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

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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 (grand mal) convulsions and convulsive status epilepticus (currently defined as a grand mal convulsion lasting at least 30 minutes) are medical emergencies and demand urgent and appropriate anticonvulsant treatment. Benzodiazepines (midazolam, diazepam, lorazepam), phenobarbitone, phenytoin and paraldehyde may all be regarded as drugs of first choice. This is an update of a Cochrane review first published in 2002 and previously updated in 2005.

Objectives

To review the evidence comparing the efficacy and safety of midazolam, diazepam, lorazepam, phenobarbitone, phenytoin and paraldehyde in treating acute tonic-clonic convulsions and convulsive status epilepticus in children treated in hospital.

Search methods

We searched the Cochrane Epilepsy Group's Specialized Register (1st July 2007), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2007), and MEDLINE (1966 to July 2007).

Selection criteria

Randomized and quasi-randomized controlled 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

Four trials involving 383 participants were included.

(1) Intravenous lorazepam is as effective as intravenous diazepam in the treatment of acute tonic clonic convulsions, 19/27 (70%) versus 22/34 (65%), RR 1.09 (95% CI 0.77 to 1.54), has fewer adverse events and rectal lorazepam may be more effective than rectal diazepam, 6/6 versus 6/19 (31%), RR 3.17 (95% CI 1.63 to 6.14)

(2) Buccal midazolam controlled seizures in 61/109 (56%) compared with 30/110 (27%) of rectal diazepam treated episodes with acute tonic-clonic convulsions, RR 2.05 (95% CI 1.45 to 2.91)

(3) Intranasal midazolam is as effective as intravenous diazepam in the treatment of prolonged febrile convulsions, 23/26 (88%) versus 24/26 (92%), RR 0.96 (95% CI 0.8 to 1.14)

(4) There is moderate evidence that intranasal lorazepam is more effective than intramuscular paraldehyde for acute tonic-clonic convulsions and patients treated with intranasal lorazepam are significantly less likely to require further anticonvulsants to control continuing seizures, 8/80 (10%) versus 21/80 (26%), RR 0.58 (95% CI 0.42 to 0.79).

Authors' conclusions

The conclusions of this update have changed to suggest that intravenous lorazepam is at least as effective as intravenous diazepam and is associated with fewer adverse events in the treatment of acute tonic-clonic convulsions. Where intravenous access is unavailable there is evidence from one trial that buccal midazolam is the treatment of choice.

PLAIN LANGUAGE SUMMARY

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

Tonic-clonic convulsions and convulsive status epilepticus are medical emergencies. In children, initial treatment is usually given in the Accident and Emergency (A&E) department of a hospital. Initial treatment may be administered in a number of ways including into a vein (intravenously), into the nasal or oral cavities (buccally) or into the rectum (rectally). The first choice anticonvulsant should be effective, work rapidly and not be associated with any serious adverse effects.

Four trials involving 383 participants were included. A review of two trials in children found evidence to inform a choice of intravenous lorazepam over intravenous diazepam as first line treatment for children presenting to an A&E department in an acute tonic-clonic convulsion. There is evidence from one trial to suggest that buccal midazolam is more effective than rectal diazepam in the initial management of convulsive status epilepticus in childhood where intravenous access is unavailable/unobtainable.

BACKGROUND

Generalized **c**onvulsive **s**tatus **e**pilepticus (CSE) may be defined as a generalized tonic-clonic convulsion lasting 30 minutes or more, or repeated tonic-clonic convulsions occurring over a 30-minute period without recovery of consciousness between each convulsion (Dodson 1993; Shorvon 1993). When the exact time of onset or duration of the convulsion is not known, any person presenting to the Accident and Emergency department in an acute tonic-clonic convulsion tends to be managed according to the definition of status epilepticus with the primary objective of stopping the convulsion, irrespective of its duration. In children, the first drug used to treat an acute tonic-clonic convulsion has, in the recent past, usually been given in the Accident and Emergency department (Garr 1999). However it is now more common that parents/carers of children with recurrent convulsions are prescribed "rescue" medications such as rectal diazepam or buccal/nasal midazolam to administer at home (or even school) to halt the convulsion at an earlier stage.

Convulsive status epilepticus is a medical and neurological emergency and if under or inappropriately treated may result in death or significant morbidity. Over-treatment may be as potentially damaging as under-treatment by causing respiratory depression/arrest (with a risk of consequent cerebral hypoxia) or a potentially fatal cardiac arrhythmia. Finally, it is generally believed that the longer the episode of CSE, the more difficult it is to terminate.

The management of CSE in children is based largely, if not wholly, on the management of CSE in adults, usually including a 'downward' extrapolation of the dosages of the anticonvulsant drugs which are used to treat CSE. This may be inappropriate for a number of reasons including a wide range of body weights and different rates of metabolism and routes of administration of the anticonvulsant drugs when treating children in CSE. In addition, the protocols that have been 'designed' and used in treating CSE in children vary considerably - and are generally based on adult protocols or on individual paediatric clinicians' personal experi-

ence and beliefs, rather than on sound evidence (Martland 1998).

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

(1) Randomized controlled trials, quasi-randomized controlled trials, blinded or unblinded.
(2) Non-randomized controlled studies.

Types of participants

Children aged between one month and 16 years presenting to an Accident and Emergency department or to a hospital ward (direct from the community) in an acute tonic-clonic convulsion and who received treatment with an anticonvulsant drug, irrespective of the duration of the presenting convulsion.
Children included those presenting *de novo* with a first convulsion and those with an established diagnosis of epilepsy. Any and all causes of the convulsion (including convulsive status epilepticus) were included in the review.

Types of interventions

In children presenting with an acute seizure including status epilepticus, we included trials if they compared one treatment (or protocol) with another or with placebo. Specific drugs included the benzodiazepines (diazepam, lorazepam and midazolam), phenytoin, phenobarbitone and paraldehyde. Different routes of drug administration were also analysed where possible, these included intra-venous, intra-nasal, buccal, rectal and intra-muscular administration.

Types of outcome measures

(1) Efficacy
(a) Whether the presenting convulsion/episode of convulsive status epilepticus was terminated with the drug(s) used.
(b) Whether convulsions recurred within 24 hours from termination of the presenting convulsion.
(c) The need to use additional antiepileptic drugs to terminate the presenting convulsion.
(d) Time taken from administration of any drug in the Accident and Emergency department to termination of the convulsion.
(2) Safety
(a) The incidence of specific adverse effects: respiratory depression/arrest; cardiac arrhythmia; hypotension and extravasation of any intravenously administered anticonvulsant.
(b) Incidence of admissions to the intensive care unit (ICU).
The timing of the appearance of adverse effects was not recorded because firstly these data were not required and secondly because the onset of the most significant adverse effect (respiratory depression) tended to be almost immediate and the times were not recorded by the observers/investigators in the studies. Where possible, admissions to ICU were analysed separately on whether admission was because of an adverse effect or because of continuing convulsive activity.

Search methods for identification of studies

We searched the Epilepsy Group's Specialized Register (1st July 2007). This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and of MEDLINE. Relevant reports are also identified by handsearching selected journals and conference proceedings. A more detailed description of this activity is given in the 'Specialized register' section of the Cochrane Epilepsy Group module.
In addition, we searched:
(1) The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2007);
(2) MEDLINE (Ovid) (1966 - July 2007) using the strategy outlined in Appendix 1;
(3) EMBASE (January 2002).

Data collection and analysis

We (Stewart Macleod and Richard Appleton) independently assessed trials for inclusion. We also extracted the outcome data specified above as well as the following data. Any disagreements were resolved by discussion.
Methodological/trial design
(a) Method of randomization.
(b) Method of double-blinding.
(c) Whether any participants had been excluded from the reported analyses.
Non-randomized controlled data
(a) Trial design (case-control, cohort, interrupted time series).
Where data were missing, we attempted to make contact with original authors for this information. Because convulsive status

epilepticus may directly result in death, any documented deaths in the studies were evaluated by analysing individual patient data.

Participant/demographic information

(a) Total number of participants allocated to each treatment group/ audited in any protocol.
(b) Age/sex.
(c) Number and type of background antiepileptic drugs.
(d) Whether any pre-hospital emergency anticonvulsant treatment was given.
(e) Duration of presenting tonic-clonic seizure/episode of convulsive status.
(f) Cause of acute tonic-clonic seizure/episode of convulsive status.

Data analysis plan

(1) RCT/Quasi-RCT/Non-randomized controlled data
(a) Data from RCTs and non-randomized controlled trials were handled in a similar way, but results for each trial methodology were handled separately.
(b) The primary analysis was by 'intention-to-treat' and included all randomized participants, analysed in the treatment group to which they were allocated, irrespective of which treatment they actually received. A secondary 'protocol correct' analysis for seizure/ status episode outcome was also undertaken.
(c) Clinical heterogeneity was assessed by reviewing the differences across trials in characteristics of recruited participants and treatment protocols. Heterogeneity was also assessed statistically using a chi squared test for heterogeneity.
(d) Dichotomous outcomes were expressed as **r**elative **r**isks (RR) with 95% **c**onfidence **i**ntervals (CIs).
(e) Continuous outcomes (ie. time to terminate the seizure/status episode) were expressed as weighted mean differences.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

In addition to the single study identified in the original review this update has identified three further studies that meet the main inclusion criteria (Ahmad 2006; Lahat 2000; McIntyre 2005). All four identified studies are hospital based studies.

The original Cochrane review (2002) identified a single study (Appleton 1995). This was a one year open, quasi-randomized study, comparing lorazepam and diazepam (with the drugs given either intravenously or rectally depending on ease of venous access). This study evaluated 102 participants, aged between one month to 16 years of both sexes, presenting with an acute tonic-clonic convulsion including established convulsive status epilepticus to an Accident and Emergency department of a large Children's Hospital. All causes of the convulsion or status, including symptomatic and idiopathic, were included in the study. No participant had evidence of acute head trauma, metabolic encephalopathy, bacterial meningitis or herpes simplex encephalitis as a cause of their presenting convulsion. No participants with known pseudo tonic-clonic convulsions or pseudo-convulsive, absence or complex partial status were included. The demography of the two treatment groups was very similar (age; sex; numbers with pre-existing epilepsy; numbers with a pre-existing neurological disorder and duration of the presenting convulsion prior to treatment with the two study drugs). Cessation of the seizure was defined as the seizure or episode of status stopping within seven or eight minutes of administration of the first dose of the study anticonvulsant. If the presenting convulsion had not stopped by eight minutes then a second dose of either lorazepam or diazepam would be given. If this seizure persisted then an additional anticonvulsant would be given, based on the hospital's protocol for managing convulsive status epilepticus (Garr 1999).

This update has identified three further studies. The first study (Lahat 2000) is a twelve month single centre randomised study comparing intranasal midazolam (0.2mg/kg) and intra-venous diazepam (0.3mg/kg) in the treatment of prolonged febrile seizures (a seizure of at least 10 minutes duration) in children aged 6 months to 5 years. The study was carried out in a paediatric emergency department within a general hospital. Patient demographics were similar in both groups. Treatment was successful if the clinical features of the seizure stopped within 5 minutes. If the seizure stopped between 5 and 10 minutes this was identified as a delayed but successful treatment. Treatment failures (continued seizure activity after 10 minutes) received intravenous diazepam and then phenobarbital as per local guidelines. Randomisation was allocated in advance by way of a random number table and investigators received an opaque envelope with each allocation at the time of administration. A total of 44 patients of both sexes with a total of 52 seizure episodes were evaluated. Children who had received an anticonvulsant or had an intravenous line sited by paramedics prior to hospital attendance were excluded from the study.

The second study (McIntyre 2005) is a 3-year 4 month, multicentre, randomised, controlled trial comparing buccal midazolam (approximately 0.5mg/kg) with rectal diazepam (0.5mg/kg) as the first line treatment of children aged 6 months to 15 years presenting to a paediatric accident and emergency department with active seizures (McIntyre 2005). The primary outcome measure was clinical cessation of the seizure within 10 minutes of drug administration without seizure recurrence within 1 hour and without respiratory depression. Patients with partial seizures or non-convulsive status epilepticus were excluded from the trial. Weekly blocks of treatment of either buccal midazolam or rectal diazepam were randomly selected in each of the four participating centres. Patient demographics were similar in either group. Locally agreed guidelines were followed in the event of continued seizure activ-

ity after the 10 minute period. The study evaluated 219 seizure episodes in 177 children of both sexes. Separate results were reported for both total episodes and first presenting episodes to minimise potential bias of patients with multiple entries. In contrast to the other studies included in this review children were not excluded if they had received anticonvulsant agents prior to their attendance at the Accident and Emergency department.

The third study (Ahmad 2006) was a 12-month, open, randomised study comparing intranasal lorazepam (0.1mg [100micrograms]/kg) and intramuscular paraldehyde (0.2mg [200micrograms]/kg) as the first line treatment of children aged 2 months to 12 years presenting to a paediatric emergency centre with a generalised convulsion continuing for a minimum of 5 minutes. The study was carried out in Malawi, Africa. Intramuscular paraldehyde is commonly used as a first line treatment of acute tonic-clonic seizures in sub-Saharan Africa but is associated with injury around the injection site, sterile abscesses and is incompatible with plastics. Patient demographics were similar in each group. Because of the geographical location of this study the majority of the children had acute symptomatic seizures mainly due to acute brain infection (cerebral malaria or bacterial meningitis in 2/3 of each of the two study groups). Randomisation was allocated in advance by computer in blocks of ten and after identification and treatment of children with hypoglycaemic seizures, investigators opened an unmarked envelope which contained details of treatment allocation. Primary outcome was clinical cessation of the seizure within 10 minutes of drug administration. Children with features of hepatic or hypertensive encephalopathy or organophosphate poisoning were excluded as were children who had received an anticonvulsant agent within one hour of presentation. For children in whom clinical seizure activity continued after 10 minutes, investigators followed a locally agreed protocol. The study evaluated 160 children of both sexes.

Risk of bias in included studies

The methodological quality of the studies included in this review are broadly similar. They are all randomised or quasi-randomised studies with the unit of randomisation being each single seizure episode. Each study compares one drug with another. None of the studies compares treatment with placebo. Given the available data on the outcome of untreated status epilepticus this approach, drug versus placebo, would be deemed unethical. The first study (Appleton 1995) also compares the same drug given by different routes, intravenous and rectal, albeit with significant differences in sample size. Outcomes are broadly similar with cessation of seizure within a given time frame (7-10 minutes) in all studies. Secondary outcomes varied somewhat, with seizure-recurrence varying from 1 hour (Lahat 2000; McIntyre 2005,) to 24 hours (Ahmad 2006). All three studies evaluate cardiorespiratory compromise.

The first paediatric study (Appleton 1995) is a single-centre, open, prospective, quasi-randomized study, using an alternate ('odd' and 'even') day approach to give two different anticonvulsants (lorazepam and diazepam). The quality of methodology of this study can be criticized. The study is not adequately randomized and is unblinded; the study population was small and there were substantial differences in the size of the two treatment groups (lorazepam - 33 participants and diazepam - 53 participants). There was an even larger discrepancy in the children who received the drug via the rectal route - rectal lorazepam (6 children) versus rectal diazepam (19 children). This clearly suggests a higher violation rate for these children who should have received rectal lorazepam. This may have been due to clinician uncertainty about the use of rectal lorazepam as this drug and route of administration are not used in routine clinical practice. Finally, there were a relatively large number of protocol violators (16 of 102 children, or 16% of the total study population) and these violators were excluded from the analyses. The analysis was therefore not an 'intention-to-treat' analysis.

The methodology of the second study (Lahat 2000) is robust. Randomisation is adequate with similar patient demographics in both groups. In addition this study evaluates a specific sub-group of children with prolonged convulsive febrile seizures. This is important as the aetiology of seizures varies across the age ranges during childhood thereby potentially affecting results. The study was unblinded.

The third study (McIntyre 2005) is adequately powered to detect clinically important differences between the study groups. There are a small number of protocol violators (4/231 or 1.7% of all seizure episodes screened). Patient demographics in both groups are similar in terms of age, sex, previous seizures, seizure duration and administration of pre-hospital treatment. It can be concluded therefore that this study is adequately randomised. The study can be criticised for being an un-blinded study. The authors acknowledge this in the paper and it was felt to be inappropriate to administer both an active drug and placebo to each patient, in what is a medical emergency.

The fourth study (Ahmad 2006) is also adequately randomised with identical numbers and similar patient demographics in either group. This study is not blinded.

Effects of interventions

Appleton 1995

One or two doses of intravenous lorazepam stopped the convulsion in 19 of 27 (70%) lorazepam and 22 of the 34 (65%) intravenous diazepam-treated participants. Relative risk (RR) and 95% confidence intervals (CI) 1.09 (95% CI 0.77 to 1.54). A single dose of rectal lorazepam stopped the convulsion in 6 of 6 participants, compared to 6 of 19 participants treated with rectal diazepam RR 3.17 (95% CI 1.63 to 6.14). 6 of the 27 intravenous lorazepam and 12 of the 34 intravenous diazepam-treated participants respectively, experienced a further convulsion within 24 hours after presentation RR 0.63 (95% CI 0.27 to 1.46). Only one of 27

participants (4%) who received intravenous lorazepam compared to 5 of 34 participants (15%) who received intravenous diazepam required additional antiepileptic drugs to terminate the presenting seizure RR 0.25(95% CI 0.03 to 2.03). A lower incidence of respiratory depression occurred in the lorazepam-treated group - one of 27 (4%) participants, compared to seven of 34 in the diazepam-treated group (21%), RR 0.18 (95% CI 0.02 to 1.37). The mean times for the presenting convulsion to stop were very similar in the two treatment groups - 29 seconds for the intravenous lorazepam and 26 seconds for the intravenous diazepam group - and almost identical for the rectal lorazepam (37 seconds) and rectal diazepam (38 seconds) group. Standard deviations for this specific efficacy or outcome measure could not be calculated because the original data were not available. None of the six and none of 27 participants treated with rectal or intravenous lorazepam respectively required admission to intensive care because of respiratory depression. However, one of the 19 (rectal) and seven of the 34 (intravenous) diazepam-treated participants did require admission to intensive care because of respiratory depression. Because there were zero participants in the lorazepam-treatment group, confidence limits could not be calculated. A Fisher exact test of these data gave a two-tailed P-value of 0.01.

Lahat 2000

Intranasal midazolam and intravenous diazepam were found to be equally effective in prolonged febrile convulsions. 23/26 (88%) in the midazolam group and 24/26 (92%) in the diazepam group, RR 0.96 (95 % CI 0.8 - 1.14). Mean time from arrival in hospital to seizure cessation was shorter in the midazolam group (6.1 minutes [6.3-6.7] versus 8.0 minutes [7.9-8.3]). Time of cessation of seizure from drug administration was shorter in the diazepam group (2.5 [2.4-2.6] versus 3.1 [2.9-3.3]). No children in either group had clinical signs of respiratory depression (as assessed by continuous pulse oximetry and 15 minute- blood pressure measurements) during or in the 60 minutes following the seizure. No adverse events, including respiratory depression were identified in either group.

McIntyre 2005

Buccal midazolam was was more effective than rectal diazepam in the emergency treatment of seizures, 61/109 (56%) versus 30/110 (27%) respectively. Relative Risk (RR) was 2.05 and 95% confidence interval (CI) was 1.45 -2.91. Results were similar for the initial presenting seizure and for total number of seizures. Fewer children in the midazolam group required intravenous lorazepam to terminate the seizure 36/109 versus 63/110 , RR 0.58 (95% CI 0.42-0.79). In the midazolam group 5/109 (5%) children had respiratory depression, 2 requiring intubation and ventilation in contrast to 7/110 (6%) children in the rectal diazepam group, 3 requiring intubation and ventilation.

Ahmad 2006

Intranasal lorazepam and intramuscular paraldehyde were equally effective in the management of prolonged seizures, with 60/80(75%) in the lorazepam group and 49/80(61%) in the intramuscular paraldehyde group successfully terminating (RR 1.9, 95% CI 0.96-3.74). 8/80 (10%) children in the lorazepam group and 21/80 (26%) in the paraldehyde group required 2 or more further anticonvulsant doses to terminate the seizures (RR 0.38, 95% CI 0.18 - 0.81). No significant difference was found between either treatment in terms of seizure recurrence within 24 hours. No difference was found between either treatment group in terms of clinically important cardiorespiratory events.

DISCUSSION

Although three further studies have been identified in this update, overall there remains a paucity of available data on the drug management of acute tonic-clonic seizures in childhood. The identified studies include a range of treatment options (midazolam, diazepam, lorazepam and paraldehyde), treatment doses and a range of routes of administration (rectal, buccal, nasal, intramuscular and intravenous). There are also significant differences in the study populations between the different trials. The study by Lahat 2000 looks at a very specific group of children with prolonged febrile convulsions only, the study by Ahmad 2006 investigated children with primarily acute symptomatic convulsions usually due to central nervous system infections and the studies of McIntyre 2005 and Appleton 1995 investigated a group of children with convulsions with a wide variety of underlying aetiologies which probably more accurately reflects the real-life and spectrum of children with acute convulsions presenting to a UK Accident and Emergency department. Although this population heterogeneity makes meaningful aggregation of data to assess efficacy problematic, some useful conclusions regarding efficacy can be made (*see* Table 1).

As regards safety, although some conclusions can be drawn from combining data there are methodological differences between the studies which pose some difficulties. In particular children who had received pre-hospital treatment (usually benzodiazepines administered by parents, carers or paramedics) were excluded from the studies by Lahat and Ahmad but included in the Mcintyre and Appleton studies. In the United Kingdom, children with recurrent prolonged seizures are often prescribed benzodiazepines for parents or carers to administer soon after the onset of a seizure (nominally 5 minutes) and the adverse effects of benzodiazepines (respiratory or cardiovascular depression) may be cumulative with additional doses (*see* Table 2, Table 3, Table 4).

A number of important conclusions can be identified from this updated systematic review :

(1) Intravenous lorazepam is at least as effective as and safer than intravenous diazepam in children. Children who receive intravenous lorazepam are less likely to (a) require additional anti-convulsant drugs to terminate the seizure, (b) develop evidence of respiratory depression and (c) require admission to a paediatric intensive care unit (Appleton 1995).

(2) Buccal midazolam is more effective than rectal diazepam in children in the emergency management of convulsive seizures (McIntyre 2005). This evidence supports the use of buccal midazolam as the first line treatment of acute tonic-clonic seizures in childhood including convulsive status epilepticus where intravenous access in unavailable. This is pertinent in childhood where intravenous access may be difficult, particularly in units not accustomed to dealing with large numbers of children. Although numbers were small, one study (Lahat 2000) demonstrated that time from hospital admission to seizure cessation was significantly faster despite the fact that intravenous diazepam was faster acting when drug administration to seizure cessation was measured. Although not stated in the paper, this presumably reflects the time to obtain intravenous access. Although not included in this review, the results of the study by Scott (1999) were also consistent with a preference for buccal midazolam over rectal diazepam.

(3) Intranasal lorazepam is more effective (less likely to require additional drugs to terminate seizure), safer and cheaper than intramuscular paraldehyde in the treatment of acute tonic clonic seizures (Ahmad 2006). This finding has relevance in economically-deprived and resource-scarce countries where seizures are often of an acute symptomatic aetiology such as central nervous system infection, when intravenous access is more difficult (often because the children are in 'shock' and where intravenous cannulae and equipment may be limited) and where prolonged seizure protection is desirable. The authors of this study also point out that lorazepam is significantly cheaper than paraldehyde.

(4) There is contrasting evidence on the safety of benzodiazepines (midazolam, diazepam, lorazepam) in children with acute tonic clonic seizures of any aetiology. In two of the studies (Lahat 2000, Ahmad 2006), respiratory depression was not reported following administration of nasal midazolam, intravenous diazepam or nasal lorazepam. In the first study (Appleton 1995), 7/34 (21%) of patients treated with intravenous diazepam showed evidence of respiratory depression, all of whom required intensive care admission, against 1/27 (4%) treated with intravenous lorazepam (this patient did not require intensive care admission). McIntyre 2005 reported an incidence of repiratory depression of 5% and 6% for buccal midazolam and rectal diazepam respectively. The discrepancy between the incidences of respiratory depression in these included studies may in part reflect the inclusion of children who had received benzodiazepines before hospital attendance between the studies; such patients were excluded from the studies of Lahat 2000 and Ahmad 2006.

Implications for practice

This updated review provides some evidence to support the use of intravenous lorazepam in the management of acute tonic clonic convulsions in childhood. It is as effective as and safer than intravenous diazepam in treating acute tonic-clonic convulsions and status epilepticus in children. It also provides evidence to support the use of buccal midazolam as the first line treatment of an acute tonic-clonic convulsion and convulsive status epilepticus in childhood where intravenous access is not available. Intranasal lorazepam is more effective, safer and cheaper than intramuscular paraldehyde in the treatment of acute tonic-clonic convulsions in childhood particularly where an acute symptomatic aetiology is suspected, for example, in seizures associated with central nervous system infection. This is of particular importance in countries with a high incidence of central nervous system infectious diseases, where children often present late and in shock (making it difficult to obtain rapid intravenous access) and where intravenous cannulae and equipment are in limited supply.

These data would support previously published open, anecdotal data. Intravenous lorazepam has become established as the first-line intravenous drug in treating an acute tonic-clonic convulsion (and established convulsive status epilepticus) in children. This followed a published consensus statement (Working Party 2000), which was based partly on the study by Appleton 1995.

Implications for research

This review has highlighted the need for additional paediatric randomized controlled data in treating acute tonic-clonic convulsions and convulsive status epilepticus. Significant gaps remain in the evidence-base for the treatment of acute tonic-clonic convulsions and convulsive status epilepticus in childhood. Potential areas for research include:

(1) Efficacy of commonly used first line treatments such as lorazepam and midazolam, mode of delivery including data on optimal drug doses and timing of interventions. The most appropriate randomised control trial would use a factorial design to compare drugs and modes of delivery efficiently.

(2) Role of pre-hospital treatment, usually benzodiazepines, administered by parents or paramedical staff.

(3) Efficacy and safety of second line treatments such as phenytoin, phenobarbitone and phosphenytoin

(4) The continuing use of rectal paraldehyde.

(5) The potential use of newer agents such as intravenous sodium valproate and levetiracetam.

AUTHORS' CONCLUSIONS

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmad 2006

Methods	RCT carried out over 12 month period in Malawi
Participants	Children of both sexes and aged 2 months to 12 years presenting to a paediatric emergency department in a generalised seizure
Interventions	Intranasal lorazepam versus intramuscular paraldehyde
Outcomes	Seizure cessation, incidence of cardiorespiratory depression, need for further anti-convulsant/s
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Appleton 1995

Methods	Quasi-RCT (odd and even days randomization of the 2 drugs) over a 12 month study period
Participants	Children of both sexes and aged (<16yrs) presenting to a single Accident and Emergency department in a tonic-clonic convulsion including established convulsive status epilepticus. Participants treated included those with an established diagnosis of epilepsy, febrile convulsions and those presenting de novo with a first convulsion
Interventions	Lorazepam versus diazepam: rectal and intravenous administration. Diazepam dose: 0.3 to 0.4 mg/kg and lorazepam dose: 0.05 to 0.1 mg/kg. These doses were used for both intravenous and rectal routes of administration
Outcomes	Seizure cessation. Seizure recurrence within 24 hours after the presenting seizure had been terminated. Additional drugs needed to control the presenting seizure. Adverse effects.
Notes	Numerous protocol violators in the study who were then excluded from analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lahat 2000

Methods	12 month RCT
Participants	Children of both sexes and aged 6 months to 5 years presenting to a paediatric emergency department with a febrile seizure
Interventions	Intravenous diazepam versus intranasal midazolam
Outcomes	Seizure cessation, time to seizure cessation, incidence of cardiorespiratory distress,
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

McIntyre 2005

Methods	Multi-centre RCT over 3 years 4 months. Randomisation of 2 drugs in weekly blocks
Participants	Children of both sexes aged 6 months to 16 years presenting to a children's accident and emergency department with active generalised tonic-clonic seizures including established convulsive status epilepticus
Interventions	Buccal midazolam versus rectal diazepam
Outcomes	Seizure cessation without recurrence within 1 hour and without respiratory depression
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

RCT: randomized controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhattacharyya 2006	Majority of seizures were simple partial seizures as opposed to generalised tonic clonic seizures. Study also included children with absence, myoclonic and atonic seizures
Scott 1999	This quasi randomised study reports the use of rectal diazepam and buccal midazolam in treating 79 seizure episodes in 18 patients with severe and refractory epilepsy in a residential institution. Reasons for excluding this study included primarily the fact that the study does not make clear how many of the 11 paediatric patients had experienced a tonic-clonic and not a complex partial or myoclonic seizure when treated with diazepam or midazolam. As the focus of this review is the treatment of only a tonic-clonic seizure, it is impossible from this study to know how many children would have fulfilled this defining criterion and so the study is excluded from this Review. The second reason for excluding this study is that only 11 of the 18 patients are aged 16 years or under

DATA AND ANALYSES

Comparison 1. Lorazepam versus diazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure stopped	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.00, 1.83]
1.1 Intravenous	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.77, 1.54]
1.2 Rectal	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [1.47, 5.55]
2 Recurrence within 24 hours of termination (intravenous)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.27, 1.46]
3 Additional drugs to terminate the presenting seizure (intravenous)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.03]
4 Respiratory depression (intravenous)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.37]

Comparison 2. Midazolam versus diazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure stopped	1	219	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.45, 2.91]
2 Incidence of respiratory depression	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.24, 2.20]
3 Required intravenous lorazepam to terminate seizure	1	219	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.42, 0.79]

Comparison 3. Intra-nasal midazolam versus intra-venous diazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure cessation	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.14]
2 Time to giving drug after arrival at hospital (minutes)	1	52	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-3.03, -0.97]
3 Time of cessation of seizure after arrival in hospital (minutes)	1	52	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-2.00, 0.20]

Comparison 4. Intranasal lorazepam and intramuscular paraldehyde

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure cessation within 10 minutes of drug administration	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.99, 1.52]
2 Seizures needing two or more rescue anticonvulsants	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.18, 0.81]
3 Seizure recurrence within 24 hours	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.31, 1.71]

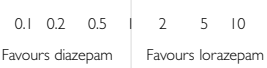
Analysis 1.1. Comparison 1 Lorazepam versus diazepam, Outcome 1 Seizure stopped.

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

Comparison: 1 Lorazepam versus diazepam

Outcome: 1 Seizure stopped

Study or subgroup	Lorazepam n/N	Diazepam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Intravenous					
Appleton 1995	19/27	22/34		85.2 %	1.09 [0.77, 1.54]
Subtotal (95% CI)	**27**	**34**		**85.2 %**	**1.09 [0.77, 1.54]**
Total events: 19 (Lorazepam), 22 (Diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 Rectal					
Appleton 1995	6/6	6/19		14.8 %	2.86 [1.47, 5.55]
Subtotal (95% CI)	**6**	**19**		**14.8 %**	**2.86 [1.47, 5.55]**
Total events: 6 (Lorazepam), 6 (Diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.10 (P = 0.0019)					
Total (95% CI)	**33**	**53**		**100.0 %**	**1.35 [1.00, 1.83]**
Total events: 25 (Lorazepam), 28 (Diazepam)					
Heterogeneity: Chi^2 = 6.37, df = 1 (P = 0.01); I^2 =84%					
Test for overall effect: Z = 1.94 (P = 0.053)					



Analysis 1.2. Comparison 1 Lorazepam versus diazepam, Outcome 2 Recurrence within 24 hours of termination (intravenous).

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

Comparison: 1 Lorazepam versus diazepam

Outcome: 2 Recurrence within 24 hours of termination (intravenous)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Appleton 1995	6/27	12/34		100.0 %	0.63 [0.27, 1.46]
Total (95% CI)	**27**	**34**		**100.0 %**	**0.63 [0.27, 1.46]**
Total events: 6 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					

Analysis 1.3. Comparison 1 Lorazepam versus diazepam, Outcome 3 Additional drugs to terminate the presenting seizure (intravenous).

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

Comparison: 1 Lorazepam versus diazepam

Outcome: 3 Additional drugs to terminate the presenting seizure (intravenous)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Appleton 1995	1/27	5/34		100.0 %	0.25 [0.03, 2.03]
Total (95% CI)	**27**	**34**		**100.0 %**	**0.25 [0.03, 2.03]**
Total events: 1 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.20)					

Analysis 1.4. Comparison 1 Lorazepam versus diazepam, Outcome 4 Respiratory depression (intravenous).

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

Comparison: 1 Lorazepam versus diazepam

Outcome: 4 Respiratory depression (intravenous)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Appleton 1995	1/27	7/34		100.0 %	0.18 [0.02, 1.37]
Total (95% CI)	**27**	**34**		**100.0 %**	**0.18 [0.02, 1.37]**
Total events: 1 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.098)					

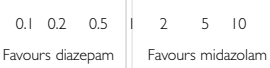
Analysis 2.1. Comparison 2 Midazolam versus diazepam, Outcome 1 Seizure stopped.

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

Comparison: 2 Midazolam versus diazepam

Outcome: 1 Seizure stopped

Study or subgroup	midazolam n/N	diazepam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McIntyre 2005	61/109	30/110		100.0 %	2.05 [1.45, 2.91]
Total (95% CI)	**109**	**110**		**100.0 %**	**2.05 [1.45, 2.91]**
Total events: 61 (midazolam), 30 (diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.05 (P = 0.000051)					

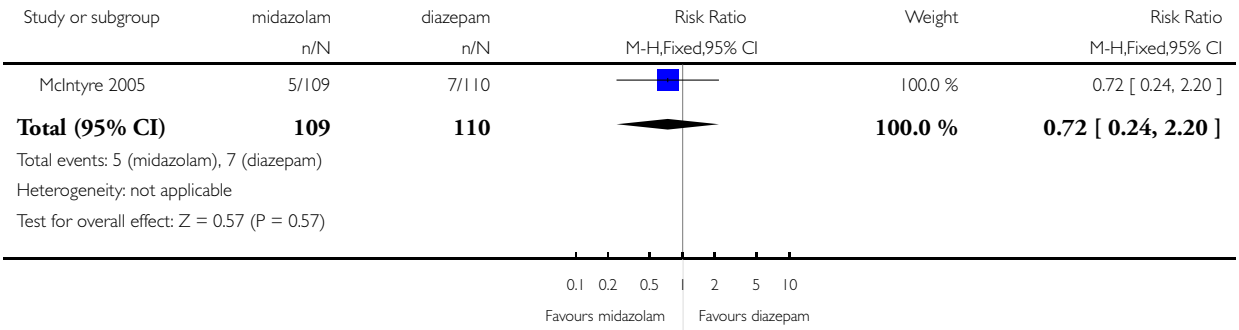


Analysis 2.2. Comparison 2 Midazolam versus diazepam, Outcome 2 Incidence of respiratory depression.

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

Comparison: 2 Midazolam versus diazepam

Outcome: 2 Incidence of respiratory depression

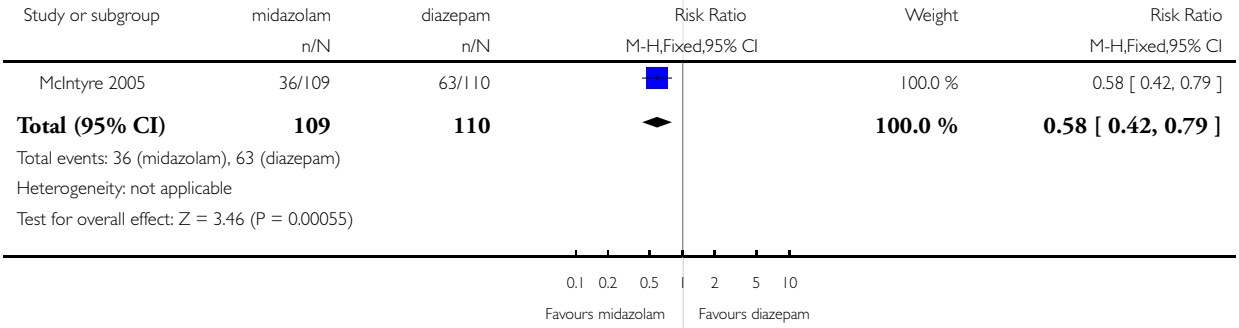


Analysis 2.3. Comparison 2 Midazolam versus diazepam, Outcome 3 Required intravenous lorazepam to terminate seizure.

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

Comparison: 2 Midazolam versus diazepam

Outcome: 3 Required intravenous lorazepam to terminate seizure



Analysis 3.1. Comparison 3 Intra-nasal midazolam versus intra-venous diazepam, Outcome 1 Seizure cessation.

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

Comparison: 3 Intra-nasal midazolam versus intra-venous diazepam

Outcome: 1 Seizure cessation

Study or subgroup	midazolam n/N	diazepam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lahat 2000	23/26	24/26		100.0 %	0.96 [0.80, 1.14]
Total (95% CI)	**26**	**26**		**100.0 %**	**0.96 [0.80, 1.14]**
Total events: 23 (midazolam), 24 (diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					

Analysis 3.2. Comparison 3 Intra-nasal midazolam versus intra-venous diazepam, Outcome 2 Time to giving drug after arrival at hospital (minutes).

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

Comparison: 3 Intra-nasal midazolam versus intra-venous diazepam

Outcome: 2 Time to giving drug after arrival at hospital (minutes)

Study or subgroup	midazolam N	Mean(SD)	diazepam N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lahat 2000	26	3.5 (1.8)	26	5.5 (2)		100.0 %	-2.00 [-3.03, -0.97]
Total (95% CI)	**26**		**26**			**100.0 %**	**-2.00 [-3.03, -0.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.79 (P = 0.00015)							
Test for subgroup differences: Not applicable							

Analysis 3.3. Comparison 3 Intra-nasal midazolam versus intra-venous diazepam, Outcome 3 Time of cessation of seizure after arrival in hospital (minutes).

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

Comparison: 3 Intra-nasal midazolam versus intra-venous diazepam

Outcome: 3 Time of cessation of seizure after arrival in hospital (minutes)

Study or subgroup	midazolam N	Mean(SD)	diazepam N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Lahat 2000	26	6.1 (3.6)	26	8 (4.1)		100.0 %	-1.90 [-4.00, 0.20]
Total (95% CI)	**26**		**26**			**100.0 %**	**-1.90 [-4.00, 0.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.78 (P = 0.076)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Intranasal lorazepam and intramuscular paraldehyde, Outcome 1 Seizure cessation within 10 minutes of drug administration.

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

Comparison: 4 Intranasal lorazepam and intramuscular paraldehyde

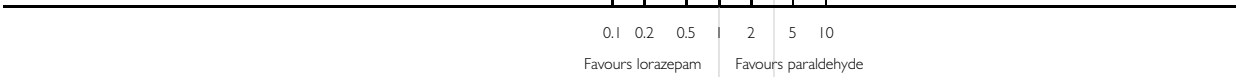
Outcome: 1 Seizure cessation within 10 minutes of drug administration

Study or subgroup	intranasal lorazepam n/N	paraldehyde n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ahmad 2006	60/80	49/80		100.0 %	1.22 [0.99, 1.52]
Total (95% CI)	**80**	**80**		**100.0 %**	**1.22 [0.99, 1.52]**

Total events: 60 (intranasal lorazepam), 49 (paraldehyde)

Heterogeneity: not applicable

Test for overall effect: Z = 1.84 (P = 0.065)

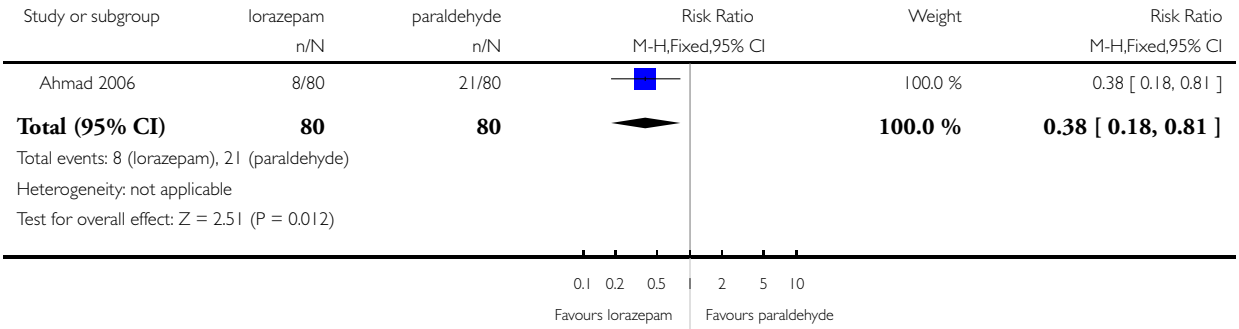


Analysis 4.2. Comparison 4 Intranasal lorazepam and intramuscular paraldehyde, Outcome 2 Seizures needing two or more rescue anticonvulsants.

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

Comparison: 4 Intranasal lorazepam and intramuscular paraldehyde

Outcome: 2 Seizures needing two or more rescue anticonvulsants

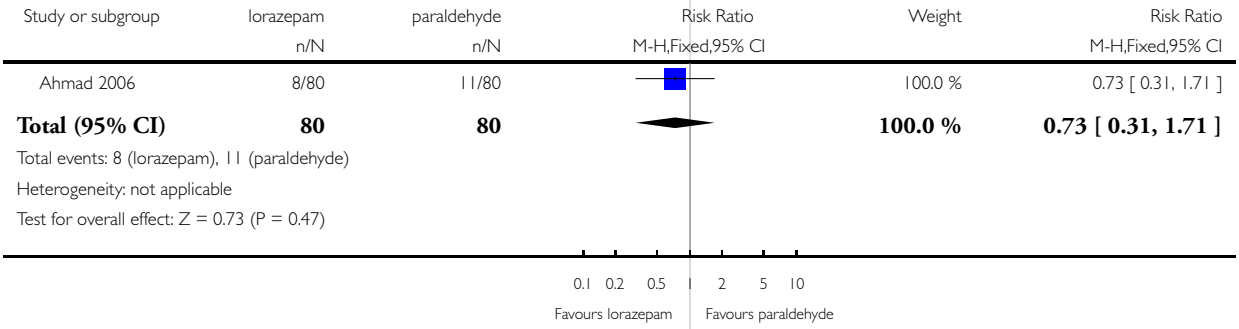


Analysis 4.3. Comparison 4 Intranasal lorazepam and intramuscular paraldehyde, Outcome 3 Seizure recurrence within 24 hours.

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

Comparison: 4 Intranasal lorazepam and intramuscular paraldehyde

Outcome: 3 Seizure recurrence within 24 hours



ADDITIONAL TABLES

Table 1. Summary of results of seizure cessation

Study	Drug	No. of cessation	No. of episodes	%
Appleton 1995	Intravenous diazepam	19	27	70%
	Rectal Lorazepam	6	6	100%
	Intravenous diazepam	22	34	65%
	Rectal Diazepam	6	19	32%
Lahat 2000	Intranasal midazolam	(23	26	88%
	Intravenous diazepam	24	26	92%
McIntyre 2005	Buccal midazolam	61	109	56%
	Rectal Diazepam	30	110	27%
Ahmad 2006	Intranasal Lorazepam	60	80	75%
	Intramuscular Paraldehyde	49	80	60%

Table 2. Summary of adverse events 1 - additional drugs to terminate seizure

Study	Drug/mode	No. of events	No. of episodes	%
Appleton 1995	Intravenous lorazepam	1	27	45%
	Intravenous diazepam	5	34	15%
	Rectal Lorazepam			
	Rectal Diazepam			
Mcintyre 2005	Buccal midazolam	39	109	33%
	Rectal Diazepam	63	110	57%
Ahmad 2006	Intranasal Lorazepam	8	80	10%
	Intramuscular paraldehyde	21	80	26%

Table 3. Summary of adverse events 2 - respiratory depression

Study	Drug/mode	No. of events	No. of episodes	%
Appleton 1995	Intravenous lorazepam	1	27	4%
	Intravenous Diazepam	7	34	21%
	Rectal Lorazepam	0	6	0%
	Rectal Diazepam	1	19	5%
Lahat 2000	Intranasal Midazolam	0	26	0%
	Intravenous Diazepam	0	26	0%
Mcintyre 2005	Buccal Midazolam	5	109	5%
	Rectal Diazepam	7	110	6%

Table 4. Summary of adverse events 3 - seizure recurrence in 24 hours

Study	Drug/mode	No. of events	No. of episodes	%
Appleton 1995	intravenous lorazepam	6	27	22%
	Intravenous diazepam	12	34	35%
	Rectal Lorazepam			
	Rectal Diazepam			
Ahmad 2006	Intranasal Lorazepam			
	Intramuscular Diazepam			

APPENDICES

Appendix 1. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp Randomized Controlled Trial/
4. exp Random Allocation/
5. exp Double-Blind Method/
6. exp Single-Blind Method/
7. exp Clinical Trial/
8. clinical trial.pt.
9. (clin$ adj trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw
11. randomi$.tw.
12. (random$ adj (allocate$ or assign$)).tw.
13. crossover.tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. epilep$.tw.
16. seizure$.tw.
17. convulsion$.tw.
18. exp Epilepsy/
19. exp Seizures/
20. 15 or 16 or 17 or 18 or 19
21. exp Epilepsy, Tonic-Clonic/
22. tonic clonic.tw.
23. status epilepticus.tw.
24. exp Status Epilepticus/
25. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 14 and 25
27. (animals not human).sh.
28. 26 not 27
29. pediatr$.tw. or paediatr$.tw
30. child$.tw.
31. exp child/ or exp child, preschool/ or exp infant/
32. 29 or 30 or 31
33. 28 and 32
34. emergency.tw.
35. 33 and 34

WHAT'S NEW

Last assessed as up-to-date: 30 June 2007.

Date	Event	Description
8 September 2010	Amended	Text added to Published notes.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2002

Date	Event	Description
11 August 2009	Amended	Copyedits made at editorial base.
21 October 2008	Amended	Search strategy amended to comply with RevMan 5 format.
8 May 2008	New search has been performed	We re-ran our searches on 1st July 2007 and found three new studies (Ahmad 2006;Lahat 2000; McIntyre 2005) with 281 participants so there are now four included studies with a total of 383 participants - all hospital based
7 May 2008	Amended	Converted to new review format.
7 May 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Stewart Macleod undertook the literature review, performed the data extraction and wrote the review. Richard Appleton undertook the literature review, reviewed the included and excluded data and commented on the draft review. Tim Martland commented on the draft review.

DECLARATIONS OF INTEREST

The lead review author of this review is the lead investigator of the study included in the original review and is a co-author of another study included in this update.

NOTES

This review is in the process of being updated. We expect the updated version to be published by early 2011.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Rectal; Anticonvulsants [*therapeutic use]; Epilepsy, Tonic-Clonic [*drug therapy]; Injections, Intravenous; Randomized Controlled Trials as Topic; Status Epilepticus [*drug therapy]

MeSH check words

Child; Humans