Seizure 2000; **9**: 537–543
doi:10.1053/seiz.2000.0447, available online at http://www.idealibrary.com on IDEAL®

A placebo-controlled, double-blind cross-over trial of adjunctive one month remacemide hydrochloride treatment in patients with refractory epilepsy

A. RICHENS[†], G. MAWER[‡], P. CRAWFORD[§] & B. HARRISON[¶]

[†]*University of Wales, College of Medicine, Cardiff CF4 4XN, UK;* [‡]*David Lewis Centre, Alderley Edge, Cheshire SK9 7UD, UK;* [§]*York District Hospital, York Y03 7HE, UK;* [¶]*Astra Charnwood, Loughborough, Leicestershire LE11 5RH, UK*

Correspondence to: Professor A. Richens, University of Wales, College of Medicine, Cardiff CF4 4XN, UK

The efficacy, safety and pharmacokinetics of adjunctive remacemide hydrochloride, a novel, low-affinity non-competitive NMDA receptor channel blocker, were investigated in 28 adult patients with refractory epilepsy. This was a randomized double-blind placebo-controlled cross-over study with five 4-week periods (baseline, treatment 1, washout, treatment 2, washout).

Baseline median seizure frequency was reduced by 33% following adjunctive remacemide hydrochloride 150 mg q.i.d. for 4 weeks compared with placebo ($P = 0.041$). Seizure frequency was reduced by $\geq$50% in 30% of patients treated with remacemide hydrochloride compared with 9% on placebo. Mean plasma concentration of concomitant carbamazepine increased by approximately 15% following adjunctive remacemide hydrochloride. There was no correlation between increased plasma carbamazepine and reduced seizure frequency.

Remacemide hydrochloride was well tolerated and only three patients withdrew due to adverse events (two remacemide hydrochloride, one placebo). Two patients died unexpectedly from their epilepsy during placebo treatment; both deaths were considered by the investigators to be unrelated to earlier remacemide hydrochloride treatment.

This first specific efficacy investigation with adjunctive remacemide hydrochloride demonstrated anticonvulsant effects in patients with refractory epilepsy. More extensive clinical investigation is justified.

Key words: clinical trials; remacemide; antiepileptic drugs; add-on therapy; seizures.

INTRODUCTION

Remacemide hydrochloride is currently in development for the treatment of epilepsy. The parent molecule and its active desglycinyl metabolite are non-competitive, low-affinity *N*-methyl-D-aspartic acid (NMDA) receptor channel blocking agents with additional significant sodium fast channel activity[1]. Non-competitive inhibition of NMDA receptors located within neuronal membrane calcium channels is thought to block the Ca^{2+} influx mediated by major excitatory neurotransmitters, principally glutamate and glycine. This results in reduced cortical neuronal activity and potentially, suppression of seizures. This mode of action appears to be different from other AEDs. Remacemide hydrochloride may therefore represent the first of a new class of AED.

Previous studies in volunteers and patients with epilepsy have shown remacemide hydrochloride administered in doses up to 600 mg day^{-1} to be well tolerated[2,3]. This was the first controlled study designed to evaluate the efficacy of adjunctive remacemide hydrochloride in patients with refractory epilepsy.

MATERIALS AND METHODS

Trial design, patient inclusion and exclusion criteria

This was a multicentre, placebo-controlled, randomized, cross-over comparison of remacemide hydrochloride 600 mg day^{-1} and placebo as adjunctive treatments in patients with refractory epilepsy. Following 28 days baseline evaluation, each patient was sequentially randomized to both treatments, administered as q.i.d. regimens for 28 days. Washout peri-

ods of 28 days followed each treatment period. All patients gave informed written consent to participate in the study and continued to take stabilized doses of either one or two pre-existing AEDs during the study period. Overall, the study duration was 20 weeks with patients seen every 2 weeks as outpatients.

Patients aged 18 to 65 taking optimal doses of up to two antiepileptic drugs (not including benzodiazepines given p.r.n.), who experienced at least four partial seizures per month in the 3 months prior to the study period, were eligible for inclusion. Seizures were defined in accordance with the International Classification of Seizures[4].

Patients excluded from entry included women of child-bearing potential; patients with a clinically significant medical condition other than epilepsy; patients with a history of pseudoseizures or chronic drug abuse; regular NSAID, antihistamine, sedative and tranquillizer users; clinically obese patients; and patients who had been involved in other experimental procedures in the previous 3 months.

Test treatments, concomitant AEDs and objectives

Identical remacemide hydrochloride 50 mg and placebo capsules were used in the study. Patients randomized to receive remacemide hydrochloride treatment initially received 50 mg q.i.d. on day one, 100 mg q.i.d. on day two and subsequently 150 mg q.i.d. for days 3–26 inclusive. The final 2 days of remacemide hydrochloride treatment involved a dose taper where 100 mg q.i.d. was administered on the penultimate day and 50 mg q.i.d. on the final day. In the event of any patient showing signs of intolerance to remacemide hydrochloride 150 mg q.i.d., the protocol allowed for dose reductions in 50 mg increments to 100 mg q.i.d. or 50 mg q.i.d.

To counter any potential treatment order effects, the order of treatment was randomized, resulting in two patient groups. Group A received placebo in the first double-blind period and remacemide hydrochloride in the second. Treatment order was reversed for group B.

Primary objectives of the study were:

(1) To assess the efficacy of 28 days adjunctive remacemide hydrochloride treatment (600 mg day^{-1}) in adult patients with poorly controlled partial seizures with or without secondary generalization.

(2) To assess the safety and tolerability of adjunctive remacemide hydrochloride (600 mg day^{-1}) during the study.

Table 1: Baseline demographics, seizure history and concomitant AEDs.

Number of patients		28
Age (years)	Mean	32.9
	Range	17–57
Sex	Male	26
	Female	2
Seizure type	Partial seizures only	24
	Generalized seizures only	0
	Partial and generalized seizures	4
Seizure frequency (No. per month)	Mean	19.3
	Median	9.0
	Range	3–90
Duration of epilepsy (years)	Mean	23.3
	Range	5–41
Concomitant AEDs[a] (No. of patients)	Carbamazepine	24
	Sodium valproate	8
	Phenytoin	4
	Clobazam	5
	Primidone	2
	Vigabatrin	3

[a] Twelve patients were taking one concomitant AED, 14 patients were taking two AEDs and two patients were receiving three AEDs.

Secondary objectives were:

(1) To measure the plasma concentrations of remacemide and the desglycinyl metabolite in the presence of concomitant AED medications.

(2) To assess the effects of adjunctive remacemide hydrochloride on seizure type during the study.

Patients remained on their pre-existing AED regimens of one, or maximally, two drugs (excluding benzodiazepines taken p.r.n.), if dosages had been stable over the 3 months prior to study entry. Plasma concentrations of background AEDs were monitored during the study. Details of concomitant AEDs are summarized in Table 1.

Assessments

The primary efficacy variable in this trial was total seizure frequency, defined as the total count of all seizure types during the 26-day treatment period following dose escalation. Secondary efficacy assessments undertaken included simple and complex partial seizure counts, secondarily generalized seizure counts, the number of seizure-free days and calculation of percentage seizure reduction during treatment periods compared with baseline.

Safety, tolerability and compliance with test medication were assessed at two-weekly outpatient visits, where adverse events and withdrawals were recorded and all patients received a detailed physical and neurological examination. Test medication was checked and

Table 2: Median seizure frequency during the study.

	Median for 26-day period				
	Baseline	Remacemide hydrochloride treatment	Remacemide hydrochloride washout	Placebo treatment	Placebo washout
Total seizures ($n = 23$)	9.0	6.0[a]	9.0	9.0	8.0
Simple partial ($n = 10$)	0.0	0.0	0.0	2.5	0.5
Complex partial ($n = 21$)	4.0	3.0	5.0	4.0	2.1
Secondary generalized ($n = 18$)	4.5	1.0	2.7	6.0	2.5

[a] Significant difference between remacemide hydrochloride and placebo ($P < 0.05$).

Table 3: Median seizure frequency during the first treatment period.

	Median for 26-day periods		
	Baseline	Treatment period	Change from baseline
Remacemide ($n = 11$)	14.0	7.0	−3.0[a]
Placebo ($n = 14$)	6.5	7.5	1.5

[a] Significant reduction in seizure frequency ($P < 0.05$) when compared to placebo (Mann-Whitney U-test).

counted. Blood and urine samples were taken at each visit for laboratory testing (haematology, biochemistry and urinalysis); blood samples for plasma remacemide and desglycinyl metabolite assay were also taken halfway through each double-blind study period. Patients were followed up by telephone contact 3 months after the study period to determine their health status.

Statistical analyses

Both parametric and non-parametric statistical methods were used in the analyses. Seizure frequency data were analysed using Koch's non-parametric two-period cross-over model[5] and also by direct comparison between the two treatment periods using the Wilcoxon Matched Pairs Signed Ranks Test. Median values for all seizure frequency data have been presented since the data were not normally distributed. Analysis of variance was used to analyse vital signs and laboratory data. All statistical tests were two-tailed and significance was determined by reference to the 5% level.

RESULTS

Patient demographics, seizure history and concomitant medication

Twenty-eight Caucasian patients entered treatment, 25 completed the first double-blind period, 23 completed both double-blind periods and 22 completed the study (including both washout periods). The baseline demographic profile, seizure history and concomitant AED details for entered patients are summarized in Table 1. The two treatment order groups were well matched with respect to demographic and seizure history variables.

Efficacy

Effects on total seizures

Analysis of the total seizures in the remacemide hydrochloride and placebo treatment periods, based on data from 23 patients who completed both treatment periods, showed a significant difference ($P = 0.041$) between the two treatment periods. Patients experienced fewer seizures during remacemide hydrochloride treatment (median seizure frequency 6.0) than during placebo treatment (median seizure frequency 9.0). There were no significant period or carryover effects seen in these data (Table 2). Analyses of individual seizure types in the study (simple partial, complex partial and secondary generalized seizures) showed no statistically significant differences.

An additional analysis of seizure data from the 25 patients who completed the first treatment period was also undertaken. This between-patient analysis would not be affected by any period effect influences. Patients treated with remacemide hydrochloride experienced a reduction in median seizure frequency of 3.0 seizures from baseline, compared with an increase of 1.5 with placebo (Table 3). This difference was statistically significant ($P = 0.029$).

Percentage reduction in seizure frequency

For all patients, the percentage reduction in seizure frequency from baseline for both treatments was calculated. There was a trend in favour of remacemide

hydrochloride treatment compared with placebo ($P = 0.068$). Median percentage reductions in total seizure frequency for both adjunctive treatment periods are summarized in Table 4.

The number and percentage of patients in both treatment groups who experienced ≥50%, ≥75% and 100% reductions in total seizures are summarized in Table 6. No patients were seizure free during placebo treatment but 13% were seizure free on remacemide hydrochloride.

Number of seizure-free days

More seizure-free days were recorded with remacemide hydrochloride treatment (21.3 days) than with placebo treatment (20.0 days) although the difference was not statistically significant.

Correlation between seizure frequency and carbamazepine plasma concentration

During this study increased plasma carbamazepine concentrations were observed during the remacemide hydrochloride treatment period. There was no correlation with reduction in seizure frequency, which suggests that increased plasma carbamazepine concentrations were unlikely to have contributed to the efficacy effects recorded.

Safety

Data from all 28 patients randomized to test treatment were included in the safety analyses: 27 patients received remacemide hydrochloride and 26 received placebo.

Adverse events

Twenty-eight patients reported adverse events during the study: 19 during baseline, 25 during remacemide hydrochloride treatment, 14 during remacemide hydrochloride washout, 16 during placebo treatment and 17 during placebo washout. Those adverse events reported by more than one patient in the double-blind treatment periods are detailed in Table 5.

The most common adverse event reported in the trial was headache but this occurred with similar frequency during remacemide hydrochloride and placebo treatment. Adverse events which occurred more frequently during remacemide hydrochloride treatment than during placebo treatment included dyspepsia, dizziness, abnormal gait, diplopia, abnormal vision, somnolence, chest pain and fatigue.

No patient withdrew as a result of CNS adverse events and no CNS adverse even were considered serious by the investigators. Compliance with test treatment was generally good. Five patients had their dose of remacemide hydrochloride reduced as a consequence of adverse events compared with two patients on placebo treatment.

The chest pains experienced by three patients on remacemide hydrochloride treatment and two patients during placebo washout were investigated further. ECG examination was unremarkable and the events were not considered to be cardiac in origin or serious.

Seven of the 23 patients (30.4%) who completed both double-blind treatment periods experienced an increase in seizure frequency during remacemide hydrochloride treatment compared with baseline. Increased seizure frequency, however, was more prevalent in the other four phases of the study: 14 patients (60.8%) had increased seizures during remacemide hydrochloride washout; 12 patients (52%) during placebo and nine (39%) during placebo washout, compared with baseline. These observations suggest adjunctive remacemide hydrochloride treatment is unlikely to have any significant pro-convulsive effects.

Serious adverse events and withdrawals

Two patients died during the study. One patient was found dead in bed after 14 days of placebo treatment and 46 days after completing remacemide hydrochloride treatment. Post-mortem examination revealed no unusual findings and cause of death was given as epilepsy. The second patient was found dead whilst mowing his lawn after 28 days of placebo treatment and 56 days after completing remacemide hydrochloride treatment. Post-mortem cause of death was given as status epilepticus with the antecedent cause as an old subdural abscess. Both deaths were considered to be unrelated to remacemide hydrochloride treatment.

A further five patients experienced other serious adverse events during the study. Two patients were hospitalized for seizures whilst receiving placebo. One patient receiving remacemide felt that a capsule of study drug had lodged in his throat and was admitted to hospital with chest pain and dysphagia. Another patient was admitted to hospital due to a prolonged seizure while taking remacemide. Both of these events were considered by the investigator to be possibly related to study treatment. Another patient became unsteady and drowsy and had double vision after 5 days of treatment with remacemide hydrochloride. The investigator considered this event was probably related to study treatment.

In addition to the two deaths, three patients discontinued the study due to adverse events. During the remacemide hydrochloride treatment period, one patient withdrew due to oesophageal pain and dysphagia and another withdrew due to abdominal pain. During the placebo treatment period, one patient withdrew due to abdominal pain and headache.

Table 4: Summary of median percentage reductions in total seizure frequency.

	Remacemide hydrochloride treatment	Remacemide hydrochloride washout	Placebo treatment	Placebo washout
All patients ($n = 23$)	20.0	−11.1	−16.7	0.0

Negative percentages indicate an increase in seizure frequency.

Table 5: Numbers (and percentage) of patients reporting adverse events.

Preferred term		Remacemide hydrochloride ($n = 27$)	Placebo ($n = 26$)
GI disorders	Nausea	3 (11.1%)	3 (11.4%)
	Vomiting	1 (3.7%)	2 (7.7%)
	Dyspepsia	3 (11.1%)	0
	Abdominal pain	2 (7.4%)	1 (3.8%)
CNS disorders	Headache	8 (29.6%)	7 (26.9%)
	Dizziness	5 (18.5%)	1 (3.8%)
	Gait abnormality	3 (11.1%)	0
Vision disorders	Diplopia	5 (18.5%)	1 (3.8%)
	Vision abnormal	4 (14.8%)	1 (3.8%)
Psychiatric disorders	Somnolence	6 (22.2%)	3 (11.4%)
Body as a whole	Back pain	2 (7.4%)	0
	Chest pain	3 (11.1%)	0
	Chest pain substernal	2 (7.4%)	0
	Death	0	2 (7.7%)
	Fatigue	4 (14.8%)	1 (3.8%)

Table 6: Number (and percentage) of patients with a greater than 50% reduction in seizure frequency.

Extent of seizure reduction	Remacemide hydrochloride $n = 23$	Placebo $n = 23$
≥50% Reduction	7 (30.4%)	2 (8.7%)
≥75% Reduction	6 (26.1%)	1 (4.3%)
100% Reduction	3 (13%)	0 (0%)

Laboratory data

There were no clinically significant changes in mean values for haematological variables between the two double-blind treatment periods. Six patients had reduced white cell counts during the study; these events were attributed to concomitant carbamazepine use. There were no further white cell decreases during remacemide hydrochloride treatment.

Clinical chemistry was generally unremarkable. Individual patient analyses revealed a number of out-of-range values during the study for sodium, potassium, urea, ALT, gamma GT, and ALP. Hepatic enzyme induction secondary to concomitant AED medication is the most probable explanation for the observed raised liver enzymes. There was no evidence of further hepatic enzyme elevation in the presence of remacemide hydrochloride or increased frequency of abnormal laboratory assessments during treatment with remacemide hydrochloride. Urinalysis was unremarkable.

Vital signs, physical and neurological examinations

No significant differences were recorded between the two treatment periods for vital signs, including systolic and diastolic blood pressure, heart rate, ECG examination, respiratory rate and temperature. Physical examinations throughout the study showed no emergence of any new physical abnormality arising as a consequence of test treatments. Neurological assessment revealed no new abnormal findings.

Pharmacokinetics

Remacemide and desglycinyl metabolite

Steady-state plasma concentrations of remacemide, measured at mid-point during the double-blind treatment periods, ranged from 22.9 to 233 μg l^{-1} at 13 hours post-dose and 3.2 hours post-dose, respectively. The terminal half-life for remacemide is approximately 3–4 hours, so variation in plasma remacemide concentrations is largely explained by individual differences in the timing of blood samples taken.

Measurement of the desglycinyl metabolite was not possible from all blood samples due to the assay method's limit of quantification (10 μg l^{-1}). Where the desglycinyl metabolite could be quantified, plasma concentrations ranged from 12.8 μg l^{-1} (4 hours post-dose) to 60.9 μg l^{-1} (2.1 hours post-dose). Less variation in metabolite concentrations, compared with the parent drug, was expected due to the longer terminal half-life and the flat steady-state profile of the desglycinyl metabolite[3].

Concomitant AEDs

Two patients were taking only sodium valproate, while all other patients were receiving enzyme-inducing AEDs. Carbamazepine was the most widely administered concomitant AED during the study (24 patients). Analysis of carbamazepine concentrations, determined during different phases of the study, identified a significantly higher mean plasma carbamazepine concentration of 12.3 mg l^{-1} during remacemide hydrochloride treatment compared with 10.7 mg l^{-1}during placebo treatment. Plasma concentrations of carbamazepine were therefore increased by approximately 15% in the presence of adjunctive remacemide hydrochloride treatment.

DISCUSSION

This study demonstrated that adjunctive remacemide hydrochloride, administered as 150 mg q.i.d. for 4 weeks, was effective to a statistically and clinically significant extent in a small population of adult patients with epilepsy refractory to long-term treatment with conventional AEDs. Although treatment duration was short and the study population small, the response rate to remacemide hydrochloride was encouraging with median seizure frequency reduced by approximately one third in the study population. Three patients who completed both treatment periods were seizure free on remacemide hydrochloride, whereas no patient was seizure free during placebo treatment.

Adjunctive remacemide hydrochloride administered at 600 mg day^{-1} was generally well tolerated. Although all patients in the study reported adverse events, most were transient and not serious. This level of reported adverse events is not unusual in a study of this duration involving patients with refractory epilepsy taking long-standing concomitant medications. The adverse events most commonly attributed to remacemide hydrochloride treatment involved the CNS and gastrointestinal tract. Gastrointestinal intolerance was responsible for the withdrawal of two patients receiving remacemide hydrochloride, although none of the CNS adverse events led to withdrawal. Remacemide hydrochloride was not associated with any clinically significant changes in neurological function, laboratory variables or vital signs compared with placebo.

Plasma concentrations of carbamazepine were increased in the presence of remacemide hydrochloride; in this study the mean plasma carbamazepine concentration increased by approximately 15%. There was no correlation between increased carbamazepine concentrations and reduced seizure frequency in individual patients ($r = 0.18$, $P = 0.43$). The absence of any correlation provides confidence that the modest increase in plasma carbamazepine concentrations did not contribute to the observed efficacy effects in the study.

The two sudden epileptic deaths in this study occurred during placebo treatment and in both cases the investigators considered death to be unrelated to earlier exposure to remacemide hydrochloride. The phenomenon of sudden unexplained death in patients with epilepsy is widely recognized and has been reported by other investigators[6,7].

CONCLUSIONS

Remacemide hydrochloride has a novel mode of action. Low-affinity NMDA receptor blocking activity is believed to contribute to its anticonvulsant effect. Adjunctive remacemide hydrochloride administered at 600 mg day^{-1} for approximately 1 month, to patients with epilepsy refractory to pre-existing regimens of either one or two conventional AEDs, was effective in reducing seizures compared with placebo. Adjunctive remacemide hydrochloride at 600 mg day^{-1} was generally well tolerated in most patients; CNS and gastrointestinal adverse events were most frequently reported during remacemide hydrochloride treatment.

ACKNOWLEDGEMENT

The authors would like to thank Dr Stephen Clegg, the Medical Writer who assisted in the preparation of this manuscript.

REFERENCES

1. Palmer, G. C., Harris, E. W., Ray, R., Stagnitto, M. L. and Schmiesing, R. J. Classification of compounds for prevention of NMDLA-induced seizures/mortality, or maximal electroshock and pentylenetetrazol seizures in mice and antagonism of MK801 binding in vitro. *Archives Internationales de Pharmacodynamie et de Therapie* 1992; **317**: 16–34.
2. Clark, B., Hutchison, J. B., Jamieson, V., Jones, T., Palmer, G. C. and Scheyer, R. D. Potential antiepileptic drugs. Remacemide Hydrochloride. In: *Antiepileptic Drugs.* (Eds R.

H. Levy, R. H. Mattson and B. Meldrum). 4th Edition: New York, Raven Press Ltd, 1995: pp. 1035–1044.
3. Leach, J. P., Blacklaw, J., Jamieson, V., Jones, T., Richens, A. and Brodie, M. J. Mutual interaction between remacemide hydrochloride and carbamazepine two drugs with active metabolites. *Epilepsia* 1996; **37**: 1100–1106.
4. International Classification of Epileptic Seizures. *Epilepsia* 1981; **22**: 489–501.
5. Koch, G. G. The use of non-parametric methods in the statistical analysis of a two-period changeover design. *Biometrics* 1972; **5**: 577–584.
6. Leestma, J. E., Kelelkar, M. B., Teas, J. J., Jay, G. W. and Hughes, J. R. Sudden unexpected death associated with seizures. *Journal of Neurology, Neuropsychology and Psychiatry* 1984; **25**: 84–88.
7. Schaeder, P. L. and Lathers, C. M. Paroxysmal autonomic dysfunction, epileptogenic activity and sudden death. *Epilepsy Research* 1989; **3**: 55–62.