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Perampanel serum concentrations in adults with epilepsy: Effect of dose, age, gender and concomitant antiepileptic drugs

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Abstract:

Background: Perampanel (PMP), a noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, is a novel antiepileptic drug (AED) licensed for the adjunctive treatment of focal and generalized epilepsy. There is limited information on PMP's pharmacokinetics and drug interaction characteristics with concomitant AEDs. We have investigated the effects of PMP dose, age, gender and co-prescribed AEDs on serum PMP concentrations.

Methods: We used the database of a therapeutic drug monitoring unit at a tertiary epilepsy referral centre to identify patients who had PMP as part of their treatment and extracted clinical information from their medical notes. Sera PMP concentrations had being determined by using liquid chromatography/mass spectroscopy.

Results: In total, 160 sera from 107 patients (66 females) aged 18-70 years and weighing 40-125 kg were identified. They were prescribed a median PMP dose of 6 mg/day (range 2-12 mg/day) and were co-prescribed a variety of AEDs including enzyme-inducing (carbamazepine and oxcarbazepine) and enzyme-inhibiting (valproic acid) AEDs. A linear relationship was observed between PMP dose and serum concentrations ($r^2 = 0.714$, $p<0.0005$). Gender and age were found not to influence PMP serum concentration. Enzyme-inducing AEDs dose-dependently decreased PMP concentrations, with carbamazepine and oxcarbazepine decreasing mean values by 69% and 37% respectively. In contrast, whilst topiramate and phenytoin also decreased mean PMP concentrations by 18% and 13% respectively, these changes did not achieve statistical significance.

Conclusions: PMP exhibits a linear dose-concentration relationship, with serum PMP concentrations being age and gender independent. Carbamazepine and oxcarbazepine can significantly decrease PMP concentrations, probably via an induction of CYP3A4-mediated metabolism.

Running title: Perampanel serum concentrations in epilepsy

Key words: new antiepileptic drug, pharmacokinetic drug-drug interactions, carbamazepine, oxcarbazepine

Introduction

Perampanel (PMP) is a novel antiepileptic drug (AED) recently licensed for the adjunctive treatment of patients with focal and generalized epilepsies aged ≥12 years of age.[1] PMP is a selective non-competitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-receptor antagonist; a unique mechanism of action for an AED.[2,3]

PMP has some pharmacokinetics properties which could be advantageous in clinical use. These include fast absorption (Tmax 0.5-2.5 hours) the extent of which is not affected by food co-ingestion, a bioavailability of 100%, and linear pharmacokinetics. Its volume of distribution is 1.1 L/kg and protein binding is 95%. PMP serum steady-state concentrations are achieved in 10-19 days. The serum elimination half-life PMP is ~48 hours in healthy volunteers and ~25 hours in both healthy volunteers and patients with epilepsy co-prescribed carbamazepine. PMP is extensively metabolised, primarily via cytochrome P450 (CYP) 3A4 but CYP3A5 may also contribute, to produce several pharmacologically inactive metabolites.[4] Clearance is reportedly unaffected by age and race[5], although it was found to be 17% slower in women compared to men.[6]

At clinically relevant concentrations, PMP in vitro is neither a potent inducer nor inhibitor of CYPs or uridine 5'-diphospho-glucuronosyltransferase (UGT) isoenzymes and thus it is not anticipated to cause pharmacokinetic interactions. However, since PMP is metabolised via CYP3A4, an isoenzyme responsible for the metabolisms of many drugs including various AEDs, would suggest that it may be susceptible to pharmacokinetic interactions. Indeed in the pooled population pharmacokinetic analysis[7] of three Phase III randomized clinical trial studies in 969 patients with focal seizures,[8-10] patients co-prescribed carbamazepine (n=379), oxcarbazepine (n=201), phenytoin (n=91) or topiramate (n=226) all experienced an increase in PMP clearance. Thus, PMP area under the serum concentration-time curves (AUC) decreased by 67%, 50%, 50% and 20% respectively for carbamazepine, oxcarbazepine, phenytoin and topiramate. For carbamazepine, a study in 20 healthy male volunteers has shown that carbamazepine administration increased the apparent oral clearance of PMP three-fold and the mean AUC values were decreased by 26%.[4]

We used serum PMP concentration data collected for therapeutic drug monitoring (TDM) in an adult population of patients with epilepsy to assess the effect of daily PMP dose, gender, age and concomitant AED therapy on steady-state serum PMP concentrations. TDM databases are particularly useful in providing robust confirmation of pharmacokinetic interactions noted by other investigative methodologies and indeed can serve to highlight as yet unknown pharmacokinetic interactions.[11]

Materials and Methods

Study Population

Data were retrospectively collected from 109 adults attending the specialist epilepsy clinics of the National Hospital for Neurology and Neurosurgery (Queen's Square and Chalfont sites), during the period January 2013 and December 2014 who had serum samples collected for AED concentration determination, as part of their of their routine clinical management. Specific ethical approval was not needed because it entailed retrospective data generated as part of their routine clinical management.

PMP Analysis

PMP concentration analysis was undertaken by high-performance liquid chromatography/mass spectroscopy (LC/MS) using a fully validated methodology in routine use within the TDM Unit at the Chalfont Centre for Epilepsy. Validation was based on the most recent versions of the guidelines on bionalytical method validation of the European Medicines Agency and the US Food and Drug Administration.[12,13] Briefly, an Agilent 1200 series automated LC with an Agilent 6400 series triple quad MS (Agilent Technologies, Stockport, Cheshire, UK) and a HiQ sil C18 column were used. Sera (24 μL) were extracted with 500 μL acetonitrile and prepared for LC/MS analysis by use of a Gilson Quad-Z215 liquid handler (Gilson Instrumentation Services, Luton, Bedfordshire, UK). Calibration curve linearity was observed over the concentration range of 2-800 μg/L. The lower limit of quantification for PMP was 2.0 μg/L and the lowest limit of detection was 1.0 μg/L. The inter-assay and intra-assay coefficient of variation was 3.7-4.6% and 1.8-2.2% respectively. The measurement uncertainty for PMP was 4.2%.

Blood samples

In total, 160 samples were collected, with some patients being sampled on multiple occasions as their PMP dose was up-titrated. As PMP is only approved as adjunctive therapy, all but 6

patients (who were on PMP monotherapy) were treated with PMP in combination with other AEDs (Table 1).

Data collection was achieved by first reviewing the TDM Unit's archived request for analysis forms and reports and secondly by searching through each individual's medical records. Information gathered included age, gender, body weight, PMP dosage and concurrent blood concentration, as well as concomitant AEDs, their doses and their concurrent blood concentrations. For AED comedication, although some blood samples were collected at trough (i.e. just before the next dose), most were collected up to 3 hours post AED ingestion and reflects every day AED TDM clinical practice. For PMP, these sampling times represented approximately 12 hours post ingestion because patients typically ingest their PMP medication at bed time the evening before. Only patients whose PMP blood concentrations were at steady-state were included in this study. Steady state was considered to occur when the same PMP dose was prescribed for 10-19 days (i.e. equivalent to PMP 5 half-life values). These values are based on a calculated effective half-life of PMP of 48 hours and simulation of a pooled Phase I model of a sample size of 1,000 volunteers receiving 4 mg/day PMP whereby 90% of subjects achieved 90% steady-state by day 19. [4]

PMP blood samples were divided into sub-groups according to AED comedication namely: A = PMP monotherapy and samples from those neither on enzyme-inducing AEDs or enzyme-inhibiting AEDs, Group B = co-prescription of enzyme-inducing AEDs, Group C = co-prescription of enzyme-inhibiting AEDs and Group D = co-prescription of both an enzyme-inducing and an enzyme-inhibiting AED (Table 1).

Statistical Analysis

Statistical analysis was undertaken using SPSS 21.0 for Macintosh. Correlations were determined by use of the Pearson's correlation statistic and variances between means were determined by use of the Levene statistic followed by the Dunnett or Bonferoni post hoc testing for multiple comparisons depending on variance significance. Results were considered statistically significant when p-values were below the 0.05 level.

Results

In total, 160 samples of serum PMP concentrations were collected from 107 individuals (66 females) (Table 1). This resulted in 68 male and 92 female serum samples. All had a

diagnosis of focal epilepsy. Mean age was 42 years (range, 18-70 years), and mean body weight was 77 kg (range, 40-125 kg). Body weight measurements were not available for all subjects. The mean PMP concentration for the 160 samples was 353 μg/L (95% CI: 306-403), and ranged 2-1621 μg/L.

For the purposes of data analysis, sera from patients co-prescribed non-enzyme-inducing AEDs, with no influence on CYP3A4/5, as well as samples from those prescribed PMP as monotherapy, were considered to be controls (n=50). Five individuals were on PMP monotherapy (median dose, 6 mg/day) with a mean (± sd) serum PMP concentration of 379 ± 223 μg/L.

PMP concentrations in the control group (Group A) exhibited dose linearity as determined by Pearson correlation analysis (0.621 $p<0.0003$; Figure 1). Linear analysis, however, did not identify any gender or age effect on PMP serum concentrations ($p=0.421$ and $p=0.393$ respectively).

Table 2 summarizes the mean PMP serum concentrations and the PMP serum concentration versus dose ratios (CDRs) in the different groups. Compared with sera from those not prescribed enzyme-inducing or enzyme-inhibiting AEDs (Group A), mean PMP serum concentrations in sera from patients co-prescribed enzyme-inducing AEDs (Group B) were significantly lower (500 ± 326 versus 217 ± 20 μg/L; $p < 00005$). The CDR values followed the same pattern.

Mean PMP serum concentrations in sera from individuals co-prescribed valproic acid, a known inhibitor of CYP enzymes (Group C), were not significantly different compared to sera from those not prescribed enzyme-inducing or enzyme-inhibiting AEDs (Group A). Consequently, comparing mean PMP serum values in Group B with that of patients co-prescribed valproic acid, Group B had significantly lower mean serum PMP concentrations ($p<0.05$). The presence of both an enzyme-inducing AED and that of valproic acid resulted in lower mean serum PMP concentrations although this did not achieve statistical significance.

In order to investigate the specific effects of individual AEDs on PMP serum concentrations, samples were sub-grouped according to which single enzyme-inducing AED was co-

prescribed. If patients were co-prescribed more than one enzyme-inducing AED, they were excluded from the analysis. As a result of these criteria, no samples were identified so as to investigate the effect of either phenobarbital or primidone; both AEDs are known to be potent enzyme inducers. For carbamazepine 28 samples were identified, for oxcarbazepine 31, phenytoin 8 and topiramate 3. Compared to control samples (50), the mean PMP concentration in those co-prescribed carbamazepine was 69% lower (mean PMP concentration 134.9 μg/L; range 105.6-159.5 μg/L; 95% CI -77% to -58%). Those co-prescribed oxcarbazepine, the mean serum PMP concentration was 37% lower (mean PMP concentration 262.2 μg/L; range 222.7-301.7 μg/L; 95% CI: -54% to -21%). Topiramate and phenytoin, mean serum PMP concentrations were not significantly lower than that of control group samples, however values were lower. Topiramate was associated with an 18% decrease in the mean PMP concentration (95% CI: -62% to 25%) whilst phenytoin was associated with a 13% decrease in PMP concentrations (95% CI: -57% to 31%). The data for carbamazepine and oxcarbazepine are illustrated in Figure 2 which show a dose-dependent effect with correlation coefficients of -0.642 ($p<0.005$) and -0.528 ($p<0.005$) respectively.

Figure 3 shows the relationship between PMP dose and serum PMP concentrations in 3 individuals who had been sampled on 3 separate occasions for TDM and were co-prescribed different concomitant AEDs. For each, PMP exhibited linear pharmacokinetics with PMP serum concentrations increasing with increasing PMP dose. The PMP serum concentrations achieved in subject 3, who was not co-prescribed enzyme-inducing AEDs, were substantially higher than for subject 1 who was co-prescribed the enzyme-inducing AED carbamazepine (a potent inducer) and subject 2 who was co-prescribed 2 enzyme-inducing AEDs, oxcarbazepine and phenytoin (moderate inducers).

Lastly, as animal data suggested that lamotrigine and levetiracetam can decrease PMP serum concentrations by 38% and 17% respectively[14] and as these AEDs are often prescribed, we sought to evaluate these potential interactions in our cohort. We identified 13 patients who were co-prescribed lamotrigine and 20 co-prescribed levetiracetam. No other AED was co-prescribed to these. Compared to mean serum PMP concentrations achieved in controls, neither lamotrigine nor levetiracetam had a significant effect on mean serum PMP concentrations (mean PMP concentration: 358.7 μg/L and 342.1 μg/L, range 54.0-945.0 μg/L and 2.0 -1143. μg/L, respectively).

Discussion

PMP dose both in terms of mg/day and mg/kg/day are linearly related to serum PMP concentrations (r^2 =0.481, p=0.0004 for mg/day vs r^2 =0.714, p=0.0001 for mg/kg/day) and these data are in agreement with those reported by Gidal et al.[7] Dose linearity is an important characteristic as this allows straightforward dosing strategies and it aids the prediction of the effect of dose titration and adjustment which may improve treatment outcome.

There is a significant relationship between increases in PMP serum concentrations and reduction in seizure frequency.[7] Increases in serum PMP concentrations may also be associated with increases in PMP-related adverse effects.[7] Also, efficacy increases with increasing PMP serum concentrations regardless of whether or not enzyme-inducing AEDs are co-prescribed.[15] This characteristic supports the strategy of dosing PMP to clinical effect guided by TDM. The current putative therapeutic range for PMP is 180-980 μg/L.[4] With regards to PMP TDM, the fact that PMP has a long half-life (48 hours), which consequently only necessitates once a day dosing, means that diurnal oscillations of serum PMP concentrations is minimal and therefore samples can be collected at any time during a dosing interval. Furthermore, the long-half life of PMP means that missing a dose should have a minimal effect on serum PMP concentrations; although consequent to the extensive metabolism of PMP in patients co-prescribed enzyme-inducing AEDs, serum PMP concentration may decline to a clinically significant extent [7] and in this setting the missed dose should be ingested upon identification of a missed dose.

An important challenge in the management of patients with epilepsy is firstly the recognition of drug-drug interactions and secondly undertaking the appropriate adjustment of doses so as to circumvent the often undesirable outcome.[16,17] At present, PMP is given as add-on therapy and therefore it is important to consider potential drug interactions. Indeed, like many AEDs, PMP appears to be susceptible to such interactions and this was first highlighted in the pooled population pharmacokinetic analysis of 969 patients with partial epilepsy who participated in three Phase III randomized clinical trial studies. Mean PMP AUC values in patients co-prescribed carbamazepine decreased by 67%, whilst those co-prescribed oxcarbazepine decreased by 50%. In those co-prescribed phenytoin and topiramate mean PMP AUC values decreased by 50% and 20% respectively.[4] Our present data, derived from a TDM database, corroborate the published population data in terms of magnitude of the different individual AEDs and their relative effects. Thus, carbamazepine has the strongest inducing effect

whereby its co-prescribing resulted in a mean 69% lower PMP serum concentration (n=23). Oxcarbazepine co-prescribing (n=25) resulted in a mean 37% lower PMP concentration. With regards to topiramate (n=3) and phenytoin (n=8), mean serum PMP concentrations were 18% and 13% lower compared to that of control group samples; but these data did not achieve statistical significance probably because the sample size was small. For carbamazepine and oxcarbazepine, their effect on decreasing PMP serum concentration was linearly related to their respective doses (r^2 = -0.642, $p<0.005$; r^2 =-0.531, $p<0.005$ respectively). These drug interactions appear to be unidirectional because *in vitro* PMP does not have a significant effect on isoenzymes responsible for the metabolism of carbamazepine, oxcarbazepine, phenytoin or topiramate[4].

Valproic acid, at clinically relevant concentrations, is a potent competitive inhibitor *in vitro* of CYP2C9 with only a slight effect on CYP2C19 and CYP3A4 activities.[18] In addition, clinical data indicate that it is a potent inhibitor of UGT1A4 activity.[19] Consequently, valproic acid inhibits the metabolism of numerous AEDs including phenytoin, phenobarbital and lamotrigine and raises their serum concentrations. Since VPA has only a slight inhibitory effect on CYP3A4, the principal isoenzyme responsible for the metabolism of PMP, it is not surprising that serum PMP concentrations were unaffected by valproic acid co-administration (Table 2).

Recently published animal (rat) data report that lamotrigine and levetiracetam can decrease PMP serum concentrations by 38% and 17% respectively.[14] However, it should be remembered that rats may metabolize AEDs via different isoenzymes, they exhibit faster metabolism and also higher drug doses are often required in rats so as to achieve serum AED concentrations typically achieved clinically.[20] In the present study, 13 and 20 patients were identified respectively who were co-prescribed lamotrigine and levetiracetam only, and not on any concomitant enzyme-inducing AED. Compared to mean serum PMP concentrations achieved in those not prescribed enzyme-inducing AEDs, neither lamotrigine nor levetiracetam had a significant effect on mean serum PMP concentrations. Our data are not surprising bearing in mind that neither lamotrigine or levetiracetam are known to affect CYP3A4 isoenzyme activity and corroborate the lack of effect of these two AEDs (n=357; n=330 respectively) reported in the population pharmacokinetic evaluation of the three Phase III randomized clinical trial studies.[4]

Analysis of PMP oral clearance values in the 1,478 subjects that participated in the three phase III studies by gender, showed that females (n=759) exhibited a mean 17% lower clearance than that of males (n=719).[6] Our data, based on steady-state PMP serum concentrations did not show any gender differences (mean ± sd): 490±344 μg/L (n=75; all patients); 501±344 μg/L (n=28; males); 484±347 μg/L (n=46; females) for Groups A+C combined. Other AEDs which exhibit gender differences with regards to their pharmacokinetics include lacosamide,[21] lamotrigine,[22] pregabalin,[23] clobazam,[24] valproic acid, [25] carbamazepine,[26] ethosuximide[27] and rufinamide.[28] Other AEDs have not been systematically studied in this regards.

It is particularly interesting to examine the cases in which multiple PMP doses and blood samples were available for analysis (Figure 3). All 3 exhibited PMP linear pharmacokinetics despite their different co-prescriptions. What is particularly noteworthy is that the slope of the curve of subject 3, who was not co-prescribed an enzyme-inducing AED, was particularly steep compared to subjects 1 and 2 who were co-prescribed enzyme-inducing AEDs. Interestingly, it would appear that co-prescribing two relative weak enzyme-inducing AEDs (oxcarbazepine and phenytoin) has approximated the same effect on PMP serum concentration as occurs with a strong enzyme-inducing AED (carbamazepine).

Conclusion

Our analyses of a PMP TDM database shows that PMP exhibits dose linearity, that concentrations were age and gender independent but were significantly affected by co-prescribed AEDs. Enzyme-inducing AEDs such as carbamazepine and oxcarbazepine resulted in lower mean PMP serum concentrations compared with those not co-prescribed such AEDs. Lower serum PMP concentrations were also observed in those co-prescribed phenytoin and topiramate, but possibly because of small serum number, these effects did not achieve statistical significance. These data concur with earlier published population pharmacokinetic data that PMP clearance can be enhanced by enzyme-inducing AEDs.

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Table 1: Sera and clinical characteristics.

Number of subjects	107
Number of sera	160
Gender (male/female)	41/66
Age (years) Mean: Range:	 41 18-70
Seizure type Partial seizures: Partial seizures with secondary Generalization:	 83 24
Body weight (kg) Mean: Range: Number of subjects with documented body weight:	 77 40-125 92
PMP dose (mg/day) Median: Range:	 6 2-12
PMP dose (mg/kg/day) Median: Range:	 0.08 0.019-0.331
Number of concomitant AEDs (samples) Group A: PMP monotherapy: Non-enzyme-inducing/non-enzyme-inhibiting AEDs in combination (CLB, CZP, ESM, GBP, LEV, LTG, LCM, PGB, RTG, VGB, ZNS): Group B: Enzyme-inducing AEDs: CBZ: OXC: PB: PHT: TPM: PRM: Group C: Enzyme-inhibiting AEDs: VPA: Group D: Enzyme-inducing and enzyme-inhibiting AEDs:	 5 45 74 31 35 7 22 3 5 25 11

CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; LCM, lacosamide; OXC, oxcarbazepine;

PMP, perampanel; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; PRM, primidone; RTG, retigabine; TPM, topiramate; VPA, valproic acid; VGB, vigabatrin; ZNS zonisamide.

Table 2: Mean serum perampanel (PMP) concentrations and serum PMP concentration versus dose ratios (CDRs) in the different groups.

Group	n-value	Mean PMP concentration (μg/L)	Group comparison	Mean PMP concentration difference (μg/L)	p-value
A	50	500 ± 326			
B	74	217± 201	A vs B	-283*	P<00005
C	25	468± 384	A vs C	-32	P=1.00
D	11	340± 167	A vs D	-160	P=0.166
	160		B vs C	251*	P<0.028
Group	n-value	Mean PMP CDR	Group comparison	Mean PMP CDR	p-value
A	29	6016± 3613			
B	38	2369± 2128	A vs B	-3648*	P=0002
C	19	7116± 3741	A vs C	1099	P=0.891
D	6	3407± 1569	A vs D	-2610	P=0.063
Total n	91		B vs C	4747*	P=002

* = statistically significant difference

A = control group (patients on PMP monotherapy + those not prescribed enzyme-inducing or enzyme-inhibiting antiepileptic drugs [AEDs].
B = patients co-prescribed enzyme-inducing AEDs
C = patients co-prescribed enzyme-inhibiting AEDs
D = patients co-prescribed both enzyme-inducing and enzyme-inhibiting AEDs

Figure Legends

Figure 1: Correlation between PMP dose (mg/kg) and PMP serum concentrations (μg/L) in Group A (PMP control group, n=29) and Group B (co-prescribed enzyme-inducing AEDs, n=38). (Group A; $r^2 = 0.621$; p=0.0003; Group B; $r^2 = 0.325$, p=0.046)

Figure 2: The relationship between PMP dose (mg/day) and PMP serum concentrations (μg/L) in the PMP control group (n=50), patients co-prescribed carbamazepine (n=31, mean dose: 1186 mg, range: 400-2200) and patients co-prescribed oxcarbazepine (OXC; n=35, mean dose: 1398 mg, range: 450-3100 mg). Co-prescription with carbamazepine (CBZ) resulted in lower PMP concentration values (mean: 135 μg/L; range 10-428 μg/L) compared to co-prescription with OXC (mean: 262 μg/L; range: 2-912 μg/L).

Figure 3: Relationship between perampanel (PMP) dose (mg/day) and PMP serum concentrations (μg/L) in 3 individuals co-prescribed different antiepileptic drugs (AEDs). For each PMP exhibited linear pharmacokinetics with PMP serum concentrations increasing with PMP dose (r^2 values were 0.983, 0.784 and 0.971 respectively). The slope of the curves was dependent on concomitant AEDs – Subject 1 (a female, aged 42, weight 73 kg) was co-prescribed carbamazepine (a potent enzyme inducer of CYP3A4) and clobazam; Subject 2: (a male, aged 36, weight 82kg) was co-prescribed phenytoin (an enzyme inducer of CYP3A4), oxcarbazepine (an enzyme inducer of CYP3A4) and levetiracetam; Subject 3 (a female, aged 40, weight 70 kg) co-prescribed valproic acid and clobazam (neither AED is known to have an effect on CYP3A4 isoenzymes).