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Predictors of the usefulness of mirogabalin for neuropathic pain: a single-institution retrospective study

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Mirogabalin is a novel, preferentially selective α2 δ-1 ligand to treat neuropathic pain. However, this agent is not always effective for patients with neuropathic pain. We therefore attempted to identify factors that could predict the efficacy of mirogabalin. The study comprised 133 patients given mirogabalin for alleviation of neuropathic pain between April and November 2019 at our hospital. Variables were extracted from medical records for regression analysis of factors associated to alleviation of neuropathic pain. We evaluated the effect of mirogabalin at two weeks after administration. Groups were categorized according to degree of improvement: poor, effective, or very effective. Multivariate ordered logistic regression analysis was conducted to identify predictors for the usefulness of mirogabalin. Threshold measures were analysed using receiver operating characteristic (ROC) curves. Maintenance dose [odds ratio (OR) = 0.90; 95% confidence interval (CI) = 0.84–0.98; P = 0.01], concomitant use of opioids (OR = 0.26, 95% CI = 0.08–0.83; P = 0.023) and Neurotropin® (NTP) (OR = 4.78, 95% CI =1.04–21.93; P = 0.044) were factors significantly correlated to the effect of mirogabalin. ROC curve analysis of the effective group indicated a threshold maintenance dose of ≤ 20 mg/day (area under the curve [AUC] = 0.53). In conclusion, maintenance dose (≤ 20 mg), concomitant use of opioids and NTP were identified as predictors for the utility of mirogabalin.

1. Introduction

Neuropathic pain is incredibly challenging to manage because of the heterogeneity of aetiologies, symptoms, and underlying mechanisms (Attal and Bouhassira 2015). Current first-line anti-neuropathic pharmacotherapy includes serotonin–noradrenaline reuptake inhibitors, tricyclic antidepressants and gabapentinoids. Gabapentinoid therapies (pregabalin and gabapentin) are effective in managing neuropathic pain, the common side effects of somnolence, headache and dizziness are linked to their interaction with the α 2 δ-2 subunit of voltage-gated calcium channels. However, traditional oral medications have been limited by negative factors such as systemic adverse effects, drug-drug interactions, slow onset of action, the need for titration, multiple daily dosing, as well as the potential risk of addiction, dependence, withdrawal symptoms and abuse (Dosenovic et al. 2017; Finnerup et al. 2015; Gilron et al. 2015; Yekkirala et al. 2017). As a result, there is an unmet medical need for management options with fewer adverse effects and high efficacy.

Mirogabalin is a novel, preferentially selective α2 δ-1 ligand used to treat neuropathic pain, currently available in Japan only (Calandre et al. 2016; Deeks 2019; Domon et al.2018a, b; Javed et al.2018). In contrast to pregabalin, a standard $\alpha_2\delta$ ligand, mirogabalin has higher binding affinities to human and rat $\alpha_2\delta$ subunits. Furthermore, the dissociation rate is slower for the $\alpha_2\delta$-1 subunit than for the $\alpha_2\delta$-2 subunit resulting in more sustained analgesia compared with traditional gabapentinoids (Deeks 2019; Domon et al. 2018a). Mirogabalin is rapidly absorbed after oral administration and the median time to maximum plasma concentration is 0.5–1.5 h (Deeks 2019b). Additionally, mirogabalin has a superior adverse events profile due to a rapid dissociation from the α 2 δ-2 subunit of voltage-gated calcium channels potentially implicated in central nervous system-specific adverse events (Deeks 2019). Several randomized controlled trials have verified the efficacy of mirogabalin for neuropathic pain such as postherpetic neuralgia and diabetic peripheral neuropathic pain (Baba et al. 2019; Kato et al. 2019; Merante et al. 2017). Mirogabalin became available for daily clinical use in Japan from April 2019 but is not always effective for patients with neuropathic pain. The aim of this study was to identify factors that could predict the usefulness of mirogabalin.

2. Investigations and results

2.1. Patients demographics

Among the 159 patients prescribed mirogabalin for alleviation of neuropathic pain between April 2019 and November 2019, 26 patients were excluded from this study: 3 due to somnolence within 2 weeks, 1 due to poor compliance, and 22 due to insufficient data. Mirogabalin was effective in 85 of 133 patients. Table 1 shows the clinical characteristics of the 133 evaluable patients, variables associated to the effect of mirogabalin, and the results of univariate analysis.

2.2. Statistical analysis

Five of these variables [starting dose of mirogabalin, maintenance dose of mirogabalin, albumin level, concomitant use of opioids and Neurotropin® (NTP)] were identified by the stepwise forward

Table 1: Patient characteristics, extracted variables, and results of univariate analyses (n = 133)

	Poorly effective (n = 48)	Effective (n = 76)	Very effective (n = 9)	*P* value	Odds ratio (95%CI)
Age (y), median (range)	65.5 (36–93)	64 (21–89)	70 (48–83)	0.995	1.00 (0.98–1.03)
Male, n (%)	21 (43.8)	29 (38.2)	5 (55.6)	0.928	0.97 (0.49–1.92)
Starting daily dosage of mirogabalin (mg), mean±SD	8.9±4.7	9.3±3.9	9.4±4.6	0.550	1.03 (0.95–1.11)
Maintenance daily dosage of mirogabalin (mg), mean±SD	15.6±8.6	14.7±7.2	13.3±8.3	0.421	0.98 (0.93–1.03)
Change from pregabalin to mirogabalin, n (%)	9 (18.8)	9 (11.8)	1 (11.1)	0.283	0.59 (0.23–1.54)
Concomitant medication					
Opioids, n (%)	12 (25)	11 (15.5)	0	0.051	0.41 (0.17–1.01)
Morphine, n (%)	0	1 (1.3)	0	-	-
Oxycodone, n (%)	1 (2.1)	0	0	-	-
Buprenorphine, n (%)	1 (2.1)	0	0	-	-
Tramadol, n (%)	10 (20.8)	10 (13.2)	0	0.109	0.46 (0.18–1.19)
Vitamin B12, n (%)	3 (6.3)	21 (27.6)	0	0.086	2.24 (0.89–5.61)
Neurotropin®, n (%)	2 (4.2)	9 (11.8)	3 (33.3)	0.016*	4.44 (1.32–14.94)
Duloxetine, n (%)	1 (2.1)	3 (3.9)	0	0.824	1.25 (0.17–9.20)
Acetaminophen, n (%)	9 (18.8)	7 (9.2)	3 (33.3)	0.626	0.79 (0.30–2.05)
NSAIDs, n (%)	19 (39.6)	29 (38.2)	5 (55.6)	0.718	1.14 (0.57–2.26)
Steroid, n (%)	1 (2.1)	5 (6.6)	0	0.538	1.69 (0.32–8.98)
Physical/physiological parameters					
Height (cm), median (range)	160.9 (140.7–185)	157.9 (135–182.3)	171.9 (149–178.5)	0.880	1.00 (0.96–1.03)
Weight (kg), median (range)	56.4 (30.6–87)	55.1 (36.7–99.8)	70 (45.1–85)	0.117	1.02 (1.00–1.05)
BMI (kg/m^2), median (range)	21.5 (14.5–30.1)	21.7 (15.8–35.8)	23.7 (20.0–27.2)	0.043*	1.10 (1.00–1.21)
Laboratory test					
Serum creatinine, mg/dL median (range)	0.71 (0.48–7.73)	0.69 (0.34–5.92)	0.8 (0.51–1.01)	0.346	0.80 (0.50–1.28)
Creatinine clearance, mL/min median (range)	68.3 (6.7–159.4)	79.9 (12.7–174.5)	84.0 (33.2–128.6)	0.218	1.01 (1.00–1.02)
ALT, U/L, median (range)	15 (8–141)	17 (3–154)	19 (10–43)	0.709	1.00 (0.99–1.02)
Albumin, g/dL, median (range)	4 (2.8–4.7)	4 (2.7–4.8)	4.1 (3.5–4.5)	0.366	1.42 (0.67–3.01)
Bilirubin, mg/dL, median (range)	0.69 (0.33-1.5)	0.77 (0.31-3.21)	0.66 (0.37-1.14)	0.521	1.43 (0.48- 4.25)
Pathology of neuropathic pain					
PHN, n (%)	2 (4.2)	9 (11.8)	0	0.441	1.64 (0.47–5.75)
Postoperative pain, n (%)	3 (6.3)	7 (9.2)	0	0.934	1.06 (0.29–3.79)
CIPN, n (%)	6 (12.5)	8 (10.5)	2 (22.2)	0.762	1.16 (0.45–2.98)
Spinal canal stenosis, n (%)	7 (14.6)	8 (10.5)	2 (22.2)	0.887	0.93 (0.34–2.54)
Lumbar spine disease, n (%)	7 (14.6)	10 (13.2)	2 (22.2)	0.870	1.08 (0.41–2.84)
Cervical spine disease, n (%)	5 (10.4)	4 (5.3)	1 (11.1)	0.455	0.62 (0.17–2.19)
Upper extremity pain, n (%)	4 (8.3)	5 (6.6)	0	0.476	0.62 (0.16–2.33)
Lower extremity pain, n (%)	6 (12.5)	7 (9.2)	0	0.323	0.57 (0.18–1.75)

	Poorly effective (n = 48)	Effective (n = 76)	Very effective (n = 9)	*P* value	Odds ratio (95%CI)
Arthritis, n (%)	1 (2.1)	3 (3.9)	0	0.824	1.25 (0.17–9.20)
Adverse effects (duplicate data)					
Dizziness, n (%)	5 (10.4)	2 (2.6)	1 (11.1)	0.189	0.38 (0.09–1.61)
Somnolence, n (%)	4 (8.3)	9 (11.8)	1 (11.1)	0.576	1.37 (0.45–4.18)
Oedema, n (%)	0	3 (3.9)	1 (11.1)	-	-
Failing vision, n (%)	0	1 (1.3)	0	-	-

NSAIDs, non-steroidal anti-inflammatory drugs; BMI, body mass index; ALT, alanine transaminase; PHN, post-herpetic neuralgia; CIPN, chemotherapy-induced peripheral neuropathy; CI, confidence interval
*P<0.05

selection procedure. These variables were then employed for multivariate ordered logistic regression analysis. Maintenance dose of mirogabalin [odds ratio (OR) = 0.90, 95% confidence interval (CI) = 0.84–0.98; P = 0.01], concomitant use of opioids (OR = 0.26, 95% CI = 0.08–0.83; P = 0.023) and NTP (OR = 4.78, 95% CI = 1.04–21.93; P = 0.044) were factors significantly associated to the effect of mirogabalin (Table 2). ROC curve analysis of the effective group indicated the threshold maintenance dose of mirogabalin was ≤ 20 mg, with 91% sensitivity and 20% specificity (area under the curve [AUC] = 0.53). Adverse effects that were identified included dizziness [8 patients (5 discontinued), 6.0%], somnolence [14 patients (9 discontinued), 10.5%], oedema [4 patients (2 discontinued), 3.0%] and failing vision [1 patient (1 discontinued), 0.8%] (duplicate data: some patients developed multiple adverse effects).

Table 2: Ordered logistic regression analysis results for variables extracted by forward selection

Variable	*P* value	Odds ratio	95%CI	
			Lower 95%	Upper 95%
Maintenance daily dosage of mirogabalin (mg)	0.010*	0.90	0.84	0.98
Starting daily dosage of mirogabalin (mg)	0.184	1.11	0.95	1.30
Opioids	0.023*	0.26	0.08	0.83
Neurotropin®	0.044*	4.78	1.04	21.93
Albumin, g/dL	0.088	2.33	0.88	6.14

CI, confidence interval
*P<0.05

3. Discussion

In this study, multivariate ordered logistic regression analysis showed that significant predictors of mirogabalin efficacy involved maintenance dose of mirogabalin, concomitant use of opioids and NTP. ROC curve analysis of factors potentially responsible for the effect of mirogabalin determined a cut-off value for the maintenance dose of mirogabalin of ≤ 20 mg.

Blood levels (measured as plasma concentration-time curve or maximum plasma concentration) of mirogabalin have been reported to increase in a dose-dependent manner (Jansen et al. 2018b). However, this study suggested that mirogabalin was poorly effective against neuropathic pain, even with maintenance dose increased to > 20 mg/day. If increasing the dose > 20 mg/day does not yield sufficient effects, clinicians should consider concomitant use of other analgesics or switching to another drug. The optimal maintenance dose of mirogabalin needs further validation in routine clinical practice.

Regarding concomitant medications, we found mirogabalin was poorly effective for neuropathic pain with opioids and was effective with NTP. Among the 24 patients prescribed opioids, 21 were received tramadol. In clinical trials, no interactions have been identified between tramadol and mirogabalin. However, a previous study reported an increased incidence of nausea and headache for combination use with mirogabalin and tramadol (Jansen et al. 2018a). Combined use of mirogabalin and opioids may increase the occurrence of adverse effects such as dizziness or somnolence, so combination of opioids with mirogabalin may be better avoided. On the other hand, NTP is a nonprotein extract isolated from the inflamed skin of rabbits inoculated with vaccinia virus and used for the treatment of neuropathic pain (Ishikawa et al. 2015). Its pharmacological and clinical efficacy has also been reported for neuropathic pain (Zhang et al. 2012; Zhu et al. 2017). NTP has no cytochrome 450 interactions limiting the potential for drug interactions. In addition, NTP has few adverse effects, and is often used in combination with other drugs in the treatment of neuropathic pain. Thus, clinicians may consider combining the use of NTP with mirogabalin.

As for the adverse effects of mirogabalin in our study, dizziness, somnolence, oedema and failing vision were encountered. These results were similar to the events seen in clinical trials (Baba et al. 2019; Kato et al. 2019; Merante et al.2017) and also similar to those of other gabapentinoids (Enke et al. 2018; Goodman et al.2019; Hamilton et al. 2016). On the other hand, kidney function did not appear to affect the effects or adverse effects in our study, unlike previous studies (Kato et al. 2018). Continuous accumulation of data from daily clinical practice is necessary.

Several limitations were associated with the present study. The retrospective nature of the survey may have decreased the validity of the data extracted. Furthermore, this study was conducted at a single institute. The current results should be confirmed in a larger multicentre study.

In conclusion, maintenance dose of mirogabalin, concomitant use of opioids and NTP were identified as significant predictors of the effects of mirogabalin. However, our results are preliminary and must be substantiated in further studies. Nevertheless, identification of predictors of the usefulness of mirogabalin for neuropathic pain may help in the development of measures to improve the quality of life of patients receiving treatment for neuropathic pain.

4. Experimental

4.1. Patients and methods

Between April 2019 and November 2019, we enrolled 159 patients who were prescribed mirogabalin for alleviation of neuropathic pain at our hospital.

4.2. Statement of ethics

The Medical Ethics Review Committee at Kyoto Prefectural University of Medicine approved this study (approval no. ERB-C-1647). All procedures were performed in accordance with the ethical standards of the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine and the 1964 Declaration of Helsinki and its later amendments. No prospective studies with human participants or animals were performed by any of the authors for this article. Due to the retrospective nature of this work, the need to obtain informed consent was waived for the individual participants included in the study, in accordance with the ethical standards of the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine. All authors declare that they have no competing interest concerning this work.

4.3. Extraction of variables

For regression analysis of factors associated to neuropathic pain, variables were extracted from medical records. Evaluated variables were factors potentially effecting

neuropathic pain: age, sex, complications, starting dose of mirogabalin, maintenance dose of mirogabalin, concomitant medication, body mass index, height, weight, pathology of neuropathic pain and adverse effects. We also extracted laboratory data that appeared to influence pharmacological effects of mirogabalin, which included liver and kidney functions. Laboratory data were extracted at the start of mirogabalin administration. Concomitant medication was defined as administration of another drug for ≥ 2 weeks at the time of evaluation of the effect of mirogabalin.

We evaluated the effect of mirogabalin two weeks after administration. Data on the effect of mirogabalin was collected by patient interviews managed by the treating physician, pharmacist, and/or primary nurse during daily medical practice. Treatment was defined as effective when mirogabalin administration resulted in subjective improvements associated with the initial complaints of patients. Among patients considered to have improved, improvement was defined as "very effective" according to patient responses of "worked well" and "much better". Degree of improvement was classified as follows: 0 = poor (no change or worsening); 1 = effective; and 2 = very effective. We also examined the frequency of adverse effects and subsequent outcomes.

4.4. Statistical analysis

Variables were analysed for multicollinearity (correlation coefficient $|r| \geq 0.7$), which can appear when correlations exist among variables, developing in the use of an inappropriate model. First, we performed univariate ordered logistic regression analysis between outcomes (the effect of mirogabalin) and each potential explanatory variable. We then constructed a multivariate ordered logistic regression model using stepwise forward selection among potential explanatory variables with a variable entry criterion of 0.25 and a variable retention criterion of 0.1. Ordered logistic regression analysis was used because the degree of improvement of neuropathic pain was evaluated on a graded scale and multiple factors possibly associated as predictors for the usefulness of mirogabalin had to be analysed simultaneously. Threshold measurements were analysed using receiver operating characteristic (ROC) curves (Akobeng 2007).

All statistical analyses were conducted using JMP® version 14.3.0 (SAS Institute, Cary, NC) with a two-sided significance level of 0.05.

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