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(Accepted for publication August 1, 2011.)

How Often Should Atenolol Be Dosed for Perioperative ß-Blockade?

To the Editor:

In "Perioperative β-blockade: Atenolol Is Associated with Reduced Mortality When Compared to Metoprolol," Wallace *et al.* make a strong case for preferring atenolol for perioperative ß-blockade.[1] As the authors note, their results are consistent with our prior meta-regression of randomized controlled trials[2] and the large observational analysis by Redelmeier.[3]

In the absence of renal insufficiency that alter the kinetics of atenolol, atenolol has favorable pharmacokinetic characteristics compared with metoprolol. However, if we are to use atenolol, we must know its optimal dosing interval. Originally, all ß-blockers were recommended for once-daily dosing[4]; however, since the early 1990s, the variable duration of ß-blockers has been recognized.[5] Some studies have found that atenolol does not provide 24 h of ß-blockade.[6,7] As Wallace *et al.* note, Freestone found that atenolol has more predictable ß-blockade at 24 h than does metoprolol.[8] However, Freestone's group also reported that atenolol's reduction of the pulse during exercise was less at 24 h than at 3 [1/2] h after dosing.[9] The INVEST study dosed atenolol twice a day if more than 50 mg per day was needed.[10]

Dr. Wallace coauthored the Multicenter Study of Perioperative Ischemia trial, which is the largest placebo-controlled trial of atenolol for perioperative ß-blockade.[11] A strength of the Multicenter Study of Perioperative Ischemia trial is continuous Holter monitoring. The Multicenter Study of Perioperative Ischemia trial dosed atenolol once per day and reported trends, although insignificant, toward increased perioperative mortality and stroke among patients treated with atenolol.[11]

Since we share Dr. Wallace's interest in atenolol, we hope he would be willing to resurrect the trial data and publish an analysis of it for diurnal variation in morbidity and electrocardiographic events in order to further evaluate the optimal dosage interval for atenolol.

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(Accepted for publication August 2, 2011.)

In Reply:

The communication from Badgett *et al.* serves to emphasize that there remain a number of important questions about how to optimize the efficacy of perioperative β blockade. While it is clear that perioperative β blocker reduces mortality,[1] unresolved issues include use of prophylactic β-blockade in moderate risk patients, choice of medication, optimal dosing intervals, optimal doses, appropriate heart rate targets (*e.g.*, maximum heart rate *vs.* average heart rate), routes of administration, optimal strategies for ensuring administration, and, most importantly, strategies to avoid medication withdrawal.[1] We

This work has been supported by the Northern California Institute for Research and Education and the Veterans Affairs Medical Center, San Francisco, California.

agree that reanalysis of heart rate data from the atenolol study[2,3] might address some questions regarding physiologic response and diurnal variation. Unfortunately, the patient population in the atenolol study was limited, with only 200 patients, and we doubt that reanalysis would have sufficient statistical power to definitively answer questions regarding optimal dosing intervals as the dosing was by protocol, and there is little variation. The optimal dosing interval problem is particularly an issue in subgroups of patients with different risk-factor profiles.

There are a number of possible hypotheses to explain the observed differences in mortality between patients treated with atenolol or metoprolol,[4] including differences in drug metabolism, appropriate dosing intervals, interactions with other medications that affect metabolism such as antidepressants, rates of missed doses, and actual differences in efficacy or pharmacodynamics of the two drugs. We have begun the process of investigating our existing data to define the mechanisms for the observed differences in mortality, but this work is currently incomplete. We do believe that future investigations of perioperative β blockade will need to be informed by an awareness of the above issues, as well as by other evolving issues in β-blockade, including the increasing use of vasodilating β blockers such as carvedilol, as well as declining use of β blockers as first-line agents for hypertension.

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(Accepted for publication August 2, 2011.)