Assessment of Hematological Toxicity in Case of Oral Administration of Metronidazole

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Metronidazole is an antibacterial agent, which is part of nitroimidazole class. It is used, particularly, in the treatment of infections caused by anaerobic bacteria and protozoa. Metronidazole, orally administered, is recommended for the treatment of infections with anaerobic germs, specifically in the genitalia area (bacterial vaginitis) and in the abdominal area (Crohn's disease, necrotising pancreatitis, gastritis) and it is a treatment prescribed in infection with Clostridium difficile (pseudomembranous colitis). Metronidazole is also frequently prescribed in the treatment of infection with Helicobacter pylori. Severe adverse effects induced by the intake of Metronidazole are known, such as: convulsive crises, encephalopathy, peripheral neuropathy, reversible neutropenia. The aim of this paper is to present the involvement of Metronidazole in the alteration of platelet function, pathology occurred in form of severe peripheral thrombocytopenia. We present the case of a 59-year old woman, diagnosed with gastritis with Helicobacter pylori, who, after having taken Metronidazole in order to fight the infection, presents severe hemorrhagic syndrome. Thrombocytopenia induced by Metronidazole is a rare adverse reaction, induced by immune mechanism. It is characterised by hemorrhagipar syndrome which occurs after primary haemostasis and clinically manifests at cutaneous-mucous level.

Keywords: toxicity, Metronidazole, thrombocytopenia, anti-platelet antibodies, haemostasis

Metronidazole is a nitromidazole medication. Due to its antibacterial action, it is prescribed in the treatment of numerous infectious pathologies, such as amoebiasis, giardiasis, infection with *Trichomonas vaginalis* [1, 2]. The surgeons, gynaecologists, dentists recommend it particularly for the treatment with anaerobic germs. The neurologists use Metronidazole in the therapy of amoebaean infections of the nervous system. It is also a first-class antimicrobial agent when it comes to curing the infection with *Clostridium difficile* or *Helicobacter pylori* [3-5].

Metronidazole is conditioned in numerous pharmaceutical forms, with different pharmacodynamics properties and bio-availability that corresponds to the effect which is desired to be obtained. Metronidazole is absorbed by the systems from injectable solutions, suspensions, pills. A local effect occurs in case of topical preparations with Metronidazole (cream, ointment, gel) and of semisolid preparations intended to be applied on mucous (suppositories, ovules) [6, 7].

Common adverse reactions (≥1% from the patients) associated with oral therapy with Metronidazole include minor digestive disturbances: nausea, taste disturbances, epigastralgia, vomits, diarrhoea. Intravenous administration is frequently associated with the apparition of thrombophlebitis. Very rarely, hypersensitivity reactions have been reported: rash, face redness, pruritus, fever, angioedema, pustular rash, glossitis, stomatitis. It has been proven that Metronidazole can cause neurological reactions, such as: transitory visual troubles, neuro-psychical reactions, cephalalgia, dizziness, confusion, convulsions, reversible neuro-encephalopathy [8-10]. In high dosage and/or long treatments, the following was reported: leukopenia, peripheral sensorial neuropathy, reversible after the interruption of the treatment. The studies on animals have proven that Metronidazole is cancer-related agent, however mechanisms standing at the basis of this hypothesis have not been very well clarified yet. Rarely, Metronidazole may induce serotoninergic syndrome in usual dosage. Symptoms occurring are: increase of cardiac frequency, chills, perspiration, eyeball dilatation, spasms, hyperthermia, confusion, reflexogenous hyperactivity, muscular rigidity, agitation, headache. The only therapeutic method is to interrupt the therapy with Metronidazole [11- 13].

By means of this study, we want to emphasise the toxic haematological potential of Metronidazole. We present the case of a 59-year old woman, who developed secondary severe thrombocytopenic purpura, after having taken Metronidazole.

Experimental part

Materials and methods

We present the case of a patient, C.S., 59 years old, female gender, coming from the rural environment, who went to the Haematological Department, of the Sf. Spiridon

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University Hospital from Ia°i, Romania, in July 2011, accusing gum and mouth bleedings, and ecchymoses, particularly at her inferior limbs, aggravated in the last 24 hours. The patient mentioned that three weeks before she had been diagnosed with gastritis with Helicobacter pylori and attended the prescribed treatment, with Amoxicillin, Controloc and Metronidazole, with the aim of fighting the infection. The treatment lasted for 5 days.

In emergency, blood samples were collected. The haematological examination revealed very severe thrombocytopenia (platelets= 0/mm^3). The peripheral blood smear showed very rare thrombocytes and platelet-related anisocytosis. The biochemical examination was within normal limits and the immunological tests showed the absence of anti-platelet antibodies. It was also excluded a liver disorder – the viral samples for B and C hepatic virus being negative; the same for the immunological markers for a collagen-related disease. The imagistic examination revealed a normal aspect of the abdominal ultrasound, the spleen being within normal limits. The clinical image was suggestive for thrombocytopenic purpura, its occurring being deemed as an adverse reaction at Metronidazole, in the conditions of excluding another pathology that could cause secondary thrombocytopenia (viral infections, autoimmune diseases, myeloproliferative syndromes).

Results and discussions

The case presented above shows the capacity of Metronidazole to induce thrombocytopenic purpura as a rare adverse reaction. In accordance with the specialty literature, medicine-induced thrombocytopenic purpura is a severe adverse reaction caused by a lot of drugs. This type of thrombocytopenia can be susceptible at all the patients where thrombocytopenia has no known aetiology. It is difficult for clinicians to put the diagnosis of medicine-induced thrombocytopenia. The incriminated substance, which causes the diseases, is difficult to find at patients associated with polimedication and the existing studies that refer to substances that give such reaction are still limited [14- 16].

The assessment of this case reveals the fact that it is atypical. The Najaro algorithm for calculating the probability of an adverse drug reaction's occurring gives Metronidazole the score = 7 and implicitly the statute of probable agent that causes thrombocytopenia.

From the chemical point of view, Metronidazole is part of nitroimidazole class.

It is also known with the name of 2- Methyl, 5-nitroimidazole 1-ethanol (fig. 1). Its molecular mass is M = 171.15396 g/mol.

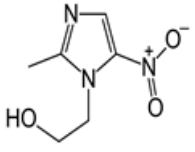

Fig. 1. Chemical structure of 2-methyl, 5-nitromidazole 1-ethanol

It is synthesised by nitrating 2-Methylimidazole, reaction from which it results 2-methyl, 4, 5-nitroimidazole-2, which, on its turn, is subject to alkylation with ethylene oxide or 2-chloroethanol [17- 19]. The synthesis reaction of Metronidazole is presented below, in figure 2.

Its colour is cream, it has crystal shape, or it comes in crystalline powder. It has no smell [20, 21]. Its melting point is = 158-160°C [22]. It is soluble in water and ethanol, a little soluble in ether, chloroform and solutions of diluted acids. It is rarely soluble in dimethylformamide. It is stable in air, but the recommendation is to keep it away from light, because its colour darkens when exposit it to light [23].

The solution of Metronidazole hydrochloride interacts with aluminium, therefore it is counter-indicated to use aluminium instruments in order to prepare drugs that contain Metronidazole. After neutralization – its usual form in injectable solutions – Metronidazole hydrochloride does not react with aluminium, if it is injected during the period of time specified by the manufacturer [24].

Metronidazole was identified in biological fluids (blood, plasma) by means of HPLC (high-performance liquid chromatography) or by means of differential impulse polarography.

Orally administered Metronidazole metabolizes in the liver, in proportion of 30-60%. There results two main metabolites subsequent to the chain oxidation reactions, hydroxylation and glucuronide conjugation. Hydroxide metabolite has a half-life of about 12 hours and it responds for about 50% from the anti-trichomonasis activity of Metronidazole. Bio-availability at oral intake is good (80%). It disseminates in the saliva, bile, seminal liquid, maternal milk, liver, bones and vaginal secretions. It also crosses encephalic barrier, being indicated in nervous system infections. The half-time a Metronidazole is between 6 and 8 hours at adults with normal liver and kidney functions [25, 26].

It is not associated with enzymatic inhibitors of coumarin anticoagulants type, as the effects of Metronidazole can be amplified. Periodical calculations, prothrombin time-type, are performed in order to know the need of adjusting anticoagulant dosages. Liver metabolism of Metronidazole can be diminished in case of associating it with enzymatic inductors, such as cimetidine. This interaction leads to the delay of eliminating Metronidazole and at the increase of its serum concentration [27].

Frequent adverse reactions occurred subsequent to the therapy with Metronidazole administered orally are: rhinitis, diarrhoea, loss of weight, abdominal pains, headache, metallic taste. Intravenous administration may induce thrombophlebitis [12]. Among the rarest adverse reactions

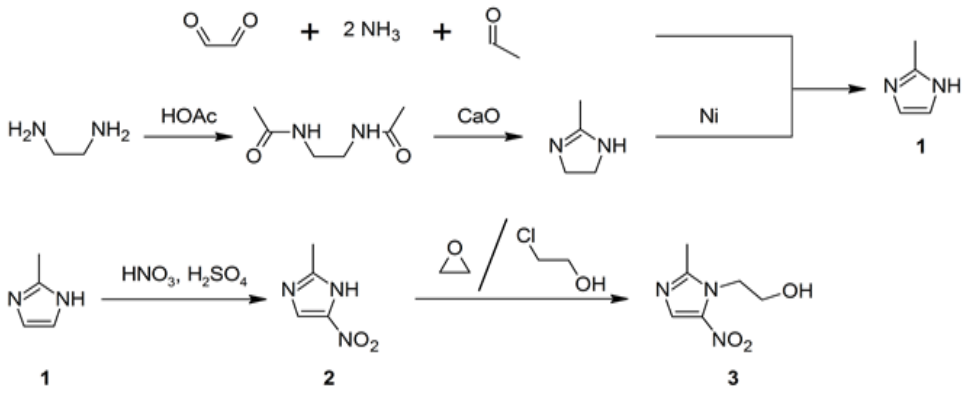

Fig. 2. Synthesis reaction of Metronidazole

occurred, we remind the following: cutaneous hypersensitivity reactions, glossitis, stomatitis, paraesthesia. High dosage taken on long periods of time may induce leukopenia, neutropenia, toxicity at the level of the nervous system.

Conclusions

With this paper, we underline the potential haematological toxicity of orally administered Metronidazole. Subsequent to the study of pharmacological and toxicological profile of this pharmaceutical substance, we have obtained significant data on pharmacodynamics, posology and studied side effects of Metronidazole. By correlating this information with the clinical and biochemical data of the patient presented above, we emphasize the interference of Metronidazole in the occurring of secondary thrombocytopenic purpura.

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