Comparative Effectiveness of Carbamazepine and Propranolol for Rage Outbursts

Jeffrey A. Mattes, M.D.

Eighty patients (randomly assigned in 51 cases) with diverse diagnoses, were prescribed propranolol or carbamazepine for temper outbursts. Results suggested that both medications were beneficial. The diagnosis of attention deficit disorder predicted preferential response to propranolol, and a diagnosis of intermittent explosive disorder predicted preferential response to carbamazepine. Results, however, were not entirely consistent and require confirmation.

(The Journal of Neuropsychiatry and Clinical Neurosciences 1990; 2:159–164)

The psychopharmacological treatment of rage outbursts is an area of increasing interest.[1] A number of medications, including carbamazepine, beta blockers, and lithium, have been reported to be beneficial in alleviating temper difficulties, though most studies to date were uncontrolled.

The rationale for using a particular drug in a particular study has varied. For example, carbamazepine has been used primarily in patients with electroencephalogram (EEG) abnormalities[2] because of its prior use as an anticonvulsant[3] and because of the hypothesis that rage outbursts may be seizure equivalents in some patients.[4] Propranolol has been used primarily in patients with known central nervous system (CNS) organic pathology.[1,5–8] The current study evaluated and compared the effectiveness of propranolol and carbamazepine in otherwise unselected patients with rage outbursts to attempt to identify predictors of differential benefit. Preliminary reports from this study have been published previously.[9]

METHODS

Subjects

Subjects were inpatients at least 16 years old who met the first two *DSM-III* criteria for intermittent explosive disorder (IED). That is, first, the patients had to have mani-

Received July 24, 1989; revised October 20, 1989; accepted October 20, 1989. From the Psychopharmacology Research Association of Princeton, Princeton, New Jersey. Address reprint requests to Dr. Mattes, Psychopharmacology Research Association of Princeton, 601 Ewing Street, Suite C-12, Princeton, NJ 08540.

fested several discrete episodes of loss of control of aggressive impulses resulting in serious assault or destruction of property; and second, they had to have exhibited behavior that was grossly out of proportion to any precipitating psychosocial stressor.

Patients did not have to meet the additional criteria for IED and could have generalized aggressiveness between episodes. Excluded were patients with diagnoses requiring other treatment (e.g., schizophrenia) and patients with contraindications to both carbamazepine and propranolol.

Treatment

Sixty-one subjects were randomly assigned to receive carbamazepine or propranolol, but only 51 patients (22 on carbamazepine and 29 on propranolol) completed a reasonable trial. The other 10 patients were considered dropouts and not included in analyses because they did not receive a trial sufficient to discern beneficial drug effects, because they complained of side effects, or because of administrative reasons (e.g., unauthorized discharge). Several dropouts felt sedated or "spaced out" on one or the other medication, and several patients on carbamazepine developed rashes that required us to discontinue their participation in the study.

The usual clinical contraindications and safeguards were followed for both drugs. Propranolol was begun at 10 mg four times a day and increased daily by 10 mg four times a day (i.e., by 40 mg a day) to a maximum of 160 mg four times a day. Dosage was reduced if blood pressure fell below 85/55 or if pulse fell below 55. Carbamazepine was begun at a dosage of 200 mg twice or three times a day and increased to reach plasma levels of 8 to 12 mg/ml.

Twenty-nine other eligible patients were not randomized but, for clinical reasons, received one of the two medications (27 of the 29 received carbamazepine) and were followed systematically, as were the others. Reasons for nonrandomization were epilepsy (n=11), because carbamazepine was clinically indicated; contraindications to one of the medications (n=7); poor tolerance to a brief trial on the other medication (n=5); treatment by a psychiatrist who was not participating in the study (n=5), and other (n=1).

Unless medication clearly did not help the patient while hospitalized, the plan was to continue medication for two to three months after discharge and then to taper off the medication to clarify the medication effect, and to restart it only if clinically indicated.

Baseline Evaluation

To identify potential predictors of response, 30 variables were evaluated. These were *DSM-III* and neurological diagnosis; CAT scan with and without contrast; at least one EEG, generally a sleep EEG with nasopharyngeal leads; neuropsychological testing, primarily for evidence of temporal and frontal lobe dysfunction; and clinical ratings, including type (verbal, assault, or destruction of property), severity and frequency of outbursts, age at onset of outbursts, amount of provocation required for outbursts, rapidity of onset and offset, amnesia and guilt for episodes, confusion, loss of control and hypersensitivity to sensory stimuli during episodes, history of perinatal difficulties and poor coordination, personal and family history of psychiatric or neurologic illness, generalized impulsivity and aggressiveness, history of legal involvement, role of alcohol and drugs in precipitating episodes, and social impairment caused by outbursts. A rating form was devised to systematically evaluate these variables.[10,11]

Evaluation of Response

Nonblind ratings by a psychiatrist, the patient, and a family member evaluated global improvement and specific areas of drug effect, as described by Mattes et al.[11] Similar ratings were performed by a research assistant blind to drug status.

Ratings were performed after stabilization on medication in the hospital and again at follow-up. The psychiatrist made a final rating of benefit after discontinuing and restarting medication.

Statistical Analyses

The primary statistical analyses were two-way analyses of variance (ANOVAs) with drug (carbamazepine or propranolol) on one axis and the potential predictor variable on the other axis. Analyses were performed both with the randomized patients alone and including all 80 patients. Initially the ANOVAs were performed on three psychiatrist ratings: global improvement in temper at discharge and follow-up, and final rating (after medication was discontinued). The blind ratings by the research assistant were intended to confirm the nonblind psychiatrist ratings. Thus, we analyzed the blind ratings only if there was a significant ($p<.05$) difference on any of the psychiatrist ratings for that predictor variable.

RESULTS

Both medications generally were well tolerated, and patients showed no serious adverse effects. The mean ±SD dosage was 486±194 mg/day for propranolol and 860±257 mg/day for carbamazepine; the mean carbamazepine plasma level at discharge was 8.61±2.32. The patients averaged 23 days on medication while hospital-

TABLE 1. Selected significant interactions between predictor variables and carbamazepine (CMZ) or propranolol (PPL)

Predictor Variable	Outcome Variable	Without Predictor (Mean±SD) CMZ	Without Predictor (Mean±SD) PPL	With Predictor (Mean±SD) CMZ	With Predictor (Mean±SD) PPL	F	p
Diagnosis of Residual ADD	Psychiatrist discharge rating	2.79±0.63 n=28	2.46±0.93 n=11	2.39±0.92 n=18	2.95±0.62 n=19	5.97	0.017
	Final psychiatrist rating of benefit	2.46±0.69 n=28	1.91±0.83 n=11	2.05±0.71 n=19	2.21±0.71 n=19	4.22	0.044
Diagnosis of IED	Psychiatrist discharge rating	2.39±0.70 n=18	3.09±0.30 n=11	2.76±0.79 n=29	2.58±0.90 n=19	5.91	0.018
	Final psychiatrist rating of benefit	2.11±0.83 n=18	2.55±0.52 n=11	2.37±0.67 n=30	1.85±0.75 n=20	7.76	0.007
Older age at onset of temper outbursts	Final psychiatrist rating of benefit	2.07±0.68 n=27	2.20±0.70 n=20	2.52±0.75 n=21	1.89±0.78 n=9	4.63	0.035
Abnormal neuropsychological testing	Psychiatrist follow-up rating	3.17±0.41 n=6	2.40±0.84 n=10	2.74±0.62 n=23	3.00±0.00[a] n=7	6.25	0.016
Guilt for episodes	Final psychiatrist rating of benefit	2.04±0.75 n=24	2.20±0.78 n=15	2.52±0.67 n=23	2.00±0.73 n=16	4.09	0.047

Note: All ANOVAs were performed on 2×2 tables of both randomized and nonrandomized patients.
[a]SD=0.0 in this cell; given the unequal ns, the p value is probably overly liberal.

ized, and the 58 patients who continued on medication after discharge averaged another 88 days on medication.

Psychiatrist ratings were available on 98% of the 80 patients at discharge and on 76% at follow-up. Blind ratings often were missing, however, either because of difficulty in reaching the patient and a relative (by phone) or because of their refusal to cooperate. Blind ratings were obtained for only 53 patients at discharge and for 29 patients at follow-up. The psychiatrist's final rating of whether the medication was beneficial was made for all 80 patients.

Diagnoses

The *DSM-III* diagnoses (averaging 2.5 diagnoses per patient) of the 80 patients included the following: attention deficit disorder (ADD), residual type (n=38); IED (n=51); alcohol abuse (n=41); drug abuse (n=43); antisocial personality disorder (n=8); unsocialized conduct disorder (n=7); and borderline personality disorder (n=11). The first four diagnoses were sufficiently frequent to be used in subsequent two-way ANOVAs (interaction of diagnosis and medication) to identify predictors of benefit.

Patient Characteristics

The characteristics mentioned below describe our sample and, more important, served as potential predictor variables in two-way ANOVAs. For the purpose of the ANOVAs, characteristics rated on 5-point scales (or variables with three possibilities—e.g., normal, borderline, and abnormal) were generally dichotomized.

Of the 80 patients, 86% were male; mean±SD age was 24.4±8.7 years. Most (61.3%) had a childhood onset of temper difficulties; 45% had spent some time in jail; and 48% had a family history of alcoholism, ADD, or antisocial personality disorder.

Eleven patients had a history of epilepsy, and 20 patients (including nine of the 11 epileptics) had abnormal EEGs. Nine of the 20 abnormal EEGs showed focal abnormalities, eight of them temporal lobe abnormalities. Only 33.8% of patients had normal neuropsychological test results, 41.5% had borderline results, and 24.6% were clearly abnormal. Of the patients with borderline or abnormal results, 33.2% showed frontal deficits, 30.2% showed temporal deficits, 28.7% showed right-hemisphere deficits, and 16.6% showed left-hemisphere deficits. Neuropsychological test abnormalities were not more common in patients with ADD. Twenty-three percent of patients had a neurological condition—such as epilepsy (n=11), traumatic brain injury (n=4), or history of brain tumor—that was judged to be probably related to their temper outbursts, but the CAT scan was abnormal in only 8.8% of patients. Twenty-three percent of patients had histories of poor coordination.

All but five patients had histories of at least moderately severe verbal outbursts, and 61 of the 80 patients had inflicted significant injuries on others (at least significant bruising); 66 patients had perpetrated at least moderate destruction of property (e.g., smashing holes in walls).

Only five patients previously had been treated pharmacologically specifically for their temper outbursts, except for occasional, as needed, use of neuroleptics or sedatives during an outburst; none of these five patients had re-

ceived good trials (i.e., adequate dose and duration).

Other characteristics rated on a 5-point scale (0=none, 1=just a little, 2=a fair amount, 3=considerable, 4=very much) were as follows. Only 3.7% of patients were rated as showing "considerable" or more amnesia, and only 28.4% reported little or no guilt. Most patients (67%) reported an abrupt onset of their episodes, 23.2% had considerable generalized aggressiveness between episodes, 82.5% could have outbursts with "just a little" provocation, and 89% reported considerable impairment in social relationships because of their temper problems. Thirty-eight percent reported that alcohol had more than "just a little" role in precipitating their episodes, although in no case did outbursts occur only under the influence of alcohol.

Overall Outcome

All ratings except the final psychiatrist rating were on a 5-point (0 to 4) scale in which 2 represented mildly improved and 3 represented much improved. Most of the mean ratings were between 2.0 and 3.0 on both medications for both psychiatrist and blind ratings (see table 1), indicating benefit for most patients. The final psychiatrist rating was on a 3-point rating scale in which 1 represented no help, 2 represented some benefit, and 3 represented considerable benefit. The mean±SD for the carbamazepine and propranolol groups were 2.46±1.27 and 2.30±1.54, respectively, also indicating benefit for most patients.

Psychiatrist ratings of severity of outbursts showed a corresponding improvement. For example, the mean severity rating at baseline for assaultiveness was 2.56 on a 5-point (0 to 4) scale in which 2 stood for mild assaultiveness (punching or slapping but no significant bruising) and 3 stood for moderate assaultiveness (significant bruising but no hospitalization required). The mean rating at follow-up was only .38. There were no overall differences between carbamazepine and propranolol.

Of the 42 patients who had been helped by medication in the hospital, who had continued into the follow-up phase, and whose medication was discontinued, 24 relapsed (eight on propranolol and 16 on carbamazepine). Of interest, 17 patients (eight on propranolol and nine on carbamazepine) seemed to have been helped by medication when first given it but did not relapse when the medication was discontinued (so it was not restarted). Only 16 of the 80 patients were still on medication at the time of the final follow-up. For an additional 21 patients, the psychiatrist felt that the benefit warranted continuing the medication, but the patient or family refused.

All patients with epilepsy received carbamazepine, so whether or not epilepsy predicted preferential response to carbamazepine could not be evaluated. However, the presence of epilepsy tended ($p=.072$) to predict a good response to carbamazepine, in terms of reducing aggressiveness. Sixty-three percent of epileptics were "definitely helped" by carbamazepine on the final psychiatrist rating, compared with 34% of nonepileptics.

Predictors of Differential Benefit

We performed a total of 236 ANOVAs (as described above). Of these, only 10 showed a main effect for the predictor variable, but—of primary interest—24 had significant interactions, indicating differential benefit for carbamazepine and propranolol. By chance, one would expect considerably fewer (only 11.7) significant interactions. Of the significant interactions, some may be chance findings. Therefore, the results presented below focus on predictor variables that led to at least two significant interactions and for which the nonsignificant interactions still were generally in the same direction.

It is important to note, however, that the significant interactions were found mainly on the psychiatrist ratings on the total sample (including both randomized and nonrandomized patients). When the sample size was reduced, either by including only randomized patients or by analyzing blind ratings, statistical significance generally was lost, although the results in most cases were in the same direction as the significant findings.

As indicated in table 1, there were two significant ($p<.05$) interactions between the diagnosis of residual ADD and outcome; these indicated that patients with residual ADD tended to do better on propranolol, whereas other patients tended to do better on carbamazepine.

Possibly related to this, there were two significant interactions between the diagnosis of IED and outcome (see table 1): Patients with IED did significantly better on carbamazepine, whereas other patients did better on propranolol.

Age of onset also predicted differential benefit (table 1), which was significant at $p=.03$ on the psychiatrist's final rating on the total sample, and almost significant ($p=.058$) on the psychiatrist's discharge rating on the total sample. Not surprisingly (because ADD has a childhood onset), patients with onset in childhood did better on propranolol. Also consistent with the impression that IED predicted superior benefit on carbamazepine, one significant interaction suggested that patients with more guilt did better on carbamazepine; more guilt, as expected, was more common in patients with IED. Consistent with the impression that ADD predicted superior benefit on propranolol, patients with poor coordination (possibly associated with ADD) did better on propranolol (although significant only on the blind ratings). Poor coordination also had a significant main effect, statisti-

cally significant ($p<.05$) in six of the 10 analyses, indicating that poor coordination predicted more benefit from either medication. Of unclear relevance to the ADD-IED distinction—because abnormal neuropsychological tests were not more common among patients with ADD—one significant ANOVA indicated that patients with abnormal neuropsychological test results did better on propranolol.

Concomitant Medication

Concomitant medication was restricted as much as possible, but some of the patients had a treating psychiatrist in addition to the research psychiatrist, who made the final decision about concomitant medications. A total of 30 patients received at least one dose of a concomitant medication at some time during this study, but this use was restricted and did not obscure the effect of carbamazepine or propranolol.

A number of patients were on a small dose of a neuroleptic or an antidepressant when they were referred for this study, and although none of these patients met current criteria for major depression, and none were schizophrenic, the treating psychiatrist in some cases was reluctant to discontinue the prior medication before beginning carbamazepine or propranolol. Therefore, as long as the concomitant medication was at a stable dosage, and the patient clearly was not responding sufficiently to it (i.e., the patient continued to have temper difficulties despite the other medication), the patient was entered into the study and treated with propranolol or carbamazepine.

In addition, a number of patients rarely (less than once per week) received an as-needed medication, either a neuroleptic or a minor tranquilizer, during an acute outburst. In these instances it was apparent that the study medication was not adequate, so the use of this as-needed medication did not obscure carbamazepine's or propranolol's effect.

Of the 30 patients who received concomitant medication during this study, 16 received neuroleptics, six received antidepressants, three received anticonvulsants, and five received other medications.

DISCUSSION

Overall, the results of this study are not definitive. Because there was no placebo group, one cannot conclude from these data that either carbamazepine or propranolol is definitely beneficial. To some extent, however, we achieved our goal of identifying predictors of differential benefit, in that the ANOVAs resulted in more significant interactions than would be expected by chance. But the fact that the significant interactions were evident primarily on the psychiatrists' ratings and on the analyses involving the total number of final subjects, including both randomized and nonrandomized patients, strongly indicates that these results must be considered as suggestive only and require confirmation. On the other hand, the theoretical consistency of the significant results is noteworthy: Variables associated with attention deficit disorder predicted superior improvement on propranolol, and variables associated with intermittent explosive disorder predicted benefit on carbamazepine.

The fact that the significant psychiatrist ratings were not confirmed by the blind ratings seems partly to have been caused by the smaller number of blind ratings caused by missing data. In addition, the psychiatrists were treating the patients clinically and inevitably obtained more information, both from other clinical staff and from relatives, than a blind rater could obtain.

These findings interdigitate relatively well with previous studies, in that one of the largest studies reporting benefit from propranolol for temper outbursts[10] involved a sample of which 83% had attention deficit disorder. Also, carbamazepine has been used primarily in patients with seizures or EEG abnormalities, and IED, as mentioned previously,[4] may be etiologically related to a seizure disorder. (In the present study, diagnosis of epilepsy and an abnormal EEG did not significantly predict benefit from carbamazepine, although results were in the expected direction.) The efficacy of carbamazepine for rage outbursts therefore may be related to its anticonvulsant activity.

The fact that several patients who appeared to respond to propranolol or carbamazepine did not relapse after discontinuation is of interest. Of course, they may not have relapsed because the medication had not helped them in the first place and because their improvement was the product of other therapies administered in the hospital. Another possibility is that the patients' behavior was shaped by the positive reinforcement received from not having temper outbursts, so that the medication, although helpful initially, became unnecessary. It may be relevant to note that propranolol's antimigraine effect may persist for at least several months after the drug is discontinued,[12] and studies reviewed by Post et al.,[13] including studies inducing epilepsy in monkeys with aluminum hydroxide paste, indicate that carbamazepine's anticonvulsant effect may persist after discontinuation of the drug. These results suggest that additional studies probably should not use a crossover design.

The equivocal nature of the current results make further speculation premature. Possible mechanisms of action for carbamazepine and propranolol in the treatment of rage outbursts have been discussed previously.[1]

Data from this study are relevant to a controversy regarding DSM-IV—specifically, whether all IED has an underlying organic etiology (Wise M, personal communication, 1989). Of our patients with IED, only four were entirely free of any evidence of organicity, based on history, neuropsychological testing, EEG, and CAT scan. However, an additional five patients were free of evidence of organicity except for borderline abnormalities on neuropsychological testing, and another patient had only borderline abnormal neuropsychological testing and a borderline abnormal EEG. Thus, many patients with IED do have evidence of organicity, but a minority do not.

In summary, this study suggests that both propranolol and carbamazepine may be helpful for patients with temper outbursts, and that propranolol may be preferable for patients with histories of attention deficit disorder, whereas carbamazepine might be preferable for patients with intermittent explosive disorder. Further work is clearly needed to substantiate these impressions.

Portions of this paper were presented at the annual meeting of the New Clinical Drug Evaluation Unit, held May 25–28, 1987, in Key Biscayne, Florida.

This research was supported in part by the Carrier Foundation. The author thanks the Carrier Foundation Research Division—particularly Craig Marsters and Sarah Robin for collection and analysis of the data—and Jean Balcom and Carol LaBracio for technical assistance.

References

1. Mattes J: Psychopharmacology of temper outbursts: a review. J Nerv Ment Dis 1986; 174:464–470
2. Stone JL, McDaniel KD, Hughes JR, et al: Episodic dyscontrol disorder and paroxysmal EEG abnormalities: successful treatment with carbamazepine. Biol Psychiatry 1986; 21:208–212
3. Reynold EH: The pharmacological management of epilepsy associated with psychological disorders. Br J Psychiatry 1982; 141:549–557
4. Mark V, Ervin F: Violence and the Brain. New York, Harper & Row, 1970
5. Elliott FA: Propranolol for the control of belligerent behavior following acute brain damage. Ann Neurol 1977; 1:489–491
6. Ratey JJ, Mikkelsen EJ, Bushnell S, et al: Beta blockers in the severely and profoundly mentally retarded. J Clin Psychopharmacol 1986; 6:103–107
7. Greendyke RM, Kanter DR, Schuster DB, et al: Propranolol treatment of assaultive patients with organic brain disease. J Nerv Ment Dis 1986; 174:290–294
8. Kuperman S, Steward MA: Use of propranolol to decrease aggressive outbursts in younger patients. Psychosomatics 1987; 28:315–319
9. Mattes JA: Carbamazepine vs. propranolol for rage outbursts. Psychopharm Bull 1988; 24:179–182
10. Williams DT, Mele R, Yudofsky S, et al: The effects of propranolol on uncontrolled rage outbursts in children and adolescents with organic brain dysfunction. Journal of the American Academy of Child Psychiatry 1982; 21:129–135
11. Mattes JA, Rosenberg J, Mayes D: Carbamazepine vs. propranolol in patients with uncontrolled rage outbursts: a random assignment study. Psychopharmacol Bull 1984; 20:98–100
12. Diamond S, Kudrow L, Stevens J, et al: Long-term study of propranolol in the treatment of migraine. Headache 1982; 22:268–271
13. Post RM, Ballenger JC, Uhde TW, et al: Efficacy of carbamazepine in manic-depressive illness, in Neurobiology of Mood Disorder. Edited by Post RM, Ballenger, JC. Baltimore, Williams & Wilkins, 1984, pp 777–816