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Research Article

Pharmacological Therapeutic Monitoring of Three Major Anti-Epileptic Drugs in Mali

Mohamed TOURE [1,2], Adama Seydou SISSOKO [2,3], Mahamadou BALLO [1], Sékou BAH [1,2]

[1] Faculty of Pharmacy, USTTB, Mali

[2] Point G University Hospital Centre

[3] Faculty of Medicine and Odontostomatology, USTTB, Mali

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For Correspondence:

Mahamadou BALLO, Faculty of Pharmacy, USTTB, Mali

Abstract

Introduction: Therapeutic drug monitoring is a means of monitoring anti-epileptic treatment. The objective of this study was to conduct therapeutic drug monitoring of the three most commonly prescribed anti-epileptic drugs in Mali.

Methods: This was a cross-sectional, prospective study conducted over an eight-month period. It focused on the pharmacological therapeutic follow-up of carbamazepine (CBZ), phenobarbital (PB), and valproic acid (VPA) in 80 epilepsy patients monitored at the Neurology Department of Point G University Hospital.

Results: The majority of participants were aged between 18 and 70 (65%). Generalised motor seizures were more common (76.20%). Carbamazepine was the most commonly prescribed drug (60.32%), followed by phenobarbital (20.63%) and valproic acid (19.05%). The combination of CBZ/PB was the most commonly observed, at 47.06%. Among patients taking carbamazepine, 2% were underdosed and 23% were overdosed. 75% of patients taking phenobarbital were underdosed. Half of patients taking valproic acid were underdosed and 5% were overdosed.

Conclusion: Pharmacological therapeutic monitoring is an indispensable tool in the management of epilepsy. However, efforts must be made to introduce this practice into routine healthcare in Mali.

Keywords: Therapeutic monitoring, Carbamazepine, Phenobarbital, Valproic acid, Mali.

INTRODUCTION

Epilepsy is a chronic neurological condition characterised by recurrent epileptic seizures in the same individual. These seizures may be related to an imbalance between excitatory and inhibitory neurotransmitters, causing excessive and hyper-synchronous neuronal discharges within the cerebral cortex [1]. The probability of an individual developing epilepsy during their lifetime varies between 3% and 5%. Newborns, children and the elderly are at greater risk of developing epilepsy [1,2,2]. Epilepsy affects approximately 50 million people worldwide, or 1 to 3% of the global population. In the US, the prevalence of epilepsy is estimated at between 330 and 380 per 100,000 inhabitants; in France, it is between 380 and 430 per 100,000 inhabitants; and in Mali, it is between 230 and 280 per 100,000 inhabitants. Sub-Saharan Africa accounts for 80% of the global epileptic population, with a prevalence of 15.4% [1,3].

Antiepileptic drugs are used to reduce the frequency and/or severity of seizures in patients with epilepsy. Most of them have shown significant pharmacokinetic variability. Most of them showed significant pharmacokinetic variability. For this reason, therapeutic drug monitoring, which involves measuring and interpreting drug concentrations in the blood in order to determine the correct dose of medication for a given patient, is recommended [4]. This individualized approach takes into account the specific characteristics of patients or their disease and optimizes treatment by maximizing efficacy and minimizing the risk of adverse effects. Pharmacological monitoring of antiepileptic drugs is most beneficial during treatment initiation, after dose adjustments, in cases of suspected drug interactions or treatment failure, as well as in cases of overdose or the appearance of clinical signs of toxicity [5]. Pharmacological monitoring of first-generation antiepileptic drugs, particularly phenobarbital (PB), carbamazepine (CBZ), and valproic acid (VPA), is already common practice in developed countries for adjusting dosages due to their narrow therapeutic margin and common neurological side effects [5,6]. Numerous studies have shown that plasma concentrations of antiepileptic drugs in some patients fall outside the therapeutic range, leading to treatment failure (due to underdosing) or toxicity (due to overdosing) [7]. In Mali, therapeutic drug monitoring remains rarely used by clinicians due to its inaccessibility

and cost, despite being recommended for most antiepileptic drugs currently used in clinical practice. Nowadays, plasma drug testing in general, and anti-epileptic drug testing in particular, cannot be performed in any of Mali's public hospitals.

METHODOLOGY

This was a prospective descriptive study focusing on the therapeutic drug monitoring of three antiepileptic drugs in epilepsy patients treated at the Neurology Department of Point G University Hospital. The study was conducted over an eight-month.

Data collection

The data were collected from survey forms that included information about the patient, their clinical and biological condition, dosage, and frequency of administration of the measured medication.

Parameters studied

We measured the residual concentrations of carbamazepine, valproic acid, and phenobarbital.

Sampling procedures

Blood samples were collected in EDTA tubes labeled with the patient's first and last name and the date of collection. Samples were taken in the morning, just before the new daily dose of treatment and after steady state had been reached. The samples were centrifuged at 3,000 rpm for 10 minutes and then stored at –20°C.

Analytical technique

The dosage of antiepileptic drugs (carbamazepine, valproic acid, and phenobarbital) was determined using the chemiluminescence immunoassay (CMIA) technique on an Abbott ARCHITECT i1000SR automated analyzer.

Therapeutic ranges

It range from 4 to 12 µg/mL; 50 to 100 µg/mL and 15 to 40 µg/mL for carbamazepine, valproic acid, and phenobarbital, respectively.

Ethical aspects

The Faculty of Pharmacy at the University of Science, Techniques and Technologies in Bamako approved the protocol. The anonymity and confidentiality of the information collected were preserved.

Data analysis

Data entry and analysis were performed using IBM SPSS Statistics version 22.0 software. Qualitative variables were expressed as percentages with numbers of subjects.

RESULTS

Sociodemographic and clinical characteristics of participants

The sociodemographic and clinical characteristics of participants are presented in Table 1. Males were the most represented gender, accounting for 57.50% of participants. 65% of participants were aged between 18 and 70 years. Generalised motor seizures were the most common (76.20%), followed by secondary generalised partial seizures (22.5%) and unspecified seizures or seizures with an unknown onset pattern (1.3%).

Table 1: Sociodemographic and clinical characteristics of participants

Characteristics		Effective	Percentage
Gender	Male	46	57.5
	Female	34	42.5
Age group	[2-12]	14	17.5
	[12-18]	11	13.8
	[18-70]	52	65
	70 and over	3	3
Types of seizures	Generalized motor seizures	61	76.2
	Focal seizures secondarily generalized	18	22.5
	Seizures with unknown onset	1	1.3

Frequency of anti-epileptic drug prescriptions and seizure progression

In most cases, anti-epileptic drugs were prescribed as monotherapy (78.80%). Carbamazepine was the most commonly prescribed drug (60.32%), followed by phenobarbital (20.63%) and valproic acid (19.05%). The combinations of antiepileptic drugs CBZ/PB and CBZ/VPA were observed in 47.06% and 29.41% of cases, respectively. Therapeutic compliance was good for 77.5% of participants. The progression of seizures was favorable in 74% of cases (Table 2).

Table 2: Frequency of anti-epileptic drug prescriptions, therapeutic compliance and seizure progression

Treatment regimen	Molecules	Effective	Percentage
Monotherapy	Carbamazepine	38	47,5
	Phenobarbital	13	16,25
	Valproic acid	12	15
Dual therapy	Carbamazepine/ Phenobarbital	8	10
	Carbamazepine/ Valproic acid	5	6,25
	Valproic acid/ Phenobarbital	3	3,75
Triple therapy	Carbamazepine/Phenobarbital/ Valproic acid	1	1,25
Therapeutic compliance	Good	62	77.50
	Not good	18	22.50
Evolution of crises	Favorable	59	74
	Unfavorable	21	26

Plasma concentrations of antiepileptic drugs

Among participants taking carbamazepine, 75% were receiving the normal dose, 2% were underdosed, and 23% were overdosed. 75% of participants taking phenobarbital were underdosed. Fifty percent of participants taking valproic acid were underdosed and 5% were overdosed (Figure 1).

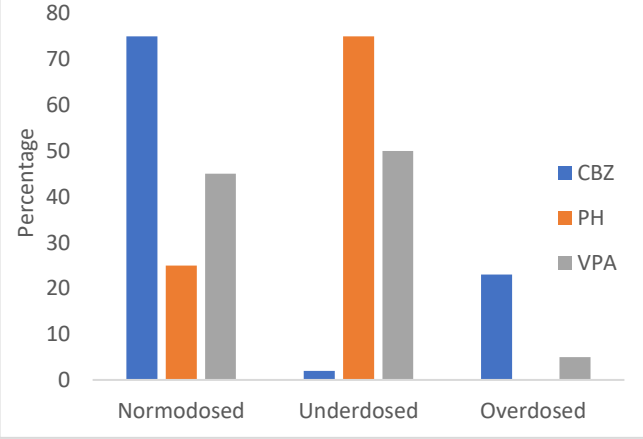

Figure 1: Categories of plasma concentration of antiepileptic drugs

DISCUSSION

At the end of this study, we found that carbamazepine was the most commonly prescribed drug, followed by phenobarbital and valproic acid. These results are consistent with those of Eshiet et al., who found in their study in Nigeria that carbamazepine was the most commonly prescribed drug, with a frequency of 48.37% [8]. However, our results differ from those reported by Gurshaw et al. in a study conducted in Ethiopia, where phenobarbital was the most commonly prescribed drug, followed by phenytoin and valproic acid [9]. In India, a study showed that valproic acid was the most commonly prescribed antiepileptic drug, followed by phenytoin and carbamazepine. These differences could be explained by factors determining the choice of antiepileptic drug, such as age, gender, comorbidities, and type of seizures [10]. In most cases, antiepileptic drugs were prescribed as monotherapy (78.8%). Our results disagree with those of a study on the use of antiepileptic drugs in India, which found that 19% of antiepileptic drugs were prescribed as monotherapy, 55% as dual therapy, and 26% as triple therapy. A study in Nigeria presented slightly similar results, with antiepileptic drugs being used as monotherapy in 54% of cases and as combination therapy in 46% of cases [10,11]. Some authors have reported that, in the management of epilepsy, combination therapy does not offer any significant advantage over monotherapy. It may increase the risk of drug interactions and could affect treatment compliance [12].

Our study showed that 75% of patients taking carbamazepine had plasma concentrations within the therapeutic range, while 23% had concentrations below this range. Grzesk et al. found similar results, with 71.0% of patients having plasma concentrations within the therapeutic range and 24.9% having concentrations below the therapeutic level [13]. However, our results differ from those of Uskur et al. in Turkey, who reported that only 27.4% of patients achieved therapeutic levels[14]. 75% of patients taking phenobarbital had subtherapeutic plasma concentrations; only 25% of them had concentrations within the therapeutic range. Our results differ from those reported by Singh et al. in India, who found that 10% of the population studied had subtherapeutic concentrations and 30% had supratherapeutic concentrations. A study conducted in Iran by Babaei and Eslamai showed that 73% of patients receiving phenobarbital had plasma concentrations within the therapeutic range [15]. Other authors have found similar results. They reported that 41% of patients taking valproic acid had normal plasma concentrations, 45% had lower concentrations, and 14% had higher than normal concentrations [5]. However, the results observed by Ozunal et al. are different. Their study showed that 76.3% of patients receiving valproic acid had plasma concentrations within the therapeutic range; 19.9% had

subtherapeutic concentrations and 3.8% had supratherapeutic concentrations [16]. Poor treatment compliance was observed in 22.5% of patients. This result is comparable to that of other authors, who observed 24% of cases of non-compliance in China and 32% in Peru [17,18].

CONCLUSION

Carbamazepine, phenobarbital, and valproic acid are widely used as first-line treatments in clinical practice in Mali. These molecules have shown significant pharmacokinetic variability. Further studies, particularly pharmacogenetic studies, are needed to better understand this pharmacokinetic variability in Mali.

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