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Journal of Pharmacology & Clinical Toxicology

Research Article

Amitriptyline Pharmacokinetics in Algerian Patients with Depressive Disorders: A Low Cyp2d6 Activity?

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Submitted: 15 May 2017

Accepted: 11 July 2017

Published: 15 July 2017

ISSN: 2333-7079

Keywords
- Amitriptyline
- Depressive disorders
- Therapeutic monitoring
- CYP2D6 system
- Interaction

Abstract

Rationale: There is a lack of knowledge about the therapeutic monitoring in the field of psychopharmacology in Algerian patients with depressive disorders.

Objectives: The aim of this work was to apply a therapeutic monitoring of Amitriptyline for Algerian patients with depressive disorders to follow the steady state plasma concentrations of Amitriptyline and its metabolite Nortriptyline, appreciate the influence of the association with neuroleptics and compare CYP2D6 activity among Algerian patients compared to those reported in the literature.

Materials and methods: A prospective study was conducted in 36 Amitriptyline- treated Algerian patients suffering from depressive disorders. Blood samples are collected 12 to 14 hours after taking the medication in case of a single daily dose, and 4 to 6 hours if divided dose. The determination of Amitriptyline and Nortriptyline concentrations is ensured by using the Chromsystems® chromatographic system.

Results: More than two thirds of the patients are outside of the therapeutic range. The study of the interaction of the Amitriptyline with neuroleptics shows that the latter inhibit CYP2D6 system involved in the hydroxylation of the Amitriptyline. Also, our study reveals a low activity of CYP2D6 system in Algerian patients, something to confirm with specific tests (e.g., debrisoquine test).

Conclusion: The therapeutic monitoring of Amitriptyline allows psychiatrists to optimize the dose and avoid concentration changes due to individual differences and drug interactions (case of associations to neuroleptics).

ABBREVIATIONS

ICD: International Classification of Diseases; AMT: Amitriptyline; NT: Nortriptyline; IMHC: Intermediate Mental Health Centres; SPE: Solid Phase Extraction; CID: Concentration/Dose ratio; CD: Concentration-Dose; WFMH: World Federation for Mental Health

INTRODUCTION

Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. Today, depression is estimated to affect 350 million people [1]. According to WHO, it will be the second leading cause of diseases and handicaps in the world in 2020. Because depression is expensive: lower profitability, reduced motivation, work stoppages, overconsumption of consultations, medicines and hospitalization [2]. In Algeria, an epidemiological study in the general population, carried out in Algiers in 2003, showed that 13% of the population (one Algerian out of ten) suffer from mental trauma or depression [3]. The hospital management remains below of needs, with a psychiatrist for 60,000 people, and a lack of processing means and therapeutic management of patients.

An early management of depression is very beneficial on evolution, but only a third of depressed persons consult within three months after the onset of signs. In addition to psychotherapy and electroconvulsive therapy, the chemotherapeutic treatment provides a considerable assistance to severe depression. Currently, chemotherapy of depression uses antidepressant

medications, generally alone or associated to neuroleptics. Among the antidepressants, Amitriptyline (AMT) (tricyclic antidepressant) is widely used because of its effectiveness and low cost compared to newer antidepressants [2]. AMT has a narrow therapeutic window with significant risks of severe drug interactions (e.g., neuroleptics) [4]. In addition, it can cause many troublesome side effects (hypotension, cardiac disorders) in case of over dosage [5].

Therapeutic drug monitoring is a reliable tool to optimise psychopharmacotherapy. When used adequately it is helpful for many psychiatric patients and in many situations [6-9]. The studies have shown a significant influence of the CYP2D6 genotype on plasma concentrations of patients taking mainly second-generation antidepressants [10,11], and it was demonstrated that monitoring therapy of tricyclic antidepressant drugs in combination with determination of the genotype seems to be more safe and effective [12,13].

The aim of our study was to apply a therapeutic monitoring of AMT in Algerian patients with depressive disorders to follow the steady state concentrations of amitriptyline and its metabolite Nortriptyline (NT), calculate the metabolic ratio NT/AMT, appreciate the influence of the association with neuroleptics and compare CYP2D6 activity among Algerian patients compared to those reported in the literature.

MATERIALS AND METHODS

Subjects

A prospective study was conducted from January to June 2011 at three Intermediate Mental Health Centres (IMHC) (IMHC of Boufarik, OuledYaïch and Bouarfa - Blida). A total of 36 algerian patients suffering from depressive disorders treated with AMT were monitored. Diagnostic confirmation of depressive episodes is based on the ICD-10 criteria, the degree of severity of depression and its evolution over time are specified by hetero (Hamilton test) or self-assessment scales. A completed information sheet based on the patient's medical file containing the patient data: age, sex, medical status, therapeutic regimen and medical history.

Blood sampling and analysis of AMT and NT

Blood samples are collected in a 5 cc dry tubes, 12 to 14 hours after taking the medication in case of single daily dose, and 4 to 6 hours in the case of divided dose. The blood is centrifuged at 3000 rpm for 5 min, the serum was collected in polypropylene tubes, because the tricyclic antidepressant may absorb on glass surfaces. Samples were stored at -20°C until the day of analysis.

The Chromsystems® reagent kit (Chromsystems Instruments & Chemicals GmbH: The determination of AMT and NT concentrations is ensured by using the chromsystems reagent kit that includes all the material necessary for analysis by HPLC (column, guard column, SPE cartridges, mobile phase, calibrators, quality controls, internal standard, sample treatment and extraction reagents), as well as the operating protocol and the chromatographic conditions. This kit allows the quantitative determination of tricyclic antidepressants and their metabolites in the serum / plasma by HPLC.

HPLC instrumentation and chromatographic conditions: Chromatographic analyses were performed with a Thermo (France) liquid chromatograph equipped with a diode array detector (*FINNING, Spectrasystem UV 6000LP*), A Rheodyne injector with a loop of 50µl, a quaternary pump (*SpectrasystemP1000XR*), A degasser (*SC Spectrasystem M1000*) and a thermostated column compartment (*Eppendorf CH-500*). The mobile phase was run at a flow rate of 0.6 ml / min and the chromatogram was monitored at 210 nm.

Statistical methods: Statistical analyses were conducted with IBM SPSS Statistics (Ver 21.0).

RESULTS AND DISCUSSION

Patient profile

Table 1 shows the two groups of patients classified according to the association with neuroleptics, the group I: patients with association with neuroleptics, Group II: patients without association with neuroleptics. This table lists the characteristics of the patients (age, sex, dosage (*mg/d*), dose (*mg/kg/d*)), the analysis results of blood samples (AMT Concentration, NT Concentration, Total Concentration (AMT+NT)). Also, the following parameters were calculated for both groups: metabolic ratio (NT / AMT), ratios concentration / dose (CID) for the AMT (CID AMT) and NT (NT CID).

Serum concentrations of AMT and NT

The results show variations in total plasma concentrations (AMT + NT). Indeed, if we refer to the limits of the therapeutic range which is between 50 - 250 ng/ml [14], the patients can be classified into three groups: Patients correctly dosed with 38.88%; Patients under-dosed with 44.45% and Patients over-dosed with 16.67%.

The range of used doses is very wide, which probably cause an important variation in the concentrations of AMT and NT. It is found that about two thirds of patients are outside of the therapeutic range with a tendency to under-dosing. These results give an idea about the therapeutic regimen adopted by psychiatrists, they try to give a dosage based on the patient's clinical condition and the treatment duration; which is insufficient for having adequate plasma concentrations knowing the interindividual variability of pharmacokinetic parameters and essentially AMT metabolism. Four patients in the group of under-dosed-patients have zero plasma concentration (n° 2,10,22,33). In general, these patients are in the acute phase of the disease (acute psychosis), and do not take their medication through ignorance or negligence.

Patients with higher concentrations generally receive a high dose (mg/kg), but can also be the result of the combination with a metabolic inhibitor, is the case of neuroleptics responsible for the inhibition of hydroxylation of the AMT and its metabolite (NT) by CYP2D6 system. Among over-dosed patients, four exceed 300 ng/ml (n° 6,7,23,34) as a result of a high dose. The patient n°23 with the highest concentration 873.42 ng/ml, has received 0.88 mg/kg, also as a result of the association with neuroleptics especially phenothiazine-like drugs. These patients should be screened for side effects, by searching some signs of AMT toxicity (cardiac arrhythmia, hypotension, etc.).

Table 1: Characteristics of the subjects.

	Mean (Min–Max) or Numb. Patients		
	Group I	Group II	*P*
Numb. samples	27	9	
Age (yrs)	44.67 ± 2.16 (26–71)	49.28 ± 4.22 (39–65)	NS
Gender (male/female)	11/16	3/6	NS
AMT dosage (mg/d)	26.04 ± 3.34 (7–75)	27.28 ± 6.36 (6–50)	NS
AMT dose (mg/kg/d)	0.34 ± 0.04 (0.12–0.8)	0.37 ± 0.07 (0.11–0.71)	NS
AMT concentration (ng/mL)	83.59 ± 24.9 (7.94–521.05)	50.38 ± 25.5 (7.76–191.81)	NS
NT concentration (ng/mL)	85.46 ± 21.6 (8.82–352.37)	30.78 ± 10.7 (4.21–83.29)	0.032
Total Concentration (AMT+NT) (ng/mL)	169.05 ± 45.1 (20.23–873.42)	81.15 ± 35.2 (11.97–275.10)	NS
AMT CDratio [(ng/mL)/(mg/kg)]	217.12 ± 38.2 (22.06–639.48)	115.79 ± 40.3 (18.32–270.15)	NS
NT CDratio [(ng/mL)/(mg/kg)] *	239.40 ± 52.7 (29.4–889.24)	75.35 ± 18.5 (17.32–142.70)	0.007
NT/AMT concentration ratio	1.18 ± 0.17 (0.38–3.72)	0.96 ± 0.33 (0.43–2.92)	NS

* The concentration of NT is corrected relative to the dose of AMT. A significant correlation was found between these two parameters (P=0.001).
N.B: Patients with nil concentration of AMT or NT were excluded in the calculation of AMT and NT mean concentration, CID AMT, CID NT, ratio NT / AMT. We think about a treatment adherence problem.
Statistical tests: t-test for the comparison of averages, the Pearson chi-square test for the comparison of percentages.
Abbreviations: AMT: Amitriptyline; NT: Nortriptyline; CID: Concentration/Dose ratio; NS: Not Significant; yrs: years.

Table 2: Appreciation of CYP2D6 activity.

Study	Concentration/Dose Ratio	Reference
	In (ng/ml)/(mg/kg)	
El-Yazigi	46.1 ± 6.5	[16]
Our study	115.79 ± 40.3	--
	In (ng/ml)/(mg)	
Baumann	0.68	[22]
Laurent	1.12	[21]
Vandel	1.01	[20]
Pfuhlmann	1.57	[7]
Jungkunz and Kuss	0.81	[22]
Beyer-Pfaff	0.67	[22]
Kupfer	0.73	[22]
Our study	2.09	--

We classified data by gender in group I, the results show that overdosed patients are represented by women in 83% (5 of 6), with a higher concentration (average 193.18 ng/ml) compared to men (average 129.83 ng/ml), but the difference was not significant. The same results were reported by Reis in his study [15]. Also, according to age the concentrations exceeding 300 ng/ml were among patients more than 48 years old. Then, knowing that neuroleptics have an inhibitory effect of the CYP2D6 system involved in the hydroxylation of AMT and its metabolite NT, leading to higher concentrations [10,11,16], we tried to evaluate the significance of variations in plasma concentrations of AMT and NT when associated with neuroleptics.

For this, the subjects were divided into two groups: group I received the AMT with a neuroleptic, and group II received the AMT alone or associated to other drugs then neuroleptics which have no action on the metabolism of AMT (e.g., benzodiazepines) (Table 1). Then, we calculated two parameters that will allow us to compare the two groups. The first parameter is the concentration/dose (CD) ratio for AMT and NT (CID AMT and CID NT), which show the plasma concentration given by a dose unit (1mg/kg). The second parameter is the NT/AMT concentration ratio, which gives an idea on the metabolism of demethylation of AMT to NT (Table 1).

Patients in group I had AMT and NT CD ratios higher than those of Group II, with a significant difference for the CID NT. The averages were 217.12 and 239.40 (ng/ml)/(mg/kg) for AMT and NT CD ratios for group I against 115.79 and 75.35 (ng/ml)/(mg/kg) for group II. We see that the value of the NT CD ratio is more than threefold among the patients of group I. Similarly, the NT concentrations were higher in patients of group I. by cons there was no significant difference in the concentrations of NT between the two groups (Table 1).

Also, there was no significant difference between the NT/AMT concentrations ratios, with a slight increase for Group I: 1.18 against 0.96 for Group II. The results show a large variation in AMT and NT plasma concentrations caused by the interaction

with neuroleptics, with a greater variation for the demethylated metabolite NT. These data confirm that neuroleptics strongly inhibit CYP2D6 system involved in the hydroxylation of AMT and NT, but this inhibition is more important for NT, whence the small deviation of the NT/AMT ratio to the increase in group I.

These results had the same trend as those of many studies on the impact of the association of AMT with neuroleptics. El-yazigi study [16], showed a significant difference in the AMT CD ratio means between the two groups, while Jerling [17], showed this difference in NT CD ratio means.

Likewise, both Gex-Fabry and Linnet studies [18,19] have shown that the association with neuroleptics gives higher concentrations of the demethyled metabolite (NT), but had no significant impact on concentrations of AMT.

Our results confirm the influence of the association with neuroleptics, which can lead to very high concentrations exposing the patient to troublesome adverse effects. For this, psychiatrists should consider these drug interactions and need to adjust the dosage in patients with co-medication by reducing the antidepressant dose. However, by comparing the administrated doses of both groups, we find that psychiatrists give the same doses on average, with 0.34mg/kg for Group I against 0.37 mg/kg for Group II (Table 1).

Appreciation of CYP2D6 activity

The results of our study showed higher AMT and NT concentrations compared to those obtained with other studies on western populations [7,20-22], and even eastern example of Saudi patients [16]. Table 2 shows the AMT Concentration/Dose ratios of the different studies. For comparability of results and depending on the availability of data, the parameters must have the same units either in [(ng/ml)/(mg/kg)] or [(ng/ml)/(mg)].

As the concentrations obtained in our study are higher than those of El-Yazigi and as the same author reports in his study that its results are not significantly different from those in Western populations, we can conclude that Algerian population is pharmacokinetically different from the others. Indeed, according to the ratios reported in Table 2, our population concentration/dose ratios are twice higher than those in other studies (populations), except the ratio of Pfuhlmann et al. (1.57 in (ng/mg)/(mg)), which is the most recent study [7].

Corona et al. (1990), had found a ratio of 1.9 (ng/ml)/(mg) very close to ours, this ratio is due to a higher bioavailability following an AMT administration by intramuscular injection [23]. In Algeria, therapeutic monitoring of antidepressants is not practiced because of lack of knowledge of this discipline. Our psychiatrists use lower doses without knowing that these doses are high enough to deliver AMT concentrations to be in the therapeutic range, they may have found clinical improvement in patients.

All this suggests that the activity of CYP2D6 is lower in Algerian patients, what requires a screening in this direction using phenotyping tests such as debrisoquine test.

CONCLUSION

The projections on next twenty years provide that mental disorders, particularly mood disorders, will increase significantly representing a growing public health problem, but also a financial problem caused by the lost of productivity and therapeutic management charges. Our study among 36 depressed patients under amitriptyline shows that more than two thirds of the patients are outside of the therapeutic range, suggesting a problem in the therapeutic regimen adopted. The study of the interaction of the AMT with neuroleptics shows that the latter inhibit CYP2D6 system involved in the hydroxylation of the AMT, as confirmed by many studies and should be considered by psychiatrists by adjusting the dosage in patients with co-medication.

Our study reveals also a low activity of CYP2D6 system in our patients, something to confirm with specific tests (e.g., debrisoquine test).Through our work, we show that the therapeutic monitoring of AMT is very important to ensure an optimal therapeutic management and avoid treatment failure or occurrence of adverse effects, due to individual differences and drug interactions (case of associations to neuroleptics). It is also essential to apply early treatment of depressed patients with a regular evaluation over conventional scales to appreciate treatment effectiveness and to track side effects.

ACKNOWLEDGEMENTS

The authors sincerely thank Souhila Melaine for her assistance in improving the use of English in the manuscript.

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Cite this article

Sobhi K, Khaldoun H, Bouda A, Ferah K, Sadouki D, et al. (2017) Amitriptyline Pharmacokinetics in Algerian Patients with Depressive Disorders: A Low Cyp2d6 Activity? J Pharmacol Clin Toxicol 5(5):1086.