PREGABALIN DOSING AND SERUM LEVELS

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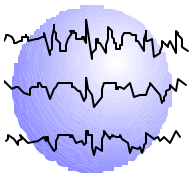

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ABSTRACT

RATIONALE: Conventional use of AEDs in the treatment of epilepsy has utilized serum levels as an indicator of appropriate daily dosage. Pregabalin (PGB), a GABA analog, which binds at the 2? subunit of voltage gated calcium receptors, has a dose response correlation for seizure reduction in phase three human studies at the two doses studied. No serum level to dose correlation has been reported. We have evaluated the effect of daily and weight-based doses on serum levels in clinical use.

METHODS: Patients received PGB as adjunctive therapy for refractory partial seizures with or without secondary generalization. Doses were empirically chosen and increased for efficacy or until side effects were experienced. Serum levels were obtained at trough if possible. Serum determinations were sent to MedTox Laboratories (St Paul, MN) for determination by HPLC. Serum levels, age, weight, daily dose, mg/kg/day dose, creatinine, efficacy and reported adverse events were evaluated by retrospective chart review.

RESULTS: Thirty-two patients ages 4-78 (mean 33.6 17.6, median 31) received PGB for two days to over seven years. Weights were 27.5 188.5 kg (mean 68.3 30.1, median 67). Total daily doses were 25 1050 mg (mean 349 212, median 300) resulting in 0.35-10.9 mg/kg/day (mean 5.1 3.1, median 4.7). Serum levels were 0.99 13.4 g/ml (mean 4.2 3.1, median 4.0). There was a significant correlation $p<.01$ for the relationship of mg/kg/day to serum concentration.

AEs reported in 11 (33%) were tiredness, weight gain, and temporary leg swelling at levels of 1-7 g/ml. Improved seizure control was reported in 56%; 1 was worse. Efficacy was seen in 7/18 at 2 g/ml or less and in 11/18 at 4-10 g/ml. Seven patients had 2 or more levels at different doses and showed linear increase in serum level.

CONCLUSION: PGB is easily utilized as adjunctive therapy in clinical practice. Doses are well tolerated up to 1050 mg/day without serious AEs. Serum levels correlate linearly with increased dosing.

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Rationale:

Conventional use of AEDs in the treatment of epilepsy has utilized serum levels as an indicator of appropriate daily dosage. Pregabalin (PGB), a new GABA analog which binds at the $\alpha 2\delta$ subunit of voltage gated calcium receptors1, has a dose response correlation for seizure reduction in phase 3 human studies at the two doses studied. 2,3,4 No serum level to dose correlation has been reported. We have evaluated the effect of daily dose and weight based doses on serum levels in clinical use since approval.

Methods:

Patients received PGB as adjunctive therapy for refractory partial seizures with or without secondary generalization. Doses were empirically chosen and increased for efficacy or until side effects were experienced. Serum levels were obtained at trough if possible. Serum determinations were sent to Med Tox Laboratories (St Paul, MN) for nearly all the specimens for determination of PGB levels as determined by HPLC. Serum levels, age, weight, daily dose, mg/kg/day, creatinine, efficacy and reported adverse events were evaluated by retrospective chart review.

Results

Fifty three patients ages 4-82 (mean 34, median 32) received PGB from 2 days to over 7 years (one patient had been started while participating in a PGB Phase 3 study). Weights were from 27.5 to 188.5 kg (mean 70.1, median 68). Total daily doses were 25 – 800 mg (mean 354, median 300). Weight based doses were calculated to be 0.35 – 13.9 mg/kg/day (mean 5.3, median 5.1). Serum levels were 0.35 to 13.4 μg/ml (mean 4.6, median 4). Sixteen patients had 2 or more levels at different doses which showed linear increases in serum levels. Two levels were obtained from National Medical Services Lab and were within 1-2 ug/ml of the Med Tox levels obtained at the same doses. There was a significant correlation ($p < 0.001$) between mg/kg/day and serum concentration (See Figure 1).

PGB was added to 0-4 concomitant AEDs (See Figures 2,3). AE's reported were tiredness, weight gain (4%), leg edema(4%), and body jerks (1.8%).

Improved seizure control was reported in 27/53 patients (51%) of whom 2 were seizure free. One patient was worse. Twenty five patients had no clear response. There was no pattern of co-AEDs in the responders. Efficacy was seen at 2 μg/ml or less in 23% of responders and between 2-14.8 μg/ml in the remaining responders. The serum level in the responders ranged from 1.1 to 14.8 ug/ml (mean 4.5, median 3.8) while non-responders ranged from 0.4 to 9.6 ug/ml (mean 3.0, median 3.8).

Discussion:

Pregabalin is reported to have a straightforward pharmacokinetic profile with >90% bioavailability independent of dose, no hepatic metabolism and no protein binding. It is renally excreted. This report confirms the correlation between the dose administered and the dose delivered as reflected by the serum level. The solid straight line in Figure 1 represents a linear model which does not extrapolate to zero, perhaps reflecting the limited number of patients enrolled and the absence of a dose of zero.

There is no clear dose or serum difference between the responding group and the non-responding group. There is no clear way to predict who may respond to this AED.

Conclusion:

PGB is easily utilized as adjunctive therapy in clinical practice. Doses are well tolerated up to 800 mg/day without serious AE's. Serum levels correlated linearly with increased dosing.

References:

1. Taylor. CNS Drug Rev 2004;10:183-188. Arroyo et al. Epilepsia 2004; 45:20-27.
3. Beydoun et als. Neurology 2005;64:475-480.
4. French et al. Neurology 2003;60:1631-1637.

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Table 1

RESPONDERS vs NON-RESPONDERS

All comparisons are non-significant

	Responders	Non-Responders
Age (years)	39.7 ± 3.1	33 ± 4.1
Weight (kg)	68 ± 3.4	72 ± 5.2
Serum Levels (µg/ml)	3.9 ± 2.5	4.8 ± 2.5

Figure 1

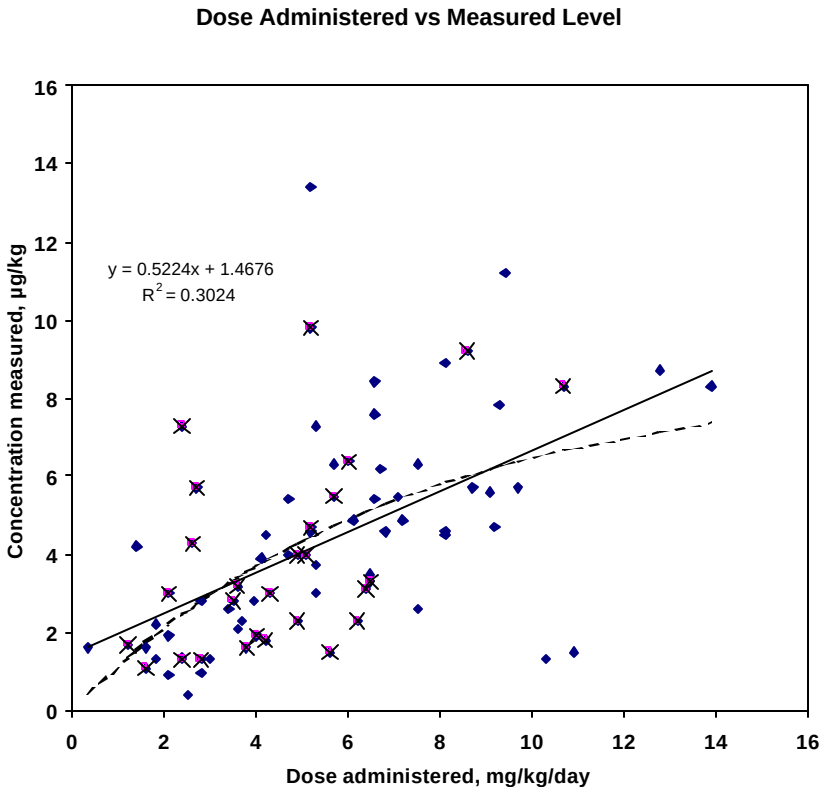

Figure 2

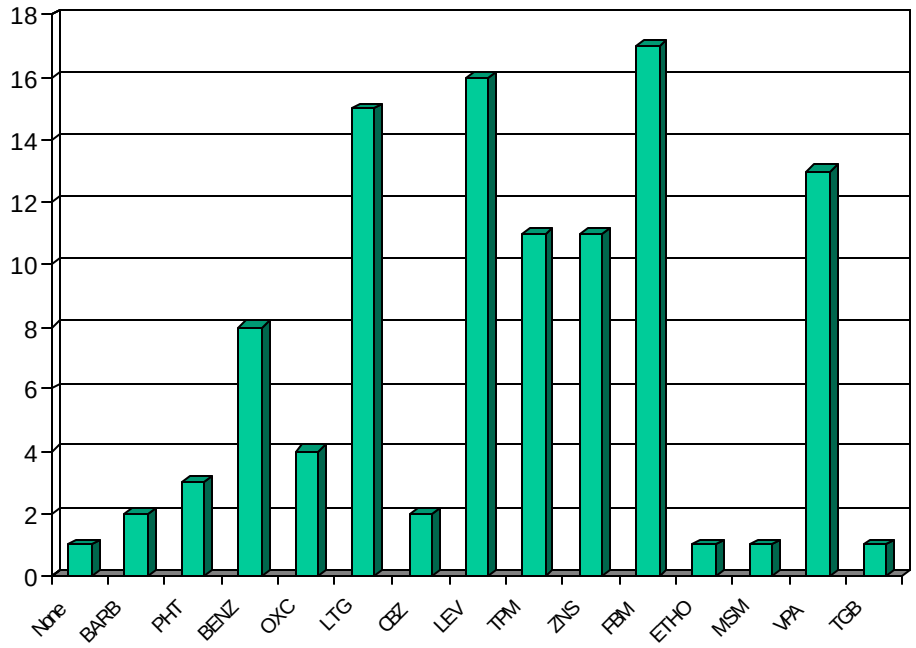

Figure 3