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METOCLOPRAMIDE – INDUCED EXTRAPYRAMIDAL SIGNS AND SYMPTOMS – BRIEF REVIEW OF LITERATURE AND CASE REPORT.

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ABSTRACT:

Introduction: Metoclopramide is a dopamine receptor agonist and well known antiemetic and gastrokynetic agent. Its usage has been restricted by European Medicines Agency (EMA), because of acute and chronic neurological adverse events. Extrapyramidal syndromes, including parkinsonism, tardive dyskinesia, akathisia and acute dystonias, are the most reported and most often drug side effects.

Contingent and methods: We present a case of 23 years old woman with a 3-year history of Metoclopramide-induced recurrent oculogyric crises.

Results: The patient suffered from examinophobia, with minimal benzodiazepine symptoms relief. She willfully took small dosages of oral Metoclopramide for nausea relief before her examinations, which lead to recurrent oculogyric crises, short after the drug intake. After a detailed explanation of drug side effects and medicine discontinuation, they disappeared. She had no significant medical and family history of neurological and psychiatric conditions. Laboratory data were normal.

Conclusions: Metoclopramide could induce acute or chronic neurological conditions and its usage should be restricted in general population to some specific conditions. Some of its adverse reactions are often misdiagnosed and improperly treated. Critical drug anamnesis with a focus on Metoclopramide usage in some cases could enhance diagnosis.

Key words: Metoclopramide side effects, dopamine antagonist, oculogyric crises.

INTRODUCTION:

Metoclopramide is well known antiemetic and gastrokynetic agent, used for treatment of nausea, vomiting, gastroparesis, gastro-esophageal reflux disease and migraine [1, 2, 3, 4]. It is a dopamine (D2) receptor antagonist with short life and mixed $5HT_3$ receptor antagonist and $5HT_4$ receptor agonist [5, 6, 7]. Although its significant effect on nausea and vomiting and widely usage in practice, on 24 October 2013 European Medicines Agency's Committee on Medical Products for Human Use recommended changes of metoclopramide containing medicines use, due to the potential risk of serious neurological side effects. [8]

Extrapyramidal side effects due to metoclopamide are the most common ones. Reported incidence is approximately 0.2%, but in aged and young patients this incidence increases up to as high as 25%, the risk in children is 6 times higher than in adults [8, 9].

They may occur earlier after treatment (most often within the first 24-72 hours), but most likely after several dosages [8, 9, 10]. Risk factors for serious neurological events are high dosages, long treatment period, and treatment of children or elderly patients [8, 9, 10]. Tardive dyskinesia and Parkinsonism are generally seen after long-term use, whereas dystonia and akathisia can occur after a single dose of metoclopramide [10].

Although the possible reason of extrapyramidal side effects presentation is a blockage of striatal D2 receptor, their exact mechanism remains unclear [9].

The most often types of extrapyramidal side effects due to Metoclopramide usage are parkinsonism, tardive dyskinesia, acute dystonias and akathisia. Metoclopramide-induced parkinsonism is not uncommon, risk factors are long-term usage, female sex, advanced age, diabetes mellitus and polypharmacy [10, 11]. Tardive dyskinesia is a syndrome characterized by persistent, potentially irreversible involuntary movements. Metoclopramide tardive dyskinesia incidence is likely to be <1%. [12, 13]. Risk factors are long term use of the medicine, increased age, female gender, pre-existing abnormal movements, diabetes mellitus, "organic" brain dysfunction and atrophy, psychiatric disorders, family history of tardive dyskinesia, polypragmasia [13]. Early syndrome recognition may improve the likelihood of remission [14]; however the treatment in some cases may be unsuccessful. Several medicines, though with variable effects could be used for the symptoms relief; they are Amantadine, Tetrabenazine, Benzodiazepines (limited results), Melatonin (high dosages at long treatment period could be effective), Vitamine E (limited results) [14]. Surgical interventions and Deep brain stimulation may be used in treatment resistant cases [14].

Incidence of acute dystonias due to metoclopramide is about 0.2% with female preponderance [15]. They are usually presented as buccolingual, torticollic, oculogyric and opisthotonic forms [15]. Risk factors are unclear, although parenteral usage and high dosages are believed to be more likely associated with acute dystonias [15]. The mechanism of their development remains unclear, but the

duration of these symptoms corresponds to T1/2 of the drug [15]. Intravenous diphenhydramine may be used for dystonia reversion [15, 16]. Sometimes the clinical picture may imitate acute encephalitis or other brain diseases [15].

The incidence of metoclopramide – induced akathisia is unknown, because of under recognition, although it is believed to be about 20-25% [17, 18]. It may present with varying grades of severity [17, 18]. Benzodiazepines, betablockers, α_2-agonists, opioids, and anticholinergics may be used for treating syndrome [17, 18].

CONTINGENT AND METHODS:

We present a case of 23 years old woman with Metoclopramide-induced oculogyric crises misdiagnosed as panic attacks. History of disease, general, neurological and psychological examinations, laboratory data are applied.

RESULTS:

The patient (23 years old student) was presented at our department with a 3- year history of unexplained oculogyric crises during some of her examinations. She suffered from long term examinophobia with anxiety and moderate autonomic signs, including nausea and vomiting, tachycardia and pallor. Small dosage of benzodiazepine (Rivotril) for acute symptom prevention was prescribed with minimal effect and she willfully stopped it. At first she complained of unexpected oculogyric crises with short duration (2 minutes), during her examination 3 years ago. This sign troubled her and she visited her outpatient psychiatrist, who diagnosed severe panic attack and sent her to psychologist. Psychotherapy was not conducted, because of patient's refusal. The same syndrome she had many times, irregularly, during some of her examinations, however the syndrome worsened with every appearance – the duration and severity of signs increased and she was unable to sit for her exams. She had no symptoms between examinations, no other significant medical or family history. At first she denied substance abuse and unprescribed medicine usage. Laboratory data were normal. She was kindly asked again for using unprescribed medications of all kinds, with a focus on dopamine-agonists. The patient confessed that she had taken 1 or 2 tablets (10-20 mg) Metoclopramide before examinations for nausea suppression. Metoclopramide side effects were explained to the patient and the medication was discontinued. Proton-pump inhibitor was prescribed for her nausea; she refused benzodiapine treatment and psychotherapy. The patient had no more oculogyric crises after the previously mentioned corrections and she passed her exams session with success.

DISCUSSION:

Oculogyric crisis is an acute dystonic reaction [15], characterized by prolonged involuntary upward deviation of the eyes, which can be associated with some drugs usage - neuroleptics and other dopamine antagonist (including Metoclopramide), carbamazepine, chloroquine, cisplatin, lithium, domperidone, nifedipine, pemoline, phencyclidine, etc. or with brain diseases. It could be recurrent and triggered by different factors (including stress and drug exposure). The syndrome is often misdisgnosed. In many cases it can mimic some neurological and psychiatric diseases, particularly in cases with short duration and mild severity, it is underdiagnosed [15]. Our patient had long history of recurrent acute Metoclopramide-induced oculogyric crises, misdiagnosed as panic attacks, with worsening of signs that lead to severe, although short-time functional disabilities and psychological distress. The signs occurred early after taking medication and disappeared without treatment, similarly to that notified by Arumugam [15]. Our patient had other psychiatric illness – examinophobia, but no history of co-morbid neurological and psychiatric conditions, no family history of dyskinesia or other neurological diseases and no polypragmasia. The explanation of drug-side effects to the patient appeared to be of great importance, because, because she obviously took and stopped medications herself, without visiting physician or reading drug instructions. In this clinical case we diagnosed the Metoclopramide – induced adverse drug reaction after a 2- month clear period and no oculogyric crises during the whole exams session. The patient remained under medical observation and according to us should undergo a psychological treatment.

CONCLUSIONS:

Metoclopramide induces acute or chronic neurological side effects and its usage in general population should be restricted to some specific conditions. Some of its adverse reactions are often misdiagnosed and improperly treated. In some cases the thorough drug history with a focus on Metoclopramide usage enhances diagnosis.

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