Review

Nutrition in Clinical Practice
Volume 25 Number 3
June 2010 265-269

10.1177/0884533610368711
http://ncp.sagepub.com
hosted at
http://online.sagepub.com

Dietary Tyramine Restriction for Hospitalized Patients on Linezolid: An Update

Martha M. Rumore, PharmD, JD, FAPhA;
Marc Roth, RPh, MS, CNSC; and Areti Orfanos

Financial disclosure: none declared.

Linezolid is a weak, reversible monoamine oxidase inhibitor. The current practice at most hospitals is to place patients receiving linezolid on a tyramine-restricted diet. This process typically involves both the hospital's pharmacy department and the food and nutrition department. A literature search assessing the interaction between linezolid and tyramine was conducted, and the amount of tyramine in a typical unrestricted diet for a hospitalized patient was reviewed. Although patients receiving linezolid should avoid consuming large amounts of foods containing high concentrations of tyramine, such foods in large amounts are not components of meals for inpatients. Therefore, dietary tyramine restriction in hospitalized patients is not generally required. (*Nutr Clin Pract.* 2010;25:265-269)

Keywords: linezolid; monoamine oxidase inhibitors; tyramine; food-drug interaction

Tyramine is an indirectly acting sympathomimetic monoamine normally found in some foods and beverages. Examples of foods that contain high tyramine levels include smoked/aged meat, aged cheeses, sauerkraut, and soy sauce.[1] Tyramine is metabolized and almost completely deaminated by monoamine oxidase (MAO). There are 2 isoforms of MAO: MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine. MAO-B preferentially deaminates phenylethylene and trace amines. Dopamine is equally deaminated by both types. MAO-A, the form predominantly expressed in the gut wall and the liver, normally serves as an enzymatic barrier to systemic tyramine circulation. In the presence of monoamine oxidase inhibitors (MAOIs), tyramine is unable to undergo metabolism (ie, deamination). This results in passage of unmetabolized tyramine into the systemic circulation and eventually potentiation of its pressor or blood pressure-raising effect. Initially described in the 1960s, when patients prescribed MAOIs for depression experienced sudden hypertensive crises,[2,3] the MAOI–tyramine food–drug interaction has become one of the most publicized in the literature. Consequently, the standard of care is to place patients receiving MAOIs on tyramine-restricted diets.

Linezolid is an oxazolidinone antibiotic possessing weak, reversible, nonselective MAOI activity. Linezolid is differentiated from other MAOIs marketed in the United States because it is a weak, reversible MAOI, whereas other MAOIs are irreversible, leading to more pronounced pressor effects when combined with small amounts of tyramine. Recommended tyramine quantities for patients receiving linezolid are <100 mg per meal,[4] whereas recommended tyramine quantities for patients receiving other MAOIs are <6 mg.[5] According to the product labeling for Zyvox (brand of linezolid, Pfizer, New York, NY), "A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content."[4] The labeling states, "Large quantities of foods or beverages with high tyramine content should be avoided while taking Zyvox. Quantities of tyramine consumed should be <100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0-15 mg tyramine per ounce); fermented or air-dried meats (0.1-8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per teaspoon); and tap beers (38 mg tyramine

From NewYork–Presbyterian Hospital, New York, New York.

Address correspondence to: Martha M. Rumore, NewYork–Presbyterian Hospital, Pharmacy Department, 622 West 168th St, New York, NY 10032; e-mail: mar9131@nyp.org.

per 12 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated."[4]

Is a Tyramine-Restricted Diet Necessary?

Acknowledging that there is a 16-fold difference between other MAOI allowances and linezolid leads to the question of whether a tyramine-restricted diet is necessary for patients taking linezolid. More specifically, is a tyramine-restricted diet necessary for hospitalized patients receiving linezolid?

Our institution, New York–Presbyterian Hospital, with > 2300 beds, may have >100 patients on linezolid at any given time. At our institution, the pharmacy department is responsible for communicating the initiation of linezolid to the department of food and nutrition. It is not practical to generate a list from our physician order entry system (Eclipsys XA, Atlanta, GA). Upon order entry of an MAOI, including linezolid, a screen appears requesting the pharmacist to contact the department of food and nutrition regarding an appropriate diet. Under the previous hospital policy titled Drug–Nutrient Interactions, the pharmacist was required to contact the clinical dietitian from the department of food and nutrition to communicate that an order for an MAOI had been received for a specific patient. The food and nutrition department then automatically instituted a tyramine-restricted diet; contacted the prescriber, if necessary, to ensure that an appropriate diet order was written; and then notified nursing. The clinical dietitian initiated diet education, when necessary, and documented this in the medical record on the Interdisciplinary Patient and Family Education Form. This process and the volume of patients placed on linezolid resulted in a significant time commitment for both the pharmacy department and the food and nutrition department. To conserve valuable resources, we investigated whether the tyramine–linezolid interaction is clinically meaningful for hospitalized patients. Our objective was to evaluate the possibility that the tyramine dietary restriction is not necessary for hospitalized patients receiving linezolid.

Literature Review

To identify pertinent literature, including but not limited to case reports describing a food–drug interaction between linezolid and tyramine, we conducted a search using MEDLINE (1996 to January 2010), PubMed, and the Google Scholar engine using the search terms *linezolid*, *tyramine*, and *reversible MAOI* and a combination of text and MeSH terms. Bibliographies of identified articles were subsequently reviewed for additional citations. The studies are summarized below. The product manufacturer was contacted for information regarding the interaction and reported cases.

No case reports were retrieved from the literature. Our search encompassed the time from discovery of linezolid in 1996, prior to Food and Drug Administration (FDA) approval in 2000, to January 2010. According to the manufacturer, no interactions were found during phase II or III clinical studies of linezolid. Since FDA approval in April 2000, only 1 case has been reported to the manufacturer. The details of the case are unknown except that the patient was receiving linezolid as an outpatient and that the event ceased when the patient stopped consuming tyramine (A. Alla, Pfizer Inc, New York, NY, personal communication, July 23, 2009). Thus, there are no documented cases of a linezolid-tyramine reaction occurring in hospitalized patients. Several clinical studies evaluating the interaction between linezolid and tyramine were retrieved.

A placebo-controlled, crossover study in 12 healthy volunteers evaluated the effect of oral linezolid on the pressor response to oral tyramine.[6] Tyramine doses were escalated at increments of 25 mg from 25 to 450 mg until an increase of at least 30 mm Hg in systolic blood pressure (SBP) was observed. Subjects received linezolid (625 mg twice daily orally), moclobemide (another reversible MAOI marketed in the United Kingdom; 150 mg 3 times daily), or placebo for up to 7 days. The pressor dose (ie, $PD_{>30}$) is the most widely used measure of sensitivity to tyramine and represents the smallest tyramine dose required to cause a 30 mm Hg increased in SBP. In the study, the $PD_{>30}$ was 100 mg with linezolid treatment and 75 mg with moclobemide treatment. At 75-mg doses, no patients reached $PD_{>30}$. In most patients, however, the smallest dose was 200 mg. Pharmacokinetic analysis revealed the mechanism to be decreased clearance of tyramine, consistent with MAOI activity. The magnitude of the effect observed was similar to moclobemide. No changes in blood pressure were observed when tyramine was given concomitantly in doses within the range of normal dietary intake (<100 mg per meal).[6] The authors concluded that restriction of normal dietary intake of tyramine-containing foods is not warranted for patients receiving linezolid.

Another study evaluated the effect of a single 600-mg dose of linezolid, 300 mg of moclobemide, or placebo on the pressor response to intravenous tyramine in 12 healthy male volunteers (age 27-46 years), with body mass index of 18-31 kg/m^2, no history of migraine or serotonin syndrome, and resting blood pressure <130/90 mm Hg at screening.[7] Tyramine doses of 1, 2, 4, 6, 8, and 10 mg were escalated until SBP increased at least 30 mm Hg. The mean intravenous tyramine dose required to achieve a 30 mm Hg increase in SBP was 5.4 mg and

Table 1. High Tyramine–Containing Foods and Quantity Required to Provide 50 mg of Tyramine

	Serving Size	Tyramine Content Per Serving, mg[a]	Quantity Required for 50 mg of Tyramine
Chicken liver, aged 9 d	1 oz	63	0.8 oz
Aged cheeses	1 oz	7.5	6.7 oz
Soy sauce	15 mL	15	50 mL
Sauerkraut	4 oz	4	50 oz
Fermented or air-dried meats	1 oz	4	12.5 oz
Tap beers	12 oz	4	150 oz
Red wine	8 oz	3	133 oz

[a]Average from references 1, 4, 15, and 16.

was 1.8 times greater with placebo than with linezolid. Again, linezolid and moclobemide had a similar pressor response to intravenous tyramine.

Although not specific to linezolid or any drugs, another study evaluated the tyramine content of previously restricted foods in typical tyramine-restricted MAOI diets.[8] The tyramine content of 51 samples was analyzed via liquid chromatography. Food samples included sausages, beverages, sliced meat products including chicken liver, raspberries, and bananas. A dangerously high concentration of tyramine was characterized as being ≥6 mg per serving. Many of the foods in the samples, although typically listed in tyramine-restricted MAOI diets, such as raspberries, bananas, beverages, and meats, were not found to be high in tyramine content. The study concluded that of the foods analyzed, only those with high tyramine content per serving should be absolutely restricted. All other foods evaluated were deemed either safe for consumption or safe in moderation. Thus, research supports the concept that current MAOI–tyramine diets are excessively restrictive and founded on poor scientific evidence.

Discussion

Although the interaction of irreversible MAOIs with foods containing high tyramine content is well known, for reversible MAOIs such as linezolid much less is known. What is known is that linezolid has in vitro MAOI activity,[9] and coadministration of linezolid with adrenergic and serotonergic agents has been associated with elevated blood pressure in normotensive patients.[10] It is also known that based on analysis of $PD_{>30}$ indices, the smallest tyramine dose required to cause a 30 mm Hg increase in SBP is 100 mg. This is reflected in the Zyvox product labeling.

Moclobemide, another reversible MAOI drug, has been extensively evaluated in tyramine pressor tests.[11,12] As a result, the potential of moclobemide to interact with food has been quantified. The magnitude of the effect observed appears to be similar to that of linezolid. Moclobemide is prescribed in the United Kingdom without dietary tyramine restriction but with a general precaution in the product labeling to avoid excessive amounts of tyramine-rich foods.[13]

The product labeling of Zyvox restricts its caution to limiting consumption of large amounts of foods or beverages with high tyramine content.[4] Unlike the Zyvox caution, the product labeling for the irreversible MAOI tranylcypromine sulfate (Parnate, GlaxoSmithKline, Research Triangle Park, NC) warns about the potential for hypertensive crises and lists combination with cheese or other foods with a high tyramine content as a contraindication.[14] Clearly, the different labeling for the reversible MAOI linezolid and the irreversible MAOI tranylcypromine reflect the 16-fold (100 vs 6 mg) difference in the amount of tyramine for $PD_{>30}$.

Our research revealed no literature reports and only 1 case in an outpatient, reported to the manufacturer, details unknown. Although a drawback of our research, in view of the nonexistent cases, we decided not to request from the FDA, under the Freedom of Information Act, postmarketing voluntary adverse event reports of linezolid that included a tyramine reaction.

A high-tyramine meal, judged from tyramine analysis of current commercially produced foodstuffs, could contain ≥40 mg of tyramine. One study assessed the tyramine content of high-tyramine meals and found concentrations ranging from about 10 to 36 mg per meal.[13] Thus, a tyramine content of ≥50 mg significantly exceeds amounts achievable from dietary tyramine sources unless high-tyramine foods are consumed such as aged chicken liver. The tyramine content of various foods is found in Table 1 in addition to the quantity required to provide 50 mg of tyramine.[1,4,15,16] The vast majority of foods on the high-tyramine list would not comprise a hospitalized patient's meal tray offerings or dietary choices—beer, wine, yeast extract, or aged or cured meats. This is especially true because hospital menus are designed to consistently meet the Recommended Daily Allowances and U.S. Dietary Guidelines. However, even if these foods were on the menu, large quantities would need to be consumed. For example, a patient would need to consume 5 oz of aged cheese to receive 100 mg of tyramine (assuming 100% bioavailability).[15] In 1 study, patients had difficulty ingesting the amounts of cheese needed to provide 400 mg tyramine.[17] Even if other foods included in Table 1 would need to be consumed in large quantities, such quantities typically would not be found in meals for hospitalized patients. Given these features, a wide tolerability margin for linezolid and dietary tyramine is expected.

Tyramine pharmacokinetics are greatly altered by food. Oral bioavailability of tyramine is estimated to be approximately 50%. The bioavailability of oral tyramine is reduced by 50% when administered with food. Studying the effect of food on the pharmacokinetics of tyramine, VanDenBerg et al[18] administered a 200-mg oral capsule of tyramine to 8 volunteers after an overnight fast. Following a 1-week tyramine-washout period, these patients also received a 200-mg oral capsule of tyramine together with a standard breakfast. Tyramine bioavailability was reduced by half (range, 32%-81%; $P < .05$), and the maximum concentration was reduced by 72% (range, 21%-96%; $P < .05$). The authors concluded that "systemic exposure to tyramine from foods is expected to be lower by approximately half compared to that obtained when tyramine is administered to fasting subjects in an experimental situation."[18,p609] In another study, 2.8 times higher oral tyramine doses were necessary to produce the pressor effect in fed vs fasted subjects.[19]

In the study on which the recommendation to limit tyramine to <100 mg per meal for patients taking linezolid was based, tyramine was not administered with a meal.[6] Additionally, the dose of linezolid used was 625 mg, not the 600-mg marketed dose. In the only other study involving administration of tyramine to subjects receiving linezolid, tyramine was administered intravenously.[7] Although linezolid coadministered with intravenous tyramine pressor testing demonstrated potentiation of SBP increases, tyramine pressor challenge tests are difficult to translate into clinical significance of drug–tyramine interactions. Much higher doses of oral tyramine are required to produce a pressor response compared with intravenous tyramine.[20]

Upon recommendation by both the pharmacy department and the food and nutrition department, the New York–Presbyterian Drug-Nutrient Interaction Policy was revised to exclude a tyramine-restricted diet requirement for linezolid. The revised policy was approved by the hospital's formulary and therapeutics committee in December 2009 and has been in effect since without reports of any problems.

Conclusion

These results suggest that the margin of safety regarding the lowest tyramine dose for $PD_{>30}$ may be greater than previously estimated. Further research is needed to confirm this. Moreover, the amount of oral tyramine for $PD_{>30}$ in the only clinical study significantly exceeds the amounts achievable from dietary sources.

Hospital dietary and pharmacy departments have policies and procedures to address the MAOI–tyramine food–drug interaction. Most hospital pharmacy departments use a mechanism to notify the nutrition department when an MAOI is prescribed, whereby the patient is then placed on a tyramine-restricted diet. A question to our hospital's Drug Information Center regarding the clinical significance of a low-tyramine diet for linezolid patients prompted a comprehensive review of available data and the literature and a query for case reports to the manufacturer. Based on our research, and interdisciplinary collaboration between the departments of pharmacy and food and nutrition, a change in policy and procedures for patients placed on linezolid was deemed appropriate.

Based on these findings, we conclude that dietary restrictions of tyramine are not necessary for hospitalized patients on linezolid.

References

1. Sen N. Analysis and significance of tyramine in foods. *J Food Sci*. 1969;34:22-26.
2. Bethune HC, Burrell RH, Culpan RH, Ogg GJ. Vascular crisis associated with M.A.O.I. *Am J Psychiatry*. 1964;121:245-248.
3. Blackwell B, Marley E, Price J, Taylor D. Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. *Br J Psychiatry*. 1967;113:349-365.
4. Zyvox [package insert]. http://media.pfizer.com/files/products/uspi_zyvox.pdf. 2008. Accessed May 3, 2010.
5. Marcason W. What is the bottom line for dietary guidelines when taking monoamine oxidase inhibitors? *J Am Diet Assoc*. 2005;105:163.
6. Antal EJ, Hendershot PE, Batts DH, Sheu WP, Hopkins NK, Donaldson KM. Linezolid, a novel oxazolidinone antibiotic: assessment of monoamine oxidase inhibition using pressor response to oral tyramine. *J Clin Pharmacol*. 2001;41:552-562.
7. Cantarini MV, Painter CJ, Gilmore EM, Bolger C, Watkins CL, Hughes AM. Effect of oral linezolid on the pressor response to intravenous tyramine. *Br J Clin Pharmacol*. 2004;58:470-475.
8. Walker SE, Shulman KI, Tailor S, Gardner D. Tyramine content of previously restricted foods in monoamine oxidase inhibitor diets. *J Clin Psychopharmacol*. 1996;16:383-388.
9. Martin JP, Herberg JT, Slatter JG, Dupuis MJ. Although a novel microliter-plate assay demonstrates that linezolid (PNU-100766) is a weak, competitive (reversible) inhibitor of human monoamine oxidase (MAOA), no clinical evidence of MAO A inhibition in clinical trials has been observed. Paper presented at: 38th Interscience Conference on Antimicrobials and Chemotherapy; September 1998; San Diego, Calif.
10. Clark DB, Andrus MR, Byrd DC. Drug interactions between linezolid and selective serotonin reuptake inhibitors: case report involving sertraline and review of the literature. *Pharmacotherapy*. 2006;26:269-276.
11. Warrington SJ. Clinical pharmacology of moclobemide: a new reversible monoamine oxidase inhibitor. *J Psychopharmacol*. 1991;5:82-91.
12. Wijnands S, Chang PC, Blauw GJ, et al. Potentiation of the pressor effect of oral and intravenous tyramine during administration of the selective MAO-A inhibitor moclobemide in healthy volunteers. *J Psychopharmacol*. 1989;3:36-44.

13. DePrada M, Zurcher G, Wuthrich I, Haefely WE. On tyramine, food, beverage and the reversible MAO inhibitor moclobemide. *J Neural Transm*. 1988;26:31-56.
14. Parnate [package insert]. Research Triangle, NC: GlaxoSmithKline; 2007.
15. Chicago Dietetic Association, The South Shore Suburban Dietetic Association, and Dietitians of Canada. Tyramine controlled diet. In: *Manual of Clinical Dietetics*. 6th ed. Chicago, Ill: American Dietetic Association; 2000.
16. Spectrum Health. Tyramine Restricted (MAOI) Meal Plan. Grand Rapids, MI: Spectrum Health Patient Education Council. April 2008:1-3.
17. Blob LF, Melvin S, Campbell BJ, et al. Effects of tyramine-enriched meal on blood pressure response in healthy male volunteers treated with selegiline transdermal system 6 mg/24 hour. *CNS Spectr*. 2007;12:25-34.
18. VanDenBerg CM, Blob LF, Kemper EM, Azzaro AJ. Tyramine pharmacokinetics and reduced bioavailability with food. *J Clin Pharmacol*. 2003;43:604-609.
19. Korn A, Da Prada M, Raffesberg W, Allen S, Gasic S. Tyramine pressor effect in man: studies with moclobemide, a novel reversible monoamine oxidase inhibitor. *J Neural Trans*. 1988;26(suppl):57-71.
20. Berlin I, Zimmer R, Cournot A, Payan C, Pedarriosse AM, Puech AJ. Determination and comparison of the pressor effect of tyramine during long-term moclobemide and tranylcypromine treatment in healthy volunteers. *Clin Pharmacol Ther*. 1989;46:344-351.