Evaluation of maximum dose intravenous midazolam used in dental intravenous sedation: a West of Scotland regional audit

Hannah Lawler*[1] and Peter Walker[2]

Key points

- British National Formulary's intravenous midazolam recommended maximum dose of 7.5 mg was exceeded without adverse events in 28% of cases.
- Intravenous midazolam doses over 7.5 mg are considered 'off-label' but are accepted as 'common practice' in dental conscious sedation where a single drug technique (midazolam) is used.
- This study demonstrates intravenous midazolam doses from 1–15 mg were administered without adverse events.

Abstract

Background Intravenous (IV) midazolam sedation is commonly used in the delivery of dentistry for phobic patients. There is currently no guidance on a maximum dose for use specifically in dentistry. Dentists practise with the British National Formulary recommended maximum dose of 7.5 mg; however, anecdotally, this is often exceeded. We aim to evaluate prescribing and propose recommendations for a maximum dose for dentists.

Method Data was collected from ten dentists across four Scottish health boards regarding their last 20 IV sedation patients, giving a total of 200. Data obtained from standard Dental Sedation Teachers Group IV logbooks included: dose of midazolam administered; justification for doses over 7.5 mg; flumazenil or supplemental oxygen usage; significant medical/social factors; and the Ramsay Sedation Score.

Results Mean midazolam dose was 6.1 mg with a range of 14 mg. The recommended maximum dose of 7.5 mg was exceeded in 28% of cases. The mean sedation score was 2.7 and there were no reported adverse events or use of flumazenil.

Conclusion IV midazolam is an effective way to achieve conscious sedation in dentistry. Acknowledgement of current off-label prescribing is important; however, 7.5 mg as a recommended maximum dose is too conservative as it is regularly exceeded without adverse events. Further investigation and expert opinion is required to set a maximum dose specifically for dentistry.

Introduction

Intravenous (IV) midazolam sedation is commonly used in the delivery of dental treatment for highly anxious or phobic patients where behavioural management creates a significant barrier to dental care.[1] With levels of dental anxiety increasing, estimated at 11.6% of the adult population in England, Wales and Northern Ireland, the demand on conscious sedation services is growing.[2] The use of conscious sedation for those medically complex and special care patients is widely accepted as an efficacious and safe alternative to a general anaesthetic, which carries greater morbidity and financial burden.[3] Conscious sedation is defined by the Department of Health as: 'a technique in which the use of a drug or drugs produces a state of depression of the central nervous system (CNS) enabling treatment to be carried out, but during which verbal contact with the patient is maintained. The drugs and techniques used to provide conscious sedation for dental treatment should carry a margin of safety wide enough to render loss of consciousness unlikely'.[4]

Midazolam is a short-acting benzodiazepine with a rapid onset and recovery times faster than that of other benzodiazepines, such as diazepam.[5] Unwanted side effects associated with IV midazolam are rare, but significant. High doses are attributable to hypoventilation and hypoxaemia due to its CNS-depressant effects.[6] In dentistry, midazolam is administered through an IV cannula that facilitates slow, incremental titration (typically 1 mg/min) to the patients' response. This method reduces the risk of respiratory depression and allows the seditionist to achieve the desired level of sedation while minimising the possibility of under- or over-sedation.[7] A recent review of the literature revealed no guidance on a maximum dose for use specifically within dentistry. Instead, sedation dentists practise with the British National Formulary (BNF) recommended maximum dose of 7.5 mg.[8,9,10] However, anecdotally, this maximum dose is often exceeded without detrimental effect. The 2008 National Patient Safety Agency's rapid response report evaluating the risk of overdose associated with midazolam evaluated 1,529 patient safety incident reports containing the terms 'midazolam' or 'flumazenil', received through the Reporting and Learning System. The report identified 498 incidents in adult patients administered midazolam between November 2004 and November 2008. Of the 1,529 reports, only two were linked to

[1]Oral and Maxillofacial Surgery, NHS Greater Glasgow and Clyde, Queen Elizabeth University Hospital, Glasgow, UK; [2]NHS Ayrshire and Arran, Public Dental Service, Ayr Hospital, UK.
*Correspondence to: Hannah Lawler
Email address: hannah.lawler2@ggc.scot.nhs.uk

Refereed Paper.
Submitted 11 October 2021
Revised 20 February 2022
Accepted 7 March 2022
https://doi.org/10.1038/s41415-022-4456-7

dentistry, with neither patient experiencing serious harm.[11] We aim to evaluate prescribing habits and risk and propose suitable next steps towards a maximum dose of midazolam when used as a single drug for use in dental conscious sedation.

Materials and method

A retrospective audit assessing the dose of IV midazolam administered to achieve conscious sedation when delivering dental treatment was completed. Ten dental practitioners providing IV midazolam sedation in primary and secondary care environments across four Scottish NHS health boards were included. Each practitioner submitted their standard Dental Sedation Teachers Group logbooks and a data *pro forma* table was completed (Appendix 1) in order to capture data for practitioners last 20 IV sedation cases. Data included: dose of midazolam administered; justification for administering doses over the recommended 7.5 mg; if flumazenil or supplemental oxygen were given; any significant medical/social factors (that is, recreational drug use, use of concurrent benzodiazepine etc); and the allocated Ramsay Sedation Score (RSS).[12] Results were accumulated in order to allow overall conclusions to be drawn.

As this audit was an evaluation of peers based on their logbooks, with no identifiable patient data included, it was advised by NHS Ayrshire and Arran that this research did not require ethical approval.

Results

In total, 200 cases were analysed over four health boards, giving a broad demographical range. The average patient age was 39 years old. The mean dose of midazolam administered was 6.1 mg with a range of 14 mg. The lowest reported dose administered was 1 mg and the highest was 15 mg. The mean dose administered to the 18 patients over 60 years old was 3.4 mg, with a median of 3 mg – this is below the recommended maximum dose of 3.5 mg for this age group. Among the over 60-year-olds; seven patients were given doses above 3.5mg. Of these, two were given supplemental oxygen and there were no adverse events or reported uses of flumazenil. Overall dosing habits demonstrated a left-shift bell curve distribution (Fig. 1).

Oxygen saturations dropped below 95% in 14% of cases, with the lowest recorded saturation being 90%. Supplemental oxygen was delivered in 74% of these cases. There were no reported uses of flumazenil. Among the cases included, 6% of the patients were known to use recreational drugs, 4% disclosed cannabis use and 5% were taking either prescribed or non-prescribed benzodiazepines. The recommended maximum dose of 7.5 mg was exceeded in 28% of all cases and justification for doing so was recorded in 21%. The mean RSS was 2.7 – this exhibited a normal bell curve distribution (Fig. 2).

Of the 25 cases where midazolam doses of 10 mg or greater were given, no patients were deemed to be 'over sedated' as per the RSS and all had their treatment completed successfully as planned. Furthermore, only 6 of the 25 patients (24%) required supplemental oxygen – this is comparable with those given lower doses of midazolam. Though, it is worth acknowledging the limitations of this small sample size.

Fig. 1 Overall IV midazolam dose distribution

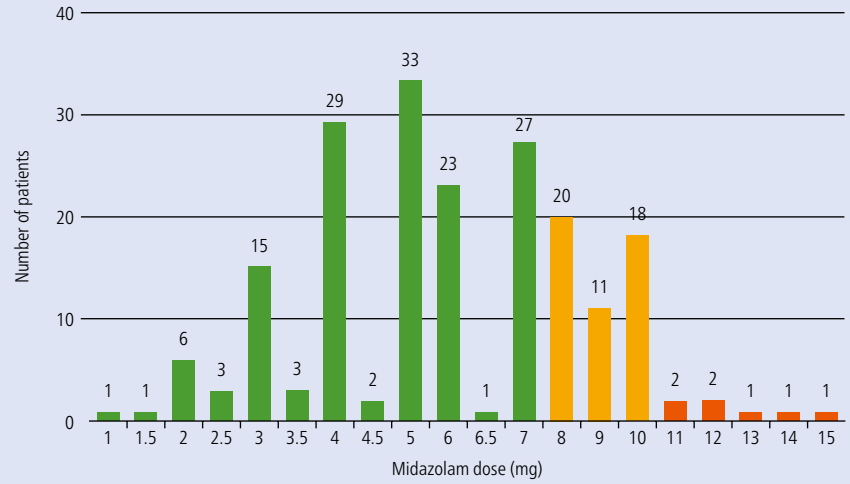
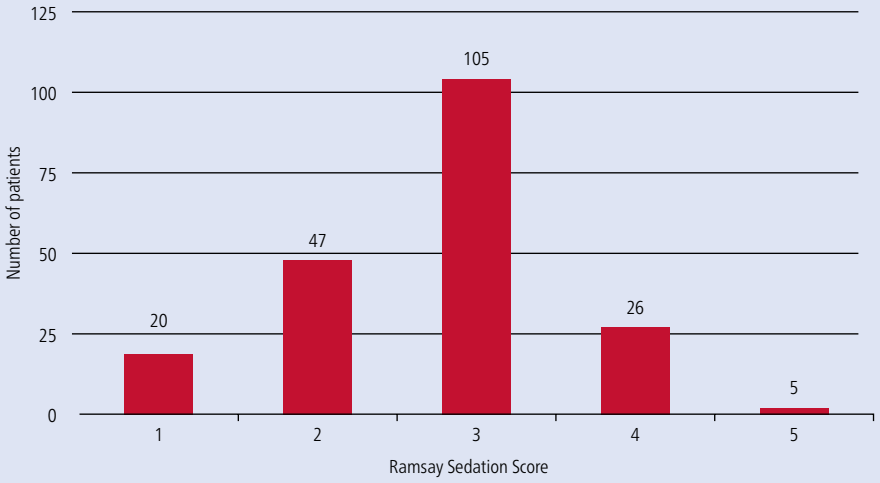


Fig. 2 Sedation score distribution



Discussion

A drug licence defines a medicine's 'term of use' and includes information such as: a summary of product characteristics, indications(s), recommended dose(s), contraindication(s), special warnings and so on. Licences give prescribers reassurance that therapeutic agents have been assessed for efficacy, safety and quality and are ultimately what is used to determine BNF dosing guidance.[13] In dentistry, some licenced drugs are recommended for treatment of conditions that are beyond the scope of the licence granted, yet their use is deemed in the patients' 'best interests' and based on 'sufficient available evidence'. Doses of midazolam above 7.5 mg are considered 'off-label' as per this definition. The licence for 1 mg/ml midazolam solution for injection states that when providing sedation, doses for adults under 60 years old should not exceed 7.5 mg and should not exceed 3.5 mg in those

over 60 years old – though it is worth noting that this guidance does not relate specifically to use within dentistry. Contradictory, the licence advises an IV dose of up to 10 mg when providing sedation for children aged 6–12 years old.[8] It is worth noting that this is not referring specifically to dentistry, though it does support the concept for a higher maximum dose in adults.

Since 2015, it is compulsory that all members of the dental team involved in the delivery of IV sedation must complete an accredited sedation course, including both didactic and practical elements. Furthermore, in Scotland, all dental practices must pass a thorough sedation inspection. To ensure patient safety, dental seditionists must record a detailed medical history before treatment, justify IV midazolam is an appropriate treatment modality and record adequate monitoring throughout treatment.[14] In addition to recording an explicit justification in the patients' clinical records for IV sedation when titrated doses exceed 7.5 mg, it is currently considered as 'off-label' and therefore the reasons why also need to be documented in the patient's notes. When obtaining consent for treatment, it is best practice to explain reasoning for prescribing 'off-label' to allow the patient make an informed decision.[15] However, in the case of midazolam conscious sedation, dentists are unable to predict the dose of midazolam required before starting. Available guidance suggests that drawing attention to drug licences when seeking consent may be unnecessary if current practice supports the use of a therapeutic agent outside the terms of its licence,[13] as we have demonstrated is the case when administering midazolam for dental conscious sedation.

This audit has demonstrated the use of IV midazolam for dental conscious sedation above the recommended dose of 7.5 mg without any adverse outcomes. Our study found that 7.5 mg of midazolam was exceeded in 56 cases which is over one-quarter of the patients treated. There were no reported adverse events or recorded uses of flumazenil, allowing us to define this as 'routine practice' within this small sample. We have also been able to demonstrate effective, complication-free use of midazolam doses up to 15 mg – we reported no adverse reactions, no increased need for supplemental oxygen and no evidence linking doses between 10–15 mg and higher RSSs. This is in keeping with available literature which also reports efficacious prescribing above the recommend maximum dose.[15,16] According to Malamed *et al*., dental seditionists should demonstrate heightened awareness at doses above 7.5 mg and should consider, after reviewing the patient's response, whether an adequate level of sedation is likely to be achievable once 10 mg is exceeded.[17] It is worth noting the impact maximum dose restrictions could have on dental sedation services, which are often a last resort for anxious or phobic patients hoping to avoid a general anaesthetic. General anaesthetics are not only attributable to increased morbidity, they also have a significantly larger financial burden[3] and are increasingly more challenging to secure during the current COVID-19 era. For treatment such as dentistry that is elective, it would be inexcusable not to consider safer alternatives, such as slow, carefully titrated, single-drug (midazolam) IV sedation. Furthermore, such a shift could lead to a number of patients being excluded, namely those deemed not fit for general anaesthetic or patient cohorts that tend to have greater tolerance to benzodiazepines.

Conclusions

Currently, IV midazolam as a single pharmacological agent to achieve conscious sedation is the most commonly used technique within dentistry. The importance of being able to sedate our patients is recognised by the General Dental Council who support that the provision of adequate anxiety control is an integral component of providing dental care.[18] In this audit, we have demonstrated that 28% of cases exceed the current recommended maximum dose of 7.5 mg. Therefore, if the maximum dose were to be strictly imposed, one can conclude that over one-quarter of the patients would be under-sedated. Consequentially, this could result in failed dental treatments and increased patient anxiety necessitating more dental general anaesthetics, as well as an unpleasant experience for many patients that could lead to avoidance of routine dental care. To avoid this, it is clear that there is a requirement for a recommended maximum dose of IV midazolam for use specifically for dental conscious sedation to be included in the BNF.

Given the data presented and that available in the literature, it is clear that 7.5 mg as an absolute limit is too conservative as it is regularly breached in 'normal practice'; however, it is worth acknowledging the relatively small sample analysed. Additionally, doses between 7.5–10 mg and those up to 15 mg, though less common, were also effective and attributable to no clinical incidents that warranted the use of flumazenil or increased use of supplemental oxygen. We propose that further investigation within a larger patient cohort and expert opinion is required to set a maximum dose of midazolam for use specifically in dental conscious sedation that is both safe and effective – when titrated slowly and carefully as a single agent – in achieving optimal sedation for most patients.

Ethics declaration

The authors declare no conflicts of interest. As this audit was an evaluation of peers based on their logbooks, with no identifiable patient data included, it was advised by NHS Ayrshire and Arran that this research did not require ethical approval.

Author contributions

Hannah Lawler: study design, data analysis, interpretation of results and draft manuscript preparation. Peter Walker: data collection and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Acknowledgements

To West of Scotland Dental Sedation Group: data provided by members in NHS Ayrshire and Arran, NHS Lanarkshire, NHS Forth Valley and NHS Highland.

References

1. Licheri L, Erriu M, Bryant V, Piras V. A Clinical Audit of Escorts' Awareness and Patients' Safety Following Intravenous Sedation In Adult Oral Surgery. *SAAD Dig* 2016; **32:** 17–22.
2. NHS Digital. Adult Dental Health Survey 2009 – Summary report and thematic series. 2011. Available at https://digital.nhs.uk/data-and-information/publications/statistical/adult-dental-health-survey/adult-dental-health-survey-2009-summary-report-and-thematic-series (accessed June 2022).
3. Jameson K, Averley P A, Shackley P, Steele J. A comparison of the 'cost per child treated' at a primary care-based sedation referral service, compared to a general anaesthetic in hospital. *Br Dent J* 2007; DOI: 10.1038/bdj.2007.631.
4. Department of Health. A Conscious Decision: A review of the use of general anaesthesia and conscious sedation in primary dental care. 2000. Available at https://www.dentalfearcentral.org/media/a-conscious-decision.pdf (accessed June 2022).
5. National Institute for Health and Care Excellence. Midazolam. 2022. Available at https://bnf.nice.org.uk/drug/midazolam.html (accessed June 2022).
6. Qadeer M A, Rocio Lopez A, Dumot J A, Vargo J V. Risk Factors for hypoxaemia during ambulatory gastrointestinal endoscopy in ASA I–II patients. *Dig Dis Sci* 2008; **54:** 1035–1040.
7. Folayan M O, Faponle A, Lamikanra A. Seminars on controversial issues. A review of the pharmacological approach to the management of dental anxiety in children. *Int J Paediatr Dent* 2002; **12:** 347–354.

8. Electronic Medicines Compendium. Midazolam 1mg/ml Solution for Injection or Infusion. 2018. Available at https://www.medicines.org.uk/emc/product/6045/smpc (accessed June 2022).
9. Intercollegiate Advisory Committee for Sedation in Dentistry. Standards for Conscious Sedation in the Provision of Dental Care (V1.1). 2020. Available at https://saad.org.uk/IACSD%202020.pdf (accessed June 2022).
10. Scottish Dental Clinical Effectiveness Programme. Conscious Sedation in Dentistry: Dental Clinical Guidance. 2017. Available at https://www.sdcep.org.uk/media/iegenn4c/sdcep-conscious-sedation-guidance.pdf (accessed June 2022).
11. NHS National Patient Safety Agency. Rapid Response Report: Reducing risk of overdose with midazolam injection in adults. 2008. Available at http://smart-ni.co.uk/downloads-2/files/NPSA%20Rapid%20Respose%20Report.pdf (accessed June 2022).
12. Rasheed A M, Amirah M F, Abdallah M, P J P, Issa M, Alharthy A. Ramsay Sedation Scale and Richmond Agitation Sedation Scale: A Cross-sectional Study. *Dimens Crit Care Nurs* 2019; **38:** 90–95.
13. UK Government. Off-label or unlicensed use of medicines: prescribers' responsibilities. 2014. Available at https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities (accessed June 2022).
14. Jacobsen P, Chávez E M. Clinical management of the dental patient taking multiple drugs. *J Contemp Dent Pract* 2005; **6:** 144–151.
15. Barker I, Butchart D G, Gibson J, Lawson J I, Mackenzie N. I.V. sedation for conservative dentistry. A comparison of midazolam and diazepam. *Br J Anaesth* 1986; **58:** 371–377.
16. Bavisha K A, Elias M, Paris S, Leon A R, Flynn P J. Comparison of patient-controlled and operator-controlled conscious sedation for restorative dentistry. *Eur J Anaesthesiol* 2004; **21:** 284–288.
17. Malamed S. Intravenous Moderate Sedation: Techniques of Administration. *In* Malamed S (ed) *Sedation: A Guide to Patient Management.* 6th ed. Philadelphia: Mosby, 2016.
18. General Dental Council. Standards for the Dental Team. 2013. Available at https://standards.gdc-uk.org/Assets/pdf/Standards%20for%20the%20Dental%20Team.pdf (accessed June 2022).

Appendix 1 IV midazolam dosing assessment *pro forma* for patients receiving dental conscious sedation

Please answer the questions below for each of your cases

Patient no.	What dose of midazolam did this patient receive?	What age is the patient?	Did the patient's oxygen saturation drop below 95%?	If yes, what was the lowest reading recorded?	Was oxygen given to the patient?	If you prescribed >7.5 mg did you record a rationale for this?	If yes, what was the rationale?	If you prescribed more than 7.5 mg, did the patient have a history of:			Sedation score	Flumazenil used?	Comments, if required:
								Use of recreational drugs?	Use of benzodiazepines, prescribed or not?	Cannabis use?			
1	9	51	No		No	Yes	Titrated to patient response	No	No	No	2	No	
2	7	23	No		No			No	No	No	3	No	
3	4	46	No		No			No	No	No	3	No	
4	8	35	No		No	Yes	Titrated to patient response	No	No	No	4	No	
5	8	18	No		No	Yes	Titrated to patient response	No	No	No	2	No	
6	6	38	No	95	Yes			No	No	No	2	No	
7	8	27	No		No	Yes	Titrated to patient response	No	No	No	1	No	
8	5	16	No		No			No	No	No	2	No	
9	4	22	No		No			No	No	No	3	No	
10	4	31	No		No			No	No	No	4	No	
11	3	34	No		No			No	No	No	3	No	
12	6	27	No		No			No	No	No	2	No	
13	5	24	No		No			No	No	No	3	No	
14	3	53	No		No			No	No	No	3	No	
15	10	40	Yes	93	Yes	Yes	Titrated to patient response	No	No	No	3	No	
16	8	56	No		No	No		No	No	No	2	No	
17	10	28	No		No			No	No	No	3	No	
18	7	23	No		No			No	No	No	4	No	
19	6	25	No		No			No	No	No	3	No	
20	10	31	No		No	Yes	Titrated to patient response	No	No	No	2	No	