Midazolam and drug–drug interactions in dental conscious sedation

Careful prescribing is paramount in clinical practice. Potential drug–drug interactions need to be considered. Midazolam is the drug of choice for the purpose of IV sedation. To ensure safe clinical practice, the patient’s current medications need to be recorded.

Clinical relevance: An update on the drug interactions relating to midazolam are worthy of scrutiny as its use becomes more commonplace in clinical practice.

Objective: The dentist should understand the possible implications for drug interactions when sedating patients using midazolam.

Introduction
Midazolam is an imidazobenzodiazepine, which was first synthesised in 1976 by Fryer and Walser. Its favourable properties include a reduced half life, high lipophilicity and a pH of 3.5, which enables it to be water soluble in the preparatory ampoule. This subsequently allowed for painless intravenous administration, in contrast with diazepam, where thrombophlebitis had been commonly reported at the site of administration. Midazolam soon became an alternative to diazepam and soon superseded it as the mainstay pharmacological agent for intravenous sedation. It has a therapeutic range of between 2mg and 7mg when administered intravenously.1 Within this range, the well recognised and desirable effects of the agent are observed – namely anxiolysis, sedation, amnesia and muscle relaxation. It does not have an analgesic effect. While the exact dosage utilised will vary between patients, the margin of safety is wide enough, when administered using a careful and controlled titration technique, to render unintended deep sedation/anaesthesia or loss of consciousness unlikely.

Midazolam is predominately metabolised by the liver, facilitated by microsomal oxidation. Each hepatocyte contains an extensive network of membrane structures, and an important enzyme located within these membranes is cytochrome P450 (CYP450). This represents a large family of enzymes that have an affinity for an array of drugs. The oxidation pathway involves binding of the CYP450 enzyme to a specific drug, carrying it through an electron transport chain, and releasing at the end of the process an oxidised form of the drug, H2O and the CYP450 enzyme. The oxidised drug is generally hydrophilic, therefore less likely to penetrate cells or be active, and is more easily excreted. These enzymes are also located in the upper gastrointestinal tract and need to be considered if oral midazolam is administered, as some of the drug is immediately deactivated. CYP3A4 is a member of the CYP450 family and is the mainstay enzyme involved in midazolam metabolism. It forms the basis for many of midazolam’s interactions.2

Before considering the reported interactions between midazolam and various other drugs
a patient may be prescribed, it is important to consider some important pharmacological concepts. Interactions are broadly classified into two categories, namely pharmacokinetic and pharmacodynamic interactions. Using a simple example of a person taking two drugs – drug A and drug B – the following explanations can be used:

1. **Pharmacokinetic interactions**: The administration of drug A alters the concentration of drug B that reaches its site of action. Within this interaction, one of the four major pharmacological processes of the drug can be affected, namely absorption, distribution, metabolism and elimination (Figure 1).

2. **Pharmacodynamic interactions**: The administration of drug A modifies the pharmacological effect of drug B, without altering its concentration.²

Two other concepts remain important, namely the therapeutic range and the concentration response curve, and these need to be considered:

1. **Therapeutic range**: This concept examines the concentration at which the therapeutic response is achieved compared to the concentration at which no effect is seen or a toxic effect is seen. A good example is warfarin, which has a narrow therapeutic range and is a common drug that dental patients take for medical reasons (Figure 2).

2. **Concentration-response curve**: This graph generally displays the response achieved for a given concentration. The steeper the curve, the greater the response for a smaller change in concentration (Figure 3).

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**Figure 1**: Pharmacokinetics of a drug. Following administration, each drug undergoes a pathway, which is predictable for most drugs. Following absorption and distribution, the drug is metabolised and excreted.

**Figure 2**: Therapeutic range of warfarin. Warfarin has a very narrow therapeutic range. For a very small change in concentration of warfarin, the therapeutic effect of the drug can be radically altered. This could create significant problems for a patient.

**Figure 3**: Concentration response curve for two drugs, A and B. Drug A displays how small changes in concentration lead to a large change in clinical effect of the drug; it has a steep concentration response curve. Drug B displays how a large change in concentration of a drug has a small effect on the clinical effect of the drug.
Pharmacokinetic interactions

Pharmacokinetic interactions can be broadly classified into two categories:

1. Enzyme inhibition – drugs or their metabolites react covalently or strongly with cytochrome (CYP), thus reducing the metabolism of the drug and therefore increasing its effect.

2. Enzyme induction – activation of genes, which leads to an increase of CYP, thus increasing the metabolism of the drug and therefore decreasing the effect of the drug.

Interactions

Inhibition of the CYP450 enzymes (more importantly CYP3A4) by any agent will result in a decrease in the rate of metabolism of a drug that is metabolised by it, i.e., the rate of metabolism of midazolam will be reduced. Put simply, more of the drug will remain actively available in the system for longer. Numerous drugs have been studied in relation to midazolam, namely groups such as the azoles (antifungals), macrolides (antibiotic), calcium channel blockers (blood pressure tablets) such as diltiazem, and human immunodeficiency virus (HIV) protease inhibitors such as saquinivir.1,4,5,6 Interestingly, many studies exist, not as a direct investigation of midazolam metabolism and its clinical effect, but using midazolam as a marker of CYP3A4 disruption by various other drugs. Midazolam is thus considered a “probe” agent. Many investigators attempt to quantify the level of CYP changes by an agent by co-administering midazolam and measuring its plasma concentrations at various intervals. The clinical impact of such interactions is often overlooked.

Antifungals/antibiotics

Ketoconazole, fluconazole and itraconazole, all azole antifungals, have displayed CYP450 inhibition.1,4,5 In a crossover study in healthy volunteers (n=12) has also displayed potent CYP3A4 inhibition; however, not to the same extent as ketoconazole. Inhibition of the CYP450 enzymes (more importantly CYP3A4) by any clinical significance; however, clarithromycin and roxithromycin are newer members of the family. They are known to be CYP450 inhibitors. It has been recommended that the dose of midazolam should be reduced by between 50% and 75% in patients concurrently taking erythromycin.4,7 Investigation of the potential interactions between midazolam and erythromycin involving 12 subjects highlighted a 54% reduction in clearance of intravenous midazolam and a four-fold increase in the area under the concentration curve when oral midazolam was administered. Both results were statistically significant (p<0.05). The subjects were given a standard dose of 500mg tds. Six of the subjects repeated the five-day course of erythromycin at the end of the five-day course of erythromycin.4,8 In vivo studies using rats have displayed a significant decrease in clearance of midazolam, both orally and intravenously, when administered with ketoconazole (p<0.005).9 Patients in the intensive care unit (ICU) will commonly be sedated and ventilated. Concentrations of midazolam were significantly increased up to four-fold after the start of flucloxacillin treatment. Unfortunately, given the high level of sedation required for the patients (10-30mg midazolam/hour), and indeed the presence of mechanical ventilation, any clinical effects were potentially masked. The authors concede that any decrease in clearance/elimination of midazolam could potentially lead to longer-lasting sedation, with a subsequent longer stay in ICU. The need for dose adjustment of midazolam is acknowledged.

The need for caution with midazolam in the presence of potent enzyme inhibitors is also recognised. In one randomised, controlled study, 40 healthy subjects received either ketoconazole, fluoxetine, fluvoxamine and nefazodone for a set period of time followed by an oral dose of midazolam at the end of that pre-defined period. The area under the curve of midazolam was increased by 771% as compared with measurements taken pre-administration of ketoconazole. Significant midazolam-related cognition impairment was also recorded.10 Posaconazole examined in a randomised, open-label crossover study in healthy volunteers (n=12) has also displayed potent CYP3A4 inhibition; however, not to the same extent as ketoconazole. Doses of 2mg oral midazolam with 0.4mg IV midazolam were administered. Bloods were checked at 24 hours following administration. It is prudent to note that the concentrations administered in subjects of a mean age of 42 years were not administered for sedative purposes. The area under the concentration curve increased to 6.2 times expected normal, and when administered with ketoconazole an 8.2-fold increase was recorded within the same study.11 Macrolides are a useful group of antibiotics, and are often the first-line choice in penicillin-sensitive individuals. It is not uncommon to prescribe a macrolide for dental infections (erythromycin) for penicillin-allergic patients. Erythromycin was the first macrolide with any clinical significance; however, clarithromycin and roxithromycin are newer members of the family. They are known to be CYP450 inhibitors. It has been recommended that the dose of midazolam should be reduced by between 50% and 75% in patients concurrently taking erythromycin.4 Macrolides are a useful group of antibiotics, and are often the first-line choice in penicillin-sensitive individuals. It is not uncommon to prescribe a macrolide for dental infections (erythromycin) for penicillin-allergic patients. Erythromycin was the first macrolide with any clinical significance; however, clarithromycin and roxithromycin are newer members of the family. They are known to be CYP450 inhibitors. It has been recommended that the dose of midazolam should be reduced by between 50% and 75% in patients concurrently taking erythromycin.
Anaesthesia was preoperatively. All patients were induced with 0.1mg/kg midazolam, randomly assigned to receive either diltiazem or a placebo 60 minutes undergoing coronary bypass grafting under general anaesthesia. Erythromycin, increases the area under the concentration curve of CYP3A4 inhibitor and, therefore, similarly to ketoconazole and increases the risk of arrhythmias and hypertension, and for the control of angina. It is a calcium channel blocker, often used for the treatment of blood pressure medication.

Diltiazem is a calcium channel blocker, often used for the treatment of arhythmias and hypertension, and for the control of angina. It is a CYP3A4 inhibitor and, therefore, similar to ketoconazole and erythromycin, increases the area under the concentration curve of midazolam. In one randomised controlled trial, 30 patients undergoing coronary bypass grafting under general anaesthesia were randomly assigned to receive either diltiazem or a placebo 60 minutes preoperatively. All patients were induced with 0.1mg/kg midazolam, 50mcg/kg alfentanil and 20-80mg propofol. Anaesthesia was maintained with alfentanil, midazolam and isoflurane. The mean halflife of midazolam was 43% longer in patients receiving diltiazem. Tracheal extubation was performed on average 2.5 hours longer in patients given diltiazem. It is important to note, however, that alfentanil metabolism is also decreased in the presence of CYP450 inhibitors, and that has to be taken into consideration when explaining the clinical effects recorded.

### Table 1: Drug–drug interactions. The list is quite expansive and needs careful attention.

<table>
<thead>
<tr>
<th>Pharmacokinetic interactions</th>
<th>Pharmacodynamic interactions</th>
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<tr>
<td>CYP Inhibitors</td>
<td>CYP inducers</td>
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<tr>
<td>Ketoconazole</td>
<td>Phenyoitin</td>
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<td>Fluconazole</td>
<td>Carbamazepine</td>
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<tr>
<td>Itraconazole</td>
<td>Rifampicin</td>
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<td>Diltiazem</td>
<td>St John’s wort</td>
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<td>Verapamil</td>
<td>Alcohol</td>
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<td>Erythromycin</td>
<td>Propofol</td>
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<td>Clarithromycin</td>
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<td>Roxithromycin</td>
<td>Etomidate</td>
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<td>Saquinavir</td>
<td>Sedative antidepressants</td>
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<td>Atorvastatin</td>
<td>H₂, antihistamines</td>
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<td>Grapefruit juice</td>
<td>Centrally acting antihypertensive drugs</td>
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0.05mg/kg. Psychomotor analysis was undertaken. The authors reported that the interaction between oral midazolam and erythromycin was statistically significant, with a time interval of between 15 minutes and six hours. These results have been supported by other investigators, who have studied the interaction between various doses of oral midazolam (namely 5mg, 10mg and 15mg) with a single dose of erythromycin or roxithromycin, both of which displayed similar interactions – erythromycin more so than roxithromycin. Clarithromycin has also been investigated, interestingly in an elderly study population, differing hugely from the typical study groups of young healthy individuals. Sixteen volunteers received clarithromycin 500mg for seven days. Two hours after finishing clarithromycin, subjects received 0.05mg/kg intravenous midazolam and 3.5mg orally. Clinical effects were not assessed. The area under the concentration curve of intravenous midazolam increased 3.2-fold and, following oral midazolam, eight-fold. Caution was advised when considering administering midazolam to a patient on clarithromycin.

### Blood pressure medication

Diltiazem is a calcium channel blocker, often used for the treatment of arhythmias and hypertension, and for the control of angina. It is a CYP3A4 inhibitor and, therefore, similar to ketoconazole and erythromycin, increases the area under the concentration curve of midazolam. In one randomised controlled trial, 30 patients undergoing coronary bypass grafting under general anaesthesia were randomly assigned to receive either diltiazem or a placebo 60 minutes preoperatively. All patients were induced with 0.1mg/kg midazolam, 50mcg/kg alfentanil and 20-80mg propofol. Anaesthesia was maintained with alfentanil, midazolam and isoflurane. The mean half-life of midazolam was 43% longer in patients receiving diltiazem. Tracheal extubation was performed on average 2.5 hours longer in patients given diltiazem. It is important to note, however, that alfentanil metabolism is also decreased in the presence of CYP450 inhibitors, and that has to be taken into consideration when explaining the clinical effects recorded.

#### Anti-retroviral medication

The oral administration of midazolam, as mentioned, can be unpredictable in the presence of an enzyme inhibitor. HIV is not an uncommon condition among dental patients today. Saquinavir, a protease inhibitor used in patients with HIV, has displayed potent inhibition of CYP3A4 enzymes. Bioavailability of oral midazolam has been shown to increase from 41% to 90% in its presence, with clinically increased sedative effects being displayed. Saquinavir also decreased the clearance of intravenous midazolam by 56%.

#### Cholesterol-reducing agents/herbal remedies

Atorvastatin, used in the treatment of hypercholesterolaemia, has also been reported as reducing the clearance of midazolam in both an in vivo and in vitro setting. These drugs are almost routine in patients over 50 years of age. While prescribed drugs often dominate the major studies, it is interesting to note interactions with various herbal remedies and, interestingly, grapefruit juice. Grapefruit juice inhibits the CYP3A4 activity in the intestinal wall, an effect that can last for 24 hours. This will invariably lead to an increase in the bioavailability of a drug such as midazolam, which undergoes pre-systemic metabolism. Oral midazolam administered following patient intake of grapefruit juice increased the area under the curve and maximum concentration by an estimated 41%, psychometric tests showing greater patient impairment in this situation. St John’s wort has been one of the most commonly used herbal remedies for mood disorders. It is recognised as a potent CYP450 enzyme inducer. It accelerates the metabolism of substrates of the CYP system, such as midazolam. While not examined in the clinical setting, a significant decrease in the area under the concentration curve was noted for oral midazolam. One can assume that decreased sedation will be a clinical outcome.

#### Anti-tuberculosis medication/anti-epileptic medications

Rifampicin, an antibiotic frequently used in the treatment of tuberculosis, and carbamazepine, a well recognised anti-epileptic drug, are both well-recognised inducers of the CYP450 enzymes. Tuberculosis is on the increase in Ireland. Trigeminal neuralgia and epilepsy are also not uncommon. In one study, carbamazepine reduced the peak concentration of midazolam to 7.4% of its value in control subjects, while reducing the area under the concentration curve to 5.7% of its normal value. Midazolam was administered orally, thus highlighting the effect of pre-systemic reduction in the bioavailability of midazolam as orchestrated through the intestinal CYP3A4 enzyme.
Pharmacodynamic interactions

Pharmacodynamic interactions have been reported with a considerable number of drugs, namely: opioids, antipsychotics, other benzodiazepines, barbiturates, alcohol, propofol, ketamine, etomidate, sedative antidepressants, H₂ antagonists, and centrally acting antihypertensive drugs. The co-administration of midazolam with other sedatives and CNS depressants will invariably lead to an increase in the risk of over-sedation and respiratory depression. For instance, one should refrain from the consumption of alcohol for at least 12 hours post receiving midazolam. Careful consideration needs to be exercised in the presence of the above medications/drugs (see Table 1).

Conclusion

Midazolam itself does not affect the pharmacokinetics of any other drug. Midazolam's metabolism and bioavailability are invariably altered by other drugs to varying extents. Given the pharmacological basis to the majority of studies, and the theoretical basis on which they are performed, the clinical effects of such interactions are not always considered. The desired effects of midazolam are ubiquitously reported as being anxiolyis, anti-convulsion, sedation and amnesia; however, these desired clinical end points occur on a spectrum with a generally wide therapeutic range (i.e., 2mg-7mg) for a 72kg healthy individual. Towards the latter end of the spectrum, it has to be recognised that respiratory depression and anaesthesia are clinical end points that are undesirable for routine dental treatment. No study, however, even when clinical effects were noted in conscious patients, reported any adverse end points such as those mentioned, although caution has been strongly advised with the use of oral midazolam and potent CYP3A4 inhibitors such as ketoconazole. To begin with, one can only make gross theoretical extrapolations from the body of literature available, to assume that certain negative interactions could lead to over-sedation of the patient leading to an un-manageable patient. The patient may remain sedated for longer as a result of the decreased clearance, or indeed develop fatal respiratory depression.

The predominant method utilised for conscious sedation is titration, which is the administration of a drug, in this case midazolam, towards a defined conscious sedation patient response. This is one potential safety net offered to sedationists, as over-sedation should not occur and dose adjustments can easily be made. The only factor that cannot be controlled is the length of sedation, as a result of decreased clearance. This may have both a staffing and a financial implication for the sedationist. It is a mandatory requirement to have a pulse-oximeter present and working for all patients who are sedated, in tandem with good clinical observation. Any drop in oxygen saturation should be quickly noted. Interactions with oral midazolam, in particular in the presence of a potent CYP450 inhibitor, is an area where extreme caution and dose adjustment need to be implemented. Following administration of oral midazolam, usually only about 40% becomes bioavailable; the remainder is either non-absorbed or metabolised by the pre-systemic CYP450 enzymes located in the intestinal cells of the small intestine. Bioavailability has been increased to as much as 80% in the presence of potent inhibitors of midazolam; that is, essentially a doubling in the serum concentration. This might have clinical effects that are detrimental. The manufacturers of midazolam give strong warning regarding such combinations. If the true clinical implications are to be discovered, more randomised controlled trials with subjects of all ages need to be performed, coupling pharmacokinetic parameters with definite sedative clinical parameters. This will remove theoretical assumptions from the equation and will give greater guidance on such interactions. What remains static, at present, is that a thorough medical and drug history needs to be taken from each and every patient, even questioning about non-prescription medication. This will highlight any potential interaction, even if not offering an insight into clinical relevance. Grapefruit juice is an interesting addition to the interaction list. Should we change preoperative instructions to advise patients to avoid grapefruit juice? It remains true that midazolam fortunately has a relatively wide therapeutic range; however, this should not be considered in isolation as good clinical practice, i.e., clinical monitoring, titration and the presence of the reversal agent flumazenil, needs to be implemented on a permanent basis.

Unfortunately, oral sedation does not allow the same degree of titration as intravenous methods allow; therefore, caution needs to be exercised if an interaction is anticipated.

References

9. Kotegawa, T., Laurijssens, B., Moltke, L., Cotreau, M., Perloff, M.


