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Title Midazolam use for dental conscious sedation: how safe are we?

In brief

- The use of midazolam for conscious sedation has an excellent safety profile in dentistry comparatively, with a low number of reported incidents
- Use of high strength midazolam is still prevalent
- Education and training of dentists regarding relevant safety reports and reporting systems is necessary to improve the safety culture of drug administration in conscious sedation.

Abstract (200 words)

Aim: To explore the safety awareness of midazolam use amongst dentist in the UK. **Materials and methods:** A cross-sectional study on 203 dentists was undertaken, 146 of whom currently practice conscious sedation using intravenous midazolam. Use of high strength midazolam; awareness of the Rapid Response Report (RRR) and the National Reporting and Learning System (NRLS); and midazolam related incidents were explored. **Results:** Formal training in conscious sedation was variable with 35.6% holding a postgraduate sedation qualification. Flumazenil administration was common practice (63%) although used very selectively. Use to reverse respiratory depression was minimal (4%). Awareness of the RRR and the NRLS was generally low but higher among those working in general dental practice ($p < 0.05$). Comparative analysis showed that high dose midazolam was administered more frequently in gastroenterology than in dentistry ($p < 0.001$) with higher incidences of overdose (12.4% Vs 4.8%) and death (8.3% Vs 0%) within a 3 year period. **Conclusions:** High strength midazolam administration remains prevalent in dentistry, despite recommendations by the DoH. Use of flumazenil for reasons other than respiratory depression in dentistry should warrant little concern. The low incidence of reported harm is positive but may be due to a lack of uptake of national reporting systems.

Introduction

The increasing level of dental anxiety in the UK population (1) has kept the demand for dental conscious sedation (CS) high. General anaesthesia (GA) is an alternative but is not without significant morbidity, and the associated expense in today's constrained health care funds make it less feasible (2). Side effects are uncommon with midazolam, although the risks associated with high doses are hypoventilation and hypoxemia (3) which can be reversed rapidly with flumazenil. Recommendations within medical guidance suggest that routine administration of flumazenil should be avoided, and use regularly audited as a marker of excessive midazolam use (4).

Recent years have witnessed a shift towards safer practices in CS using midazolam- the result of key published documents (5). In 2004, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) showed an increase in sedation related mortality/morbidity in the elderly resulting from high doses of benzodiazepines (6), further highlighted when 498 incidents of midazolam overdose were recorded on the National Reporting and Learning System (NRLS) between 2004-2008. The rapid response report (RRR) that ensued recommended high strength midazolam restriction to GA, palliative care and in risk assessed areas and that routine use of flumazenil should be avoided (7).

Costing over £5m to develop, the NRLS has enabled nationwide incident reporting with the intention of learning in a blame free environment (8). When an incident occurs in an NHS Trust, the onus is on staff to record information on a safety management system. Sensitive information is anonymised,

electronically sent to the NPSA (9) and stored in the NRLS' data fields that include location, specialty, qualitative descriptions of the incident and level of harm: (1)No harm; (2)low harm; (3)moderate harm; (4)severe harm; (5)death (10). In April 2010, it became compulsory to report all serious harm or death following a serious patient safety incident to the NPSA who forward the data to the Care Quality Commission (11).

Whilst there have been numerous studies exploring the safety of midazolam in medicine, little is known about the number of non-death related incidents nationally within dentistry. To date, the safety awareness of midazolam use amongst dentists in the UK has not been established and the aim of this paper is to explore this and to follow on from previously published work that focused on safety in gastroenterology (12).

Materials and Methods

a. Data collection regarding the midazolam safety awareness in dentistry- questionnaire

A cross sectional survey was distributed via an electronic portal to dentists practising intravenous sedation (IV) in the UK (Table 1). Ethical approval was sought from City, University of London ethics committee. Questions explored background, use of different midazolam strengths (and high dose midazolam as specified by the Department of Health's Never Events list) and flumazenil, adverse events, and awareness of the RRR and NRLS. There was an option to express comments on questions for the online questionnaire should any participant feel they needed to add further information or clarify answers. The survey was also distributed during various national sedation meetings (SAAD conference and SAAD weekend courses) in order to capture the target group. Dentists currently practicing intravenous sedation (IVS) in the UK were included in the study. All participants were able to withdraw from the study at any time. As sedation is not recognised as an independent specialty, eliciting the numbers of sedation dentists in the UK from the General Dental Council register was impossible. Nevertheless, the minimum sample size was based on a similar previous report that studied sedation incidents in gastroenterology (12).

b. Comparative analysis with gastroenterology

Questions used in a previously published study (12) that explored midazolam related incidents in gastroenterology were incorporated into our survey to allow raw data comparisons between gastroenterology and dentistry. The involvement of one of the authors in this previous study enabled access to raw data, facilitating comparative analysis.

Data from questionnaires was analysed with SPSS v21 using Pearson's Chi-square (χ^2) to identify differences in practice, awareness and occurrence of incidents between groups in methods a and b (comparing IVS dentists with non IVS dentists; and dentists with gastroenterologists). Differences were considered statistically significant when $P < 0.05$. All 'don't know' responses were included in the analysis of data.

c. Analysis of incident data from the NPSA

Incidents in dentistry from the NRLS database were requested from NHS England. The NRLS database was examined for midazolam related dental incidents from 1st January 2005 to 4th October 2015 using the following keyword searches: MIDAZALOM, MIDAZELAM, MIDAZILEM, MIDAZOLAM, MIDIZOLAM, MIDOZALAM, MIDOZOLAM, HYPNOVAL, HYPNOVEL, FLUMAZENIL, FLUMAZIMIL,

ANEXATE, ANNEXATE combined with DENTISTRY, DENTAL, DENTIST. Details of incidents such as type of incident, level of harm and details of incident were analysed and summarised in the results below. Removal of duplicate incidents and inspection of free-text legends confirmed the relevance of the incident for analysis.

Results

Responses received totalled 212, with 9 incomplete submissions which were omitted from analysis. Of the remaining 203 responses, 146 dentists stated that they currently carry out IVS. As some of the data was collected during the SAAD weekend course, there were some participants who were new to conscious sedation practice and had no experience of IVS or were not regularly practicing IVS. Participants who stated that they 'never' carry out IVS were included in the data analysis for comparative purposes, dividing the data into two groups: IVS dentists (71.9%, n=146) and non IVS dentists (28.1%, n=57).

The total rate of response is unknown as the link to the survey was originally sent to a defined number of people but was then subsequently disseminated via email to an unknown number of recipients.

Survey responses amongst dentists

Background of clinicians

The median number of years since qualification for both groups was 9.5 years (s.d.=9.44, IQR 4.0-16.3yrs) amongst IVS dentists, and 5.0yrs (s.d.= 8.4 years, IQR 3.0-15.0 years) amongst non IVS dentists. General dental services, GDS, (46.6%, n=68) were the most common place of work for participants in the IVS group, followed by hospital dental services, HDS, (30.8%, n=45), with smaller numbers practicing in community dental services, CDS, (15.8%, n=23) and specialist dental practices, SDS (2.7%, n=4). The majority of non IV sedation dentists were in hospital dental services (57.9%, n=33) and in GDP (17.5%, n=10)

Training and experience

Training in conscious sedation amongst IVS dentists was mainly via a weekend course (IVS dentists 39.0%, n=57; non IVS dentists 93%, n=33) hosted by SAAD, the biggest sedation society in the UK. Those with a postgraduate sedation qualification comprised 35.6% of IVS dentists (n=52). The remainder of participants had in house training or had attended a CPD course in sedation. A postgraduate qualification in sedation was more common amongst dentists in GDS (n=30, 20.5%) than HDS (n=11 7.5%), but this difference was not statistically significant ($\chi^2(4)=4.81$, $p=0.307$, $\phi=0.182$). Those with a postgraduate qualification were significantly more likely ($U=1826.5$, $p=0.011$) to have been qualified for longer (median=11years, IQR=3-15.25 years) than those without (median=7years, IQR=6.25-18.75) (Figure 1).

The experience of IVS dentists was variable, with many carrying out sedation less than 20 times a year (32.9%, n=48) or more than 80 times a year (31.5%, n=46). General dental practitioners provided the majority of IV sedation compared to hospital practitioner who were more likely to carry out less than 20 sedation treatments a year ($\chi^2(16)=27.79$, $p=0.034$, $\phi=0.436$).

Drug administration

Some sedation dentists declared that low strength midazolam was not available for use intravenously in their clinics (17.8%, n=26). Most reported no midazolam related incidents (93.8%, n=137) that required major intervention, and in those who did- none reported any level of harm or death. There was no significant difference between place of work and use of high strength midazolam ($\chi^2(12)= 15.184$, $p=0.232$, $\phi=0.322$) or availability of low strength midazolam

($\chi^2(8)=12.840$, $p=0.117$, $\phi=0.297$). Over a third (32.9%) of IVS dentists used high strength midazolam intravenously (21.9%, $n=32$), and orally as a pre-medication prior to IV administration (10.96%, $n=11$). Intravenous administration of high strength midazolam was significantly ($\chi^2(9)=21.162$, $p=0.012$, $\phi=0.381$) more common in those qualified in the last 5 years (43.8%) than practitioners qualified for over 15 years (28.1%) but the majority of those using it orally as a pre-medication had been qualified over 10 years (90.9%). There was no statistically significant association between use of high strength midazolam and midazolam related incidents ($\chi^2(6)=1.925$, $p=0.926$)

Flumazenil use

Flumazenil administration was common practice (53% of responses) (Figure 2) with its main uses including prolonged chairside recovery (22%, n=45), and for patients with learning disabilities (15%, n=32) and mobility problems (12%, n=26). Reversal of respiratory depression was the reason for delivery in 4% of cases (n=9).

Awareness of the RRR guidance

Only 47.3% (n=66) of IVS dentists were aware of the RRR compared to 22.8% (n=13) of non IVS dentists (Fisher's exact p=0.001). They were also significantly more likely to know who their RRR lead was (31.5%, n=46 Vs 12.3%, n=7; Fisher's exact p=0.011) and were more aware of the NRLS reporting system (44.5%, n=65 Vs 22.8%, n=13; Fishers Exact p=0.006). Awareness of the RRR ($\chi^2(4)=14.054$, p=0.007, $\phi=0.310$) and NRLS ($\chi^2(4)=14.117$, p=0.007, $\phi=0.311$) was higher in GDS and those with a postgraduate qualification (RRR: Fisher's exact=24.764 p<0.001, $\phi=-0.413$; NRLS Fisher's exact=4.109 p=0.043, $\phi=-0.168$).

Comparative data with gastroenterology

High dose midazolam was administered more frequently in gastroenterology than in dentistry ($\chi^2(4)=57.4$, p<0.001). No significant differences were observed between the two professions in reference to midazolam strengths and incidents, despite reported incidents being higher in gastroenterology, with one incident of long term harm or death (Table 2). Gastroenterologists were significantly more likely to have administered high strength midazolam in the last 3 years

Data from the NRLS

After excluding data that was repeated or unrelated to dentistry, a total of 57 incidents were obtained from the NRLS over a 10year period. Incidents occurred mainly in GDS (49.12%, n=28) and HDS (43.86%, n=25), with a minority in CDS (7.02%, n=4). No harm was reported in 87.72% (n=50) of patients, low harm in 8.77% (n=5) and moderate harm in 3.51% (n=2). Serious harm or death was not reported in any cases. Qualitative data entries were analysed in detail to elicit whether the level of harm assigned corresponded with the details of the incident. These were all individually validated for consistency by the authors, all experts in the field of sedation, incident reporting, patient safety or medical error reviews. The two cases of moderate harm were: a fit and faint that occurred after administration of 2mg midazolam; and shaking with wheezing after administration of local anaesthesia sometime after 7mg midazolam was administered.

The main findings of the reported incidents are summarised in Table 3. Incidences of respiratory depression was very low (2%, n=1). The most frequently cited incident was shattering of the midazolam ampoule (33%, n=19). Flumazenil was wrongly administered instead of midazolam in 9% of incidents but in all these cases, treatment was carried out as planned without subsequent administration of midazolam and the patient was informed. In one case, the confusion was due to the similarity in the appearance of the midazolam and flumazenil ampoules. Resedation after 40minutes of flumazenil administration was recorded in one incident. The patient was monitored and fully recovered thereafter.

Discussion

Historically, anaesthetists have scrutinised the use of conscious sedation drugs in dentistry, advocating the sole use by medical professionals (13,14,15). This may partly be due to the limited evidence regarding the safety record of midazolam administration in dentistry, a prime objective of this study.

The NPSA guidance was significant, with the hope that it would reduce incidents in CS. It is surprising that the awareness of the report was low, though this finding relates to the name of the guidance and not knowledge regarding best practice procedures that resulted from the RRR's recommendations i.e. the replacement of high strength with low strength midazolam. However, our results showed the concentrated formulations are still widely used irrespective of sector. Although some dentists were using high strength midazolam orally as a premedication to allow cannulation in special care patients, a high proportion (32.9%) used it intravenously. Absence of low dose midazolam as declared by 17.8% of our sample may be due to cost implications, with the concentrated formulations being cheaper per unit ml (10mg/2ml ampoules=63p; 10mg/5ml= 65p; 5mg/5ml=60p). Comparative data with gastroenterology showed that dentists were using significantly less high strength midazolam, which may be why there were less reported incidents (4.8% compared to 12.4% in gastroenterology) in dentistry. This could also be due to the low reporting culture within dentistry, especially in primary care which contributes just 5% to all incident reports to the (16). Nevertheless, the low number of incidents suggest that midazolam as a CS drug in dentistry is safe, concurring with a recent systematic review focusing on the safety of oral midazolam in paediatric patients (17). We suggest that alternatives for pre-medications such as

2.5mg/ml oral syrup should be explored. It should also be noted that the use of intranasal midazolam (40mg/ml) was not explored in this survey, and is therefore a limitation of this study.

We intended to explore purchasing data of midazolam and flumazenil to ascertain reductions in purchasing of high strength midazolam since the RRR guideline, but the NHS Purchasing and Supply Agency that had provided global purchasing data within the NHS in a previous study (12) was dissolved in 2010. Data was thus requested from various pharmaceutical companies for the period of 2008-2015, however we received no response.

Serious harm or death resulting from high strength midazolam (5mg/ml; 2mg/5ml) overdose during conscious sedation is a UK Department of Health 'Never Event' (18) which must be reported, most commonly through a tool such as the NRLS (19). However, our data highlighted flaws with this system. For example, the qualitative data described medical emergencies that ensued following administration of the drug, which may in fact be two isolated incidents. Thus, the taxonomy may confuse or hide incidents (20). Furthermore, NLRs reports refer to incidents for patients receiving NHS funded care. Exclusion of the private sector can account for the low number of reported incidents compared to medicine. A tailored systematic monitoring safety system within dentistry would provide a more reliable evidence base, and may incentivise its use. Improvements in reporting could increase the number of incidents in the long term as reflected in the data received by NHS England which exhibited a 6% increase in incidents in one year (21). Furthermore, the statutory duty of candour which emphasises the need to be transparent to patients when an incident occurs and to report it may increase incident reporting (22).

Although the RRR suggested that administration of flumazenil is indicative of a benzodiazepine overdose, its use in dentistry is for reasons other than to reverse respiratory depression as indicated in all our data, supporting earlier findings (23). Flumazenil can prevent sedation-related accidents after dental procedures in those with mobility problems and severe learning disabilities, who have been shown to be at an increased risk of falls and injury (24). Hence concerns regarding use of flumazenil as a surrogate marker of midazolam overdose requiring reversal should not be a deterrent for its administration in dentistry provided it is justified with appropriate measures to avoid errors. The NRLS data showed that there were 9% of incidents involving wrong administration of flumazenil instead of midazolam, which is similar to reported national medicines administration errors of 3-8% (25). Similar drug packaging may contribute to human factor error, as explained in one data entry from the NRLS. For example, flumazenil and midazolam are available from manufacturers in packaging of a similar colour (Figure 3) which has previously been identified as increasing the risk of medicines administration errors (26), (27) (7).

A strong primary care base of dentists qualified and experienced in carrying out CS is essential in view of recent NHS sustainability reports (28) and our results are encouraging as they showed more dentists with a PG qualification in general practice carrying out sedation. Over a third (35.6%) of our sample had a sedation PG qualification, which is similar to the documented uptake of sedation training by medical non-anaesthetists (29). The impact of new UK conscious sedation guidelines is likely to enhance the uptake of PG accredited training programmes within dentistry, thereby improving knowledge and awareness of safety practices recommended in key documents such as the RRR.

Although the results are positive, we appreciate that this study is not without limitations/challenges. There was no way of identifying exactly the number of dentists currently practicing sedation and we cannot therefore elicit to what extent our survey sample represents the views of all IVS dentists. However, we believe that we maximised the number of responses by utilising our dental professional network which has been shown to be an effective method of information gathering (30)

We also recognise that there are limitations with self-reporting of adverse events in dentistry, which is in part due to: (1) failure in incident recognition, (2) apprehension of medico-legal liability (3) behavioural inclinations not to publicly acknowledge adverse (4) lack of knowledge about the processes of reporting (31,32,33). Despite this, our collection of incident and awareness data provides a useful and informative snapshot that illustrates the safety of midazolam use in dentistry

Conclusion

The absence of reported harm and the low number of incidents suggest that midazolam as a conscious sedation drug in dentistry is safe. Although there is little advice available on use of flumazenil for reasons other than respiratory depression, the use of flumazenil in dentistry should warrant minimal concern, as it is used selectively. The low awareness of the NRLS and RRR emphasises the need to act and learn from patient safety incidents in a blame free environment through improved incident reporting. In view of recent published guidance, more training programmes need to be made available to coordinate the delivery of training in safe sedation practice in dentistry and increase awareness of key policies and reports

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Declaration of interests

Nil

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Figure Legends

Figure1 Box plot showing that dentists with a postgraduate qualification in sedation were more likely to have been qualified longer (11 years Vs 7 years) (U=1826.5, p=0.011)

Figure 2: Bar chart showing the clinical situations in which flumazenil is used. Most clinicians reported never using flumazenil, with the smallest percentage reporting its use to reverse respiratory depression

Figure 3: Flumazenil and midazolam drug ampoules (5ml) manufactured by Hameln Pharmaceuticals, Gloucester, UK. The similarity between the packaging could account for the miss selection drug errors

Tables

About you
Year of graduation:
Place of work: (Tick all that apply) <ul style="list-style-type: none"> <input type="radio"/> General Dental Practice <input type="radio"/> Community Dental Service <input type="radio"/> Hospital Dental Service <input type="radio"/> Other (please specify)
Have you attended any post-graduate training courses in conscious sedation? Please tick all that apply: <ul style="list-style-type: none"> <input type="radio"/> SAAD course <input type="radio"/> Certificate in conscious sedation <input type="radio"/> Diploma in conscious sedation <input type="radio"/> MSc involving conscious sedation <input type="radio"/> Other (please specify) <input type="radio"/> Comments
Your Experience
How often do you treat patients under intravenous sedation <ul style="list-style-type: none"> <input type="radio"/> Never <input type="radio"/> Less than 20x/year <input type="radio"/> 21-40x/year <input type="radio"/> 41-60x/year <input type="radio"/> 61-80x/year <input type="radio"/> 80+ times/year
Have you administered intravenous high-strength midazolam in the last 3 years for conscious sedation (10mg in 2ml, 10mg/5ml)? <ul style="list-style-type: none"> <input type="radio"/> Yes, intravenously <input type="radio"/> Yes, as an oral pre-medication <input type="radio"/> No <input type="radio"/> Don't know
Is intravenous low-strength midazolam (5mg /5ml) routinely available in your dental clinic? <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Don't know <input type="radio"/> Details
Have you been involved in a midazolam overdose incident in the past 3 years whereby the patient failed to respond to simple measures of opening the airway, oxygen therapy and tactile stimulation? <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Don't know
If you answered yes to the previous question, did this incident result in death or long-term harm to the patient? <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Comments
In what circumstances have you had to use flumazenil in the past? (* tick all that apply) <ul style="list-style-type: none"> <input type="radio"/> Never used flumazenil <input type="radio"/> For prolonged chairside recovery <input type="radio"/> For those travelling long distances <input type="radio"/> For patients with mobility problems <input type="radio"/> For patients with learning disabilities (to assist carers) <input type="radio"/> To reverse respiratory depression <input type="radio"/> other- please specify below in comments box
Prior to this survey, were you aware the National Patient Safety Agency had issued an Rapid Response Report regarding midazolam? <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Comments
Do you know who the lead for implementing this Rapid Response Report is in your organisation/practice? <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Comments
Were you aware of the National Patient Safety Agency's national reporting and learning system for recording patient incidents? <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Comments

Table 1 Questionnaire distributed to dentists across the UK

Profession	Question		
	Have you administered high strength midazolam in the last 3 years?*		
	<i>Yes % (n)</i>	<i>No</i>	<i>Don't know</i>
<i>Dentistry</i>	32.9 (48)	67.1 (98)	0.0 (0)
<i>Gastroenterology</i>	68.0 (66)*	30.9 (30)	1 (1)
	Is low strength midazolam available in your clinic?		
	<i>Yes</i>	<i>No</i>	<i>Don't know</i>
<i>Dentistry</i>	79.5 (116)	17.8 (26)	2.7 (4)
<i>Gastroenterology</i>	81.4 (79)	16.5 (16)	2.1 (2)
	Have you been involved in a midazolam related overdose in past 3 years?		
	<i>Yes</i>	<i>No</i>	<i>Don't know</i>
<i>Dentistry</i>	4.8 (7)	93.9 (137)	1.4 (2)
<i>Gastroenterology</i>	12.4 (12)	86.6 (84)	1 (1)
	If you answered yes, did this result in long term harm or death?		
	<i>Yes</i>	<i>No</i>	<i>Don't know</i>
<i>Dentistry</i>	0	100.0	0.0
<i>Gastroenterology</i>	8.3 (1)	91.7 (11)	0.0

*Significant difference observed between gastroenterology and dentistry

Table 2 Comparative responses between gastroenterologists and dentists regarding midazolam and incidents

Medication Error Category	% (n)
Re-sedation after flumazenil	2 (1)
High strength midazolam wrongly administered	4 (2)
Flumazenil mistakenly administered	9 (5)
Shattering of ampoule	33 (19)
Medical emergency	18 (10)
Respiratory depression	2 (1)
Expired drug not administered	9 (5)
Expired drug administered	2 (1)
Missing drug unaccounted for	12 (7)
Other	11 (6)
Total	100 (57)

Table 3: *Incidents relating to midazolam sedation in dentistry reported to the NRLS between 2007-2015*