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Multiple adverse drug reactions and genetic polymorphism testing

A case report with negative result

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Abstract

Rationale: Defects in drug metabolic pathways could explain why some patients have a history of multiple adverse drug reactions (ADR); therefore we aimed to analyze genetic polymorphisms in a patient with multiple ADR related to drugs with a common hepatic metabolic pathway through CYP2D6.

Patient concerns: We report a patient with psychosis and hypertension related to amitriptyline, tramadol, and duloxetine within a 2-year period.

Interventions and Outcomes: A pharmacogenetic test was performed to assess the causative role of the CYP2D6 enzyme, but did not demonstrate a metabolic deficiency.

Lessons: Although negative results in the reported case; typing for cytochrome P450 isoenzyme polymorphisms could be a useful diagnostic tool in some patients with a history of multiple ADR.

Abbreviations: ADR = adverse drug reactions, EM = extensive metabolizer, IM = intermediate metabolizer, MDIS = multiple drug intolerance syndrome, PM = poor metabolizer, UM = ultrarapid metabolizer.

Keywords: adverse drug reactions, CYP2D6, drug metabolism, genetic polymorphism, multiple drug intolerance syndrome

1. Introduction

The multiple drug intolerance syndrome (MDIS) is characterized by adverse drug reactions (ADR) to more than 2 chemically unrelated drugs, with or without a known immunologic or other mechanism responsible.[1,2] Its estimated prevalence varies from 2.1% to 4.9% of patients with any history of an ADR, and is more likely in females with anxiety and patients with other comorbidities.[3,4] The management of these patients can be difficult, because reliance on medication avoidance may limit optimal first-line therapy. The pathogenic of MDIS is complex and not well understood.[5] Our hypothesis is that patients with *CYP450* enzyme genetic polymorphisms could present with MDIS, if drugs they used share this common metabolic pathway and the ADR are related to drug mechanism of action. To our knowledge, there is little data describing an association between the metabolic pathways of medications and clinically apparent MDIS. We describe a case of MDIS with intolerance to 4 different nervous system drugs manifested by episodes of drug-associated psychosis, hypertension, and skin eruption.

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2. Case description

The patient reported here is a 56-year-old Caucasian female with only a medical history of neuropathic pain due to T2-T3 transverse myelitis in treatment with multiple analgesic drugs in the outpatient Pain Clinic. She started treatment with amitriptyline 10 mg/d, and between 1 and 2 weeks later, she presented transitory episodes of visual hallucinations, and amitriptyline was switched to gabapentin (1200 mg/d) ceasing the hallucinations. Almost a year later, because the pain persisted, tramadol (100 mg/d) was added to the treatment. One month later, the visual hallucinations reappeared accompanied by delusional ideation, leading to a decrease in the dose of tramadol to 50 mg/d. Thereafter, to control the neuropathic pain, the dose of gabapentin was increased (2200 mg/d). Two months later, she developed a generalized skin rash with itching. Gabapentin was suspected to be the responsible drug; the dose was reduced to its previous of 1200 mg/d. The rash progressively disappeared within 2 weeks. The hallucinations and paranoia persisted for almost a year and the patient had to take a sick leave from work. At that moment, the patient was evaluated by a psychiatrist who diagnosed a drug-induced psychotic disorder that required treatment with olanzapine, and tramadol was stopped as it was suspected to be related to the psychosis. Her pain was then controlled with gabapentin 1500 mg/d and acetaminophen 1 g

Table 1

Characteristics of the adverse drug reactions (ADR).

ADR	Involved drug	Drug metabolic pathway	Naranjo algorithm score	ADR treatment
Psychosis	Amitriptyline	*CYP2D6, CYP2C19*	4 (possible)	—
	Tramadol	*CYP2D6, CYP3A4*	5 (probable)	Olanzapine
Hypertension	Duloxetine	*CYP2D6, CYP1A2*	5 (probable)	Captopril or enalapril
Skin eruption	Gabapentin	Not hepatic metabolism	5 (probable)	—

TID. One month later, because of anxiety and depression, the psychiatrist prescribed duloxetine (30 mg/d). Two days later, she was admitted to the emergency room for symptomatic hypertension (blood pressure up to 166/105 mm Hg) that normalized with captopril. Duloxetine was switched to escitalopram without new ADR and afterward stopped. The psychosis disappeared after withdrawal of tramadol and temporary treatment with olanzapine. Currently, the pain is controlled with gabapentin and acetaminophen, and the hypertension with enalapril. This case was reported to the Spanish Pharmacovigilance System.

All the ADR (psychosis, hypertension, and skin eruption) fulfill the criteria of causality: a plausible time between exposure to drugs and onset of symptoms, the disappearance of these symptoms following the withdrawal of the drugs and the evidence in the literature associating the reactions to the drugs. After applying the Naranjo's ADR probability algorithm,[6] the score was 5 points (probable causal association) for tramadol-induced psychosis, for duloxetine-induced hypertension, and for gabapentin-induced skin rash; and the score was 4 points (possible causal association) for amitriptyline-induced psychosis (Table 1).

Neuropsychiatric effects of tramadol and amitriptyline, as well as cardiovascular effects of duloxetine could be explained by their own mechanism of action through binding to opioid receptors and/or increasing neurotransmitters such as norepinephrine (type A adverse reactions).[7] Unfortunately plasma concentrations of drugs were not available in this patient. Because a common hepatic metabolic pathway through *CYP2D6* was shared by those drugs, a poor metabolism of the *CYP2D6* isoenzyme was suspected. Therefore, some of the most common alleles for *CYP2D6* in Spanish population (**2,*3,*4,*6,*10,*35,* and **41*) were analyzed by real-time PCR using TaqMan assays (Table 1), after the informed consent was signed by the patient. The PCR conditions were a 10-minute pre-incubation at 95°C to activate the Taq DNA polymerase, followed by 40 cycles of denaturation at 92°C for 15 seconds and then by primer annealing and extension for 1 minute at 60°C. Moreover, *CYP2D6*5* and *CYP2D6* multiplications were analyzed by XL-PCR as described in detail elsewhere.[8] In addition, *CYP2C9* and *CYP2C19* genes were also assessed using TaqMan assays (Table 2). The amplification conditions were the same as for the *CYP2D6* alleles. The results of the pharmacogenetic test revealed that the patient was homozygous for all the 3 isoenzymes (wild type).

3. Discussion

As a result, no metabolic deficiencies for *CYP2D6* were confirmed in the pharmacogenetic test. The main reason that could explain those results could be the limited assessed alleles in the pharmacogenetic test. Other reasons could be the fact that other factors influencing the pharmacokinetic of the drug, such as drug transporters, would be implicated in the occurrence of ADR.

One out of every 15 persons treated with drugs at standard doses may have either no therapeutic response or an exaggerated response to the pharmacological treatment leading to an ADR. Some of this variability could be explained by *CYP450* enzymes genetic polymorphisms.[9] The different allelic variants translate into 4 major enzyme hydroxylation capacity groups: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultrarapid metabolizer (UM).[10] About 7% to 10% of European Caucasian population is PMs, and about 5% of Spaniards are UMs.[11,12] In those cases, the pharmacogenetic test can elucidate the problem related to the therapeutic response. Recently, a Pharmacogenetic Decision

Table 2

***CYP2D6*, *CYP2C19*, and *CYP2C9* alleles studied in this patient.**

Gene	Allele	SNP ID	Genetic polymorphism	Enzyme activity	TaqMan SNP genotyping assay
CYP2D6	*CYP2D6*2*	rs1080985	−1584C>G	Normal	C__32407252_30
	*CYP2D6*3*	rs35742686	2549delA	Null	C__32407232_50
	*CYP2D6*4*	rs1065852; rs3892097	100C>T; 1846G>A	Null	C__11484460_40; C__27102431_D0
	*CYP2D6*5*	–	*CYP2D6* deletion	Null	–
	*CYP2D6*6*	rs5030655	1707delT	Null	C__32407243_20
	*CYP2D6*10*	rs1065852	100C>T	Reduced	C__11484460_40
	*CYP2D6*35*	rs1080985;	−1584C>G; 31G>A	Normal	C__32407252_30; C__27102444_80
	*CYP2D6*41*	rs769258	2988G>A	Reduced	C__27102444_80
	*CYP2D6*1/*2xN*	—	—	Enhanced	–
CYP2C9	*CYP2C9*2*	rs1799853	430C>T	Reduced	C__25625805_10
	*CYP2C9*3*	rs1057910	1075A>C	Very reduced	C__27104892_10
	*CYP2C9*6*	hCV32287221	818delA	Null	C__32287221_20
CYP2C19	*CYP2C19*2*	rs4244285	681G>A	Null	C__25986767_70
	*CYP2C19*4*	rs28399504	1A>G	Null	C__30634136_10

Algorithm designed to simplify the decision-making of clinicians about when to perform a pharmacogenetic test has been proposed, and it can be useful for selecting the right patient that could benefit from it.[13]

The *CYP2D6* is a highly polymorphic isoenzyme with >100 allelic variants and subvariants described. There are ethnic differences in allele frequencies.[14] About 7% of white persons and 2% to 7% of black persons are PM of *CYP2D6*.[5] This enzyme is known to metabolize as many as 25% of commonly prescribed drugs, such as antidepressants, antipsychotics, analgesics, cough suppressants, beta adrenergic blocking agents, antiarrhythmics, and antiemetics.[9] PM of *CYP2D6* have a high risk for ADR due to progressive accumulation of the drug.[11] When prodrugs like tramadol and codeine that require activation by *CYP2D6* are used, a lack of this enzyme results in reduced effectiveness of drug therapy.[11,15]

Amitriptyline, a tricyclic antidepressant, is metabolized by demethylation through the isoenzyme *CYP2C19* to the active compound nortriptyline and also by *CYP2D6* to hydroxyl metabolites. Nortriptyline then is metabolized by *CYP2D6* to an inactive metabolite.[16] Neuropsychiatric adverse reactions reported with amitriptyline are anxiety, cognitive dysfunction, confusion, delusions, disorientation, dizziness, drowsiness, mania or hypomania, hallucinations, insomnia, lack of concentration, nightmares, restlessness, and sedation.[17]

Tramadol, an opioid agonist receptor, is metabolized primarily by *CYP2D6* to a pharmacologically active metabolite *O*-desmethyltramadol, and also by the *CYP3A4* isoenzyme. The variability in therapeutic response is closely related to the *CYP2D6* genotype. A *CYP2D6* PM has a worst pain control because a reduction of metabolism to *O*-desmethyltramadol before pain-relieving effects is observed.[9] Psychiatric adverse reactions of tramadol are frequent (10% of all the ADR). These are hallucinations, confusion, sleep disturbances, delirium, anxiety, nightmares, panic attacks, depersonalization, and paranoia. Tramadol-induced hallucinations have been described in few case reports that recovered quickly after withdrawal.[18,19]

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is metabolized by the *CYP1A2* and *CYP2D6* isoenzymes and is also a moderate inhibitor of the *CYP2D6*.[20] Because duloxetine increases the noradrenergic system, it could increase blood pressure, mainly in patients with previous hypertension.[21]

In the revised literature, only a case report has been identified examining the influence of genetic polymorphisms in a patient with multiple ADR related to psychotropic medications. This patient had drug metabolizing deficiencies for *CYP2D6*, *CYP2C19*, and *CYP2C9*, suggesting that adverse events were drug induced.[22]

4. Conclusion

Although pharmacogenetic testing did not demonstrate a metabolic deficiency in the reported case; we suggest that typing for cytochrome P450 isoenzyme polymorphisms could be a useful diagnostic tool in some patients with a history of multiple ADR, helping physicians to manage pain or other conditions with a better safety profile drug.

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References

[1] Schiavino D, Nucera E, Roncallo C, et al. Multiple-drug intolerance syndrome: clinical findings and usefulness of challenge tests. Ann Allergy Asthma Immunol 2007;99:136–42.
[2] Antoniou S, Saxena M, Hamedi N, et al. Management of hypertensive patients with multiple drug intolerances: a single-center experience of a novel treatment algorithm. J Clin Hypertens (Greenwich) 2016;18:129–38.
[3] Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. Ann Allergy Asthma Immunol 2012; 108:88–93.
[4] Omer HM, Hodson J, Thomas SK, et al. Multiple drug intolerance syndrome: a large-scale retrospective study. Drug Saf 2014;37:1037–45.
[5] Patriarca G, Schiavino D, Nucera E, et al. Multiple drug intolerance: allergological and psychological findings. J Investig Allergol Clin Immunol 1991;1:138–44.
[6] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30:239–45.
[7] Rawlins MD, Thompson JW. Davies DM. Mechanisms of adverse drug reactions. Textbook of Adverse Drug Reactions Oxford University Press, Oxford:1991;18–45.
[8] Dorado P, Cáceres MC, Pozo-Guisado E, et al. Development of a PCR-based strategy for CYP2D6 genotyping including gene multiplication of worldwide potential use. Biotechniques 2005;39:S571–4.
[9] Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician 2007; 76:391–6.
[10] Johansson I, Ingelman-Sundberg M. Genetic polymorphism and toxicology—with emphasis on cytochrome p450. Toxicol Sci 2011; 120:1–3.
[11] Gardiner SJ, Begg EJ. Pharmacogenetics, drug metabolizing enzymes, and clinical practice. Pharmacol Rev 2006;58:521–90.
[12] Naranjo ME, de Andrés F, Delgado A, et al. High frequency of CYP2D6 ultrarapid metabolizers in Spain: controversy about their misclassification in worldwide population studies. Pharmacogenomics J 2016;16:485–90.
[13] Alzghari SK, Blakeney L, Rambaran K. Proposal for a pharmacogenetic decision algorithm. Cureus 2017;9:e1289.
[14] Hicks JK, Swen JJ, Thorn CF, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther 2013;93:402–8.
[15] Ingelman-Sundberg M. Pharmacogenetics of cytrochrome P450 and its applications in drug therapy: the past, present and future. Trends Pharmacol Sci 2004;25:193–200.
[16] Steimer W, Zöpf K, von Amelunxen S, et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. Clin Chem 2005;51:376–85.
[17] Fiori MG. Tricyclic antidepressants: a review of their toxicology. Curr Dev Psychopharmacol 1977;4:71–110.
[18] Keeley PW, Foster G, Whitelaw L. Hear my song: auditory hallucinations with tramadol hydrochloride. BMJ 2000;321:1608.
[19] Devulder J, De Laat M, Dumoulin K, et al. Nightmares and hallucinations after long-term intake of tramadol combined with antidepressants. Acta Clin Belg 1996;51:184–6.
[20] Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J 2005;5:6–13.
[21] Wernicke J, Lledó A, Raskin J, et al. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. Drug Saf 2007;30:437–55.
[22] Ruaño G, Blair CL, Bower B, et al. Somatic complications of psychotropic medications in a patient with multiple CYP2 drug metabolism deficiencies. Conn Med 2007;71:197–200.