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Review Article

Midazolam for rapid tranquillisation: its place in practice

Caroline Parker

Consultant Pharmacist, Adult Mental Health, Central and North West London NHS Foundation Trust

Abstract

Benzodiazepines are mainstay medicines in rapid tranquillisation. Midazolam is a short acting benzodiazepine. It is not available for oral administration as this route of administration leads to poor bioavailability. It has recently become available in a new formulation specifically designed for buccal administration, and is also available as a solution for injection.

The absorption of intramuscular midazolam is erratic and it has an unpredictable propensity for causing profound oversedation. Healthcare providers who include IM midazolam in their rapid tranquillisation guidelines or policies need to ensure that clinicians using it have the necessary knowledge, skills and competencies surrounding its use including clinical sequelae and the use of the 'antidote' flumazenil.

This brief review describes midazolam's potential role in rapid tranquillisation via these routes, and discusses the risks and benefits of these options in order to help readers consider their places in regular clinical practice, particularly in light of the shortage of lorazepam injection.

Keywords

Rapid tranquillisation; midazolam; buccal; intramuscular

INTRODUCTION

Rapid tranquillisation (RT) is the use of medicines to quickly calm the severely agitated patient in order to reduce the risk of imminent and serious violence to self or others rather than to treat the underlying psychiatric condition (Parker et al. 2013). RT is widely used across psychiatric services (Innes & Sethi 2013). It should only be used once non-pharmacological options have been explored and failed. According to National Institute for Health Care Excellence (2005, 1.8.4.8) guidelines 'All medication given in the short-term management of disturbed/violent behaviour should be considered as part of rapid tranquillisation (including pro re nata [PRN] medication…'. Therefore the definition of which medicines constitute RT is dependent on the indication for which they were given, rather than a defined list of medicines.

Although RT practice varies across the UK (Pereira et al. 2005), the currently recommended medicines are antipsychotics and benzodiazepines, and specifically lorazepam (National Institute for Clinical Excellence, 2005). A number of other agents such as the sedating antihistamine promethazine are also used but to a lesser extent (Innes & Sethi, 2013).

Correspondence to: Dr Caroline Parker, CNWL NHS Foundation Trust, Pharmacy, St Charles Mental Health Unit, Exmoor St, London, W10 6DZ. E-mail: caroline.parker@nhs.net
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Since May 2005 there have been ongoing difficulties with the supply of the only licensed formulation of lorazepam injection (Ativan®, Pfizer), leading trusts to source alternative supplies such as unlicensed formulations from outside of the UK.

This brief review considers the potential role of midazolam in this context.

Routes of administration of RT

Currently the medicines used for RT in the UK are generally administered orally (and absorbed via the gastrointestinal tract) or by intramuscular (IM) injection (Innes & Sethi 2013). A number of the antipsychotics are available as orodispersible tablets (aripiprazole, risperidone and olanzapine) and liquids (haloperidol, amisulpride, aripiprazole and risperidone). The medication is not buccally absorbed from these formulations; the tablets disperse in the saliva, and after swallowing are absorbed via the gastrointestinal tract.

In general, intravenous (IV) RT is no longer recommended due to specific risks with individual medicines, as well as difficulties and risks associated with the actual administration of slow IV boluses to a struggling and restrained patient, and the availability of staff trained to administer IVs (Parker et al. 2013).

Loxapine has recently been licensed for RT as a breath actuated inhalation, and is due to be launched in the UK in 2014 (Adasuve®; European Medicines Agency, 2013). Loxapine is a well-established first generation antipsychotic available in for oral and IM administration in several countries (excluding the UK; Keating 2013). Loxapine for inhalation for the management of mild to moderate agitation could potentially allow for a change in practice for a certain group of patients. However NICE's Technology Appraisal was terminated, and so it has not been approved (National Institute for Health and Care Excellence, 2013).

BENZODIAZEPINES IN RT

Benzodiazepines as a group are all active at the 'benzodiazepine' $GABA_A$ receptor complex. They all exhibit sedative, anxiolytic, anticonvulsant and muscle relaxant properties to varying extents. The choice of benzodiazepine for use in RT is guided in part by the formulations available, their method of delivery, and by their relative pharmacodynamic and pharmacokinetic properties (including rate of absorption, onset of effect and duration of effect). Respiratory depression is a potential risk with all benzodiazepines.

Parenteral benzodiazepines used alone are at least as effective as using an antipsychotic alone for RT (Gillies et al. 2013). Using a benzodiazepine alone is as effective as the combination of a benzodiazepine plus an antipsychotic for parenteral RT, although the combination may have other benefits (National Institute for Clinical Excellence, 2005; Isbister et al. 2010; Gillies et al. 2013). Benzodiazepines give rise to fewer extrapyramidal side effects than first generation antipsychotics (Huf et al. 2007; Gillies et al. 2013). For a very recent comprehensive review of the place or parenteral benzodiazepines in RT, see Gillies et al. 2013. The authors undertook an extremely extensive literature search for benzodiazepine administered via any route in RT. They did not identify any suitable trials of oral benzodiazepines for RT, which is notable as oral RT is recommended prior to parental RT (National Institute for Clinical Excellence, 2005). All of the 21 trials included used IM benzodiazepines except one, which used IV midazolam (Knott et al. 2006). Gillies et al. (2013) did not find any trials to directly compare the efficacy of one benzodiazepine over another. They found that the evidence for comparisons between various groups of drugs for RT was poor. Gillies et al. (2013, p. 5) concluded:

> 'Overall, there is insufficient information in these 21 studies to support or refute the use of benzodiazepines (alone or in combination with other drugs, where emergency drugs are needed)… However, there was good evidence to suggest that benzodiazepines are at least as effective as antipsychotics in reducing the agitation associated with mental illness… There was also some evidence that the combination of benzodiazepines with antipsychotics was superior to either drug alone and may also reduce side effects.'

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Lorazepam is widely used for RT. It has the advantages of being short acting, it is reliably absorbed after IM injection and does not have any active metabolites, and although hepatically metabolised this is not significantly impaired by hepatic dysfunction. With the shortages of lorazepam injection in the UK, attention has turned to finding another suitable benzodiazepine.

Diazepam is not a very suitable alternative for RT. It is long-acting, with several active metabolites including one very long-acting one (N-desmethyldiazepam with a half life of 30–100 hours) giving a prolonged terminal elimination phase of one to two days (Wockhardt, 2008). Therefore there is a risk of accumulation and so greater risk of respiratory depression. It is slowly and erratically absorbed after IM injection and may give lower peak plasma concentrations than obtained than with oral administration, as such it has no advantage over the oral route (Joint Formulary Committee 2013, Wockhardt Ltd, 2008). It has previously been used IV, however this route is no longer recommended, plus there is a high risk of thrombophlebitis after IV administration due to precipitation, although this can be minimised by the use of the emulsion formulation (Diazemuls®).

Clonazepam is also not very suitable for RT, although it has been used (IM; Benazzi et al. 1992). It is a long acting benzodiazepine with active metabolites, with an elimination half-life of between 20 and 60 hours (mean 30 hours; Roche Products Ltd, 2013) therefore there is a risk of accumulation and so greater risk of respiratory depression. It can cause significant postural hypotension. In the UK it is only licensed for IV administration in status epilepticus when it should be diluted with water for injection prior to giving by slow IV injection (over 30 seconds).

Midazolam is a short acting benzodiazepine with a quick onset of action and 'off-set' of action. It is extensively hepatically metabolised but its metabolites have only minor clinical activity and are renally excreted. Its half-life is longer in obese patients and those with cirrhosis. It is highly lipophilic and distributes widely. In the UK, midazolam is available as an injection and as a solution for buccal administration. It is not available for oral use as it has low bioavailability when administered orally due to extensive first pass metabolism. Although trial data was available at the time, it was not included in the 2005 NICE guidelines on the management of violence, however randomised controlled trial data on its use will be considered in the current review (National Institute for Health and Care Excellence, 2012).

Midazolam IM

Midazolam injection is unlicensed for RT in the UK, it is licensed for conscious sedation prior to procedures, anaesthesia, sedation in intensive care units (Roche Products Ltd, 2012). Both IV (Knott et al. 2006; Isbister et al. 2010) and IM use have been investigated for RT. It is widely used in some countries, often where the requirement to store lorazepam injection in refrigerated conditions inhibits its use. Recently IM midazolam has been incorporated into a number of UK trust RT policies and guidelines (5 out of 45; Innes & Sethi, 2013) including for use in children and adolescents (Taylor et al. 2012). Absorption from the muscle tissue is rapid and complete, absolute bioavailability is very high (over 90%). Maximum plasma concentrations are achieved within 30 minutes. It has a half-life of 1½ to 2½ hours in healthy adults. IM injection is painful (Roche Products Ltd, 2012).

For RT it has been used alone and in combination with the antipsychotics droperidol (Isbister et al. 2010) and haloperidol (Baldacara et al. 2011). IM midazolam has a faster onset of sedation than IM lorazepam (Nobay et al. 2004; Huf et al. 2007) and some antipsychotics (Martel et al. 2005; Nobay et al. 2004) and the combination of IM haloperidol plus promethazine (at 20 minutes; TREC Collaborative Group, 2003). It has similar efficacy to lorazepam or haloperidol (Nobay et al. 2004) and droperidol (Isbister et al. 2010) and other agents (Baldacara et al. 2011). Following IM administration plasma concentrations peak at approximately 5–15 minutes and sedation is usually noted within 20 minutes. But the desired sedative effects are shorter lived, wearing off earlier than

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with other medicines (at 45 minutes; Nobay et al. 2004; Martel et al. 2005) leading to the need for further doses to treat the re-emerging agitation (Martel et al. 2005; Isbister et al. 2010; Baldacara et al. 2011).

The doses used for RT have varied; commonly 5–10 mg has been given, although some studies used higher doses such as 7.5–15 mg (TREC Collaborative Group, 2003). The recommended doses for IM use as an anaesthetic pre-medication are similar, ranging from 4.9–7 mg for a 70 kg adult (Roche Products Ltd, 2012).

Midazolam, in common with all benzodiazepines, can cause sedation and respiratory depression which is more likely with higher doses (Joint Formulary Committee, 2013). In some RT trials, IM midazolam unpredictably led to respiratory depression requiring active intervention (TREC Collaborative Group, 2003; Martel et al. 2005) and excessive sedation (Baldacara et al. 2011), more frequently than other non-benzodiazepine medicines. In view of this, it has been recommended that IM midazolam should only be used in scenarios where services are fully confident in observing for and managing the consequences of respiratory depression (Care Quality Commission 2011; TREC Collaborative Group, 2003; Gillies et al. 2013). Managing the consequences of respiratory depression includes the use of oxygen and flumazenil, a benzodiazepine antagonist. As flumazenil must be administered intravenously, this would usually be done by a doctor as Registered Mental Health Nurses are not trained to administered IVs. In services where IM midazolam is administered, medical staffing needs to be such that in an emergency a doctor competent to administer IVs can be called to see the patient at a few minutes notice. These concerns have been highlighted by the CQC who have taken the unusual step of giving specific guidance on the use of a medicine to their second opinion approved doctors (SOADs) who authorise treatment plans for patients detained under the Mental Health Act 1983. The CQC suggests to SOADs that they should be 'especially mindful of midazolam's licensed indications, and of the potential harm that may result'. The CQC goes on to say that SOADs 'are likely to wish to satisfy themselves that the provider clinicians are fully aware of the risks, have adequate training in, and equipment for, resuscitation, and that the risks are outweighed by such clear benefits not obtainable from a more mainstream preparation…' (Care Quality Commission, 2011). In a recent survey of UK trusts' RT policies and guidelines it was found that, in keeping with NICE guidelines (National Institute for Clinical Excellence, 2005), the vast majority did specify that respiratory rate is one of the required physical health monitoring parameters to be checked following administration of RT (Innes & Iyeke, 2012). However, the recommended frequency of monitoring varied considerably. Infrequent monitoring of respiratory rate after midazolam IM could be insufficient to detect swift and erratic onset of respiratory depression. When looking at actual clinical practice after RT, few trusts can demonstrate adherence to their own physical health monitoring requirements (Loynes et al. 2013); monitoring may occur in as few as 16% of cases (Choudhury et al 2011), and CPR is not initiated as often as indicated, sometimes due to lack of equipment (Windfuhr et al. 2011).

If IM midazolam is to be used in psychiatry for RT then healthcare providers should pay attention to the National Patient Safety Agency's (2008) rapid response report. This alert addressed the risk of unintentional overdose with IV midazolam for conscious sedation. Ampoules of midazolam for injection are available in three strengths and three volumes. The contents of the two higher strength ampoules frequently exceeds the dose a patient requires, presenting a risk of administering a whole ampoule and so overdosing the patient. The alert recommended that high strength ampoules should be restricted to specific general medical settings. However the lower strength would necessitate the use of volumes that are excessively large for IM administration. It would be advisable for healthcare providers recommending the use of IM midazolam for RT to formally assess the risks in view of this risk alert (a risk assessment tool is provided).

Midazolam buccal and sublingual

Sublingual midazolam is quickly absorbed via the buccal mucosa, reaching peak plasma concentrations within 30 minutes (as per IM administration).

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Absolute bioavailability is lower than with IM administration but still high (about 75% in adults) and gives reliable plasma concentrations (Schwagmeier et al. 1998; ViroPharma, 2013). The elimination half-life in children is between 27 minutes and 3 hours 24 minutes (ViroPharma, 2013).

The buccal and sublingual administration of midazolam have been studied in a number of populations and scenarios, mostly in paediatrics and in patients with learning disabilities, as an alternative to rectal diazepam as an emergency antiepileptic for prolonged seizures where the speed of onset of action is crucial (Sweetman, 2011). Until recently, it was only available as a solution for injection which was given orally despite its bitter taste. This was not ideal, and involved snapping open a narrow glass ampoule and drawing up the correct amount of solution in an oral syringe prior to administration. Since 2011, a formulation specifically designed for oromucosal administration (Buccolam® 10 mg▼; ViroPharma Ltd, 2013) as pre-filled oral syringes, has been available in the UK. This is licensed for the treatment of seizures in patients aged under 18 years. It is not licensed for any indication in adults (ViroPharma Ltd, 2013). The Buccolam®▼ solution should be slowly inserted into the space between the cheek and gum, approximately half the solution on each side of the mouth. The syringes are all the same strength but available in a range of volumes thereby easily facilitating the safe administration of the dose using a whole syringe (0.5 ml = 2.5 mg, 1 ml = 5 mg, 1.5 ml = 7.5 mg, and 2 ml = 10 mg; ViroPharma Ltd, 2013). (NB ▼ indicates a product that is subject to additional monitoring.)

There is minimal data available regarding its efficacy in RT via this route and it has only been incorporated into a minority of UK trust RT policies/guidelines (2 out of 45; Innes & Sethi 2013; Taylor et al. 2012). In one small study (n = 27) in two English psychiatric intensive care units for men buccal midazolam 10–20 mg was used for RT instead of routine IM practice over a six month period. Sedative effects were noted at the first time point (15 minutes) peaking at 30 minutes, and lasting at least 1 hour (no further measures taken). In over a third of cases further doses of RT were required within 24 hours, which is in keeping with midazolam's short duration of action. Most patients were already prescribed regular oral benzodiazepines and received the buccal midazolam in addition to these. There was one case of over sedation (Taylor et al. 2008).

Clearly buccal midazolam is not a suitable alternative in the face of shortages of lorazepam injection as it requires the patient to comply with administration. But for patients who are, by definition, less disturbed and willing to accept a medicine given by mouth, buccal midazolam may be an appropriate choice instead of oral tablets. It has a faster onset of action compared with medicines absorbed via the gastrointestinal tract. However it has drawbacks, including a paucity of evidence when used via this route for this indication in this population. The oromuccosal solution is intended to be held in the mouth and absorbed there, however if it is swallowed the efficacy will be greatly reduced due to extensive first pass metabolism resulting in low bioavailability. Secondly, this formulation requires a member of staff to gently and slowly administer liquid directly from an oral syringe into the mouth of the patient. Given the likely agitation and aggression of the patient this may present practical difficulties, as they would be unlikely to sit reasonably still for a couple of minutes to allow this. Cost of medicines for RT is rarely a major concern as RT use is relatively infrequent and the purchase cost of medicines is insignificant compared to the cost of one night's admission to a psychiatric ward. As a newly licensed medicine, Buccolam®▼ is relatively expensive (ranging from £20.50 to £22.88 plus VAT per syringe depending on the dose), compared with the cost of a standard alternative oral RT, (lorazepam 2 × 1 mg tablets at 22p plus VAT; Joint Formulary Committee, 2013). Despite this hundred-fold difference in cost, this is probably not a deciding factor when considering the role in clinical practice of the newer product. If this intervention could be used to reduce a patients' duration of stay, and therefore cost, the cost of the medication would be more likely to be viewed positively.

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SUMMARY

Benzodiazepines remain mainstay options for RT, specifically lorazepam with haloperidol when IM administration is required. The shortages of lorazepam injection over the past few years have encouraged psychiatric services to consider alternatives. Healthcare organisations recommending the use of buccal or IM midazolam need to carefully balance the potential risks (clinical, medico-legal, poor evidence base) and advantages against those of the alternatives. As with any new initiative or practice, the initial risks are likely to be higher due to lack of familiarity and training needs.

Potential place in RT of IM midazolam

Midazolam is a short acting benzodiazepine that can be safely administered intramuscularly. Absorption following IM administration is erratic and it has an unpredictable propensity for causing profound over sedation. This is in the context of services that may be less skilled and equipped than they should be to manage such scenarios. Therefore healthcare providers who include IM midazolam in their RT guidelines or policies need to ensure that clinicians using it have the necessary knowledge, skills and competencies surrounding its use including clinical sequelae and the use of the 'antidote' flumazenil. They also need to consider the medico-legal risks of approving the use of IM for an 'off-licence' indication, and the implications of the NPSA (2008) alert.

Potential place in RT of buccal midazolam

Buccal midazolam may be a useful addition to the choices currently available for patients who are willing to comply and take RT medicines into their mouth. It has the advantage of a quicker onset of action than medicines to be swallowed. If a patient is refusing to open their mouth to accept oral medication, then they are also likely to refuse to buccal medication, and so a parenteral agent may be indicated.

Widespread use of buccal midazolam for this 'off-licence' indication is not yet recommended, as there is very little evidence to substantiate its efficacy and safety in adults or for this indication. Organisations recommending it need to give careful consideration to the practicalities of safe administration to appropriate patients, and guidance should be given to staff. The problems of using it in aggressive adults with the potential risk of staff being bitten during administration, and the dose being swallowed resulting in reduced efficacy, and the concept of attempting to administer a dose to a restrained patient, need to be carefully addressed. However these issues are not insurmountable.

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