

Antiepileptic Drugs and neuropathic pain: Comparative analysis of CNS-active derivatives of valproic acid in the (rat) spinal nerve ligation model

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Antiepileptic drugs (AEDs) are widely utilized in the management of neuropathic pain. The AED valproic acid (VPA) holds out particular promise as it is engaging a variety of different anticonvulsant mechanisms simultaneously. However, the clinical use of VPA is limited by two rare but potentially life-threatening side effects: teratogenicity and hepatotoxicity. We synthesized VPA's corresponding amide: valpromide (VPD), two of VPA's isomers and their corresponding amides; valnoctic acid (VCA), valnoctamide (VCD), diisopropyl acetic acid (DIA), diisopropylacetamide (DID) and VPD's congener N-methyl-VPD (MVPD). VCD, DID and VPD are non-teratogenic, potentially non-hepatotoxic, and exhibit better anticonvulsant potency than VPA. In addition, we have synthesized several tetramethylcyclopropyl analogues of VPA amides that are non-teratogenic, and non-hepatotoxic, that exhibit good antiepileptic efficacy. In this study we have assessed the antiallodynic activity of these compounds in comparison to VPA and gabapentin (GBP) using the rat spinal nerve ligation (SNL) model of neuropathic pain. VCA and MVPD were inactive. However, VPD (20-100 mg/kg), VCD (20-100 mg/kg) and DID (20-90 mg/kg), produced dose-related reversal of tactile allodynia with ED₅₀ values of 61, 52 and 58 mg/kg, respectively. All the amides were more potent than VPA (ED₅₀=269 mg/kg). The antiallodynic effect of VPA, VPD, VCD and DID was obtained at plasma concentrations of 125 mg/L, 24 mg/L, 18 mg/L and 7 mg/L, respectively, with a good pharmacokinetic-pharmacodynamic correlation and a minimal lag response. The following tetramethylcyclopropyl analogues of VPA amides showed dose-related reversal of tactile allodynia: TMCA (2,2,3,3-tetramethylcyclopropanecarboxylic acid, 100-250 mg/kg), TMCD (2,2,3,3-tetramethylcyclopropanecarboxamide, 40-150 mg/kg), MTMCD (N-methyl-TMCD, 20-100 mg/kg), and TMCU (2,2,3,3-tetramethylcyclopropanecarbonylurea, 40-240 mg/kg), with i.p-ED₅₀ values of 181, 85, 41, and 171mg/kg, respectively. All were more potent than VPA (ED₅₀=269 mg/kg). An antiallodynic effect was obtained for TMCD, MTMCD and TMCU at plasma concentrations as low as 23 mg/L, 6 mg/L and 22 mg/L, respectively. VCD and DID were found to have minimal motor and sedative side effects at analgesic doses, and were equipotent to GBP, currently the leading drug in neuropathic pain treatment. MTMCD was also found to be non-toxic, non-sedative and equipotent to GBP. Consequently, VCD, DID, MTMCD and TMCU have potential to become a new series of drugs for neuropathic pain treatment.

References

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