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[Intervention Review]

Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children

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ABSTRACT

Background

Tonic-clonic convulsions and convulsive status epilepticus (currently defined as a tonic-clonic convulsion lasting at least 30 minutes) are medical emergencies and require urgent and appropriate anticonvulsant treatment. International consensus is that an anticonvulsant drug should be administered for any tonic-clonic convulsion that has been continuing for at least five minutes. Benzodiazepines (diazepam, lorazepam, midazolam) are traditionally regarded as first-line drugs and phenobarbital, phenytoin and paraldehyde as second-line drugs. This is an update of a Cochrane Review first published in 2002 and updated in 2008.

Objectives

To evaluate the effectiveness and safety of anticonvulsant drugs used to treat any acute tonic-clonic convulsion of any duration, including established convulsive (tonic-clonic) status epilepticus in children who present to a hospital or emergency medical department.

Search methods

For the latest update we searched the Cochrane Epilepsy Group's Specialised Register (23 May 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO, 23 May 2017), MEDLINE (Ovid, 1946 to 23 May 2017), ClinicalTrials.gov (23 May 2017), and the WHO International Clinical Trials Registry Platform (ICTRP, 23 May 2017).

Selection criteria

Randomised and quasi-randomised trials comparing any anticonvulsant drugs used for the treatment of an acute tonic-clonic convulsion including convulsive status epilepticus in children.

Data collection and analysis

Two review authors independently assessed trials for inclusion and extracted data. We contacted study authors for additional information.

Main results

The review includes 18 randomised trials involving 2199 participants, and a range of drug treatment options, doses and routes of administration (rectal, buccal, nasal, intramuscular and intravenous). The studies vary by design, setting and population, both in terms of their ages and also in their clinical situation. We have made many comparisons of drugs and of routes of administration of drugs in this review; our key findings are as follows:

(1) This review provides only low- to very low-quality evidence comparing buccal midazolam with rectal diazepam for the treatment of acute tonic-clonic convulsions (risk ratio (RR) for seizure cessation 1.25, 95% confidence interval (CI) 1.13 to 1.38; 4 trials; 690 children). However, there is uncertainty about the effect and therefore insufficient evidence to support its use. There were no included studies which compare intranasal and buccal midazolam.

(2) Buccal and intranasal anticonvulsants were shown to lead to similar rates of seizure cessation as intravenous anticonvulsants, e.g. intranasal lorazepam appears to be as effective as intravenous lorazepam (RR 0.96, 95% CI 0.82 to 1.13; 1 trial; 141 children; high-quality evidence) and intranasal midazolam was equivalent to intravenous diazepam (RR 0.98, 95% CI 0.91 to 1.06; 2 trials; 122 children; moderate-quality evidence).

(3) Intramuscular midazolam also showed a similar rate of seizure cessation to intravenous diazepam (RR 0.97, 95% CI 0.87 to 1.09; 2 trials; 105 children; low-quality evidence).

(4) For intravenous routes of administration, lorazepam appears to be as effective as diazepam in stopping acute tonic clonic convulsions: RR 1.04, 95% CI 0.94 to 1.16; 3 trials; 414 children; low-quality evidence. Furthermore, we found no statistically significant or clinically important differences between intravenous midazolam and diazepam (RR for seizure cessation 1.08, 95% CI 0.97 to 1.21; 1 trial; 80 children; moderate-quality evidence) or intravenous midazolam and lorazepam (RR for seizure cessation 0.98, 95% CI 0.91 to 1.04; 1 trial; 80 children; moderate-quality evidence). In general, intravenously-administered anticonvulsants led to more rapid seizure cessation but this was usually compromised by the time taken to establish intravenous access.

(5) There is limited evidence from a single trial to suggest that intranasal lorazepam may be more effective than intramuscular paraldehyde in stopping acute tonic-clonic convulsions (RR 1.22, 95% CI 0.99 to 1.52; 160 children; moderate-quality evidence).

(6) Adverse side effects were observed and reported very infrequently in the included studies. Respiratory depression was the most common and most clinically relevant side effect and, where reported, the frequency of this adverse event was observed in 0% to up to 18% of children. None of the studies individually demonstrated any difference in the rates of respiratory depression between the different anticonvulsants or their different routes of administration; but when pooled, three studies (439 children) provided moderate-quality evidence that lorazepam was significantly associated with fewer occurrences of respiratory depression than diazepam (RR 0.72, 95% CI 0.55 to 0.93).

Much of the evidence provided in this review is of mostly moderate to high quality. However, the quality of the evidence provided for some important outcomes is low to very low, particularly for comparisons of non-intravenous routes of drug administration. Low- to very low-quality evidence was provided where limited data and imprecise results were available for analysis, methodological inadequacies were present in some studies which may have introduced bias into the results, study settings were not applicable to wider clinical practice, and where inconsistency was present in some pooled analyses.

Authors' conclusions

We have not identified any new high-quality evidence on the efficacy or safety of an anticonvulsant in stopping an acute tonic-clonic convulsion that would inform clinical practice. There appears to be a very low risk of adverse events, specifically respiratory depression. Intravenous lorazepam and diazepam appear to be associated with similar rates of seizure cessation and respiratory depression. Although intravenous lorazepam and intravenous diazepam lead to more rapid seizure cessation, the time taken to obtain intravenous access may undermine this effect. In the absence of intravenous access, buccal midazolam or rectal diazepam are therefore acceptable first-line anticonvulsants for the treatment of an acute tonic-clonic convulsion that has lasted at least five minutes. There is no evidence provided by this review to support the use of intranasal midazolam or lorazepam as alternatives to buccal midazolam or rectal diazepam.

PLAIN LANGUAGE SUMMARY

Drug management for acute tonic-clonic convulsions (fits), including convulsive status epilepticus in children

Review question

This review aimed to assess whether the use of different anticonvulsant drugs, given by different routes of administration, have an impact on how quickly an acute tonic-clonic-convulsion (fit) can be stopped. The review also investigated whether different anticonvulsant drugs were accompanied by less frequent or different serious side effects.

Background

Tonic-clonic convulsions and convulsive status epilepticus are medical emergencies. In children, the first anticonvulsant drug is usually given in the Accident and Emergency (A&E) Department of a hospital. This drug may be administered in a number of ways, including into a vein (intravenously), into the mouth and between the cheeks (buccally), into the nostrils (intranasally) or into the rectum (rectally). The first-choice drug should be effective, work rapidly and not be associated with any serious adverse effects. Research is important to try and find the most effective and the safest anticonvulsant drug in this clinical situation.

Study characteristics

We carried out a review of all available and relevant evidence on the effectiveness and safety of anticonvulsant drugs used in the first-line treatment of tonic-clonic convulsions in children who attended hospital A&E departments. This review examined data from 18 randomised controlled trials (RCTs); RCTs provide the most reliable evidence. They investigated the use of different anticonvulsant drugs and given by different routes.

Key Results

The review included 18 RCTs involving 2199 children, and investigated many different anticonvulsant drugs, doses of the drugs and routes of administration of the drugs. The studies also had some differences in their designs, their settings and the populations of children included, in terms of their ages and their clinical situation (such as how long their convulsion had been going on when they were recruited into the trial).

Analysis of two trials found no clear evidence of a different effect between intravenous lorazepam and intravenous diazepam in stopping a tonic-clonic convulsion taken to an Emergency Department. There is uncertainty about whether buccal midazolam is more effective than rectal diazepam as the first management of a tonic-clonic convulsion or convulsive status epilepticus when intravenous access is unavailable. There is no good evidence that the intranasal route is as effective as the intravenous route. Consequently there is no evidence that it can be used as an alternative route of administration.

Although medications such as midazolam, lorazepam and paraldehyde can reduce breathing rates, this is not a common complication and was not seen very often in the included studies. Rates of serious side effects of these medications are generally very low.

Quality of the evidence

Many of the trials used different drugs, different dosages and different routes of administration. This has to be taken into account when looking at the overall conclusion of this review. Most of the trials took place in large children's hospitals or in large children's departments in a general hospital. This means that the results found in this review are probably relevant for similar clinical situations throughout the world.

The quality of the evidence provided in this review ranged from very low to high. The quality of the evidence provided for some outcomes is low to very low, due to imprecise results where limited information was available for analysis. There were also variability and problems within the designs of some studies, which may have influenced the findings. The quality of evidence was lower in some study settings which were specific to the country in which they were conducted, so the results may not reflect clinical practice worldwide.

The evidence is current to May 2017.