Influence of CYP1A2 and CYP2C19 polymorphisms on clozapine exposure in Tunisians schizophrenic patients

H. Ammar¹, Z. Chedly¹, A. Mhalla², S. Khouaja², I. Hannachi¹, M. Alsheikeid¹, N. Ben Fadhl¹, N. Ben Fredj¹, A. Chaabane¹, N. Boughattas¹, L. Zarrouk², L. Gaha², K. Aouam¹.

¹Faculty of Medicine of Monastir- University of Monastir, Department of pharmacology, Monastir, Tunisia.

²Fattouma Bourguiba Hospital, Department of Psychiatry, Monastir, Tunisia.

Introduction

- ❖ **Clozapine** : Resistant schizophrenia +++
- ❖ Interindividual variability & narrow therapeutic index ➔ **Therapeutic Drug Monitoring (TDM)**+++
- ❖ CYP1A2 & CYP2C19 : mainly responsible for the metabolism of clozapine
- ❖ Activity of these enzymes : several Single Nucleotide Polymorphisms (SNPs) ➔ Interethnic variability
- ➔ Study allele and genotype frequencies of CYP1A2 & CYP2C19 polymorphisms (SNPs) in Tunisian schizophrenic patients receiving clozapine and compare them with those of healthy volunteers
- ➔ Study the impact of CYP1A2 & CYP2C19 on clozapine pharmacokinetics .

Patients & Methods

- ❖ **Cross sectional study** : Pharmacology Department & Psychiatry Department of University hospital center of Monastir
- ❖ Schizophrenic patients receiving clozapine
- ❖ **Clozapine dosing** : High-performance liquid chromatography (HPLC)
- ❖ **Trough concentration**: C0(Therapeutic range(TR)) : 350 et 600 ng/ml)
- ❖ **Genotyping** CYP1A2 & CYP2C19 : PCR-RFLP
- ❖ **SNPs** : CYP1A2*1F - CYP1A2*1C - CYP2C19*2

- ❖ **Phenotypic study** : Genotype combination of CYP1A2 & CYP2C19

Table I : Phenotypic repartition of the studied population

Phenotype	Genotype combination
Poor Metabolizers (PM)	CYP1A2*1C (GA or AA)
	+ CYP1A2*1F (CC or CA or AA)
Intermediate Metabolizer (IM)	CYP1A2*1C (GG)
	+ CYP1A2*1F (CC)
Extensive Metabolizer (EM)	CYP1A2*1C (GG)
	+ CYP1A2*1F (CA or AA)

Results

- ❖ 25 patients & 50 healthy subjects (HS) : included.
- ❖ Characteristics of the study population :

Table II : Characteristics of patients

Demographic Characteristics	Mean ± Standard deviation (extremes)
Age (years)	33,2±7,1 (23-48)
Weight (Kg)	80±12,3 (50-115)
Sex ratio : M/F	5,25 (21/4)

- ❖ Comparaison of allelic repartition between patients & HS :

Table III : Comparaison of allelic repartition between patients & HS

SNP	Allele	Frequency Patients	HS	P
CYP1A2*1F	C	42%	38%	0,93
	A	58%	62%	
CYP1A2*1C	G	96%	96%	1
	A	4%	4%	
CYP2C19*2	G	88%	84%	0,9
	A	12%	16%	

- ❖ Repartition of the trough concentration of clozapine:

Figure 1 : Repartition of the trough concentration of clozapine

- ❖ Phenotypic repartition of the studied population :

Table IV : Phenotypic repartition of the studied population

Phenotypic groups	Genotype combination	Number (percentage)
Poor Metabolizers (PM)	CYP1A2*1C (GA)	2
	+ CYP1A2*1F (CA or AA)	(8%)
Intermediate Metabolizer (IM)	CYP1A2*1C (GG)	5
	+ CYP1A2*1F (CC)	(20%)
Extensive Metabolizer (EM)	CYP1A2*1C (GG)	18
	+ CYP1A2*1F (CA or AA)	(72%)

Discussion

- **CYP1A2*1F & CYP1A2*1C** : Controversial subject
- **Meta-analysis** (August 2018)¹ :
CYP1A2*1F: absence of impact
CYP1A2*1C: non conclusive

- **CYP2C19*2**:
 - The majority of studies² : Influence on the C0 of clozapine
 - Asian study³ : non-significant difference in C0/D between the genotypes of CYP2C19 .

Conclusion

- ❖ First study in the south Mediterranean population : the influence of the CYP1A2 and CYP2C19 genotype on pharmacokinetics of clozapine
- ❖ 3 SNPs studied : No influence
- Inclusion of more patients & others SNPs / genes : CYP1A2*1D, CYP2C19*17 / CYP2D6
- Better to study the role of pharmacogenetic on the TDM of clozapine in Tunisian patients.

- ❖ Impact of SNPs studied on pharmacokinetic (PK) of clozapine :

Figure 2 : The variation of C0/D ratio according to CYP1A2*1F genotypes

Figure 3 : The variation of C0/D ratio according to CYP1A2*1C genotypes & CYP2C19*2 genotypes

- ❖ Influence of genotype combinations on pharmacokinetics of clozapine:

Figure 4 : The variation of C0/D ratio according to CYP1A2 Genotype combinations

- ❖ **Univariate & Multivariate analysis** :

- **CYP1A2*1F** :

- Univariate analysis : a significant correlation between the C0/D ratio of clozapine and CYP1A2*1F (p=0,015)
- Multivariate analysis : do not correlate with the C0/D variation
- **CYP1A2*1C & CYP2C19*2** : absence of significant correlation between these SNPs and the variability of C0/D.
- **Caffeine consumption** : 17% of clozapine PK variability.