ORIGINAL ARTICLE

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 administered 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 0.132 [95% CI 0.030 to 0.578]; P=0.0072), age (OR 3.137 [95% CI 1.220 to 8.066]; P=0.0177) and maintenance dose (OR 0.437 [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 neurotropin (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 associés à la prégabaline administrée pour soulager la douleur neuropathique

HISTORIQUE : L'administration de prégabaline est parfois abandonnée en raison d'événements indésirables comme la somnolence, les étourdissements, le déséquilibre, la prise de poids et l'œdème. Cependant, les causes exactes des différences en matière d'événements indésirables attribuables à la prégalabine ne sont pas établies.
OBJECTIF : Déterminer les facteurs indicateurs d'événements indésirables associés à l'administration de prégabaline pour soulager la douleur neuropathique.
MÉTHODOLOGIE : La présente analyse rétrospective portait sur 208 patients atteints d'une douleur neuropathique qui avaient été traités à la prégabaline à la clinique de la douleur de l'hôpital des auteurs entre juillet 2010 et septembre 2011. Les chercheurs ont tiré les variables des dossiers cliniques pour effectuer l'analyse de régression des facteurs liés à la survenue d'événements indésirables associés à l'administration de prégabaline. Ils ont utilisé l'analyse de régression logistique multivariée pour examiner le lien entre divers facteurs prédictifs et les événements indésirables.
RÉSULTATS : Les facteurs prédictifs étaient la durée du traitement (RR 1,684 [95 % IC 1,179 à 2,406]; P=0,0042) pour la somnolence, les anti-inflammatoires non stéroïdiens (RR 0,132 [95 % IC 0,030 à 0,578]; P=0,0072), l'âge (RR 3,137 [95 % IC 1,220 à 8,066]; P=0,0177) et la dose d'entretien (RR 0,437 [95 % IC 0,217 à 0,880]; P=0,0205) pour le déséquilibre, la créatinine sérique (RR 6,439 [95 % IC 1,541 à 26,902]; P=0,0107) pour la prise de poids et la neurotropine (RR 8,538 [95 % IC 1,159 à 62,901]; P=0,0353) et la créatinine sérique (RR 6,912 [95 % IC 1,118 à 42,726]; P=0,0375) pour l'œdème.
CONCLUSIONS : D'après les résultats de la présente étude, des soins s'imposent pour résorber la somnolence causée par la longue durée du traitement, le déséquilibre est attribuable à l'âge avancé plutôt qu'à un événement indésirable lié à la dose, la prise de poids est secondaire au taux de créatinine sérique élevé et l'œdème est imputable au taux de créatinine élevé associé à l'utilisation de neurotropine. L'innocuité de la prégabaline combinée aux anti-inflammatoires non stéroïdiens a également été invoquée.

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

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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, mean ± SD (median)	11 (5.3)	4.45±1.98 (4.0) (2.6–9.0)
Edema	9 (4.3)	
Demographic factors		
Male sex	88 (42.3)	
Age, ≥60 years	145 (69.7)	63.3±15.4 (19–91)
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 (0/1/2/3)	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)	
Neurotropin	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)	
Target diseases		
Postherpetic neuralgia	75 (36.1)	
Cancer-related neuropathic pain	18 (8.7)	
Failed back surgery syndrome	14 (6.7)	
Trigeminal neuralgia	12 (5.8)	
Complex regional pain syndrome	8 (3.8)	
Spine disease	21 (10.1)	
Spinal canal stenosis	11 (5.3)	
Osteoarthritis	7 (3.4)	
Hernia	3 (1.4)	
Diabetic peripheral neuropathy	3 (1.4)	
Others	57 (27.4)	

TABLE 1 – CONTINUED
Patient characteristics and extracted factors that may affect effectiveness or adverse effects associated with pregabalin for neuropathic pain (n=208)

**Binary scales were: female = 0 and male = 1 for sex; <60 years of age = 0 and ≥60 years of age = 1 for age; <1.0 mg/dL (88.4 µmol/L) = 0 and ≥1.0 mg/dL (88.4 µmol/L) = 1 for serum creatinine level; <100 mg/day = 0 and ≥100 mg/day = 1 for 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 = 0; >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*

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 = 0; ≥60 years = 1); serum creatinine level (<1.0 mg/dL [88.4 µmol/L] = 0; ≥1.0 mg/dL [88.4 µmol/L] = 1); initial dose (<100 mg/day = 0; ≥100 mg/day = 1); maintenance dose (<150 mg/day = 0; ≥150 mg/day = 1); and other variables (no = 0; yes = 1). Ordinal scales were ≤2 weeks = 0; >2 weeks but ≤1 month = 1; >1 month but ≤2 months = 2; and >2 months = 3 for duration of therapy. All potential predictive variables were screened for multicollinearity, which was defined as a correlation coefficient >0.7 between any two predictors. A lack of multicollinearity ensured the appropriate use of the multivariate regression model. Variables were further screened with the forward selection procedure, after which multivariate logistic regression analysis was performed using the selected variables. Threshold measures were examined using an ROC curve (16). All statistical analyses were performed using JMP version 9 (SAS Institute, USA) at a two-sided significance level of P<0.05.

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 1.684 [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 8.066]; P=0.0177) and maintenance dose (OR

TABLE 2
Results of logistic regression analysis for variables extracted by forward selection

Variable	Estimated value	SE	χ^2	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	0.782	0.581	1.81	0.1781	2.186	0.700–6.826
Response Y = unsteadiness (accuracy = 159/208)						
NSAIDs	−2.027	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	4.364	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*

0.437 [95% CI 0.217 to 0.880]; P=0.0205) for unsteadiness; serum creatinine level (OR 6.439 [95% CI 1.541 to 26.902]; P=0.0107) for weight gain; and neurotropin (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. Accuracy refers to the ratio of patients whose expected value is equal to the observed value (Table 2). Using an ROC curve with a creatinine threshold >0.83, the highest sensitivity (67%) and specificity (73%) were obtained for the occurrence of weight gain (area under the curve = 0.68); with a creatinine threshold >1.02, the highest sensitivity (63%) and specificity (91%) were obtained for the occurrence of edema (area under the curve = 0.78).

DISCUSSION

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, NSAIDs are independently associated with significant adverse effects, particularly in elderly patients (eg, unheralded gastrointestinal bleeding); clinicians should, therefore, be alert to combined use of pregabalin and NSAIDs in elderly patients. The safety of the combination of the agents would require more detailed study. In addition, pregabalin shows a linear pharmacokinetic profile (18). However, unsteadiness did not occur in a dose-dependent manner. Clinicians should, therefore, be alert to initial unsteadiness when prescribing pregabalin.

Elevated serum creatinine level was identified as a predictive factor for weight gain. Pregabalin is eliminated primarily unchanged by renal excretion (19); therefore, accumulation of pregabalin due to delayed elimination through the kidney may cause weight gain. Stephen et al (20) identified dose-related weight gain due to pregabalin; our results support that finding. Clinicians should be cautious when prescribing pregabalin to patients with altered renal function.

Elevated serum creatinine level and combination use with neurotropin were identified as predictive factors for edema. Cumulative dosage of pregabalin due to delayed elimination through the kidneys may cause edema in addition to weight gain, reinforcing the need for clinicians to exercise care regarding renal function when prescribing pregabalin. Neurotropin, a nonprotein extract isolated from inflamed rabbit skin after inoculation with vaccinia virus, acts on the descending pain inhibitory system and has been widely used in Japan for the treatment of disorders associated with chronic pain (21-23). Edema due to neurotropin has been reported infrequently; thus, the possibility of edema arising in combination use of pregabalin and neurotropin needs to be considered.

In our study, dizziness was observed in 2.9% of patients. 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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