A NEW ANTICONVULSANT ON THE HORIZON: HOW DOES IT MEASURE UP?

Dose–Response Trial of Pregabalin Adjunctive Therapy in Patients with Partial Seizures

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BACKGROUND: Pregabalin (PGB) is an [alpha]$_2$-[delta] ligand that has anxiolytic, analgesic, and anticonvulsant properties.

OBJECTIVE: To establish the efficacy, safety, and tolerability of PGB administered twice daily (b.i.d.) without dose titration as adjunctive treatment in patients with partial seizures and to confirm the dose–response relation.

METHODS: This 76-center, double-blind, randomized, placebo-controlled, parallel-group study consisted of an 8-week baseline and a 12-week double-blind phase. Patients with refractory partial seizures taking one to three antiepileptic drugs were randomly assigned to one of five treatment groups (placebo or 50, 150, 300, and 600 mg/d PGB, all administered b.i.d.). Efficacy was assessed by using seizure-frequency reduction and responder rate (≥50% seizure reduction from baseline). Pharmacokinetic parameters were estimated.

RESULTS: A total of 453 patients were included in the intent-to-treat analysis. The median baseline seizure rate was 10 per month. Seizure-frequency reductions from baseline were 7% (placebo; $n = 100$), 12% (50 mg/d; $n = 88$), 34% (150 mg/d; $n = 86$), 44% (300 mg/d; $n = 90$), and 54% (600 mg/d; $n = 89$). Responder rates (≥50% seizure reduction) were 14% (placebo), 15% (50 mg/d), 31% (150 mg/d), 40% (300 mg/d), and 51% (600 mg/d). Discontinuation rates due to adverse events were 5% (placebo), 7% (50 mg/d), 1% (150 mg/d), 14% (300 mg/d), and 24% (600 mg/d). The 150-, 300-, and 600-mg/d PGB groups were associated with greater reductions in seizures ($P \leq .0001$) and greater responder rates compared with the placebo group ($P \leq .006$). There was a favorable dose–response trend for both seizure reductions ($P \leq .0001$) and responder rate ($P \leq .001$).

CONCLUSIONS: Adjunctive therapy with PGB, 150, 300, and 600 mg/d, given in twice-daily doses without titration, is significantly effective and well tolerated in the treatment of patients with partial seizures as demonstrated in patients with refractory partial seizures.

COMMENTARY

Despite the approval of six new anticonvulsant drugs (AEDs) in the last 10 years, many patients still have refractory epilepsy. Many of these patients are not surgical candidates and are searching for new therapies. The study by French and colleagues reports a large multicenter trial of pregabalin (PGB). This molecule binds to an $\alpha 2-\delta$ calcium channel subunit and has analgesic, anxiolytic, and anticonvulsant activity against several epilepsy models in rodents. Pharmacokinetic analysis shows more than 90% bioavailability, which is independent of dose and not dependent on gastrointestinal transport systems, and no protein-binding or hepatic metabolism. There is renal clearance, and PGB has a half-life of 5.5 to 6.7 hours.

The patients randomized in this outpatient double-blind, parallel-group designed study had epilepsy for a mean of 25 years, were aged 14 to 75 years, had a mean of 10 seizures per month, and 80% were taking two or three other antiepileptic drugs (AEDs), not including gabapentin (GBP). Patients received placebo or 50, 150, 300, or 600 mg/day in divided doses, which were added to concurrent AEDs without titration. Efficacy, using the response ratio (RR), and safety were assessed. The RR is a statistical tool used in the studies on GBP and directly transforms the percentage of change in seizure frequency from baseline to treatment period by normalizing the seizure data: $RR = [(T - B)/(T + B)] \times 100$. An RR of -33 equates to a 50% reduction in seizure frequency; 0 equates to no effect; and $+33$ equates to a doubling of seizure frequency from baseline to treatment period. Intent-to-treat analysis was performed for 453 patients, with each treatment group consisting of 86 to 100 patients.

In this refractory-patient group, PGB treatment resulted in a reduction in seizure frequency from baseline of 12% to

54% and an RR of −6% to −37% for doses of 50 mg to 600 mg/day, respectively. Responder rates in active treatment were greater than in placebo (patients with ≥50% reduction in seizures) for doses of 150 mg/day or more. Adverse events (e.g., dizziness, ataxia, and somnolence, usually at treatment initiation) were mild to moderate and appeared to be dose related and transient, resolving in the first few weeks. Behavioral or cognitive side effects were rare. Weight gain was dose related and ranged from a mean of 0.5 kg at 50 mg/day to 2.28 kg at 600 mg/day.

PGB, in this study of refractory epilepsy patients, when initiated without titration, appeared to be safe and effective at doses starting at 150 mg/day. An analysis of efficacy findings from similar trials of new AEDs, before approval, shows comparable results, although not strongly superior. This study was performed by using a well-recognized study design to prove that new agents have efficacy in refractory epilepsy patients. How clinicians will use PGB in actual clinical practice with less-refractory patients is not clear. Experience with other newly approved drugs studied in similar-protocol designs suggests that PGB would be better tolerated if starting doses are low and the add-on titration is performed more slowly. Efficacy may be better in general clinical practice with patients who are less refractory.

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