Drug Monitor

Levothyroxine for Hypothyroidism: How High Can You Start?

Currently, there is no consensus on starting doses for levothyroxine in primary hypothyroidism. Although concerns about an association between ischemic heart disease and hypothyroidism keep many clinicians following a "start low and go slow" approach, that may be unnecessarily conservative for patients with low cardiovascular risk, say researchers from Medical Centre Rijnmond-Zuid and Erasmus Medical Centre in Rotterdam, the Netherlands and Academic Medical Centre in Amsterdam, the Netherlands.

In the first prospective study of levothyroxine starting doses in primary hypothyroidism, the researchers enrolled newly diagnosed patients who had no history of cardiac disease and were taking no cardiac drugs. They randomly assigned the 50 patients to begin levothyroxine treatment at either the full replacement dose (1.6 µg/kg) or a low dose (25 µg). Doses were adjusted, based on monitoring of serum thyrotropin and free thyroxine (FT_4) levels, in 25-µg increments at four-week intervals for the first 24 weeks and at 12-week intervals thereafter.

Both groups experienced comparable improvements in quality-of-life scores and, for the first 24 weeks, in clinical and symptom scores. The median serum thyrotropin level normalized significantly more quickly, however, in the full dose group compared with the low dose group (by week four versus week 16). Similar results were seen with FT_4 levels.

During the study, no patients experienced adverse cardiac events, needed interim dose adjustments due to adverse effects, or withdrew from the study protocol. None experienced anginal symptoms during bicycle ergometry at 12 and 24 weeks or showed electrocardiographic evidence of ischemia or serious arrhythmias.

Although the mean age of patients in the study was relatively young (47 years), both groups included patients over age 65. Therefore, the researchers say their findings suggest that it may be safe to treat older patients who have no history of ischemic heart disease with the full dose of levothyroxine from the start. In patients—of any age—with concurrent cardiac disease, however, starting low is still the prudent choice.

Source: *Arch Intern Med.* 2005;165:1714–1720.

ACE Inhibitors and ARBs for Diabetes Prevention

Findings from a meta-analysis of 11 randomized, controlled trials involving 66,608 patients show that blocking the renin-angiotensin system with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) significantly reduces the odds of developing type 2 diabetes. This effect was comparable regardless of whether an ACE inhibitor or an ARB was used and whether it was given for hypertension, coronary artery disease, or heart failure. The analysis showed no impact on short-term cardiovascular, cerebrovascular, or mortality outcomes in either the group as a whole or in the subgroup with hypertension—though there was a benefit in the two coronary artery disease trials. Nevertheless, the researchers say, simply preventing diabetes might have important long-term benefits.

Source: *Diabetes Care.* 2005;28:2261–2266.

Impact of Sedatives in the ICU

It's a common practice to give patients in the intensive care unit (ICU) a sedative or neuromuscular blocking (NMB) agent to improve tolerance of mechanical ventilation. But could these drugs be hurting at the same time they're helping?

To find out, the International Mechanical Ventilation Study Group analyzed data on 5,183 patients who received mechanical ventilation in ICUs in 20 countries. Of these patients, 3,540 (68%) received a sedative at some point during their mechanical ventilation, for a median duration of three days. The most commonly used sedatives were benzodiazepines, opioids, and propofol—with many patients receiving a combination of drugs.

Compared to patients who didn't receive a sedative, those who did had significantly longer durations of mechanical ventilation, weaning, and ICU stay. They also had a higher mortality rate, but this association did not hold up after adjusting for other variables.

By contrast, NMB agents, which were given to 13% of the patients, were independently associated with higher mortality—as well as more days of mechanical ventilation, more weaning days, and a longer ICU stay. The researchers speculate that, since NMBs were most likely to be given to patients with severe respiratory failure, they probably were used as a last resort in the sickest patients. They also acknowledge that, despite these findings, the benefits of sedatives and NMB agents in facilitating mechanical ventilation and improving patient comfort may outweigh the drawbacks in many cases. They call for prospective studies

to address these issues and clarify the findings.

Source: *Chest.* 2005;128:496–506.

Inappropriate Prescribing in Elderly Vets

"Despite many previous studies, we are only beginning to understand the phenomenon of inappropriate prescribing," say researchers from the Veterans Evidence-based Research Dissemination and Implementation Center at the Audie L. Murphy Memorial Veterans Hospital, San Antonio, TX; the Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA; Boston University School of Public Health, Boston, MA; the Inner City Health Research Unit and University of Toronto, Toronto, Canada; the VA Pharmacy Benefits Management Strategic Health Group, Hines, IL; and the University of Illinois at Chicago College of Pharmacy. Taking advantage of the availability of a comprehensive national data source to look closer at a problem that has been discussed often but not yet solved, these researchers found that about one third of elderly veterans may be exposed to potentially inappropriate drugs.

The study relied on a list of 11 "always-avoid" drugs, eight "rarely appropriate" drugs, and 14 "some-indications" drugs developed by an expert panel at the Agency for Healthcare Research and Quality (AHRQ). The panel also specified situations in which use of a rarely appropriate or some-indications drug is proper. The researchers applied these criteria to prescribing data from all VA patients who had at least one outpatient visit in fiscal year 2000.

Of the 1,265,434 patients (most of whom were male and white), 33% were found to be receiving a potentially inappropriate medication. Specifically, 0.8% received at least one always-avoid drug, 8.9% received at least one rarely appropriate drug, and 15.5% received at least one some-indications drug. In addition, 16% received at least one drug for which a lower geriatric dose is recommended, with digoxin being most common (10%).

After the researchers adjusted for situations in which potentially inappropriate drugs might be allowed, the rate of inappropriate prescribing fell to 23%. And only 29% of the patients prescribed dose-limited drugs were actually taking inappropriate dosages. Nevertheless, the fact that most cases of potentially inappropriate prescribing were validated as improper using the AHRQ criteria underscores the reality of the problem, the researchers say.

Given the preponderance of inappropriately prescribed pain relievers and muscle relaxants, the researchers suggest that it may be useful to explore the role of chronic pain in inappropriate prescribing and to focus on developing interventions to improve adherence to pain management guidelines that do not include these agents.

The study also indicated a "prolonged" duration of some drugs. Although the researchers acknowledge that some patients need long-term treatment, they caution that long-acting benzodiazepines and other psychotropic drugs are associated with falls, altered cognition, depression, new institutionalization, and traffic accidents. Many of these drugs' adverse effects, they warn, are subtle and may arise only after prolonged use. ●

Source: *J Am Geriatr Soc.* 2005;53:1282–1289.