Drug Monitor

Amiodarone Use and Risk of Pacemaker Insertion in Patients with AF

Amiodarone has been shown to be more effective than other antiarrhythmic agents at maintaining sinus rhythm in patients with atrial fibrillation (AF). A previous retrospective study of elderly patients with prior myocardial infarction, however, found a link between the drug and the occurrence of bradyarrhythmia requiring permanent pacemaker insertion. This study also suggested that the increased risk of pacemaker insertion might be greater among women than men—though this finding was statistically nonsignificant.

To determine whether the association would persist in a general AF population, and to learn more about possible sex differences, researchers from McGill University Health Center, Montreal, Québec, Canada; Beth Israel Deaconess Medical Center, Boston, MA; University of Ottawa Heart Institute, Ottawa, Ontario, Canada; University of Iowa Hospitals, Iowa City, IA; and Rhode Island Hospital, Providence, RI performed a prospective analysis of a cohort of patients enrolled in the Fibrillation Registry Assessing Costs, Therapies, Adverse Events, and Lifestyle (FRACTAL) trial. Of 1,005 patients with new-onset AF, 32 were excluded for having a pacemaker or pacemaker-defibrillator implanted before the study. The 973 patients included in the analysis were followed up for a mean of two years from AF diagnosis to first pacemaker insertion, death, or study's end.

Using multivariable Cox regression, the researchers found that amiodarone was, indeed, associated with an increased risk of pacemaker insertion (hazard ratio [HR], 2.01; 95 % CI, 1.08–3.76). Age and atrial flutter also were associated independently with pacemaker insertion, but other antiarrhythmic agents (sotalol or class 1 drugs) were not. The researchers suggest that amiodarone's substantially longer half-life (more than 30 days, compared with less than one day for the other medications) may contribute to the problem by reducing the chances that simply lowering the dosage or stopping the drug will reverse bradycardia.

The results also showed a significantly (P = .02) higher risk of pacemaker insertion in women (HR, 4.69; 95% CI, 1.99–11.05) as opposed to men (HR, 1.05; 95% CI, 0.42–2.58;)—even after adjusting for weight, body mass index (BMI), weight-adjusted amiodarone dose, and use of other antiarrhythmic or rate control drugs. Additionally, there was a nonsignificant trend toward an increased risk with amiodarone doses greater than 200 mg/d.

The researchers say their study was limited by the lack of randomization (antiarrhythmic or rate control medications were prescribed at the discretion of the providers). Furthermore, other than adjusting separately for weight and BMI, the researchers could not quantitatively evaluate any sex differences in amiodarone's pharmacokinetic properties because they did not measure serum and tissue drug concentrations.

Although the reasons for the higher risk of pacemaker implantation in women remain unclear, the researchers say their findings indicate a need for extra caution when prescribing amiodarone to this population. They recommend using lower loading and maintenance doses, particularly in elderly women.

Source: *Arch Intern Med.* 2007:167(15):1648–1653.

Do Fixed-Dose Regimens Improve Drug Adherence?

Optimal management of chronic conditions often requires the use of multiple medications. Polypharmacy and complex treatment regimens, however, are two causes of decreased adherence. While the efficacy and safety of fixed-dose combination products are well established, the data are not so clear on how well the use of such products helps improve adherence.

Researchers from St. Luke's-Roosevelt Hospital and Columbia University, both in New York, NY, conducted a meta-analysis of studies that compared medication adherence when using a fixed-dose combination product versus the individual components of the fixed-dose product (free-drug regimen). A Medline search revealed nine studies, including 20,042 patients, that examined adherence among patients with hypertension, diabetes, HIV, and tuberculosis.

Statistical analysis of the extracted data showed that fixed-dose combination products reduced the risk of nonadherence by as much as 26 % (P < .0001). Although only three studies had efficacy outcomes, results from these three suggested that fixed-dose combination products worked equally well or better than the free-drug regimens.

The researchers acknowledge that the meta-analysis format did not allow them to control for possible confounding variables. They further caution that the definition of adherence was not uniform. Nevertheless, they say their findings support the use of fixed-dose combination products, when available and appropriate, for patients with chronic conditions. ●

Source: *Am J Med.* 2007;120(8):713–719. doi:10.1016/j.amjmed.2006.08.033.