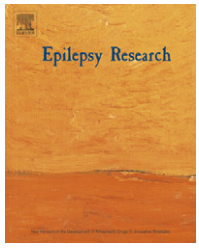
Epilepsy Research (2007) **73**, 75—84

journal homepage: www.elsevier.com/locate/epilepsyres



Anticonvulsant activity, neural tube defect induction, mutagenicity and pharmacokinetics of a new potent antiepileptic drug, *N*-methoxy-2,2,3,3-tetramethylcyclopropane carboxamide

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Received 4 May 2006; received in revised form 22 August 2006; accepted 22 August 2006
Available online 25 September 2006

KEYWORDS
N-Methoxy-2,2,3,3-tetramethylcyclopropane carboxamide;
Valproic acid;
Anticonvulsant activity;
Induction of exencephaly;
Mutagenicity;
Pharmacokinetics

Summary *N*-methoxy-2,2,3,3-tetramethylcyclopropane carboxamide (OM-TMCD) is a methoxyamide derivative of a cyclopropyl analogue of valproic acid (VPA). The structural considerations used in the design of OM-TMCD were aimed to enhance OM-TMCD anticonvulsant potency (compared to VPA) and to prevent VPA's two life-threatening side effects, i.e., induction of neural tube defects (NTDs) and hepatotoxicity. Following i.p. administration to rats OM-TMCD demonstrated a broad spectrum of anticonvulsant activity and showed better potency than VPA in the maximal electroshock seizure and subcutaneous pentylenetetrazole tests as well as in the hippocampal kindling model. OM-TMCD was inactive in the mouse 6-Hz test at 100 mg/kg dose. Teratogenicity studies performed in a SWV/Fnn-mouse model for VPA-induced-exencephaly showed that on the equimolar basis OM-TMCD possesses the same fetal toxicity and ability to induce NTDs as VPA, but since OM-TMCD is a much more potent anticonvulsant its activity/exencephaly formation ratio appears to be much more beneficial

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0920-1211/$ — see front matter
doi:10.1016/j.eplepsyres.2006.08.004

than that of VPA. OM-TMCD was found to be non-mutagenic and non-pro-mutagenic in the Ames test. It showed a beneficial pharmacokinetic profile in rats, having a high oral bioavailability of 75% and satisfactory values of clearance and volume of distribution. These results support further studies to fully characterize the therapeutic potential of OM-TMCD.

1. Introduction

Valproic acid (VPA, Fig. 1) is one of the most prescribed antiepileptic drugs (AEDs). As a broad spectrum AED, it is widely used in patients with multiple seizure types (Bourgeois, 2002). VPA is also approved for the treatment of migraine prophylaxis and the management of bipolar disorders (Silberstein, 2002; Swann, 2002). Among the leading AEDs, phenytoin, carbamazepine, topiramate and lamotrigine, VPA is the least potent and possesses two rare but potentially life-threatening side effects, hepatotoxicity and teratogenicity that restrict its clinical use in children and women of childbearing age (White et al., 2002; Konig et al., 1999; Kaneko et al., 1999). VPA-associated hepatotoxicity is thought to be caused by two minor metabolites with a terminal double bond: 4-ene-VPA and 2,4-diene-VPA (Fig. 1) (Konig et al., 1999; Zimmerman and Ishak, 1982; Rettie et al., 1987; Baillie, 1992). Unlike hepatotoxicity, VPA-induced exencephaly is caused by the parent compound and not by one of its metabolites (Nau et al., 1991). The incidence of neural tube defects (NTDs) and especially spina bifida increases from 0.1% in unexposed offspring to about 2% in children born to mothers treated with VPA during pregnancy (Lindhout and Schmidt, 1986). A well-established murine model of NTDs showed that the percent of fetuses displaying this congenial malformation is strongly related to the chemical structure of the tested compound (Hauck and Nau, 1989). In this regard, structure—teratogenicity relationship studies revealed that the free carboxylic group along with hydrogen on the α-carbon to the carbonyl group and branching of the alkyl substituents are essential requirements for inducing NTDs by VPA and its derivatives or analogues (Nau et al., 1991).

The major therapeutic goal in the development of follow-up compounds to VPA or new AEDs that will be second-generation to VPA, is to design non-hepatotoxic, non-teratogenic new CNS-active VPA derivatives or analogues more potent than VPA and while retaining VPA's broad spectrum of antiepileptic activity.

N-methoxy-2,2,3,3-tetramethylcyclopropane carboxamide (OM-TMCD, Fig. 1), is a *N*-methoxy derivative of the amide of 2,2,3,3-tetramethylcyclopropanecarboxylic acid (TMCA, Fig. 1), a cyclopropyl analogue of VPA (Sobol et al., 2004). Since OM-TMCD has two quaternary carbons at the β-positions to the carbonyl it cannot be biotransformed to the potentially hepatotoxic metabolites with a terminal double bond, analogous to VPA. In addition, being an amide, OM-TMCD does not fulfill the aforementioned structural requirements for the VPA derivatives and analogues having an ability to induce NTDs (Nau et al., 1991).

In previous studies, OM-TMCD was evaluated in the maximal electroshock (MES) and metrazol-induced (scMet) seizure tests following intraperitoneal administration to mice and oral administration to rats (White et al., 2002; Sobol et al., 2004). A comparative presentation of the ED_{50} values of OM-TMCD and VPA was outlined previously (Sobol et al., 2004). A special advantage of OM-TMCD over VPA was observed following its oral administration to rats. OM-TMCD was found to be 4.5 and 18.5 times more potent than VPA in the rat MES and scMet tests, respectively, and its protective indexes (PI, $PI = TD_{50}/ED_{50}$) in these tests were 2 and 8 times higher than those of VPA in the corresponding tests, respectively (Sobol et al., 2004).

The aims of the present study were: (a) to extend the evaluation of the anticonvulsant activity of OM-TMCD in the MES, scMet tests and hippocampal kindling model of partial seizures following i.p. administration to rats, and 6-Hz test following i.p. administration to mice; (b) to analyze the potential of OM-TMCD to induce NTDs in comparison to VPA; (c) to evaluate the mutagenic potential of OM-TMCD; (d) to evaluate the pharmacokinetic profile of OM-TMCD in rats.

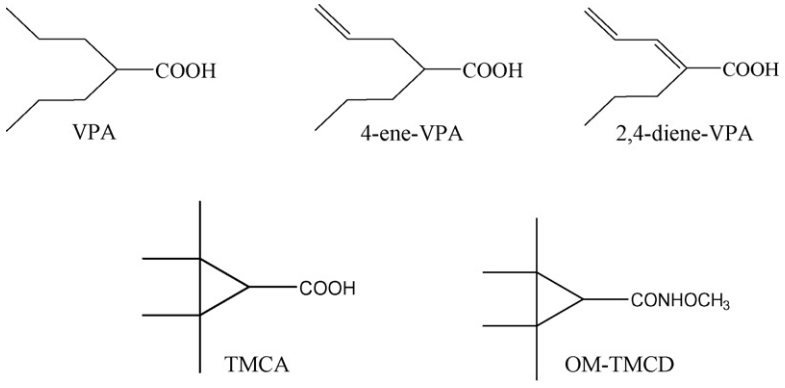

Figure 1 Chemical structures of VPA, 4-ene-VPA, 2,4-diene-VPA, TMCA and OM-TMCD.