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What are the best ways to deliver benzodiazepines in children/patients with prolonged convulsive seizures?

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ABSTRACT – Aetiology is the main determinant of morbidity and mortality in convulsive status epilepticus (CSE) but longer seizure durations may also increase risk of worse outcome. Thirty minutes of seizure activity is usually the time period used in longstanding definitions of CSE but it is not acceptable to wait for 30 minutes before treatment. Whilst intravenous therapy is best, pre-hospital treatment by a non-intravenous route is most practical in treating children. Benzodiazepines are the main class of first-line emergency antiepileptic drugs. This review will examine the available data on benzodiazepines according to: stability in the conditions of the emergency room services, drug absorption *via* non-intravenous route, clinical efficacy and safety, and ease of delivery and social acceptability.

Key words: benzodiazepine, children, seizure

Convulsive status epileptics (CSE) is associated with increased morbidity and mortality (Raspall-Chaure *et al*., 2006). Whilst underlying aetiology is the main determinant of morbidity and mortality, experimental and clinical data indicate that longer seizure durations also increase the risk of a worse outcome (Lothman, 1990). Thirty minutes of seizure activity is the time from which permanent brain injury can be observed and hence the reason why this time period is used in longstanding definitions of status epilepticus, particularly for epidemiological studies. However, it is not acceptable to wait for 30 minutes before treatment. Since 80% of seizures that do not stop within five minutes of onset continue for at least 30 minutes (Shinnar, 2007) and the longer seizures continue the more difficult they are to stop, there has been the emergence of an operational definition of CSE for treatment purposes to be based around a 5-minute threshold (Lowenstein *et al*., 1999). Since most seizures start outside of the hospital/clinical setting (Raspall-Chaure *et al*., 2007), it is imperative that in order to minimise seizure duration, treatment should be started prior to arrival at the hospital (Treiman *et al*., 1998; Chin *et al*., 2004a; Chin *et al*., 2008).

Whilst there is clear evidence that intravenous therapy is best (Yoong *et al*., 2009), pre-hospital treatment

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by a non-intravenous route is most desirable since intravenous access poses a major challenge in a child experiencing seizures, particularly in children under the age of 5 years, when CSE is most common (Chin *et al*., 2004b; Chin *et al*., 2006). Benzodiazepines are the main class of first-line antiepileptic drugs (AEDs) used for the emergency treatment of seizures because they have a rapid onset of action, have good efficacy, and are easy to prepare and administer by non- intravenous routes.

The first licensed non-intravenous benzodiazepine preparation was rectal diazepam, and for many years was considered the gold standard for pre-hospital treatment (Shorvon, 2013). However, new benzodiazepines have emerged (midazolam, clonazepam, and lorazepam) with alternative delivery routes (intranasal, buccal/oromucosal, sublingual, and intramuscular). This review will examine the available data according to:

– stability in the conditions of the emergency room services (EMS);
– rapid drug absorption via non-intravenous route ;
– proven clinical efficacy and safety;
– ease of delivery route and social acceptability.

Stability in the conditions of the EMS

Rectal diazepam gel is stable under the temperature and light exposure conditions found in ambulances. When exposed to a freeze-thaw cycle, hard freeze (-30°C for 72 hours), extreme light exposure, and long-term evaluation at either 30°C or 40°C, diazepam gel concentration always exceeded 95% of label, with no substantial changes in excipients or physicochemical properties (Alldredge *et al*., 2002).

Similarly, when exposed to ambient ambulance conditions during the spring/summer months in 14 metropolitan areas across the United States, midazolam and lorazepam were generally stable. There was no degradation in a non-commercially available parenteral, liquid, autoinjector preparation of midazolam after 60 days (mean relative concentration: 1.00; 95% confidence interval [CI]: 1.00-1.00); it was stable across temperature exposures (adjusted R2: -0.008). Under the same conditions, there was minimal degradation of a commercially-available, parenteral, liquid preparation of lorazepam (mean relative concentration: 0.99; 95% CI: 0.98-0.99), but degradation correlated to increasing mean kinetic temperature (adjusted R2: 0.278). Whilst there was a statistically significant difference ($p<0.001$) in the temperature dependence degradation between both drugs, both maintained clinically acceptable concentration levels of the active drug (McMullan *et al*., 2013). McMullan and colleagues have now confirmed that these findings remain consistent even when storage under EMS conditions is increased to 120 days (McMullan; *personal communication*). These findings are important since they provide evidence against the long held view that parenteral, liquid lorazepam requires refrigerated storage, and therefore justify the possibility of its usage in the pre-hospital setting.

Rapid drug absorption and action *via* non-intravenous route

Table 1 summarises the bioavailability, time to maximum blood concentration (T_{max}), and plasma half-life ($T_{1/2}$) of buccal midazolam, intranasal midazolam, sublingual lorazepam, sublingual clonazepam drops, and rectal diazepam (Wermeling *et al*., 2006; Riss *et al*., 2008; Viropharma, 2011). Generally, there is high bioavailability amongst all, with greatest bioavailability of 90% or more for sublingual FDDF lorazepam and rectal diazepam. Whilst T_{max} for buccal and intranasal midazolam, as well as rectal diazepam, is within 30 minutes (the shortest being 10 minutes for intranasal midazolam), that of clonazepam drops and sublingual FDDF lorazepam is longer, between 1-4 hours.

Table 1. Bioavailability, time to maximum blood concentration (T_{max}), and plasma half life ($T_{1/2}$) of buccal midazolam, intranasal midazolam, sublingual lorazepam, sublingual clonazepam drops, and rectal diazepam.

	Oromucosal midazolam hydrochloride (Viropharma, 2011)	**Intranasal midazolam** (Wermeling *et al*., 2006)	**Clonazepam drops** (Tassinari, 1998; Greenblatt, 1982)	**Fast-dissolving drug formulation Lorazepam** (Riss *et al*., 2008)	**Rectal diazepam** (Riss *et al*., 2008)
Bioavailability	75%†– 87%‡	72.5%	>80%	94%	90%
T_{max}	<30 min*	10.3 min	1–4 hours	2.3 hours	10–45 min
$T_{1/2}$	27 min-3.4 hours	3.25 hours	19-60 hours	7-26 hours	21-70 hours

*In children; †In healthy adults; ‡In children with severe malaria and convulsions.

For both children and adults, there is some evidence of inter- and intra-subject variability with regards to the effective dose and speed of onset of sublingual lorazepam (Greenblatt *et al*., 1982; Camu *et al*., 1988; Yager and Seshia, 1988). In a study of 10 children, 8 had a latency of 30-60 minutes in terminating serial seizures (Yager and Seshia, 1988). In a randomised, single, five-way crossover study comparing the pharmacokinetics of two forms of sublingual lorazepam compared to intravenous, intramuscular, and oral lorazepam, 10 healthy adult volunteers each received a modest dose of 2 mg of lorazepam administered by each route, with sequential phlebotomy to assess levels. Of those given standard oral tablets of lorazepam administered sublingually, there was a lag time of 22.7±5.1 minutes from administration to the start of absorption in nine of the 10 volunteers. When they were given a special tablet preparation delivered sublingually, 8 showed delayed absorption of 14.9±3.5 minutes. There was no lag time for the intravenous nor intramuscular delivery routes. All subjects reported mild to moderate discomfort when given the drug intramuscularly. All routes exhibited similar peak drug concentrations, with the pharmacokinetics of the sublingual routes being similar to that of the oral route, which in turn, had a slower time-to-peak concentration compared to intramuscular lorazepam, although this was not statistically significant (Greenblatt *et al*., 1982). This study suggests that if a preparation of lorazepam that undergoes rapid dissolution is available, it may be a useful clinical alternative to intramuscular/intravenous lorazepam. Fast-dissolving drug formulation (FDDF) lorazepam may be one such preparation but its absorption can be variable.

In a study comparing the pharmacokinetics of FDDF and intravenous lorazepam as anaesthetic premedication, 8 adult surgical patients were given 4 mg sublinguales FDDF lorazepam and 8 were given 4 mg intravenous lorazepam. The absorption of sublingual FDDF lorazepam was rapid in half of the patients and provided a high plasma concentration of lorazepam (Cmax: 61.8±16.2 ng/mL) in a short time interval (Tmax: 58±39 min). However, in the other half, the absorption was slow with a low plasma concentration (Cmax: 39.5±17.2 ng/mL) with a variable lag time (Tmax: 360±69 min). This variability in absorption might explain why premedication with FDDF lorazepam is sometimes less effective than expected (Camu *et al*., 1988), and could theoretically result in similar problems in the acute treatment of seizures.

In a study on the pharmacokinetics of buccal midazolam, 10 healthy adult volunteers were given 10 mg of buccal/sublingual midazolam hydrochloride. There was a rapid increase in venous blood concentrations for the first 20-30 minutes following treatment. However, preceding the venous spike, spectral analysis identified EEG changes at 8- to 30-Hz frequencies, 5-10 minutes into the test, but not in control subjects (Scott *et al*., 1998). These data prove that there is a rapid cerebral effect of midazolam hydrochloride and this occurs before a detectable venous surge. This may be attributable to the highly lipophilic, closed-ring form that midazolam hydrochloride assumes when it becomes absorbed into the circulation (Scott *et al*., 1998). To the author's knowledge, there is, to date, no peer-reviewed similar published data on buccal midazolam maleate.

Proven clinical efficacy and safety

The duration of action of rectal diazepam is less than 2 hours, for buccal midazolam hydrochloride is 3 to 4 hours, and is longer for clonazepam drops (24 hours), and even longer for sublingual FDDF lorazepam (up to 72 hours). Duration of action is not correlated with the plasma concentration-time profiles of these drugs (Rey *et al*., 1999). In principle, the longer duration of action of midazolam, clonazepam, and lorazepam may favour the use of these as alternatives to diazepam, particularly if they are available in a suitable non-intravenous rapidly absorbable form. In support of this, a metanalysis of six studies comparing non-intravenous midazolam and rectal or intravenous diazepam showed that midazolam was superior to diazepam in achieving seizure cessation (risk ratio: 1.52; 95% CI: 1.27-1.82). However, there are few randomised controlled trials that compare the different benzodiazepines and different administration routes for efficacy and safety in the emergency treatment of seizures in children. Those available are summarised below.

Intranasal midazolam *versus* rectal diazepam

In a prospective randomised study comparing intranasal midazolam *versus* rectal diazepam for the home treatment of acute seizures in paediatric patients with epilepsy, 358 children who attended a paediatric neurology clinic were prescribed home emergency treatment for their next seizure (Holsti *et al*., 2010). Carers were randomised to use either 0.2 mg/kg of intranasal midazolam up to a maximum of 10 mg or 0.3 to 0.5 mg/kg of rectal diazepam, up to a maximum of 20 mg RD (maximum, 20 mg) for their child's seizure at home if it lasted more than five minutes. Ninety-two carers gave emergency treatment and completed the study; 50 administered intranasal midazolam and 42 gave rectal diazepam. Four died

during the study without having used emergency medication, 254 did not receive emergency medication during the study, and 8 withdrew from the study. There was no statistically significant difference in time to treatment administration, time from treatment to seizure cessation, or efficacy between intranasal midazolam and rectal diazepam. Using an 11-point nominal scale to investigate ease of administration and overall carer satisfaction, carer scores were higher with intranasal midazolam compared to rectal diazepam for both ease of administration (10 *vs*. 9; p=0.02) and satisfaction (9.3 *vs*. 7.3; p=0.02). Four children (8%) treated with intranasal midazolam required oxygen or intubation for respiratory complications, compared to one (2%) treated with rectal diazepam (the difference was not statistically significant).

Intranasal midazolam *versus* intravenous diazepam

Table 2 summarises the results of two studies that have compared intranasal midazolam hydrochloride to intravenous diazepam (Lahat *et al*., 2000; Mahmoudian and Zadeh, 2004). In both, the end point was seizure termination within 10 minutes of treatment. The study by Lahat and colleagues was restricted to febrile seizures whilst Mahmoudian and Zaden included febrile and afebrile seizures. Both studies found remarkably high seizure termination rates when either drug was used. In particular, the study by Mahmoudian and colleagues reported seizure termination within 10 minutes of treatment in 100% of patients treated with either intranasal midazolam or intravenous diazepam. This is much higher than that found in any other study examining the efficacy of either drug for the emergency treatment of seizures.

Both studies found that buccal midazolam was quicker to administer than intravenous diazepam. However, Mahmoudian and Zadeh found that the interval between treatment and seizure termination was longer with those treated with buccal midazolam (3.6 minutes) compared to those given intravenous diazepam (2.9 minutes) (p=0.007).

Increased blood flow to the nasal mucosa during an upper respiratory tract infection may aid drug absorption but nasal secretions may theoretically dilute the midazolam solution, thereby reducing contact with the absorptive nasal mucosal surface (Lahat *et al*., 2000). In the study by Lahat and colleagues, most of the 26 children treated with intranasal midazolam had an upper respiratory tract infection, of which only 3 had poor seizure control which was attributable to presumed ineffective absorption, however, there were

Table 2. Randomised controlled trials of intranasal midazolam hydrochloride *versus* intravenous diazepam for the emergency treatment of seizures.

	Lahat *et al*., 2000		**Mahmoudian and Zadeh, 2004**	
No. patients	47		70	
Type of seizures	Febrile only		Febrile and Afebrile	
Age range	0.5-5 years		0.17-15	
Treatment[a]	Nasal Midazolam 0.2 mg/kg	IV Diazepam 0.3 mg/kg	Nasal Midazolam 0.2 mg/kg	IV Diazepam 0.2 mg/kg
No. of episodes (no. of patients)	26	26	35	35
Seizure termination within 5-10 mins (%)	23 (88)	24 (92)	35 (100)	35(100)
p for difference in proportions	(NS)		(NS)	
Time to administer[c]/min (range)	3.5 (0-7)	5.5 (1.5-9.5)	Not analysed but reported to be shorter for nasal midazolam compared to intravenous diazepam	Not analysed but reported to be shorter for nasal midazolam compared to intravenous diazepam
Time to response[c] /min	6.1	8.0	3.6	2.9

NS: significant; IV: intravenous.

no confirmatory drug levels. Nasal irritation was not investigated in either of the trials on intranasal midazolam described above (Lahat *et al*., 2000; Mahmoudian and Zadeh, 2004; Holsti *et al*., 2010). However, there is a potential for irritation to the nares, including burning sensation and lacrimation attributable to the acidic pH (3.5) of midazolam solution (Lugo *et al*., 1993).

Buccal midazolam *versus* rectal diazepam

Table 3 summarises studies comparing buccal midazolam *versus* rectal diazepam for emergency seizure treatment (Scott *et al*., 1999; McIntyre *et al*., 2005; Mpimbaza *et al*., 2008; Ashrafi *et al*., 2010). Except for the study by Ashrafi and colleagues in which buccal midazolam maleate was used, all the studies used buccal midazolam hydrochloride. In all the studies, the primary endpoint was clinical cessation of motor activity within 5-10 minutes of administration. Together, these data provide strong evidence that buccal midazolam is superior or, at the very least, as effective as rectal diazepam. Amongst these studies, one was carried out in a residential school for children with severe epilepsy, whilst the others were carried out in the accident and emergency setting where participants are likely to have difficult-to-control seizures because of the length of seizure activity prior to arrival at hospital. Thus, although there are no trials based on the general population, it would be reasonable to surmise from the available data that buccal midazolam would be better for out-of-hospital treatment. The results of the Ugandan study (Mpimbaza *et al*., 2008), which arguably had the best design since it was blinded and had the largest sample size, show that buccal midazolam was superior to diazepam in children without malaria but not in those with malaria. These findings highlight aetiology as playing a substantial role in effectiveness of treatment. In all the studies, respiratory depression was similar or less frequent with treatment with buccal midazolam, compared to treatment with rectal diazepam.

Buccal midazolam *versus* intravenous diazepam

A hospital-based study of 120 children (82 males; age range: 0-12 years) compared seizure termination within five minutes after treatment with 0.2 mg/kg of buccal midazolam *versus* 0.3 mg/kg of intravenous diazepam, irrespective of seizure duration or cause (Talukdar and Chakrabarty, 2009). Of the children treated with buccal midazolam, 85% had seizure termination within five minutes of treatment, compared to 93% in those treated with intravenous diazepam (p=0.142). Although treatment with buccal midazolam was initiated quicker than that with intravenous diazepam, the time required to control seizures was shorter in those treated with intravenous diazepam. For up to 10 minutes post-treatment, no patients in either group had unusual CNS depression, respiratory depression, apnoea, or cardiac dysrhythmia. These data highlight that intravenous treatment is better, but buccal midazolam would be a reasonable option if intravenous access proves problematic.

Intramuscular midazolam *versus* intravenous diazepam

Chamberlain and colleagues carried out a prospective, randomised study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures with a duration of at least 10 minutes in 24 children (Chamberlain *et al*., 1997). The 13 children in the midazolam group received medication earlier (3.3±2.0 *vs*. 7.8±3.2 minutes, respectively; p=0.001) and their seizures terminated earlier (7.8±4.1 *vs*. 11.2±3.6, respectively; p=0.047) than those of the 11 children treated with diazepam.

Intramuscular midazolam *versus* intravenous lorazepam

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study was a double-blind, randomised, non-inferiority trial of the effectiveness of intramuscular midazolam *versus* intravenous lorazepam in seizure management in the out-of-hospital setting for all age groups (Silbergleit *et al*., 2012). In total, 145 paediatric patients among 893, overall, were enrolled. For those who were seizure-free upon arrival at hospital, there was no statistical difference among those treated with intramuscular midazolam (73%) *versus* treatment with intravenous lorazepam (63%), however, the rate of hospitalisation was lower in the intramuscular midazolam group (57.6 *vs*. 65.6%, respectively; relative risk: 0.88). This study highlights the potential for another non-intravenous out-of-hospital route of administration. However, the authors admitted that the cost of study autoinjectors, that were not commercially available and had been funded through the USA's Department of Defense, would have been prohibitively expensive for general usage. Respiratory depression (14%) and hypotension (1-2%) were comparable in both treatment groups.

Intramuscular diazepam *versus* placebo

Abou-Khalil *et al*. carried out a double-blind, randomised, placebo-controlled trial of a diazepam autoinjector administered by caregivers to patients with epilepsy who required treatment for acute

Table 3. Studies comparing buccal midazolam *versus* rectal diazepam for emergency seizure treatment.

	Scott *et al.*, 1999		**McIntyre *et al.*, 2005**		**Mpimbaza *et al.*, 2008**		**Ashrafi *et al.*, 2010**	
Blinding	None		None		Single-blinded		None	
Setting	High-income, Western European country.		High-income, Western European country.		Low-income, African country		Middle-high income, Middle Eastern country	
Sites	Single		Multi-centre		Single		Two	
Pre-hospital/ Hospital	Pre-hospital. Residential school for young people with severe epilepsy.		Hospital (emergency department of 3 children's hospitals and one general hospital)		Hospital (paediatric emergency department of referral centre)		Hospital (emergency department of 2 paediatric referral centres)	
Aetiology	Convulsive seizures in a patient with epilepsy		Convulsive seizures of any aetiology		Convulsive seizures of any aetiology. Most malaria-related		Convulsive seizures of any aetiology	
No. patients	28		177		330		98	
Age range	5-19 years		1-6 years		3 m-12 years		Not given but median age 24 months in midazolam group and 48 months in the rectal diazepam group	
Treatment	Mid 10 mg	Dia 10 mg	Mid 0.5 mg/kg	Dia_r 0.5 mg/kg	Mid 0.5 mg/kg	Dia 0.5 mg/kg	Mid 0.3-0.5 mg/kg	Dia 0.5 mg/kg
No. of episodes (no. of patients)	40 (14)	39 (14)	109 (92)	110 (85)	165 (165)	165 (165)	49 (49)	49 (49)
Seizure termination within 5-10 mins (%)	30 (75)	23 (59)	61 (56)	30 (27)	115 (70)	94 (57)	49 (100)	40 (82)
p for difference in proportions	0.16		<0.0001		0.016		<0.001	
Mean or Median Time to administer/min (range)	2 (1-4)	2 (1-3)	-	-	-	-	2	3
Mean or MedianTime to response /min	6.00	8.00	8.00	15.00	4.75	4.35	4	5
Recurrence >1 hour post treatment/%	-	-	14	33	39	46	-	-
Time to recurrence/ hours (IQR)	-	-	<1	<1	5.1 (1.1-10)	1.8 (0.9-3.5)	-	-

repetitive seizures (Abou-Khalil, 2013). Among the 234 subjects enrolled, 81/110 were given placebo and 82/124 given diazepam. Those given intramuscular diazepam had a longer time to next seizure with a hazard ratio of 0.55 (95% CI: 0.34-0.88; p=0.012) and a lower number of seizures experienced during the 12-hour post-dose period (median: 0.0), compared to placebo (median: 1.0; p=0.010). Injection site pain was similarly common in both groups (15% for placebo *vs*. 17% for diazepam), as was injection site haemorrhage (6% for placebo *vs*. 5% for diazepam).

Whilst there are no randomised trials for lorazpam or clonazepam delivered sublingually, buccally or intranasally, there is anecdotal evidence of their effectiveness by these routes in the acute treatment of seizures.

Midazolam delivered buccally or intranasally has a relatively short half-life of up to 3.4 hours, compared to the other benzodiazepines included in *table 1* which may have a half-life of a day or longer. Long elimination half-life increases the risk of a hangover effect. In the randomised trials of intranasal/buccal midazolam *vs*. rectal diazepam described above, the risk of respiratory depression was similar or less in children treated with midazolam, compared to rectal diazepam.

Ease of delivery route and social acceptability

There is overwhelming evidence of a preference for nasal/oromucosal midazolam over rectal diazepam by families, carers, and affected children themselves (Wilson *et al*., 2004; Terry *et al*., 2007; Sofou *et al*., 2009). The preference is mainly due to better personal dignity for those being treated, the fact that buccal/intranasal routes are more socially appropriate, ease of administration for wheelchair users, and a perceived quicker response relative to rectal diazepam. A US 2003-2004 survey found that 19% (8/43) of parents reported that schools had refused to administer rectal diazepam, citing legal concerns behind their refusal (Terry *et al*., 2007). A recent European review revealed that fear of liability was a critical issue for treatment with rectal diazepam by non-parental carers (Wait *et al*., 2013).

Early in the placebo-controlled trial of a diazepam autoinjector, the study was put on hold because three caregivers accidentally injected themselves while attempting to administer study medication to subjects. Thus, in addition to the common complications of pain at the site and haemorrhage in patients given intramuscular treatments, there is the potential for needle stick/injection injuries to care-givers.

Conclusion

Midazolam, clonazepam and lorazepam are all in principle viable options to diazepam for the treatment of prolonged seizures in children. For practical reasons, non-intravenous delivery options must be the mainstay of early emergency treatment of children with seizures out of hospital, and include treatment rectally, intranasally, buccally (*via* oromucosa), sublingually (*via* oromucosa), or intramuscularly. The evidence, thus far, is that buccal midazolam is superior to rectal diazepam, but beyond that, there are limited conclusions that can be made because of the limited randomised controlled trials comparing benzodiazepines delivered by different routes.

There is marked diffidence towards treatment by the rectal route, and alternatives are at least as effective in seizure termination. There is rapid absorption by the nasal route but treatment by this route can theoretically be associated with marked nasal irritation, although this would be less of an issue in an acute convulsing child. There are also concerns surrounding this route of delivery because of a theoretical reduced absorption in children with upper respiratory tract infections, but this has to be counterbalanced by increased blood flow that may aid absorption. These theoretical concerns do not seem to have been borne out in practice, as a randomised controlled trial restricted to children with febrile seizures, many of whom had upper respiratory tracts, reported a high proportion of children successfully treated with nasal midazolam. However, why aim for a smaller moving target in the nares of children to deliver an intranasal preparation when there is a much bigger and easily accessible option close by for delivery of a buccal preparation? There is a theoretical risk of aspiration with buccal treatment but none of the studies on buccal midazolam above have reported this as a complication. Intramuscular injections cause local haemorrhage and are painful which would be a major deterrent for use in children, especially in those who require recurrent usage.

It is evident from the studies included in this review that the optimum dose for the individual drugs, according to the varied delivery route options, remains unclear. The long-term effects of these medications and whether they have a neuroprotective effect beyond seizure termination is not known. Further studies in these areas, particularly randomised controlled trials, are needed. □

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