Factors predicting adverse events associated with pregabalin administered for neuropathic pain relief

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BACKGROUND: Pregabalin administration is occasionally abandoned due to adverse events such as somnolence, dizziness, unsteadiness, weight gain and edema. However, the exact causes of these differences in adverse events associated with pregabalin have not been elucidated.

OBJECTIVE: To identify factors predicting adverse events associated with pregabalin administration for neuropathic pain.

METHODS: The present study was a retrospective analysis involving 208 patients with neuropathic pain who had been treated with pregabalin in the pain clinic at the authors’ hospital between July 2010 and September 2011. Variables were extracted from the clinical records for regression analysis of factors related to the occurrence of adverse events associated with pregabalin administration. Multivariate logistic regression analysis was used to examine the relationship between various predictive factors and the adverse events.

RESULTS: Predictive factors were: duration of therapy (OR 1.684 [95% CI 1.179 to 2.406]; P=0.0042) for somnolence; nonsteroidal anti-inflammatory drugs (OR 0.332 [95% CI 0.230 to 0.578]; P=0.0072), age (OR 3.137 [95% CI 1.220 to 8.066]; P=0.0177) and maintenance dose (OR 0.457 [95% CI 0.217 to 0.880]; P=0.0205) for unsteadiness; serum creatinine (OR 6.439 [95% CI 1.541 to 26.902]; P=0.0107) for body weight gain; and neuropotropin (OR 8.538 [95% CI 1.159 to 62.901]; P=0.0353) and serum creatinine (OR 6.912 [95% CI 1.118 to 42.726]; P=0.0375) for edema.

CONCLUSIONS: The results of the present study indicate that care is warranted regarding long durations of therapy for somnolence, advanced age rather than dose-dependent adverse events for unsteadiness, elevated serum creatinine level for weight gain, and elevated serum creatinine level and combination use of neurotropin for edema. The safety of the combined use of pregabalin and nonsteroidal anti-inflammatory drugs were also suggested.

Key Words: Adverse events; Body weight gain; Neuropathic pain; Pregabalin; Somnolence; Unsteadiness

Les facteurs prédictifs d’événements indésirables

Pregabalin, a specific ligand of the alpha-2-delta type 1 and 2 subunits of voltage-gated calcium ion channels, is used in the treatment of various types of intractable neuropathic pain (NP) such as postherpetic neuralgia (PHN) (1-9), diabetic peripheral neuropathy (DPNP) (5-13) and cancer-related NP (14). However, pregabalin administration is occasionally abandoned due to adverse events. The most commonly reported adverse events data (all-causality) with pregabalin (regardless of dose) in Japan were dizziness (PHN 31.1%; DPNP 24.6%), somnolence (PHN 28.6%; DPNP 25.7%), peripheral edema (PHN 12.5%; DPNP 15.1%) and weight gain (PHN 11.7%; DPNP 13.4%) (15). However, the exact causes of these differences in adverse events of pregabalin have not been elucidated. Therefore, the aim of the present study was to identify predictive factors for adverse events of pregabalin, which will help to establish evidence-based guidelines for the optimal use of pregabalin.

METHODS

Study term and participants

The present study was a retrospective analysis involving 208 patients with NP who had been treated with pregabalin in the pain clinic at the University Hospital at Kyoto Prefectural University of Medicine (Kyoto, Japan) between July 2010 and September 2011. The study protocol was approved by the ethics review boards of Kyoto Prefectural University of Medicine.

Statistical analysis

Multivariate logistic regression analysis was used to examine the relationships among various predictive factors and adverse events associated with pregabalin administered for the relief of NP. Analyzed adverse events were somnolence, unsteadiness, weight gain and edema. The occurrence of adverse events was recorded by pain clinicians.
TABLE 1  Patient characteristics and extracted factors that may affect effectiveness or adverse effects associated with pregabalin for neuropathic pain (n=208)

| Characteristic | n (%) | Mean ± SD (range) |
|---------------|-------|-------------------|
| Adverse events | 118 (56.7) | |
| Somnolence | 62 (29.8) | |
| Dizziness | 6 (2.9) | |
| Unsteadiness | 49 (23.6) | |
| Weight gain, kg. | 11 (5.3) | 4.45±1.98 (4.0–9.0) |
| Edema | 9 (4.3) | |
| Physical examination finding | | |
| Body mass index | | 22.4±3.5 (15.2–34.5) |
| Dose and duration of pregabalin therapy | | |
| Initial dose, mg/day, mean ± SD (median) | 149 (71.6) | 112.9±48.8 (100) (25–375) |
| Maintenance dose, mg/day, mean ± SD (median) | 111 (53.4) | 152.2±96.4 (150) (25–450) |
| Duration of therapy | 9 (4.3) | 34/25/31/118 |
| Laboratory tests | | |
| AST, U/L | 24.3±13.6 (9–111) | |
| ALT, U/L | 20.4±20.3 (4–236) | |
| Blood urea nitrogen | | |
| mmol/L | 5.7±2.1 (2.0–17.7) | |
| mg/dL | 16.0±6.0 (5.6–49.5) | |
| Albumin, g/L | 40.8±5.1 (16–51) | |
| Bilirubin | | |
| µmol/L | 12.8±12.0 (3.9–157.1) | |
| mg/dL | 0.75±0.70 (0.23–9.19) | |
| Serum creatinine | | |
| µmol/L | 22 (10.6) | 66.3±27.4 (30.1–231.6) |
| mg/dL | 0.75±0.31 (0.34–2.62) | |
| Concomitant medications | | |
| Opioids | 27 (13.0) | |
| Morphine | 2 | |
| Oxycodone | 9 | |
| Fentanyl | 7 | |
| Tramadol | 1 | |
| Others | 8 | |
| NSAIDS | 43 (20.7) | |
| Neurtropin | 12 (5.8) | |
| Benzodiazepine | 44 (21.2) | |
| Tricyclic antidepressant | 22 (10.6) | |
| Combination therapies | | |
| Nerve block | 62 (29.8) | |
| Epiduroscopy | 24 (11.5) | |
| Phototherapy | 40 (19.2) | |

Adverse events were observed in 118 patients (56.7%). Pregabalin was discontinued due to adverse events in 32 patients (15.4%). These adverse events comprised somnolence in nine patients, dizziness in two, unsteadiness in 16, weight gain in two and edema in four (some patients experienced two or three adverse events). All patients showed full resolution of symptoms after discontinuation of pregabalin. Table 1 summarizes the clinical characteristics of the patients administered pregabalin, as well as the selected predictors related to adverse events of pregabalin. Predictive factors for adverse events were identified using logistic regression analysis. Predictive factors were: duration of therapy (OR 1.689 [95% CI 1.179 to 2.406]; P=0.0042) for somnolence; nonsteroidal anti-inflammatory drugs (NSAIDs) (OR 0.132 [95% CI 0.030 to 0.578]; P=0.0072), age (OR 3.137 [95% CI 1.220 to 8.666]; P=0.0177) and maintenance dose (OR based on interviews with the patients in daily clinical practice. The occurrence of an adverse event of grade ≥1 according to the Common Terminology Criteria for Adverse Events version 4.0 was regarded as a positive event. Variables were extracted from the clinical records for regression analysis of factors related to the occurrence of adverse events associated with pregabalin administration. Predictive variables included sex, age, body mass index, dose and duration of pregabalin therapy, laboratory tests, concomitant medications, combination therapies and target disease. Target diseases were PHN, cancer-related NP, failed back surgery syndrome, trigeminal neuralgia, complex regional pain syndrome, spine disease (spinal canal stenosis, osteoarthritis, hernia), DPNP and others. Concomitant drug use was defined as the administration of another drug for ≥2 weeks at the time of evaluation for adverse events. Body mass index and laboratory tests were extracted at the time of last evaluation. Binary scales were used for sex (female = 0; male = 1); age (<60 years of age = 0; ≥60 years of age = 1); serum creatinine level (<1.0 mg/dl [88.4 µmol/L] = 0; ≥1.0 mg/dl [88.4 µmol/L] = 1); initial dose (<150 mg/day = 0 and ≥150 mg/day = 1) for maintenance dose; and absent = 0 and present = 1 for others. Ordinal scales were: ≥2 weeks but ≤1 month = 1; >1 month but ≤2 months = 2; and >2 months = 3 for duration of therapy. ALT Alanine aminotransferase; AST Aspartate aminotransferase; NSAIDS Nonsteroidal anti-inflammatory drugs

Results

Adverse events were observed in 118 patients (56.7%). Pregabalin was discontinued due to adverse events in 32 patients (15.4%). These adverse events comprised somnolence in nine patients, dizziness in two, unsteadiness in 16, weight gain in two and edema in four (some patients experienced two or three adverse events). All patients showed full resolution of symptoms after discontinuation of pregabalin. Table 1 summarizes the clinical characteristics of the patients administered pregabalin, as well as the selected predictors related to adverse events of pregabalin. Predictive factors for adverse events were identified using logistic regression analysis. Predictive factors were: duration of therapy (OR 1.689 [95% CI 1.179 to 2.406]; P=0.0042) for somnolence; nonsteroidal anti-inflammatory drugs (NSAIDs) (OR 0.132 [95% CI 0.030 to 0.578]; P=0.0072), age (OR 3.137 [95% CI 1.220 to 8.666]; P=0.0177) and maintenance dose (OR
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| Variable                | Estimated value | SE     | χ²    | P     | OR    | 95% CI     |
|-------------------------|-----------------|--------|-------|-------|-------|------------|
| **Response Y = somnolence (accuracy = 125/208)** |                 |        |       |       |       |            |
| Duration of therapy     | 0.521           | 0.182  | 8.21  | 0.0042*| 1.684 | 1.179–2.406|
| TCA                     | −0.811          | 0.669  | 1.47  | 0.2259 | 0.445 | 0.120–1.651|
| Opioid                  | 0.662           | 0.513  | 1.67  | 0.1968 | 1.938 | 0.710–5.295|
| Serum creatinine        | 0.792           | 0.581  | 1.81  | 0.1781 | 2.186 | 0.700–6.826|
| **Response Y = unsteadiness (accuracy = 159/208)** |                 |        |       |       |       |            |
| NSAIDs                  | −0.027          | 0.755  | 7.21  | 0.0072*| 0.132 | 0.030–0.578|
| Age                     | 1.143           | 0.482  | 5.63  | 0.0177*| 3.137 | 1.220–8.066|
| Maintenance dose        | −0.828          | 0.357  | 5.37  | 0.0205*| 0.437 | 0.217–0.880|
| **Response Y = body weight gain (accuracy = 164/208)** |                 |        |       |       |       |            |
| Neurotropin             | 1.473           | 0.914  | 2.6   | 0.1068 | 4.346 | 0.728–26.156|
| Serum creatinine        | 1.862           | 0.730  | 6.52  | 0.0107*| 6.439 | 1.541–26.902|
| **Response Y = edema (accuracy = 164/208)** |                 |        |       |       |       |            |
| Neurotropin             | 2.144           | 1.019  | 4.43  | 0.0353*| 8.538 | 1.159–62.901|
| BUN                     | 0.0958          | 0.053  | 3.28  | 0.0701 | 1.101 | 0.992–1.221|
| Serum creatinine        | 1.933           | 0.929  | 4.33  | 0.0375*| 6.912 | 1.118–42.726|

*P<0.05. BUN Blood urea nitrogen; NSAIDs Nonsteroidal anti-inflammatory drugs; TCA Tricyclic antidepressant

Our findings indicate that predictive factors for the occurrence of adverse events were: duration of therapy for somnolence; use of NSAIDs, age and maintenance dose for unsteadiness; serum creatinine for weight gain; and use of neurotropin and serum creatinine for edema.

Duration of therapy was identified as a predictive factor for somnolence. This result showed that pregabalin does not induce any tolerance for somnolence. The only predictor Frame et al (17) identified for the time to first nonzero dizziness or drowsiness score due to pregabalin was the daily titrated dose. Thus, clinicians need to consider reducing the dose of pregabalin if patients report feeling very sleepy. Tricyclic antidepressants (TCAs) showed a low, but not significant, OR for somnolence; this finding may suggest the safety of the combined use of pregabalin and TCAs. The combination of pregabalin and TCAs may be associated with reduced somnolence.

No administration of NSAIDs and advanced age were identified as significant factors for unsteadiness. Unsteadiness occurred even with relatively low maintenance doses. These findings suggest the safety of the combined use of pregabalin and NSAIDs. Clinicians need to exercise caution when administering pregabalin to elderly patients, due to the risk of unsteadiness. Addition of NSAIDs to the regimen of an elderly patient on pregabalin may mitigate the risk of unsteadiness. On the other hand, previous studies have concluded that dizziness in patients treated with pregabalin occurred in 17% to 46% (24,25). It may also be due to the difference in drug metabolism between Japanese and Caucasian patients, the difference in disease, or the low maintenance dose in the present study because the daily dose of our subjects was 152.2±96.4 mg whereas the dose used in previous studies was 300 mg to 600 mg (24,25). The present study had several limitations. First, the retrospective nature of the investigation may have decreased the reliability of the data collected. Second, the present study was performed at a single centre and involved a relatively small number of patients; therefore, the results should be confirmed in a further multicentre study.

CONCLUSION

We used a statistical approach to identify factors predicting adverse events associated with administration of pregabalin for NP. Our findings indicate that care is warranted regarding long duration of therapy for somnolence, advanced age rather than dose-dependent adverse events for unsteadiness, elevated serum creatinine level for weight gain, and elevated serum creatinine level and combination use of neurotropin for edema. Our study also demonstrated the safety of the combined use of pregabalin and NSAIDs. These findings should be considered preliminary and in need of further refinement and study. However, statistical identification of predictive factors should contribute to establish optimal protocols for pregabalin use.

DISCLOSURES: The authors have no conflicts of interest to declare.
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