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Remacemide hydrochloride: a placebo-controlled, one month, double-blind assessment of its safety, tolerability and pharmacokinetics as adjunctive therapy in patients with epilepsy

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Forty patients (33 male, 7 female) with refractory epilepsy were randomized to receive ascending weekly doses of adjunctive remacemide hydrochloride in a b.i.d. or q.i.d. regimen, or placebo for up to 1 month. Assessments included routine physical examination and laboratory tests, recording of adverse events and seizure frequency, and neuropsychological tests. Trough plasma concentrations of concomitant AEDs were measured at weekly intervals. Trough plasma concentrations of remacemide and its desglycinyl metabolite were measured before each dose increment, and complete 24-hour profiles were measured at steady state following administration of 600 mg day^{-1} and 1200 mg day^{-1}.

A daily dose of 1200 mg was well tolerated in a q.i.d. regimen and up to 800 mg was well tolerated in a b.i.d. regimen. The most common adverse events were dizziness, diplopia, dyspepsia and abdominal pain. On some occasions, these were considered to be related to raised concentrations of concomitant AEDs. No adverse effects were observed on seizure frequency. Neuropsychology tests revealed no significant changes. Remacemide and the desglycinyl metabolite demonstrated dose proportional pharmacokinetics over the dose range tested.

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

INTRODUCTION

Remacemide hydrochloride and its principal active desglycinyl metabolite are low-affinity *N*-methyl-D-aspartic acid (NMDA) receptor channel blocking agents with additional significant sodium fast channel blocking 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. The anticonvulsant properties of remacemide hydrochloride have been demonstrated in a variety of animal models[2]. Remacemide hydrochloride may, therefore, represent the first of a new class of AED.

In a previous study in adult patients with epilepsy[3], remacemide hydrochloride capsules were generally well tolerated in doses up to 600 mg day^{-1} in a q.i.d. regimen. In addition, it was observed that the metabolism of remacemide hydrochloride was induced by co-administration of hepatic enzyme-inducing AEDs such as carbamazepine and phenytoin[4,5]. Furthermore, remacemide hydrochloride, in turn, inhibited the metabolism of some of these enzyme-inducing AEDs.

The purpose of this study was to evaluate the safety, tolerability and pharmacokinetics of ascending doses of adjunctive remacemide hydrochloride, in b.i.d. or q.i.d. regimens, compared with placebo in adult patients with refractory epilepsy.

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MATERIALS AND METHODS

Trial design, patient inclusion and exclusion criteria

This was a two-centre, double-blind, randomized, three-way parallel group comparison of adjunctive remacemide hydrochloride, administered in b.i.d. or q.i.d. regimens, and placebo, over 28 days, in patients with epilepsy. All patients gave written informed consent to participate in the trial and continued to take a fixed dose of one or two AEDs, including either carbamazepine or phenytoin, during the study period. The study was planned for a minimum of 12 patients per treatment group. A total of 45 patients were recruited at the two centres between 3 January and 27 April 1992, the last patient completing the study on 25 June 1992.

Reasons for exclusion from the study included a history of pseudoseizures, a clinically significant medical condition other than epilepsy, a history of alcohol or drug abuse, and regular use of antidepressants, tranquillizers or non-steroidal anti-inflammatory drugs. Women of child-bearing potential and patients who had received an investigational drug within 3 months prior to screening were also excluded.

Test treatments and assessments

Six tablet formulations of identical appearance were used in the study: placebo, 50 mg, 100 mg, 150 mg, 200 mg, and 300 mg remacemide (base content). All treatments were administered in a q.i.d. regimen at 08:00, 12:00, 16:00 and 20:00 hours, with patients in the remacemide hydrochloride b.i.d. treatment group receiving placebo each day at 1200 and 1600 hours to preserve blinding.

Those patients randomized to the adjunctive remacemide hydrochloride b.i.d. or q.i.d. treatment groups, initially received a single introductory dose of 200 mg on day one of the study period. Thereafter, an ascending dose schedule was followed in both groups; the daily dose was increased after 1 week at each dose level. Dosage commenced at 400 mg day^{-1} for the first week, followed by 600, 800 and 1200 mg day^{-1} during weeks 2, 3 and 4.

Patients were hospitalized 24 hours prior to receiving the first increased dose at each phase of the study, and physical examinations, neurological assessment, ECG measurement, recording of vital sign, neuropsychological testing, and blood and urine sampling for laboratory analyses were scheduled at this point. Adverse events, the nature and frequency of seizures experienced, and compliance to dosage instructions were recorded at each visit, following patient questioning and examination of patient diary cards by the investigators. Patients remained as inpatients for up to 24 hours after the first increased dose was administered, in each weekly phase.

Those patients who, in the opinion of the investigator, showed intolerance to remacemide hydrochloride during weeks 2–4 were down-titrated to a lower dose and continued at the reduced dose for the remaining study period. Any patient intolerant of the lowest dose of remacemide hydrochloride was withdrawn from the study. At the end of 4 weeks, remacemide hydrochloride treated patients were gradually withdrawn from the drug over a six-day period.

Pharmacokinetic objectives for the study were to measure the steady-state trough plasma concentrations of remacemide and the desglycinyl metabolite at each dose level, and to examine the plasma profiles over 12 hours at the 600 mg day^{-1} dose, and at the end of the highest dose used. Comparisons between the b.i.d. and q.i.d. dosing regimens could then be made. Concomitant AED plasma concentrations (carbamazepine and phenytoin) were monitored throughout the study.

Patients recorded their medication usage, adverse events and seizures on diary cards throughout the study. Seizures were classified according to the International Seizure Classification of Epilepsy as simple partial, complex partial, secondary generalized and primary generalized tonic–clonic seizures.

At screening, a physical and neurological examination was carried out, together with an ECG and vital signs measurements, and neuropsychological tests were performed. The neuropsychological tests comprised finger tapping, stroop and digit cancellation, digit span and logical memory, list learning, design recall and design learning. In addition, blood samples were taken for clinical laboratory tests and plasma concentrations of remacemide, the desglycinyl metabolite and concomitant AEDs. These measurements were repeated at periodic intervals during the study. At each study visit, adverse events were recorded following examination of the diary card and direct questioning of the patient. Compliance was assessed by examining the diary card, by patient questioning, and by tablet counts.

Any patient who withdrew from the study due to an adverse event was followed up until the event had resolved and any relationship to the study treatment was established.

Statistical methods

Both parametric (analysis of variance) and non-parametric (Kruskal–Wallis test) statistical methods were used to analyse data from the three treatment groups. All statistical tests were two-tailed and

Table 1: Baseline patient demographics and seizure history.

Patient details		Remacemide HCl b.i.d.: $n = 13$	Remacemide HCl q.i.d.: $n = 13$	Placebo group: $n = 14$
Age (years)	Mean	36.3	36.2	40.4
	Range	20–53	22–60	23–66
Sex	Male	9	12	12
	Female	4	1	2
Duration of epilepsy (years)	Mean	23.5	22.2	21.9
	Range	4–41	4–40	4–54
Types of seizure experienced:				
• Simple partial		8	4	4
• Complex partial		10	10	12
• Secondary generalized		8	8	9
• Primary generalized		1	1	2
Number of seizures during baseline 7 day period	Mean	5.1	2.8	7.8
	Range	0–17	0–17	0–62

Table 2: Summary of patient withdrawals.

Treatment group	Days on treatment	Dose at time of withdrawal	Reason for withdrawal	Relationship to test treatment
Remacemide hydrochloride b.i.d.	16	800 mg day^{-1}	Intercurrent illness; patient choked on food and required hospitalization	Unlikely
Remacemide hydrochloride b.i.d.	18	400 mg day^{-1}	Nausea despite dose reduction	Possible
Remacemide hydrochloride q.i.d.	1	400 mg day^{-1}	Low neutrophil count prior to receiving test treatment	None
Placebo	5	Placebo	Deterioration in epilepsy status	Unlikely

carried out to determine statistical significance at the 5% level. The three treatment groups were compared at baseline and at subsequent timepoints using the Mack–Skillings statistic[6] to adjust for centre differences. Where an overall significant difference between treatment groups was established, pairwise comparisons of the three treatment groups were performed using Mann–Whitney U-tests.

RESULTS

Patient entry, exposure and concomitant medications

Forty patients were randomized to receive test medication. The summary demographic profile and seizure history for patients randomized to each treatment group is presented in Table 1.

The treatment groups were comparable with respect to demographic data, seizure type and concomitant AEDs. All patients were receiving other AEDs during the study; these comprised carbamazepine (29 patients), phenytoin (17), valproate (8), vigabatrin (8), clobazam (6), lamotrigine (4), phenobarbital (3) and primidone (1).

Safety analyses

Withdrawals, dose adjustments and compliance

Four patients were withdrawn from the study; three were receiving remacemide hydrochloride, and one patient was in the placebo group. Details are summarized in Table 2.

Compliance with the test treatments was generally good. Sixteen patients who received remacemide hydrochloride and 12 patients who received placebo completed the study and received all the dose increments as specified in the protocol (Table 3). Seven patients treated with remacemide hydrochloride (five b.i.d., two q.i.d.) required dose adjustments due to intolerance during the study. Of these, two patients were reduced from 1200 to 800 mg day^{-1} in the b.i.d. treatment group and four patients were reduced from 800 to 600 mg day^{-1} (two b.i.d., two q.i.d.). A further patient in the b.i.d. treatment group was reduced from 800 to 400 mg day^{-1}. One patient remained on remacemide hydrochloride at 600 mg day^{-1} in the b.i.d. treatment group to the end of the study period due to intolerance beyond this dose. There were no major protocol violations.

Table 3: Flow chart showing progress of patients through the study.

Number of patients entered in study	45		
Number of patients excluded prior to randomization	5		
Total number of patients randomized to test treatment	40		
	Remacemide hydrochloride		Placebo
	b.i.d.	q.i.d.	
Number of patients randomized to each treatment group	13	13	14
Number of patients withdrawn	2	1	1
Number of patients completing study (receiving all doses)	6	10	12
Number of patients completing study (but on reduced dose)	5	2	1

Adverse events

Thirty eight patients (25 remacemide hydrochloride, 13 placebo) experienced adverse events during the study. The most commonly reported adverse events associated with remacemide hydrochloride were dizziness, ataxia, fatigue, diplopia, abnormal vision, abdominal pain and dyspepsia. The adverse events experienced by 10% or more of patients are listed in Table 4.

There were seven serious adverse events; five of these were experienced by patients treated with remacemide hydrochloride and two by patients in the placebo treatment group. These events resulted in hospital admission or in extension of hospitalization. Two of these events were considered by the investigator to be possibly related to study treatment; one patient in the remacemide hydrochloride q.i.d. group experienced tonic–clonic seizures 2 days after completing the treatment phase of the study and one patient in the placebo group experienced severe vomiting followed by status epilepticus. The other serious adverse events were hospitalization for physical injury following a seizure (1), post-ictal drowsiness (1), dysphagia (1) and worsening seizures (2).

Laboratory analyses: haematology, biochemistry and urinalysis

A high proportion of patients (15 remacemide hydrochloride and nine placebo) entered the study with abnormal haematological parameters, notably haematocrit and red cell count outside the normal range. These values may have been affected by pre-existing and concomitant carbamazepine treatment. No further clinically significant changes in these parameters occurred during the study.

Most patients entered the study with high plasma gamma glutamyl transpeptidase (GGT) due to pre-existing AED medication. These concentrations remained elevated, although no clinically significant changes from these baseline concentrations were observed during the study. Similarly, 50% of patients entered the study with elevated plasma cholesterol concentrations; these remained elevated throughout the study but showed no clinically significant changes from baseline throughout the study. There were increases from baseline in mean alanine amino transferase (ALT) concentrations in the remacemide hydrochloride treated patients of $2.9 \pm 4.8\ \mathrm{IU\,l^{-1}}$ whereas in the placebo group there was a decrease in mean ALT concentrations. This difference in the treatment groups was statistically significant ($P = 0.019$). In one patient the increase was considered clinically significant but it was attributed by the investigator to concomitant medication.

With the exception of one patient diagnosed with maturity onset diabetes who had marked glycosuria, urinalysis changes following the test treatments were unremarkable.

Neuropsychological tests and neurological examination

No consistent or significant effects on neuropsychological function attributable to remacemide hydrochloride or placebo treatment were detected.

Nine patients (five, remacemide hydrochloride, four placebo) entered the study with nystagmus which continued throughout the study period. Otherwise, no consistent neurological changes of clinical significance were observed in the patient population.

Physical examination and vital signs

No clinically significant changes were detected during weekly and follow-up physical examinations in any of the patients in the study. Additionally, no clinically significant differences were seen in vital signs among the three treatment groups following dosing and throughout the study.

Pharmacokinetic data

Remacemide and desglycinyl metabolite

A reasonable degree of dose proportionality for remacemide and the desglycinyl metabolite was

Table 4: Summary of numbers of patients experiencing the most common (≥10%) adverse events.

Preferred term	Remacemide hydrochloride			Placebo:
	b.i.d.: $n = 13$	q.i.d.: $n = 13$	b.i.d. and q.i.d.: $n = 26$	$n = 14$
Hypoaesthesia	1	1	2 (7.7)	2 (14.3)
Impaired concentration	0	2	2 (7.7)	3 (21.4)
Vomiting	4	0	4 (11.5)	2 (14.3)
Ataxia	2	2	4 (15.4)	0
Abnormal vision	2	3	5 (19.2)	1 (7.1)
Somnolence	1	5	6 (23.1)	5 (35.7)
Dyspepsia	3	5	8 (30.7)	1 (7.1)
Fatigue	3	5	8 (30.7)	2 (14.3)
Diplopia	4	4	8 (30.7)	2 (14.3)
Abdominal pain	6	4	10 (34.6)	3 (7.1)
Headache	7	6	13 (30.7)	7 (50)
Dizziness	8	6	14 (46.2)	3 (21.4)

apparent for area under the plasma concentration time curve over the dosing interval (AUCτ) after both b.i.d. and q.i.d. dosing. Details are summarized in Table 5.

Table 5: AUCτ determination for remacemide and desglycinyl metabolite.

Remacemide hydrochloride dose regimen	Mean and (SD) of AUCτ (ng h ml^{-1})	
	Remacemide	Desglycinyl metabolite
300 mg b.i.d. ($n = 11$)	2028 (808)	427 (270)
600 mg b.i.d. ($n = 5$)	4880 (1941)	701 (229)
150 mg q.i.d. ($n = 10$)	737 (327)	91 (46)
300 mg q.i.d. ($n = 10$)	1571 (808)	234 (123)

A similar pattern was found for C_{max} despite considerable interpatient variability. Details are summarized in Table 6.

Those patients who required a dose reduction during the study tended to be in the b.i.d. treatment group. There was no clear correlation, however, between plasma concentrations and the nature, severity or time of onset of the adverse events reported during the study.

Plasma concentrations of concomitant carbamazepine and phenytoin

Plasma concentrations were evaluated in 29 patients taking concomitant carbamazepine. Baseline plasma concentrations of carbamazepine in remacemide hydrochloride treated patients varied widely at study entry, ranging from 4.8 to 14.8 μg ml^{-1}. Both remacemide hydrochloride treated groups (b.i.d. and q.i.d.) were associated with statistically significantly increased carbamazepine plasma concentrations at the 800 mg day^{-1} dose, whereas the placebo treated patients were not. Increased plasma carbamazepine concentrations were also associated with remacemide hydrochloride at 600 mg day^{-1}, compared with placebo, but were not statistically significant.

Clinically significant increases (defined as >30%) in carbamazepine plasma concentrations were recorded in 16 of the 20 patients treated with remacemide hydrochloride and carbamazepine. The greatest individual percentage increase in plasma carbamazepine recorded was 106%. A trend was apparent where increasing doses of remacemide hydrochloride resulted in correspondingly higher plasma carbamazepine concentrations. The sample size, however, was too small to provide the basis for a formal statistical correlation analysis. In five remacemide hydrochloride treated patients the dose of concomitant carbamazepine was reduced due to symptoms of carbamazepine toxicity.

In the placebo treated group, carbamazepine plasma concentrations for most patients (two exceptions) remained within ±30% of the mean baseline value (9.9 μg ml^{-1}). Carbamazepine dose adjustments were necessary for two of these patients during the study: one patient received an increased dose of carbamazepine from 600 to 800 mg day^{-1}, and one patient was down-titrated from 1000 to 900 mg day^{-1} due to symptoms of carbamazepine toxicity.

Analysis of concomitant phenytoin plasma concentrations from 17 patients showed greater variation than with carbamazepine. No significant differences between the three treatment groups were detected, although the analysis was based on very small patient numbers. In the 10 patients who received remacemide hydrochloride and concomitant phenytoin, seven had plasma phenytoin concentrations ≥50% higher than baseline. Phenytoin dose reductions were required by two patients treated with remacemide hydrochloride compared with no phenytoin adjustments in the placebo group.

Table 6: C_{max} concentrations for remacemide and desglycinyl metabolite.

Remacemide HCl dose regimen	*n*	Remacemide mean C_{max} (range) ng ml^{-1}	Desglycinyl mean C_{max} (range) ng ml^{-1}
300 mg b.i.d.	11	785 (156–1602)	66 (21–150)
600 mg b.i.d.	5	1416 (673–2136)	87 (54–128)
150 mg q.i.d.	10	394 (108–826)	30 (13–51)
300 mg q.i.d.	10	796 (238–1695)	78 (35–117)

Table 7: Analysis of median seizure frequency (all seizures) by dose of treatment.

	Baseline	Difference from baseline					
		400 mg	600 mg	800 mg	1200 mg	Dose-titration	Follow-up
Remacemide (b.i.d.)	2.5	−0.5	0.0	0.0	−1.0	−1.0	1.0
Remacemide (q.i.d.)	1.0	0.0	0.0	1.0	0.0	1.0	0.0
Placebo	2.0	2.0	2.0	2.0	1.0	2.0	3.5
Kruskal–Wallis statistic (df.)	0.85 (2)	5.79 (2)	3.55 (2)	2.88 (2)	1.96 (2)	4.07 (2)	4.33 (2)
P-Value	0.65	0.055	0.17	0.24	0.37	0.13	0.11

Efficacy assessment

This study was primarily a safety study. Efficacy assessments based on investigation of changes in patients' seizure frequency and type of seizure experienced were included as secondary variables.

There were no statistically significant differences among the three treatment groups in total seizure frequency. Patients in the two remacemide hydrochloride treatment groups, however, had a consistently lower median seizure frequency than placebo treated patients (Table 7). This difference narrowly failed to reach 5% significance at the remacemide hydrochloride 400 mg day^{-1} dosing phase compared with placebo treatment.

No patient experienced a change in seizure type during the study; there were no statistically significant differences among the three treatment groups when the data relating to individual seizure types were examined.

Two patients, both receiving remacemide hydrochloride, experienced clinically relevant increases in seizure frequency during the study: one experienced an increase in seizure frequency which was attributed by the investigator to a reduction in phenytoin dose. This patient had reported symptoms of phenytoin toxicity earlier in the study and the dose of concomitant phenytoin had been reduced. The second patient had an increase in seizures during the withdrawal phase.

DISCUSSION

This study established that remacemide hydrochloride was generally well tolerated in ascending q.i.d. doses to 1200 mg day^{-1} and b.i.d. doses to 800 mg day^{-1}, as adjunctive therapy to either carbamazepine or phenytoin. On the basis of the clinical observations and safety data provided by this study, it is recommended that future efficacy or definitive dose ranging studies adopt adjunctive doses of 800 mg day^{-1} b.i.d. or 1200 mg day^{-1} q.i.d.

Four patients were withdrawn from the study due to adverse events. Of the three withdrawn patients treated with remacemide hydrochloride, two withdrawals were considered by the investigator to be unrelated to the study treatment. These events were dysphagia resulting from choking on a piece of food and granulocytopenia; the granulocytopenia was present at baseline and the patient had been entered in error. The third remacemide hydrochloride treated patient who withdrew due to an adverse event experienced nausea which was considered by the investigator to be possibly related to study treatment.

Of the seven adverse events classified as serious, only one event, a seizure during the withdrawal phase, was considered by the investigator to be possibly related to the study treatment. Analysis of the non-serious adverse events revealed that patients treated with remacemide hydrochloride experienced more CNS and gastrointestinal events than placebo treated patients. The level of reporting of these adverse events escalated with increasing doses of remacemide hydrochloride and as the plasma concentrations of remacemide and the desglycinyl metabolite increased.

Those patients who required a dose reduction of remacemide hydrochloride had the highest peak plasma concentrations of remacemide and desglycinyl metabolite. Despite large interpatient variability, remacemide and its desglycinyl metabolite fol-

lowed predictable pharmacokinetics across the dose range and regimens evaluated in this study. Dose reduction was a more frequent requirement in the b.i.d. group than in the q.i.d. group.

Neuropsychological testing did not reveal any consistent effects of remacemide hydrochloride on cognitive or psychomotor functions. Physical examination, vital signs and neurological tests were also clinically unremarkable during the study and at follow-up.

The plasma concentrations of concomitant carbamazepine and phenytoin increased to a clinically significant, but variable, extent in the presence of adjunctive remacemide hydrochloride treatment. This interaction probably contributed to the reported adverse event profile in the study. Diplopia, in most cases, was attributed by investigators to concomitant carbamazepine.

This study was not powered to assess the effects of remacemide hydrochloride on seizure activity. However, fewer seizures were seen in the remacemide hydrochloride treatment groups compared with placebo, although a statistically significant, overall difference was not achieved among these groups. No adverse effects on seizure frequency or type were observed in any of the remacemide hydrochloride treated patients.

CONCLUSIONS

Maximum well tolerated daily dosing regimens (300 mg q.i.d. and 400 mg b.i.d.) for adjunctive remacemide hydrochloride were determined for further evaluation in longer term efficacy and safety studies. Carbamazepine and phenytoin should be monitored when co-administered with remacemide hydrochloride in future trials. Such precautionary measures will help prevent incorrectly attributing efficacy or toxicity to remacemide hydrochloride when elevated plasma concentrations of concomitant AEDs are a confounding factor. Remacemide hydrochloride, in common with other anticonvulsant drugs, should be withdrawn gradually to prevent the possibility of rebound seizures occurring.

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