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THERAPY

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Anticonvulsant drugs in migraine prophylaxis

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Abstract Anticonvulsant drugs have been used in migraine prophylaxis since 1970. In recent years, new antiepileptic compounds have given rise to much interest in pain control. Migraine prophylaxis is still based on old drugs, and physicians facing this condition are always prompted to use any new possible choice. The most studied drug over last decade has been divalproex sodium, and many papers showed its efficacy in the treatment of episodic migraine, chronic migraine, transformed migraine, and related conditions. Valproate is well tolerated and many dosages have been used successfully. For the newer drugs, such as gabapentin, lamotrigine or topiramate, the evidence is less strong but rapidly increasing in the last 3-4 years. We review the principal characteristics of their use, according to dosages, duration of treatments, side effects, and significant efficacy.

Key words Anticonvulsant drugs • Carbamazepine • Divalproex • Gabapentin • Lamotrigine • Topiramate • Migraine prophylaxis

Introduction

Migraine prophylaxis is still an open problem. In 1997, Ramadan et al. [1] reviewed all published English reports of randomized, double-blind, placebo-controlled trials of migraine prophylactic drugs and wrote that "most reported trials have doubtful scientific merit and have been poorly reported. Also, an agent that provides more than 50% improvement in migraine headache frequency is still awaited". In their review, the authors considered β-blockers, tricyclics, calcium channel blockers, anticonvulsants (divalproex sodium and carbamazepine), anti-serotonin agents, clonidine and selective serotonin reuptake inhibitors (SSRIs). They finally stated that "the recent trials of divalproex are steps in the right direction but they have not provided us yet with the answer to migraine prevention".

Anticonvulsants for migraine prophylaxis have been tested since 1970 [2], but most studies have been performed in last decade. Carbamazepine was the first drug used. Since 1988, divalproex sodium has been the antiepileptic drug more studied in clinical trials. In recent years, the new anticonvulsant drugs (e.g. lamotrigine, gabapentine, topiramate, oxcarbazepine) have been employed to treat migraine condition.

Carbamazepine

Rompel and Bauermeister [2], in a cross-over, randomized, double-blind, placebo-controlled trial using three tablets per day (strength not specified), showed that 38 of 45 patients improved compared with 13 of 48 on placebo. No other study has investigated carbamazepine (CBZ) until 2000,

when Krusz [3] presented his work at the "Headache 2000" congress, helded in London. In this open study, 40 patients were treated with a mean dosage of 550 mg/day for 2–6 months; 30 patients reported a reduction of almost 70% in the frequency of their migraine headaches, and headaches in the remaining migraines were about 40% less severe.

Divalproex sodium

In all of the clinical studies, whether open, retrospective or placebo-controlled and double-blind, divalproex sodium was an effective preventive treatment for migraine. Divalproex sodium has been studied as a prophylactic medication for migraine without aura [4], migraine with and without aura [5–7], transformed migraine [8, 9] refractory migraine [10, 11], persistent migraine aura [12], and pediatric migraine [13, 14]. The efficacy of divalproex sodium has been compared with that of propanolol [15] and flunarizine [16].

Several reviews have summarized the clinical benefit of divalproex sodium in migraine [17–19]. Most patients received a dosage of 500–1000 mg, although the drug was also effective at low (400 mg/day) and high (2500 mg/day) dosages [7, 8, 20]. Before starting treatment, is useful obtain baseline laboratory data, including complete blood count and serum chemistry with liver enzymes. These should be repeated at two and six months, particularly in patients receiving polytherapy [17]. Recommended starting dose is 500 mg/day, with titration to 1000 mg/day in case of failure. Higher dosages are not indicated [19]. Divalproex sodium safety has been extensively studied and documented. Adverse events were usually mild or moderate in severity and transient. Nausea was the most common side effect, followed by alopecia, tremor, asthenia, dyspepsia, somnolence, and weight gain. In an open-label, long-term study, Silberstein et al. [21] noted that side effects were distinguishable in three groups: (a) nausea, vomiting, dizziness, and dyspesia were generally greatly reducted during treatment; (b) somnolence, asthenia, and diarrhea were reduced by approximately 50% or more; and (c) other adverse events, such as tremor and weight gain, remained relatively constant over time.

Recently, a new indication for divalproex sodium has been explored: as a drug for acute treatment of migraine crises [22–25]. Intravenous sodium valproate (300–1000 mg) has good efficacy with minimal side effects: unusual taste sensation, somnolence, burning at injection site, nausea, and dizziness [25]. When compared with intravenous dihydroergotamine, the efficacy was similar but divalproex sodium caused significantly fewer adverse events.

Finally, divalproex sodium may be considered in the prophylaxis of migraine in children. A retrospective study found great clinical efficacy in children receiving a daily dosage of 15–45 mg divalproex sodium per kilogram body weight: 50% or more reduction in headache frequency was seen in 78.5% of patients after 4 months of treatment and 9.5% of the patients became pain free [13]. A second, open-label study [14] testing a daily dosage of 250–1125 mg divalproex sodium (3.09–32.89 mg/kg body weight) also found great clinical efficacy: a 50% or greater reduction in headache frequency was seen in 60% of patients (the treatment duration was not indicated), and 15% of the patients became headache free. These studies strongly support the efficacy of divalproex sodium in young people but, unfortunately, the lack of controlled design makes these data not fully reliable.

Lamotrigine

The first report on the use of lamotrigine in migraine prophylaxis was published in 1997 [26]. To date, this is the only study regarding patients with both migraine with and without aura. In the study, 37 patients were randomized to placebo and 40 to treatment with lamotrigine. Active treatment either was started at the full dose of 200 mg/day (18 patients) or with a slow dose-escalation (19 patients) to avoid skin reaction. Improvement was greater on placebo and these changes, not statistically significant, indicated that lamotrigine is ineffective for migraine prophylaxis.

In 1999, Lampl et al. [27] enrolled 15 patients with migraine with aura or aura without migraine and treated them for a period of 4 months, with a 3-month follow-up. Lamotrigine was slowly titrated up to 100 mg/day. Aura symptoms were significantly reduced from baseline to month 4. In all 15 cases, increases in aura frequency and duration were observed following cessation of treatment.

D'Andrea et al. [28] studied 24 patients affected by migraine with aura with a high frequency of attacks. The patients underwent 3 months of therapy with lamotrigine at 100 mg/day. Of the 21 patients who completed the study, 13 were symptom-free at the third month of therapy. Only one patient was completely unresponsive to the drug.

In all 3 of the previously discussed studies, adverse events were mild or moderate, and were mainly skin rash, paresthesias, dizziness, and sleep disturbances.

Gabapentin

Gabapentin has only been recently employed in the treatment of migraine with or without aura. A double-blind, randomized, placebo-controlled study was carried on 63 patients (35 treatment, 28 placebo) at the dosage of 1200

mg/day for 3 months [29]. Adverse events were mild and transient, and no patient withdrew because of side effects. Somnolence, dizziness, tremor, ataxia, and fatigue were the major compliants and occurred in 13 patients (27%). All 3 study groups (placebo, migraine with aura, migraine without aura) obtained significant improvement at the third month of therapy vs. baseline. No significant difference was observed between active treatment and placebo.

Mathew et al. [30] treated 98 patients with gabapentin, administered in increasing dosages up to 2400 mg/day after 4 weeks. A significant response was observed in these patients compared to 45 who received placebo: there was a 50% reduction of migraine in 46.6% of treated and 16.1% of placebo patients. Adverse events were similar to those in the previous study, but led to withdrawal of 16.3% of treated patients and 8.9% of placebo patients.

Topiramate

After the report of the efficacy of topiramate in cluster headache patients [31], many studies were presented at the "Headache 2000" congress. From these reports, no definitive conclusions can be drawn about the efficacy of topiramate. Only two studies were double-blind and placebo-controlled [32, 33], and their results are controversial, with less than 50% of patients experiencing an improvement in headache frequency. Two open-label studies reported a low rate of improvement [34] or insufficient data and few patients [35]. Two other studies were retrospective [36, 37], with different dosages, no clear end-point indicators and insufficient data. Finally, one report analyzed topiramate in combination with other drugs [38], and the last study demonstrated only that topiramate is associated with weight loss [39].

Oxcarbazepine

An open-label study treated over 30 refractory migraine patients [40] with oxcarbazepine, titrated to an average of 1800 mg/day. The author reported seven early successes, but it is not clear what happened to the other patients.

Cochrane review

Published in 2000, the Cochrane review of "anticonvulsant drugs for acute and chronic pain" [41] considered only three placebo-controlled studies of migraine prophylaxis, during the period from January 1966 to February 1994. Two studies [2, 5] showed greater effect with the anticonvulsant than with placebo. The authors stated that "these studies showed anticonvulsants to be effective".

References

1. Ramadan NM, Schultz LL, Gilkey SJ (1997) Migraine prophylactic drugs – proof of efficacy, utilization and cost. Cephalalgia 17:73–80
2. Rompel H, Bauermeister PW (1970) Aetiology of migraine and prevention with carbamazepine (Tegretol): result of a double-blind, cross-over study. S Afr Med J 44:75–80
3. Krusz JC (2000) Carbamazepine, controlled-release, is effective in reducing chronic headaches. Cephalalgia 20:422 (abstract)
4. Jensen R, Brinck T, Olesen J (1994) Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 44:647–651
5. Hering R, Kuritzky A (1992) Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 12:81–84
6. Mathew NT, Saper JR, Silberstein SD et al (1995) Migraine prophylaxis with divalproex. Arch Neurol 52:281–286
7. Klapper J, on behalf of the Divalproex Sodium in Migraine Prophylaxis Study Group (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 17:103–108
8. Mathew NT, Ali S (1991) Valproate in the treatment of persistent chronic daily headache. An open label study. Headache 31:71–74
9. Rothrock JF, Mendizabal JE (2000) An analysis of the "carry-over effect" following successful short-term treatment of transformed migraine with divalproex sodium. Headache 40:17–19
10. Erdemoglu AK, Ozbakir S (2000) Valproic acid in prophylaxis of refractory migraine. Acta Neurol Scand 102:354–358
11. Ghose K, Niven B (1998) Prophylactic sodium valproate therapy in patients with drug-resistant migraine. Meth Find Exp Clin Pharmacol 20(4):353–359
12. Rothrock JF (1997) Successful treatment of persistent migraine aura with divalproex sodium. Neurology 48:261–261
13. Caruso JM, Brown WD, Exil G et al (2000) The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. Headache 40:672–676
14. Pakalnis A, Greenberg G, Drake ME Jr et al (2000) Paediatric migraine prophylaxis with divalproex. Cephalalgia 20:388 (abstract)
15. Kaniecki RG (1997) A comparison of divalproex with propanolol and placebo for the prophylaxis of migraine without aura. Arch Neurol 54:1141–1145

16. Mitsikostas DD, Polychronidis J (1997) Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. Funct Neurol 12:267–276
17. Silberstein SD (1996) Divalproex sodium in headache: literature review and clinical guidelines. Headache 36:547–555
18. Rothrock JF (1997) Clinical studies of valproate for migraine prophylaxis. Cephalalgia 17:81–83
19. Landy SH, McGinnis J (1999) Divalproex sodium – review of prophylactic migraine efficacy, safety, and dosage, with recommendations. Tenn Med 92:135–136
20. Coria F, Sempere AP, Duarte J et al (1994) Low-dose sodium valproate in the prophylaxis of migraine. Clin Neuropharmacol 17:569–573
21. Silberstein SD, Collins SD, for the Long-term Safety of Depakote in Headache Prophylaxis Study Group (1999) Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study. Headache 39:633–643
22. Mathew NT, Kailasam J, Meadors L et al (2000) Intravenous valproate sodium (Depacon) aborts migraine rapidly: a preliminary report. Headache 40:720–723
23. Norton J (2000) Use of intravenous valproate sodium in status migraine. Headache 40:755–757
24. Robbins L (2000) Intravenous valproate for prolonged migraine headache. Cephalalgia 20:333 (abstract)
25. Mathew NT, Kailasam J (2000) Repetitive intravenous administration of valproate sodium in intractable migraine: comparison with intravenous dihydroergotamine. Cephalalgia 20:351 (abstract)
26. Steiner TJ, Findlej LJ, Yuen AWC (1997) Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 17:109–112
27. Lampl C, Buzath A, Klinger D et al (1999) Lamotrigine in the prophylactic treatment of migraine auara – a pilot study. Cephalalgia 19:58–63
28. D'Andrea G, Granella F, Cadaldini M et al (1999) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 19:64–66
29. Di Trapani G, Mei D, Marra C et al (2000) Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. Clin Ter 151:145–148
30. Mathew NT, Rapoport A, Saper J et al (2001) Efficacy of gabapentin in migraine prophylaxis. Headache 41:119–128
31. Wheeler SD, Carrazana EJ (1999) Topiramate-treated cluster headache. Neurology 53:234–236
32. Potter DL, Hart DE, Calder CS et al (2000) A double-blind, randomized, placebo-controlled study of topiramate in the prophylactic treatment of migraine with and without aura. Cephalalgia 20:305 (abstract)
33. Edwards KR, Glantz MJ, Norton A (2000) Prophylactic treatment of episodic migraine with topiramate: a double-blind, placebo-controlled trial in 30 patients. Cephalalgia 20:316 (abstract)
34. Shuaib A (2000) Efficacy of topiramate in prophylaxis of frequent severe migraines or chronic daily headaches: experience with 68 patients over 18 months. Cephalalgia 20:423 (abstract)
35. Di Trapani G, Mei D, Marra C et al (2000) Use of topiramate as prophylactic treatment in migraine: results of a pilot study. Cephalalgia 20:426 (abstract)
36. Wilson MC (2000) Efficacy of topiramate in the prophylactic treatment of intractable chronic migraine: a retrospective chart analysis. Cephalalgia 20:301 (abstract)
37. Von Seggern RL, Mannix LK, Adelman JU (2000) Efficacy of topiramate in prophylactic treatment of migraines in patients refractory to preventive intervention: a retrospective chart review in a tertiary clinic. Cephalalgia 20:423 (abstract)
38. Drake ME Jr, Greathouse NI, Pakalnis A (2000) An open label study of topiramate for migraine prevention. Cephalalgia 20:421 (abstract)
39. Young WB, Hopkins MM, Sanchez Del Rio M et al (2000) The effect of topiramate on weight in chronic daily headache and episodic migraine patients. Cephalalgia 20:353–354 (abstract)
40. Krusz JC (2000) Oxcarbazepine is effective in chronic migraine prophylaxis. Cephalalgia 20:425 (abstract)
41. Wiffen P, McQuay H, Carroll D et al (2000) Anticonvulsant drugs for acute and chronic pain (Cochrane review). In: The Cochrane Library, Issue 1. Update Software, Oxford