Epilepsy & Behavior 64 (2016) 29–36

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Review

Is intravenous lorazepam really more effective and safe than intravenous diazepam as first-line treatment for convulsive status epilepticus? A systematic review with meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 3 June 2016
Revised 16 July 2016
Accepted 8 September 2016
Available online 11 October 2016

Keywords:
Diazepam
Efficacy
Lorazepam
Meta-analysis
Status epilepticus

ABSTRACT

Background: Some guidelines or expert consensus indicate that intravenous (IV) lorazepam (LZP) is preferable to IV diazepam (DZP) for initial treatment of convulsive status epilepticus (SE).
We aimed to critically assess all the available data on efficacy and tolerability of IV LZP compared with IV DZP as first-line treatment of convulsive SE.
Methods: Systematic search of the literature (MEDLINE, CENTRAL, EMBASE, ClinicalTrials.gov) to identify randomized controlled trials (RCTs) comparing IV LZP *versus* IV DZP used as first-line treatment for convulsive SE (generalized or focal). Inverse variance, Mantel–Haenszel meta-analysis to obtain risk ratio (RR) with 95% confidence intervals (CI) of following outcomes: seizure cessation after drug administration; continuation of SE requiring a different drug; seizure cessation after a single dose of medication; need for ventilator support; clinically relevant hypotension.
Results: Five RCTs were included, with a total of 656 patients, 320 randomly allocated to IV LZP and 336 to IV DZP. No statistically significant differences were found between IV LZP and IV DZP for clinical seizure cessation (RR 1.09; 95% CI 1.00 to 1.20), continuation of SE requiring a different drug (RR 0.76; 95% CI 0.57 to 1.02), seizure cessation after a single dose of medication (RR 0.96; 95% CI 0.85 to 1.08), need for ventilator support RR 0.93; 95% CI 0.61 to 1.43, and clinically relevant hypotension.
Conclusion: Despite its favorable pharmacokinetic profile, a systematic appraisal of the literature does not provide evidence to strongly support the preferential use of IV LZP as first-line treatment of convulsive SE over IV DZP.

1. Introduction

Status epilepticus (SE), clinically defined as an abnormally prolonged seizure, represents a neurological and medical emergency with an estimated crude incidence of 10–41/100.000 patients per year, an age-standardized incidence ranging from 4.61/100,000 [1] to 18.3/100,000 [2] and an overall mortality of 20% [3–5]. Being life threatening, SE requires prompt recognition and treatment SE to reduce mortality and neurological sequelae due to enduring seizure activity.

By definition, the time limit was reduced from 30 min and is currently set at 5 min for generalized convulsive SE [6]. The choice of adopting this limit for convulsive SE is consistent with previous reports demonstrating that generalized tonic–clonic seizures usually do not last longer than 2 to 3 min [7–10].

The first-line treatment of SE relies on the use of benzodiazepines. These drugs act by increasing the channel opening frequency of the γ-Aminobutyric acid (GABA)-A receptors, with increased chloride conductance and neuronal hyperpolarization, and overall enhancement of inhibition [3,11].

The benzodiazepines usually used as first-line treatment of SE are intravenous (IV) lorazepam, diazepam or clonazepam, or intramuscular midazolam [3,5,12–14].

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http://dx.doi.org/10.1016/j.yebeh.2016.09.020
1525-5050/

The IV use of lorazepam has been widely advocated as preferable to IV diazepam, because of pharmacokinetic differences between the two drugs: lorazepam is less lipid-soluble than diazepam (their octanol/water partition coefficient is, respectively, 73 and 2.8) [15] and, hence, is less prone to rapid redistribution into peripheral tissues. This might result in longer duration of action with higher efficacy in terms of cessation of epileptic activity [5,11].

Conversely, because of its high lipophilicity, diazepam crosses the brain–blood barrier much more rapidly than lorazepam, but is then redistributed into peripheral tissues [16] with only 3–5% of the total dose remaining in the brain [17]. This pharmacokinetic property has been claimed responsible for a possible rapid, but transient antiepileptic effect of this benzodiazepine.

For the above-mentioned reasons, some guidelines or expert consensus statements [18–20] indicate IV LZP as preferable to IV DZP for initial treatment of convulsive SE. Recently, the World Health Organization (WHO) has published a recommendation stating that, for the first-line treatment of adults with acute convulsive seizures, "Intravenous lorazepam (if available) may be preferred over intravenous diazepam because of slightly superior benefit-risk profile." [21].

The aim of this systematic review with meta-analysis was to critically assess all the available data on efficacy and tolerability of LZP compared with IV DZP as first-line treatment of convulsive SE, using an evidence-based approach.

2. Methods

2.1. Criteria for considering studies for this review

All randomized controlled trials (RCTs) comparing the efficacy and the safety profile of IV LZP *versus* IV DZP used as first-line treatment for convulsive SE (generalized or focal) were included.

Patients from any age group diagnosed with SE, clinically defined as convulsive seizures lasting more than 5 min [6,22], were included. Both generalized and focal convulsive subtypes of SE were included. Focal SE cases without enough information on the presence of convulsive activity as well as nonconvulsive SE were excluded.

We included all RCTs, either blinded or not blinded. Uncontrolled and nonrandomized trials were, instead, excluded.

The following electronic databases and data sources/*thesauri* were systematically searched, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [23]:

1. MEDLINE (from inception–24th of November 2015), accessed through PubMed;
2. Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, *The Cochrane Library*, December 2014) (accessed on 24th of November 2015);
3. Excerpta Medica dataBASE (EMBASE) (accessed on 24th of November 2015);
4. ClinicalTrials.gov (available at: https://clinicaltrials.gov/; accessed 24th of November 2015);
5. Hand-searching of the references quoted in the identified trials.

Search strategy adopted for all databases mentioned above is reported in Appendix 1.

All resulting titles and abstracts were evaluated, and any relevant article was considered.

No language restrictions were adopted.

2.2. Study selection

Retrieved articles were independently assessed for inclusion by two review authors (F.B., R.N.); any disagreement was resolved through discussion and consensus meetings.

2.3. Methodological quality assessment

Trials were scrutinized, and the methodological quality of all included studies was evaluated. The randomized trials were judged on the risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] [24].

2.4. Data extraction

The following trial data were independently extracted by two review authors (F.B., R.N.): main study author and year of publication; country; definition of SE applied in the study; type of participants (children, adults, or both); total number, age, and sex of participants for each treatment group; SE type; intervention details (dose, route of administration); definition of successful treatment adopted in each trial; and proportion of seizures controlled after drug administration in each treatment group.

2.5. Outcomes

We chose dichotomous primary outcomes to have hard outcome measures of both treatment efficacy and safety.

In particular, we evaluated efficacy as (1) the proportion of patients in each group with clinical seizure cessation within 15 min after the start of drug administration, (2) the proportion of patients in each group with continuing seizure activity after benzodiazepine administration requiring the use of a different antiepileptic drug, and (3) the proportion of patients in each group with clinical seizure cessation within 15 min after the start of drug administration and requiring only a single dose of study medication to have SE controlled.

Safety was evaluated as (1) the proportion of patients in each group with need for ventilator support and (2) the proportion of patients in each group who developed hypotension, defined as a systolic blood pressure below 90 mm Hg following drug administration and until seizure cessation.

Subgroup analyses were made including either RCTs conducted in adults or children.

2.6. Statistical analyses

A quantitative synthesis (conventional meta-analysis) of RCTs comparing IV LZP with IV DZP as first-line treatment for SE was performed using inverse variance, Mantel–Haenszel (MH) weighted meta-analysis [25]. The outcomes of interest were analyzed by calculating risk ratio (RR) with 95% confidence intervals (CIs) and weighted treatment effect across trials.

Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. Homogeneity among trial results was evaluated using a standard Chi-squared test rejecting the hypothesis of homogeneity with p-value lower than 0.10.

Statistical heterogeneity was assessed by means of the I-squared (I^2) statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error [26]. The I^2 statistic for heterogeneity was interpreted according to Higgins and Green [24]. Results from RCTs were pooled together using a fixed effect model unless there was a significant heterogeneity, in which case we summarized results using a random effects model.

An intention-to-treat (ITT) primary analysis was made to include all patients in the treatment group to which they were allocated, irrespective of the treatment they actually received.

Publication bias for each outcome was assessed by visually inspecting the asymmetry of the funnel plots.

Analyses were conducted using RevMan 5.3.