

Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial

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Summary

Background In sub-Saharan Africa, rectal diazepam or intramuscular paraldehyde are commonly used as first-line anticonvulsant agents in the emergency treatment of seizures in children. These treatments can be expensive and sometimes toxic. We aimed to assess a drug and delivery system that is potentially more effective, safer, and easier to administer than those presently in use.

Methods We did an open randomised trial in a paediatric emergency department of a tertiary hospital in Malawi. 160 children aged over 2 months with seizures persisting for more than 5 min were randomly assigned to receive either intranasal lorazepam (100 µg/kg, n=80) or intramuscular paraldehyde (0·2 mL/kg, n=80). The primary outcome measure was whether the presenting seizure stopped with one dose of assigned anticonvulsant agent within 10 min of administration. The primary analysis was by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00116064.

Findings Intranasal lorazepam stopped convulsions within 10 min in 60 (75%) episodes treated (absolute risk 0·75, 95% CI 0·64–0·84), and intramuscular paraldehyde in 49 (61·3%; absolute risk 0·61, 95% CI 0·49–0·72). No clinically important cardiorespiratory events were seen in either group (95% binomial exact CI 0–4·5%), and all children finished the trial.

Interpretation Intranasal lorazepam is effective, safe, and provides a less invasive alternative to intramuscular paraldehyde in children with protracted convulsions. The ease of use of this drug makes it an attractive and preferable prehospital treatment option.

Introduction

Acute protracted convulsions in children are one of the most common medical emergencies in sub-Saharan Africa. In areas with endemic malaria and a heavy burden of infectious diseases, including bacterial meningitis, and where resources are scarce, the incidence of seizures is many times greater than in well-resourced countries.¹ Timely interventions are necessary to maintain cardiorespiratory function, stop the seizure, and diagnose and treat the underlying disorder. Failure to provide such interventions could lead to a protracted seizure episode that is more difficult to control, increasing the likelihood of death or long-term neurological sequelae.^{2,3}

In the prehospital setting in developed countries, rectal diazepam is the most commonly used first-line agent in childhood seizures. However, concerns over social acceptability and convenience of rectal administration have led to a search for alternatives. Two randomised trials have shown buccally-administered midazolam is better than, or at least as effective as, rectal diazepam in childhood seizures.^{4,5}

In developing countries, the context of care and the challenges faced in medical emergencies are different from those in developed countries. Patients often present late in an illness because of an absence of organised

prehospital emergency services, the cost of transport, and the distances to travel. Many seizures at presentation are protracted and need several doses of anticonvulsant agents to be controlled. The risks of benzodiazepine-induced respiratory depression are substantial if the drug is given in excessive doses or in combination with other sedative agents, especially when provision of oxygen therapy might be scarce, or skills and resources for short-term ventilatory assistance are unavailable.⁶ Seizures are frequently due to acute central nervous or severe systemic infections, whereas in developed countries protracted febrile convulsions or poorly controlled idiopathic recurrent seizures are most common.⁵ The risk of recurrent seizures is great, and seizures might take place on wards that are inadequately staffed to monitor and manage them. Resource limitations reduce the availability of equipment such as appropriately sized cannulae, and so emergency therapy is often delivered by non-intravenous routes.

The ideal first-line anticonvulsant agent would be one that can be given safely and easily at a primary health-care facility. The anticonvulsant should be quick acting, have minimum cardiorespiratory side-effects, have a longlasting effect, and be inexpensive.

In view of its favourable pharmacokinetics and potential practical advantages, we wished to assess the

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See [Comment](#) page 1555

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efficacy and safety of intranasal delivery of lorazepam compared with intramuscular paraldehyde, which is our first-line anticonvulsant agent in the treatment of acute seizures in children.

Methods

Patients

Between July, 2004, and June, 2005, we did an open randomised trial comparing the efficacy and safety of intranasal lorazepam with intramuscular paraldehyde in consecutive patients with acute seizures presenting to the paediatric emergency department at the Queen Elizabeth Central Hospital, a teaching and referral hospital in Blantyre, southern Malawi. Participants were children aged between 2 months and 12 years who presented with generalised convulsions continuing for a minimum of 5 min. Generalised convulsions were defined as the presence of rhythmic twitching of the arms, legs, trunk, or facial muscles, tonic eye deviation, or nystagmoid eye jerking in a comatose child. Exclusion criteria were any child who had received an anticonvulsant agent within an hour of presentation, whose seizure had stopped with cooling or correction of hypoglycaemia, or who had features consistent with hepatic or hypertensive encephalopathy or organophosphate poisoning. The study was done in the resuscitation room at the paediatric emergency department of the Queen Elizabeth Central Hospital during its opening hours of 0730–1700, when it is operated by medical and nursing staff trained in paediatric emergency medicine.

Most children attending the emergency department live within the Blantyre region, and are not referred by a doctor. Fewer patients attend the paediatric emergency department outside the usual opening hours; however, patient characteristics in terms of diagnostic spectrum and seizure duration are similar to those who arrive during the day. The emergency department is a dedicated children's emergency unit that sees at least 75 000 patients a year, of whom around 30% need admission. About 1000 children are triaged as priority one (needing immediate emergency care) every year, and managed in the resuscitation room.

Staff of the paediatric department were fully informed of our study before it began. Rapid seizure control was our first priority. Informed consent for the participants was obtained in accordance with the code of federal regulations section 50.24 and 50.25 for clinical research operations (the ethical regulation on emergency trials).⁷ While the child was being assessed and medications drawn up, the guardian was informed of the procedures, and detailed descriptions of care took place in real time so as not to delay treatment. Informed consent after a full explanation was requested from the guardians as soon as the child was stable. All guardians gave written informed consent for their children to participate. Anonymous HIV spot testing was done and was not linked to any patient identification data in the final analysis. The

results were available to those who wished to know the HIV status of their child after full counselling before and after the test was done. The trial was approved by the research and ethics committee of the College of Medicine, University of Malawi (P03/04/248).

Study design

Children arriving to the emergency department who were convulsing or developed convulsions within the department were immediately taken to the resuscitation room. All convulsing patients were managed according to advanced paediatric life support guidelines⁸ up to the point of choice of anticonvulsant agent. Children diagnosed as hypoglycaemic (bedside glucostix ≤ 2.6 mmol/L, Roche Diagnostics, Boehringer Mannheim, Germany) had intravenous or intra-osseous access established and were given glucose. Those with continuing seizures were then randomly allocated to receive the named therapeutic options. Blocked randomisation was done in advance by a computer that randomly generated a table of numbers in batches of ten, and treatment allocations were sealed in unmarked identical envelopes. Investigators were masked to these allocations before the point of patient treatment. Study randomisation envelopes were kept in a so-called seizure control tray along with emergency drugs and equipment in the resuscitation room. All children who attended the emergency department were either weighed on arrival or had their weight estimated by use of a locally modified Broselow tape.⁹

Study envelopes were opened and the named medication was given by the study investigators (SA or EM). For administration of lorazepam, 100 μ g/kg was drawn up in a 1 mL syringe (4 mg/mL vial, Ativan, Wyeth-Ayerst, Philadelphia, USA), attached to a mucosal atomisation device (Wolfe Tory Medical, Salt Lake City, Utah, USA) and squirted rapidly into a nostril. To attain maximum bioavailability of intranasal lorazepam, we kept the child's head in the recovery position while placing the atomisation device firmly into one nostril and directing it upwards during administration. Intramuscular paraldehyde, 0.2 mL/kg (10 mL vial, Medicopharma UK, Romford, UK) was drawn up into a syringe and delivered immediately into the buttock or thigh after sterilisation of the injection site.

During seizure activity, humidified oxygen from an oxygen concentrator was provided through a mask or nasal cannula if the patient arrived with or developed an oxygen saturation reading of 92% or less. Oxygen saturation was monitored continuously for 30 min and recorded on arrival, every 2 min until 10 min after arrival, then every 5 min until 30 min. Blood pressure was measured and recorded according to the same time schedule after administration of the assigned anticonvulsant agent (Drager Dialog 2000 monitor type no 5706200, Medizintechnik GbmH, Lubeck, Germany, with a Nellcor pulse oximeter sensor, 800 series, Pleasanton, CA, USA). The end of a seizure was defined

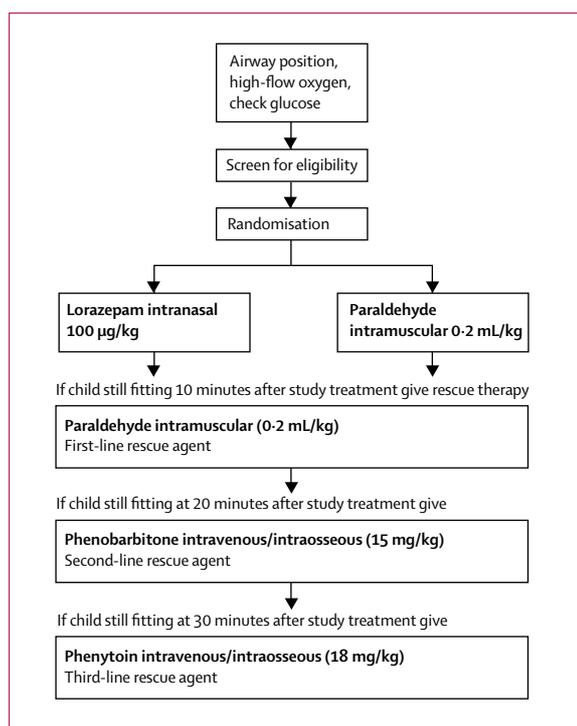


Figure 1: Study treatment algorithm

as cessation of all visible convulsive activity. Treatment was regarded as successful if one dose of the assigned treatment stopped the presenting seizure within 10 min of administration. If the seizure continued beyond 10 min, the treatment was judged ineffective and a rescue regimen was followed (figure 1). All children had a thick blood film taken for detection of malaria parasitaemia. Lumbar puncture with cerebrospinal fluid analysis was done if there were no contraindications (such as irregular respirations, posturing, or other signs of acute raised intracranial pressure). Plasma electrolytes were analysed with a point of care device (i-STAT1 handheld portable clinical analyser, Abbott Laboratories, IL, USA). HIV-1 and HIV-2 test cards (Determine, Abbott Laboratories, Tokyo, Japan) were used to assess HIV serological status. After leaving the emergency department, all patients were admitted to a ward for high-dependency care.

The primary outcome measure was whether the presenting seizure stopped or not with one dose of assigned anticonvulsant agent within 10 min of administration. We chose this time for further action to remain consistent with current standard treatment algorithms for acute paediatric convulsions.^{8,10} We also obtained data for several secondary outcome measures: these included time between seizure onset and drug administration, time between opening the study envelope and drug administration, time from drug administration to cessation of convulsion, frequency of episodes needing two or more rescue anticonvulsant agents, development

of hypotension (5 mm Hg or more reduction from that at enrolment for systolic and diastolic pressures) or hypoxia (oxygen saturation $\leq 92\%$) for 30 min after drug administration, and whether seizures recurred within 24 h of termination of the presenting convulsion. Final diagnosis of the presenting convulsion was made once all the available diagnostic and demographic data had been assessed. All patients were followed-up until discharge or death. Patients needing two or more rescue agents represent a group with seizures that were difficult to control, and so this outcome measure is also useful in indicating those patients likely to need further resources in terms of drugs and high dependency nursing care.

Statistical analysis

We anticipated, from previous clinical experience, that about 25% of children in the paraldehyde group would need a second dose of anticonvulsant after 10 min. We were unable to accurately anticipate the results with intranasal lorazepam, but using the findings reported in a Cochrane review of the use of rectal lorazepam, we assumed that 5% would need a second dose of anticonvulsant.¹¹ Using these estimations, we calculated that a total sample size of 154 people was needed to measure a 20% difference in primary outcome, with 90% power (β) and 5% significance (α). Data were entered on study proforma and double entered into a Microsoft Access file. We used Stata version 8 for analysis of the data. We used the following summary statistics: Wilcoxon's rank sum test to compare medians, Fisher's exact test to look for associations between variables, and χ^2 tests for absolute risk. The primary analysis was on an intention-to-treat basis.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

All 160 children randomised were followed up with no protocol violations by the end of the study. Of the 42 children excluded, most (29 episodes) stopped convulsing before randomisation and their convulsions were attributed to fever or hypoglycaemia (figure 2). Between treatment groups, children were similar for sex, age, median seizure duration pretreatment, median time to drug delivery, underlying cause, and HIV status. Seizures were exclusively due to acute brain infection secondary to cerebral malaria or bacterial meningitis in 51 (64%) of 80 children in the intranasal lorazepam group, and 53 (66%) of 80 children in the intramuscular paraldehyde group (table 1).

The presenting seizure stopped within 10 min of the assigned study drug in three-quarters of children in the

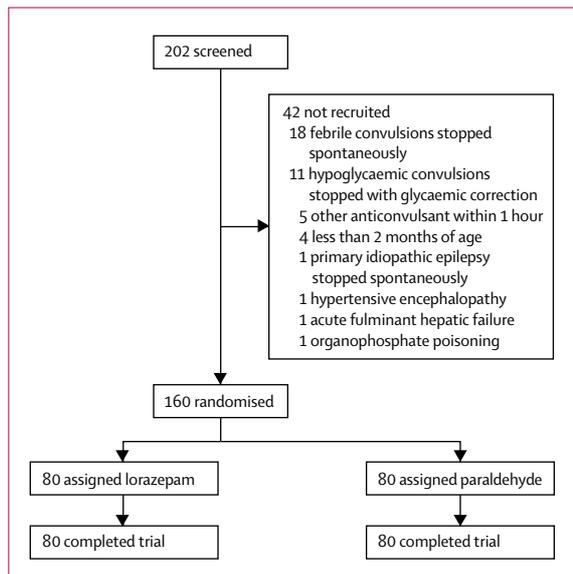


Figure 2: Trial profile

intranasal lorazepam group and in about 60% of those on intramuscular paraldehyde (table 2). The median time for the presenting seizure to stop after drug administration did not differ between groups (table 2). However, the number of children needing two or more rescue anticonvulsant agents was significantly lower in the intranasal lorazepam group than in the intramuscular paraldehyde group. Logistic regression analysis showed that only the difference in treatment was significant, and that none of the diagnoses were statistically important in affecting the need for two or more rescue agents either alone or in interaction with the intranasal lorazepam group or the intramuscular paraldehyde group (5% level of significance, odds ratio 6.33, 95% CI 1.64–24.45, $p > 0.007$). Only eight of 80 (10%) children in the intranasal lorazepam group and 11 of 80 (14%) children in the intramuscular paraldehyde group had a further convulsion within 24 h of presentation (table 2).

Median oxygen saturation at enrolment was 98% (IQR 95–99) in the intranasal lorazepam group and 99% (97–99) in the intramuscular paraldehyde group. After treatment the median readings were 99% (97–100) and 99% (97–99), respectively. In the intranasal lorazepam group, there were 15 children in whom systolic blood pressure fell by at least 5 mm Hg, with a median reduction of 7 mm Hg (range 5–20 mm Hg) and 12 children in whom diastolic blood pressure fell by at least 5 mm Hg with a median of 7.5 mm Hg (5–16 mm Hg). In the intramuscular paraldehyde group, there were 16 children with a systolic blood pressure reduction of at least 5 mm Hg with a median of 6.5 mm Hg (5–10 mm Hg) and four children with a diastolic blood pressure reduction of at least 5 mm Hg, median 6.5 mm Hg (5–20 mm Hg). In the lorazepam group, two children had a fall in oxygen saturation to

92% after treatment. In both these children oxygen saturations remained below 92% for 10 min and needed supplemental oxygen only. In the paraldehyde group, one child de-saturated to 92% after two doses of paraldehyde and one dose of phenobarbitone. This child needed oxygen therapy for 2 h to maintain normal oxygen saturations. Hypoxaemia preceded the administration of allocated treatment in eight cases, which was attributed to severe malarial anaemia (four cases), co-existent pneumonia (two), near drowning (one) and lung aspiration of gastric contents before presentation at hospital (one). The 95% exact binomial CI for the proportion of cardiorespiratory events is 0–4.5% in each group.

The recorded number of deaths from underlying causes was small and much the same between the randomised groups. 75 children had a pretreatment-seizure duration of less than 2 h, eight of whom died (absolute risk 0.1, 95% CI 0.04–0.2). Of the 85 patients with a pretreatment-seizure duration of greater than 2 h, 20 died (absolute risk 0.23, 95% CI 0.15–0.34; RR 0.45, 95% CI 0.21–0.86, $p = 0.03$). 19 children were found to be infected with HIV at presentation. Of these children, eight were male, 11 female, and the median age was 18 months (IQR 7–48). In HIV-infected children, eight of 19 had an underlying diagnosis of acute bacterial meningitis versus 13 of 141 in children not infected with HIV (4.57, 2.18–9.56 $p = 0.0001$). The proportion of deaths was also greater in those with HIV infection. Seven deaths occurred in the 19 HIV-infected children compared with 21 of 141 non-infected (RR 2.51, 95% CI 1.23–5.10, $p = 0.02$). There was no significant relation between HIV status and allocated treatment efficacy or safety.

Discussion

Intranasal lorazepam stopped three-quarters of the presenting seizures in less than 10 min. Intramuscular paraldehyde was effective in two-thirds of children within 10 min. This difference was not significant, although significantly fewer patients receiving intranasal lorazepam needed two or more rescue anticonvulsant agents than did those who received paraldehyde. There were no clinically important cardiorespiratory events, suggesting both treatment options were safe. There were fewer recurrent seizures in the intranasal lorazepam group but the difference was not significant.

In several children, the severity of tonic-clonic activity diminished over time after initial treatment, and the initially allocated drug could well have taken more than 10 min to effectively stop the presenting seizure. Our study endpoint, the visible cessation of all convulsive activity, was tightly defined and therefore waiting beyond 10 min in selected children would have introduced performance bias. In the absence of continuous electroencephalogram (EEG) monitoring, we did not think that breaking the study protocol was safe. Overall, the number of seizures controlled within 20 min

requiring first-line rescue therapy (intramuscular paraldehyde) was ten episodes in the intranasal lorazepam group and 11 episodes in the intramuscular paraldehyde group.

Children who needed two or more rescue anticonvulsant agents were more likely to have been initially allocated to receive intramuscular paraldehyde than intranasal lorazepam. As a measure of efficacy, this difference is notable. It might indicate poorer availability of blood-borne paraldehyde circulating to the brain, as a result of slower absorption and systemic release when given intramuscularly, or intranasal lorazepam might have a more favourable synergistic effect with first-line rescue therapy than intramuscular paraldehyde. Overall, 19 (12%) of 160 patients had further seizures within 24 h of initial convulsion, of whom ten (53%) children had cerebral malaria. 16 (84%) of 19 patients with seizure recurrence had not received second or third-line rescue anticonvulsant agents. These data suggest that prophylactic therapy should be considered in selected patients. Another randomised controlled study of phenobarbitone prophylaxis has been done in childhood cerebral malaria in a similar setting (Kilifi, Kenya) to our study. It showed a reduction in seizure frequency but with an unacceptable doubling of mortality.¹² This finding is important, and needs further study.

Paraldehyde is the first-line or second-line anticonvulsant agent in many countries in sub-Saharan Africa because of its favourable safety and efficacy profile.^{10,13,14} Paraldehyde acts within 5–10 min and can last up to 8 h. The major disadvantages of paraldehyde are a potential for local injury when given intramuscularly, incompatibility with plastics, and substantial cost. At around US\$30 per 10 mL vial, the cost of the drug alone for one intramuscular dose at 0.2 mL/kg for a child weighing 10 kg is \$6.¹⁵ This amount compares poorly with the cost of lorazepam, which at roughly \$1 per 4 mg/mL vial for the same sized child as one intranasal dose at 100 µg/kg is \$0.25.¹⁵ Paraldehyde given intramuscularly is preferred over the rectal route since it is absorbed quicker, is easier to administer, and avoids the risk of bowel irritation or perforation, potential complications if mixed inappropriately or given in decomposed form.¹⁶ In those allocated to receive

	Lorazepam (n=80)	Paraldehyde (n=80)
Demographic characteristics		
Sex		
Boy	44 (55%)	43 (54%)
Girl	36 (45%)	37 (46%)
Age (months, median, IQR)	18.5 (9–33)	19 (10.5–36)
Seizure duration before treatment (min, median, IQR)	127 (66.5–220)	120 (35.5–252)
Time to drug delivery once study envelope opened (seconds, median, IQR)	60 (60–60)	60 (60–60)
HIV infected	8 (10%)	11 (14%)
Cause of seizure (final diagnosis)*		
Cerebral malaria	39 (49%)	44 (55%)
Protracted febrile convulsion	16 (20%)	15 (19%)
Metabolic derangement (serum Na <130 or >145 mmol/L)		
Alone	5 (6%)	6 (7.5%)
Co-existing	7 (9%)	6 (7.5%)
Acute bacterial meningitis	12 (15%)	9 (11%)
Primary idiopathic epilepsy	3 (4%)	3 (4%)
Drug toxic side-effect	2 (2.5%)	4 (5%)
Pre-existing neurological abnormality	1 (1%)	2 (2.5%)
Aseptic meningitis	1 (1%)	1 (1%)
Post head injury	1 (1%)	0
Hypoxic brain injury	1 (1%)	0
Tuberculosis meningitis	1 (1%)	0
Cerebral abscess	1 (1%)	0
Data are number (%) unless otherwise stated. *Some children had two or more co-existing conditions.		

Table 1: Baseline characteristics of treated children

intramuscular paraldehyde, 61% had seizure control within 10 min. Our anticipated control of 75% of seizures by one dose of paraldehyde was an educated guess after years of experience of using this drug in sub-Saharan Africa. Our results, however, suggest intramuscular paraldehyde was not as effective as we had anticipated, and we acknowledge that our estimate might have been overoptimistic.

Midazolam administered buccally or nasally is effective for initial seizure control;^{4,5,17,18} however, in view of its shorter duration of action (3–4 h) than lorazepam (12–18 h) we were concerned midazolam might not act for long enough to prevent seizure recurrence. Such a short-lived effect is a major concern in settings in which seizures are

	Lorazepam (n=80)	Paraldehyde (n=80)	Absolute risk (95% CI)		p
			Lorazepam	Paraldehyde	
Presenting seizure stopped within 10 min	60 (75%)	49 (61%)	0.75 (0.64–0.84)	0.61 (0.49–0.72)	0.06
Seizures needing two or more rescue anticonvulsant agents	8 (10%)	21 (26%)	0.1 (0.04–0.19)	0.26 (0.17–0.37)	0.007
Seizure recurrence within 24 h	8 (10%)	11 (14%)	0.1 (0.04–0.19)	0.14 (0.07–0.23)	0.46
Died	15 (19%)	13 (16%)	0.19 (0.11–0.29)	0.16 (0.08–0.26)	0.68
Time for fit to stop (min, median, IQR)	7.5 (4.5–11.5)	8 (5–21)	0.06*
Data are number (%) unless otherwise stated. *Wilcoxon's rank-sum test.					

Table 2: Primary and secondary outcome measures

often caused by continuing pathological changes in the central nervous system. Lorazepam is effective in acute seizure control and has few clinically important adverse effects when given intravenously.^{19,20} In the absence of intravenous access, buccal or intranasal routes for lorazepam are appealing alternatives. We chose the intranasal route for delivery because in our clinical practice we see children with pronounced salivation. We do not know if excessive salivation can cause dilution or delayed absorption, but did not want to have that doubt if the buccal route was unsuccessful. In similar previous studies^{4,5} undertaken in the UK, many children had coryza and upper respiratory tract infections and the researchers did not wish that to affect the results of absorption if the intranasal route was used. There were 11 convulsive episodes in our study in which children had evidence of nasal congestion, six in the intranasal lorazepam group and five in the intramuscular paraldehyde group. All cases responded to their allocated treatment within 10 min. We used an atomisation device (connected to a 1 mL syringe) that aerosolised the treatment solution. Aerosolisation compared with dripping a solution into the nasal cavity with a syringe has improved particle distribution, and targets a larger surface area of olfactory epithelium, thus increasing benzodiazepine maximum plasma concentration from about 50% to 80% of that reached when given intravenously.²¹ We used an undiluted lorazepam 4 mg/mL solution, thus gaining maximum concentration while keeping volumes low. We did not find access to the nasal cavity difficult with the mucosal atomisation device, even in the youngest children. In no children was there evidence of nasal discharge of the drug or aspiration when this technique was used. We acknowledge that the number of children who had protracted seizures with evidence of upper respiratory tract infection was small in our study. Whether in a developed or resource poor setting, in view of the differences in patient characteristics, there are valid theoretical concerns over the routes of absorption. We need to compare benzodiazepines given nasally, buccally, and via intravenous routes to see if all routes are as safe and effective as each other.

Neural connections, both intraneuronal and extraneuronal between the olfactory epithelium and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS. The intraneuronal pathway involves axonal transport and needs hours to days for drugs to reach the brain, whereas the extraneuronal pathway is thought to rely on bulk flow transport through perineural channels, delivering drugs directly to the brain within min.²² Experimental study with nerve growth factor has shown direct entry into the brain via extraneuronal pathways involving olfactory and trigeminal sensory nerves, thus bypassing the slower penetration of the blood-brain barrier.²³ We postulate a similar mechanism for intranasal lorazepam's rapid entry and delivery to cerebral tissue.

A large number of patients in our study had continuous seizures for longer than 2 h before treatment. Longlasting continuous seizures or those refractory to treatment and continuing for 2 h or more have a mortality of between 0% and 32% in well-resourced settings. Worse outcomes are associated with an acute symptomatic cause or progressive encephalopathy, multifocal or generalised abnormalities on initial EEG, age under 12 months, and duration of seizure pretreatment of 2 h.^{24–27} In our study, 28 (17.5%) of 160 children died. This high rate of death is likely to indicate a protracted seizure duration pretreatment and incidence of progressive encephalopathy predominantly of infective origin.

In comparison with previous studies in an emergency setting, which have been heavily weighted with febrile convulsions and known epilepsies, we treated more convulsions due to infectious causes. This group might be perceived to be more difficult to control, but we were nevertheless encouraged by the success of intranasal lorazepam. However, we acknowledge the limitations of clinical assessment alone in defining cessation of seizure activity, and that we were unable to exclude subclinical persisting electroconvulsive activity in our setting.

Lorazepam delivered intranasally fulfils many of the criteria for an ideal combination of drug and delivery system for the treatment of protracted seizures in a cost-restrained setting. Its favourable cost compared with paraldehyde and its efficacy and safety should make it a preferred option within the benzodiazepine family before and during hospital care.

Contributors

S Ahmad, J C Ellis, H Kamwendo and E Molyneux designed the study and cared for patients clinically. S Ahmad, J Ellis, and E Molyneux collected and entered the data. S Ahmad maintained the database. S Ahmad and E Molyneux analysed the data. All investigators contributed to the writing of the final draft of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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