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METOCLOPRAMIDE-INDUCED ACUTE DYSTONIC REACTION IN TWO PATIENTS, CYP2D6 *4/*4, *10/*10 (POOR) AND *1/*5 (INTERMEDIATE) METABOLIZERS

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INTRODUCTION

Metoclopramide is a strong postsynaptic dopamine D(2) receptor blocker and a weak 5-HT3 and 5-HT4 agonist for its prokinetic effect. Metoclopramide stimulates acetylcholine receptors accelerating gastric emptying. Major side effect of metoclopramide is an acute dystonic reaction (ADR) that usually occurs within 24 to 72 hours of drug administration and depends on the plasma concentration of the drug. Metoclopramide is metabolized by CYP2D6 and is a reversible inhibitor but not inactivator of CYP2D6 under conditions of varying concentration (Livezey et al 2014).

By this article, we point out that in addition to CYP2D6 poor metabolizers (PM), which have already been described in the literature, intermediate metabolizers (IM) who take metoclopramide also have an increased risk of developing metoclopramide-induced acute dystonic reaction (MIADR).

TWO CASES OF METOCLOPRAMIDE--INDUCED ACUTE DYSTONIA

Case A

A 20-year-old female of European descent, was admitted to Neurology Clinic due to headaches and nausea. Her medical history revealed that at the age of 11 she had developed episodes of torticollis three days after starting metoclopramide at a dose of 30 mg daily due to gastritis-associated nausea.

The possibility that the patient may be manifesting a MIADR was considered, according to the DSM-5 criteria. Other conditions were excluded by laboratory tests, thyroid function and immunological tests, brain MRI and EEG. Her symptoms improved upon administration of 5 mg biperiden intravenously.

Case B

A 30-years-old female Caucasian, was admitted to Neurology Clinic due to vertigo-associated nausea. She has a history of chronic gastritis. Five years ago, she felt neck pain, stiffness and inability to move her head several hours after the administration of the 20 mg of metoclopramide. Based on the drug history, sudden onset and rapid progression of the symptoms, a diagnosis of MIADR was established. Her symptoms had disappeared immediately upon administration of 5 mg biperiden intravenously.

Both patients was recommended to avoid metoclopramide and to use if needed, all other CYP2D6 substrates with caution.

GENETIC ANALYSIS

The participants consented to provide a blood sample for pharmacogenetic testing. Genotyping of *CYP2D6*3*4*5*6*,*10,*41* and duplications were performed by polymerase chain reaction (PCR) based methods on the 7500 Real-Time PCR System, using TaqMan® Drug Metabolism Genotyping Assays, and on the Gene Amp PCR System 9700 (Applied Biosystems, Carlsbad, CA, USA) as previously published (Ganoci et al. 2017).

RESULTS

The patient A was a carrier of *CYP2D6 *4/*4* and *CYP2D6*10/*10* genotypes, while patient B had *CYP*1/*5* genotype, predisposing for PM and IM, respectively. Both the *CYP2D6 *4* and *5* are non-function alleles, while allele *10* predispose for reduced CYP2D6 activity (reduced-function allele).

DISCUSSION

MIADR is a neurologic condition frequently reported in the literature with an incidence of 0.5-1%. The effects of CYP2D6 gene variants on the pharmacokinetics of metoclopramide were evaluated previously (Bae JW et al. 2020). However, only two case reports highlighted the relevance of CYP2D6 activity for MIADR. One, reported two patients who were given metoclopramide for chemotherapy-induced nausea (van der Padt A et al. 2006). Both patients were poor metabolizers, carriers of inactivating CYP2D6 alleles (*4/*4 and *4/*5 genotype, respectively. The second article refers to two pregnant women who were taking oral metoclopramide for pregnancy-associated nausea (Chua EW et al. 2019). Both patients were homozygous for *CYP2D6*4* allele. It was assumed that deficient CYP2D6 function increased exposure to metoclopramide increasing the risk of MIADR. Furthermore, authors provided new insights into the relation between CYP2D6 poor metabolism, pregnancy-related hormonal changes and chemotherapy as other predisposing risk factors.

Together with *CYP2D6* gene deletion (allele *5*), variants *3* and *4* account for most instances of poor metabolizer (PM) phenotypes in Caucasians. The frequency of the *5* allele is similar in both populations (2-6%), while *10* allele is more frequent in Asians (40%).

Several factors were proposed to contribute to the risk of developing side effects of metoclopramide in the form of MIADR. Cases reported provided evidences that the CYP2D6 impaired function alone is not sufficient, but the role of other mediated factors such as hormonal changes and concomitant therapy by other CYP2D6 drug substrates like neuroleptics, antidepressants, opioids and chemotherapy may provoke MIADR (Chua et al. 2019, van der Padt et al. 2006). Our two patients, apart from gastritis, had no peculiarities in their medical histories and were not treated with any other drugs. MIADR are believed to be due to inhibition of specific dopamine receptors that are related to poor elimination of metoclopramide while others are independent of the elimination rate (van der Padt et al, 2006, Silferer et al, 2012). Inactivation of CYP2D6 may be due to different interaction of metoclopramide with some CYP2D6 genotypes (van der Padt et al, 2006, Silferer et al, 2012). Furthemore, CYP2D6 could also interact with other polymorphic enzymes including monoamine oxidases, glucuronosyltransferases, sulfotransferases, and others (Livezey et al, 2014). Pharmacogenomic research showed that duplication of a non-functional CYP2D6 alleles has the same clinical function as a single copy. The activity is also decreased in subjects heterozygous for the deletion (Kato D et al, 2005). Since there is a lack of reports on patients CYP2D5 IMs who manifested MIADR, this case should further alert clinicians. Furthemore, CYP2D6 variants may be associated with biochemical changes in the brain and personality due to their role in the metabolism of tyramine to dopamine and regeneration of serotonin from 5-methoxytryptamine (Peñas-Lledó & Llerena 2014). CYP2D6 may participate in the central dopaminergic regulation, and the CYP2D6 PM may have decreased 5-HT activity, allowing increase in the dopaminergic tone (dopamine hypersensitivity) (Yu AM et al. 2003). Understanding the role of CYP2D6 inactivation or inhibition in MIADR can aid in metoclopramide prescription.

Limitation of the present study is that is not a case-control study but only a case report. Further research is needed to elucidate the direct association of different CYP polymorphisms with the occurrence of MIADR.

CONCLUSION

Risk for MIADR existed in patients with CYP2D6 PM and IM phenotype due to impaired metabolic function and prolonged bioavailability of metoclopramide. Pharmacogenetics is a powerful tool in personalized treatment by indentifying individuals at increased risk of developing adverse events due to impaired metoclopramide metabolism, which can cause serious extrapyramidal symptoms.

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