International Journal of Community Medicine and Public Health
Agbanlinsou AC et al. Int J Community Med Public Health. 2022 Jul;9(7):3023-3029
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20221777

Review Article

Drug misuse by teenagers in schools in Benin and genetic polymorphism of cytochrome p450: interest and perspectives of cytochrome p450 genotyping

Arnaud Coffi Agbanlinsou*, Ibrahim Cisse, Anatole Laleye

Department of Histology, Reproductive Biology, Cytogenetics and Medical Genetics, Faculty of Health Sciences, Cotonou University of Abomey-Calavi, Benin

Received: 18 May 2022
Revised: 08 June 2022
Accepted: 09 June 2022

***Correspondence:**
Arnaud Coffi Agbanlinsou,
E-mail: arnaudagbanlinsou@yahoo.fr

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

The misuse of psychoactive substances by students is a reality in Beninese schools. These students are exposed to experimentation with these substances with or without prescriptions. The systematic genotyping of cytochromes in these students and in general in subjects exposed to the use of psychoactive substances would be an asset in their therapeutic management and more specifically in the adaptation of dosages and will also allow us to add a particular touch during sensitizations on the experimentation of substances. To achieve this, we checked the availability of drugs that metabolize by cytochromes 2D6 and 3A4 and that are in pharmacies in Benin. What would happen when they consume one or more substances that are metabolized by two cytochrome? PharmGKB is a pharmacogenomics knowledge base that provides information on how human genetic variation affects drug response by collecting information on clinically relevant gene-drug associations and genotype-phenotype relationships. For dosage individualization in therapeutics, the use of the PharmGKB knowledge base preceded by cytochrome genotyping in exposed subjects are assets that clinicians should make use of today for disease treatment.

Keywords: Misuse, Psychoactive substances, Cytochromes, Students, PharmGKB

INTRODUCTION

The management of medicines is a complex process that relies on the organisation of the medication circuit. Its objective is to ensure that the right patient receives the right medicine, in the right dosage, by the right mean, under the right conditions and at the best cost.[1] Human and organisational components, environmental factors, evaluation of professional practices and risk situations are the factors to be taken into account in the implementation of drug management.[1]

In Benin, the school environment has become a place for the use and misuse of drugs and especially addictive substances with a propensity for abuse, coming from the formal and informal sectors. Stress, the quest for physical performance, the reinforcement of cognitive potential, the search for a social and generational identity are the main reasons leading school teenagers to engage in this practice.[2] The majority of these adolescents construct their own uses of different pharmaceutical classes of drugs for various purposes and through multiple consolidation networks. Their practice is based on self-medication which has progressively given rise to the phenomenon of diversion of medicines.[2] They are therefore exposed to poly-drug and psychotropic drug use which can lead to drug interactions. Drug interactions are a major source of accidents or therapeutic failures, particularly in the case of polymedication, especially when they are not detected.[3,4] They are responsible for

one third of hospital admissions due to adverse events, 4% to 7% of emergency admissions and 1% of all hospital admissions.[5-7] Responses to drugs may differ from patient to patient in terms of both therapeutic efficacy and adverse effects. This variability may be a limitation to the use of certain drugs, as it is difficult to predict.[8-10] These variabilities are due to genetic, hormonal, physiological, pathophysiological and environmental factors as well as poor compliance and drug interactions.[9] During the last decades, the genes responsible for drug metabolism and transport as well as their most common functional variants have been identified and characterised. Pharmacogenetics provides a better understanding of the genetic basis for the pharmacokinetic and pharmacodynamic interindividual variability of many analgesic drugs.[11] Enzymes responsible for drug metabolism, drug transporters or drug targets themselves are indeed subject to genetic polymorphism defined by differences in gene expression with a frequency greater than 1% of the population.[12] These enzymes responsible for drug metabolism form the cytochrome p450 superfamily. Polymorphisms in cytochrome p450 genes can lead to altered metabolic activity towards a plethora of clinically important drugs. Thus, nucleotide variants and copy number variations in cytochrome genes are major determinants of drug pharmacokinetics and toxicity and are pharmacogenetic biomarkers for drug dosage, efficacy and safety.[13] This article aimed to show how cytochrome profiling would be an asset for treatment in high school and college students in Benin who already had a regular use of psychoactive substances and in whom the risk of becoming addicted to these substances was already high.

CYTOCHROMES P450

Cytochromes p450 are the most studied enzyme system not only because of their importance in drug metabolism and elimination, but also because of their ability to activate promutagenic and procarcinogenic substances.[14] They are membrane enzymes located mainly in the endoplasmic reticulum membrane of hepatocytes. Other sites of expression are organs that are in contact with the external environment: lungs, intestine, skin and kidneys. They catalyse the oxidation of endogenous or exogenous lipophilic substances (drugs), transforming them into more polar products and facilitating their elimination.[15]

The CYP superfamily contains 74 gene families, 35 of which in humans are classified into 14 families.[12] Members of subfamilies representing a particular gene are then designated by a number according to the description of the subfamily.[12] Taking into account the clinical implications of pharmacogenetic polymorphisms and their role in the individual response of patients to drugs, treatments can be better explained both from the point of view of their toxicities and therapeutics, especially the failures that occur with standard doses.

DRUGS PRESENT IN BENINESE PHARMACIES AND METABOLISED BY CYP P450 2D6 AND 3A4

Cytochromes P450 (CYP) are now well known as an enzymatic system very much involved in drug metabolism.[16] Of all the isoforms, CYP2D6 and CYP3A are most importantly involved in opioid metabolism.[16] CYP2D6 is involved in the metabolism of about 25% to 30% of drugs while CYP3A is involved in the metabolism of about 50% of drugs.[17] The drugs available in Beninese pharmacies and the cytochromes responsible for their metabolism are summarized in (Table 1).

GENETIC POLYMORPHISM OF CYP P450

According to the work of Sim et al there are 57 active CYP genes in the human genome (classified into 18 families), and variation in these genes results in several phenotypes defined as ultrafast, extensive, intermediate and slow metabolisers.[19] In general, an ultra-rapid metaboliser carries duplicate or multiple gene copies of the same allele, while intermediate and slow metabolisers carry one and two defective alleles respectively (by gene inactivation or deletion).[19] The black American population has fewer polymorphic variants than the Caucasian populations.[20] That is, genetic variation is greater in African populations than in Asian and Caucasian populations. Therefore, the African continent cannot be treated as a single entity in drug research and development, as is the African-American population, which is considered an adequate indicator of pharmacogenetic differences across Africa.[21] There are very few primary studies on the frequencies of CYP 450 allelic variants in Africa, particularly in West Africa.[22] Zhoul et al have found that the distribution of cytochrome alleles differs considerably between populations, which has important implications for drug therapy and personalised healthcare programmes.[13] However, further research is needed to confirm these distributions and to identify populations at potentially higher risk of drug-induced adverse events or drug inefficacy.[21] To provide a global distribution map of clinically relevant cytochrome alleles, Zhoul and colleagues had integrated whole genome and exome sequencing data from 56945 unrelated individuals from five major human populations (European, African, East Asian, South Asian, Mixed American). By combining this dataset with population-specific linkage information, they obtained frequencies of 176 cytochrome haplotypes, providing an extensive resource for key genetic determinants of drug metabolism.[13] CYP p450 alleles were identified that may be unique to Africa or for which data on African populations are limited and regions where additional data need to be collected. It is likely that polymorphisms in other enzymes and transporters contribute to the diversity of drug response observed in Africa. Therefore, the involvement of clinicians in genomic research will facilitate this process of genomic knowledge transfer, helping to ensure that patients are treated with effective doses of therapeutic drugs.[21]

Table 1: Substrates of the cytochromes CYP2D6 and CYP3A and their presence in Beninese pharmacies.[4,18]

Substrate	CYP2D6	CYP3A4	Presence
Alfentanil			No
Alprozolam			Yes
Amiodarone			Yes
Amitriptyline			Yes
Amlodipine			Yes
Amprévanir			No
Atorvastatine			Yes
Bisoprolol			Yes
Bromocriptine			Yes
Bupivacaïne			No
Buprénorphine			No
Buspirone			No
Caféine			Yes
Cabarmazépine			Yes
Célécoxibe			Yes
Clorpromazine			Yes
Ciclosporine			No
Cisapride			No
Citalopram			No
Clarithromycine			Yes
Clomipramine			Yes
Clonazépam OUI			Yes
Clopidogrel			Yes
Clozapine			No
Cocaine			No
Codeine			Yes
Colchicine			Yes
Cortisol			No
Cyclophosphamide			No
Dapsone			No
Délavirdine			No
Désogestrel			No
Desaméthasone			Yes
Dexthrométhorphane			Yes
Diazepam			Yes
Dihydrocodéïne			No
Dihydroergotamine			No
Diltiazem			Yes
Dolasetron			No
Donépezil			No
Ecstasy (MDMA)			No
Efavirenz			Yes
Ergotamine			Yes
Erythromicine			Yes
Escitalopram			No
Esoméprazole			Yes
Ethanol			Yes
Ethinylestradiol			Yes
Ethosuximide			No
Etoposide			No
Felbamate			No
Felodipine			No
Fentanyl			No
Finastéride			Yes
Flécaïdine			No

Continued.

Substrate	CYP2D6	CYP3A4	Presence
Flunitrazépam			No
Fluoxétine			Yes
Flutamide			No
Fluvastatine			No
Fluvoxamine			No
Galantamine			No
Gestodène			No
Granisétron			Yes
Halofantrine			No
Halopéridol			Yes
hydrocodone			No
Isofamide			No
Imatinib			No
Imipramine			No
Indivanir			No
Israpidine			No
itraconazolz			Yes
Kétoconazole			Yes
Lansoprazole			Yes
Lévomépromazine			Yes
Lidocaïne			Yes
Lopinavir			Yes
Loratadine			Yes
Losartan			Yes
Maprotiline			No
Medroxyprogest			No
Mefloquine			Yes
Méloxicam			Yes
Méthadone			No
Méthyl prednisolone			Yes
Métoprolol			Yes
Miansérine			No
Midazolam			Yes
Mifépristone (RU486)			Yes
Mirtazapine			No
Montélukast			Yes
Natéglinide			No
Néfazodone			No
Nelfinavir			No
Névirapine			Yes
Nifédipine			Yes
Nimodipine			No
Nisoldipine			No
Nitrendipine			Yes
Noréthistérone			Yes
Nortriptyline			No
Olanzapine			No
Oméprazole			Yes
Ondansetron			Yes
Oxybutinine			Yes
Oxycodone			No
Paclitaxel			No
Pantoprazol			Yes
Paracétamol			Yes
Paroxétine			Yes
Phenylbutazone			No
Pioglitazone			No

Continued.

Substrate	CYP2D6	CYP3A4	Presence
Pravastatine			No
Prednisolone			Yes
Proguanil			Yes
Prométhazine			Yes
Propafénone			No
propanolol			Yes
Quétiapine			No
Quinidine			No
Quinine			Yes
Réboxétine			No
Répaglinide			No
Rifabutine			No
Rispéridone			Yes
Ritonavir			Yes
Saquinavir			Yes
Sertraline			No
Sildénafil			Yes
Simvastatine			Yes
Sirolimus			No
sufentanil			No
Tacrolimus			No
Tamoxifen			Yes
Tamsulosin			Yes
Tégaserod			No
Terbinafine			Yes
Testostérone			Yes
THC			No
Thioridazine			Yes
Timolol			Yes
Toltérodine			No
Tramadol			Yes
Trazodone			No
Triazolam			No
Trimipramine			No
Tropisetron			No
Venlafaxine			No
Verapamil			Yes
Vinblastine			No
Vincristine			No
Vindesine			No
Warfarin			No
zalepon			No
Zolpidem			Yes
zopiclone			No

-Major metabolic pathways, -minor metabolic pathways.

Considering patients' genotype as a complementary tool to therapeutic algorithms could potentially assist clinicians in not only evidence-based but also risk stratification decision making.[23] However, the performance of the suggested practical approach needs to be rigorously evaluated or validated in clinical studies, and the clinician's judgement remains paramount when making decisions.[24,25] The polymorphic nature of the cytochrome p450 gene largely affects an individual's response to the drug and adverse drug reactions.[26] With the decrease in sequencing costs and the next generation sequencing analyses can now be performed at the population level. This allows the whole landscape of pharmacogenetic variability to be mapped. Importantly, the functional interpretation of these rare variants cannot be based on experimental data and the development of tools to reliably translate these variants into clinical guidance is therefore an interesting frontier in contemporary pharmacogenomics.[27] Therefore, scientific evidence suggests that gene polymorphisms can explain differences in outcomes after drug administration and that pharmacogenomics-guided treatments are possible, but

controlled clinical trials are needed to substantiate this claim.[23]

ISSUES AND HOPES FOR INDIVIDUALISATION OF DOSING IN DRUG THERAPY

Published literature entitled drug interactions and cytochromes P450, shows us that several drugs that exist in pharmacies in Benin are metabolised by both cytochrome 2D6 and cytochrome 3A4.[4] Also in this review, the authors showed that a drug can be metabolised mainly by one or both of these CYPs.[4] The first questions that may arise from these different possibilities of metabolism are the following: *in vivo*, how would the metabolism of a drug metabolised predominantly by both CYP2D6 and CYP3A4 proceed? Would there be competition between these two cytochromes in the metabolism of this drug? If so, what are the parameters that will come into play to define the main metabolic pathway of this drug? What will happen in the event of enzymatic induction and/or inhibition of a cytochrome by this substrate? The work of Kpatchavi and Adounkpe in 2016 reveals that one of the most commonly used opioids in schools is Tramadol.[2] Between CYP2D6 and CYP3A4 which one would be responsible for the metabolisation of Tramadol in a Beninese school adolescent who experiments with this drug and who expresses these two cytochromes.

Systematic genotyping of the cytochromes in these adolescents and in general in subjects exposed to the use of psychoactive substances would be an asset in their therapeutic management and more specifically in the adaptation of dosages. The subject may be a slow metaboliser with one cytochrome and at the same time be a normal or fast metaboliser with another cytochrome. Indeed, opioids that require bioactivation by a cytochrome subject to genetic polymorphisms, such as 2D6, are not the analgesic treatments of choice in slow metabolizers for this enzyme.[16] Thus a teenager who is a normal metaboliser of a drug or substrate may become a slow metaboliser when exposed to poly-drug use. The PharmGKB is a pharmacogenomics knowledge base. It is an NIH (National Institutes of Health) funded resource that provides information on how human genetic variation affects drug response. This knowledge base collects, organises and disseminates information on clinically relevant gene-drug associations and genotype-phenotype relationships. Prescribing information provided by PharmGKB includes clinical guidelines on how to adjust the treatment of certain drugs based on a person's genetic information. Several organisations around the world write these guidelines and PharmGKB provides annotations on its website.[28]

CONCLUSION

For a better care and for dosage individualisation in therapy of subjects exposed to the misuse and use of psychoactive substances, the use of the PharmGKB knowledge base preceded by cytochrome genotyping in exposed subjects are assets that clinicians should make use of nowadays for disease treatment.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Certification of health care organisations, educational sheet-Medicines: Evaluation of drug management drug management according to the certification standard. Available at: https://www.who.int/publications/. Accessed on 20 October 2021.
2. Kpatchavi AC, Adounkpe F. Drug Use and Addictive Substances Among Adolescents in Benin: A Survey of High Schools in Cotonou. Ann Univ Lomé, SérieLett. 2016;4:239-49.
3. Tripathi N, Mousa OY. Hepatitis B. Treasure Island, FL: StatPearls Publishing; 2022.
4. Jules D. Importance of cytochromes P450: pharmacogenetics and drug interactions. Pharma-Flash. 2010;37:7-10.
5. Charlotte AJ. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf. 1993;9(1):51-9.
6. Pirmohamed M, James SM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Lat Am J Pharm. 2004;329:15-8.
7. Sultana J, Cutroneo PGT. Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother. 2013;4(1):73-8.
8. Ingelman-Sundberg MO. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. TIPS. 1999;20(1):342-8.
9. Lhermitte M, Allorge D, Broly F, Launois B. Xenobiotic-metabolizing polymorphic enzymes. An opportunity for individualized drug treatment. Bull Acad Natl Med. 2006;3:42.
10. Sundberg M. Pharmacogenetics: An opportunity for a safer and more efficient pharmacotherapy. J Intern Med. 2001;250(3):186-200.
11. Samer CF, Valérie Piguet PD. Analgesia, the importance of cytochrome P450 2D6 genetic polymorphism in therapeutic individualisation. Douleurs Analg. 2004;2:63-6.
12. Samer CF, Valérie Piguet PD. Genetic polymorphism and drug interactions: Their importance in pain management. Can J Anesth. 2005;52(8):806-21.
13. Zhou Y, Ingelman-Sundberg M, Lauschke V. Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects. Clin Pharmacol Ther. 2017;102(4):688-700.
14. Aigrain E, Panserat S, Sica RK. Molecular genetics of cytochrome P450 llD: abnormalities in drug metabolism. Rev Française d'allergologie d'Immunol Clin. 1995;35(5):462-9.

15. Rogers JF, Nafziger AN. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450-metabolized drugs. Am J Med. 2002;113(9):746-50.
16. Marsousi N, Ancrenaz V, Rudaz S, Samer C, Desmeules J. Influence of genetic polymorphisms on the response variability to opioids. Douleur Analg. 2013;26(4):203-8.
17. Bertz RJ, Granneman GR. Use of in Vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmocokinet. 1997;32(3):210-58.
18. Zone industrielle d'Akpakpa, Cotonou. Available at: http://www.promopharma-benin.com/fr/. Accessed on 20 October 2021.
19. Sim SC, Ingelman-Sundberg M. The Human Cytochrome P450 (CYP) Allele Nomenclature website: a peer-reviewed database of CYP variants and their associated effects. Hum Genomics. 2010;4(4):278-81.
20. Kozyra M, Ingelman-Sundberg M, Lauschke VM. Rare genetic variants in cellular transporters, metabolic enzymes, and nuclear receptors can be important determinants of interindividual differences in drug response. Genet Med. 2017;19(1):20-9.
21. Rajman I, Knapp L, Morgan T, Masimirembwa C. African genetic diversity: implications for cytochrome P450-mediated drug metabolism and drug development. EBio Med. 2017;17:67-74.
22. Kabre E, Karfo RBK. Genetic polymorphism of cytochromes p450: a systematic review of primary studies in the African population. J la Société Biol Clin du Bénin. 2017;27:38-46.
23. Daniel LH. Polymorphisms of cytochrome P450 are potential candidates that could potentially help clinicians on the treatment of cardiovascular diseases among Asian populations. Indian Heart J. 2017;69(5):655-6.
24. Anne LB. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenom. 2002;3(2):229-43.
25. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. J Am Med Assoc. 2016;316(1):70-8.
26. Bagheri A, Haghshenas BKM. Prevalence of the CYP2D6, Iranians of different ethnicities. Drug Des Devel Ther. 2015;9:2627-34.
27. Volker M. Lauschke MIS. Prediction of drug response and adverse drug reactions : From twin studies to Next Generation Sequencing. Eur J Pharm Sci. 2019;130(1):65-77.
28. PharmGKB. Available at: https://www.pharmgkb.org/whatIsPharmgkb. Accessed on 20 October 2021.

Cite this article as: Agbanlinsou AC, Cisse I, Laleye A. Drug misuse by teenagers in schools in Benin and genetic polymorphism of cytochrome p450: interest and perspectives of cytochrome p450 genotyping. Int J Community Med Public Health 2022;9:3023-9.