Disturbance of consciousness induced by isotretinoin and azithromycin: A case report

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ABSTRACT

Almost every drug has side effects. Adverse drug reactions occur in 2 to 21% of hospital admissions. An important factor in the occurrence of several drug interactions that can result in drug toxicities, adverse effects and reduced pharmacological effect is genetic polymorphism of cytochrome P450 (CYP), responsible for the biotransformation of several drugs. The aim of this paper is to present the case of a 16-years-old male who developed acute psychosis during isotretinoin therapy for acne and azithromycin therapy due to upper respiratory tract infection. The results indicated normal CYP enzymes activity. However, because of occurrence of symptoms after applying of isotretinoin and azithromycin that are metabolized by CYP 450 the effect of this treatment was taken into account. This patient is probably the second case of delirium during azithromycin therapy among children. This case brings to mind the importance of accurate medical history, especially of information regarding medication and knowledge of possible side effects and drug interactions during diagnostics.

Key words: Delirium, adverse reaction, cytochrome P450.

INTRODUCTION

Almost every drug has side effects. Adverse drug reactions occur in 2 to 21% of hospital admissions (Chan et al., 2016). An important factor in the occurrence of several drug interactions that can result in drug toxicities, adverse effects and reduced pharmacological effect is genetic polymorphism of cytochrome P450 (CYP) (Ogu and Maxa, 2000).

Cytochrome P450 is a family of isoenzymes responsible for the biotransformation of several drugs. Recognizing whether the drugs involved act as enzyme substrates, inducers or inhibitors is very important in preventing clinically significant interactions. Optimal response with minimal adverse effects is possible due to avoiding co-administration or anticipating potential problems and adjusting a patient’s drug regimen early in the course of therapy.

The aim of this paper is to present the case of a 16-years-old male who developed acute psychosis during isotretinoin therapy for acne and azithromycin therapy as a result of upper respiratory tract infection and to discuss metabolism of these drugs and role of cytochrome p450 in this process.

CASE REPORT

16-years-old male, first grade IT technician student visited the SPDSK Hospital Emergency Ward for neurological consultation before hospitalization in Psychiatric Department due to psychiatric disorders. Two weeks earlier the healthy young male suddenly developed auditory hallucinations, periodically increasing anxiety and restlessness with vegetative symptoms (palpitations, intensive sweating and generalized tremor). Thereafter, the sleep disorder in the form of insomnia followed.

This patient had no previous psychiatric history or family psychiatric history. The patient has never shown any disturbing psychopathological symptoms. He was a good student and he never had social problems. He was suffering from acne vulgaris from puberty and treated with
Table 1: Genetic test for CYP polymorphism.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Differentiated alleles</th>
<th>Test result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>*1 wild *3, *4 conditioning the lack of enzyme activity *1x2 gene duplication *5 gene deletion</td>
<td>*1/*1</td>
<td>Effective substrates CYP2D6 metabolism</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1 wild *2, *3 conditioning changed enzyme activity</td>
<td>*1/*1</td>
<td>Effective substrates CYP2C9 metabolism</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1 wild *2, *3 conditioning reduced enzyme activity *17 conditioning increased gene transcription</td>
<td>*17/*17</td>
<td>Effective substrates CYP3A4 metabolism (studies shows that presence of *17 allele is related with increased enzyme activity)</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1 wild *22 conditioning reduced enzyme activity</td>
<td>*1/*1</td>
<td>Effective substrates CYP3A4 metabolism</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*1 wild *3, conditioning the lack of enzyme activity</td>
<td>*3/*3</td>
<td>The lack of CYP3A5 activity (genotype predominant in the population - *3/*3 genotype occurs in more than 90%)</td>
</tr>
</tbody>
</table>

isotretinoin initially 20 mg/day and thereafter, 30 mg/day for 4 months prior to the admission. The treatment was recommended for 6 months. A few days before the onset of psychopathological symptoms the fever and symptoms of upper respiratory infection appeared. For this reason, he was treated with azithromycin 500 mg/day for 6 days. After the onset of psychopathological symptoms and consultation with the dermatologist, isotretinoin was withdrawn.

On admission to the Department of Neurology he was in average general condition with auto- and allopsychic disorientation, amimical face and elated mood. He answered questions belatedly. He knew he was in the hospital, but he did not know the date. He knew his name, but did not know his age. The symptoms were intermittent. The patient was periodically self-critical and upset because of his problems with answers to the questions. Somatic symptoms of anxiety like tachycardia, increased sweating without correlation with the situation was also observed. He confirmed the occurrence of visual and auditory hallucinations. The visual and auditory hallucinations included hearing the voice of his father who was not present at the time. He denied any suicidal ideation. He denied self-harm and willingness to harm others. He denied any abuse of illicit drug.

On physical examination acne on his face was noted. In addition, there was no significant deviation from the norm. The neurological examination found no abnormalities.

In the early days of hospitalization anxiety states alternated with periods of silence or sometimes immobility and auditory hallucinations was observed. These symptoms intensified in the evening. They were accompanied by sleep disorders- the patient had problem with falling asleep and initially he could not sleep at all. After falling asleep, he often woke up. He slept briefly, four to five hours. In the differential diagnosis organic causes, metabolic illness and cytochrome P450 enzyme block due to time correlation with medication used was considered.

The patient underwent many laboratory, toxicological and metabolic (GC/MS, MS/MS) tests, EEG and brain MRI. All results were correct and provided evidence to exclude with high probability the organic causes and metabolic illness. Due to the suspicion of CYP enzyme activity disturbance he was not treated with neuroleptics. If needed, he received lorazepam with good effect because this drug is not metabolized through the cytochrome P450 system. Fluid therapy was applied and the patient state improved. His verbal responses were coherent - he spoke spontaneously, his statements were logical. Sleep disorders and increased anxiety in the evening were no longer observed.

Genetic test for polymorphism CYP was done (Table 1), because genes from CYP family are responsible for the metabolism of xenobiotics. The results indicated normal CYP enzymes activity. However, because of occurrence of symptoms after applying isotretinoin and azithromycin
metabolized by CYP 450, the effect of this treatment was taken into account. 
The therapy used in the hospital resulted in the disappearance of symptoms. The patient was discharged home with improved clinical condition and diagnosis of delirium resulting from possible drugs interaction.

RESULTS AND DISCUSSION

Cytochrome P450 belongs to the isoenzymes group responsible for many drugs biotransformation by oxidation. This group consists of 57 isoenzymes from 3 families CYP1, CYP2 and CYP3. They metabolize about 70 to 80% of drugs (Zanger and Schwab, 2013). The most important among them are isoenzymes CYP3A4 and CYP2D6. These are membrane proteins located at smooth endoplasmic reticulum expressed predominantly in the liver and also in the small intestine, lungs, kidneys and placenta. Their expression is dependent on many mechanisms and factors like genetic polymorphism, xenobiotics, cytokines, hormones, clinical condition, age and gender (Zanger and Schwab, 2013; Lynch and Price, 2007).

Multiallelic genetic polymorphism, which strongly depend on ethnicity, play a major role in the function of CYP 2D6, 2C19, 2C9, 2B6, 3A5 and 2A6. It leads to distinct pharmacogenetic phenotypes termed as poor, intermediate, extensive and ultrarapid metabolizers (Zanger and Schwab, 2013). Drug metabolism through the cytochrome P450 is an important determinant of several drugs interaction that can result in drug toxicities, reduced pharmacological effect and adverse reactions (Ogu and Maxa, 2000).

During the diagnostics of the described patient the fact that he took two drugs metabolized in the liver by this cytochrome in the same time was taken into account. Isotretinoin (13-cis retinoic acid) is a stereoisomer of tretinoin (all-trans retinoic acid) and belongs to 1 generation monoaromatic retinoids - vitamin A active forms. Isotretinoin binds in 99.9% with albumins and is metabolized mainly in the liver. The process consists of oxidation and shortening the chain which leads to formation of metabolites easily eliminated by the kidneys and with the gall. Few CYP isoenzymes participate in this process.

According to the characteristics of the drug, no enzyme plays a dominant role and isotretinoin with its metabolites has no significant effect on cytochrome P450 isoenzymes activity. Isotretinoin is retinoid occurring physiologically in organism. Levels characteristic for endogenic retinoids were obtained two weeks after the end of treatment. It has many adverse reactions like inter alia psychiatric adverse reactions demonstrated an increased risk of depression, attempted suicide and suicide following isotretinoin treatment. A few studies suggest a possible link between isotretinoin and psychosis (Lynch and Price, 2007; Ludot et al, 2015).

Azithromycin is an azalide and belongs to macrolide antibiotics which are strong CYP3A4 inhibitors. Although azithromycin is an exception among macrolides - it does not inhibit CYP3A4 or has no significant effect on it; this effect cannot be excluded in patients who are treated with azithromycin. However, Preisner et al. (2010) noticed that azithromycin is CYP3A4 substrate and can be CYP3A4, CYP2A6 and CYP1A2 inhibitor. To azithromycin adverse reactions belong to inter alia anxiety, irritability and aggressive behaviors.

During the period of using simultaneous drugs with narrow therapeutic index and metabolized by cytochrome p450, special attention is recommended. All these informations allow suspecting the occurrence of non-typical pharmacokinetic phenotype causing slow substrates metabolism that could cause adverse effects of these drugs occurrence. Table 1 shows the genetic test for polymorphism of selected genes. The genotype test did not indicate slower drug metabolism. However, one should bear in mind that only 5 from more than 50 isoenzymes were tested. The patient's clinical condition improved after intense fluid therapy, discontinuation of isotretinoin and azithromycin and avoiding drugs metabolized by cytochrome P450 in treatment.

The informations earlier maintained and the fact that the patient had no family history or previous history of mental disorders could suggest adverse drug reaction as a cause of patient symptoms. The Naranjo adverse drug reaction probability scale which can be helpful in determining whether a particular side-effect is due to a specific medication was used. In this patient, the score was 7/13 which describes casualty as "probable" (Naranjo et al., 1981).

Several cases of isotretinoin adverse reactions in the form of mental disorder have been described (Villalobos et al., 1989; Duke, 1993; Cott and Wisner, 1999). Rajagopal (2014) described the case of a 27 years old female who developed acute psychosis after 5 days of isotretinoin administration. Barak et al. (2005) and Luca et al. (2016) described the cases of manic psychosis during isotretinoin treatment. Most of the descriptions concerned young people as the appearance of acne and use of isotretinoin is most frequent in this age group. Side effects occurred at different times since the beginning of the treatment. To the best of our knowledge, it is the first published case of delirium during isotretinoin treatment.

Cone et al. (2003) reported two cases of delirium resulting from azithromycin therapy in two geriatric patients who were treated for lower respiratory tract inflammation. Case 1: A 78-year-old male on third azithromycin treatment day started experiencing visual hallucinations and 24 h later the azithromycin was discontinued. Over the next 72-h his visual hallucinations resolved. Case 2: A 88-year-old female on the fourth day of
azithromycin therapy became confused and had visual hallucination with paranoia. Azithromycin was discontinued and within 24 h and the visual hallucinations resolved but confusion and paranoia resolved 2 days later (Cone et al., 2003).

Baranowski (2009) reported probably the first case of delirium in a child with therapeutic doses of azithromycin. A 6-years-old girl without family history of neurological and mental disorders, who was treated for acute otitis media with azithromycin after second dose of the antibiotic started presenting symptoms of acute confusional state. She had visual and auditory hallucinations. The antibiotic was identified as the only possible cause of her symptoms. All psychotic symptoms subsided within 48 h after azithromycin discontinuation (Baranowski, 2009).

CONCLUSION

This patient is probably the second case of delirium during azithromycin therapy among children. However in this case, it cannot be clearly defined which drug (azithromycin or isotretinoin) or drugs interaction caused occurrence of his symptoms. This case brings to the remembrance the importance of accurate medical history, especially regarding information about medication and knowledge of possible side effects and drug interactions during diagnostics.

REFERENCES


