



Clinical value of saliva therapeutic drug monitoring of newer antiseizure medications

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ABSTRACT

Introduction: Saliva is a promising option for therapeutic drug monitoring, with studies since the 1970s indicating a good correlation between plasma and saliva levels for early anti-seizure medications, although limited data exist for newer generation drugs.

Objectives: To evaluate the reliability and predictive power of saliva as a minimally invasive surrogate marker of plasma concentration for the routine therapeutic drug monitoring (TDM) of newer anti-seizure medications (ASM).

Methods: We collected blood samples at steady state in patients at least 6 h post-dose, paired with unstimulated saliva samples. We evaluated the correlation between plasma and saliva drug levels and the positive and negative predictive value for plasma values extrapolation from saliva levels. A very low saliva level was defined as below half the plasma lower reference limit.

Results: 294 adult patients (53 % male) with a mean age of 40 (SD: 16) were enrolled and 589 paired saliva-plasma samples were quantified. The highest significant correlations between saliva and plasma were observed for zonisamide (R^2 : 0.92) perampanel (0.91), brivaracetam (0.87), followed by topiramate, lamotrigine, lacosamide (0.76–0.68), and rufinamide, levetiracetam, pregabalin (0.63–0.55). No significant correlation was found for the active mono-hydroxy derivative of oxcarbazepine. Despite a good correlation coefficient, the correlations between saliva and plasma levels were generally loose, resulting in a broad predicted range of plasma levels for a given saliva level. Nonetheless, very low saliva levels exhibited strong specificity in predicting low plasma levels, with 87 % to 100 % accuracy, and when saliva levels fell below the limit of quantification, all corresponding plasma levels were below reference ranges.

Conclusions: This large newer ASM paired plasma-saliva collection allows to precise the potential use of saliva in the management of epilepsy, especially for commonly used ASM such as lamotrigine and levetiracetam. Although they correlate well, extrapolating plasma levels from saliva samples is still an imprecise approximation, making it inadequate for fine dosage adjustments. Yet, a very low saliva level has an appreciable discriminative ability for low plasma level. Unstimulated saliva represents a convenient non-invasive alternative to plasma, to readily identify compliance issues or major drug-drug interactions.

1. Introduction

The majority of people with epilepsy (>70 %) are treated with antiseizure medications (ASM) on the long course [1]. In clinical practice, ASM dosage adjustment remains mostly empirical. Therapeutic drug monitoring (TDM or “therapeutic concentration monitoring”),

aims at adjusting the drug dose according to circulating drug levels measured in plasma for achieving pre-defined reference ranges, in which efficacy and tolerability are most likely. The International League Against Epilepsy has proposed specific situations in which TDM is indicated, including doubtful compliance, toxicity issues, suspected drug-drug interaction, or malabsorption [2–4]. Important intra- or

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inter-individual variabilities in pharmacokinetics can be modulated by age, comorbidities, pathophysiological alterations (pregnancy, hepatic or renal impairment), or co-medications that may alter drug metabolism or plasma protein binding [3,5].

Circulating concentrations of ASM determined in plasma are generally used for assessing drug patients' exposure, but alternate biological matrices such as tears, hair, cerebrospinal fluid, dried blood spot, sweat or saliva have been also considered. Among them, saliva has emerged as an attractive matrix for TDM [6,7], as it is non-invasive, and its collection procedure does not require trained medical staff, with potentially favourable economic implications [8]. Yet, the use of saliva for TDM has some issues including unknown or shorter half-life for some drugs as compared to plasma [5], and risk of sample alteration by last ASM pill intake or food residues. There are also technical issues, including sometimes the tedious analyses of small volume of viscous saliva.

The use of saliva for TDM has been evaluated since the 1970s, generally demonstrating a good correlation between plasma and saliva levels for the first-generation ASM like phenytoin and carbamazepine [4]. More recently, studies on correlations between saliva and plasma have been also reported for newer ASM, such as lamotrigine (LTG), oxcarbazepine (OXC) and levetiracetam (LEV) [4,9]. However, there is still a limited number of reports regarding lacosamide (LCM) or topiramate (TPM) [5], and only scarce data for zonisamide (ZNS) [10], brivaracetam (BRV) [11], rufinamide (RUF) [12], pregabalin (PGB) [13], and perampanel (PER) [14,15]. As newer generation ASM are increasingly preferred over older, less well-tolerated options, there is a clear need to examine the strength of correlation between saliva and plasma also for these compounds, and to assess whether saliva constitutes a valid surrogate of plasma in clinical applications [16].

The aim of this study was therefore to correlate paired plasma-saliva specimens in a large panel of newer ASM, and to assess the reliability of using saliva as a tool for TDM during the follow-up of patients with epilepsy. Users of older ASMs were not included in the study due to their small numbers.

2. Methods

Consenting adults with epilepsy were prospectively recruited between June 2016 and December 2018 from our tertiary outpatient ward. Participants for this saliva-plasma sub-study were enrolled either within the frame of a randomized controlled two-arm clinical trial comparing *systematic* versus *rescue* TDM [17], or in a cross-sectional observational prospective cohort study [18], both approved by the local ethics committee (ID: 2015-00799).

2.1. Saliva and plasma sampling

Samples were collected during a steady state, defined as a period occurring after at least five times the plasma half-life of the ASM following the last dosage change. Venous blood samples were collected during the routine visit at least 6 h after the last ASM dosing. Unstimulated saliva samples of 1–2 ml were collected by spitting into a Falcon® tube within 15 min following the venepuncture. Individuals unable or refusing to spit were excluded from the analysis. Visual observation and technical issue were recorded for saliva samples. Published ASM plasma reference ranges are summarised in Table S1 (supplementary material). Thresholds to define very low saliva levels were arbitrary set as lying below half of the lower plasma reference range level of Table S1 (supplementary material).

2.2. LC-MS/MS analysis

The blood and saliva samples were stored at 4 °C before being processed by the laboratory of clinical pharmacology at CHUV, Switzerland. In a pilot study, we showed significant correlation for some ASMs, therefore, in the present study only total ASM levels were measured

[19]. ASM concentrations were measured using modified in-house methods with liquid chromatographic coupled to a triple quadrupole mass spectrometer (LC-MS/MS), (see Tables S1–S2, supplementary material) [20]. Saliva samples were diluted in purified H₂O using a Milli-Q® UF-Plus apparatus (Millipore Corp., Burlington, MA, USA), and protein precipitation with methanol and isotopically-labelled internal standards were used for quantification. Chromatographic analyses were performed using a X-Select HSS T3, 2.1 × 75 mm, 3.5 µm column (Waters, Milford, MA, USA) by applying an 8-min water-acetonitrile gradient program distributed at 300 µl/min on a LC Vanquish pump with a MS/MS detection performed using a TSQ Quantiva (both from Thermo Scientific, USA) (see Tables S2–3 supplementary material). Metabolite of OXC (10-hydroxy-carbamazepine or mono-hydroxy derivative, MHD), were also quantified. Quality control tests demonstrated no significant matrix effect, ensuring specificity, and the laboratory participates in external proficiency programs (<https://www.lgcstandards.com/>) to further validate the accuracy of its analyses. In terms of sensitivity settings, saliva or plasma samples below the lower limit of quantification (LLOQ) were considered as half the LLOQ (see Table S2, supplementary material), the ones undetectable as 0 mg/l, and saliva/plasma (S/P) ratios were excluded in case of undetectable plasma value.

2.3. Statistical analysis

For an initial description, we summarized all data as both percentiles and geometric means, and we calculated saliva to plasma ratios (S/P) for each ASM by dividing the concentration in saliva (C_{saliva}) by the respective simultaneous plasma (C_{plasma}) value, collected within 15 min. To characterise their relationship, we first performed a linear regression of saliva along plasma levels to compute Pearson's correlation coefficient (R) and the coefficient of determination (R^2) for each drug. Chi-squared tests were used to compare categorical variables. To evaluate the prediction performance of saliva levels for plasma concentrations, we estimated a conversion factor relating C_{plasma} with C_{saliva} for each ASM. In this intent, we transformed all values into natural logarithms to normalize their distribution and fitted them with a linear regression forced through zero (Eq. (1)). The conversion factor (F_{conv}) was defined as the intercept of the regression equation on logarithms, assuming a constant slope of 1, (Eq. (2)).

Finally, the antilog of the intercept (i.e. antilog of $\text{Log}(F_{\text{conv}})$) was considered as a rough estimates to predict C_{plasma} based on measured C_{saliva} .

Based on this result, the uncertainty of a single future observation from a population was calculated by the 95 % prediction interval using the standard error of the estimate.

The equations are as follows:

$$C_{\text{plasma}} = C_{\text{saliva}} * F_{\text{conv}} \quad (1)$$

$$\text{Log}(C_{\text{plasma}}) = \text{Log}(C_{\text{saliva}} * F_{\text{conv}}) = \text{Log}(C_{\text{saliva}}) + \text{Log}(F_{\text{conv}}) \quad (2)$$

The described logarithmic regression models between paired plasma and saliva samples were shown on linear data with their corresponding 95 % prediction interval. Calculations and plots were done with GraphPad Prism 3.0 (GraphPad Software, San Diego, CA, USA). Residual graphs were generated with the *QQ plot* function on for visual control (Figure S1).

We finally evaluated the predictive performance of “very low” saliva samples, defined as below half the value corresponding to the plasma lower reference limit, to predict “low” plasma levels, i.e., below the reference range (Table S1, supplementary material). Paired saliva and plasma samples were categorized in 2 by 2 tables into congruent and discordant saliva and plasma samples according to those criteria. Sensitivity, specificity, prevalence, and positive/negative predictive values were calculated for each ASM using the *diagti* function (package *sbe 36.2*) of Stata 14.2 (StataCorp, College Station TX, USA). The same

evaluation was also performed for a saliva threshold as twice the minimum plasma level to predict confidently a plasma concentration within the reference range.

3. Results

A total of 294 patients (53 % male) were recruited between June 2016 and December 2018 (follow-up study: $n = 136$ and cross-sectional study: $n = 158$). Table 1 describes the demographic characteristics of the studies population.

In total, 589 paired plasma-saliva and 586 S/P ratios were analysed in both studies. Only few saliva samples were excluded because of an excessive viscosity of the collected material ($n = 2$), insufficient volume ($n = 5$), or when corresponding plasma level was undetected (plasma $n = 3$). Detailed number of the paired plasma-saliva samples for ASM can be found in Table 2.

Because of its short half-life and the requested minimum delay of 6 h before sampling, 96 % plasma and 57 % saliva OXC samples were either undetectable, or below the LC-MS/MS lower limit of quantification (LLOQ). Therefore, the MHD metabolite levels only was considered in the model.

3.1. Correlation analysis

Fig. 1 and Table S4 (supplementary material) show the linear regression between log-transformed paired plasma and saliva samples plotted on linear scales, and on log scales for LTG and LEV. The highest coefficients of determination were observed for PER (R^2 0.92) and ZNS (R^2 0.91), followed by BRV (R^2 0.87), then TPM (R^2 0.76), LTG (R^2 0.71), LCM (R^2 0.68), RUF (R^2 0.63), LEV (R^2 0.60) and PGB (R^2 0.55). No significant correlation was found for MHD-OXC. For a given saliva level, an important variability in patients' plasma levels was observed for all studied ASM (Fig. 1A). Higher levels were found in plasma than in saliva (i.e. S/P ratio <1 , between 0.03 and 0.83) for LTG, MHD-OXC, PER, PGB and RUF. Conversely, the levels of BRV, LCM and LEV were higher in the saliva than in the plasma compartment (i.e. S/P ratio between 1.2 and 1.7). Finally, the concentrations of ZNS and TPM were similar in both matrices (Table S5, supplementary material). Of note, no time-dependent, nor dose-dependent variations of the S/P ratio were observed in the study (data not shown).

3.2. Plasma prediction and diagnostic performances

Fig. 1 shows the predicted plasma level for a given saliva sample, and Tables S4–5 (supplementary material) illustrate the results of the

Table 1
Patients' characteristics at baseline among those who provided or declined giving a saliva sample with the plasma sample.

Variables	No saliva sample	Saliva sample	Total	Missing / N (%)
n (%)	14 (4.8)	280 (95.2)	294 (100.0)	0 / 294 (0.0)
Age years, mean (sd)	41.9 (15.9)	39.9 (16.2)	40.0 (16.1)	0 / 294 (0.0)
BMI kg/m ² , mean (sd)	26.5 (5.0)	24.7 (4.6)	24.7 (4.6)	29 / 294 (9.9)
Age years, at onset, mean (sd)	27.8 (14.5)	27.6 (19.6)	27.6 (19.3)	21 / 294 (7.1)
Number of previous antiepileptic drugs, mean (sd)	0.7 (0.7)	1.7 (1.8)	1.6 (1.7)	28 / 294 (9.5)
Female, n (%)	8 (5.8)	130 (94.2)	138 (100.0)	0 / 294 (0.0)
Monotherapy, n (%)	5 (3.0)	164 (97.0)	169 (100.0)	0 / 294 (0.0)
Pharmacoresistant epilepsy, n (%)	4 (3.1)	127 (96.9)	131 (100.0)	23 / 294 (7.8)

Table 2

Antiseizure-medication (ASM) saliva-plasma paired sample. Details can be found in Tables S5.

ASMs	Sample nb.	
Brivaracetam	Saliva	10
	Plasma	10
MHD (HO-Oxcarbazepine)	Saliva	23
	Plasma	23
Lacosamide	Saliva	20
	Plasma	21
Lamotrigine	Saliva	223
	Plasma	226
Levetiracetam	Saliva	154
	Plasma	155
Perampanel	Saliva	6
	Plasma	6
Pregabalin	Saliva	43
	Plasma	43
Rufinamide	Saliva	5
	Plasma	5
Topiramate	Saliva	31
	Plasma	32
Zonisamide	Saliva	74
	Plasma	75

regression model including r , R^2 and an extensive study on the level for ASM in a real-life patient setting. A wide range of plasma levels were related to a given level of saliva concentration, resulting in a wide prediction interval for plasma levels. Fig 1B shows the logarithmic regressions between paired plasma and saliva samples, plotted on logarithmic scales for the two most frequent ASM, LTG and LEV with 95 % prediction intervals (95PI). For instance, only LTG salivary levels falling within the range 3–5 mg/l are associated with 95 % probability of finding the corresponding plasma value in the reference range. Conversely, a plasma value in the reference range has 95 % chances to correspond to salivary values in the interval of 0.8–20 mg/l. No salivary levels were found within the 95PI plasma reference range for levetiracetam (Fig. 1B). All ASM scattered plots on log scale are shown in Figure S1.

On the other hand, the defined threshold for a very low saliva level had a fair predictive value for a low plasma level (below the references ranges). For the most abundant ASM namely LTG, 94 % plasma levels were below the reference range when a very low saliva level was identified (see positive predictive value, PPV, in Table 3). The prevalence of plasma levels below reference ranges ranged between 0 and 80 % (Table 3) depending on the ASM considered. Overall, when all ASMs are combined, 165 samples fall into both the very low saliva group and the below reference group (87.8 %). Considering the negative predictive values (NPV, i.e. a saliva level above the defined very low level and a paired plasma level within the reference range), the value of the test is also high for LTG, at 85 %. Sensitivity and specificity of the test for LTG were 0.73 and 0.97, respectively. Table 3 showed all diagnostic test parameters each ASM. The analysis could not be performed for the others ASM as all saliva values fall in a single group after categorisation (PGB, MHD, BRV, PER, RUF) or were insignificant (LCM). Additionally, a second higher threshold was calculated for a saliva plasma level twice the minimum of the reference plasma range. We observed in that case that the sensitivity increased while the specificity decreased. In that case, it is the negative predictive value that is very accurate.

4. Discussion

This study examines the correlation between newer generation ASM concentrations in plasma and saliva within a substantial clinical cohort. Our findings demonstrate a fair correlation between plasma and saliva samples across most ASM, in line with previous studies involving patients on a single ASM or healthy volunteers, albeit with minor differences in correlation values [10–15,21–37]. Discrepancies in correlation

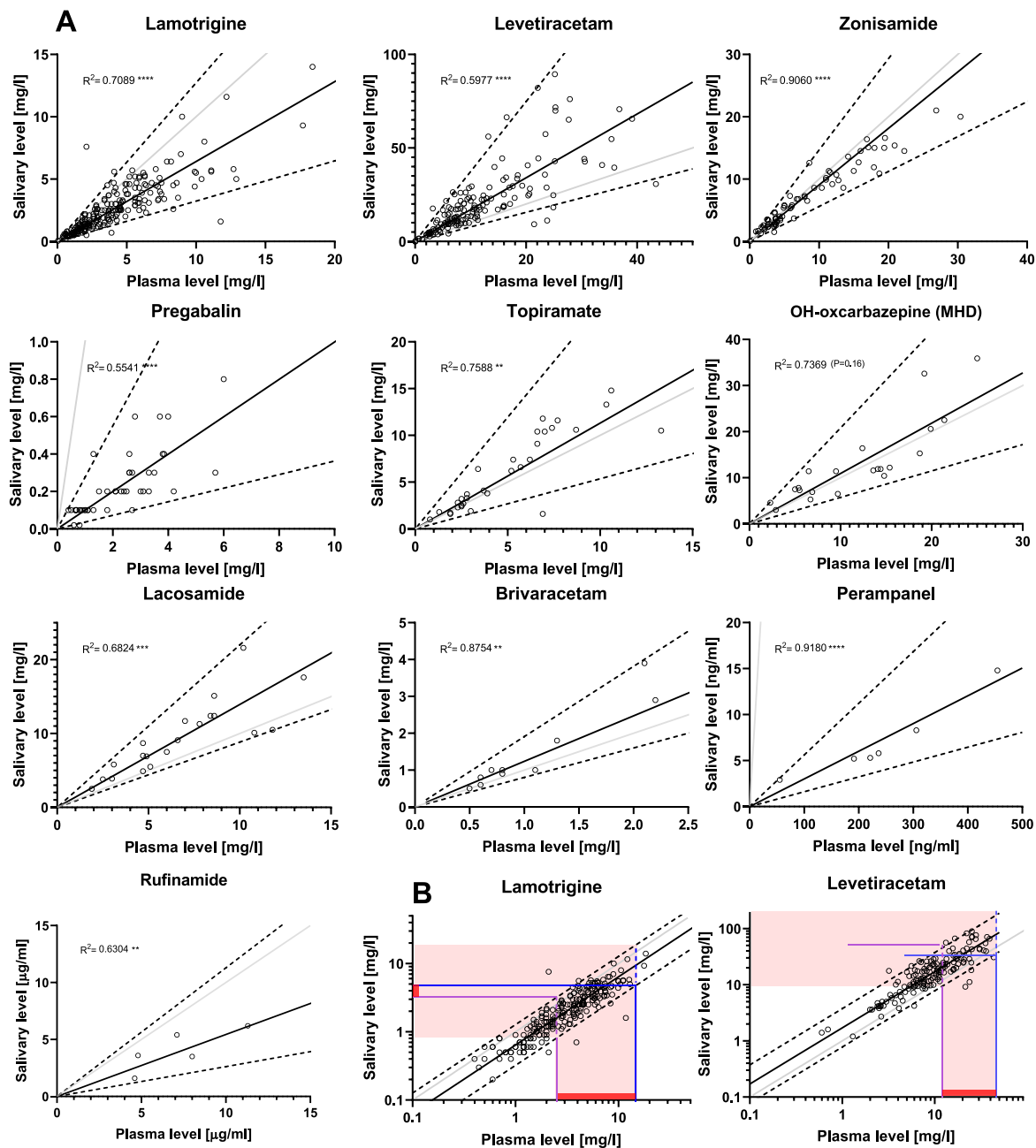


Fig. 1. Scatter plot.

A. Logarithmic regression between paired plasma and saliva samples for the antiseizure medications (ASMs) showed on linear data. The black circles represent the paired plasma and saliva samples. The black line shows the regression performed on log-level transformed data with the 95 % prediction interval (95PI, dotted lines); and, the grey line shows the line of identity. Coefficient of determination (R^2) and P-values (ns: not significant, $P < 0.05$ *, $P < 0.01$ **, $P < 0.001$ ***, and $P < 0.0001$ ****) are showed.

B. The same logarithmic regressions between paired plasma and saliva samples for the ASMs are shown on a log scale data for two ASMs. The x-axis red lines indicate the reported ASMs plasma reference ranges. The red surfaces show the salivary levels compatible at 95 % probability with a plasma value in the reference range. The y-axis red line indicates the salivary concentration interval of lamotrigine reflecting with 95 % certainty a plasma concentration in the reference range. Such an interval does not exist for levetiracetam.

coefficients may stem from variations in the studied population, sample size, timing of sample collection, and analytical techniques. Our study used LC-MS/MS associated with isotopically labelled for ASM quantification, providing high selectivity for discriminating the parent drug from its metabolites and high sensitivity for detecting very low levels of quantification (LLOQs), compared to immunoassays. However, in the case of MHD-OXC, we observed a lack of significant correlation, which may be attributed to factors such as dose-dependent variation in

saliva-plasma concentration, the short half-life of the active metabolite (MHD) [39], and the limited number of samples available. Previous reports have also highlighted a poor predictive value of saliva for MHD [40].

It is widely acknowledged that ASM distribution in saliva primarily occurs through passive diffusion of the unbound drug across tissue cell membranes [4,9,38]. The ASM saliva-to-plasma (S/P) ratios indirectly indicate the extent of drug protein-binding and tend to reflect free

Table 3

Accuracy of the diagnostic test of using different thresholds for low saliva level for the detection of antiseizure medications (ASMs) inferior to the reference range plasma levels. The threshold is defined as A) half the minimum plasma reference range level, and B) twice the minimum plasma reference range level. The ASMs are ordered by their sample size (cf. Table S5). Prevalence of inferior reference range plasma levels is reported for all ASMs. Other statistical tests, including the positive (PPV) and negative (NPV) predicted values could be performed only for ASMs with samples in the different defined categories (cf. Material and Method – Diagnostic). The 95 % confidence intervals are indicated in brackets.

A. Very low saliva level.					
ASMs	Sensitivity (%)	Specificity (%)	Prevalence (%)	PPV (%)	NPV (%)
Lamotrigine	72.7 (62.2–81.7)	97.0 (92.6–99.2)	39.5 (33.0–46.2)	94.1 (85.6–98.4)	84.5 (77.8–89.8)
Levetiracetam	22.8 (15.0–32.2)	100.0 (93.3–100.0)	65.6 (57.5–73.0)	100.0 (85.2–100.0)	40.5 (32.0–49.4)
Zonisamide	70.8 (55.9–83.0)	100.0 (85.8–100.0)	66.7 (54.6–77.3)	100.0 (89.7–100.0)	63.2 (46.0–78.2)
Pregabalin			72.1 (56.3–84.7)		
Topiramate	50.0 (24.7–75.3)	93.3 (68.1–99.8)	51.6 (33.1–69.8)	88.9 (51.8–99.7)	63.6 (40.7–82.8)
MHD			9.5 (1.2–30.4)	.	
Lacosamide	25.0 (7.3–52.4)	100.0 (39.8–100.0)	80.0 (56.3–94.3)	100.0 (39.8–100.0)	25.0 (7.3–52.4)
Brivaracetam			.		
Perampanel			16.7 (0.4–64.1)		
Rufinamide			.		
B. Confidently above threshold saliva level.					
ASMs	Sensitivity (%)	Specificity (%)	Prevalence (%)	PPV (%)	NPV (%)
Lamotrigine	98.9 (93.8–100.0)	17.8 (11.7–25.3)	39.5 (33.0–46.2)	43.9 (36.9–51.2)	96.0 (79.6–99.9)
Levetiracetam	94.1 (87.5–97.8)	71.7 (57.7–83.2)	65.6 (57.5–73.0)	86.4 (78.5–92.2)	86.4 (72.6–94.8)
Zonisamide	100.0 (92.6–100.0)	4.2 (0.1–21.1)	66.7 (54.6–77.3)	67.6 (55.5–78.2)	100.0 (2.5–100.0)
Pregabalin			72.1 (56.3–84.7)		.
Topiramate	100.0 (79.4–100.0)	60.0 (32.3–83.7)	51.6 (33.1–69.8)	72.7 (49.8–89.3)	100.0 (66.4–100.0)
MHD	100.0 (15.8–100.0)	94.7 (74.0–99.9)	9.5 (1.2–30.4)	66.7 (9.4–99.2)	100.0 (81.5–100.0)
Lacosamide	100.0 (79.4–100.0)	25.0 (0.6–80.6)	80.0 (56.3–94.3)	84.2 (60.4–96.6)	100.0 (2.5–100.0)
Brivaracetam			.		
Perampanel			16.7 (0.4–64.1)		
Rufinamide			.		

Abbreviations: MHD: monohydroxy derivative, the active metabolite of oxcarbazepine, also called 10-hydroxy-carbazepine or 10, 11-Dihydro-11-hydroxycarbamazepine.

plasma concentration [41–43]. For instance, BRV, LCM and LEV concentrate into the saliva compartment (S/P ratio 1.2–1.7), as opposed to MHD-OXC, LTG, PER, PGB and RUF (S/P ratio 0.03–0.83), which concentrate more in plasma, while and TPM, ZNS (S/P ratio 0.9–1.1) seem equally distributed in both matrices (see Table S5, supplementary material). The low S/P ratio of PGB, despite its minimal protein binding in plasma, can be attributed to its zwitterionic nature, facilitating diffusion through membranes with saturable membrane L-amino acid transporters [4]. Our results corroborate previously reported S/P ratios for most ASM [10–15,21–37].

Despite a significant overall correlation between paired saliva-plasma, we observed a considerable inter-sample variability, meaning that a given saliva level may correspond to a wide predicted range of plasma levels (Fig. 1).

This observation holds clinical relevance, as saliva TDM may not be clinically useful in situations where only limited (i.e. ± 50 %) alteration in ASM levels is expected, such as in pregnancy follow-up, moderate pharmacokinetic interactions, or cases of kidney or liver dysfunction. On the other hand, we noted a robust association between very low saliva levels (i.e., half of the lower boundary of the plasma reference range, as shown in Table 3.A) and plasma levels below the reference ranges. This qualitative rather than quantitative approach to saliva TDM may be particularly useful in cases of extreme values, such as severe drug interactions or issues with adherence or malabsorption. In such instances, saliva levels may be more likely to detect clinically relevant deviations.

In this study, we used a pragmatic and convenient approach to saliva collection, involving simple spitting, that is well accepted by patients and healthcare staff [8,44]. This approach is particularly suitable for centres lacking trained personnel and accommodates children and individuals with limited mobility or cognitive impairment. However, it may present challenges for those with low saliva production. Methodologically, using unstimulated saliva avoids potential dilution issues [25,28] and maintains a more natural pH balance compared to stimulated saliva, without influencing the S/P ratio [42]. The stability of ASM concentrations at room temperature [20] allows for convenient sample transportation via surface mail from patients' homes or general

practitioners' offices not equipped with laboratory facilities [41,43]. Saliva sampling is often preferred to blood testing by patients, caregivers and paediatric neurologists [8,44]. The approach used in this study with only 7/589 collected samples discarded for technical reasons, might thus be an interesting option.

Several limitations should be acknowledged. We compared saliva levels with total plasma levels rather than free plasma levels, given the highly significant correlation found in a pilot study on lacosamide, lamotrigine, levetiracetam, topiramate and zonisamide [19]. Free plasma levels are not routinely measured so we used total plasma level as a more widely available comparator for the salivary level. Analysis of free levels might lead to a better correlation between saliva and plasma levels, but this would not reflect on clinical practice. Our method cannot also exclude that saliva samples were contaminated by the presence of residues of orally administered drug or blood smearing from gums. Clinical value of saliva TDM was assessed more thoroughly for lamotrigine and levetiracetam given the greater sample size for these ASMs, limiting the generalisability of our results for the other less represented ASM. These ASM are however the most widely prescribed and those for which TDM need is best established. Lastly, the absence of plasma levels exceeding reference ranges precludes the estimation of PPV and NPV of saliva levels for predicting supratherapeutic plasma exposure or toxicity associations. Further prospective studies are also needed to define ASM salivary pharmacokinetics better, in terms of correlation between salivary and plasma AUC or peak (C_{max}) concentrations and half-life.

5. Conclusion

This large study pairing plasma/saliva levels for newer ASM showed an acceptable correlation between plasma and saliva ASM levels. For all ASM except OXC-MHD, unstimulated saliva can be used to measure saliva level in an outpatient setting. Saliva TDM may be useful for evaluating patient compliance, and possibly for monitoring large deviations of the expected exposure but is not suitable for fine ASM dosage modification.

Author contribution

EC (design, data acquisition and interpretation, analyses, writing and revision), PV (data acquisition and interpretation, writing and revision), IAR (design, data acquisition and interpretation, revision), CS (revision), PA (revision), AOR (design, data interpretation and revision) TB (design, data interpretation, writing and revision), JN (design, data acquisition and interpretation, writing and revision), LAD (design, data acquisition and interpretation, writing and revision).

Declaration of competing interest

All authors declare that they have no conflict of interest.

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Data availability statement

Anonymised data will be shared upon request from any qualified investigator.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.seizure.2025.01.013](https://doi.org/10.1016/j.seizure.2025.01.013).

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