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Original Contributions

Assessment of Double-blindness at the Conclusion of the β-Blocker Heart Attack Trial

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• **At the conclusion of a double-blinded, randomized clinical trial of propranolol hydrochloride, but before unblinding, the patients and clinic personnel were asked to guess the treatment group assignment of each patient. While 79.9% of the patients receiving propranolol correctly identified their treatment group assignment, 57.2% of the patients receiving placebo incorrectly guessed that they were also in the propranolol group. No specific mechanism was identified to explain why more patients receiving propranolol were better able to guess their group assignment. Clinic physicians correctly identified the group assignment of 69.9% of the patients receiving propranolol and 68.8% of the patients receiving placebo. Clinic coordinators correctly identified the group assignment of 67.1% of the patients receiving propranolol and 70.6% of the patients receiving placebo. For clinic personnel, heart rate level and heart rate change seem to be the mechanisms employed to identify their patients' treatment assignment.**

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THE ELIMINATION, or at least the reduction, of bias is a primary objective in the design of a clinical trial. Blinded designs can help to meet this objective by preventing the conscious or subconscious prejudices of the study patients and/or investigators from influencing how they behave. Although a double-blinded design is the preferable type of design in almost all placebo-controlled clinical trials, it is not always possible. For example, agents with known and fairly specific pharmacologic effects, such as β-blocking agents, present special problems for double-blinded trial designs. When such agents are employed, the blindness of the trial may be questioned.

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This is a report of an analysis examing this question in a double-blinded trial of propranolol hydrochloride, the β-Blocker Heart Attack Trial (BHAT).

METHODS

The BHAT was a multicentered, double-blinded, randomized, placebo-controlled trial designed to test the efficacy of the β-blocker propranolol in reducing mortality during a two- to four-year period in post-myocardial infarction (MI) patients. Men and women, aged 30 through 69 years old, were eligible for enrollment into the BHAT five to 21 days after hospital admission for an acute MI. During a two-year period, 3,837 patients were randomized into the trial: 1,916 into the propranolol group and 1,921 into the placebo group. All patients were followed up at regular visits for 12 to 40 months (mean, 25 months). Because of the demonstrated benefit of propranolol treatment, the trial was terminated nine months ahead of schedule. The design of the trial, the baseline characteristics of the patients, and the primary results of the trial are described elsewhere.[1-4]

All study medications, propranolol or placebo, were made to look identical. However, propranolol has many known pharmacophysiological effects, some of which may be detected without special tests by clinic personnel and patients. This made true blinding difficult. For example, in many patients the drug lowers heart rate and blood pressure,[5,6] two parameters that were to be routinely measured during the course of the trial. Other side effects associated with propranolol treatment include fatigue, nightmares, and depression.[7] These were known and accepted at the beginning of the study as unavoidable consequences of the nature of the drug. However, the decision was made to conduct a double-blinded trial because individual variations in response and the likelihood of physiological changes in at

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least some of the placebo participants because of nondrug factors made it less likely that the clinic personnel and patients could be certain of treatment group assignment in individual cases.

At the conclusion of the trial, after the final interview and physical examination were completed but before the patients and clinic personnel were unblinded, the patients were asked the following questions: "What treatment do you think you were prescribed in this study? (A) I am certain I was prescribed propranolol; (B) I think I was probably prescribed propranolol; (C) I have absolutely no idea which medication I was assigned; (D) I think I was probably prescribed placebo; (E) I am certain I was prescribed placebo. If you answered the above as, 'I have absolutely no idea which medication I was assigned,' which medication would you guess? (A) propranolol; (B) placebo."

The BHAT clinic personnel (ie, the patient's clinic physician and the clinic coordinator) were asked to state their opinion in a similar manner. The patient, physician, and clinic coordinator answered these blindness questions in private and without knowledge of the others' responses. Each patient's form was sealed in an envelope and sent directly to the coordinating center for the trial.

This present analysis examined the perception of treatment group assignment by both the BHAT patients and clinic personnel *v* the patients' actual treatment group assignments. Patient characteristics associated with correct and incorrect guessing were sought. Because of the large number of subgroup analyses conducted with the BHAT data and the probability of finding a statistically significant difference by chance alone, we are not reporting tests of significance.

Table 1.—Percent Frequency Distribution of Patients' Perception of Treatment Group Assignment

Patient Guess	Actual Treatment Group Assignment: Propranolol Hydrochloride (n=1,649)		Placebo (n=1,581)	
Response to First Blindness Question				
Certainly propranolol	23.1	63.6	10.7	40.7
Probably propranolol	40.5		30.0	
Have absolutely no idea	26.3		32.8	
Probably placebo	8.6		21.3	26.5
Certainly placebo	1.5		5.2	
Total	100.0		100.0	
Response to Second Blindness Question				
Propranolol	62.0		50.3	
Refused to speculate	8.5		10.6	
Placebo	29.5		39.1	
Total	100.0		100.0	

Table 2.—Patients' Mean Heart Rates (Beats/min) by Actual Treatment Group Assignment and Guesses of Treatment Group Assignment

Actual Assignment	Patient Guess of Treatment Group Assignment: Certainly Propranolol	Probably Propranolol	No Idea	Probably Placebo	Certainly Placebo
Patients receiving propranolol					
Baseline visit	74.9	75.6	76.7	77.0	76.5
6-mo visit	62.5	64.0	66.3	66.5	69.2
Patients receiving placebo					
Baseline visit	75.2	75.0	75.4	75.8	75.8
6-mo visit	73.4	73.1	73.8	74.2	73.1

RESULTS

Blindness data were obtained from 1,649 propranolol patients (93% of the propranolol group survivors) and from 1,581 placebo patients (or 91% of the placebo group survivors). Table 1 gives the frequency distribution of the initial responses given by the BHAT patients. Of the propranolol group patients, 63.6% either were certain that they were in the propranolol group or believed it was probable that they were in this group. Among the 26.3% of the propranolol patients who first stated that they did not know their treatment group assignment, 62% correctly guessed that they were receiving propranolol when pressed to take a guess (Table 1, bottom half). When these patients are combined with the patients who either were certain or felt it was probable that they were receiving propranolol, a total of 79.9% of the propranolol group patients correctly guessed or had some sort of feeling for their treatment group assignment.

Although 26.5% of the placebo group patients either were certain or felt it was probable that they were in the placebo group, 40.7% incorrectly felt that they were in the propranolol group (Table 1, top half). Furthermore, slightly more placebo group patients initially stated that they did not know their treatment group assignment compared with propranolol group patients (32.8% *v* 26.3%). When these placebo patients were asked in the second question to guess their assignment, slightly more than 50% of them still incorrectly guessed propranolol, while only 39% guessed placebo (Table 1, bottom half). When the responses to the two questions were combined, 57.2% of the placebo group patients incorrectly guessed that they were receiving propranolol. This contrasts with the 39.3% who correctly guessed their group assignment.

Certain subgroups of the propranolol and placebo groups were better able to correctly identify their treatment group assignment than were other subgroups. Among the propranolol group patients, when the "certain" and "probable" answers are combined, men were slightly better identifiers of their treatment group assignment than were women (65% *v* 56%), as were those patients who were employed (65% *v* 59% for the unemployed), those who were married (66% *v* 54% for the unmarried), and those with at least a high school education (72% *v* 58% for those with no high school diploma). Among the placebo group patients, patients younger than 60 years were slightly better identifiers of their group assignment than were those aged 60 years and older (28% *v* 24%), as were those who were employed (29% *v* 18% for the unemployed), those with at least a full high school education (34% *v* 21% for those with no high school diploma), and those with no MI prior to the BHAT MI (27% *v* 22% for those with a prior MI). No subgroup of placebo group patients had at least 50% of the patients correctly guess-

Table 3.—Percent Frequency Distribution of Physicians' and Clinic Coordinators' Perception of Patients' Treatment Group Assignment

Guess of Clinic Personnel	Actual Treatment Group Assignment: Propranolol Hydrochloride — Physician Guess (n=1,721)		Propranolol Hydrochloride — Coordinator Guess (n=1,789)		Placebo — Physician Guess (n=1,677)		Placebo — Coordinator Guess (n=1,763)	
Certainly propranolol	16.4	60.6	8.9	52.2	2.6	22.2	1.7	18.1
Probably propranolol	44.2		43.3		19.6		16.4	
Have absolutely no idea	18.2		27.1		21.0		29.7	
Probably placebo	18.8		19.5		46.1	56.8	45.4	52.1
Certainly placebo	2.3		1.2		10.7		6.7	
Total	100.0		100.0		100.0		100.0	

Table 4.—Patients' Mean Heart Rates (Beats/min) by Clinic Personnel Guesses of Treatment Group Assignment

	Guess of Clinic Personnel: Certainly Propranolol Hydrochloride	Probably Propranolol	No Idea	Probably Placebo	Certainly Placebo
Propranolol Patients Only					
Physician guess					
Baseline visit	73.9	75.2	77.3	78.5	80.9
6-mo visit	59.7	63.3	68.5	69.8	73.6
Coordinator guess					
Baseline visit	75.1	75.3	76.6	77.4	77.7
6-mo visit	59.7	63.0	65.8	69.8	72.4
Placebo Patients Only					
Physician guess					
Baseline visit	71.8	72.0	75.5	76.2	79.1
6-mo visit	67.5	69.2	71.9	75.0	78.0
Coordinator guess					
Baseline visit	72.5	75.0	75.4	75.8	77.0
6-mo visit	67.2	70.8	72.9	74.7	76.8

ng their treatment group.

lo specific purported side effect of pranolol was identified to explain y the patients receiving propranowere better identifiers of their atment group assignment than re the patients receiving placebo. ring the follow-up period, patients o correctly guessed their treatnt group assignment had, comed with patients who incorrectly ssed, similar rates of fatigue, htmares, hallucinations, and dession.

lowever, propranolol group paits who correctly guessed their atment group assignment had lowmean heart rates at six months n did those who guessed incorrect(Table 2). Also, the more certain propranolol group patients were t they were receiving the β-blockthe lower were their mean heart es. This relationship between sixnth heart rate and level of certy was not seen in the placebo up patients at all. There was no ong association between baseline heart rate and level of certainty for either treatment group.

Compared with their patients, the BHAT clinic personnel were better able to differentiate the patients receiving propranolol and placebo. The frequency distributions of the guesses made by the patients' BHAT physician and clinic coordinator are given in Table 3.

Physicians correctly identified 60.6% of the patients receiving propranolol, and the coordinators correctly identified 52.2%. When pressed to take a guess about the treatment group assignment of those whom they initially had no opinion about, propranolol was still the most common response for both physicians and coordinators, 51% and 55%, respectively. When these guesses were combined, the patterns of treatment group identification were similar for both physicians and coordinators, with more than two thirds of the patients receiving propranolol being correctly identified (69.9% by physicians and 67.1% by coordinators).

Physicians and coordinators also correctly identified more than half of the patients receiving placebo, 56.8% and 52.1%, respectively (Table 3). When pressed to take a guess about the treatment group assignment of those about whom they initially had no opinion, 57% of the physicians and 62% of the coordinators correctly guessed placebo. When these guesses are added to those they already had an opinion about, again more than two thirds of the patients receiving placebo were correctly identified (68.8% by physicians and 70.6% by coordinators).

The mechanism by which the high proportions of correct treatment group identifications were made appears to be through the observation of the heart rate level after six months of treatment and/or the reduction of heart rate level from that at the time of the baseline examination. As shown in Table 4 (top half), for both physicians and coordinators, the patients receiving propranolol correctly identified as such had much lower mean heart rates at six months than did the patients incorrectly identified as receiving placebo. The former patients also experienced a greater reduction in mean heart rate level from that at the time of the baseline examination. A gradient of certainty exists, in that the more certain the clinic staff were that a patient was receiving propranolol, the lower was the six-month heart rate level and the greater was the reduction in heart rate level from baseline examination to six months. These differences also existed at the time of baseline examination, before the patients were even randomized, although the differences were not as great as they were at six months.

The corresponding data for the placebo group patients are given in Table 4 (bottom half). Again, for both physicians and coordinators, the patients receiving placebo incorrectly identified as patients receiving propranolol had lower mean heart rates at six months as well as a greater reduction in heart rate than did the patients correctly identified as receiving placebo.

COMMENT

Propranolol is known to reduce heart rate.[5,6] Given this effect, the

results of the guesses by the clinic personnel are not surprising. However, because during the course of the trial there were no group differences in drug and visit compliance or in the prescription of concomitant therapy,[3] the ability of the personnel to correctly identify treatment group assignment did not appear to have influenced the successful conduct of the trial. Also, if clinic personnel were completely unblinded, it would be expected that their guesses would have been correct 100% of the time. If the trial were completely blinded, it would be expected by chance that the guesses would have been correct 50% of the time. In the BHAT, the staff correctly guessed at levels in between these two extremes.

The pattern of treatment group identification was not as clear for the patients. Most patients, regardless of actual treatment assignment, guessed that they were prescribed propranolol. The mechanism for this could not be determined but could be a reflection of "wishful thinking."

Only a few double-blinded clinical trials report the success or failure of blinding. If reported at all, the assessment of blindness is usually noted in three or four sentences in the primary report of the trial.[8-10] Other reports that specifically deal with blindness concentrate on how the active and placebo agents were similar or dissimilar. Usually this type of report is restricted to the physical description and/or the taste of the agents."

This report is different from most other reports because the agent under study, propranolol, has pronounced pharmacophysiological effects that are easily measured. The active agents in other studies often did not have pronounced and/or easily measured characteristics. For example, in another double-blinded, placebo-controlled clinical trial of post-MI patients, aspirin was the studied agent. In an analysis of patient blindness at the conclusion of that trial,[12] it was found that 46.7% of the true aspirin group patients correctly guessed that they were taking aspirin and that 43.4% of the true placebo group patients correctly guessed that they were taking placebo. These figures contrast with the 63.6% correct propranolol guesses and 26.5% correct placebo guesses in the BHAT. As another example, at the conclusion of a clinical trial of cholestyramine resin given to asymptomatic hypercholesterolemic men, it was reported that 56.0% of the treatment group and 54.6% of the placebo group correctly identified their treatment assignment. Similarly, clinic personnel in that study correctly identified 55.2% of the patients receiving cholestyramine and 52.9% of the patients receiving placebo.[13]

In summary, double-blindness was not fully achieved in the BHAT. The clinic personnels' observation of the patients' heart rate level and/or heart rate level change appears to have been at least partly responsible for the correct identification of treatment group. Although ideal blindness was not achieved, this did not appear to influence the successful conduct of the trial because during the course of the trial there were no group differences in drug and visit compliance and in the use of concomitant therapy.

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