SODIUM VALPROATE AND CARBAMAZEPINE EFFECTS ON IMPULSIVITY IN BIPOLAR PATIENTS

L'IMPULSIVITE CHEZ LES BIPOLAIRES : EFFET DU VALPROATE DE SODUIM ET DE LA CARBAMAZEPINE

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Abstract

Objectives : Sodium Valproate and Carbamazepine are mood stabilizers used as a treatment for bipolar disorder and have an anti-impulsive action. Drugs' blood testing are sometimes recommended to evaluate the therapeutic observance or the intolerance to the treatment. In our study, we are proposed to measure the effect of Sodium Valproate and Carbamazépine on the impulsive dimension of bipolar patients based on the blood tests of these two drugs. Methods: This was a descriptive and analytical cross-sectional study of 30 bipolar patients who have been in remission for at least 3 months. They benefit of monitoring blood tests.
Results : The mean age was 36.1 years with a male predominance of 73.3%. Seventy percent of patients used Sodium Valproate and average dose was 21.9 mg/kg. Thirty used Carbamazepine and average dose was 12.9 mg / kg. The average of the blood level of Sodium Valproate was 47, 51 mg/l .The mean blood level of Carbamazepine was 5,7 mg/l.The change in the impulsivity score is inversely proportional to the blood level of Valproate(r=-0,966) and inversely proportional to the blood level of Carbamazepine(r=-0,696) Conclusion : It seems that Sodium Valproate has a greater anti-impulsive action than Carbamazepine.

Key-words: Bipolar disorder ; Carbamazepine;Impulsivity ;Sodium Valproate

Résumé

Introduction : Le Valproate de sodium et la Carbamazepine sont des thymorégulateurs utilisés dans le traitement du trouble bipolaire et ont une action anti-impulsive. Notre but est de comparer les effets du Valproate de sodium et de la Carbamazepine sur la dimension impulsive chez les bipolaires en se basant sur les dosages sanguins de ces deux médicaments. Méthodes : Il s'agit d'une étude transversale descriptive et analytique réalisée auprès de 30 patients bipolaires en rémission depuis au moins 3 mois. Ils ont bénéficié de dosages sanguins. Résultats : L'âge moyen était de 36,1 ans avec une prédominance masculine de 73,3%. Soixante-dix pour cent des patients étaient sous Valproate de sodium avec une dose moyenne de 21,9 mg/kg, et trente pour cent sous Carbamazépine avec une dose moyenne de 12,9 mg/kg. Tous les patients ont bénéficié d'un dosage de la dépakinémie (taux moyen de 47,51 mg/l) ou de la carbamazepinémie (taux moyen de 5,7 mg/l). La variation du score d'impulsivité est inversement proportionnelle à la dépakinémie (r=-0,966) et inversement proportionnelle à la carbamazepinémie (r=-0,696). Conclusion : Il semble que le Valproate de sodium a une action anti-impulsive plus importante que la Carbamazépine.

Mots-clés : Carbamazépine ; Impulsivité ; Trouble bipolaire ; Valproate de sodium

ملخص

الأهداف: فالبروات الصوديوم وكاربامازيبين هما مثبتات في الحالة المزاجية تستخدم في علاج الاضطراب الثنائي القطب ولها عمل مضاد للاندفاع.في دراستنا، اقترحنا مقارنة آثار فالبروات الصوديوم وكاربامازيبين على البعد الدافع لدى المرضى ثنائي القطب بناءً على اختبارات الدم لهذين الدواءين. الطريقة: هذه دراسة وصفية وتحليلية مستعرضة وقعت عبر دراسة 30 مريضا يعانون من أعراض القطبين والذين كانوا في حالة استقرار ونقاهة لمدة 3 أشهر على الأقل، وقد استفادوا من اختبارات الدم. تم تقييم البعد الدافع باستخدام مقياس الاندفاع بارات BIS11. النتائج: كان متوسط العمر 36.1 عامًا مع غلبة الذكور بنسبة 73.3٪، وكان سبعون في المائة من المرضى معالجون بفالبروات الصوديوم. وثلاثين في المئة بالكاربامازيبين. وكان متوسط الجرعة المقررة من فالبروات الصوديوم 21.9 ملغم / كغم. وكان متوسط الجرعة المقررة من كاربامازيبين 12.9 ملغ / كغ، وتلقى جميع المرضى جرعة من دياكينيميا أو كاربامازيبين. كان متوسط ديباكينيميا 47.51 ملغم / لتر وكان متوسط كاربامازيبين الدم 5.7 ملغم / لتر.التغير في درجة الاندفاع يتناسب عكسيا مع دياكينيميا (ص = -0.966).التغيير في درجة الاندفاع يتناسب عكسيا مع الكاربامازيبين (ص = -0.696).التغيير في درجة الاندفاع يتناسب عكسيا مع الكاربامازيبين (ص = -0.696).
الخلاصة: يبدو أن فالبروات الصوديوم له تأثير مضاد للاندفاع أكبر من كاربامازيبين

الكلمات المفاتيح : كاربامازيبين ; الاندفاع ; الاضطراب الثنائي القطب ; فالبروات الصوديوم

INTRODUCTION

Impulsivity is a behavior found in several psychiatric pathologies, especially in bipolar disorder (BD) – in which it is considered as an exacerbating factor. Indeed, impulsivity is considered as one of the dimensions underlying the link between mental pathology and the risk of violence [1, 2]. As a consequence, prescribing mood-stabilizing drugs is the rule in bipolar disorder. It allows to reduce the frequency, duration, and intensity of mood episodes and to alleviate the quality of symptom-free remission periods. Anti-epileptic drugs, such as Sodium Valproate and Carbamazepine, are widely prescribed as mood-stabilizers [3] with an anti-impulsive effect [4]. However, the narrow therapeutic indexes of Sodium Valproate and Carbamazepine, and their inter- and intra-individual pharmacokinetic interaction variations make their plasma level monitoring primordial, especially in case of an intolerance to treatment and for the assessment of patients' drug adherence [5].
Hence, this study aims to compare the effects of Sodium Valproate and Carbamazepine on the impulsive dimension in bipolar patients based on the blood test levels of these two drugs and the patients' clinical evolution.

PATIENTS AND METHODS

This is a cross-sectional, descriptive and analytical study conducted on outpatients at the Psychiatric C Department of Hedi Chaker University Hospital in Sfax, Tunisia, during the month of April, 2018.
Inclusion Criteria:
Were included all the patients suffering from bipolar disorder under Sodium Valproate or Carbamazepine treatment, who had been in remission for at least 3 months and who presented to the outpatient service of the psychiatric ward C during the month of April, 2018.
Exclusion Criteria:
Were excluded all the patients presenting with psychiatric comorbidities.
For each patient, we collected the sociodemographic and clinical data on a pre-established file. We evaluated:
- Impulsivity using Barratt's scale (BIS11) [6], translated into (Tunisian) dialectal Arabic. It consists of a 30-question auto-questionnaire, exploring the three dimensions of impulsivity (motor impulsivity, cognitive impulsivity and non-planning impulsivity). A score above 72 means a high degree of impulsivity, with the maximum score being at 120.
- Drug adherence using Morisky's 8-item Medication Adherence Scale [7]. A high adherence corresponds to a score of 8, a medium adherence score ranges between 6 and 8, and low adherence is attributed to a score below 6.
The patients have also benefited from Sodium Valproate or Carbamazepine blood tests using the immuno-enzymatic method. These analyses were carried out at the laboratory of pharmacology of the University of Medicine, Sfax, Tunisia.

RESULTS

The mean age of our study population was 36.1 years, with extremes of 22 and 48 years, and a standard deviation (SD) of 6.78.
Our sample included 22 men and 8 women, i.e. a sex ratio (M/W) of 2.75. The patients were single in 73% of the cases and married in 27%.
The patients had a primary school educational level in 36.6% of the cases (n=11), secondary in 40% (n=12), and tertiary in 23% (n=7).
Among our patients, 53.5% were smokers and 40% were alcohol consumers. The patients said they had not consumed any other psycho-active substances.
Only one patient had a somatic history (i.e. 3.3% of the sample). He suffered from diabetes and hypertension.
As far as psychiatric pathologies are concerned, bipolar disorder I (BD I) was diagnosed in 23 patients and BD II in seven. The mean age of onset of the disorder was 28.7 years (SD=6.19). The average duration of evolution of the disease was 7.37 years (SD=5.92).
The average number of previous episodes was 2.8 (SD=1.64). These were manic episodes in 68% of BD type I cases, and depressive episodes in 73% of BD II cases.
Among our patients, 13.3% had previously been taking a mood-stabilizer other than the one taken during the study period. This change in medication came as a result of adverse effects such as an important weight gain and digestive problems following Sodium Valproate intake, and dizziness and drowsiness for Carbamazepine. The latest mood episode occurred, on average, 2.5 years earlier (SD=2.5). It is manic in 50% of the cases, hypomanic in 6.7%, mixed in 10%, and depressive in 33%.
According to Morisky's scale [7], twenty-four patients had a high therapeutic adherence. A medium adherence was observed in 3 patients,

while the remaining 3 patients' adherence was qualified as low. Twenty-one patients were under treatment with Sodium Valproate, and 9 were taking Carbamazepine. The average dosages are reported in Table I.

The average duration of treatment intake was 5.43 years (SD=5.08). In our sample, 58.6% of the patients were on mood-stabilizing mono-therapy. Neuroleptic intake was recorded in 17.2% of the cases, against 24.1% for atypical neuroleptics.

Twenty patients, among whom 14 were on Valproate and 6 on Carbamazepine, had blood concentration levels within the therapeutic range. Nine had blood levels below the therapeutic range, and only one had a level below the therapeutic range. Average Valproate blood concentration was at 47.5mg/l (SD=22.49%) while that of Carbamazepine was at 5.7mg/l (SD=2.9).

In our sample, all the patients had high impulsivity scores across all three dimensions (Table II).

The statistical analysis showed that the variation in the impulsivity score is inversely proportional to Valproate and Carbamazepine blood concentration levels by, respectively, (r=-0.966; p=0.000 and r=-0.696; p=0.037), which implies a stronger link between Valproate blood concentration levels and impulsivity.

Indeed, among the patients whose dosages are within the therapeutic ranges (N=20), those who were on Valproate (N=14) had impulsivity scores lower than the scores of patients on Carbamazepine (N=6) (75.93% versus 89.50%; p=0.011).

Patients with high drug adherence levels, according to Morisky's scale, had the lowest impulsivity scores compared to less adherent patients (with medium to low drug adherence scores according to Morisky's scale) (81.35% versus 96.00%; p=0.000).The other variables – especially sex, age, educational level, intake of psychoactive substances, type of bipolar disorder, evolution of the disease, dominant polarity, type of the last episode, and the prescribed mood-stabilizer dosage – did not correlate with the impulsivity score.

Table I : Mean doses of Sodium valproate and carbamazépine

	Mean doses in mg/j	Standard Deviation	Mean doses in mg/kg/j	Standard Deviation
sodium Valproate	1547,61	357,23	21,9	5,26
Carbamazépine	1044,44	296,27	12,9	3,20

Table II: Impulsivity scores

	middle score	Standard Deviation	minimum score	High impulsivity scores
Impulsivity scores	84,77	10,43	72	104
motor impulsivity	31,17	2,57	27	35
cognitive impulsivity	19,77	5,36	14	28
non-planning impulsivity	33,83	4,78	25	42

DISCUSSION

Our results are consistent with the results of other studies. A study conducted by Swann et al. [8] on 10 BD I patients who did not present any depressive or manic episodes for 3 months, against 12 healthy controls, concluded to an impulsivity score which is significantly higher in bipolar patients than in controls, in all three dimensions.

In 2006, the study by Peluso et al. [9], carried out on 24 depressed bipolar patients, 12 euthymic bipolar patients, 10 euthymic unipolar patients, and 51 healthy controls, showed that the latter had a BIS11 score significantly lower than that of the other groups in the three dimensions of impulsivity.

In 2011, another study [10], conducted on 71 patients with bipolar disorder in clinical remission, found out that bipolar patients were more impulsive than the control group in all the studied dimensions of impulsivity.

In one meta-analysis of 17 studies with 1469 participants – using Barratt's BIS11 – over a period ranging from 1980 to 2012, 15 studies found an increase in the total score of impulsivity in the bipolar group in comparison to the control group. Only two studies reported negative results. Concerning the three dimensions of Barratt's scale, the majority of the studies have shown that the high level of impulsivity concerned all three of them [2].

In our work, we have addressed impulsivity amongst bipolar patients in clinical remission. This impulsivity is commonly known as "Trait Impulsivity" in patients suffering from bipolar disorder. The relatively high level of impulsivity found in euthymic bipolar patients could be a constant parameter in bipolar disorder and not a simple manifestation of the mood patient's state. Impulsivity could be a consequence of frequent acute episodes or due to a biological risk factor of the disorder. This dimension could influence the clinical presentation of the disease, as well as its treatment, since high impulsivity during a euthymic phase could lead to a low therapeutic adherence, which could in turn lead to an adverse outcome [10, 11].

Other studies [12, 13] addressed the "impulsivity state" which is present during decompensation periods. According to these studies, "impulsivity state" and "trait impulsivity" would be associated in perpetual continuity in bipolar disorder.

As far as age is concerned, it does not seem to be a factor correlated to impulsivity scores in our study; a result which was also reported in a study by Ekinci et al. [10].

Other studies have found that age could increase the non-planning impulsivity score on the Barratt scale without increasing the total impulsivity score [1].

Overall, it seems that young people have a greater tendency toward impulsivity than older patients. These controversial findings would be explained by the heterogeneity of the studied populations and impulsivity degrees [6].

In our study, sex was not correlated to impulsivity, either, which is consistent with the majority of the studies that made no distinction between the two sexes [10]. The most frequently cited hypothesis is that sexual hormones would not be involved in the pathogenesis of impulsivity [14].

As far as education is concerned, we did not find a correlation between the level of education and impulsivity. This finding is in line with the results of a study by Ekinci et al. [10]. Another study [1] found a low inverse correlation between the level of education and impulsivity. However, overall, these studies have noted that bipolar patients had a lower level of education compared to the control group [10].

Furthermore, there was no correlation between impulsivity scores and psychoactive substance intake. This finding contradicts the results of other studies [2, 15, 16] which have found that the patients who consumed psychoactive substances had higher impulsivity scores compared to non-consumers. Our small sample size might explain this divergence. The high levels of impulsivity found in psychoactive-substance consumers could be explained by neuronal lesions caused by these substances [17].

In contrast to the findings of Swann et al. [1], our study has shown that the age of the patient at the onset of the disorder does not seem to influence impulsivity scores, which is in line with Ekinci's findings [10]. If there were a link between the level of impulsivity and the early age of onset, it would be due to other factors such as increased substance abuse, suicidal behavior etc. [1]

In our study, the duration of the disorder was not correlated to the impulsivity scores. Other researchers [1, 10] have found an increase not only in the non-planning impulsivity score but also in the overall impulsivity score according to Barratt's scale. These studies [1, 10] have suggested that the duration of the complaint could affect the different aspects of impulsivity through biological and neuro-anatomic modifications.

The number of previous episodes was not correlated to impulsivity in our study, unlike what

was reported by Jiménez et al. who stated that the number of previous episodes was in correlation with higher scores of impulsivity [18]. The reason behind this increase would most likely be the lesions caused to the neurons by the recurrence of acute episodes [1].

Our study has shown that the dominant polarity during the previous episodes was not correlated to impulsivity scores. Ekinci's study, on the other hand, showed that bipolar patients suffering from depression had significantly higher scores on all impulsivity scales. In fact, most of the studies conducted on this subject are cross-sectional, thus, it is not possible to determine with precision the factors correlated with high impulsivity scores or to distinguish between the impact of the previous episodes and the predominance of a particular polarity with respect to the inherent characteristics of the patient himself/herself [1].

In contrast to Dervic's study [19], which reported that BD I patients had higher impulsivity scores than those suffering from BD II, we have found no correlation between impulsivity scores and the type of BD; our small sample size could explain this disagreement. In fact, several explanations may be suggested to establish a link between BD I and impulsivity. Psychoactive-substance intake, eating disorders and unemployment would be more frequent among BD I patients than among BD II patients, and these factors would also be correlated to a higher level of impulsivity [18]. Moreover, BD I patients have significantly higher scores on the BPRS (Brief Psychiatric Rating Scale, which evaluates the global functioning of subjects), thus, suggesting that the alteration in the global functioning in BD I would be associated with impulsivity.

BLOOD TESTS AND MOOD-STABILIZERS

Many studies [20] have shown the importance of determining the concentration levels of Sodium Valproate and Carbamazepine in the blood given their narrow therapeutic range (50-100 mg/l for Sodium Valproate, and 4-10 mg/l for Carbamazepine) [21], the significant intra- and inter-individual variability of their pharmacokinetics depending on the patient's age, his/her physio-pathological condition, and the numerous drug interactions [5, 22].

Overdose signs could show as soon as the plasmatic concentrations of the drug exceed the therapeutic range [21]. These signs include: consciousness disorder, asthenia, anorexia and abdominal pain – due to a liver disease – for Sodium Valproate; and neuromuscular, cardiovascular (tachycardia, bradycardia, hypotension, atrio-ventricular conduction disorders) and respiratory disorders for Carbamazepine [23,24]. A retrospective study [25] about blood-level tests for Sodium Valproate, Carbamazepine and Phenobarbital, carried out between April 1995 and April 2015, has shown that the requests for such blood tests remain low in comparison with the number of patients on epileptic drugs. The motives behind these blood-test requests were mainly the occurrence of adverse effects and doubts on drug adherence.

However, some studies [5,26] have shown that the therapeutic monitoring of drugs used in psychiatric treatments is a vital tool which is used to optimize them given the variation of the drug metabolism in the body due to pharmaco-genetic and environmental factors. For the particular case of mood-stabilizers, the pharmacological therapeutic monitoring would be a means to manage their side effects, to detect over- or under-dosing in the concentration levels of these substances in the blood – which could be due to age or caused by other physiological and/or pathological factors – and to evaluate patients' drug adherence [25].

In our study, 80% of the patients had a good adherence to treatment. Overall, patients' adherence in bipolar disorders is often insufficient, thus, leading to mood relapses. The pretexts spontaneously brought up by the patients to justify their poor drug adherence concern mainly the lack of information about the disease and the treatment, the drug's sedative effect, its extended effect duration, the fear of drug dependency, the denial of the disease, and forgetfulness [27].

Drug adherence could be accessed through blood tests, even though the latter might be limited by pharmacokinetic biases and the considerable inter-individual variability. In our study, the most drug-adherent patients had the lowest impulsivity scores compared to the least adherent. This finding has already been reported by other studies. Impulsivity would thus be associated with poor drug adherence [28].

In our study, we assessed the effects of Sodium Valproate and Carbamazepine on impulsivity. Several studies have confirmed the anti-impulsive action of these two antiepileptics [29].

Several hypotheses have been put forward in order to explain their neurobiological effect on impulsivity.

Impulsivity is due to a reduction in serotonin transmission reflected in the lack of cerebral serotonin levels in impulsive subjects.

Recent findings show that impulsivity scores may increase when dopamine acts on the nucleus accumbens and that it may decrease when it acts on the orbitofrontal cortex. Other hypotheses now suggest that the decrease in glutamate transmission could be involved in impulsivity symptoms, focusing on the particular role of the pre-frontal medial cortex [30].

These mood-stabilizers act on the neurotransmissions that are involved in the pathogeny of impulsivity. Sodium Valproate adjusts the transmission of dopamine, serotonin and glutamate [31]. Carbamazepine is also known to act on the serotonergic, glutamatergic, and dopaminergic systems [3].

One meta-analysis [4] carried out in 2011, with the purpose of evaluating the efficacy of mood-stabilizers as a treatment for aggressivity and impulsivity in adult patients, has shown a significant reduction in these two symptoms among patients treated with Phenytoin, Lithium and Carbamazepine but there was no significant decrease in patients on Valproate or Levetiracetam. However, many studies included within this meta-analysis had inclusion and methodological biases. Some statistical analyses which included only studies with rigorous methodology have reported that there was not any significant advantage of one mood-stabilizer over another when it comes to aggressivity or impulsivity management [4].

In this study, the variation in the impulsivity score was inversely proportional to Valproate and Carbamazepine blood concentration levels.

The studies that investigated the relationship between blood concentration levels and clinical response yielded inconsistent results. The study by Allen et al. [32] that included 374 patients suffering from BD in the acute phase of mania showed the existence of a linear link between Valproate serum concentrations and the therapeutic response, and that Valproate concentration levels in the blood should be above 94mg/l for a better response during a manic episode.

A study by Chbili et al. [33] which included 13 patients on Carbamazepine in clinical remission showed that the optimal thymo-regulatory action was reached with Carbamazepine plasma concentrations of around 7mg/l. several hypotheses could explain this divergence of results, such as the heterogeneity of subjects, sample sizes, and dosage techniques [32, 34].

The link between the average dosages of the prescribed drugs, blood concentration levels and anti-impulsive effect has been addressed in Stanford's study [34] (Table III).

In our work, the prescribed dosages were well above those prescribed in this study. However, the blood concentration levels reported in both studies were rather similar.

In Stanford's study [34], an anti-impulsive action was reached even with sub-therapeutic threshold blood concentration levels. Similar results have also been found in previous studies (31).

The variation found in Sodium Valproate and Carbamazepine blood concentration levels would be related to the patient's genetic profile. Several studies, one of which is Tunisian, have also come to the same conclusion [33, 35]

Table II: the relationship between dosage, serum concentartion of valproate sodium and carbamazepine and their anti-impulsive effect

	Number of patients take Valproate	Number of patients take Carbamazépine	Mean dose of Valproate (mg/j)	Mean dose of Carbamazépine (mg/j)	Serum concentration of sodium valproate (mg/l)	Serum concentration of Carbamazepine (mg/l)	Comparison of the effect of Valproate and Carbamazepine on the impulsive dimension
Stanford's study 2005 [34]	7	7	450	750	39,2	4,3	Same effect on impulsivity but the effect of Carbamazepine is delayed compared to Valproate
Our study, 2018	21	9	1547	1044	47 ,5	5,7	Valproate would be more effective than Carbamazepine on the impulsive dimension

CONCLUSION

Measures aiming at reducing impulsive behavior among bipolar patients – including the prescription of mood-stabilizers, psychotherapeutic management, and the identification of at-risk patients – could significantly help optimize the quality of life of BD patients. This study yielded results that highlight the importance of Sodium Valproate and Carbamazepine blood test levels given their narrow therapeutic range, the significant intra- and inter-individual variability of their pharmacokinetics, and their extensive drug-drug interactions. An inversely proportional relationship between blood concentration levels and impulsivity scores was found to be much more important for Sodium Valproate in comparison with Carbamazepine. The anti-impulsive effect of these mood-stabilizers could be dependent on the genetic profile of the patients, which might explain this discrepancy in the different studies' results concerning the link between mood-stabilizer intake and anti-impulsive effect. To confirm this, further pharmaco-genetic studies focusing on the anti-impulsive effect of mood-stabilizers on large samples have to be carried out.

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