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Influence of seasonal variation and gender on anti-epileptic drugs pharmacokinetics

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Summary. Therapeutic drug monitoring of anti-epileptic drugs is widely used for the management of epilepsy and to avoid treatment ineffectiveness or to explain the onset of adverse events. In this study, we explored the role of months and seasons of withdrawal for the plasma quantification of oxcarbazepine, lamotrigine, phenytoin and levetiracetam pharmacokinetics and the prediction of the outcome cut-offs. One hundred and seventy-five adult patients were enrolled. Drugs plasma concentrations were measured by HPLC-UV methods. We reported that oxcarbazepine concentrations in autumn and winter were higher than those registered in spring and summer. In a logistic regression model, warm seasons have been considered as predictive factors of a negative therapeutic range. If we separately evaluate males and females, the influence of seasons on oxcarbazepine concentration remains only in male patients, also considering the logistic regression analysis. No factors significantly influenced lamotrigine, phenytoin and levetiracetam concentrations or were considered in regression models as predictive factors of treatment outcomes. These results suggest for the first time the effect of seasons on oxcarbazepine. Applying a seasonal- and sex-specific approach should be the key to optimize treatment in each patient, in each period of their life.

Keywords. Sex, gender pharmacology, epilepsy, oxcarbazepine, 10-OH-carbazepine, vitamin D.

Introduction

Epilepsy defines a wide group of central nervous system disorders, characterized by sudden seizures, which determine the alteration of the brain integrative activity pattern. However, its exact etiology is still subject of debate. Different factors have been associated with epilepsy: brain trauma, stroke, brain cancer, drug and alcohol abuse and genetics. Different antiepileptic drugs with different molecular targets have been developed, and many of them cause adverse events or treatment failure. The reasons for treatment-related toxicity could be drug overexposure, due to an inappropriate dosage or to abnormal elimination. Treatment ineffectiveness could be related to a lower dose or, possibly, to drug resistance or patient non-adherence.

Therapeutic Drug Monitoring (TDM) is an important approach to determine drug concentrations, while considering the characteristic of each single patient, to diagnose drug intoxication, to assess therapy adherence, to reach the therapeutic range, to avoid drug-drug interactions, to revise dose regimens in patients with renal or hepatic failure, to monitor drugs' plasma concentrations with non-linear kinetics, to understand any differences in clinical characteristics and for the adjustment of the administered dose, particularly during pregnancy, in elderly patients, after significant changes in body weight or during children growth.[1] Among the factors associated to the treatment outcome, sex and gender seem to play a key role. Gender differences in epileptic seizure susceptibility and the distribution of circadian seizures have been already demonstrated.[2] Moreover, it has been observed that the onset frequency and severity of spasms is higher in winter and in winter-born subjects; the incidence of spasms in children increases in the days of the year with less daylight hours.[3-5] While evaluating drugs, circannual rhythms have been studied in animals, and a reduced effectiveness has been reported in late winter and early spring.[6] Based on these observations, we investigated whether sex and seasons could play a role in oxcarbazepine, lamotrigine, phenytoin or levetiracetam pharmacokinetics and in the prediction of the outcome cut-offs.

Patients and methods

Patients and inclusion criteria

We performed a monocentric study in adult patients with one or more focal onset seizure or generalized tonic-clonic seizures treated with oxcarbazepine, lamotrigine, phenytoin or levetiracetam.

The study protocol ("*PkPG_N03A. Studio retrospettivo di valutazione farmacocinetica e farmaco-genetica dei farmaci antiepilettici*", registration number 138/2016) was approved by the local Ethics Committee of the San Luigi Gonzaga University Hospital in Orbassano (Turin, Italy). A written informed consent for the study was obtained from each subject. Data available were sex, age, drug administered and date of withdrawal for TDM.

Pharmacokinetics analysis

Plasma drug concentrations were evaluated from samples collected at the end of the dosing interval (C_{trough}). Blood samples were centrifuged at 2,500 rpm for 10 minutes and plasma was stored at -20 °C before the experiments. Drug concentrations were determined using a high performances liquid chromatography system, coupled with an ultraviolet detector (HLPC-UV). To quantify oxcarbazepine and 10-OH-carbazepine metabolite, lamotrigine and phenytoin, a simple protein precipitation extraction procedure was applied. To the plasma samples (500 µL), 50 µL of internal standard (phenytoin 50 µg/mL for oxcarbazepine, 10-OH-carbazepine metabolite and lamotrigine protocols and oxcarbazepine 50 µg/mL for phenytoin) and 750 µL of methanol (HPLC grade, VWR, Milan, Italy) were added; after centrifugation, the surnatant was injected in the HPLC system. Chromatographic separation was achieved on a C18 (5 µm) reversed phase column (LiChroCART, Merck KGaA, Darmstadt, Germany) and eluate (50 µL of injection) was monitored at 220 nm, with 16 minutes of analytical run (1 mL/min). The mobile phase consisted of 70% solvent (water with 0.1% triethylamine – VWR, Milan, Italy – adjusted to a pH value of 7) and 30% acetonitrile (HPLC grade, VWR, Milan, Italy). The lower limit of quantification for oxcarbazepine and 10-OH-carbazepine metabolite, lamotrigine and phenytoin is 0.625 µg/mL.

To quantify levetiracetam, the ClinRep® HPLC Complete Commercial Kit (RECIPE, Munich, Germany) was used. The lower limit of quantification for levetiracetam is 0.46 µg/mL.

Statistical analysis

Kruskal-Wallis test has been used to evaluate the influence of months and seasons on pharmacokinetics. Mann-Whitney test has been used to evaluate the influence of cold seasons (autumn and winter) and warm seasons (summer and spring) on pharmacokinetics. Spring runs from March 21 to June 21; summer runs from June 22 to September 22; autumn runs from September 23 to December 22; winter runs from December 23 to March 20. Significant differences of drug concentrations in different seasons were determined by Games-Howell comparison test. The considered level of statistical significance was p value <0.05. Any predictive power of the considered variables was finally evaluated through univariate logistic (considering therapeutic range) regression analysis. Dependent variable was therapeutic range: drug concentrations included in the range and concentrations under or over the defined range; independent variables were: age, sex, warm seasons and cold season.

All the tests were performed with IBM SPSS Statistics 25.0 for Windows (Chicago, Illinois, USA).

Results

Study population

One hundred and seventy-five adult Italian patients treated with levetiracetam (Table 1), oxcarbazepine (Table 2), lamotrigine (Table 3) and phenytoin (Table 4) were enrolled.

Effect of months and seasons on oxcarbazepine concentrations and treatment outcomes

Performing the Kruskal-Wallis test, we observed that seasons (p = 0.049, Figure 1, upper figure) affected oxcarbazepine concentrations: in autumn (N = 12; median 14.44 µg/mL, interquartile range - IQR - 9.88-16.57 µg/mL) and winter (N = 12; median 14.70 µg/mL, IQR 12.31-19.49 µg/mL), drug concentrations are higher than those reported in spring (N = 10; median 10.61 µg/mL, IQR 7.18-14.09 µg/mL) and summer (N = 11; median 11.53 µg/mL, IQR 8.80-14.83 µg/mL). According to the results of the Games-Howell test, the concentrations of oxcarbazepine in spring and summer (p = 0.999) and in winter and autumn (p = 0.853) were statistically the same (Figure 1, lower figure).

With the Mann-Whitney test, seasons were merged and the obtained p-value was 0.007 (Figure 2), thus confirming the previous difference: in autumn and winter (N = 24; median 14.70 µg/mL, IQR 12.15-16.82 µg/mL) drug concentrations are higher than in spring and summer (N = 21; median 11.53 µg/mL, IQR 8.20-14.59 µg/mL). In the logistic regression model, warm seasons (summer and spring) have been considered as predictive factors for obtaining a negative therapeutic range (p = 0.007; odds ratio = 0.162; 95% CI = 0.043-0.607).

Evaluating male and female patients separately, we observed the influence of seasons on oxcarbazepine concentration only in males (p = 0.014): in cold seasons (N = 14; median 15.01 µg/mL, IQR 11.92-17.52 µg/mL) drug concentrations are higher than in warm seasons (N = 8; median 9.40 µg/mL, IQR 6.18-11.57 µg/mL) (Figure 3). Also, in the male population the logistic regression model reported that warm seasons were predictive factors for obtaining a negative therapeutic range (p = 0.010; odds ratio = 0.039; 95% CI = 0.003-0.453).

Effect of months and seasons on lamotrigine, phenytoin and levetiracetam concentrations and on treatment outcomes

No factors significantly influenced lamotrigine, phenytoin and levetiracetam concentrations, or were considered in the regression analysis as predictive factors of treatment outcomes.[7,8]

Table 1. Demographic, clinical and pharmacokinetic characteristics of patients undergoing levetiracetam treatment

Levetiracetam	**N = 72 (41.1%)**
Gender	
Male, n (%)	26 (36.1)
Female, n (%)	46 (63.9)
Age (years)	
Median (IQR)	66.8 (44.52-73.16)
Ethnicity	
Caucasian, n (%)	72 (100)
Other, n (%)	0
Month of withdrawal	
January, n (%)	2 (2.8)
February, n (%)	5 (6.9)
March, n (%)	6 (8.3)
April, n (%)	8 (11.1)
May, n (%)	6 (8.3)
June, n (%)	8 (11.1)
July, n (%)	5 (6.9)
August, n (%)	9 (12.5)
September, n (%)	11 (15.3)
October, n (%)	7 (9.7)
November, n (%)	3 (4.2)
December, n (%)	2 (2.8)
Season of withdrawal	
Autumn, n (%)	14 (19.4)
Winter, n (%)	13 (18.1)
Spring, n (%)	21 (29.2)
Summer, n (%)	24 (33.3)
Drug concentration	
Median µg/mL (IQR)	17.46 (12.01-34.53)
Therapeutic range	
$C_{through}$ <10 µg/mL, n (%)	13 (7.4)
$C_{through}$ ≥10 AND ≤40 µg/mL, n (%)	46 (26.3)
$C_{through}$ >40 µg/mL, n (%)	13 (7.4)

Table 2. Demographic, clinical and pharmacokinetic characteristics of patients undergoing oxcarbazepine treatment

Oxcarbazepine	**N = 45 (25.7%)**
Gender	
Male, n (%)	22 (48.9)
Female, n (%)	23 (51.1)
Age (years)	
Median (IQR)	51.67 (38.86-60.82)
Ethnicity	
Caucasian, n (%)	45 (100)
Other, n (%)	0
Month of withdrawal	
January, n (%)	5 (11.1)
February, n (%)	2 (4.4)
March, n (%)	4 (8.9)
April, n (%)	4 (8.9)
May, n (%)	2 (4.4)
June, n (%)	5 (11.1)
July, n (%)	2 (4.4)
August, n (%)	4 (8.9)
September, n (%)	4 (8.9)
October, n (%)	2 (4.4)
November, n (%)	6 (13.3)
December, n (%)	5 (11.1)
Season of withdrawal	
Autumn, n (%)	12 (26.7)
Winter, n (%)	12 (26.7)
Spring, n (%)	10 (22.2)
Summer, n (%)	11 (24.4)
Drug concentration	
Median µg/mL (IQR)	13.19 (9.52-16.25)
Therapeutic range	
$C_{through}$ <12 µg/mL, n (%)	18 (10.3)
$C_{through}$ ≥12 AND ≤35 µg/mL, n (%)	27 (15.4)

Table 3. Demographic, clinical and pharmacokinetic characteristics of patients undergoing lamotrigine treatment

Lamotrigine	**N = 35 (20.0%)**
Gender	
Male, n (%)	6 (17.1)
Female, n (%)	29 (82.9)
Age (years)	
Median (IQR)	35.85 (26.72-73.71)
Ethnicity	
Caucasian, n (%)	35 (100)
Other, n (%)	0
Month of withdrawal	
January, n (%)	6 (17.1)
February, n (%)	4 (11.4)
March, n (%)	1 (2.9)
April, n (%)	0
May, n (%)	3 (8.6)
June, n (%)	3 (8.6)
July, n (%)	1 (2.9)
August, n (%)	2 (5.7)
September, n (%)	5 (15.3)
October, n (%)	4 (11.4)
November, n (%)	2 (5.7)
December, n (%)	4 (11.4)
Season of withdrawal	
Autumn, n (%)	13 (37.1)
Winter, n (%)	11 (31.4)
Spring, n (%)	5 (14.3)
Summer, n (%)	6 (17.1)
Drug concentration	
Median µg/mL (IQR)	2.89 (2.03-5.30)
Therapeutic range	
$C_{through}$ <3 µg/mL, n (%)	20 (11.4)
$C_{through}$ ≥3 AND ≤15 µg/mL, n (%)	15 (8.6)

Table 4. Demographic, clinical and pharmacokinetic characteristics of patients undergoing phenytoin treatment

Phenytoin	**N = 23 (13.1%)**
Gender	
Male, n (%)	20 (87.0)
Female, n (%)	3 (13.0)
Age (years)	
Median (IQR)	57.04 (53.94-66.14)
Ethnicity	
Caucasian, n (%)	23 (100)
Other, n (%)	0
Month of withdrawal	
January, n (%)	2 (8.7)
February, n (%)	1 (4.3)
March, n (%)	2 (8.7)
April, n (%)	1 (4.3)
May, n (%)	3 (13.0)
June, n (%)	3 (13.0)
July, n (%)	2 (8.7)
August, n (%)	2 (8.7)
September, n (%)	3 (13.0)
October, n (%)	1 (4.3)
November, n (%)	1 (4.3)
December, n (%)	2 (8.7)
Season of withdrawal	
Autumn, n (%)	3 (13.0)
Winter, n (%)	6 (26.1)
Spring, n (%)	7 (30.4)
Summer, n (%)	7 (30.4)
Drug concentration	
Median µg/mL (IQR)	10.41 (7.79-13.40)
Therapeutic range	
$C_{through}$ <10 µg/mL, n (%)	10 (5.7)
$C_{through}$ ≥10 AND ≤25 µg/mL, n (%)	13 (7.4)

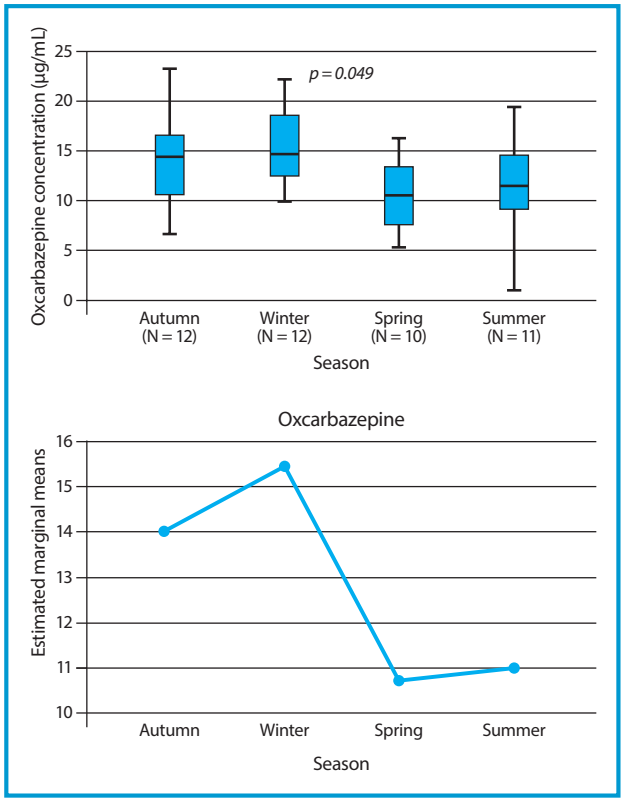

Figure 1. Influence of seasons on oxcarbazepine plasma concentration at the end of dosing interval (C_{trough}) [µg/mL] (p = 0.049).

Upper figure. Box plot of seasonal influence on oxcarbazepine plasma concentration at the end of the dosing interval (µg/mL); boxes and black lines in boxes represent interquartile ranges (IQR) and median values, respectively; open dots and stars represent outlier values. Median values (horizontal line), IQR (bars), patient values (black square), highest and lowest value (whiskers) and p value are shown.

Autumn: N = 12; median 14.44 µg/mL, IQR 9.88-16.57 µg/mL
Winter: N = 12; median 14.70 µg/mL, IQR 12.31-19.49 µg/mL
Spring: N = 10; median 10.61 µg/mL, IQR 7.18-14.09 µg/mL
Summer: N = 11; median 11.53 µg/mL, IQR 8.80-14.83 µg/mL

Lower figure. Statistical analyses by Games-Howell comparison test.

Autumn-Spring standard error: 1.838, p = 0.307, 95% CI: -1,853; 8,435
Autumn-Summer standard error: 2.078, p = 0.485, 95% CI: -2,798; 8,822
Autumn-Winter standard error: 1.778, p = 0.853, 95% CI: -6.374; 3.524
Spring-Summer standard error: 1.995, p = 0.999, 95% CI: -5.906; 5.348
Spring-Winter standard error: 1.679, p = 0.050, 95% CI: -9.429; -0.002
Summer-Winter standard error: 1.940, p = 0.137, 95% CI: -9.900; 1.027

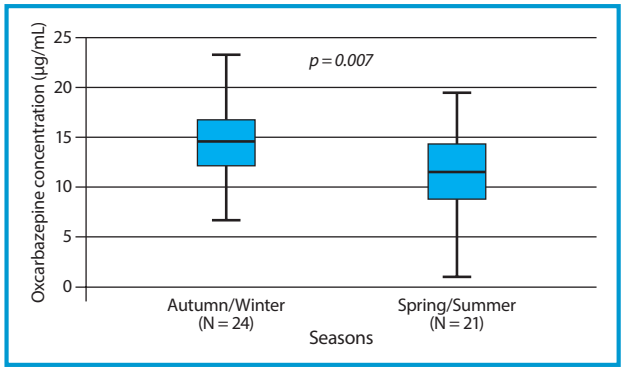

Figure 2. Influence of cold vs warm seasons on oxcarbazepine plasma concentration at the end of the dosing interval (C_{trough}) [µg/mL] (p = 0.007). Box plot of cold vs warm seasons' influence on oxcarbazepine plasma concentration at the end of the dosing interval (µg/mL); boxes and black lines in boxes represent interquartile ranges (IQR) and median values, respectively; open dots and stars represent outlier values. Median values (horizontal line), IQR (bars), patient values (black square), highest and lowest value (whiskers) and p value are shown.

Autumn and winter: N = 24; median 14.70 µg/mL, IQR 12.15-16.82 µg/mL
Spring and summer: N = 21; median 11.53 µg/mL, IQR 8.20-14.59 µg/mL

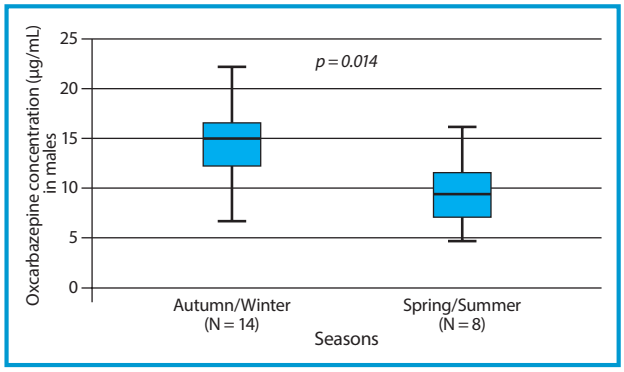

Figure 3. Influence of cold vs warm seasons on oxcarbazepine plasma concentration at the end of the dosing interval (C_{trough}) [µg/mL] in males (p = 0.014). Box plot of cold vs warm seasons influence on oxcarbazepine plasma concentration at the end of the dosing interval (µg/mL) in male patients; boxes and black lines in boxes represent interquartile ranges (IQR) and median values, respectively; open dots and stars represent outlier values. Median values (horizontal line), IQR (bars), patient values (black square), highest and lowest value (whiskers) and p value are shown.

Autumn and winter: N = 14; median 15.01 µg/mL, IQR 11.92-17.52 µg/mL
Spring and summer: N = 8; median 9.40 µg/mL, IQR 6.18-11.57 µg/mL

Discussion

Chronopharmacokinetics studies dosing time- as well as season-dependent changes in the parameters that affect drug pharmacokinetics. In particular, it is related to changes in drug absorption, distribution, metabolism, excretion and effectiveness, as well as adverse reactions (chronodynamics). This is important above all for lipophilic drugs, which reach higher serum concentration and in a shorter time in the morning, due to higher gastrointestinal perfusion rates and faster gastric emptying times during the days with more sunshine. While evaluating the plasma protein binding of drugs, circadian rhythms have been reported for different mood stabilizers, such as valproic acid, 5-fluorouracil, ketoprofen, carbamazepine, diazepam, lidocaine, prednisone and cisplatin, which register the peak plasma concentration during the night. Chronopharmacodynamics studies the variations or rhythmic changes in the susceptibility or

sensitivity of the different targets or sites of action of drugs, such as receptors, cells, tissues or organs. These sites of action have a variable sensitivity, depending on the circadian rhythm, consequently the pharmacodynamic characteristics of a receptor (affinity or intrinsic activity) will depend on the phase where it is within its rhythm of activity. Therefore, the sensitivity of a receptor for the same dose of medication varies according to the time of administration over the 24 hours, due to the circadian nature of the activity of all the biological systems of the organism.[9] Several drugs can produce changes in the circadian rhythms, leading to altered homeostatic regulation. The alteration of the biological rhythm is a new concept in terms of adverse effects. This can be minimized by optimizing the dosing schedule. Moreover, significant sex-related differences in the chronopharmacokinetics of several drugs have been observed in humans.[10] In addition, medical conditions – such as seasonal affective mood disorder, premenstrual dysphoric disorder and depression – could also be, albeit minimally, due to circadian time-keeping abnormalities.[11]

In our study, we observed an influence of seasons on oxcarbazepine concentrations and treatment outcomes. In particular, we reported lower drug concentrations in spring and summer and a lower probability to reach the optimal concentration for the therapeutic range. Evaluating males and females separately, these results persisted only for male patients. For lamotrigine, phenytoin and levetiracetam, no factors statistically affected drug concentrations or were considered in the regression analysis.

Oxcarbazepine is a sodium-channel blocker, used alone or within a combination therapy for partial seizures; 10-OH-carbazepine is its pharmacologically active metabolite. The main pathway of the oxcarbazepine metabolism is via glucuronidation; 28% of the pro-drug is metabolized by cytochrome P450 (CYP). It is rapidly absorbed orally, with a volume of distribution of 0.75 L/kg; the time to maximum plasma concentration is 3-6 hours post-dose; its reported half-life is 8-15 hours. Oxcarbazepine is a CYP3A4 inducer, resulting in a reduced effect of oral contraceptives, and a CYP2C19 inhibitor, determining a higher phenytoin exposure during the combination therapy. The recommended initial daily dose is 150 mg twice a day; the highest dose used is 1,200 mg twice a day. To achieve therapeutic goals, the recommended plasma concentration range is 12-35 µg/mL.[1] The adverse effect reported are: headache, blurred vision, fatigue, diplopia, dizziness, nausea, vomiting, drowsiness, ataxia, rash (probably predicted by human leukocyte antigens-B1502 allele) and hyponatremia. Because of the higher inter-individual variability in plasma exposure and active metabolite concentration, the oxcarbazepine TDM is important to individualize the treatment and to reach the efficacy cut-offs, also considering genetics, sex and body weight. A study by Borowicz et al. reported cholecalciferol (at subject-protective doses) potentiating the effect of oxcarbazepine and lamotrigine, without changing their brain concentrations, suggesting a pharmacodynamics interaction. Aksoy and colleagues observed reduced calcium and 25-OH vitamin-D3 levels in patients treated with oxcarbazepine, compared to the control group.[12] Moreover, an increased duration of oxcarbazepine treatment seems to decrease calcium and calcidiol levels.[13] Since sunlight has a key role in supplying the sufficient amount of vitamin D to the body, these data suggest a possible role of sun exposure on the epilepsy treatment; several studies reported a severe vitamin D deficiency in patients with this disease.[14] Calcitriol is an important immunomodulator that exerts its function through vitamin D receptors (VDR), a transcriptional factor activated by the ligand. In liver, provitamin D (cholecalciferol) is converted to calcidiol by 25-alpha-hydroxylation through the action of a series of hydrolases with different cellular locations; part of calcidiol is then converted by renal 25-hydroxyvitamin D 1-alpha-hydrolase (CYP27B1) into calcitriol, or is inactivated in 24,25-dihydrosivitamin D by 1,25-dihydrosivitamin D 24-hydrolase (CYP24A1). Vitamin D is transported by the vitamin-D-binding protein to different compartments. Antiepileptic drugs reduce vitamin D levels, inducing CYPs: this mechanism is mediated by the pregnane X receptor (PXR) activation, resulting both in the induction of CYP2 and CYP3 and – since PXR and VDR share DNA-binding domains – in the increase of CYP24 expression, thus decreasing the active form of vitamin D levels. In particular, enzyme-inducing drugs, such as phenytoin, carbamazepine and oxcarbazepine, are known to have an induction effect on the CYP system, which determines the catabolism of vitamin D. In the present work, the oxcarbazepine levels are lower in seasons with more sunlight hours. In addition, when we considered gender separately, the seasonal effect is not observed in female patients. Sex differences in drug pharmacokinetics and treatment response and related toxicity have still been reported: in women, factors as body size and composition, hormonal variations, metabolism and access to care systems and therapy could strongly influence treatment outcomes.[15] Considering oxcarbazepine treatment, reduced testosterone, estrogen and progesterone and increased dehydroepiandrosterone and androstenedione levels have been reported.[16-18] Progesterone and estrogens, contrary to androgens, inhibit the liver microsomal enzymes, and progesterone is also an enhancer of the activity of the hepatic enzyme.[19] Lastly, CYP3A4, CYP2A6 and CYP2B6 show a higher activity in women; CYP1A2, CYP2E1 and uridine 5'-diphospho-glucuronosyltransferase showed a reduced activity in females.[20]

The lack of statistically significant results, considering the other drugs, could be probably due to the reduced

number of patients (23 for phenytoin) or to a different distribution of the sample in the different seasons: 27 versus 46 for levetiracetam and 24 versus 11 for lamotrigine, considering winter/autumn and spring/summer, respectively. Another explanation could be the different type of epilepsy of the patients treated; and indeed a correlation between the seizure timing and the localization and semiology of seizures has been proposed.[21,22] It has been noted that generalized seizures tend to happen more frequently in the morning, but temporal lobe seizures seem to happen more frequently in the afternoon, with a possible additional morning peak. Not much data is available for the less frequent occipital and parietal lobe seizures, but they may happen more frequently in the afternoon and in the morning, respectively. Frontal lobe seizures are more common in the early morning.[23-25]

Limitations

Our study was characterized by a few limitations: it was monocentric and retrospective and, despite the large sample size, some correlations were weak. Moreover, data regarding diagnosis, drug dosing, concomitant antiepileptic drugs, seizure frequency and drug co-administration were not collected. Antiepileptic therapy is highly predisposed to drug-drug, drug-dietary and drug-food interactions.[16] It is well known that more than 1,000 drugs and natural products interact whit antiepileptics' pharmacokinetics and/or pharmacodynamics, leading to adverse drug reactions and loss of seizure control.[26-28] Therefore, it is important to study drug interactions, in terms of pharmacological effects and therapy-related patient behaviors. Therefore, an expansion of our analyses is necessary, to better describe our cohort and the data obtained.

Further studies, including body mass index information, female hormonal phase, fat percentage distribution and quantification of cholecalciferol, 25-hydroxicalciferol, 24,25-dihydroxicalciferol and 1,25-dihydroxicalciferol could clarify the data obtained. In addition, a high number of patients and a more frequent drug quantification over the year are warranted, in order to verify our preliminary observations.

Conclusions

These results suggest the effect of sex and seasons on oxcarbazepine therapy. Applying a seasonal- and gender-specific approach could be the key to optimize treatment in each patient, in each period of their life.

Key messages

- Among the factors associated with epilepsy, sex and gender seem to play a key role.
- In males, oxcarbazepine concentrations are higher in autumn and winter.
- Warm seasons have been considered as predictive factors of a negative therapeutic range in both sexes.
- Applying a seasonal- and gender-specific approach could be the key to optimize treatment in each patient, in each period of their life.

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Ethics approval: the study protocol ("PkPG_N03A. Studio retrospettivo di valutazione farmacocinetica e farmaco-genetica dei farmaci antiepilettici", registration number 138/2016) was approved by the local Ethics Committee of the San Luigi Gonzaga University Hospital in Orbassano (Turin, Italy).

Informed consent: a written informed consent for the study was obtained from each subject. Data available were sex, age, drug administered and date of withdrawal for TDM.

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