meta-analysis. BMJ 1997; 314:1526-9.
2. Rosenfeld R, Vertrees J, Carr J, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials. J Pediatr 1994; 124:355-67.
3. Appelman CLM, Claessen JQPJ, Touw-Otten FWMM, et al. Co-amoxiclav in recurrent acute otitis media: placebo-controlled study. BMJ 1991; 303:1450-2.

Treatment of Restless Leg Syndrome with Pergolide

Earley CJ, Yaffee JB, Allen RP. Randomized double-blind placebo-controlled trial of pergolide in restless leg syndrome. Neurology 1998; 51:1599-602.

Clinical question **Is pergolide effective in the treatment of restless leg syndrome?**

Background Restless leg syndrome (RLS) affects between 2% and 15% of the population. Disturbances in the dopaminergic system are thought to play a role in the etiology of RLS. Levodopa, which demonstrated significant benefit in small randomized controlled trials, can cause a paradoxical worsening of symptoms (levodopa augmentation). Other agents that augment dopaminergic action (pramipexole, ropinirole, bromocriptine, and pergolide), as well as the anticonvulsant gabapentin, are currently being investigated for the treatment of RLS.

Population studied Patients presenting to a sleep center who met standard criteria for the disease and who had a minimum of 15 periodic limb movements of sleep per hour (PLMSs/hr) were considered for enrollment. The first 16 consecutive patients presenting to the center who met these inclusion criteria and who had not previously been treated with pergolide were enrolled. Seven of those 16 had not previously been treated for RLS, 5 were being treated with levodopa/carbidopa, 2 with propoxyphene, and 1 each with clonazepam and alprazolam.

Study design and validity Patients stopped their previous treatment regimens for RLS 4 days before the baseline assessment. They were then randomized in a double-blind fashion to pergolide or placebo. During the first 14 days, patients in each group were instructed to increase the dose taken at dinner and at bedtime until (1) the patient felt the benefits from the medication were adequate; (2) the maximum dose had been reached (0.65 mg per day); or (3) adverse effects occurred. After day 14, the dose remained constant for 5 days. The final pergolide dose could be from 0.05 mg twice daily to 0.3 mg at dinner and 0.35 mg at bedtime. All-night polysomnograms and a log of RLS symptom duration were obtained at baseline and on day 17 or 18.

Outcomes measured The primary outcome was the global improvement score (0% to 100% improvement) on day 18. Secondary outcomes included the number of PLMSs per hour and the number of hours per day with RLS symptoms.

Results Baseline characteristics (PLMSs per hour, sleep efficacy, age, and symptom duration) were not statistically different between groups. The median final daily dose of pergolide in the treatment group was 0.35 mg (7 capsules). Global improvement scores were 61% improved in the pergolide group compared with 19% in the placebo group (P = .009). The placebo group showed no statistically significant change from baseline for any of the secondary outcome variables. For patients treated with pergolide, however, the PLMSs decreased from 48.9 per hour to 14.5 per hour (P <.001) and the duration of RLS symptoms decreased from 7.0 hours per day to 1.8 hours per day (P = .036). Mild adverse events were common in both groups (unfortunately, "mild" was not defined by the authors). Adverse events rated as "severe" occurred in 4 patients in the pergolide group (stomach pain, increased dreaming, and constipation) compared with 2 in the placebo group (bad taste in the mouth and itchy eyes). RLS rebound or augmentation was not seen in either group. None of the patients discontinued treatment or had to decrease the dose of medication because of adverse events.

Recommendations for clinical practice **This study demonstrates the efficacy of pergolide in the treatment of RLS. Unfortunately, the number of patients studied was small and the follow-up period was short. It is still unknown whether treatment of RLS with pergolide will result in the same augmentation of RLS symptoms seen with levodopa/carbidopa. Given the difficulty of treating RLS, the known adverse effects of augmentation seen with levodopa/carbidopa, and the significant improvements in both objective and subjective measures seen in this clinical trial, long-term trials comparing the efficacy of pergolide with other agents that augment dopamine are needed.**

Karen Gunning, PharmD
Christopher Gay, MD
University of Utah
Salt Lake City
E-mail: kgunning@pharm.utah.edu

Initiating Warfarin Therapy

Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. Arch Intern Med 1999; 159:46-8.

Clinical question **Is it better to initiate warfarin therapy with a 5-mg or a 10-mg dose?**

Background Initiation of warfarin therapy usually takes 4 to 5 days, until a therapeutic international normalized ratio (INR) has been maintained for 2 consecutive days. Various loading doses have been recommended, ranging from 5 to 40 mg. In a previous study by the same investigators,[1] a 10-mg loading dose was found to have the potential to make patients hypercoagulable early in therapy because of suppressed protein C levels, yet also make them hypocoagulable several days *after* beginning warfarin. Patients on a 5-mg starting dose were less likely to have these problems. The purpose of this study was to compare the relative effectiveness of the 5-mg and 10-mg starting does of warfarin in achieving therapeutic INR levels.

Population studied The study subjects were 53 consecutive patients (25 men, 28 women) from a thromboembolism unit who had warfarin initiated, with a target INR of 2.0 to 3.0.

Study design and validity Patients were randomized to receive either 5-mg or 10-mg warfarin doses on days 1 and 2 of the study. Warfarin was taken in the evening, and INR levels were measured every morning. Warfarin doses were adjusted by study nurses using published dosing nomograms (Table).[2] The laboratory staff performing the INR testing were blinded to the treatment allocation, but the nursing staff and physicians were not.

Outcomes measured The primary outcome was the achievement of a stable INR between 2.0 and 3.0 on 2 consecutive days within the first 5 days of therapy. Other outcomes measured included the number of patients with INR values above 3.0 on day 4 of the study and the need for vitamin K treatment.

Results Twenty-one patients were assigned to the 10-mg group and 31 to the 5-mg group, because of an error in the random number table used. Five patients (3 in the 10-mg group and 2 in the 5-mg group) did not complete the required blood testing. One patient in the 5-mg group received vitamin K for an INR value of 5.1 on day 2 of the study. No patients in the 10-mg group required vitamin K therapy.

The proportion of patients with therapeutic INR values was consistently higher at all times in the 5-mg group than in the 10-mg group. The primary outcome—2 consecutive therapeutic INR reports within the first 5 days of therapy—was achieved by 24% of the patients in the 10-mg group compared with 66% in the 5-mg group (relative risk [RR] = 2.2; 95% confidence interval [CI], 1.3-3.7). These results did not change significantly using a worst case scenario in which all 3 of the patients with incomplete follow-up in the 10-mg group and neither of the 2 patients in the 5-mg group were assumed to have reached the primary end point. Although not statistically different, more patients in the 10-mg group (24%) than in the 5-mg group (7%) had INR values greater than 3.0 on day 4 of the study (RR = 0.8; 95% CI, 0.6-1.1).

Recommendations for clinical practice **This study, though small, shows that a 5-mg starting dose of warfarin is twice as likely as a 10-mg starting dose to result in a stable therapeutic INR level by the fifth day of therapy. The 10-mg dose also had a higher (although not statistically significant) risk of supratherapeutic INR at day 4 and, theoretically, has the potential for hypercoagulability in the first 3 days of therapy. Thus, for both safety and efficacy, warfarin therapy should be initiated with a 5-mg loading dose and adjusted following the published algorithm.**

Michael Schooff, MD
Clarkson Family Practice Residency Program
Omaha, Nebraska
E-mail: Mschooff@nhsnet.org

TABLE. Algorithm for Adjusting Warfarin Doses According to International Normalized Ratio (INR) Levels

Day	INR	Dose, in mg
1		5.0
2	<1.5	5.0
	1.5 to 1.9	2.5
	2.0 to 2.5	1.0 to 2.5
	>3.0	0.0
3	<1.5	5.0 to 10.0
	1.5 to 1.9	2.5 to 5.0
	2.0 to 2.5	0.0 to 2.5
	2.5 to 3.0	0.0 to 2.5
	>3.0	0.0
4	<1.5	10.0
	1.5 to 1.9	5.0 to 7.5
	2.0 to 3.0	0.0 to 5.0
	>3.0	0.0
5	<1.5	10.0
	1.5 to 1.9	7.5 to 10.0
	2.0 to 3.0	0.0 to 5.0
	>3.0	0.0
6	<1.5	7.5 to 12.5
	1.5 to 1.9	5.0 to 10.0
	2.0 to 3.0	0.0 to 7.5
	>3.0	0.0

REFERENCES

1. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997; 126:133-6.
2. Crowther MA, Harrison L, Hirsh J. Warfarin: less may be better. Ann Intern Med 1997; 127:332-3.