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Cefixime-Induced Dystonia and Hypothermia in a 12-Year Old Boy: A Need for Safe Prescribing

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Abstract: This study report a case of adverse reaction to cefixime; a newly promoted drug in Nigeria, manifesting as dystonia and hypothermia in a 12-year old boy. The reaction was delayed, as it occurred after the second dose of the drug. The symptoms abated after cefixime was discontinued without causing any sequelae. Neurotoxicity of cefixime was initially uncommon and not reported during its clinical trial, but in recent time it has emerged and is on the increase, especially in adults with renal failure. The neurotoxicity reported in adults ranged from encephalopathy to coma, which were reversible after discontinuation of the drug. Dystonia and hypothermia had neither been reported in adults nor children following use of cefixime at therapeutic dose or in children with renal failure. This report is, therefore, made to alert health care providers that adverse drug reaction in children is not a rare problem in Nigeria and to highlight the significance of evidence based medicine, safe and rational prescribing in preventing adverse reaction to drugs.

Key words: Cefixime, adverse reaction, rational prescribing, hypothermia, dystonia

INTRODUCTION

Cefixime, a third-generation cephalosporin with a broad antibacterial spectrum, is a commonly used antibiotic for the treatment of serious hospital infections in the developed countries (Fernandez-Torre, 2006). A very good advantage of this drug is that, being available as an oral formulation, it allows early switch from one form of parenteral third-generation cephalosporin to an enteral therapy, without necessarily changing the antibiotic group. In addition, prolonged hospitalisation and tremendous cost of treatment are much reduced. Gastrointestinal symptoms have been its major adverse effects; diarrhoea being the commonest (Taketomo *et al*., 2004). However, case report of cefixime-induced colitis had been made many years ago (Gremse *et al*., 1994) and in recent time, cefixime-induced neurotoxicity; ranging from encephalopathy to coma (Capparelli *et al*., 2005; Fernandez-Torre, 2006) which were reversible. These neurologic disorders were reported in uremic and elderly patients whose serum cefixime levels were elevated.

Until recently, cefixime was rarely used in Nigeria. Prescribing information is scanty on the drug as it is not listed in both the essential drug list and the national drug formulary. Therefore, the prescribers are likely to rely on the scanty information from the drug promotion or the information booklet supplied by the marketing companies which are, by far, inadequate for safe prescribing (World Health Organization, 2004).

Despite the many potential adverse effects of cefixime, none has been reported in children. People are not aware of any neurotoxicity of cefixime at therapeutic dose, manifesting as dystonia, especially in children. Hence, this report of a twelve-year old boy that developed dystonia and hypothermia following his treatment with cefixime at the paediatric outpatient clinic of the Lagos State University Teaching Hospital (LASUTH), Ikeja.

CASE REPORT

AA, a 12-year old boy, initially presented to the general paediatric outpatient clinic of the Lagos State University Teaching Hospital, Ikeja, with a 4-day history of fever, headache and reduced appetite. The fever was high grade, intermittent with chills and rigors, and reduced by using paracetamol tablets. Constitutional symptoms such as cough, vomiting, body ache; neck and joint pains were absent. He tolerated both liquid and solid feeds without pain on swallowing, the ears were not discharging pus and his genitourinary system was asymptomatically non-constitutional. Physical

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examination was essentially normal except a high axillary temperature of 39.8°C. His body weight was 40 kg, he had never used any form of herbal medicines since birth; neither had he used any drug, except paracetamol, two weeks before presentation.

A presumptive diagnosis of malaria to rule out early sepsis was made. Having ascertained that the boy had used artemesinin based combined antimalarials in the past without any adverse effect; he was prescribed a combination of artesunate with amodiaquine, to be taken as 100/300 mg twice daily for 3 days. He was also prescribed cefixime capsules, 400 mg daily and paracetamol tablets, 1000 mg thrice daily, both to be taken for 5 days. The drugs were purchased from the fee paying pharmacy of the hospital and used according to the pharmacist's instruction.

While taking the drugs, his mother noticed him to have improved clinically; the headache and fever had subsided, and appetite for food was increased. On the third day of treatment, he, suddenly, developed abnormal movement of the body; characterised by intermittent twisting motion of the whole body, hyper-extension of the neck and spine with outward posterior curves, bilateral abnormal posturing of the lower extremities with the feet assuming extended and rotated position that made the boy to tip-toed while walking. The facial muscles were rigid with upward gaze; speech and swallowing were impaired during the attack but no loss of consciousness. There was no history of use of metoclopramide, promethazine or chlorpromazine. Each episode lasted about 10 min at 30 min interval. He has had three episodes of the attack before presenting to the children emergency room (CHER). After the first episode, he was taken to a private hospital where his axillary temperature was reported as 33.2°C but all other vital signs were not documented in the referral note. He was given only i.v 5% dextrose in saline, 500 mL fast and subsequently referred to us. At presentation in the CHER, his axillary temperature was 35.1°C, heart rate 110 beats per min respiratory rate 30 cycles per min and blood pressure 100/60 mmHg. Other physical examination findings were essentially normal except twisting motion of the body, hyper-extended neck and tip-toed walk, which were observed but appeared transiently.

An assessment of idiosyncratic drug reaction was entertained and was further supported by the results of full blood counts, electrolyte and urea, cerebrospinal fluid analysis which were essentially normal. He was closely monitored at the CHER while on admission for 4 days. Cefixime was discontinued and last dose of the artesunate/amodiaquine administered, he was also maintained on i.v 5% dextrose in saline, 500 mL every 8 h. and trihexphenidyl (artane) 2 mg daily, per oral was given until he was discharged home. He was followed up at the paediatric outpatient clinic weekly for three weeks and found physically and mentally fit. He was advised not to use cefixime again, before finally discharged from the clinic.

DISCUSSION

This report is intended to inform health care providers, especially those attending to children, that adverse drug reaction among children is not a rare problem in Nigeria and to highlight the significance of evidence based medicine, safe and rational prescribing in averting preventable adverse drug reaction (Oshikoya *et al*., 2006).

Fever was one of the presenting symptoms of the patient and a recent history of fever is enough a criterion for diagnosis of uncomplicated malaria (Ogun, 2006), this, therefore, explains the empiric treatment with an antimalarial. The choice of artesunate/amodiaquine in this patient must have been informed by the change in national guidelines for uncomplicated malaria treatment in Nigeria (Federal Republic of Nigeria, 2005) where, artemesinin based combined antimalarial is recommended as the first line drug for uncomplicated malaria treatment. The fact that both artesunate/amodiaquine and cefixime used by the patient are relatively new drugs in Nigeria and their clinical trials not done in children might have made it very difficult to properly identify the culprit drug. However, cefixime was more favoured as the culprit drug because amodiaquine alone has not been reported to be neurotoxic at therapeutic dose and its use predates the other drugs (Parikh *et al*., 2007). Even though, an idiosyncratic reaction may occur to amodiaquine, the fact that the observed reaction did not continue with further use of amodiaquine further eliminated it as the culprit drug. Artesunate and its derivatives, on the other hand, have been reported to be neurotoxic in animals but not in human (Woodrow *et al*., 2005), however, many physician are sceptical about the use of artesunate because of the fear of neurotoxicity, despite no official report of this in human. They are of the opinion that, while, pharmacovigilance continues on the drug, it should be used prudently. The fact that the patient had used the combined antimalarial before, without showing any adverse reaction and the condition not worsened upon re-introducing the drug, possibly exonerates artesunate too as the culprit drug.

Literature abounds on the neurotoxicity of cefixime, especially in adults with renal impairments and increased serum levels of the drug (Capparelli *et al*., 2005; Fernandez-Torre, 2006). Surprisingly, no similar report has been made in children from both developed and developing countries; probably as a result of lack of clinical trials of drugs in children.

The uniqueness of this report is that it is very likely to be the first of its kind in children, the adverse reaction occurred at therapeutic dose of the drug, and the neurological manifestation was dystonia; which was completely different from those reported in adults (Capparelli *et al*., 2005; Fernandez-Torre, 2006). Like other neurologic manifestations, the dystonia was completely reversible after cefixime was discontinued. It is, therefore, very likely that the drug has some extrapyramidal effects; possibly a competitive antagonistic property on the dopamine receptors.

Irrational drug use is one of the major causes of preventable adverse drug reaction (Oshikoya and Njokanma, 2007) and was the cause of this patient's problem. Cefixime prescription to this patient has not been justified by the history of the ailment. Moreso, it is a new drug just promoted to the doctors in the last few months. The prescription must have been motivated by gratification from the detailed product sales representative to the hospital. The influence of sales representatives on the doctors' prescription had earlier been reported in this hospital (Oshikoya *et al*., 2006). Patients with generalised dystonia, irrespective of their causes, have been known to respond to large doses of trihexphenidyl (Johnston, 2004). However, we chose to treat the patient with low dose of the drug because the symptoms of dystonia have tremendously reduced at presentation.

We have been unable to find a plausible explanation for the mild hypothermia observed in this patient. An extensive literature search has not shown an association between dystonia and hypothermia; however it is not impossible that the mechanism by which cefixime produces hypothermia is similar to that of neuroleptics, sedative-hypnotics, and benzodiazepines (Mofenso, 1998) since these drugs are known to predispose to developing hypothermia. These drugs, especially the neuropletics, are known to exert some effects on the hypothalamus or pituitary that may involve dopamine. This therefore explains the hyper-prolactinaemia that may complicate neuroleptic use (Baldessarini, 1996). However, involvement of dopamine in the thermoregulatory function of hypothalamus has not been documented.

A high index of suspicion is required especially if the patient is on multiple drugs.

CONCLUSION

Practising evidence based medicine, caution in prescribing new drugs, shunning pressure from detailed sales representatives lurking around the hospital, and a sound knowledge of the pharmacology of the drugs will go a long way in averting preventable adverse reaction, especially to new drugs.

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