Interpreting the Azithromycin Versus Amoxicillin Preoperative Surgical Prophylaxis Issue

It is important for clinicians to read peer-reviewed research papers and then properly digest what the results and conclusions purport. Recently the *Journal of Periodontology* published "Comparison of azithromycin and amoxicillin prior to dental implant placement: an exploratory study of bioavailability and resolution of postoperative inflammation" by Escalante et al.[1] This paper has piqued the interest of implant clinicians. Several clinicians have mentioned that after reading this paper, they have concluded that all implant patients would be better served by the use of azithromycin versus amoxicillin as a single preoperative antibiotic surgical prophylaxis. The authors provided results and offered conclusions for their interesting and relevant research. However, readers must be cautious not to overextend the authors' conclusions and apply them to all clinical situations. Therefore, there are two concerns with the paper that we will address. The first is pharmacological, and the second is statistical.

Pharmacologically, the purpose of a surgical antibiotic prophylaxis is to prevent a systemic bacteremia or localized infection following an oral surgical procedure. The serum and tissue levels of the antibiotic should be gone within 24 hours of wound closure. The authors have correctly noted that there is evidence that prophylactic antibiotics can assist in preventing localized infections and enable more predictable dental implant outcomes. This is especially true for patients with diabetes, a history of smoking, and/or compromised localized bone environments.[2–5] The authors also have stated the purpose of their research was "to assess the resolution of postoperative peri-implant inflammation during early healing in the presence of two different systemic antibiotic regimens…".[1]

The study provides evidence that azithromycin (with its antimicrobial activity) was still present at the surgical site on postoperative day 6 and that proinflammatory cytokine and chemokine markers (G-CSF, IL-8, MIP-1β, and IP-10) in the peri-implant crevicular fluid were significantly decreased. Both of these findings are not surprising when one considers the pharmaco-dynamics and -kinetics of azithromycin. The antimicrobial prophylaxis action was present for more than desired and intended 24 hours following wound closure. Additionally, there is an issue of azithromycin-induced fatal cardiac arrhythmias.[6,7] Azithromycin carries the risk of inducing a prolonged QTc interval (torsade de pointes). This can result in potentially serious cardiovascular conditions or sudden cardiac death. However, this complication is less of an issue for patients not affected by cardiovascular disease or those receiving a single azithromycin dose versus prolonged treatments.[8]

The authors conclude, "preoperative azithromycin may enhance resolution of postoperative inflammation to a greater extent than amoxicillin". This is not surprising since amoxicillin does not possess anti-inflammatory action, as azithromycin does. Many clinicians will provide anti-inflammatory coverage for dental implant surgeries by administering a glucocorticosteroid, such as dexamethasone, perioperatively. When a glucocorticosteroid is administered, one would have to question the benefit of using azithromycin as the surgical prophylaxis for its anti-inflammatory action. Unfortunately, a side effect of the systemic administration of glucocorticosteroids is increased blood glucose levels. This may be the ideal selective opportunity for using azithromycin as the preoperative surgical prophylactic antibiotic. Uncontrolled diabetes mellitus is an absolute contraindication (or at the minimum, a relative contraindication in the well-controlled diabetic) for the use of systemic glucocorticosteroids. Therefore, the use of azithromycin as the preoperative surgical antibiotic prophylaxis may be the drug of choice in the patient with diabetes and no existing cardiovascular disease. One would reap the benefits of the prolonged antimicrobial action and the anti-inflammatory effects without the risk of increasing blood glucose levels. The prolonged antimicrobial affect would be of value in the diabetic patient because of their compromised ability to combat infections.

While respecting the limitation of text to communicate in professional publications, there are questions about the statistical analysis. The variance, sphericity, of the differences between all combinations of related groups is an assumption for the ANOVA, and problems with sphericity may be more problematic with small and unequal group sizes. The current study used 7 amoxicillin control group participants and 6 azithromycin experimental group participants. The use of several one-way repeated measures ANOVAs is a concern with a sample size this small, especially with unequal group sizes. Additionally, a one-way repeated measures ANOVA requires the dependent variable to follow a normal distribution. With a sample size of 7 in one group and 6 in the second group, it is difficult to demonstrate a normal distribution.

Time-varying covariates as possible intervening variables are also a concern. The authors may have had a stronger argument for the outcome of the study had they used an ANCOVA (assuming that mathematical assumptions were met) and addressed possible intervening variables. Additionally, for the family of parametric and non-parametric statistical contrasts that were performed in this study, how was the family-wise alpha level controlled throughout the study to avoid one or more Type I errors? Therefore, with respect to subject selection (a required statistical assumption), the number of subjects included in the study, and the data analysis and data interpretation, there are concerns for the external validity of the study.

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In conclusion, this study has value. However, given the pharmacological and statistical concerns presented above, its interpretation should not be overextended nor should the well-accepted concept of using amoxicillin (or another beta-lactam antibiotic) for surgical prophylaxis and a systemic glucocorticosteroid to control postoperative inflammation be abandoned. Azithromycin may be the ideal presurgical antibiotic prophylactic agent in the diabetic patient who does not have existing cardiovascular disease.

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References

1. Escalante MG, Eubank TD, Leblebicioglu B, Walters JD. Comparison of azithromycin and amoxicillin before dental implant placement: an exploratory study of bioavailability and resolution of postoperative inflammation. *J Periodontol*. 2015;86:1190–1200.

2. Palma-Carrió C, Maestre-Ferrín L, Peñarrocha-Oltra D, Peñarrocha-Diago MA, Peñarrocha-Diago M. Risk factors associated with early failure of dental implants. A literature review. *Med Oral Patol Oral Cir Bucal*. 2011;16: e514–e517.

3. Koldsland OC, Scheie AA, Aass AM. Prevalence of implant loss and the influence of associated factors. *J Periodontol*. 2009;80:1069–1075.

4. Esposito M, Grusovin MG, Loli V, Coulthard P, Worthington HV. Does antibiotic prophylaxis at implant placement decrease early implant failures? A Cochrane systematic review. *Eur J Oral Implantol*. 2010;3:101–110.

5. Alsaadi G, Quirynen M, Michiles K, Teughels W, Komárek A, van Steenberghe D. Impact of local and systemic factors on the incidence of failures up to abutment connection with modified surface oral implants. *J Clin Periodontol*. 2008;35:51–57.

6. US Food and Drug Administration. FDA drug safety communication: azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms. Available at: http://www.fda.gov/drugs/drugsafety/ucm341822.htm. Accessed August 25, 2015.

7. Wynn RL. Azithromycin associated with a small increased risk of cardiovascular death: A review. *Gen Dent*. 2013;61:8–9.

8. Hancox JC, Hasnain M, Vieweg WV, Crouse EL, Baranchuk A. Azithromycin, ardiovascular risks, QTc interval pro-longation, torsade de pointes, and regulatory issues: a narrative review based on the study of case reports. *Ther Adv Infect Dis*. 2013;1:155–165.