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REVIEW

REMACEMIDE – A NOVEL POTENTIAL ANTIEPILEPTIC DRUG

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Remacemide – a novel potential antiepileptic drug. R. MAŁEK, K.K. BOROWICZ, Ż. KIMBER-TROJNAR, G. SOBIESZEK, B. PISKORSKA, S.J. CZUCZWAR. Pol. J. Pharmacol., 2003, 55, 691–698.

Epilepsy belongs to common diseases of the brain. It affects approximately 1% of the population. The aim of epilepsy therapy is to keep the patient free of seizures without interfering with normal brain function. Unfortunately, about 30% of all epilepsies remain without control. In this situation patients require polytherapy which is usually a combination of antiepileptic drugs (AEDs) acting *via* different mechanisms of action. Many potential AEDs have been developed but the proportion of patients failing to respond to drug treatment has not been fundamentally changed. The aim of this review was to assemble current literature data on remacemide, a novel AED, which is suggested for the treatment of epilepsy. Remacemide hydrochloride is a low-affinity NMDA receptor blocker as well as Na^+ fast-channel blocker. The drug exerts anticonvulsant activity both in various animal seizure models and in clinical studies. In addition to its antiseizure properties, the drug seems to provide neuroprotection. Remacemide holds promise to serve as neuroprotectant not only in seizures but perhaps in other neurodegenerative conditions in humans as well.

Key words: *remacemide, antiepileptic drugs, seizures, refractory epilepsy, neuroprotection*

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Abbreviations: AEDs – *antiepileptic drugs,* Co Q10 – *coenzyme Q10,* CYP_{450} – *cytochrome P450,* HD – *Huntington's disease,* MES – *maximal electroshock,* NMDA – *N-methyl-D-aspartate,* PD – *Parkinson's disease,* PTZ – *pentetrazole*

Introduction

Epilepsy is one of the most common diseases of the brain, which has chronic and sometimes progressive character with periodic and unpredictable occurrence of seizures [31]. It affects approximately 1% of the population. The aim of therapy with an antiepileptic drug (AED) is to keep the patient free of seizures without interfering with normal brain function. There has been a progress in the pharmacotherapy of epilepsy, including the introduction of various new AEDs and improved formulations of older drugs [3, 34]. As monotherapy is not sufficient in one third of all epileptic patients [25], second drug is usually used as an alternative to monotherapy. When this option is still unsuccessful, polytherapy is another choice [15]. The most successful polytherapy involves the use of AEDs acting *via* different mechanisms of action. This situation requires combinations of conventional with novel AEDs. The application of two drugs as a combined therapy is considered as rational polytherapy when toxic interaction between the two AEDs is infra-additive with the simultaneous additive antiepileptic interaction or when the toxicity is additive with the supra-additive antiepileptic interaction. Unfortunately, even this procedure does not guarantee a full success. In spite of adequate AED therapy, seizures remain uncontrolled in at least 30% of all patients with epilepsy. Neurodegeneration may contribute to decreased long-term efficacy of AEDs [60]. The refractory epilepsy seems to be a multifactorial process [32]. In response to this problem, many potential new drugs are being developed particularly as adjuvants. Nevertheless, the proportion of patients failing to respond to drug treatment has not been fundamentally changed. [32]. New AEDs with better safety, lesser toxicity, and higher efficacy are still needed. Remacemide appears to be one of them. The aim of this review was to assemble current literature data on this drug.

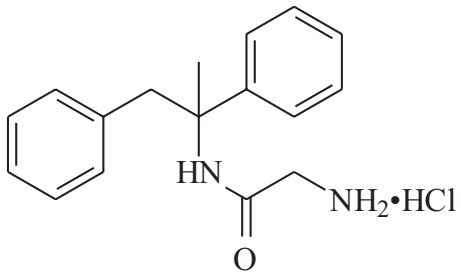
Structure of the drug

Remacemide hydrochloride [(±)-2-amino-N-(1-methyl-1,2-diphenylethyl)-acetamide monohydrate] (Fig. 1) is a racemate. The two enantiomers R(+) and S(–) have been isolated for preclinical testing in pharmacological models. The (–) isomer turned out to be more potent than (+) isomer in maximal electroshock (MES) test in mice [42]. Remacemide has nine identified and five putative metabolites [41]. The major route of metabolism of remacemide involves desglycination. The more active metabolite desglycinyl-remacemide [(±)-1-methyl-1,2-diphenylethylamine] is the result of this alteration. Desglycinyl-remacemide has higher brain concentration and longer elimination half-life (11–19 h vs. 3–4 h) than the parent compound [11, 48, 50, 56]. According to Santangeli et al. [50], there is a rapid conversion to desglycinyl-remacemide after administration of remacemide. Remacemide is believed to exert its effects, at least partially, *via* its desglycinyl metabolite [30]. There is even a strong suggestion that anticonvulsive properties of remacemide are mainly due to activity of desglycinyl-remacemide [49].

Mechanisms of action

Remacemide and its principal active desglycinyl metabolite have dual mechanism of the anticonvulsant action. They are low-affinity N-methyl-D-aspartate (NMDA) receptor blockers [41, 59], and both remacemide and its metabolite have been shown to be potent Na^+ fast-channel blockers [6, 35, 38, 51, 62]. It is likely that synergism between these two actions occur. A possible partial blockade of potassium channels has also been considered [38].

A number of studies reported the influence of remacemide and desglycinyl metabolite on NMDA receptor, which is a subtype of ionotropic glutamate receptors. Both compounds displaced [^{3}H]dizocilpine binding from rat brain homogenates, which



Remacemide

Fig. 1.

suggests the interaction with the NMDA receptor ion channel complex [41]. In cultured rat hippocampal neurons, remacemide and metabolite its inhibited NMDA-evoked currents [59]. In comparison with competitive NMDA blockers, uncompetitive ones (such as remacemide) show better therapeutic indices, which seem to be due to strong voltage dependency and rapid blocking kinetics [43].

Several electrophysiological studies reported use- and voltage-dependent blockade of Na^+ channels. Remacemide and its metabolite inhibited the sustained repetitive firing in rat hippocampal slices [38] as well as in cultured mouse spinal cord neurons [62], which is indicative of partial blockade of voltage-sensitive Na^+ channels. In rat cortical synaptosomes remacemide and desglycinyl-remacemide reduced veratridine-stimulated Na^+ influx to 30.7% and 13.2% of control, respectively. Furthermore, desglycinyl-remacemide (1 and 10 μM) significantly increased or (1000 μM) significantly decreased resting Na^+ concentration. Santangeli et al. [51] suggested that the action of desglycinyl-remacemide *via* an unidentified ion transport system might account for this influence on resting internal Na^+ concentration but this assumption needs further investigation.

Desglycinyl-remacemide is a two-fold more potent Na^+ channel blocker and a 100-fold more potent non-competitive NMDA channel antagonist [11, 14, 41, 51, 56, 59, 62] and exhibits a greater efficacy than remacemide itself in a variety of animal seizure models [41]. There is even a hypothesis that without the conversion to its desglycinyl-derivative, remacemide would be rather poor anticonvulsant agent [7, 49]. Thus, remacemide can be unhesitatingly considered as a prodrug.

Remacemide has been tested for its effectiveness in the treatment of epilepsy. Owing to its reported cerebroprotectant properties, studies have also been conducted in other indications including Parkinson's disease [PD] and Huntington's disease [HD]. Expectedly, NMDA-blocking mechanism may contribute to this activity [2].

Toxicology

Both remacemide and desglycinyl-remacemide demonstrate no sedative effect. Stagnitto et al. [58] concluded in their study that remacemide was devoid of central depressant-hypnotic action in mice. Preclinical studies suggest a low level of toxicity of remacemide. This is probably due to its low affinity for the NMDA receptor [14]. There were, however, reports on dose-related impaired neurological and motor function in rats as well as emesis and occasional seizures in dogs. Remacemide seems to be safe in terms of teratogenicity and genotoxicity in animals [6]. Popke et al. [45] assessed the potential toxicity of remacemide in juvenile rhesus monkeys. The drug was well tolerated and produced no treatment-related effects during two years of dosing and observation.

Efficacy and tolerability

Remacemide is absorbed rapidly from the gastrointestinal tract [14]. It reaches the peak concentration within 0.5–1 h, whereas it takes 2–3 h for desglycinyl-remacemide to reach its maximum level. The parent drug has a relatively short half-life of 3–4 h compared with 12–15 h for the metabolite [36]. Both compounds exhibit linear pharmacokinetics.

Generally, remacemide has been well tolerated in humans [10, 22]. Adverse experiences are dose-dependent and affect mostly the gastrointestinal system (nausea, vomiting, dyspepsia and abdominal pain) and the central nervous system (dizziness, fatigue, somnolence and diplopia). The study by Besag et al. [5] showed that the pharmacokinetic profiles of remacemide and desglycinyl-remacemide as well as adverse effects in children are similar to those reported in adults.

Remacemide also turned out not to affect driving performance, unlike carbamazepine, which can produce mild but sufficient impairment putting epileptic patients at risk when driving [46].

Drug interactions

In interaction studies, remacemide increases both carbamazepine and diphenylhydantoin blood levels in co-medicated patients. These changes are explained on the basis of interactions at the cytochrome P450 (CYP_{450}) level. Conversely, the induction of hepatic enzymes reduces the brain concentration of both remacemide and desglycinyl-remacemide but the latter is more susceptible to this process [26, 28, 56]. The decrease in concentrations of remacemide and its metabolite amounts to 25–50% and 65–75%, respectively [63]. Sills et al. [56] reported that pre-treatment with phenobarbital, which is connected with CYP_{450} induction,

decreased brain concentrations of remacemide and desglycinyl-remacemide in mice and, thus, attenuated anticonvulsant activity of remacemide in MES test.

Administration of remacemide increases carbamazepine and diphenylhydantoin blood levels in co-medicated patients [28, 47]. Leach et al. [26, 28] reported that remacemide inhibited carbamazepine and diphenylhydantoin metabolism, which induced that of remacemide and its active metabolite but apparently this mutual interaction is predictable and should not limit their clinical use in combination. Chadwick et al. [10] as well as Jones et al. [22] showed in their trials that plasma concentrations of carbamazepine and diphenylhydantoin were well controlled during add-on therapy with remacemide and remained within target ranges. Leach et al. [27] in their study conducted in epileptic patients showed that remacemide did not interfere with the pharmacokinetics of valproate and *vice versa*.

Activity profile in seizure models

Remacemide was originally targeted for generalized tonic/clonic seizures and complex partial epilepsy [41]. The studies have confirmed that remacemide exhibits efficacy against MES-induced seizures [18, 41, 58]. Stagnitto et al. [58] reported that the therapeutic indices of orally administered remacemide in MES test in mice seemed to be more favorable than valproate, phenobarbital or carbamazepine. Interestingly, the potency of remacemide in MES test in mice was lower than that found after administration of the (–) stereoisomer but higher than for the (+) stereoisomer [42]. In contrast, in MES test in rats Garske et al. [18] observed equal potency of remacemide and the (–) stereoisomer, while the (+) stereoisomer was still less potent. The duration of protection against MES, after oral administration of remacemide, is dose-dependent and longer than carbamazepine and valproate but shorter than diphenylphenytoin or phenobarbital. This protection is rapidly attenuated and not present by 3 h [58].

Remacemide also proved to be efficacious in seizures induced by NMDA, kainic acid, electrical kindling and 4-aminopyridine [12, 18, 40]. In cocaine-induced convulsions remacemide produced dose-dependent protection [19]. The compound also inhibited convulsions in mice prone to audiogenic seizures [11, 37, 58]. Remacemide and its metabolite suppressed spike-and-wave discharges (SWDs) in the WAG/Rij rats and in the GAERS rats, which constitute a genetic model of absence epilepsy [37, 61]. However, in this model desglycinyl-remacemide turned out to act faster and was more potent in reducing the number of spike-wave discharges but, unlike remacemide, had tendency to prolong their mean duration [61].

Conversely, remacemide affords little or essentially no protection against bicorneal kindled seizures and those induced by pentetrazole (PTZ), bicuculline, picrotoxin, strychnine [18, 41, 58] or by acute heat stress [39]. As regards convulsions elicited by PTZ and picrotoxin in mice, only large oral doses were partially effective while intraperitoneal dosing was inactive [58]. Interestingly, unlike remacemide, its metabolite significantly reduced (to 42.4% of control) zero Mg/4-aminopyridine-induced epileptiform discharges in the rat hippocampal slice [49]. This discrepancy could be explained by the relatively lower potency of parent compound in Na^+ channel blockade and NMDA channel antagonism [49].

In conclusion, the presented data confirm wide range of antiepileptic activity of remacemide.

Clinical considerations

Remacemide was investigated as adjuvant in many clinical studies with refractory epilepsy patients. Generally, it has shown a good profile of safety and tolerability. Undesired effects of remacemide are usually mild and moderate in severity [10]. The most common adverse events of remacemide are: dizziness, abnormal gait, gastrointestinal disturbance, somnolence, diplopia and fatigue [10].

Chadwick et al. [10] reported placebo-controlled trial, where remacemide was applied as an add-on therapy at the three dose levels (300, 600 and 1200 mg/day) in a q.i.d. regimen. Remacemide significantly increased the percentage of responders (defined as, at least, 50% reduction in seizure frequency) when compared with placebo. In individuals treated with the drug at 1200 mg /day, 23% of the patients were responders compared with 7% in placebo-treated group. The overall treatment outcomes differed at $p = 0.038$. It should be mentioned that the adult patients with refractory epilepsy taking part in this trial were already taking up to three AEDs, including hepatic enzyme-inducers. Simi-

larly, Jones et al. [22] reported their trial showing that adjunctive remacemide treatment at 800 mg/day was associated with a higher, dose-related responder rate than that observed in placebo-administered patients.

Also Devinsky et al. [16] concluded from their study that remacemide at a dose of 600 mg/day exhibited therapeutic activity as monotherapy in patients with refractory epilepsy following presurgical assessment. On the contrary, Brodie et al. [8] reported significantly lower effectiveness of remacemide compared to carbamazepine in newly diagnosed epilepsy. Having reviewed clinical trials with localization related epilepsy, Leach et al. [29] have concluded that it is rather unlikely that remacemide will be developed as an AED. Also Marson et al. [33] questioned efficacy of remacemide.

Neuroprotective properties

Neuroprotection afforded by remacemide is mainly due to its non-competitive antagonism at NMDA receptor [14]. Calabresi et al. [9] suggested that inhibition of Na^+ channels also contributed to this effect. Halonen et al. [21] reported that remacemide significantly decreased pyramidal cell damage in the CA3 and CA1 hippocampal regions in a perforant pathway stimulation model of status epilepticus in rats.

Remacemide demonstrated also neuroprotection in animal models of hypoxia and ischemic stroke. It reduced significantly ($p < 0.02$) the ischemic damage in a cat model of focal cerebral ischemia [2]. Remacemide proved to reduce cortical lesion volume following brain trauma in the rat ($p < 0.05$) [57]. Arrowsmith et al. [1] reported a significant remacemide-induced neuroprotection observed during coronary artery bypass grafting.

Kieburtz et al. [23] indicated that remacemide may be also advantageous in HD. In their trial, the authors observed a trend toward improvement in chorea among subjects healed with remacemide at the dose of 200 mg/day. Moreover, the concomitant application of coenzyme Q10 (Co Q10) with remacemide is presently being studied as a potential combination treatment for HD. Beal [4] reported that Co Q10 occurred useful in animal models of amyotrophic lateral sclerosis (ALS) and HD. The Co Q10/RMC combination showed additive efficacy in a model of HD. In another transgenic model of HD in mice, combination of Co Q10 and remacemide resulted in beneficial effects on motor performance [52]. Furthermore, Ferrante et al. [17] found that oral administration of either Co Q10 or remacemide significantly extended survival and delayed the development of weight loss, motor deficits, cerebral atrophy as well as neuronal intranuclear inclusions in the R6/2 transgenic mouse model of HD. It should be underlined that the combined treatment proved to be more efficacious than either compound alone. On the contrary, in the clinical trial conducted in order to determine the influence of remacemide/Co Q10 on the functional decline in early HD, neither of these compounds was effective [24]. On the other hand, desglycinylremacemide and lamotrigine (both at low concentrations) demonstrated additive neuroprotective effect on excitotoxicity induced by glutamate agonists in isolated chick retina [44].

Remacemide turned out to exhibit antiparkinsonian action in rodent and primate models of PD [20]. However, in patients with early PD there was no evidence for a symptomatic effect of remacemide monotherapy [53]. Various preclinical studies suggest that glutamate antagonists help ameliorate motor fluctuations in patients with PD treated with levodopa. Nevertheless, in a randomized, controlled trial for motor fluctuations in PD, remacemide did not show significant improvements [55]. In another clinical study of PD, remacemide demonstrated safety and tolerability. However, such a treatment did not result in any demonstrable improvement or worsening in dyskinesia measures [54]. As it was only a small pilot trial, the authors concluded that larger trials are unavoidable to determine the influence of remacemide on parkinsonian impairment and dyskinesias.

Conclusions

In this review we tried to assemble current available data on remacemide. Remacemide belongs to new potent AEDs. It also may have some potential applications in neurodegenerative diseases.

Remacemide occurred to be effective in numerous experimental seizure models such as MES test, hippocampal kindling and convulsions induced by NMDA, 4-aminopyridine, kainic acid. It was also active in audiogenic and absence seizures.

There were also several clinical trials confirming the efficacy of remacemide in patients with generalized or partial tonic/clonic convulsions and

complex partial seizures. Additionally, in the course of adjunctive therapy of refractory epilepsy, remacemide was well tolerated and showed good safety. However, because of its interference with pharmacokinetics of hepatic enzyme inducers, such as carbamazepine or diphenylhydantoin, some authors question the effectiveness of remacemide in add-on therapy.

In conclusion, remacemide appears to be a promising drug with several applications. As glutamate receptor antagonists are being thoroughly studied at the moment as potential adjuvant AEDs [13], remacemide adjunctive therapy in refractory epilepsy seems to be particularly interesting. However, definite evidence for the efficacy of remacemide necessitates further clinical investigations.

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