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Neurological adverse events of new generation sodium blocker antiepileptic drugs. Meta-analysis of randomized, double-blinded studies with eslicarbazepine acetate, lacosamide and oxcarbazepine

Gaetano Zaccara [a,*], Fabio Giovannelli [a], Dario Maratea [b], Valeria Fadda [b], Alberto Verrotti [c]

[a] U.O. Neurologia, Azienda Sanitaria di Firenze, Firenze, Italy
[b] HTA Unit, Regional Health System, ESTAV-Centro, Italy
[c] Department of Pediatrics, University of Chieti, Chieti, Italy

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ABSTRACT

Purpose: Analysis of overall tolerability and neurological adverse effects (AEs) of eslicarbazepine acetate (ESL), lacosamide (LCM) and oxcarbazepine (OXC) from double-blind, placebo-controlled trials. Indirect comparisons of patients withdrawing because of AEs, and the incidence of some vestibulocerebellar AEs between these three antiepileptic dugs (AEDs).

Methods: We searched MEDLINE for all randomized, double-blind, placebo-controlled trials investigating therapeutic effects of fixed oral doses of ESL, LCM and OXC in patients with drug resistant epilepsy.

Withdrawal rate due to AEs, percentages of patients with serious AEs, and the proportion of patients experiencing any neurological AE, nausea and vomiting were assessed for their association with the experimental drug.

Analyses were performed between recommended daily doses of each AED according to the approved summary of product characteristics (SPC). Risk differences were used to evaluate the association of any AE [99% confidence intervals (CIs)] or study withdrawals because of AEs (95% CIs) with the experimental drug. Indirect comparisons between withdrawal rate and AEs dizziness, coordination abnormal/ataxia and diplopia were estimated according to network meta-analysis (Net-MA).

Results: Eight randomized, placebo-controlled, double-blind trials (4 with ESL, 3 with LCM, and 1 with OXC) were included in our analysis.

At high doses (OXC 1200 mg, ESL 1200 mg and LCM 400 mg) there was an increased risk of AE-related study withdrawals compared to placebo for all drugs. Several AEs were associated with the experimental drug. Both number and frequency of AEs were dose-related.

At high recommended doses, patients treated with OXC withdrew from the experimental treatment significantly more frequently than patients treated with ESL and LCM. Furthermore, the AEs coordination abnormal/ataxia and diplopia were significantly more frequently observed in patients treated with OXC compared to patients treated with LCM and ESL.

Conclusions: The overall tolerability of AEDs and the incidence of several neurological AEs were clearly dose-dependent. Indirect comparisons between these AEDs, taking into account dose-effect, showed that OXC may be associated with more frequent neurological AEs than LCM and ESL.

1. Introduction

Neurological adverse events (AEs) are frequently observed in patients treated with antiepileptic drugs (AEDs) and are often responsible of treatment failure and poor quality of life.[1,2] Amongst these AEs, the most common is sedation, which is observed with almost all AEDs, and brain stem, and vestibulocerebellar AEs, which are most often observed with voltage-gated sodium channels (VGSC) blocker AEDs.[3]

Vestibulocerebellar AEs may be characterized by objective involvement of gait and motor coordination (which in clinical trials are named ataxia, unsteadiness, abnormal gait, balance disturbance, imbalance, coordination disturbance)[4] or by subjective signs such as dizziness or vertigo. Other signs expression of brain stem involvement are those affecting ocular motor functions such as diplopia, blurred vision, and nystagmus.[3]

* Corresponding author at: Unit of Neurology, San Giovanni di Dio Hospital, Via Di Torregalli 3, Azienda Sanitaria di Firenze, 50143 Firenze, Italy.
Tel.: +39 055 7192476; fax: +39 055 7192280.
E-mail addresses: gaetano.zaccara@asf.toscana.it, gaetanozaccara@yahoo.it (G. Zaccara).

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This meta-analysis aimed to evaluate the differences in the neurological tolerability profile of oxcarbazepine (OXC) and two other recently approved VGSC blockers AEDs – lacosamide (LCM) and eslicarbazepine acetate (ESL) – at their recommended daily dosages for the adjunctive treatment of partial-onset seizures (POS) in adults, based on data from phase III clinical studies performed with each drug in this patient population.

2. Methods

2.1. Criteria for considering studies for this review

We included randomized, double-blinded, placebo-controlled trials investigating therapeutic effects of fixed doses of oral ESL, LCM and OXC as adjunctive therapy of POS in adults. Full journal publication was required, with brief abstracts not included. All other types of studies, including non-randomized trials, case reports, or clinical observations, were excluded.

We focused this meta-analysis on adjunctive treatment of POS, since tolerability of these drugs in patients with other diseases than epilepsy and as monotherapy is different from that observed in drug resistant epileptic patients.[5,6]

We searched in PubMed oxcarbazepine OR Trileptal, lacosamide OR Vimpat and eslicarbazepine acetate OR Zebinix with limits: ''Randomized controlled trial (or Clinical trial)'' and ''Humans''. Additional studies were sought in reference lists of retrieved articles and in The National Institutes of Health (NIH) clinical trial registry (www.clinicaltrial.gov). Eligibility was determined after reading each study identified by our search. All studies were read independently by two authors (G.Z. and A.V.) and agreement for inclusion/exclusion was reached after discussion

2.2. Comparison between recommended therapeutic dosages

Since neurological AEs are dose-dependent,[3,7,8] we considered that tolerability profile of the AEDs under analysis should be performed at equi-effective dosages. However, equally effective dosages are not available in the literature and therefore we decided to compare the tolerability profiles taking mainly into account the recommended daily dosages of each agent for the treatment of POS in adults, based on the approved summary of product characteristics (SPC).[9–13]

For the purpose of comparisons performed in this meta-analysis we have set the minimum effective recommended daily dosages to be OXC 600 mg, ESL 800 mg, and LCM 200 mg; the highest effective recommended daily dosage was set as OXC 1200 mg, ESL 1200 mg, and LCM 400 mg. Separate analyses per dose were performed (each dose arm was compared with placebo arm).

2.3. Outcome measures

Our primary outcome of interest was identification of specific neurological AEs and our secondary outcome was the comparison of percentages of patients withdrawing due to any AE. However, the secondary outcome will be discussed first.

2.3.1. Withdrawal rate due to AEs

We calculated placebo-subtracted percentages of patients withdrawing because of AEs. In a second step, we made an indirect comparison of placebo-subtracted percentages of patients withdrawing because of AEs.

2.3.2. Proportion of patients experiencing neurological AEs

We identified all neurological AEs significantly associated with the experimental drug in double-blinded studies with these AEDs. We included nausea and vomiting as neurological AEs because at least in some cases they are a consequence of neurological toxicity. We also performed an indirect comparison of placebo-subtracted percentages of three out of the most important AEs caused by vestibulocerebellar involvement: dizziness, coordination abnormal (or ataxia), and diplopia between these three AEDs.

These analyses were performed after the identification of synonyms – grouped under one main term – and the exclusion of rare AEs (i.e. those AEs observed in <5 patients among those randomized to the experimental drug or placebo).

2.4. Statistical analysis

Statistical heterogeneity was assessed using the I^2 test, with an $I^2 > 70\%$ indicating heterogeneity.[14] Provided that no significant heterogeneity was detected ($I^2 < 70\%$), analyses were carried out using a fixed-effect model. When I^2 was >70%, a random-effect model was used.

Risk differences (RDs) were used to estimate withdrawal rate and to identify AEs significantly associated with the experimental drug. A 95% confidence interval (CI) was used for the analysis of withdrawal rate and 99% (CI) for the analysis of AEs. In the last case, this conservative approach was aimed at minimizing the error rate.

All analyses were carried out with RevMan version 5.1.[15]

The statistical models for the indirect comparisons were based on the frequentist model described by Bucher and colleagues.[16] No heterogeneity was assessed for indirect comparisons; this assessment was restricted to direct comparisons (see I^2 test).

The RD (with 95% CI) for each indirect comparison was estimated according to the ITC software (Canadian Agency for Drugs and Technologies in Health, Indirect Treatment Comparison software, Ottawa, Ontario, Canada). This approach allows an indirect RD (with 95% CI) to be estimated upon the condition that both treatments included in the indirect comparison have been compared in actual trials against a common comparator (which in our case was placebo). Graphs were plotted using GRNETMA.EXE software (Società Italiana di Farmacia Ospedaliera, Milan, Italy) (www.osservatorioinnovazione.org).[17]

3. Results

3.1. Description of studies

3.1.1. Studies search results

A total of 95 references were identified through electronic databases searches (see Appendix 1). From this initial sample, we excluded non double-blinded studies, abstracts, active comparator-controlled studies, studies in which these drugs were administered intravenously, studies performed on children, healthy volunteers, or for indications other than epilepsy. Eight randomized, placebo-controlled, double-blind trials (1 with OXC, 3 with LCM and 4 with ESL) were carefully evaluated and included in our analysis (Table 1). For a detailed description of included studies see Appendix 2.

3.1.2. Characteristics of studies

The 8 studies included a total of 2732 subjects, 1858 of whom were randomized to active drug and 874 to placebo (Table 1). In all studies, patients received placebo or were titrated to a fixed dose regimen of the experimental drug.

In the 4 studies performed with ESL, 855 subjects were treated with active drug and 337 with placebo. Nine hundred-forty-four subjects were treated with LCM and 364 with placebo in the 3 LCM study. Finally, 519 subjects were treated with OXC and 173 with placebo in the OXC study.