After SCI, Short Sleep Duration Raises Stroke Risk

BY DAN HURLEY

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF HYPERTENSION

NEW YORK — Getting fewer than 7.5 hours of sleep significantly raised the risk of clinically overt stroke in hypertensive patients with a history of silent cerebral infarct, according to multicenter study.

The study, designed to settle some of the controversy regarding the relation between sleep duration and stroke, found a modest but nonsignificant increasein risk in those without evidence of silent cerebral infarct (SCI).

By contrast, after 5 years of follow-up, those who slept less than 7.5 hours per night and had SCI had about a 1-in-4 risk of stroke, compared with a 1-in-10 risk in those who slept longer than 7.5 hours. After adjustment for age, sex, body mass index, smoking, diabetes, and other risk factors, the researchers found that the hazard ratio for stroke in patients who slept less than 7.5 hours per night and had a prior SCI was 2.52.

Dr. Kazuo Eguchi, professor of cardiovascular medicine at Jichi Medical University in Tochigi, Japan, and colleagues performed ambulatory BP monitoring in 1,268 hypertensives with a mean age of 70.4 and followed them for an average of 50 months. Brain MRI performed in 932 of these patients showed that 517 had prior SCI and 415 did not. A multivariate Cox analysis showed that, among all these patients, those who slept at least 7.5 hours per night had a significant, 20% reduced risk of stroke events, Dr. Eguchi said at the meeting. ■

Disclosures: *Dr. Eguchi reported having no relevant financial conflicts.*

---

administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and measures to ensure a patent airway may be necessary.

Discontinue aliskiren immediately in patients who develop angioedema and do not readminister.

5.3 Hypotension
An excessive fall in blood pressure (hypotension) was rarely seen (<0.5%) in patients with uncomplicated hypertension treated with Valturna in controlled trials.

In patients with an activated renin-angiotensin-aldosterone system, such as volume- or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to the administration of Valturna, or start the treatment under close medical supervision.

Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If an excessive fall in blood pressure occurs with Valturna, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.4 Patients with Severe Renal Impairment
Valturna
Patients with severe renal impairment were excluded from clinical trials with Valturna in hypertension.

Aliskiren
Patients with severe renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension. Safety information with aliskiren and the potential for other drugs acting on the renin-angiotensin-aldosterone system to increase serum creatinine and blood urea nitrogen are not available.

Valsartan
In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume depleted patients. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

5.5 Patients with Hepatic Impairment
Valsartan
As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs).

5.6 Patients with Congestive Heart Failure and Post-Myocardial Infarction
Valsartan
Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Include assessment of renal function when evaluating patients with heart failure or post-myocardial infarction.

5.7 Serum Electrolyte Abnormalities
Valturna
In the short-term controlled trials of various doses of Valturna, the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was about 1%-2% higher in the combination treatment group compared with the monotherapies aliskiren and valsartan, or with placebo.

In a long-term, uncontrolled study with median treatment duration of about one year, about 4% of the patients had at least one serum potassium >5.5 mEq/L at some time during the study; about 0.8% of patients discontinued study treatment and had a high serum potassium at some point during the study. Patients with hyperkalemia were older (median age 65 vs. 55) with slightly lower mean baseline estimated creatinine clearance compared to patients without hyperkalemia. While about 25% of the hyperkalemic episodes occurred in the first two months, other initial episodes were reported throughout the study.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.

Caution is advised with concomitant use of Valturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.

5.8 Renal Artery Stenosis
Aliskiren
No data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Valsartan
In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

5.9 Cyclosporine
Aliskiren
When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
The following serious adverse reactions are discussed in greater detail in other sections of the label:
- Risk of fetal/neonatal morbidity and mortality *[see Warnings and Precautions (5.1)]*
- Head and neck angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Valturna
Valturna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 1.4% of patients treated with Valturna versus 2.7% of patients given placebo.

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valturna and at a higher incidence than placebo included fatigue (2.6% vs. 1.4%), nasopharyngitis (2.6% vs. 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs. 0.3%).

Hyperkalemia has been observed as a serum electrolyte abnormality in Valturna clinical trials *[see Warnings and Precautions (5.7)]*.

Aliskiren
Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.