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Brief Communication

Oro-mucosal midazolam maleate: Use and effectiveness in adults with epilepsy in the UK

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ABSTRACT

Background: Oro-mucosal midazolam maleate (OMM) with suitable training to family and carers is being increasingly recognized as the treatment of choice to mitigate the development of status epilepticus in non-hospital community settings. There are no studies to describe the use, effectiveness, and suitable dosing of OMM in adults with epilepsy in community settings.
Purpose: To describe the use, effectiveness, and dosing of OMM in the emergency treatment of epileptic seizures in community settings.
Methods: A retrospective observational study (2016–17) design was used with participant recruitment from four UK NHS secondary care outpatient clinics providing epilepsy management. Study sample was of adult people with epilepsy (PWE) having had a recent seizure requiring OMM. Data on patient demographics, patient care plans, details of a recent seizure requiring emergency medication, and dose of OMM were collected from medical records.
Results: Study data from 146 PWE were included. The mean age of PWE was 41.0 years (SD 15.2) and mean weight was 64.8Kg (SD 18.2). Fifty-three percent of PWE were recorded as having intellectual disability. The most frequently used concomitant medications were lamotrigine (43%). The majority of seizures occurred at people's homes ($n = 92$, 63%). OMM was most often administered by family/professional care-givers ($n = 75$, 48.4%). Generalized (tonic/clonic) seizures were recorded in most people ($n = 106$, 72.6%). The most common initial dose of OMM was 10 mg ($n = 124$, 84.9%). The mean time to seizure cessation after administration of this initial dose was 5.5 minutes (SD = 4.5, Median 5.0, IQR 2.1–5.0). Only a minority of seizures led to ambulance callouts ($n = 18$, 12.3%) or hospital admissions ($n = 13$, 9%).
Conclusion: This is the first observational study describing the use and effectiveness of OMM in adults in community settings. Minimal hospital admissions were reported in this cohort and the treatment was effective in ending seizures in adults in community settings.

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1. Introduction

Prolonged seizures and status epilepticus are neurological emergencies that pose a significant risk of morbidity and mortality [1]. Benzodiazepines are widely used as first line as rescue medications for prolonged seizures because of their efficacy and rapid onset of action [2]. Midazolam, a benzodiazepine derivative can be administered through different routes (oral/oromucosal, rectal, nasal, intramuscular and intravenous) [3–5]. Studies comparing the efficacy of midazolam have observed that nasal and oromucosal routes are non-inferior and more acceptable than intravenous or rectal routes of administration in community settings [6–9].

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Previous evidence suggests that intravenous lorazepam and intramuscular midazolam are most effective; however, similar comparative clinical studies on the effectiveness of oromucosal midazolam maleate (OMM) are lacking [10]. Several studies have evaluated the effectiveness of midazolam in children as the incidence of epilepsy and status epilepticus is much more common in this population than in adults [11–13]. Though the use of OMM has been studied in adults generally there has be no systemic in adults with epilepsy in non-hospital community settings [14].

The aim of this study was to describe the most common dose of OMM used to treat adults with epilepsy and evaluate its effectiveness in community settings.

2. Methods

This retrospective, observational, cross-sectional study, using the STROBE guidance was done in 2016–17. It was conducted in four NHS (National Health Service, UK) secondary care centers providing services for treatment and management of people with epilepsy in the UK community. This study received a favorable ethical opinion from the East Midlands - Nottingham Research Ethics Committee (reference: 15/EM/0492), and was approved by the local research and development department of each participating trust/health board.

The inclusion criteria for this study were: [1] Participants aged 18 years or greater at time of most recent seizure requiring emergency treatment [2] Participants with written patient care plans for administration of OMM (Epistatus®, Veriton Pharma Limited, UK) as rescue medication for seizure.

Eligible participants were identified retrospectively from medical records. In order to minimize selection bias, participants were selected in reverse consecutive order from the date they were last seen for an out-patient appointment until the center's recruitment target had been achieved. To describe the use of OMM in community settings ("real life"), data on each person's most recent episode of a seizure requiring emergency medication were used for this study. Data collected included: participant demographics, duration and type of seizure, administered dose of OMM, time to cessation of seizure, and need for ambulance call out or subsequent hospital admission. Data were extracted from clinical records by members of the direct care team to maintain patient confidentiality. Data were forwarded to the research team after anonymization. Statistical analysis was performed using Microsoft Excel®, using available results with no imputation of missing data. Quantitative variables were presented as mean (standard deviation [S.D]) or median (interquartile range [IQR]) and categorical data are presented as frequency percentage. A sample size of 120–200 was chosen to ensure reliability and precision in estimating the most common dose of OMM, in line with similar studies.

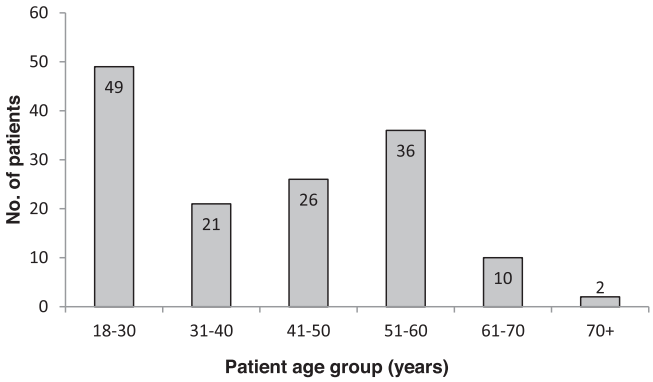

Fig. 1. Distribution of participant age at the time of most recent seizure.

3. Results

3.1. Patient characteristics

Data from medical records of a total of 146 participants were included in the study (81/146, 55% were male). Fig. 1 describes that the mean age of participants at the time of the most recent seizure when OMM was administered was 41.0 years (S.D. = 15.2).

The mean body weight of these patients, at the time of most recent seizure was 64.8 Kg (S.D. = 18.2, range 30 kg to 110Kg, available for 71, 48.6%). Intellectual disability was the most common comorbidity (77/146, 52.7%). The most commonly used concomitant medications were lamotrigine (63, 43%), levetiracetam (60, 41%) and sodium valproate (53, 36%). Participants' recent seizure frequency at the time of the rescue medication use is described in Fig. 2.

The most common location for administration of OMM was recorded as home (92, 63.0%). The drug was most often administered by a professional care-giver (75, 48.4%). Generalized tonic-clonic seizure was the most common type of seizure treatment with rescue medication (106, 72.6% Table 1).

Fig. 2. Distribution of seizure frequency in the year preceding the date of data collection.

Table 1
Distribution of types of seizure and cumulative dose of OMM administered.

Type of Seizure	No. of patients	% (n = 146)	Mean cumulative dose (mg)	SD
Generalized seizure (Tonic/Clonic)	106	72.6%	10.3	3.5
Focal seizure	19	13.0%	9.7	1.1
Myoclonus	4	2.7%	10	0.0
Other	2	1.4%	7.5	3.5
Not recorded	15	10.3%	11.3	3.5
Total	**146**		10.3	3.3

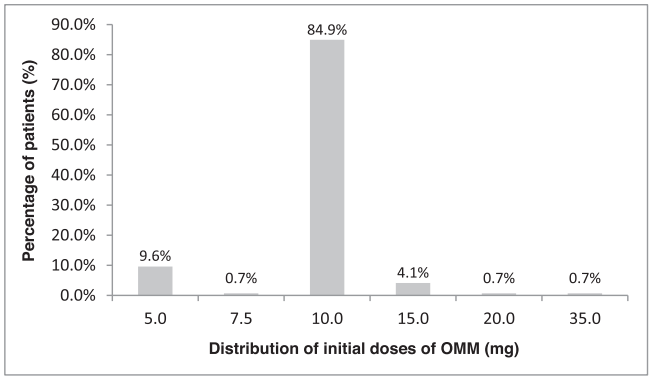

Fig. 3. Distribution of initial dose of OMM administered during most recent seizure.

3.2. Oromucosal midazolam maleate dose distribution

The most common initial dose of OMM administered to participants was 10 mg. This was used for 84.9% (n = 124) of seizures recorded in this study. The distribution of initial doses of OMM is shown in Fig. 3. Use of an initial dose of five mg was reported for 9.6% (n = 14) of seizure episodes. The mean cumulative dose recorded for this patient cohort was 10.3 mg (S.D = 3.3 mg, range of 5 to 35 mg, Table 1). The mean cumulative dose of OMM administered according to type of seizure is described in Table 1.

The mean length of time until cessation of seizure was 17.9 minutes (n = 4, S.D = 11.8, Median 19.8, IQR 13.3–24.4) following a 5-mg dose of OMM and 5.5 minutes (n = 38, S.D = 4.5, Median 5.0, IQR 2.1–5.0) following a 10-mg dose of OMM.

Table 2
Distribution of OMM dose according to duration and frequency of seizures in the year preceding data collection (as prescribed in individual patient care plans).

Usual duration of seizure (min)	Number of seizure care plans*	Mean dose (mg)	SD
0 to 2	40	10.32	2.70
2 to 4	58	9.64	2.31
4 to 6	58	10.29	1.83
6 to 8	4	11.67	2.58
8 to 10	2	12.50	5.00
10+	32	9.64	2.09
Cluster seizures	4	10.00	-
Not known	22	8.57	3.06
Seizure frequency (No. per month)	**No. of patients**	**Mean dose (mg)**	**SD**
0 to 2	43	9.36	2.11
0 to 3	31	9.10	1.94
7 to 10	10	10.77	1.88
11 to 20	10	10.59	1.66
over 20	27	10.33	2.90
Not known	25	11.11	2.11

*Total N numbers reflect patients who were given more than one seizure care protocol.

Table 3
Ambulance call outs and hospital admissions following OMM administration.

Ambulance call out	No. of patients	% (n = 146)
Yes	13*	9%
No	120	82%
Not known	13	9%
Total	**146**	
Hospital admissions**	**No. of patients**	**% (n = 146)**
Admitted to ED or Acute Admissions Unit (following ambulance call out)	10	7%
No admission	129	88%
Not known	7	5%
Total	**146**	

*Of 13 call outs, medications administered were recorded in 3 patients: one had an unknown dose of midazolam, one given 5 mg of oromucosal midazolam maleate and an unknown dose of diazepam; one was given 5 mg of oromucosal midazolam maleate (these doses are not represented in previous tables).** Hospital medications were recorded in four admitted patients: one given unknown dose of IV lorazepam plus an unknown dose of levetiracetam, one given an unknown dose of paraldehyde, one given an unknown dose of phenytoin, one given 3 mg of lorazepam plus 1 g of phenytoin.

Time to cessation of seizure was not recorded for 71.2% (n = 104) of participants. An initial dose of OMM was sufficient to achieve cessation of seizure in 82.9% (n = 124) of participants, while 10 participants required additional doses (data were unavailable for 12 remaining participants).

The mean prescribed dose of OMM in patient care plans (for all types of seizures) was 10.0 mg (S.D. = 2.3). Mean prescribed dose according to seizure frequency and duration is shown in Table 2.

An initial dose of 10 mg was administered in 65.5% (n = 19/29) with body weights between 30Kg and 60 kg and in 83.3% (n = 35/42) with body weights ranging from 60 kg to 110Kg.

Seizures requiring post rescue medication ambulance call outs was 9% (n = 13/146) three of four of whom required hospital admission (7%, 10/146). Further details about these participants are described in Table 3.

4. Discussion

This retrospective observational study on the use of OMM in adults with epilepsy in community settings shows that a 10-mg dose of OMM was well tolerated and usually effective in achieving seizure cessation. The demographics of our study population and the high prevalence of generalized tonic/clonic seizures are consistent with previous reports [15].

A 10-mg dose of OMM was effective in ending seizures within an average of 5.5 minutes (Median 5.0) in our study sample.

This is consistent with previous observations on the rapid onset of action and relatively short half-life of OMM [3,16]. Most participants who received an initial 10-mg dose of OMM reported seizure cessation. However, since time to cessation of seizure following first dose of OMM was recorded for only 28.8% of

patients in our study sample, further studies with more complete data may be needed to confirm this result. Larger patient cohorts are also needed to evaluate the relationship between patient characteristics such as age, body mass index, and midazolam dose responsiveness.

It is worth noting that our study population was comprised of a large number of people with intellectual disability. This is a relatively under-represented patient group in clinical studies and it is useful that the results of this study may help inform therapeutic strategies for this patient cohort particularly likely to require rescue medication [17].

Despite the fact that our study focused on a participant population with difficult-to-treat epilepsy (as evidenced by the fact that all participants had emergency treatment plans and had been prescribed rescue medications), a relatively small number of seizures (less than 10%) led to hospital admissions and ambulance call outs. It would be unethical to carry out a randomized controlled study to evaluate how often OMM can stop prolonged seizures and obviate the involvement of emergency services. However, previous studies showing that suspected epileptic seizures are one of the commonest neurological reasons for emergency admission to hospital suggest that the use of OMM had a significant effect on emergency healthcare usage in the population studied here [18,19]. Our observations were based on data from a single recent episode of seizure where OMM was used as rescue medication. Further studies on the use of OMM as rescue medication for adults with epilepsy would be of interest to assess its impact on healthcare resource use [20,21].

5. Conclusion

The results of this study show that a 10-mg dose of oromucosal midazolam maleate is used most often as rescue medication for adults with epilepsy and is effective when administered in community settings.

Conflict of interest

All authors have the potential conflict of interest to disclose.

The study was sponsored by Veriton Pharma (previously Epistatus), adopted onto the National Institute of Health Research (NIHR) portfolio. The sponsors had no influence on the design, delivery, and analysis of the study. The payments of the study were made to the NHS institutions participating. No direct conflict of interest is recognized.

Disclosure

RS has received institutional and research support from LivaNova, GW pharma, UCB, Eisai, Veriton pharma, Averelle and Destin outside the submitted work. MR has received funding for research projects from UCB Pharma, commercial research paid for by LivaNova and personal payments from Elsevier as Editor-in-Chief of Seizure - European Journal of Epilepsy. All other authors declare no conflict of interest. The study was sponsored by Veriton Pharma (previously Epistatus), adopted onto the National Institute of Health Research (NIHR) portfolio. The sponsors had no influence on the design, delivery, and analysis of the study. The payments of the study were made to the NHS institutions participating. All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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