Netherlands
The Journal of Medicine

CASE REPORT

Acute dystonic reaction to metoclopramide in patients carrying homozygous cytochrome P450 2D6 genetic polymorphisms

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ABSTRACT

Background: Extrapyramidal syndromes (EPS) are clinically relevant side effects of metoclopramide which are often not anticipated.

Patients and methods: Two patients who received metoclopramide developed an acute dystonic reaction. Symptoms disappeared after biperiden or trihexyphenidyl were given. Molecular analysis of the CYP2D6 gene was performed using a PCR-based method.

Results: Both patients were homozygous for inactive CYP2D6 alleles (CYP2D6*4/*4 and CYP2D6*4/*5), which are associated with slow drug metabolism.

Conclusion: Metoclopramide-induced acute dystonic reactions may occur in patients carrying a CYP2D6 genetic polymorphism.

KEYWORDS

Acute dystonic reaction, chemotherapy, CYP2D6, metoclopramide

INTRODUCTION

Metoclopramide is a selective dopamine antagonist (D2-R) with central and peripheral antidopaminergic effects. Metoclopramide increases peristaltic movements of the gut, it induces pyloric relaxation and has a direct antiemetic effect.[1-3] Extrapyramidal syndromes (EPS) are clinically relevant side effects of metoclopramide, which are often not anticipated. We report two cases of an acute dystonic reaction to metoclopramide in two patients treated with chemotherapy who were homozygous carriers of CYP2D6 variant alleles, making them CYP2D6 poor metabolisers.

CASE REPORTS

Patient A, a 25-year-old female, was diagnosed with acute myeloid leukaemia (AML), French-American-British (FAB) classification AML-M1. She was treated with cytosine arabinoside and idarubicin (chemotherapy). Granisetron (1 mg intravenously) was given as prophylactic antiemetic drug. Because of persisting granisetron-refractory nausea after four days, metoclopramide 10 mg was prescribed intravenously four times daily. After two days, the patient felt cramps in her mouth and right hand, twisting of her neck to the right in combination with turning of her eyes to the right and above and she was unable to speak. After a short period of relaxation, her head and hand turned in the compulsion position again. She remained fully consciousness during this episode.

An acute dystonic reaction was considered. The symptoms disappeared immediately upon administration of 5 mg biperiden (akineton) intravenously. No further dystonic reactions were noticed after stopping metoclopramide.

Patient B, a 34-year-old male, was diagnosed with diffuse large B-cell non-Hodgkin lymphoma and was treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). Metoclopramide tablets (10 mg) were prescribed for nausea. The next day the patient developed episodes of torticollis every five minutes. He had cramps in his neck and head to the left and backwards lasting for seconds to five minutes. During these episodes

he could not rotate his neck; he remained fully conscious. There were no signs of urinary incontinence, tongue bite injuries or tonic-clonic seizures.
An acute dystonic reaction (torticollis) was diagnosed, due to metoclopramide. Trihexyphenidyl (artane) 1 mg was administered, upon which the symptoms disappeared. The symptoms did not recur after metoclopramide was stopped.

METHODS

Genomic DNA was isolated from EDTA (Ethylene Diamine Tetra Acetic) blood. Detection of the *4 allele was performed using 5 ng of DNA in a polymerase chain reaction (PCR) with primers 5'-TCATGGCCACGCGCACGTGC-3' and 5'-ACTCCTCGGTCTCTCGCTCC-3', for 35 cycles with conditions [1 min 94°C, 1 min 60°C, 1 min 72°C]. The 460 bp PCR product was digested with BstN1 for two hours at 37°C. The *4 allele will give a specific 347 bp band. For the *5 allele, 20 ng of genomic DNA was amplified with primers 5'-ACCGGGCACCTGTACTCCTCA-3' and 5'-GCATGAGCTAAGGCACCCAGA-3' in a 35 cycle PCR with conditions [1 min 94°C, 30 sec 65°C, 5 min 68°C]. The appearance of a 3.5 kb PCR product indicates the presence of a *5 allele.

RESULTS

Patient A was genotyped as CYP2D6*4/*5 and patient B was genotyped as CYP2D6*4/*4. Both the *4 and *5 alleles encode nonfunctional CYP2D6 enzyme, making both patients poor metabolisers of CYP2D6.

DISCUSSION

Nausea can be induced in several ways. The vomiting centre receives signals from the gut, the vestibular labyrinths and the 'chemoreceptor trigger zone (CRT)', which is located in the area postrema of the medulla oblongata.[4] The dopamine (type 2), serotonin (type 3), histamine (type 1) and muscarine receptors are located here. Emesis is induced when these receptors are activated by their respective neurotransmitters. Specific antagonists of these receptors are used to treat symptoms of nausea.[5]
Metoclopramide is used for treatment of oesophageal reflux, dyspepsia, gastroparesis and for chemotherapy-related nausea.[1,2,6] Metoclopramide blocks the dopamine receptor (D2-R) both centrally as well as peripherally. It stimulates the acetylcholine receptors, which are located on the musculature of the stomach.[7] When metoclopramide is prescribed at a high dose it has an antagonistic effect on the serotonin (5-HT3) receptors.[8] This observation triggered the development of selective 5-HT3-antagonists.[7,9] The antagonistic effects of ondansetron are 100 times more potent than metoclopramide at the chemoreceptor trigger zone.[10]

EPS due to metoclopramide are observed in 1:500 patients.[6,11] Persons at risk are young women, patients with a family history of neurological disorders and those who are treated with neuroleptics.[12]
EPS which have been associated with metoclopramide include tardive dyskinesia, drug-induced parkinsonism, akathisia, malignant neuroleptic syndrome and an acute dystonic reaction.[6,11]
An acute dystonic reaction is defined as sustained muscular spasms producing twisting, squeezing and pulling movements.[6] Specific clinical symptoms are torticollis, opisthotonus, blepharospasms and ocular crises. Respiratory and swallowing problems can lead to life-threatening situations.[6,13] Symptoms often start within 24 hours after administration of a dopamine antagonist and 94% of these symptoms occur within 72 hours.[14]
Several studies indicate that these reactions especially occur in women aged between 12 and 19 years. They have three to four times more chance of developing these side effects.[6,13,15] Acute dystonia is rarely observed in the elderly, due to loss of dopamine receptors.[6]

Metoclopramide is an inhibitor as well as a substrate of the hepatic cytochrome P450 enzyme, subclass CYP2D6. Drug-induced EPS are more frequently observed in patients with a genetic polymorphism in the gene coding for CYP2D6, resulting in an absent enzyme activity.[16,17] Molecular analysis of this gene was therefore performed using a PCR-based method. Both patients were homozygous for inactive CYP2D6, alleles (CYP2D6*4/*4 and CYP2D6*4/*5), making them poor metabolisers. Of the Caucasian population, 5 to 10% are poor metabolisers of CYP2D6. However, the incidence of EPS due to metoclopramide is only 1:500 patients.[17] It is hypothesised that simultaneous use of metoclopramide with drugs that are metabolised by CYP2D6 such as antidepressants and neuroleptics, may provoke EPS. The metabolism of metoclopramide may then be affected more seriously in patients who carry homozygous CYP2D6 nonfunctional alleles, leading to drug accumulation and related toxicities such as EPS.[18]
Both patients were treated with chemotherapy, idarubicin and doxorubicin respectively, which are metabolised by CYP2D6. Therefore, they are more at risk for developing an acute dystonic reaction.
Searching for nonfunctional CYP2D6 would be interesting if a patient is at risk for EPS and if there is no good alternative treatment for metoclopramide. However, there is not much written in the literature about the incidence of patients developing an acute dystonic reaction who are

known as poor metabolisers of CYP2D6. There is a rational relation considering our two patients. More research is necessary before it can be tested routinely.

There are several therapeutic options for acute dystonic reactions after administration of metoclopramide. First of all, metoclopramide should be stopped. Secondly, various therapeutic interventions can be considered. Dysbalance between agonists and antagonists of musculature is seen when a dopamine antagonist, such as metoclopramide, is administered. Through other neurotransmitters (gamma-aminobutyric acid (GABA) and acetylcholine) an extra activation will take place and induce muscular spasms.[19] Blocking these neurotransmitters will inhibit the dystonic reaction. However, GABA derivates (for example baclofen) and dopamine agonists (for example bromocriptine) are only available for oral use, which will produce a delayed effect after 30 minutes.
Direct intravenous administration of anticholinergics (for example biperiden 5 mg or promethazine 25-50 mg) is the treatment of choice for acute dystonic reaction since they provide an immediate effect. Benzodiazepines (diazepam 2 to 20 mg iv or im) induce immediate muscle relaxation and can be used in combination with anticholinergics.[20]
Although both patients are poor metabolisers, they remained free of symptoms after one dose of biperiden and trihexyphenidyl, respectively. Normally the half-life of metoclopramide is four to six hours and for the other drugs 16 to 33 hours and 6 to 12 hours, respectively. The blood level of metoclopramide is probably reduced when biperiden or trihexyphenidyl are eliminated, so that the dystonia does not return.

CONCLUSION

Metoclopramide is an antiemetic drug which can cause a severe adverse event, such as an acute dystonic reaction, especially in patients carrying homozygous CYP2D6 genetic polymorphisms. If a patient is at risk for an acute dystonic reaction and there is a good alternative, metoclopramide use should be avoided. The most rapid treatment of an acute dystonic reaction by metoclopramide is administration of anticholinergics or benzodiazepines intravenously or intramuscularly.

ACKNOWLEDGEMENT

We would like to thank Dr A.F.C. Schut (Ikazia Hospital, Department of Internal Medicine) for reading the manuscript critically.

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