A review of the use of intranasally administered midazolam in adults and its application in dentistry

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Abstract

Dental treatment for adults with a severe learning disability can be complicated due to lack of cooperation. This often results in treatment being provided under general anaesthesia (GA) with exodontia rather than restorative care and maintenance (Holland and O'Mullane, 1990). Supportive care and periodontal maintenance is also difficult (British Society for Disability and Oral Health, 2009). Midazolam has anxiolytic, muscle relaxant, anticonvulsant, hypnotic and amnesic properties and is commonly used in dentistry by trained sedationists as an intravenous conscious sedation agent. Where cannulation for adult patients has not been possible, midazolam has been administered orally or intranasally to facilitate cannulation and subsequent administration of additional midazolam intravenously. These combined approaches have enabled the provision of dental treatment in many cases that would otherwise only have been possible under GA. This paper reviews the use of intranasally administered midazolam in adults, the safety of the technique and its application in dentistry, particularly as an alternative to the use of GA for adults who are unable to comply with conventional dental care.

Key words: *Administration, intranasal, nasal, midazolam, adults, learning difficulties, dentistry, general anaesthetic*

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Introduction

Conscious sedation has been encouraged as an alternative to general anaesthesia (Standing Dental Advisory Committee, 2003; Standing Committee on Sedation for Dentistry, 2007; National Institute for Health and Clinical Excellence, 2010; Scottish Dental Clinical Effectiveness Programme, 2012; Academy of Medical Royal Colleges, 2013; Intercollegiate Advisory Committee for Sedation in Dentistry, 2015). Conventional conscious sedation techniques are widely used in dentistry but for some patients, including those with a severe learning disability, these techniques may not be possible due to lack of patient cooperation and challenging behaviour especially during cannulation for intravenous sedation (Fukata et al., 1993; Manley et al., 2008).

Midazolam has been administered via oral, rectal, intramuscular, intravenous and transmucosal routes including oral administration via the buccal sulcus (Nordt and Clark, 1997). There are disadvantages associated with these routes. Unreliable onset of action and low midazolam systemic bioavailability has been reported via the oral route (Allonen *et al.*, 1981). The rectal administration of midazolam is associated with pharmacokinetic disadvantages (Balaguer-Fernández *et al.*, 2010) and adverse attitudes of carers and patients (Sheepers *et al.*, 2000). Furthermore, midazolam administered intramuscularly may be painful (Balaguer-Fernández *et al.*, 2010) and intravenous access may be impossible in uncooperative patients (Hollenhorst *et al.*, 2001).

Midazolam can also be administered intranasally with significant potential advantages for dentistry (Manley *et al.*, 2008). The scientific basis and evidence for the use of intranasal midazolam is discussed in this review.

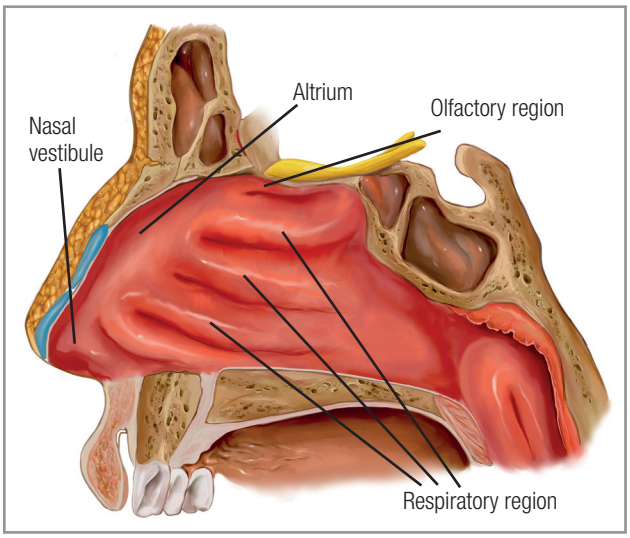
Intranasal drug administration

Anatomy of the nasal cavity

The nasal cavity is divided by the nasal septum into two symmetrical halves, opening at the nostrils and extending posteriorly to the nasopharynx.

Both halves consist of four areas, the nasal vestibule, atrium, respiratory region and olfactory regions (*Figure 1*). The cavity is lined with nasal mucosa that has a total surface area of approximately 150 cm^2 (Mygind and Dahl, 1998). With the largest surface area, the nasal respiratory mucosa is

Figure 1: Anatomy of the human nasal cavity. (from Pires *et al.*, 2009).



considered the most important section for systemic drug delivery. Its epithelium consists of pseudostratified columnar epithelial cells, goblet cells, basal cells and mucous and serous glands (Chien and Chang, 1987). The vascularity of the nasal mucosa significantly influences systemic drug absorption. The vascularisation of the vestibule and atrium areas is low whereas the respiratory and olfactory regions are highly vascularised (Pires *et al.*, 2009).

Volume of the nasal cavity

The nasal cavity has a total volume of 150-200 µL (Pires *et al.*, 2009). Due to mucociliary clearance and the limited amount of available water as a solvent, drugs for intranasal application are best administered as solutions in an ideal volume range of between 25 - 150 μL with an upper limit of 200 µL per nostril (Romeo *et al.*, 1998). If the drug volume delivered exceeds the recommended volume, low viscosity solutions tend to flow into the nasopharynx and are swallowed (Suter-Zimmermann, 2008).

Mucociliary clearance

Many epithelial cells of the nasal respiratory mucosa are covered with microvilli and fine projections called cilia. Microvilli enhance the respiratory surface area while cilia are essential to transport nasal mucus posteriorly toward the nasopharynx (Merkus *et al.*, 1998).

Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretory glands and goblet cells. This layer plays an important role in the defence of the respiratory tract as agents adhering to the mucus layer are transported by ciliary action to the nasopharynx and eventually to the gastrointestinal tract. This process is known as mucociliary clearance (MCC) and significantly influences nasal drug absorption (Pires *et al.*, 2009).

Method of administration

The method of intranasal administration used affects the site of drug deposition and subsequent absorption. Methods include aerosol sprays, drops and a liquid stream. The position of a patient in an upright or supine position during intranasal administration may be important especially when larger volumes of drops or liquid applications are administered.

The use of drops and liquid streams which deposit solutions more posteriorly will result in more rapid drug removal due to MCC and swallowing and decreased intranasal absorption (Pires *et al.*, 2009). Nasal sprays that deposit drug solutions more anteriorly result in slower drug removal and increased absorption as the drug remains within the nasal cavity for longer (Pires *et al.*, 2009). It is also possible to administer a more precise volume of solution and a more accurate dosage (Romeo *et al.*, 1998).

Intranasal absorption of midazolam

Midazolam is an imidazobenzodiazepine whose structure affects its physicochemical properties. In an acidic pH < 4, its benzepine ring structure is open, resulting in increased water solubility (Nordt and Clark, 1997) but at a physiological pH of approximately 7.4, the benzepine ring shuts and midazolam becomes highly lipophilic allowing rapid absorption across the nasal mucosa (Reves *et al.*, 1985) and a rapid onset of action (Kanto and Allonen, 1983).

Obstacles to drug absorption are limited time in the cavity due to MCC (Pires *et al.*, 2009) and potential metabolism before reaching the systemic circulation. Midazolam is mainly metabolised by the cytochrome mono-oxygenase P450-3A4 but this enzyme has not been detected in nasal mucosa so no midazolam nasal metabolism is expected here (Suter-Zimmermann, 2008).

Midazolam is rapidly absorbed directly into the systemic circulation bypassing the portal system and avoiding hepatic first pass elimination (Hollenhorst *et al.*, 2001). Consequently, the systemic bioavailability of midazolam following intranasal administration is higher than that which occurs following oral administration with a more rapid onset of action (Burstein *et al.*, 1997).

Literature search

A systematic search of the available literature was carried out using a Boolean search strategy to identify studies published between 1947 and 2014 on the use of intranasally administered midazolam in adults. The Ovid MEDLINE (R), Embase, AMED, PubMed, Web of Science, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials databases were searched.

Search strategy

Key words: Administration, intranasal, nasal, midazolam, adults

1. exp Administration, Intranasal
2. intranasal.tw
3. nasal.tw
4. 1 OR 2 OR 3
5. exp Midazolam
6. Midazolam.tw
7. 5 OR 6
8. 4 AND 7

9. limit 8 to (English language and humans and "young adult (19-24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") and (comparative study or controlled clinical trial or randomized controlled trial or meta-analysis)).

A total of 25 studies that met the inclusion criteria were included in this review (*Appendix 1*). The criteria for inclusion were studies written in English on the sole use of intranasally administered midazolam on adults, that were meta-analyses, randomised controlled trials, systematic reviews, controlled clinical trials or comparative studies.

The quality of the evidence provided by each study was assessed in accordance with recognized standards (*Appendix 2*) and the levels of evidence used (*Appendix 3*) were taken from SIGN 50 A Guideline Developer's Handbook (Scottish Intercollegiate Guidelines Network, 2011).

Pharmacokinetics and pharmacodynamics

Method of intranasal midazolam application

Several different methods of intranasal midazolam administration were used in this review (*Appendix 4*). In most studies using nasal drops or liquids, the application process and patient position were poorly described and considerable variation in administration occurred. Studies using nasal sprays reported high midazolam bioavailabilities (*Table 1*) and the only study using nasal drops that recorded midazolam bioavailability (Burstein *et al.*, 1997) noted the lowest bioavailability.

Volume of intranasal midazolam

Studies in the review used solutions in volumes ranging from 90 µL to 4000 µL. By increasing the solubility of midazolam by using co-solvents, low volume, high concentration midazolam solutions can be formulated to deliver a dose within the upper limit nasal capacity of 200 µL per nostril (Gudmundsdottir *et al.*, 2001).

Systemic bioavailability of midazolam

The systemic bioavailability of midazolam following oral administration has been measured as only 44% following oral administration (Allonen *et al.*, 1981), whereas the mean bioavailabilities of midazolam after intranasal administration recorded in this review varied from 50 to 85% (*Table 1*). These figures are consistently higher than the bioavailability reported after oral administration.

The use of low concentration, high volume midazolam solutions may result in a significant amount of the solution being swallowed and not absorbed intranasally. Burstein *et al.*, (1997) administered 1,000 µL of an intravenous 5 mg/mL midazolam solution and recorded midazolam bioavailability of only 50%. Higher midazolam bioavailability figures were recorded after the use of nasal sprays using low volume, high concentration midazolam formulations.

Plasma concentration of midazolam

The mean midazolam peak plasma concentrations (MPPCs) after intranasal administration recorded in this review (*Table 2*) varied from 28-257 µg/L, excluding the very high figure of 1,743.9 µg/L recorded by Braun *et al.*, (2008) that may have been an error.

Effect of excipients *(Appendix 5)*

Midazolam has limited solubility in aqueous solution. Its solubility and dose concentration can be increased by the addition of co-solvents such as propylene glycol (Veldhorst-Janssen *et al.*, 2001; Knoester *et al.*, 2002; Wermeling *et al.*, 2006), polyethylene glycol (Wermeling *et al.*, 2009) and hydroxypropyl methylcellulose (Gudmundsdottir *et al.*, 2001; Loftsson *et al.*, 2001).

Cyclodextrins can be used to form inclusion complexes with a lipophilic midazolam moiety to increase aqueous solubility and form high concentration solutions without affecting pharmacological properties (Gudmundsdottir *et al.*, 2001; Loftsson *et al.*, 2001; Dale *et al.*, 2006; Tschirch *et al.*, 2008; Haschke *et al.*, 2010; Hardmeier *et al.*, 2012). They also increase drug stability and act as absorption enhancers as they are able to change the permeability of biological

Table 1: Systemic bioavailability of midazolam.

Study	Administration	Concentration	Mean Bioavailability
Burstein *et al.*, 1997	1000 µL / minute syringe and tube	5mg/mL	50%
Gudmundsdottir *et al.*, 2001	200–300 µL / spray	17 mg/mL	64%
Loftsson *et al.*, 2001	200–300 µL / spray (s)	17 mg/mL	73%
Knoester *et al.*, 2002	90 µL / spray(s)	28 mg/mL	83%
Wermeling *et al.*, 2006	100 µL / spray(s)	25 mg/mL	73%
Dale *et al.*, 2006	100 µL / spray(s)	17 mg/mL	63%
Wermeling *et al.*, 2009	100 µL / spray(s)	25 mg/mL	59–61%
Haschke *et al.*, 2010	100 µL / spray	5–30 mg/mL	76–85%
Veldhorst-Janssen *et al.*, 2011	100 µL / spray	50 mg/mL	82%
Hardmeier *et al.*, 2012	100 µL / spray(s)	30 mg/mL	76–81%

Table 2: Plasma concentration of midazolam.

Study	Volume / method of administration	Midazolam		
		IN solution concentration	Mean time (Min)	Mean peak plasma concentration (*μg*/L)
Burstein *et al.*, 1996	Syringe and tube drops	5 mg/mL	26	156.2
Burstein *et al.*, 1997	1000 *μ*L per minute syringe and tube	5 mg/mL	25	147
Fukata *et al.*, 1997	Syringe without a needle	40 mg/mL	20	157 / 257
Gudmundsdottir *et al.*, 2001	200–300 *μ*L nasal spray(s)	17 mg/mL	10–15	42
Loftsson *et al.*, 2001	200–300 *μ*L nasal spray(s)	17 mg/mL	15	54.3
Knoester *et al.*, 2002	90 *μ*L / spray(s)	5 mg/mL	14	71
Wermeling *et al.*, 2006	100 *μ*L / spray(s)	5 mg	10	80
Dale *et al.*, 2006	100 *μ*L / spray(s)	17 mg/ml	15	41–51
Braun *et al.*, 2008	100 ml (x 2) micropipette	5 mg/mL	Not stated	1743.9
McCormick *et al.*, 2008	Needleless syringe and nebulizer	5 mg/mL	10	50–140
Ivaturi *et al.*	1 mL / drops	5 mg/mL	22	62.8
Wermeling *et al.*, 2009	100 *μ*L / spray(s)	25 mg/mL	10	43.0–83.9
Haschke *et al.*, 2010	100 *μ*L / spray(s)	5, 10, 30 mg/mL	7.2–13	28.1–80.6
Veldhorst-Janssen *et al.*, 2011	100 *μ*L / spray	50 mg/mL	44 After 5 minutes	78 / 31
Hardmeier *et al.*, 2012	Nasal spray(s)	30 mg/mL	7.6–8.4	52–98

membranes (Costantino *et al.*, 2007) and facilitate paracellular transport of drugs (Illum, 2007).

The use of co-solvents and cyclodextrins enable the formulation of high concentration midazolam solutions that can be used in low volumes to avoid the possibility of some solution being swallowed and subsequent gastrointestinal absorption of midazolam (Hardmeier *et al.*, 2012). Midazolam undergoes metabolism in the liver via cytochrome mono-oxygenase P450-3A4 to form its metabolites 1- and 4-hydroxymidazolam (Arendt and Greenblatt 1984). Cytochrome mono-oxygenase P450-3A4 has not been detected in nasal mucosa, so low levels of midazolam metabolites would be expected after intranasal administration (Suter-Zimmermann, 2008).

Several studies in this review recorded low plasma levels of 1-hydroxymidazolam (Bjorkman *et al.*, 1997; Knoester *et al.*, 2002; Dale *et al.*, 2006; Wermeling et al 2006; Wermeling *et al.*, 2009; Haschke *et al.*, 2010; Veldhorst-Janssen *et al.*, 2011; Hardmeier *et al.*, 2012) indicating absorption via the nasal mucosa is almost complete. One study by Braun *et al.*, (2008) recorded a very high plasma level of 1-hydroxymidazolam. This was the only study to record a significant level of 1-hydoxymidazolam.

Chitosan enhances the absorption of midazolam and MPPCs were reached faster in studies using 0.5% chitosan (Haschke *et al.*, 2010; Hardmeier *et al.*, 2012) than with other intranasal formulations. This is of great significance in the development of an intranasal midazolam solution that is able to achieve a MPPC in the shortest time for emergency seizure management or sedation for a patient with challenging behaviour. Chitosan appears to significantly increase midazolam MPPC but may cause more local discomfort (Haschke *et al.*, 2010).

Sedation

Allonen *et al.*, (1981) suggested that the threshold level at which midazolam begins to produce effective sedation starts at 40 *μg*/mL. Crevoisier *et al.*, (1983) found that the minimum concentration at which midazolam becomes effective ranged from 30-100 *μg*/mL. Persson *et al.*, (1988) found that sedation and amnesia were pronounced in patients undergoing surgical procedures until midazolam concentrations fell below 75-100 *μg*/mL.

In this review, the midazolam MPPCs reported ranged from 28.1-257.0 *μg*/L, excluding the suspect figure reported by Braun *et al.*, (2008). The available evidence indicates that effective sedation can be provided by the use of intranasally delivered midazolam to allow a range of interventions to be effectively delivered. An effective level of sedation appears to be reached within approximately 10 minutes in most cases.

The technique does suffer from the fact that the midazolam dose is not titrated to the patient's response. This may mean in some cases that a patient may become over sedated. This suggests that this technique should only be used by appropriately trained and experienced clinical teams (Academy of Medical Royal Colleges 2013).

Time taken to reach maximum midazolam plasma concentration

The times taken to achieve maximum midazolam plasma concentrations (MPPC) ranged from 6.5-25 minutes with 10-15 minutes being the most frequently reported interval. Apart from the study by McCormick *et al.*, (2008) in which 10 minutes elapsed until a midazolam MPPC was reached, other studies involving the use of nasal drops or solutions by Burstein *et al.*, (1996, 1997), Fukata *et al.*, (1997) and Ivaturi *et al.*, (2009) all had lengthy reported times of 26, 25, 20 and

22 minutes respectively. This may have been due to the possibility that the relatively large volumes of intranasal solutions used had resulted in some midazolam being swallowed, followed by delayed absorption. The fastest times (7.2-13 and 7.6-8.4 minutes) to reach midazolam MPPC's were recorded by studies using intranasal formulations incorporating 0.5% chitosan (Haschke *et al.*, 2010; Hardmeier *et al.*, 2012).

Indications of use

Use of intra-nasal midazolam in dentistry

The serum concentration time profile for midazolam following intranasal administration and the effect of midazolam on anxiety on healthy adults about to undergo third molar extractions was investigated by Burstein *et al.*, (1996). Midazolam was administered as 5 mg/mL solution nose drops and a mean midazolam MPPC of 156.2 μg/L was recorded. The mean time to reach the MPPC was 26 minutes. The use of intranasal midazolam was associated with reduced anxiety in those patients with baseline anxiety but the conclusions of this study were limited due to lack of blinding of subjects and investigators, the lack of a control group and a small sample size.

Karst *et al.*, (2007) investigated the use of auricular acupuncture compared to non-invasive placebo auricular acupuncture, intranasal midazolam and no treatment in the management of anxiety during dental treatment for adults. Patient compliance as assessed by the dentist was significantly improved if auricular acupuncture or intranasal midazolam had been administered. Both techniques were similarly effective for the management of dental anxiety.

Manley *et al.*, (2008) audited data from four dental treatment centres in the UK on the use of intranasal midazolam in the dental management of adult patients with learning disability for whom conventional intravenous sedation had not been possible. Participants received low volumes of a high concentration intranasal midazolam solution via a fine aerosol spray followed by intravenous midazolam as needed. The effectiveness of the sedation process was assessed in terms of enabling dental treatment provision using a modified scale of operative conditions devised by the Dental Sedation Teachers Group (DSTG).

A total of 140 patients were included in this audit with 222 episodes of sedation. Of this total, 128 (57.65%) were fully cooperative (DSTG 1), 75 (33.78%) presented minimal interference (DSTG 2) and 19 (8.55%) were impossible to treat (DSTG 4) and were referred for treatment under GA. Where dental treatment was carried out, a wide range of treatments was possible and were well described as well as any adverse events.

Ransford *et al.*, (2010) carried out a prospective audit following the study by Manley *et al.*, (2008) to further validate the technique of intranasal midazolam administration followed by intravenous midazolam as required, in the management of adult dental patients with learning disabilities. A total number of 316 treatment episodes involving 289 patients were included. Of these, 71.2% patients (225) had varying degrees of learning disability. Cannulation was achieved after administration of intranasal midazolam in 96.2% (304) of treatment episodes. In 88.0% of cases, 10 mg of intranasal midazolam was used and in 8.2% of patients a higher dose of up to 20 mg was used. Where additional intravenous midazolam was administered, 44% of cases had doses of 0-5 mg, 46.3% had 6-10 mg, 6% had 11-15 mg and 4% had 16-20 mg of midazolam. Dental treatment was carried out successfully without major interference from the patient in 78.8% treatment episodes. Adverse sedation events occurred in 6.0% of treatment episodes, the most frequent being oxygen desaturation.

Control of seizures

Several studies investigated the use of intranasal midazolam in epileptic seizure control and found that midazolam is safe and effective when administered intranasally to adults in the event of an epileptic seizure as an alternative to rectal diazepam (Scheepers *et al.*, 2000; de Haan *et al.*, 2010). de Haan *et al.*, (2010) reported that intranasal midazolam successfully stopped seizures after 4.6 minutes.

It should be noted that UK Resuscitation Council guidance recommends the use of buccal midazolam in the control of prolonged or recurrent epileptic seizures in adults, and rectal diazepam is not used in the UK.

Management of panic disorders

Schweizer *et al.*, (1992) investigated the safety and efficacy of the use of intranasal midazolam in the management of adults diagnosed with panic disorder. The technique was found to be safe and effective. Several studies investigated the effect of midazolam nasal spray on anxiety and image quality in adults undergoing magnetic resonance imaging (MRI) examination (Hollenhorst *et al.*, 2001; Tschirch *et al.*, 2007; Tschirch *et al.*, 2008). The technique was found to be safe and effective in significantly reducing the numbers of examinations stopped due to patient panic and in improving the MRI image quality.

Intranasal midazolam in gastrointestinal endoscopy

Uygur-Bayramicli *et al.*, (2002) compared the acceptance and efficacy of intranasally and intravenously administered midazolam in healthy adults undergoing upper gastrointestinal endoscopy. The authors concluded that although intranasal midazolam did not achieve as effective sedation as intravenous midazolam, it was almost as effective in terms of the amnesia produced and significantly better in terms of producing less side effects. Intranasal midazolam appeared to offer an interesting alternative to intravenous midazolam during gastrointestinal endoscopy.

Abuse liability of intra-nasal midazolam

Braun *et al.*, (2008) investigated intranasal midazolam abuse liability in adult subjects with a history of inhaled cocaine abuse. The results suggested that the use of the intranasal route did not seem to pose any risks for non-psychiatric individuals.

The study's methodology description was not clear and the figures obtained for serum levels of midazolam MPPC and metabolite levels suggested possible error.

Adverse effects of use

Local effects of intranasal midazolam

Studies reported local side effects of intranasal midazolam that included nasal burning and irritation, lacrimation, discomfort in the throat, bad taste, sneezing, coughing and dry mouth. All local effects resolved in 5-30 minutes but one study (Wermeling *et al.*, 2006) reported local effects lasting up to 90 minutes.

It is not clear whether local discomfort is due to midazolam itself or some other agent in the in formulations used. Several possible reasons were suggested to explain the local effects of intranasal midazolam. These included the pH of the solution (Tschirch *et al.*, 2008), benzoyl alcohol preservative (Knoester *et al.*, 2002; Tschirch *et al.*, 2007) and the volume of solution administered (Burstein *et al.*, 1996).

Available midazolam preparations for intravenous use have a low concentration of midazolam and a low, acidic pH of 3.3. By formulating midazolam solutions with a cyclodextrin and hydroxypropyl methylcellulose, Gudmundsdottir *et al.*, (2001) not only achieved a solution with high midazolam solubility and concentration but also a higher pH of 4.3. Subject discomfort in this study was scored as mild to moderate and not as severe as reported by other studies in the review.

Propylene glycol has been reported to cause irritation of the nasal cavity (Wermeling *et al.*, 2006) but this was discounted by de Haan *et al.*, (2010) who over 10 years of use, reported no serious side effects of intranasal solutions incorporating propylene glycol. Administration of a chitosan-containing midazolam formulation by Haschke et al (2010) was described as being more unpleasant than formulations not containing chitosan.

Manley *et al.*, (2008) and Ransford *et al.*, (2010) used midazolam formulations that included lignocaine hydrochloride. The effectiveness of including lignocaine into the intranasal formulation was not fully evaluated in these studies.

Assessment of the local effects of intranasal midazolam was carried out using participant evaluation. This is clearly subjective and open to individual variation. For example, in the study by Haschke *et al.*, (2010), some study participants described intranasal administrations as tolerable (65%) or unpleasant (25%) but others were indifferent (10%). No long-term local effects were reported in this review.

Safety

Several studies reported on the safety of use of intranasal midazolam.

Oxygen desaturation was the most common type of adverse incident reported (Fukata *et al.*, 1997; Manley *et al.*, 2008; McCormick *et al.*, 2008; Ransford *et al.*, 2010) and was successfully managed in most cases by either airway management or supplemental oxygen; however, reversal appears to have been necessary in several cases in the study by Ransford *et al.*, (2010).

Burstein *et al.*, (1997) reported 1 case of possible over-sedation that necessitated reversal whilst Dale *et al.*, (2006) reported 2 cases of nausea with no adverse outcome.

Ransford *et al.*, (2010) reversed sedation in 62 out of 316 episodes involving adults with severe disabilities, including learning disability. The majority of these reversal episodes (69%) were elective, either to manage agitated behaviour or to aid safe physical transfer of the patient out of the surgery. Only one case involved reversal to manage an unrousable patient. A greater incidence of reversal could have been expected in this patient group and Ransford *et al.*, (2010) did not think that this should be considered a sign of over-sedation or unsafe technique.

In the other dental study which evaluated the use of intranasal midazolam followed by intravenous midazolam in adults with severe learning disability (Manley *et al.*, 2010), only one case of desaturation occurred which was managed by the use of supplemental oxygen. No elective reversals occurred, so this technique may reflect particular clinician preference.

Conclusions

Acceptability - Grade of recommendation A

Intranasal midazolam administration technique offers a needle-free, patient-friendly means of drug delivery, more acceptable to those patients who are needle phobic and unable to allow intravenous cannulation. The relative simplicity of intranasal midazolam delivery also provides carers with a means of rescue medication for the control of epileptic seizures that is easier to apply and more acceptable than rectal, oral or buccal drug administration routes. As previously mentioned, rectal diazepam is no longer used in the UK in the control of prolonged or recurrent epileptic seizures and the UK Resuscitation Council guidance recommends the use of 10 mg of buccal midazolam for seizure control in adults.

Local side effects - Grade of recommendation A

Intranasally administered midazolam causes relatively short-lived local discomfort. It is not clear whether this discomfort is due to midazolam itself or some other agent in the intranasal formulations used. The local irritation experienced by patients during the administration of midazolam may be considered of secondary importance compared to the potential benefit of this needle-free drug delivery option that provides rapid onset of therapeutic effect.

Method of administration - Grade of recommendation A

The use of an intranasal spray technique to deliver a high concentration midazolam formulation of low volume, ideally 25-150 μL per nostril, offers the most effective means of delivery and reduces the amount of midazolam swallowed. Midazolam metabolite serum concentrations following intranasal administration are very low, indicating almost complete absorption.

Bioavailability – Grade of recommendation A

The use of high concentration midazolam formulations reliably results in systemic midazolam bioavailability in

excess of 80%. This is sufficient to produce therapeutic anxiolytic, sedative and anticonvulsive effects.

Plasma concentration - Grade of recommendation A

Studies reported maximum midazolam plasma concentrations ranging from 28.1-257.0 μg/mL. If it is accepted that the threshold level at which midazolam begins to produce effective sedation ranges from 30-100 μg/mL, it can be concluded that midazolam delivered by the intranasal route can reliably produce plasma drug levels that in many cases are more than adequate to produce sedative effects.

As plasma levels in excess of those required to produce sedation can result, over sedation may occur following the initial intranasal dose.

Time taken for sedation - Grade of recommendation A

Midazolam maximum plasma concentrations reaching the postulated threshold for sedation were reached within 10 minutes in most cases following intranasal administration. This suggests that clinical sedation can be more rapidly and reliably attained than in the case of oral sedation with midazolam.

Intranasal midazolam formulation - Grade of recommendation A

Solubilisers and absorption enhancers, including cyclodextrins, can facilitate compounding of aqueous preparations with high midazolam concentrations to allow application of therapeutic doses of minimised volume (100 μL) by nasal application.

The use of chitosan can promote transmucosal nasal absorption of midazolam and result in a reduced time to produce sedation. The efficacy of lidocaine in reducing any local irritation caused by intranasal midazolam was not fully evaluated.

Sedation - Grade of recommendation A

Effective sedation can be provided by the use of intranasally delivered midazolam to allow a range of clinical interventions to be effectively delivered. An effective level of sedation appears to be reached within 10 minutes in most cases, allowing treatment to be provided or supplemental midazolam to be given following intravenous cannulation.

There is a potential for over sedation. It should therefore be mandatory that all patients who are treatment planned to receive midazolam via the intranasal delivery technique should be assessed in terms of ease of venous cannulation and that only a clinician with competent cannulation skills should use this technique in case of over sedation and the subsequent need for reversal with an intravenous benzodiazepine antagonist.

Only staff members and teams who are appropriately trained in the use of conscious sedation should use this technique and carry out careful patient monitoring, including pulse oximetry, during the procedure. Full emergency equipment should be available and the team using the technique must be fully trained in the management of complications, including the use of appropriate emergency techniques and drugs.

Seizure control - Grade of recommendation C

The available evidence indicates that intranasal midazolam is a safe and effective method for the treatment of acute seizure exacerbations. It also appears to offer a more acceptable means of providing a rescue medication for both caregivers and the patient.

Safety - Grade of recommendation A

The available evidence suggests that the use of intranasal midazolam is a safe technique. Apart from local side effects that include nasal and nasopharyngeal discomfort that appear to be short-lived and relatively acceptable, the main complication reported in the studies included in this review was that of oxygen desaturation.

In all cases episodes of desaturation were corrected using simple airway management procedures, supplemental oxygen and in a small number of cases the use of a benzodiazepine antagonist. In all cases the patients concerned made a full recovery. The incidence of oxygen desaturation during the use of intranasal midazolam may be explained by the potential for over sedation due to the high midazolam plasma concentrations that can be achieved.

Appropriate training and access to drugs and equipment needed for the management of complications including over sedation and desaturation is mandatory. The intranasal route reduces the risk of needle stick injuries and biohazardous waste is reduced.

Use in dentistry - Grade of recommendation B

Several of the studies included in this review evaluated the use of intranasal midazolam during dental treatment and concluded that this was a safe and acceptable treatment modality.

A wide range of dental treatments were safely and successfully provided for patients who included those with disproportionate anxiety regarding dental care and others with an inability to tolerate treatment due to conditions such as a learning disability. In many cases, it was possible to provide dental care for patients who would otherwise only have been manageable using GA.

Patient groups - Grade of recommendation B

Intranasal administration of midazolam would benefit patients who are unable or unwilling to undergo intravenous cannulation. These groups include patients with disproportionate anxiety and severe needle phobia, a severe learning disability, movement disorders and those who require rapid seizure control.

Appendix 1: Studies identified for inclusion in the review.

Study	Administration
Schweizer *et al.*, 1992	Controlled clinical trial
Burstein *et al.*, 1996	Controlled clinical trial
Burstein *et al.*, 1997	Randomized controlled trial
Fukuta *et al.*, 1997	Randomized controlled trial
Sheepers *et al.*, 2000	Controlled clinical trial
Gudmundsdottir *et al.*, 2001	Controlled clinical trial
Hollenhorst *et al.*, 2001	Randomized controlled trial
Loftsson *et al.*, 2001	Controlled clinical trial
Knoester *et al.*, 2002	Randomized controlled trial
Uygur-Bayramicli *et al.*, 2002	Controlled clinical trial
Dale *et al.*, 2006	Controlled clinical trial
Wermeling *et al.*, 2006	Randomized controlled trial
Karst *et al.*, 2007	Randomized controlled trial
Tschirch *et al.*, 2007	Randomized controlled trial
Braun *et al.*, 2008	Randomized controlled trial
Manley *et al.*, 2008	Comparative study
McCormick *et al.*, 2008	Randomized controlled trial
Tschirch *et al.*, 2008	Randomized controlled trial
Ivaturi *et al.*, 2009	Controlled clinical trial
Wermeling *et al.*, 2009	Randomized controlled trial
de Haan et al., 2010	Comparative study
Haschke *et al.*, 2010	Controlled clinical trial
Ransford *et al.*, 2010	Comparative study
Veldhorst-Janssen *et al.*, 2011	Randomized controlled trial
Hardmeier *et al.*, 2012	Randomized controlled trial

Appendix 2: Quality of evidence of studies included in the review.

Author(s)	Study	Bias Risk	Level of evidence
Schweizer *et al.*, 1992	CCT	High	2-
Burstein *et al.*, 1996	CCT	Low	2+
Burstein *et al.*, 1997	RCT	High	1-
Fukuta *et al.*, 1997	RCT	High	1-
Sheepers *et al.*, 2000	CCT	High	2-
Gudmundsdottir *et al.*, 2001	CCT	Low	2++
Hollenhorst *et al.*, 2001	RCT	Low	1+
Loftsson *et al.*, 2001	CCT	Low	2++
Knoester *et al.*, 2002	RCT	Low	1+
Uygur-Bayramicli *et al.*, 2002	CCT	Low	2+
Dale *et al.*, 2006	CCT	Low	2+
Wermeling *et al.*, 2006	RCT	Low	1+
Karst *et al.*, 2007	RCT	Low	1+
Tschirch *et al.*, 2007	RCT	High	1-
Braun *et al.*, 2008	RCT	High	1-
Manley *et al.*, 2008	CS	Low	2+
McCormick *et al.*, 2008	RCT	High	1-
Tschirch *et al.*, 2008	RCT	Low	1+
Ivaturi *et al.*, 2009	CCT	High	1-
Wermeling *et al.*, 2009	RCT	Low	1+
de Haan *et al.*, 2010	CS	High	2-
Haschke *et al.*, 2010	CCT	High	1-
Ransford *et al.*, 2010	CS	Low	2+
Veldhorst-Janssen *et al.*, 2011	RCT	Low	1+
Hardmeier *et al.*, 2012	RCT	Low	1+

Key: CCT – Controlled clinical trial; RCT – Randomised controlled trial; CS – Comparative study

Appendix 3: Levels of evidence and grades of recommendations.

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation	
This relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

From: *SIGN 50 A Guideline Developer's Handbook* (Scottish Intercollegiate Guidelines Network 2011).

Appendix 4: Methods of intranasal midazolam application.

Drug administration	Study
Spray	Gudmundsdottir *et al.*, 2001; Hollenhorst *et al.*, 2001; Loftsson *et al.*, 2001; Knoester *et al.*, 2002; Dale *et al.*, 2006; Wermeling *et al.*., 2006; Karst *et al.*, 2007; Tschirch *et al.*, 2007; Manley *et al.*, 2008; Tschirch *et al.*, 2008; Wermeling *et al.*, 2009; de Haan *et al.*, 2010; Haschke *et al.*, 2010; Ransford *et al.*, 2010; Veldhorst-Janssen *et al.*, 2011; Hardmeier *et al.*, 2012
Bi-directional airflow device	Dale *et al.*, 2006
Nebulizer	McCormick *et al.*, 2008
Syringe and flexible tube	Burstein *et al.*, 1997
Syringe without a needle	Fukata *et al.,* 1997; McCormick *et al.,* 2008
Drops	Schweizer *et al.*, 1992; Uygur-Bayramicli *et al.*, 2002; Braun *et al.*, 2008; Ivaturi *et al.*, 2009
Syringe and flexible tube/drops	Burstein *et al.*, 1996; Scheepers *et al.*, 2000

Appendix 5: Formulations of intranasal preparations.

Study	Formulation
Schweizer *et al.*, 1992	Aqueous solution of 5 mg/mL midazolam hydrochloride (only details)
Burstein *et al.*, 1996	5 mg/mL midazolam hydrochloride, benzyl alcohol 1%, disodium edetate 0.01% and sodium chloride 0.8%
Burstein *et al.*, 1997	5 mg/mL midazolam (only details)
Fukata *et al.*, 1997	40 mg/mL midazolam (only details)
Scheepers *et al.*, 2000	5 mg/mL midazolam (only details)
Gudmundsdottir *et al.*, 2001	17 mg/mL of midazolam with sulfobutylether-β-cyclodextrin, hydroxypropyl methylcellulose, benzalkonium chloride, ethylenediamine tetra-acetic acid and phosphoric acid
Hollenhorst *et al.*, 2001	Aqueous solution of midazolam (5 mg/mL) with 1% benzyl alcohol, 0.8% sodium chloride and 0.01% edetate disodium (pH 2.5-3.7)
Loftsson *et al.*, 2001	17 mg/mL of midazolam with sulfobutylether-β-cyclodextrin, hydroxypropyl methylcellulose, benzalkonium chloride, ethylenediamine tetra-acetic acid and phosphoric acid
Knoester et al., 2002	28 mg/mL midazolam hydrochloride in aqueous solution with propylene glycol (pH 4) with benzyl alcohol (1%)
Uygur-Bayramicli *et al.*, 2002	Aqueous solution of midazolam (5 mg/mL) with 1% benzyl alcohol, 0.8% sodium chloride and 0.01% edetate disodium (pH 2.5-3.7)
Dale *et al.*, 2006	17 mg/mL midazolam in aqueous solution with sulfobutylether-β-cyclodextrin sodium, hydroxyl-propyl methylcellulose, benzalkonium chloride, ethylenediamine tetra-acetic acid and phosphoric acid (pH 4.20–4.35)
Wermeling *et al.*, 2006	25 mg/mL midazolam in non-aqueous solution with polyethylene glycol 400, butylated hydroxytoluene, saccharin and propylene glycol
Karst *et al.*, 2007	Aqueous solution of midazolam (5 mg/mL) with 1% benzyl alcohol, 0.8% sodium chloride and 0.01% edetate disodium (pH 2.5-3.7)
Tschirch *et al.*, 2007	Aqueous solution of midazolam (5 mg/mL) with 1% benzyl alcohol, 0.8% sodium chloride and 0.01% edetate disodium (pH 2.5-3.7)
Braun *et al.*, 2008	5 mg/mL midazolam hydrochloride in aqueous solution (only details)
Manley *et al.*, 2008	40 mg/mL of midazolam hydrochloride and 20 mg/mL of lignocaine hydrochloride (only details)
McCormick *et al.*, 2008	Aqueous solution of 5 mg/mL midazolam hydrochloride, sodium chloride, hydrochloric acid and sodium hydroxide (pH 3.3)
Tschirch *et al.*, 2008	0.5% midazolam solution with benzalkonium chloride and sodium ethylenediamine-tetra-acetic acid (pH 3.0-3.5) or 1% solution of midazolam hydrochloride and 4% RMβ-cyclodextrin
Ivaturi *et al.*, 2009	5 mg/mL midazolam (only details)
Wermeling *et al.*, 2009	25 mg/mL intranasal midazolam in non-aqueous solution with polyethylene glycol 400, butylated hydroxytoluene, saccharin and propylene glycol
de Haan *et al.*, 2010	Aqueous solution of 28 mg/mL midazolam hydrochloride, propylene glycol and benzyl alcohol (pH 4)
Haschke *et al.*, 2010	Midazolam hydrochloride (ranging from 5 to 30 mg/mL) in aqueous solution with RMβ-cyclodextrin, sodium chloride and chitosan hydrochloride
Ransford *et al.*, 2010	40 mg/mL of midazolam hydrochloride and 20 mg/mL of lignocaine hydrochloride (only details)
Veldhorst-Janssen *et al.*, 2011	50 mg/mL of midazolam with propylene glycol
Hardmeier *et al.*, 2012	30 mg/mL midazolam containing 0.5% chitosan, 12% RMβ-cyclodextrin

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