



Oral midazolam – grapefruit juice drug interaction

Curt Goho DDS

Dr. Goho is the staff pediatric dentist, Department of Pediatric Dentistry, U.S. Army Dental Activity, Ft. Lewis, WA. Correspond with Dr. Goho at gohocurtis@hotmail.com

Abstract

Oral midazolam is a frequently used sedative in pediatric dentistry. Although an oral form of midazolam is now commercially available, some practitioners continue to use the IV midazolam as an oral medication. If the injectable form of midazolam is administered orally, its bitter taste requires the use of a flavoring agent. Grapefruit juice is contraindicated for this purpose as it inhibits cytochrome P450 (CYP) 3A4. CYP 3A4 is located in the intestine and liver. Inhibition of this cytochrome results in delayed absorption and reduced first pass effect on midazolam. This results in increased blood plasma levels of midazolam of 56% and increased midazolam bioavailability of 35%. This can result in excessive levels of sedation for the pediatric patient. Grapefruit juice is therefore contraindicated for use with oral midazolam. (Pediatr Dent 23:365-366, 2001)

Midazolam (Versed, Roche Pharmaceuticals, Nutley, NJ) is a short-acting benzodiazepine that has gained popularity as an oral sedative and anxiolytic. It is frequently used by pediatric dentists for pharmacologic behavior management.¹ Although a relatively safe medication, overdose has been associated with respiratory depression and respiratory arrest. For this reason, established doses of 0.3-0.75 mg/kg for oral administration should not be exceeded.²

Until recently, midazolam was only available in an injectable form, in concentrations of 5 mg/ml, in 1 ml, 2 ml, and 10 ml vials, and 2 ml syringes. Intravenous midazolam has been used orally, however, it has an extremely bitter taste. For use as an oral medication, a flavoring solution is therefore needed to mask the bitterness. Examples of flavoring agents mixed with the injectable midazolam include pharmacy prescribed flavorings such as Ora-Sweet (Paddock Laboratories, Minneapolis, MN, NDC #0574-0304-16), Acetaminophen elixir (Pharmaceutical Associates, Greenville, SC), presweetened Kool-Aid (Kraft General Foods), and grapefruit juice. In 1999, Roche Pharmaceuticals introduced an oral syrup form of midazolam, at 2mg/ml concentration, in a 118 ml bottle.

Although an oral form of midazolam is now available, some health care providers still use the IV medication as an oral sedative, mixing it with a flavoring agent. This is often due to the convenience of the "unit doses" of the injection vials, or the reluctance to have a pharmacy stock the comparatively larger and more expensive bottle of liquid midazolam for only infrequent use. The wholesale cost of oral midazolam syrup is \$1.67 per milligram, while the injectable form of midazolam costs approximately \$0.33 per milligram. The fact that the oral midazolam syrup costs over five times more than the injectable form can also be a factor in practitioners continuing to

use the injectable midazolam for oral use. Practitioners who continue to use the injectable midazolam for oral use need to be aware that one common flavoring agent – grapefruit juice – has been contraindicated for use with midazolam.

Grapefruit juice inhibits the action of cytochrome P450 3A4 (CYP3A4). This cytochrome is found in both the intestine and the liver. Studies suggest that a combination of flavinoids and other compounds unique to grapefruit cause this inhibition of CYP3A4. The effect is not noted from other citrus juices.^{3,4} In the intestine, CYP3A4 is responsible for the absorption of many medications, including midazolam.^{5,6} Decreased absorption from the intestine results in a prolonged onset time of midazolam. Grapefruit juice also inhibits hepatic CYP3A4, which is a catalyst for the breakdown of midazolam into its metabolite x-hydroxymidazolam. This results in a decreased first pass effect on midazolam and increases midazolam's bioavailability in the blood.⁵

When oral midazolam is given with grapefruit juice, the clinical effect of inhibited CYP3A4 is a 56% increase in peak plasma concentration (C_{max}) of midazolam and a 79% increase in the time required to reach the peak plasma concentration (t_{max}) (from 0.62 hours to 1.11 hours). Clearance and elimination of midazolam are not affected. The end result of the various inhibitions of CYP3A4 is an increase in the bioavailability of midazolam by 35%, leading to the possibility of excessive sedation.^{4,5,7}

The ramifications of these findings for pediatric dentists are significant. Excessive sedation can result from the administration of midazolam with grapefruit juice. This is due to the increased peak plasma levels and the prolonged bioavailability of the drug. Therefore, the best way to prevent adverse drug interactions when midazolam is administered orally is to use the commercially available oral syrup form of the drug. If a practitioner chooses to mix a flavoring agent with the injectable midazolam and administer it orally, grapefruit juice should not be used.

References

1. Henry RJ, Ruano N, Casto D, Wplf RH. A pharmacokinetic study of midazolam in dogs: nasal drops vs. atomizer administration. *Pediatr Dent* 20(5):321-326, 1998.
2. Kupietzky A, Houpt M. Midazolam: a review of its use for conscious sedation of children. *Pediatr Dent* 15(4):237-240, 1998.
3. Fuhr U. Drug interactions with grapefruit juice. Extent, probable mechanism and clinical relevance. *Drug Safety* 18(4):251-272, 1998.

Received April 5, 2001 Revision Accepted June 12, 2001

4. Kupferschmidt H, Ha H, Ziegler W, et al. Interaction between grapefruit juice and midazolam in humans. *Clin Pharmacol Ther* 58:20-28, 1995.
5. Kane G, Lipsky J. Drug-grapefruit interactions. *Mayo Clinic Proceedings* 75(9):933-942, 2000.
6. Bailey D, Malcolm J, Arnold O, Spence J. Grapefruit juice-drug interactions. *Brit J Clin Pharm* 46(2):101-110, 1998.
7. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinetics* 38(1):41-57, 2000.

ABSTRACT OF THE SCIENTIFIC LITERATURE



Fluoride levels retained following applications of topical fluoride products

The purpose of this study was to determine relative salivary retention rates, relative ingestion rates and elevation in blood fluoride levels associated with a variety of topical fluoride materials in adult patients. Subjects were asked to use, under supervision, various delivery methods and concentrations of fluoridated dentifrices, mouth rinses and gels. At set time intervals salivary and venous blood samples were collected. Reported results included: (1) fluoride retention in saliva from toothpaste was proportional to the amount used; (2) for mouth rinses the salivary retention was proportional to the concentration of fluoride ion in the mouth rinse used; (3) for gels, salivary retention did not vary for commercial versus custom trays, however custom trays did reduce the amount of gel swallowed; (4) fluoride blood levels remained near baseline regardless of the type of tray used. The authors concluded that, when safe clinical procedures are followed, these fluoride products are safe for adult patients.

Comments: Although the safety of these fluoride products has long been accepted, this study did attempt to link safety with measurable parameters (blood levels, etc...). However the results must be examined carefully since the study population was quite small (for example, only 3 subjects had blood levels checked). MM

Address correspondence and requests for reprints to: Dr. J. McIntyre, Department of Dentistry, The University of Adelaide, South Australia 5005

Analysis of fluoride levels retained intraorally or ingested following routine clinical applications of topical fluoride products.

Heath K, Singh V, Logan R, McIntyre J: *Austral Dent J* 46: 24-31, 2001
9 references

ABSTRACT OF THE SCIENTIFIC LITERATURE



The purpose of this retrospective study was to examine studies on fluoride and bone, published since 1991, and to report on the effect, if any, of fluoride on bone strength, mass and fracture rate. Using a Medline search and predetermined exclusion criteria, 31 articles were examined. These articles were divided into animal feeding studies and human ecological studies. For animal studies, the authors reported no decrease in bone strength in rats treated with less than 50 ppm fluoride (or up to 150 times greater than 1 ppm in a 60kg person). Human studies indicated that 1 ppm fluoride did not increase the incidence of fractures or decrease bone mineral density. The authors concluded that drinking fluoridated water had no adverse effect on bone; instead, evidence suggested it may be beneficial.

Comments: Since this is a review of the literature, not all aspects of the examined studies are reported. Therefore the results should be considered with caution. MM

Address correspondence and requests for reprints to: Dr. Martha I. Sinclair, Department of Epidemiology and Preventive Medicine, Monash Medical School, Alfred Hospital, Commercial Road, Prahran, Victoria 3181

Water fluoridation, osteoporosis, fractures- recent developments.

Demos L, Kazda H, Cicuttini F, Sinclair M, Fairley C: *Austral Dent J* 46: 80-87, 2001.
43 references