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Abstract

Diazepam has been used for the acute management of status epilepticus outside of hospital since its introduction in 1963 (Roche, 2007). Although known to be an effective treatment for the termination and subsequent prophylaxis of seizures (Dreifuss et al., 1998), there have been a number of developments in benzodiazepine production since its emergence, leading to the discovery of alternative agents.

The Human Medicines Regulations (2012) provides registered paramedics with legal exemption in relation to the administration of diazepam, but does not allow for the autonomous use of any other benzodiazepine medications. Therefore, unless patient specific or patient group directions exist, diazepam remains the only benzodiazepine generally available to ambulance clinicians despite the presence of alternatives that may be more effective. This article compares and contrasts the available literature regarding the qualities of diazepam with those of lorazepam in the setting of managing convulsive status epilepticus.

The authors found that lorazepam is often reported to be more effective in terminating seizures than diazepam. Lorazepam may offer a more effective, safer and cheaper treatment option for the management of seizures in the pre-hospital environment.

Key words: diazepam, lorazepam, seizure, pre-hospital, paramedic, ambulance.

Key points

- Lorazepam may offer a more efficacious option for pre-hospital seizure management than diazepam.
- Lorazepam could be a safer pharmacological agent for use in the management of convulsions.
- Amendments to The Human Medicines Regulations (2012) may be required to support advances in patient care.
- Ambulance service led controlled trials are needed to ensure pre-hospital care is designed around the current evidence base.

Introduction

Managing prolonged seizures in the pre-hospital setting is an undertaking that presents significant challenges to clinicians. Patients can present with airway and breathing compromise, transport can be dangerous and there is the potential for refractory (medication resistant) status epilepticus, which has been shown to become more likely as 'onset to drug' time increases (Goodkin and Kapur, 2003).

Medications of the benzodiazepine class are psychoactive, all acting to increase the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Pertinent to pre-hospital care is the potent anti-convulsant effect of these medications, the efficacy of which varies across different formulations which are further categorised depending on their duration of action.

National ambulance service guidelines stipulate that the first-line paramedic led treatment for generalised seizures lasting in excess of five minutes should be 10 milligrams (mg) of intravenous diazepam, with the per rectum (PR) route considered where intravenous (IV) access is difficult (Joint Royal Colleges Ambulance Liaison Committee, 2016). Diazepam is known to be effective in the termination of seizures in 50 to 80% of cases (Treiman, 1989), although the drug redistributes into adipose tissue quickly and as such has a short duration of action of approximately 20 minutes (Greenblatt and Divoll, 1983). In addition, it has been shown that seizure recurrence occurs in up to 50% of patients, leading to the administration of repeat diazepam doses (Cock, 2002).

Upon review of the clinical evidence in support of benzodiazepine (BZD) use for the termination of seizures, there is a general consensus that no single drug of this class is particularly superior in terms of efficacy. However, there may be other reasons to look into the use of BZD medications other than diazepam as an alternative first-line treatment option for paramedics.

Pathophysiology of seizures

Status epilepticus is the manifestation of a disorder in which the mechanisms of seizure termination fail. It is complex condition in itself, and is by no means limited to convulsive seizures. To demonstrate this, Shorvon (1994) proposed the following definition; 'Status epilepticus is a disorder in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms, and with a highly variable pathophysiological, anatomical, and aetiological basis.'

The mechanism by which seizure activity initiates and terminates is not well understood, but there is general consensus that the most likely cause is an imbalance between excitatory and inhibitory neurotransmission. These imbalances are thought to lead to

abnormal chaotic neural impulses which then start a seizure. Convulsive seizures have long been associated with cellular damage that is significant enough to render a patient with life-limiting or life-threatening brain dysfunction. It is thought that this is due in part to the failure of homoeostatic compensation that is seen after approximately 30 minutes of active convulsions (Fountain and Lothman, 1995), which inevitably leads to cerebral hypoxia.

Pharmacodynamics of benzodiazepines

BZDs target the allosteric sites of the GABAα receptor. These receptors are ligand gated ion channels (LGICs), that exist in all neuronal tissues, and as such play a part in almost all aspects of brain function. The receptors function when activated is to open a pore and allow chloride anions to reach the associated neuron. The result of this ion influx is a stabilisation or hyperpolarisation of the neuronal cell, making depolarisation by excitatory neurotransmitters (and therefore the generation of action potential) less likely.

The endogenous ligand of GABAα receptors is the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Benzodiazepines act to increase the affinity of the GABA molecule at the receptors α subunit by modifying the molecular structure of the receptor itself. Drugs such as DZP therefore indirectly inhibit excitation, and have particular value in controlling the excessive neuronal activity that is commonly associated with seizures.

Review methods

The focus of this review is towards the comparative benefits of diazepam and lorazepam in the pre-hospital care setting. As there is limited evidence in that specific field the search criteria was widened to allow data from other medical settings. The search plan and search strategy are shown below (see table 1, table 2).

Table 1. Search plan.

Research topic
To compare the effectiveness of diazepam to that of lorazepam in the management of convulsive status epilepticus in adults.

Category definitions
Population and/or problem   Adult patients with a presenting complaint of active convulsive seizures.   *Intervention*   Diazepam IV OR diazepam IM OR diazepam PR.   *Comparison*   Lorazepam IV OR lorazepam IM OR lorazepam PR.   *Outcome*   Efficacy of each drug by each route for the termination of seizures, ease of use of each drug in paramedic practice, practical   considerations for the use of each drug in the clinical setting.

Research question
Is diazepam or lorazepam the most effective benzodiazepine for use in paramedic management of convulsive seizures in adults?

Search restrictions
Databases were accessed using both the Oxford Brookes University library and South Central Ambulance Service OpenAthens   portal to ensure full text versions of each article could be reviewed. Only studies published in English were included in this   review.

Search start: January 2016 at 10:32.

A search was undertaken in January 2016 across the databases CINAHL and PubMed (inclusive of MEDLINE). These databases were primarily targeted as they contain a sufficient breadth of indexed journals to provide for quality data. This means that there was a reduced likelihood of omitting high quality papers from this review as a result of poor indexing.

CINAHL provides an extensive index of 3000 English language journals and 2.3 million records focused on nursing and allied healthcare from North America and Europe. CINAHL was selected for this review due to its wide selection of indexes, which includes 27 titles identified within the CINAHL 'coverage list' (EBSCO, 2016), that contain the search teams; 'Paramed*', 'Emergency', 'Pre-hospital', 'Prehospital' and 'Pharmacology'.

The PubMed database contains in excess of 25 million publications including those indexed by MEDLINE, additional life science journals and biomedical literature. Indexing also includes those publications not yet included in the MEDLINE database, which consequently improves coverage of recently submitted research.

Table 2. Search strategy.

Inclusion criteria
Studies that compared diazepam and lorazepam.
Studies that compared diazepam and lorazepam in seizure management.

Exclusion criteria
Studies published prior to 1963.
Studies that recruited non-human subjects.
Studies that recruited human subjects under the age of 16 years.
Studies that did not constitute randomised controlled trials or retrospective audits.

Search string
(diazepam AND lorazepam AND (seizure* OR convuls* OR fit* OR generalised OR generalized OR status epilepticus)) NOT (child OR paediatric OR pediatric)

Search results
CINAHL
The above search returned 29 results of which 4 were directly relevant to the research question. 1 of these results was a 'best evidence topic report (BET)' and was excluded.
4 papers were identified in this search and considered for review.
PubMed
The above search returned 179 results of which 12 were directly relevant to the research question. 7 were literature reviews and, after examination for references, were excluded.
5 papers were identified in the search and considered for review.

Directly comparative studies

Table 3. Study Comparison.

Author, date and country	Patient group	Cohort size	Trial type
Alldredge et al., (2001). United States.	Adults (> 18 years) with an out of hospital diagnosis of status epilepticus.	205 patients.	RCT.
Treiman et al., (1998). United States.	Adults (> 18 years) with an in-hospital diagnosis of overt or subtle status epilepticus.	384 patients (verified overt SE).	RCT.
Leppik (1983). United States.	Adults (>18 years) with convulsive, absence or partial status epilepticus.	70 episodes.	RCT.
Cock and Schapira (2002). United Kingdom.	Patients >16 years of age with diagnostic code; 'epilepsy', 'fits' or 'status epilepticus'.	72 episodes.	Retrospective case note audit.

Table 4. Study Findings and Weaknesses.

Author, date and country	Outcomes	Key results	Weaknesses
Alldredge et al., (2001). United States.	Termination of convulsive seizure activity by the time of ED arrival.	Lorazepam effective in 59.1% of cases. Diazepam effective in 42.6% of cases. Placebo effective in 21.1% of cases. (p=0.001)	Outcome measure timescales are not quantitively defined. No measure of benzodiazepine administration prior to the arrival of a study paramedic. Continuation of study protocol following hospital arrival is not rigidly enforced.
Treiman et al., (1998). United States.	Treatment successful if all clinical and pre-defined electrical (EEG) evidence of seizure activity stopped within 20 mins of the start of infusion, and if there was no recurrence between 20-60 minutes' post-treatment.	Lorazepam effective in 64.9% of verified overt SE cases. Diazepam with phenytoin effective in 55.8% of verified overt SE cases. (p=0.02)	Conducted in the hospital environment. Study dosages are tailored to each individual patient's weight (mg/Kg) – does not represent prehospital stat bolus administration characteristics. Outcomes are recorded at 20 minutes – arguably this places at least one study drug at a disadvantage due to the need to administer phenytoin slowly.
Leppik (1983). United States.	Seizure termination following one or two IV doses of study drug.	Lorazepam effective in 89% of cases. Diazepam effective in 76% of cases.	Conducted in the hospital environment. Accurate analysis of 'duration of action' is not possible; phenytoin is administered in an undefined number of cases post-diazepam. No set criteria for the administration of additional doses of the study drug.
Cock and Schapira (2002). United	Cessation of seizures without	Lorazepam effective in 64.7% of cases.	Conducted in the hospital environment.

Kingdom.	recurrence within the following 12 hours.	Diazepam effective in 60.9% of cases. (p=0.042)	Several incidences of benzodiazepine administration prior to arrival at hospital (and study enrolment) noted. Difficulty with data retrieval – significant proportion of the potential cohort (18%) do not have notes examined.

Alldredge et al., (2001) conducted the only study in this series which presents results from the out of hospital environment. Recruitment into the trial was based on a paramedic-led diagnosis of status epilepticus in the presence of generalised tonic-clonic convulsive activity lasting 5 minutes or more.

Alongside its primary outcomes, this study also measured the occurrence of functional cardiorespiratory changes prior to arrival at hospital, finding that lorazepam and diazepam administration related to complications in 10.6% and 10.7% of cases, respectively. In contrast, 22.5% of cases treated with placebo presented with complications meeting the same criteria (p=0.08). As the team identify, this suggests that cardiorespiratory complications are less likely to occur when patients are treated with benzodiazepines.

No significant differences were found in rates of survival to discharge and quality of neurological outcome between groups, however patients arriving at hospital still in status epilepticus were more likely to require intensive care admission than those in which pre-hospital termination of seizures had been successful (73% vs. 32% respectively, chi-square <0.001). Odds ratio for the successful outcome measure was 1.9, 95% CI (0.8 – 4.4) in the lorazepam versus diazepam comparison. Lorazepam versus placebo and diazepam versus placebo ratios were 4.8, 95% CI (1.9 – 13.0) and 2.3, 95% CI (1.0 – 5.9) respectively.

In the study conducted by Treiman et al., (1998), direct comparison between medications is not possible due to diazepam and phenytoin being administered consecutively as a single study agent. Despite this, the results demonstrate significant differences in success across the treatment regimes studied (p=0.02). In a pairwise comparison, lorazepam was effective on many more occasions than phenytoin alone (p=0.002), whereas the latter versus diazepam with phenytoin demonstrated no significant difference.

Leppik's results suggest that lorazepam demonstrated better efficacy for the termination of seizures of all types when compared to diazepam, however this difference reportedly does not attribute statistical significance. (Unfortunately, the basis for statistical significance in relation to this study is not documented). There was an equal incidence of adverse clinical effects (defined as respiratory depression or arrest) of 13% (41) vs. 12% (40) across the two study groups.

Cock and Schapira conduct the only UK based study in this series as a retrospective case note audit. The authors identify significant differences between groups receiving diazepam or lorazepam, with the latter offering a higher likelihood of treatment success where it is the first benzodiazepine administered in hospital (p=0.042). It should be noted that there was no difference in seizure termination efficacy, but recurrence after 12 hours was less likely in the lorazepam group (p=0.005). Interestingly, the team identify that problems with guideline implementation may affect adherence to new evidence-based protocols relating to seizure management, and suggest that more extensive use of lorazepam by paramedic staff may help to increase familiarity with the agent and foster its widespread adoption.

Additional observations

Efficacy - seizure termination

In several studies, lorazepam has been shown to successfully terminate seizures in a greater number of patients than diazepam (Treiman et al., 1998), (Alldredge et al., 2001). A literature review by Appleton, Macleod and Martland is supportive of lorazepam's efficacy in children when compared to other common benzodiazepines, and presents a case for intranasal use (2008).

Cock and Schapira (2002) found that both drugs were similarly effective in the termination of convulsive status epilepticus, however there were less recurrences of seizures (and therefore less repeat dosages required), and less occurrences of pharmacological sedation and endotracheal intubation due to refractory SE where lorazepam was used. This provides clinical evidence as to the real-world benefits of lorazepam's extended half-life when compared to diazepam - a result of the different distribution characteristics of the drug (Greenblatt and Divoll, 1983).

Timing - administration to action delay

Both drugs have a rapid duration of onset when administered as an IV bolus, with negligible differences in terms of the time taken in achieving a meaningful clinical effect (Trinka, 2009), (Greenblatt et al., 1989), (Treiman et al., 1998). The biggest differences occur when the two medications are delivered by IV infusion.

Administration routes

Both drugs can be administered by a variety of routes with differing absorption and distribution characteristics (Lowenstein and Cloyd, 2007). IV is the most commonly recommended and utilised in pre-hospital care, and as such forms a part of current clinical guidelines (Joint Royal Colleges Ambulance Liaison Committee, 2016).

Both drugs are rapidly absorbed into the brain, reaching peak plasma concentrations within a time frame of 1-5 minutes when administered intravenously (Arendt et al., 1983). However, diazepam is known to rapidly redistribute into adipose tissue due to its high lipid solubility, which accounts for its reduced duration of action in comparison with lorazepam (see below). Alternative routes suitable for emergency administration such as buccal, nasal, rectal, oral/sublingual and intramuscular are compatible with both drugs. Time to maximum plasma concentrations following IM administration of diazepam and lorazepam is reportedly delayed (Greenblatt et al., 1982), (Wermeling et al., 2001), which limits the potential for 'auto-injector' type device development.

Rectal administration of anticonvulsants is well documented and researched. Diazepam is more rapidly absorbed via this route due to its higher lipid solubility (Malinovsky et al., 1993), (Scott et al., 1998), (Wermeling et al., 2001), reaching therapeutic blood plasma concentrations within 15 minutes in adults (Lombroso, 1989), (Cloyd et al., 1998).

Studies that have considered intranasal administration of anticonvulsants demonstrate advantages in the rapid absorption of diazepam over lorazepam (Malinovsky et al., 1993), (Burstein et al., 1997), (Wermeling et al., 2001), (Knoester et al., 2002), (Riss, Kriel and Croyd, 2006), however in relation to the comparatively large volume of diazepam required to reach effective plasma concentrations it has been found that resultant leakage decreases the amount of agent absorbed (Burstein et al., 1997), (Knoester et al., 2002).

Duration of action

Mitchell and Crawford (1990) demonstrate that lorazepam has a much longer duration of action than diazepam, which leads to an improvement in outcome for patients treated with the drug. It is thought that this is due to the marked reduction in seizure recurrence associated with lorazepam administration alongside the lesser need for repeat doses of the drug in order to maintain a seizure-free state. Secondary to this results a reduced incidence of pharmacological sedation and intubation/mechanical ventilation retrospectively. It should be noted however, that diazepam pharmacokinetics relies on the microsomal oxidation pathway. This implicates a number of highly active metabolites with extended half-lives (primarily desmethyldiazepam), of which clearance is highly dependent on variables such as age and liver function (Breimer, Jochemsen and von Albert, 1980). In contrast, lorazepam is metabolised via the glucuronidation pathway and has no active metabolites. Together these observations make any differences in

absolute peak plasma concentrations less significant in terms of therapeutic efficacy. Additionally, it could be suggested that lorazepam presents a lower risk of undesired substrate interaction which improves its safety profile.

Safety

Both drugs are strong benzodiazepines and as such carry the primary risk of respiratory depression and arrest if used in high doses. There are documented cases of both adverse effects occurring (often resulting in ITU management), however incident monitoring suggests that lorazepam results in fewer adverse events that diazepam. Appleton et al, (2008) documents a reduction in lorazepam linked respiratory depression in context, with no comparable differences in unexpected physiological side effects such as anaphylaxis.

Storage

There are no regulatory constraints on the pre-hospital storage of diazepam or lorazepam with regards to environmental control, however studies have been conducted specifically focused on pre-hospital systems that demonstrate a much improved stability profile in lorazepam than diazepam across a wide range of operating temperatures. Gottwald et al (1999) demonstrated that lorazepam maintained 90% of its original concentration after 120 days of unrefrigerated on-ambulance storage, compared with diazepam retaining the same concentration at a maximum of 30 days in a study conducted in San Francisco. In addition, Gottwald showed that if LZP was refrigerated between 4-10 degrees Celsius, a 0% reduction in concentration could be achieved at 210 days in comparison to a 17% concentration loss in DZP.

Cost

The per-ampoule dose of each drug varies;

Diazepam as an emulsion (Diazemuls) 5mg/mL (presented as 10mg in 2mL) costs £0.91 per ampoule.

Lorazepam 4mg/mL costs £0.35 per ampoule.

All prices correct as of 01/09/16. (Joint Formulary Committee, 2016).

Limitations

Although these studies have a tendency towards lorazepam as the more effective agent, the dosages used between studies vary. There is no officially documented equivalent dose of lorazepam to diazepam although the latter is commonly administered in greater quantities or in combination with other anticonvulsants such as phenytoin.

There is a lack of literature comparing anticonvulsant therapies out of hospital. Studies suggest that significant challenges exist in evidence translation between in-hospital and out of hospital based research, particularly when risk/benefit ratios are considered in the often more complex working environments presented to ambulance professionals (Bigham and Welsford, 2015). A useful measure of efficacy in the pre-hospital environment is cessation of seizure activity prior to arrival at the emergency department which consequently reduces the risk of cardiorespiratory complications which present challenges to paramedics.

The use of midazolam for CSE management was not considered in this review. However, with its short duration of action and promising absorption profile via intramuscular, buccal and intranasal routes, midazolam could provide an efficacious alternative to intravenous benzodiazepine therapy in status epilepticus.

Summary

Most clinical guidelines throughout the world (including those published by NICE in the UK), recommend lorazepam as the first line benzodiazepine treatment for status epilepticus. As shown above, there is much evidence in support of lorazepam when compared to diazepam in the treatment of the condition. Previous reviews have collated evidence on this topic, and there is a tendency to support lorazepam as a more effective and safer treatment option (Prasad et al., 2005), (Rogalski and Rogalski, 2015), however there still exists some ambiguity as to whether lorazepam should replace diazepam in practice (Brigo et al., 2016).

Although diazepam and lorazepam are the focus of this review, there is emerging evidence to support the use of pre-hospital midazolam, which is more commonly associated with sedation and anaesthesia. Preliminary results from a trial conducted by Silbergleit et al (2012) in the United States appear promising. Silbergleit has demonstrated that the use of intramuscular midazolam is safe and potentially as effective as intravenous benzodiazepines in the control of convulsive seizures.

Conclusion

Research in the realm of pre-hospital care is a relatively new venture for the paramedic profession. Randomised controlled trials offering reliable evidence of pre-hospital pharmacological interventions are very limited, and as such clinical guidelines and legislation may benefit from review in light of new developments in pharmacology.

Lorazepam and alternative benzodiazepines already exist as first-line treatments for convulsive status epilepticus in preference to diazepam, and although ambulance guidelines facilitate some variation in practice legislation prohibits the autonomous use of these alternatives. Facilitation of randomised controlled trials that directly compare anticonvulsants in the pre-hospital environment should be encouraged, in the interest of continuous guideline and legislative review towards maintaining high standards of patient care.

Conflicts of interest

The authors declare no conflicting interests.

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