesting approval of sustained release procainamide on the basis of bioavailability studies, PARKE-Davis requested a meeting with the Cardiorenal Division to clarify what would be required for approval of their proposed bid procainamide.

During the first meeting, 3 December 1987, Division recommended a single clinical trial of parallel titrated design comparing the proposed new formulation with an approved procainamide formulation and placebo across a wide dose range.

FDA Office of Drug Evaluation Director Robert Temple himself outlined in 1982 the problems which arise with a two-arm active medicine trial in the absence of placebo.

1. It is more difficult to prove statistically that two results are the same than that they are different. If both treatments yield the same effect, there is no test to establish that a statistically significant similarity exists...

2. Since the investigator does not wish to observe a difference between treatments, there is no incentive to conduct the trial well. In fact the more poorly it is conducted, the more likely that the data will be the same with both medicines...

3. There is no accepted statistical means of demonstrating either medicine worked if there is no statistically significant difference between them in results obtained. If both medicines are approximately equal in the effect they elicit, it does not prove that either medicine is truly efficacious.[2]

Furthermore, in the case of procainamide there is so little understanding of the relationship between dose, serum levels, and effect that it is impossible to specify what serum levels of two preparations would be close enough to be deemed "bioequivalent."

For these reasons - statistical principles relating to the comparison of two drugs and specific properties of procainamide - FDA officials advised the sponsors that the bid preparation should demonstrate ectopic suppression demonstrated by Holter monitor throughout the proposed dosing interval comparable to that achieved by an existing preparation (by preference the original immediate release preparation) and better than placebo.

An increase in adverse effects in the bid as opposed to the qid preparation would not be accepted as the price for the increased length of action.

A year and a half later the sponsors requested a further meeting to discuss a clinical study along the lines discussed previously. The sponsor submitted the following schematic

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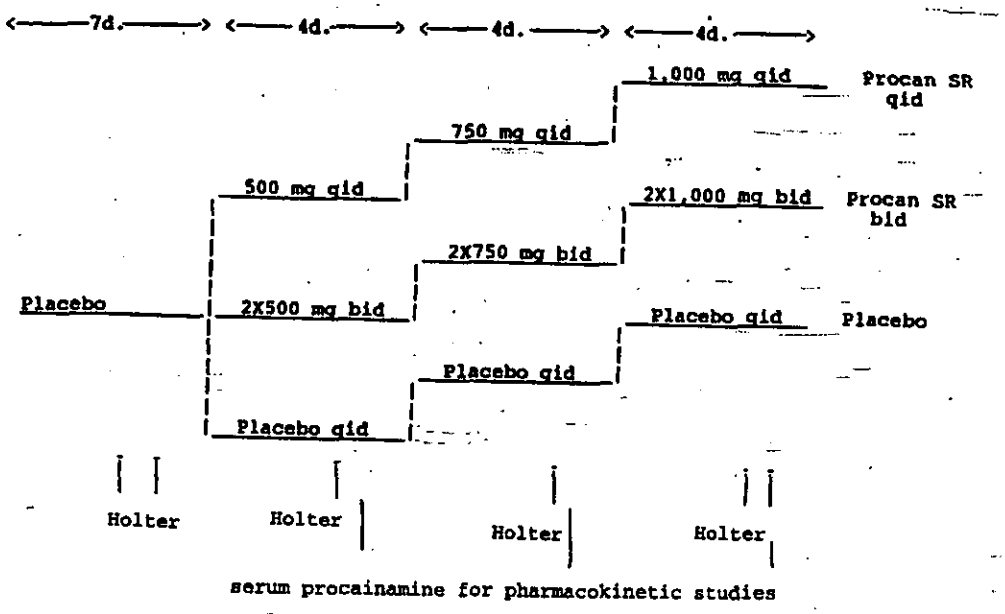
[2] Spilker, Bert, **Guide to Clinical Trials**, New York, 1991; p.721.

illustrating their plan at this point (15 June 1989.)[3]



This trial envisioned enrolling sixty patients in each treatment arm and thirty-two in the placebo arm. It was judged adequate to demonstrate efficacy vs. placebo with 95% power at the 0.05 level.

The Division promised scrutiny of monitoring hour by hour

[3]NDA 20-545, 1.1, attachment 3.

to establish suppression over entire dosing interval. Neither decreased efficacy at the end of the dosing period nor increase side effects at the beginning would be accepted as the price for bid dosing.

Sponsors asked whether enrolled patients must suffer from symptomatic ventricular ectopy (according to the contemporaneous labeling change) or could they also accept patients with asymptomatic ventricular arrhythmias. Division's advice was "not to hold out for symptoms."[4]

On 6 July 1990 the sponsor met again with the Cardiorenal Division. Sponsor now understood Division's approval of inclusion of asymptomatic patients but misunderstood Division's requests with respect to Holter monitoring -- 48 hours after the first dose and 72 hours commencing the last day of dosing.

Not long after (24 Oct 1990) sponsor filed IND[ ]and proceeded straightaway with the clinical trial (protocols 610-43 and 44) since Division deputy director waived the 30-day waiting period as requested.

However the protocols were of a design quite unlike that discussed with the Division during the previous years. Instead of a parallel design - three (bid, qid, placebo) arms x 60 patients each subjected to increasing doses of the same preparation - it was a crossover design. The arms were now defined by dose: placebo, 1000 mg, 2000 mg, 4000 mg per day. The comparison between preparations was now to be by crossover with no washout period. The patients taking qid would switch to bid and vice versa. The new design is schematized thus:[5]

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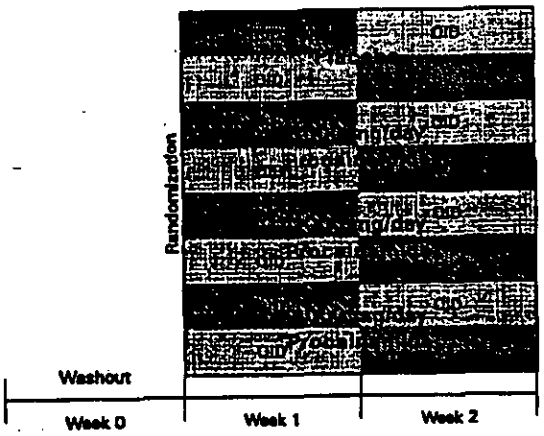
[4]NDA 20-545, 1.1, attachment 3.

[5] NDA 20-545;1.24:16.



Because of the possibility of carryover antiarrhythmic effect it is only in the pre-crossover period that the treatment arms are completely comparable. This design weakness (to be more fully discussed later) brings into question the adequacy of the trial.

The Division's safety meeting held 30 Nov 1990 did not discuss the design change -- which did not affect safety -- but did decide "the proposed study protocol is acceptable and the study may proceed."

Division Medical Officer Sughok K. Chun expressed concern at this point that a longer acting procainamide might lead to increased hematologic sequelae especially relating to leukocyte formation. To follow through on this concern the sponsor was requested to prepare an epidemiological analysis to evaluate previous frequency of such events.

At a later date (3 June 1991) Division questioned the statistical power of the protocol to sufficiently demonstrate VPD suppression. In response to protocol amendment #1 received 29 May 1991 Dr. Chun expressed by phone her view that "calculated sample size and power considerations with respect to primary objective and hypothesis probably is incorrect."[6] Details of amendment and criticism will be discussed below.

IV. NON-CONCERNS AND CONCERNS ABOUT APPROVING PROCAINAMIDE BID NOW

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[6] IND 2.1: Medical Officer's Review, 29 June 1991.

1. Non-concerns as Stated by the Division

A. Toxicology and Human Safety

Procainamide has been used clinically in humans for more than 40 years. For this reason this application does not require animal or human toxicology studies.

B. Testing on Asymptomatic Subjects

Suppression of nonsymptomatic ventricular premature depolarizations (VPD) in patients proven responsive to and tolerant of procainamide is taken as a surrogate marker for efficacy in a population with life-threatening arrhythmias, that is, in the population for which the drug is currently approved.

C. The Future Clinical Place of Procainamide and Other Antiarrythmics

Recent epidemiology (**CAST**, etc.) deprecates the value of arrhythmia suppression in the absence of severe symptoms. The sponsor clearly recognizes this in conservative labeling indicating proposed use only in life-threatening arrhythmias.[7]

Thus, although bid procainamide would be far less used in the current environment than if it had appeared forty years ago, there is no intent to question that the parent drug has a place in the pharmacopeia.

2. Concerns

A. The Trial Design

There are three objectives that should be met in order to demonstrate equivalence in suppressing VPD's over the entire dosing range:

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[7]"PROCANBID tablets are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia that in the judgement of the physician, are life-threatening. Because of the proarrythmic effects of procainamide, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular depolarizations should be avoided."

(1) the active control (procainamide qid) should distinguish itself from placebo (If not, equivalence is unconvincing).

(2) procainamide bid also should be better than placebo and

(3) the study should be of sufficient power to show a difference between the approved and the new preparations if a difference exists.

The real question is whether the crossover design has adequate power to permit these demonstrations.

B. The Dose Range

But logically prior to consideration of adequacy of design the adequacy of the dosing range must be considered. The protocol used doses of 1000/2000/4000 mg daily. As stated above, dosing needs to be empiric; serum levels are not reliable guidelines of efficacy. Nonetheless the sponsor recommends (in the Procan SR PDR monograph) an initial total daily oral dose for younger patients with normal renal function 50 mg / kg; i.e. 3500 mg/day. A study contemporaneous with the approval of Procan SR began with doses of 3500 mg and increased to 7500 mg as required.[8] Mean maximal and minimal concentrations of procainamide and NAPA were 10.4/12.0 and 6.8/8.7 micrograms/ml respectively.

"Therapeutic" plasma range of procainamide traditionally has been regarded as 4 to 10 micrograms / minute with 10-15 micrograms / minute required for some arrhythmias.[9] Inspection of the graph "Procainamide Concentration vs Time" in section IX, "Pharmacokinetic Outcomes" reveals that only the 4000 mg daily dose achieved plasma concentrations in the "therapeutic" range. Doses below 2000 mg / day turned out not to beat placebo in suppressing VPD's; in fact statistically appear to increase VPDs.

Although a low arguably sub-therapeutic dose range may minimize adverse drug effects, it also makes it more difficult to

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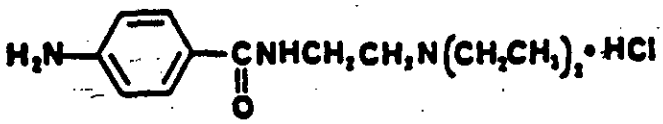
[8] EGV Giardina et al, Efficacy, Plasma Concentrations and Adverse Effects of a New Sustained Release Procainamide Preparation, AJ Card, November 1980; 46.855-862.

[9] Anderson, JL, Conventional and Sustained-Release Procainamide: Update on Pharmacology, Clinical Pharmacology 1985, 7:5.618-40.

demonstrate dose-related efficacy. The FDA advised the sponsor in a letter dated 14 August 1991 summarizing the 6 July meeting that they must "study all useful dosages."[10] This was not done.

V. CHEMISTRY

Procainamide Hydrochloride is formally named Benzamide,4-amino-N-[(2-diethylamino)ethyl]-,monohydrochloride or p-Amino-N-[2-(diethylamino)ethyl]benzamide monochloride.



The molecular formula of procainamide hydrochloride is $C_{13}H_{21}N_3O.HCl$. The molecular weight of the anhydrous monochloride is 271.79 and of the anhydrous free base 235.33. See the chemist's review for a detailed discussion of chemistry.

VI. CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

See the Biopharmacological review for detailed discussions of clinical pharmacokinetics. Here are a few considerations:

Absorption of oral procainamide appears to be a first order process taking place at all levels of the small intestine; the rate of absorption varies among individuals.

The most important clinical consequences of procainamide metabolism are (1) the formation of the active metabolite N-acetyl procainamide (NAPA), (2) the bimodal genetic distribution of fast and slow acetylators in the population, and (3) changes in metabolism with changes in body function and concurrent medication.

NAPA itself has significant anti-arrhythmic activity with a half-life of approximately seven hours in normal volunteers. It has been investigated for possible use as an antiarrhythmic because it

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[10]IND

seems less prone to cause the lupus syndrome than the parent drug. NAPA is cleared to a greater extent by the kidneys than the parent compound (85% vs. 50%) so it accumulates faster with decline in renal function.

About half the population of the United States - black and white - acetylate procainamide and other drugs - isoniazid, sulfamethazine, dapsone, sulfapyridine - quickly; the other 50% are slow acetylators.

With respect to this trial it was decided not to stratify by acetylator type but to depend on random selection to randomize for that characteristic.

Metabolism and serum levels are also affected by glomerular filtration rate, and in congestive heart failure, liver disease, obesity and by concurrent therapy with such drugs as amiodarone, cimetidine, and trimethaprim.

Eleven studies were conducted in healthy volunteers to:

(1) assess the pharmacokinetics of procainamide tablets bid vs. qid tablets and the effect of food on absorption[11]

(2) assess the dose-proportionality of the bid tablets -- leading to the rejection of the 750 mg bid preparation and

(3) assess the bioequivalence of the bid formulations prepared for the clinical trial, "clinical study tablets," with those

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[11]610-35 12 volunteers; bioavailability of bid compared with Procan SR qid; effect of food on bioavailability of bid. single -dose, non-blind, 3-period crossover; bioavailability of 1000 mg bid tablets equivalent to 1000 mg Procan SR. Negligible effect of high-fat meal on bid absorption.

610-38 identical to above comparing bioavailability of 500 mg bid vs. Procan SR 500 mg.

610-39 18 volunteers; 1000 mg bid vs. Procan SR 500 mg. Bid showed similar absorption, and increased release time.

610-40 identical to above comparing 500 mg bid vs. Procan SR 500 mg.

prepared for eventual sale, "market image tablets."[12]

Brief comment on biopharmacokinetic findings of the clinical trial appear following discussion of its design.

VII. DESIGN OF THE CONTROLLED TRIAL (PROTOCOLS 610-43 AND 610-44)

SUMMARY: The protocols comprise a single multi-center trial evaluating VPD suppression, bioequivalence, and safety.

Fourteen centers in Florida, Illinois, Kansas, Michigan, Minnesota, Ohio, and Virginia participated. The first patient entered the two-week double-blind crossover on 6 December 1990 and the last patient finished 30 December 1992.

All the centers participated in the double-blind, placebo-controlled, dose-response, formulation crossover pitting the new bid preparation against the approved qid Procan SR and against placebo.

The primary objective was to demonstrate equivalent suppression of ventricular premature depolarizations with an equivalent side-effect profile. Secondary objective was to evaluate procainamide and NAPA pharmacokinetics as a function of dose and formulation and to characterize the relationship between plasma concentration and VPD suppression. Six of the fourteen

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[12]610-47 24 volunteers: 500 mg bid clinical trial formulation compared to 500 mg market-image bid; Bioequivalence.

610-49 24 volunteers; dose proportionality of market-image bid; comparison of absorption kinetics with Pronestyl; 750 mg bid releases drug faster than 500 mg, 1000 mg bid.

610-51 24 volunteers; demonstrating equivalent bioavailability of 1000 mg clinical study bid vs. 1000 mg market-image bid.

610-52 23 volunteers; dose-proportionality of market-image 500 mg, 750 mg, 1000 mg bid; drug release was faster and greater from 750 mg.

610-53 24 volunteers; 500 mg market image bid vs. clinical study 500 mg bid; extent of absorption similar but C max of market image slightly higher; absorption of clinical study tablets slower than expected due to altered manufacturing conditions.

610-54 24 volunteers; dose proportionality and bioequivalence of market-image 500 mg bid vs 1000 mg bid

described in Protocol 610-43.

Protocol 610-44, identical to 610-43, but without bioequivalence studies, applied to the remaining eight centers. In other respects the two protocols make up a single study with pooled data.

Statistical analysis shows that there was no significant treatment x center interaction.

After completion of the two-week double-blind crossover, these same patients (including those treated with placebo) were invited to use the new preparation for one year to evaluate safety and adverse events - Protocol 610X (with respect to the six centers which had studied bioequivalence) and Protocol 610-44X (with respect to those which had not).

PROTOCOL:

The original protocol is dated 26 July 1990. It was amended three times: 2 October 1990, 10 May 1991, 14 October 1991.

The following description is that of the protocol as amended unless otherwise noted.

Since the patients for the "open-label" extension safety trial flowed out of the double-blinded crossover, they had already been screened for the same enrolment and exclusion criteria and thus all the specifications enumerated below applied in equal measure.

▸ **Enrollment criteria:**

To enter the first week, procainamide washout leading up to receiving active drug (or placebo), each patient had to be

(a) 21 years or older

(b) if female, post-menopausal or proven non-pregnant

(c) currently responding to and tolerating procainamide SR

therapy for the indication of frequent VPD[13] and

(d) total dose of procainamide SR 4000 mg or less.

▸ **Qualifying criteria:**

In order to enter the double-blind period the patients must:

(a) demonstrate at least 30 VPD per hour[14] on a 48 -hour Holter recording

(b) of these, at least 40 hours must be evaluable.

▸ **Exclusion criteria:**

So far as was possible all entrants were stable and not likely to become emergent. Specifically the following were grounds for exclusion:

1. documented history of life-threatening ventricular arrhythmias[15] or syncope of cardiac origin

2. history of acute myocardial infarction, coronary angioplasty or open heart surgery within the previous three months

3. NYHA Class III or IV heart failure

4. pacemaker dependence or internal defibrillator affecting evaluation of Holter records[16]

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[13]This was amended to allow inclusion of patients with previously untreated VPDs: They were briefly treated with procainamide to prove that their arrhythmia was responsive.

[14](revised to 20 VPD/hour.)

[15](hemodynamically unstable ventricular tachycardia or sustained ventricular tachycardia or fibrillation requiring cardioversion.)

[16] Later amendment admitted non-pacemaker-dependent patients.

5. Patients with known accessory bypass tracts

6. Patients with 2nd degree (Type II Mobitz) or 3rd degree AV block, QTc > 550 msec, or symptomatic bradycardia

7. Systolic blood pressure <90 mm Hg or uncontrolled hypertension defined by a systolic blood pressure >170 mm Hg or a diastolic blood pressure >110 mm Hg

8. Unstable angina

9. Significant hepatic disease (AST or ALT 2X upper limit of normal)

10. Significant renal disease (BUN 2X upper limit of normal or creatinine > 2 mg/dL)

11. any condition which could result in significantly altered absorption, distribution, accumulation, or excretion of procainamide

12. previous treatment with amiodarone

13. treatment with barbiturates within 4 weeks prior to entry into study

14. current or recent illicit drug use/alcohol abuse

15. current or recent treatment with any investigational drugs

▸ **Concurrent medication**

Patients continued their current medications with the exception of alternative antiarrythmics. The antihypertensives verapamil and sotalol which have antiarrhythmic action were excluded.

▸ **Treatment regimen:**

On study day 1 after history, examination, clinical

laboratory and EKG, eligible patients began a week unblinded "wash-out" off procainamide. From day 5 to 7 they were Holtered for 48 hours to establish VPD level.

Eventually ninety-nine patients randomized to eight groups began the active treatment stage, day 8.

There were eight groups as follows:

1. qid placebo crossed-over to bid placebo,
2. bid placebo crossed-over to qid placebo,
3. 1000 mg total daily dose of procainamide: qid preparation crossed-over to bid,
4. bid preparation crossed over to qid,
5. 2000 mg total daily dose of procainamide: qid preparation crossed-over to bid,
6. bid preparation crossed-over to qid
7. 4000 mg total daily dose of procainamide: qid preparation crossed-over to bid, and
8. bid preparation crossed over to qid.[17]

The medications were compounded and dispensed so that neither investigator nor patient could determine whether active or placebo was being given, whether the dosing was bid or qid or what dosage level was being dispensed.

All tablets were coated grey. A large placebo tablet (designated PL in the table below) mimicked the 1000 mg preparation, a small placebo tablet (designated PS) the lower doses.

The bid-qid blind was maintained by giving all patients bottles labelled "A" and " B" from which they were to draw medication consecutively.[18]

Thus regimens for the four crossover pairs were as follows:

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[17]NDA 20-545; 1.24:125,127.

[18]IND 1.1:313 ff.

Placebo crossover (1 and 2 above):

Large qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets from bottle B bid.

	Bottle A	Bottle B	vs. Bottle A	Bottle B.
6 am	PL	PL	PS	PL PL
12 noon	PL		PS	
6 pm	PL	PL	PS	PL PL
12 midnight	PL		PS	

1000 mg total daily dose crossover (3 and 4 above):

Large qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets from bottle B bid.

	Bottle A	Bottle B	vs. Bottle A	Bottle B
6 am	PL	500bid	250SR	PL PL
12 noon	PL		250SR	
6 pm	PL	500bid	250SR	PL PL
12 midnight	PL		250 SR	

2000 mg total daily dose pair (5 and 6 above):

Small qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets from bottle B bid.

	Bottle A	Bottle B	vs. Bottle A	Bottle B
6 am	PS	1000bid	500SR	PL PL
12 noon	PS		500SR	
6 pm	PS	1000bid	500SR	PL PL
12 midnight	PS		500SR	

4000 mg total daily dose crossover:

Large qid tablet from bottle A, large bid tablet from bottle B alternating with small qid tablet from bottle A, two large tablets bid from bottle B

	Bottle A	Bottle B	vs. Bottle A	Bottle B
6 am	1000SR	PL	PS	1000bid 1000bid
12 noon	1000SR		PS	
6 pm	1000SR	PL	PS	1000bid 1000bid
12 midnight	1000SR		PS	

It is only the 2000 mg total daily dose bid sequence which breaks total symmetry. Placebo, dose and interval are well blinded.

Holter monitoring was performed for the first 24 hours

beginning 30 minutes before the first procainamide dose and again for 48 hours from day 12 to 14 at the end of the first cycle.

At the end of this 48 hour Holter, the bid and the qid groups received their first dose of the alternative "crossed-over" preparations, day 14. No "washout" procainamide-free interval was provided and no Holter was performed during the initial phase of the second cycle.

On day 19, the sixth day of the second cycle, 48 hour Holter monitoring commenced. Medication ceased with the second dose on day 20, the seventh day of the second cycle, so this Holter overlapped the withdrawal from medication. A further 24 hour Holter was carried out from day 21 to day 22, off procainamide.

Demographics and Treatment Group Comparability:

The protocol's patient population was not diverse. The requirement of ventricular ectopy makes it not surprising that the mean age was 67 years. Little gender or racial diversity was achieved: eighty-three percent were white men.

Recruiting in fact became more difficult in the course of the study as concerns about the safety of antiarrythmics increased. This necessitated the protocol amendments already mentioned.

APPEARS THIS WAY
ON ORIGINAL

Study 610-43/44: Characteristics of Patients Randomized to Treatment

Characteristics	Combined BID and QID Forms (mg/day)								Formulation Sequence			
	Placebo N = 25		1000 N = 24		2000 N = 28		4000 N = 22		BID→QID N = 50		QID→BID N = 49	
Gender, N (%)												
Women	3	(12)	4	(17)	6	(21)	4	(18)	10	(20)	7	(14)
Men	22	(88)	20	(83)	22	(79)	18	(82)	40	(80)	42	(86)
Race, N (%)												
White	21	(84)	20	(83)	26	(93)	20	(91)	44	(88)	43	(88)
Black	3	(12)	3	(13)	1	(4)	1	(5)	4	(8)	4	(8)
Other	1	(4)	1	(4)	1	(4)	1	(5)	2	(4)	2	(4)
Age, yr												
Median	67		68.5		66		68		67.5		67	
Min, Max	51, 93		51, 80		38, 83		56, 77		38, 80		51, 93	
Distribution by Age, N (%)												
<65 years	8	(32)	8	(33)	13	(46)	6	(27)	18	(36)	17	(35)
≥65 years	17	(68)	16	(67)	15	(54)	16	(73)	32	(64)	32	(65)
Number of VPBs/hr												
Median	127		180		199		156		183		165	
Min, Max	24, 1461		23, 1010		20, 2886		23, 1445		23, 2886		20, 1445	

VPD = Ventricular premature depolarization.

As shown in the table above[19], the various dosage groups seem to be well balanced with respect to gender, race, age, and VPD rate. It is true that very few women or blacks were included.

▸ How Much of a Difference in VPD Reduction Would Constitute a Disproof of Equivalence?

Statistical analysis begins with the null hypothesis that there is no difference between the evaluated populations. In this case the objective is to prove rather than disprove equivalence;

[19]NDA 20-545;1.24.25.

that with respect to VPD suppression procainamide bid is equivalent to the approved formulation. To be convincing, the study must have enough power to detect a difference if it exists.

The final draft of the original protocol (26 July 1990) stated

> It is expected that the mean reduction in VPDs for the Procan SR/QID treated patients will be 50% over the three dose levels. 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, two-tailed, is 100 evaluable, or 25 patients per each of the three active treatment groups and 25 patients in the placebo group. This calculated sample size is based on the assumption that the standard deviation of percent reduction in VPDs for within patient groups is 25%. [20]

▸How much VPD suppression to distinguish active treatment from placebo?

In order to validate an equivalence study, to demonstrate that acceptance of the null hypotheses is not due simply to wide variance, the active treatments must stand out against placebo. Once again the degree of difference it is desired to detect between the treated and untreated groups affects the power of the study, number of patients required, to detect it. Protocol amendment of 2 October 1990 reads

> It is expected that the mean percentage reduction in VPDs for the high dose of procainamide bid will be **70%**. The mean response of the placebo group is expected to be 10%. The total number of patients required to detect the difference between the high dose of procainamide BID and placebo with 95% power at the 0.05 level, two-tailed, is 88 evaluable or 22 patients per treatment group. This calculated sample

[20]NDA 20-545; 1.24:95.

> size is based on the assumption that the standard deviation of percent reduction in VPDs for between patients is 25%. Twenty- two patients per group will also provide information about the similarity of the two formulations (relative difference between formulations within 30% by confidence interval analysis).[21]

As previously mentioned, division medical officer Sughok K. Chun in her IND review of this amendment dated 3 June 1991 took exception. She felt that sponsor was underestimating placebo response and therefore underestimating patient numbers required to achieve statistical significance:

> Sponsor calculated the sample size with expectation that the mean percent reduction in VPDs at high dose of procainamide BID will be 70%. The mean response in the placebo group is expected to be 10%. However, the placebo response in VPD reduction is around 30% (20-40%) in various antiarrhythmic studies that calculated sample size and power considerations with respect to the primary objective. Hypothesis testing is probably incorrect.[22]

VIII. WHAT DATA ARE USABLE?

(1) How many patients qualify for evaluation?

The original parallel trial design envisaged 270 patients necessary to achieve adequate statistical power; the crossover design first envisaged 100 patients. This was, contrary to Division advice, revised down to eighty-eight. In the end the data from only 77 patients was judged evaluable. The scheme below illustrates the process.[23]

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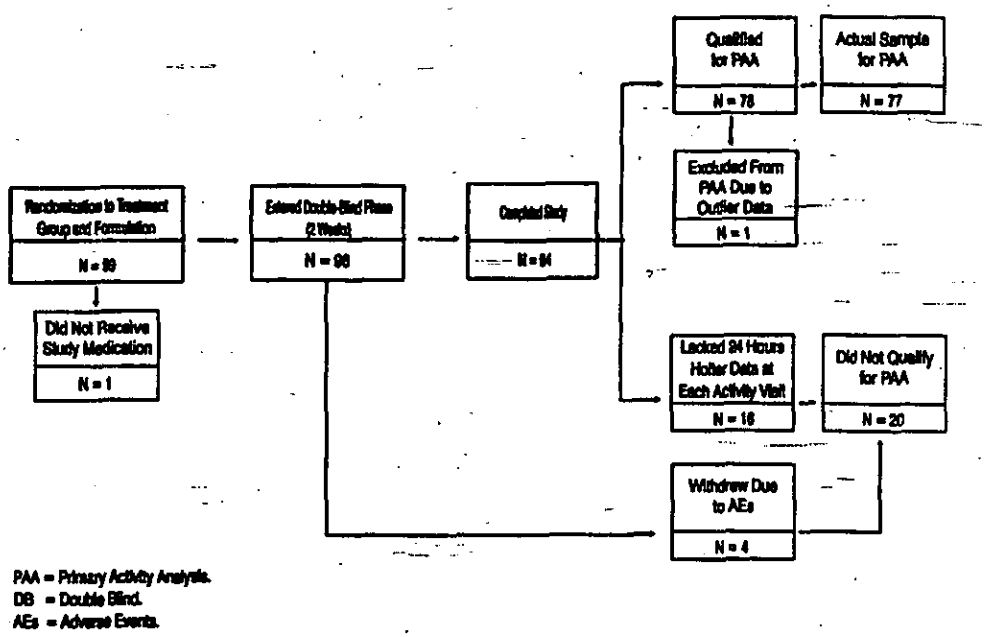
[21]NDA 20-545;1.24:104.

[22]IND 2.1:N(PI)004/5/29/91.

[23]NDA 20-545;1.24:34.



(2) How good is the Holter data?

As may be seen above, 16 patients were excluded from analysis for failure to have 24 hour Holter data at baseline or at either double-blind visit. But sponsor had been advised in writing on 14 August 1991 of the need for 48 hours after the first dose and 48 hours after the last dose plus 48 additional hours to observe return of VPDs (total 72 hours), so what was provided was substantially short of what was deemed requisite by the Agency.[24]

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[24] IND 2.1, 14 August 1991.

It is uncertain from the protocol how rigid was the timing of the Holters in relation to the protocol dosing schedule. According to the protocol, "To allow flexibility in scheduling patient appointments ... the start of Holter ECG recordings ... may be scheduled 1 day earlier or later than the day shown in the flowchart."[25]

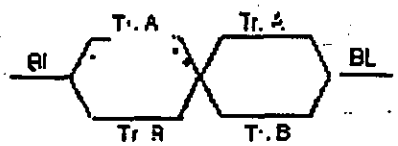
So there is some doubt about the quantity and timing precision of the Holter data.

(3) Is the Post-crossover Data Evaluable?

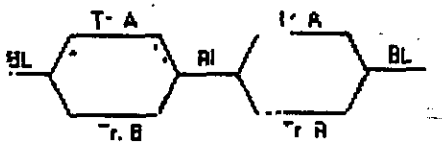
When sponsors presented their IND they substituted for the parallel trial earlier discussed a crossover design with no provision for washout; in other words, used the first of the two designs illustrated below.[26]

The possibility that data in the post-crossover phase may be contaminated by what has happened in the pre-crossover phase is a well-known weakness of the crossover design.

1. SINGLE CROSSOVER WITH NO INTERVENING BASELINE
(i.e., No Washout Interval)



2. SINGLE CROSSOVER WITH INTERVENING BASELINE



There are two mechanisms for post-crossover contamination. The first is biopharmacological. Antiarrythmics in particular may continue a

[25] NDA 20-545;1.24:84.

[26] Spilker, Bert, Guide to Clinical Trials, New York, 1991, p.33.

therapeutic effect for a time even as serum levels decline after cession of treatment. The second is statistical. "Period x treatment interaction" may indicate a carryover effect, confounding analysis despite biological implausibility.

What should be done at this point to evaluate this application for approval? One authority says, "the only acceptable option ... is to view the first part of the clinical trial as a parallel design and to compare the data of the two groups."

"This approach," he continues, "is invariably unsatisfactory because fewer patients were originally enrolled in each treatment group than would have been enrolled if the clinical trial were initially designed as a parallel trial." [27]

--If the VPD suppression outcomes need to be recomputed using pre-crossover data the evaluable patients will be reduced to ten on 4000 mg, thirteen on 2000 mg, ten on 1000 mg, daily doses of procainamide bid. These may be compared to similar numbers receiving procainamide qid and seventeen receiving placebo. [28]

A strong argument in favor of accepting the post-crossover data is that Holter recording performed after the second active treatment week, that is, on completion of the study, VPDs of patients on active treatment (squares and empty circles) reached the level of the placebo patients (solid circles) within 24 hours. [29]

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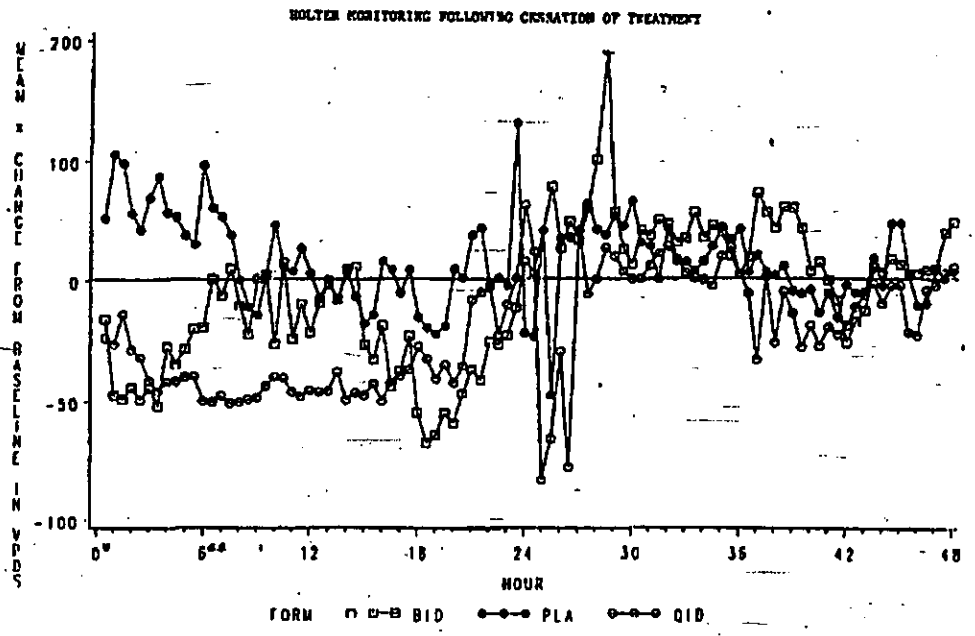
[27] Spiker, Bert, Guide to Clinical Trails, New York, 1992, p. 32.

[28] NDA 20-545;1.24.246.

[29] NDA 1.24:239.



* PATIENTS TOOK THE LAST BID DOSE
** PATIENTS TOOK THE LAST QID DOSE

Since the Holter data for the post-crossover period was taken at the end, it can be argued that in fact pre-crossover drug effect contamination may have been small. This argument does not address the "period x treatment" interaction" objection.

VIII. VPD SUPPRESSION OUTCOMES

Computations on patients accepted by the sponsor for primary activity analysis were done as follows:

To be included in the primary analysis, a subject had to have at least 24 hours Holter at screening (48 hours, on day 5 to 7 per protocol), 24 hours at the end of the first period (48 hours on day 12 to 14 per protocol) and 24 hours at the end of the second period (48 hours on day 19 to 21 per protocol).

Note that the 24 hour post-second-period 24 hour "washout" Holter is not required. Note also that Holters may be one day early or one day late from protocol time.

Seventy-eight patients met the above criteria; one patient was removed as a statistical outlier -- because his VPD were extremely increased on both preparations -- leaving Holter data from 77 patients.

1. Percent Change in Baseline vs. Placebo

The main efficacy measure analyzed was percent change from baseline in mean VPD per hour. This was calculated for each monitoring period as follows:

% change = 100 * (VPD-Baseline)/Baseline

where VPD = VPD/hr and Baseline = VPD/hr during baseline Holter.

Negative values represent decrease in VPD, the desired result of treatment.[30]

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[30]NDA 20-545 1.24:36.

PERCENT CHANGE IN VPDs BY PREPARATION AND DOSE[31]

Placebo	No. of PATIENTS 18 (7 B TO Q, 11 Q to B)	BID 20.35 (-13.85, 54.54)	QID 0.58 (-33.61,34.77)
1000 mg/day	19 (10 B to Q, 9 Q to B)	-14.66 (-48.35,19.03)	-19.68 (-53.37,14.00)
2000 mg/day	21 (13 B to Q, 8 Q to B)	-40.52* (-74.87,-6.18)	-35.81 (-70.15,-1.46)
4000 mg/day	19 (10 B to Q, 9 Q to B	-59.39* (-86.65,-20.12)	-29.91 (-63.18,3.35)

*indicates that the mean is significantly different than the corresponding mean in the placebo group.

Inspection of the above table[32] reveals the goal of 70% VPD suppression at the 4000 mg daily dose of the bid preparation is not reached. Nonetheless the 95% confidence limits for the 2000 mg and 4000 mg doses are negative, suggesting statistically significant suppression as compared to placebo.

The lower confidence levels of placebo ranged between -13.85 and -33.61. The Division had noted that the placebo effect as seen in current studies was 20% - 40%.

Whether statistical review will support and find significant sponsor's interpretation of nearly 60% reduction remains to be seen.

The fact that the bid preparation at 1000 mg and the qid preparation at all doses fail to achieve statistical significance in VPD suppression is, I believe, due to failure of the protocol to provide an adequate therapeutic dose range. The VPD

[31] prepared from data presented in NDA 20-545;1.24:241 and 246.

[32] NDA 20-545;1.24:247.

suppression efficacy of the approved preparation is not in question.

2. Comparison of VPD Suppression between Preparations

The difference between the qid and bid preparations with respect to VPD reduction was calculated by

D =(bid % change) - (qid % change).

Therefore positive D favors qid and negative D favors bid. This data is presented in the following table.[33]

FORMULATION DIFFERENCES AND ASSOCIATED CONFIDENCE INTERVALS FOR PERCENT CHANGE IN VPDs

INTENT-TO-TREAT ANALYSIS

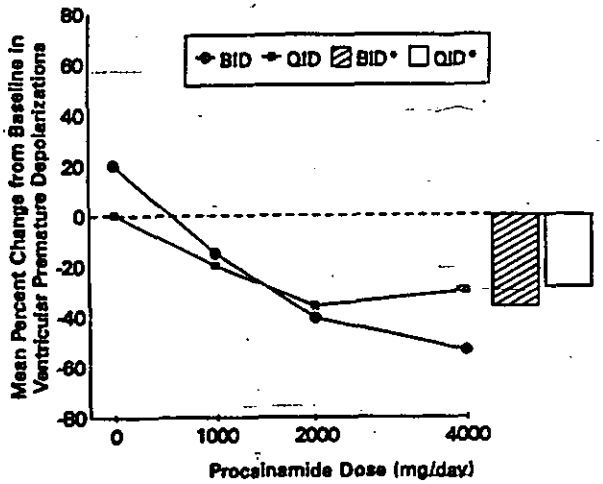
Dose Group	Difference (BID-QID) 95% Confidence Int.
1000 mg/day	30.10 (- 3.81, 64.02)
2000 mg/day	9.33 (-21.42, 40.09)
4000 mg/day	-19.64 (-54.35, 15.06)
All Active Doses	- 6.60 (-12.55, 25.75)

In this case the objective is to prove lack of difference, that is, the closer the mean is to zero, the stronger the study hypothesis. The study design had asserted that equivalence with respect to VPD suppression would be established if the 95% confidence interval for the absolute difference between the bid and qid formulations fell within +30% and -30%. The recorded confidence interval (+25.55% to -12.55%) more than meets this preset standard. In fact the data seems to support greater equivalent dose efficacy of the bid preparation.

Once again, the weight of this computations awaits statistical review.

[33]compiled from tables contained in NDA 20-545;1.24:246 and 247.

This information is presented graphically. [34]



IX. PHARMACOKINETIC OUTCOMES

Pharmacokinetic (serum level) studies were conducted on only 43 of the 77 patients who were analyzed for VPD reduction. These were trial patients at six of the fourteen centers. These studies are specified in Protocol 610-43.

These studies

(1) evaluating procainamide and N-acetylprocainamide pharmacokinetics as a function of dose and formulation and

(2) characterizing by pharmacokinetic/pharmacodynamic methods f the relationship between plasma concentration and pharmacologic effect

contained in NDA 20-545, volumes 1.13 and 1.14 respectively are interestingly reviewed by Olof Borga, PhD., biopharmacologist.

A. Procainamide Concentration vs. Time by Preparation and Dose[35]

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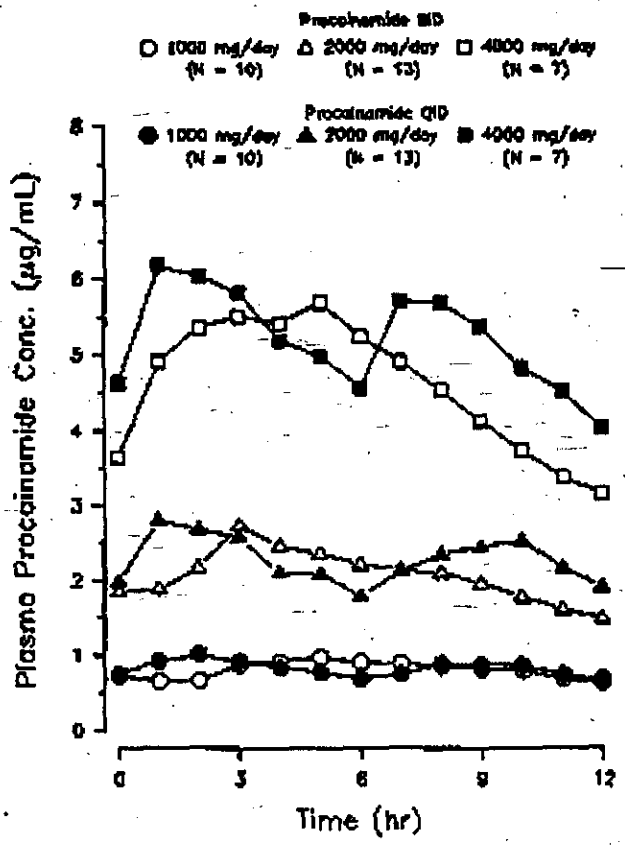
[34] IND 2.1, 14 August 1991.

[35] NDA 20-545;1.1:100.



Mean Plasma Procainamide Concentration-Time Profiles at Steady State Following Administration of Procainamide BID Tablets q12h or Procainamide QID Tablets q6h at Each Dose Level. Data from Visits 5 and 7 were pooled to calculate mean values by formulation (Protocol 610-43)

Sponsor submits the data from which after elaborate statistical analysis the above graph is drawn in appendix D, volume 1.13. Their own conclusion is that "Minimum plasma

concentrations following administration of procainamide BID tablets every 12 hours are slightly lower than those for administration of Procan SR tablets every 6 hours."[36]

The argument is made however that the overall pharmacokinetics are equivalent.

> Despite the fact that the study design and patient population were suboptimal for bioavailability comparisons across formulations, 90% confidence intervals for ratios of dose-normalized mean C_{max} and mean AUC values were within or virtually within an 80% to 125% interval indicative of bioequivalence of the two treatments. When data from all dose groups were combined, procainamide BID tablets were bioequivalent to QID tablets with respect to maximal observed concentration and extent of absorption. Mean C_{min} values for BID tablets were lower than corresponding values for QID tablets.[37]

According to FDA standards however, bioequivalence means that the outer 95% confidence limit (not the mean) of the tested drug be within 20% of the mean of the standard.

B. Relationship Between VPD Rate and Plasma Concentration of Procainamide and NAPA[38]

The following graphs presented by the sponsor of VPD suppression vs. procainamide and NAPA suppression are difficult

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[36]NDA 20-545;1.13:17.

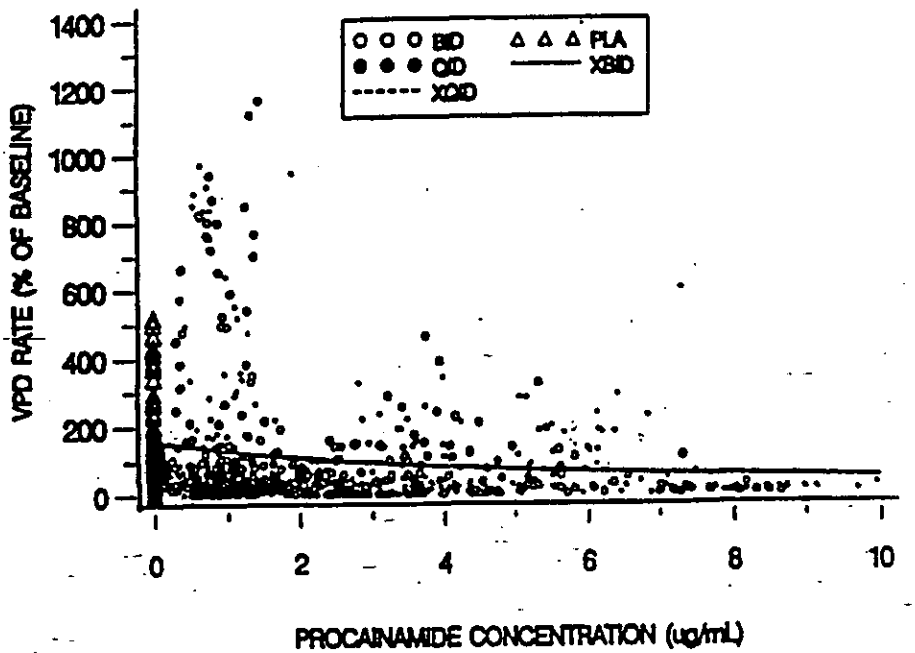
[37]NDA 20-545;1.1:99.

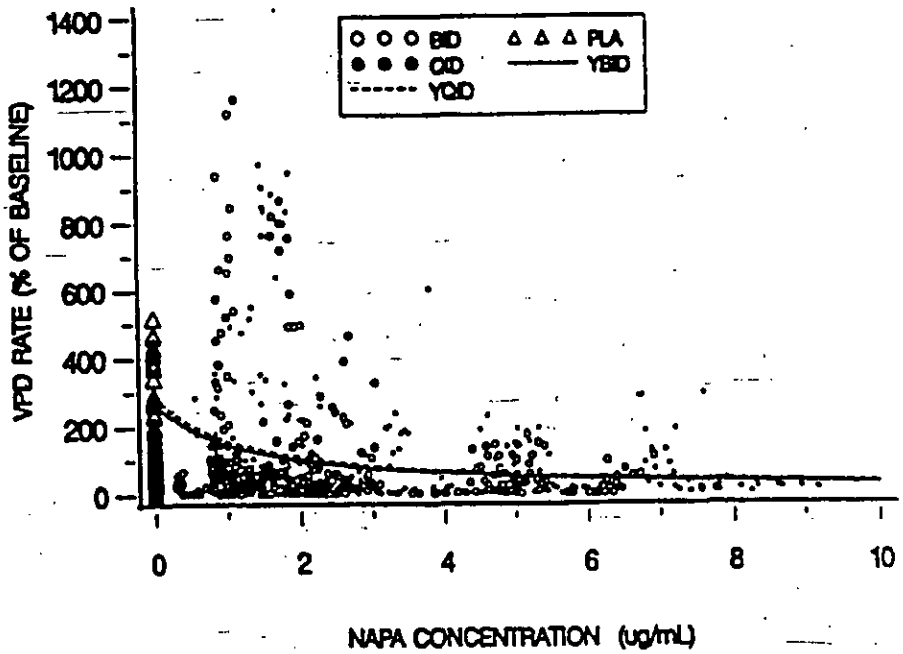
[38]NDA 20-545;1.1:130.

to analyze.[39]

APPEARS THIS WAY
ON ORIGINAL

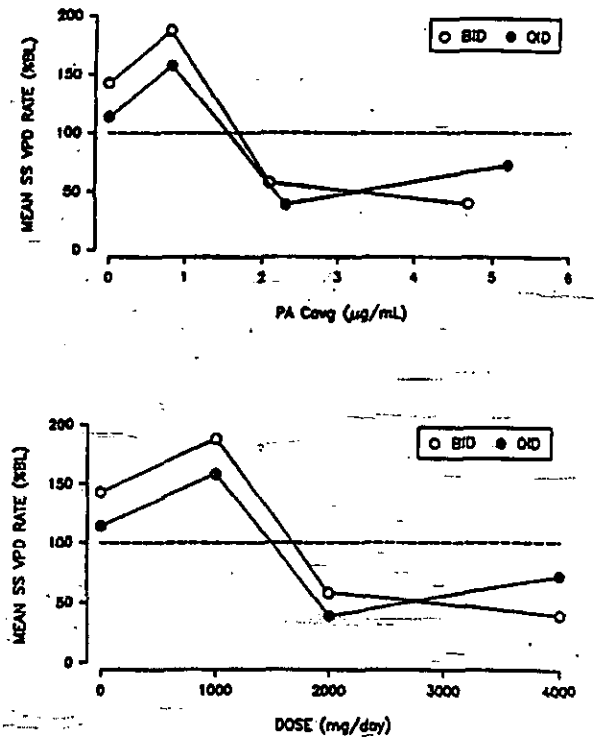
[39] NDA 20-545, 1.1:130 and Dr. Borga's draft review.





Efforts to model this data to achieve a concentration-

response relationship have been unsuccessful. One serious difficulty in constructing a consistent statistical model is that the mean VPD rate graphed vs dose actually shows the VPD rate increased above placebo at the 1000 mg dose in the 43-patient sample who were assayed pharmacologically.[40] This is not true in the overall analysis of 77 patients which showed 19.68% (-53.57, 14.00) reduction at the 1000 mg dose. The only tentative finding is a decrease in clinical effect with increasing age.



Steady-state VPD Rate vs. Mean Procainamide Concentration and Dose

Dr. Borga therefore feels that because the plasma concentration-time profiles of the two preparation are "far from identical" the sponsors' claim of equivalence with respect to VPD suppression[41] is not accurate. He believes that the failure to establish concentration-effect relationship is due to "(1) a large intra- and inter-subject variability of the effect at a particular concentration and (2) a weak response to the drug." The anomalous finding of VPD increase at the 1000 mg dose appears to be due to an unfortunate population sample and a subtherapeutic dose.

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[40] prepared by Dr. Borga from sponsor's data.

[41] NDA 20-545; 1.1: 131.

X. REVIEW OF CLINICAL OUTCOMES

The new preparation came short of its stated goal for demonstrating suppression of VPDs although at least accepting post-crossover patients, it is significantly more active than placebo.

In the clinical trial a new drug (procainamide bid) was pitted against active control (procainamide qid) and placebo.

The questions to which the trial should have provided affirmative answers leading to an affirmative answer to the application are:

(1) Is the active control (Procan SR) better than placebo in this trial?
(2) Is procainamide bid better than placebo?
(3) Is the study powerful enough to tell a difference if one exists?

The approved drug is ipso facto better than placebo but may not have been so demonstrated under the conditions of this trial. The dose range was far lower than that used for previous trials leading to approval. The anomalous increase of VPD's in a subset at the 1000 mg dose is partially explained by being subtherapeutic..

The answer to the second question is that data as analyzed does show bid superiority to placebo. But if data is discarded, will it still be possible to make the same demonstration?

The third question - does the study have enough power to show a difference? - awaits further analysis.

XI. SAFETY OUTCOMES

The sponsor provides (1) elaborate documentation of laboratory parameters and complaints during the two-week crossover period and more significantly, reports (2) one-year follow up of a subset of these same patients maintained on the study medication.

In response to Division's request, sponsor also prepared (3) an epidemiologic survey of procainamide-related bone marrow suppression.

1. The Two Week Crossover Period

In evaluating the safety data from the crossover study period one should keep in mind the particulars of the study:

(a) patients were already proven tolerant to procainamide

(b) patients were selected for stability and absence of risks

(c) the short time involved.

Assuming therefore that this new preparation of a drug widely used for forty years was not grossly toxic, drug-related significant untoward events were not very probable.

64 patients reported a total of 154 adverse events.[42]

The most frequent complaints were asthenia, dizziness, chest pain, palpitation, and dyspnea. Chest pain occurred more frequently in the procainamide group than placebo, arrhythmia and palpitations evenly distributed across dosage groups and formulations. There were no malignant arrhythmias.

Not mentioned above are two patients with proarrythmias -- one patient increased his VPD rate 4 times on Procan SR and 10 times on Procanbid; another increased his VPD 4-fold on Procan SR.

Three patients on active drug were beset by serious adverse events during the two week trial.[43]

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[42] NDA 20-545; 1.24:46.

[43] NDA 20-545;1.24:51-53.

1. A 72 year old man with CHF, angina, ventricular ectopy, suffered a non-Q-wave myocardial infarction after two days of qid procainamide 2000 mg qd. He continued procainamide and made a good recovery and completed the study.

2. A 74 year old man receiving bid procainamide 4000 mg total daily dose was hospitalized for two days after 6 days of treatment for recurrent chest pain. He was withdrawn from the study after 13 days of treatment. His angina continued after withdrawal of procainamide which he had tolerated for several years.

3. A 68 year old man with CHF secondary to cardiomyopathy was hospitalized due to worsening of his condition after less than a day on procainamide bid 2000 mg/day. He was diuresed, released, and completed the study.

The sponsor's judgement that none of these events were related to study medication seems justified.

▸ **Summary**

There was no serious or unexpected toxicity related to procainamide bid in the two-week blinded study.

2. The One Year Open-Label Continuation Safety Trial (Protocols 610-43x, 610-44x)

Patients completing the double blind crossover trial were given the option to continue on the new preparation for one year to assess safety and side effects.

Sixty-eight patients entered this phase; twenty withdrew from the study, nine for adverse events, eleven for other reasons. One patient died, leaving 47 patients who completed the year's therapy.

Since this study was a continuation of the blinded trial, it had the same inclusion and exclusion criteria, and roughly the same demographic profile: most of the patients were white men over 65.

Twenty-five percent of the participants had been treated with placebo during the trial; hence all participants received 24 hour Holter monitoring two weeks into the study.

Monitoring was focussed on development of (1) hematological and immunological abnormalities, especially antinuclear antibody titer (2) proarrythmias and (3) adverse symptoms.

Baseline laboratory values were taken to be those at the beginning of the double-blind clinical trial.

Although one patient received procainamide bid 1500 mg daily, the remainder received 1000 mg daily (864 patient days), 2000 mg daily (11,625 patient-days), 3000 mg daily (5900 patient days) or 4000 mg daily (3073 patient-days).[44]

Thirteen (20%) had possibly clinically important deviations from baseline in hemoglobin, hematocrit, platelets and eosinophils. All but one occurred during 2000 and 3000 mg bid therapy and most during the first six months of open-label therapy. One of these withdrew from the study due to gastrointestinal hemorrhage thought probably drug related.

One patient died, a 68 year old man with congestive heart failure, frequent VPD, and hypertension after hospital admission following excessive salt intake and non-compliance with his medicines. The exacerbation of CHF and subsequent death was judged not due to study medication.

Three (5%) had clinically important antinuclear antibody (ANA) rise. Clinically important was defined as (a) 4-fold increase in titer relative to base value if screening titer was <1:40 and (2) a 2-fold change if screening = or >1:40. Thus eight patients who converted to ANA positivity <1:20 during the study were not included.

▸ **Summary:**

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[44]NDA 20-545;1.28:16.

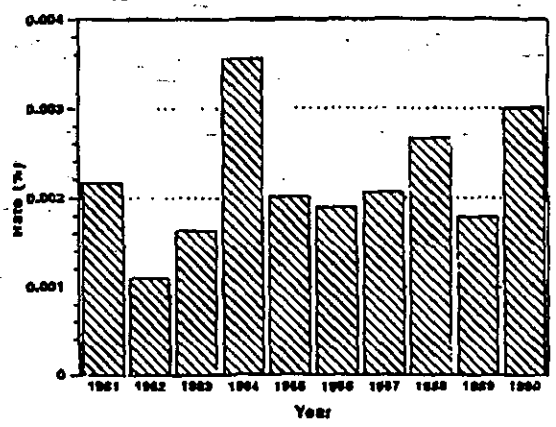
The safety experience of procainamide bid over the one year open-label trial presented no surprises.

3. Procainamide-associated Blood Dyscrasias

At Division request the sponsor performed an epidemiological study from 1981 to 1990 of procainamide-associated blood Dyscrasias indicative of bone marrow suppression --agranulocytosis, granulocytosis, neutropenia, pancytopenia, aplastic anemia.

The three hundred cases identified represent approximately 0.0022% of new prescriptions written; the annual rates ranged from 0.0011% to 0.0036%[45].

The higher rate in 1984 was associated with a study population largely post-thoracotomy and hence with an incidence of bypass and transfusion complications such as thrombocytopenia, and CMV infection. It is further suggested that many cases may be caused by concomitant medications: 71% were receiving such, and of these 81% known to cause bone marrow suppression[46].



Annual Rate of Reported Cases of Procan SR-Associated Blood Dyscrasias

It was assumed that the reporting rate was greatly less than the incidence; assuming one in one hundred reported, sponsor suggests that a fairer incidence might be 0.22% of prescriptions written.

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[45]NDA 20-545;1.23.10.

[46]NDA 20-545;1.23.12.

▸ **Summary:**

This may have not been a very useful study because of an uncertain population in the denominator; prescriptions written differ from new prescriptions differ from patients or patient years. Nonetheless results suggest that procainamide administration rarely causes bone marrow suppression.

XI. Conclusions

Twenty-five years ago a plausible new preparation for an established drug would have, like sponsor's qid preparation, have been approved on the basis of serum assays.

A changed regulatory climate and new knowledge about antiarrythmics led the Division from 1987 on to request clinical trial data to support claims of satisfactory procainamide activity and side effect profile.

The sponsor and the Division reached agreement on an appropriate parallel trial design.

There should have been a straight-forward run to completion and approval.

The sponsor's change to a crossover design weakens the data. Because of the possible residual effect following crossover, fully half of rhythm data is suspect.

Even the patient numbers that sponsor brings forward for primary analysis may not give the study sufficient power.

Furthermore the study was crippled in its effort to show efficacy because much of its dosing range was sub-therapeutic.

The overall shape of the data suggests the sponsor's contention that what their bid preparation performs with the efficacy and side-effect profile inherent to the drug.

XII. RECOMMENDATIONS

From a clinical point of view, if one accepts that oral procainamide still has a useful place in medical practice (by definition "life-threatening" arrhythmias cry out for treatment), then the increased ease of compliance with a bid preparation make its approval in the public interest. The clinical trial establishes efficacy (although much less well than a parallel design with adequate dosing could have done); both clinical and pharmacological investigations establish safety. I therefore recommend approval.

/S/ 11 Apr 95

Gerald E. Bunker, MD, PhD Date
Medical Officer

cc: HFD-110 division file, CSO (HFD-110), R. Fenichel (HFD-110) , G.Bunker (HFD-110).