



Evaluation of perampanel in patients with intellectual disability and epilepsy



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ABSTRACT

Introduction: Initial registration studies of perampanel (PMP), an AMPA receptor antagonist, have now been followed up by 'clinical' studies that confirmed its efficacy and safety in patients with refractory epilepsy. Publications on the use of PMP among patients with intellectual disability (ID) are still limited. This study extends our knowledge with respect to the relevance of PMP for patients with both ID and epilepsy, and furthermore specifies the behavioral side effects of PMP in this specific population.

Methods: Retrospective evaluation of medical records at 3, 6 and 12 months of follow-up after the initial start of PMP.

Results: 62 patients were included. 21 patients (33.9%) were female. All patients had complete data of 6 months follow-up and we were able to review 42 patients with a 1-year follow-up. Level of ID varied from borderline to profound, and mild ID was most common (43.5%). The mean maximum daily dosage of PMP was 5.6 mg (range 1–12 mg). Retention rates for PMP were 87.1% and 67.7% after three and six months. A trend indicated a longer mean retention time in patients with a more severe ID (borderline-mild-moderate ID: 205 days, severe-profound ID: 275 days). Seizure reduction was achieved in 53.2%. 36 patients (58.1%) experienced adverse effects, 80.6% of those within 3 months. 45.2% of the patients experienced somatic adverse effects. Most common were fatigue & sleep problems, motor problems & unsteadiness, and gastrointestinal problems. Behavioral adverse effects were present in 40.3%. Most common were aggression, agitated behavior, disruptive behavior, and mood symptoms. Reasons for discontinuation of PMP were lack of efficacy in 14.8%, intolerable adverse effects in 44.4%, and a combination of both in 40.7%.

Altogether, 24.2% (15/62) of the patients achieved seizure reduction without experiencing adverse effects, though none reached seizure freedom.

Conclusions: The use of PMP might lead to an effective seizure reduction without adverse effects in a minority of patients with both epilepsy and ID. Pre-existing behavioral problems or polypharmacy do not predict the occurrence of additional behavioral adverse effects, implying that these patients need not be excluded from the introduction of PMP when clinically indicated. Patients should, ideally, be monitored at a multidisciplinary clinic.

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1. Introduction

Epilepsy is a common health problem among people with intellectual disability (ID). The estimated prevalence of epilepsy in people with ID ranges from 15% to 30%, while the prevalence of epilepsy in the general population is estimated at 0.6–1% [1].

The treatment of epilepsy in patients with both epilepsy and ID might be complicated. Over the past few years, various antiepileptic

drugs (AEDs) with new modes of action were introduced. Usually, patients with ID and epilepsy are excluded from the initial registration studies of these new drugs as studies with these patients are complicated for both practical and medical ethical reasons. An example of a relatively new AED is perampanel (PMP), a non-competitive α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist. PMP was approved in 2012 as add-on AED for partial-onset seizures in patients aged twelve years or above by the European Medicines Agency (EMA). The efficacy and safety of PMP was analysed in three randomized controlled trials [2–4]. The 50% responders rates were 28.5% (PMP 4 mg), 35.3% (PMP 8 mg), and 35.0% (PMP 12 mg).

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PMP was fairly well tolerated in these studies with a small number of patients suffering from generally mild side effects. The most frequently reported side effects were somnolence, fatigue, dizziness, nausea, and falls. The reported neuropsychiatric adverse effects were aggression, depression, and irritability [5].

The initial registration studies of PMP have now been followed up by studies concerning clinical experience, which confirmed the efficacy and safety of PMP in patients with refractory epilepsy [6–9]. However, publications on the use of PMP among patients with ID are still limited. There is one case report [10] and one recent study from Shah [11] that included a subgroup of patients with “learning disabilities” that was not further specified. Still, efficacy might be different in patients with both epilepsy and ID as this group also includes the often highly resistant ‘epileptic encephalopathies’. Furthermore, adverse effects might be more pronounced or, conversely, might be inconspicuous, due to the fact that their presentation is influenced by polypharmacy and extensive co-morbidity. These co-morbidities in patients with both epilepsy and ID include behavioral problems with an estimated prevalence between 10% and 20% [12,13]. This is even more relevant as behavioral side effects have now been recognized as one of the potential most serious side effects of PMP in the population of patients with epilepsy without ID. In order to extend our knowledge with respect to the relevance of PMP for patients with both ID and epilepsy, we studied the effect of this AED in patients with ID at our institute. Furthermore, we sought to specify the behavioral side effects of PMP in this specific population.

2. Material and methods

2.1. Subjects

All patients with both epilepsy and ID, who were treated with PMP between July 2014 and January 2016, living at or visiting the outpatient clinic of Kempenhaeghe, a tertiary epilepsy centre in The Netherlands, were included in this study.

2.2. Data collection

The required information for the study was retrospectively retrieved from patient charts by a research student (SF) with a double check by two of the authors (JvO, FS). The baseline data included demographics (age, sex, ethnicity), level of intellectual disability according to the ICD-10 classification [14], epilepsy type, age at onset of epilepsy, and previous and concomitant AEDs. PMP dosage, the duration of PMP treatment, the reasons for discontinuation of PMP, seizure frequency, and adverse effects were also assessed after a follow-up of three, six, and twelve months. The outcome with respect to seizure frequency was purely descriptive: a decrease in seizure frequency (seizure reduction), no change, or an increase in seizure frequency. Whether PMP caused a reduction or not was based on the documented (written) clinical judgment of the consultant neurologist. To identify changes in seizure frequency, we used a time-frame of 1 month of clinical data before each evaluation (baseline, 3 months, 6 months, and 12 months).

The information was obtained by case study. There was no standard questionnaire. This study was approved by the local medical ethical committee. Due to the retrospective nature and the anonymous analyses of the data, formal consent was not required. However, each included patient gave a general consent to future use of their data for research purposes at their admission to Kempenhaeghe.

3. Results

Demographic and clinical characteristics are shown in Table 1. A total of sixty-two patients treated with PMP were included, of whom 21 (33.9%) were female. All patients had complete data of six months follow-up after the start of PMP and we were able to review 42 patients with a 1-year follow-up. The mean age was 27.4 years (3.2–66.8 years).

Table 1
Demographic and clinical characteristics (N = 62).

Characteristics	Values
Male	66.1%
Mean age, years (SD);	27.4 years (17.2); range 3.2–66.8
Children (< 18 years)	32.3%
Adults (> 18 years)	67.7%
Level of ID	
Borderline	4.8%
Mild	43.5%
Moderate	16.1%
Severe	25.8%
Profound	9.7%
Mean age at onset of epilepsy (SD)	6.0 years (6.1); range 0–26
Epilepsy type	
Localized	74.2%
Generalized	25.8%
History of AEDs (SD)	3.8 (2.9); range 0–11
Mean no. concomitant AEDs (SD)	3.0 (1.0); range 1–6
1 AED	6.5%
2 AEDs	22.6%
3 AEDs	43.5%
> 3 AEDs	27.4%
Length of PMP treatment, days	6–365
< 3 months	12.9%
3–5.9 months	19.4%
6–8.9 months	8.1%
9–11.9 months	3.2%
≥ 12 months	29.0%
	(27.4% had lack of follow-up data after 6 months)

AEDs = antiepileptic drugs; ID = intellectual disability; PMP = perampanel.

The mean age at onset of epilepsy was 6.0 years (range 0–26 years). Level of ID varied from borderline to profound, and mild ID was most common among patients (43.5%). 46 subjects (74.2%) were diagnosed with localization-related epilepsy and sixteen (25.8%) with generalized epilepsy. The average number of AEDs used by patients prior to this study was four (range 0–11). The polypharmacy at the start of the study was impressive with, apart from PMP, an average of three (range 1–6) AEDs. The most commonly used concomitant AEDs were valproic acid (53.2%), clobazam (45.2%), and lamotrigine (40.3%). The initial PMP dose ranged from 0.5 mg (children) to 2 mg once a day. The titration rate was guided individually by the treating neurologist. The mean maximum daily dosage PMP was 5.6 mg (range 1–12 mg).

3.1. Efficacy

At the end of the study, seizure reduction was achieved in 53.2% of the patients. The mean PMP dosage in these patients was 6.1 mg, which is significantly higher than the mean dosage in those who did not show a seizure reduction (difference = 1.0 mg; Mann-Whitney *U* test: $p = 0.045$). Seizure reduction varied over time with 48.4% of the patients showing seizure reduction within three months and 17.7% of the patients between three and six months. The seizure reduction was not significantly associated with the type of epilepsy or the level of ID. No patient became seizure-free for a substantial period of time with PMP as add-on treatment.

The retention rates for PMP were 87.1% and 67.7% after three and six months, respectively. There was a trend that indicated a longer retention time in patients with a more severe ID, although this did not reach statistical significance (borderline-mild-moderate ID: 205 days, severe-profound ID: 275 days, Mann-Whitney *U* test: $p = 0.062$; see Fig. 1).

Eight patients discontinued PMP within three months, twelve patients between three and six months, and six patients between six and twelve months. Reasons for discontinuation of PMP were lack of efficacy in 14.8%, intolerable adverse effects in 44.4%, and a combination of both in 40.7% of patients. Patients who discontinued PMP had a significant

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