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Case Study

METRONIDAZOLE INDUCED SEIZURES

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ABSTRACT

This is a case report of a four year old female patient who was admitted to pediatrics ward at Owaisi Hospital and Research Centre with chief complaints of abdominal pain and burning sensation while micturition since 2 days, associated with frequent straw colored urination and nausea. The condition was diagnosed as Cystitis, for which antibiotics were started. Three days post administration of Metronidazole, seizures were experienced by the patient. This ADR has scored 6 on naranjo algorithm, which indicates the reaction as probable. This is a rare case of metronidazole induced seizures in a pediatric patient. The reason behind the event could be the dose of metronidazole, which was slightly higher than the calculated dose according to the weight of the patient.

Keywords: metronidazole, seizure, ADR, drug induced convulsions

INTRODUCTION

A seizure is a paroxysmal clinical event of the central nervous system, characterized by an abnormal electrical discharge and associated with a change in the usual functioning. A seizure occurs when there is a sudden imbalance between the excitatory and inhibitory inputs to a network of neurons in the cerebral cortex, so that there is overall excessive excitability.[1] Almost every drug and toxin can produce seizure. Some drugs such as tramadol and TCA cause seizure more commonly. Withdrawal from opioids, ethanol, and some benzodiazepines and phenobarbitals may cause late seizure. Standard treatment in seizure due to unknown toxin is done with a benzodiazepine firstly and then phenobarbital or phenytoin. There are also special treatments, for example, pyridoxine in isoniazid-induced seizure, naloxone in propoxyphene-induced seizure, and glucose in seizure due to hypoglycemia.[2] Metronidazole is a 5-nitroimidazole (as shown in figure 1) with potent activity against anaerobic bacteria and several protozoa, including Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis and Balantidium coli. This is the drug of choice for giardiasis and initial treatment of invasive amoebiasis.[3]
Metronidazole is classified in the WHO Essential Medicines List as antiamoebic, antigiardiasis, and antibacterial.[4] It is used in combination with other antibiotics and either bismuth compounds or proton pump inhibitors for treatment of peptic ulcer disease caused by Helicobacter pylori.[5] Metronidazole is, in general, very well tolerated, has a wide therapeutic index, and its serum and tissue concentrations do not require routine determination.[5,6] The common side effects include mild abdominal pain, headache, nausea and a persistent metallic taste. Other serious and rare side effects include pseudomembranous colitis, seizures and encephalopathy.[3] Less frequent untoward effects in the digestive tract include an unpleasant metallic taste and vomiting.[7,8] Metronidazole is absorbed rapidly with a bioavailability (BA) of higher than 90% and approaching toward 100%.[8,9] According to Simms-Cendan, metronidazole is passively transported through mammalian cells.[5] Metronidazole is widely distributed and appears in most body tissues and fluids. Less than 20% of the circulating metronidazole is bound to plasma proteins. The distribution volume ranges from 0.51 to 1.1 L/kg. Metronidazole is metabolized in the liver.[8-10]

Convulsive episodes are associated with the use of a number of antimicrobial agents. Although seizures may be a feature of the disease being treated, antibiotics should be considered possible

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causes of seizures, particularly if suggested by temporal relationships between seizure activity and drug administration. The astute clinician should be aware of the clinical settings in which antibiotic-induced seizures occur, be familiar with likely agents and their mechanisms of toxicity, and be prepared to institute appropriate management directed at this adverse effect of antimicrobial therapy.[11] Metronidazole in high cumulative doses has been associated with convulsions.[12]

Convulsions induced by short- term metronidazole therapy used in conventional doses for Clostridium difficile colitis in an elderly patient with Chronic Renal Failure was also reported.[13] The estimation of the probability that a drug caused an adverse clinical event is usually based on clinical judgment. Lack of a method for establishing causality generates large between-raters and within-raters variability in assessment. There are several methods to assess causality, which includes WHO probability scale, Naranjo's scale, Karch & Lasagna scale, Spanish quantitative imputation scale, Kramer's scale, Jones scale, European ABO system and Bayesian system.[14]

CASE REPORT

A four year old female patient was admitted to pediatrics ward at Owaisi Hospital and Research Centre with chief complaints of abdominal pain and burning sensation while micturition since 2 days, associated with frequent straw colored urination and nausea. At the time of admission, the patient's blood pressure, pulse rate and temperature were normal and the treatment was started with antibiotics as given in table 1. CBP, CUE and urine dipstick test were advised to the patient. On the second day, test reports were obtained which are given in table 2, 3 & 4. Pain and abdominal tenderness were observed. The condition was diagnosed as Cystitis, same therapy was continued on the day two. An episode of seizure was experienced on the third day. Vitals were stable with persistent abdominal pain and tenderness. Inj. Eptoin (Phenytoin) was given to prevent further episodes of convulsions and Tab. Cyclospasmol was added in the therapy to lower the pain. On the fourth day, Metronidazole was suspected to be the cause of Seizures. Hence, it was replaced by Ampicillin to treat the infection. On the next day, pain was slightly decreased and the same treatment was continued as that of day four. There was much improvement in the symptoms on the fifth day as a result, the patient was discharged.

DISCUSSION

Metronidazole is generally considered to be a safe drug with less adverse effects. This is a a rare case of metronidazole induced seizures in a pediatric patient. The reason behind the event could be the dose of metronidazole, which was slighlt higher than the calculated dose according to the weight of the patient. The present adverse drug reaction has scored 6 on Naranjo Algorithm, a scale for assessing causality, which categorises the ADR as "Probable" as given in table 5.

Surviving with Seizures: Children with epilepsy often need to make lifestyle changes to minimize the frequency of seizures and possible dangers associated with seizures. Parents should teach their child to avoid biking, skating, and skateboarding on streets with heavy traffic. All children need to wear protective gear, including a helmet, during these activities. Activities at heights (eg, climbing a tree or rope) should be avoided to prevent serious falls if the child has a seizure while climbing. Always children should be supervised around water, Children with epilepsy should wear a medical identification bracelet or necklace at all times. If a seizure occurs and the child is unable to explain their condition, this will help responders give the proper care as quickly as possible. Children should be encouraged to sleep well and take medications on time.

CONCLUSION

Metronidazole induced seizures is a rare adverse drug reaction, the present case report can elevate the evidence against metronidazole for causing Seizures. Further studies can be carried out to establish a link between this drug and the disease. If possible, Metronidazole should be avoided in the patients with past history of convulsions.

CONFLICT OF INTEREST

Authors state that there is no conflict of interest.

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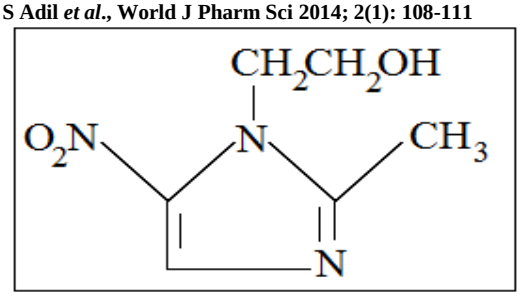

Figure 1: Structure of Metronidazole

Table 1: Therapy on day one

Brand name	*Generic name*	*Dose*	*Route*	*Frequency*
Inj. C.Tri	Cefuroxime	1gm	iv	BD
Inj. Metrogyl	Metronidazole	40ml	iv	TID
Tab. Tyfy	Paracetamol	300mg	oral	TID
IVF Iso-P	Multi-Electrolytes	500ml	iv	TID
Inj. Zofer	Ondansetron	2cc	iv	BD
Inj. Rantac	Ranitidine	1cc	iv	BD

Table 2: CBP

Parameter	*Test value*	*Normal range*
RBC	$4.4 \times 10^6/mm^3$	3.9 – 5.3
Hb	11.9g/dL	11.5 – 15.5
PLT	$401 \times 10^3/mm^3$	150 – 450
WBC	$7.96 \times 10^3/mm^3$	5.5 – 15.5
Neutrophils	55.9%	23 – 45
Lymphocytes	36.4%	35 – 65
Erythrocytes	4.7%	3 – 6
Monocytes	2.1%	0 – 3
Basophils	0.75%	0 – 1

Table 3: CUE

Characteristic	*Test*
Color	Straw
Transparency	Slight
Specific gravity	1.03
pH	6.5
Albumin	Trace
Sugar	Trace
Epithelial cells	2 – 3
Pus cells	2 – 4

Table 4: Bacterial Dipstick Test

	Dipstick Test
Bacteria presence	Positive

Table 5: Naranjo Algorithm values

Score	*Type of ADR*
≥9	Definite
5 – 8	Probable
1 – 4	Possible
0	Doubtful

LIST OF ABBREVIATIONS:

Abbreviation	*Full Form*	*Abbreviation*	*Full Form*
ADR	Adverse Drug Reaction	mg	Milligram
BD	Twice a day	ml	Millilitre
CBP	Complete Blood Picture	PLT	Platelet
CUE	Complete Urine Examination	RBC	Red Blood Cell
dL	Decilitre	Tab	Tablet
gm	Gram	TID	Thrice a day
Inj	Injection	WBC	White Blood Cell
iv	Intravenous	WHO	World Health Organization

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