CASE-REPORT

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Refractory Status Epilepticus due to Ranolazine Toxicity in a Young Child.

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ABSTRACT

Ranolazine is used as an anti-anginal and anti-arrhythmic drug in adults. Its use as antiepileptic is still under trial. We report a case of refractory status epilepticus due to accidental ingestion of ranolazine in a 3 year old child.

INTRODUCTION

Ranolazine is novel anti-anginal, anti-arrhythmic drug with favourable effect on glycaemic index. It is used for chronic stable angina. Ranolazine is a new anti-anginal drug approved by United States Food and Drug Administration US FDA in 2006 for use in adults with chronic stable angina or stable ischemic heart disease (SIHD), either as a first line agent or as an add on therapy. Ranolazine also has other non anginal effects, like on glycaemic control and as an antiarrhythmic agent. [1] The most common side effects of ranolazine are headache, dizziness, nausea, and constipation. Less common side effects include tremors, syncope, paraesthesia, hypoesthesia, hallucination, bradycardia, hypotension, palpitation and prolonged QT interval. [2] Adverse paediatric neurological outcome associated with ranolazine in a young child has not yet reported. We present a case of 3 year old child with refractory status epilepticus following accidental ingestion of tablet ranolazine.

CASE REPORT

A three year old female child was brought to emergency unit with the history of repeated convulsions within two hours of accidental ingestion of two tablets of ranolazine

(each 1000mg), which was prescribed to her aunt for chronic angina. The child had multiple episodes of convulsions, which were generalized tonic-clonic with up rolling of eyeballs, frothing from mouth and loss of consciousness. Child was absolutely alright before this episode. There was history of Pica but no history of fever, headache, vomiting or head injury. There was no past history of convulsions and her development was normal. On examination she was unconscious with Glasgow Coma Scale (GCS) score of 7, laboured breathing and weak peripheral pulses. She was treated immediately with normal saline (NS) bolus and artificial ventilation. Her stomach wash revealed the pieces of ranolazine tablets. She was treated with phenobarbitone, phenytoin and midazolam infusion. Her random blood sugar and ionic calcium were 119mg/dl and 1.2mmol/l respectively. Electrocardiogram did not show prolongation of QT interval. Her complete blood count, arterial blood gas, serum electrolytes and renal function test were normal but liver enzymes were deranged which normalized over a period of week. Toxicological screen for this new drug was not available. After 36 hours of clinical seizure free period, child was weaned off from ventilator and transferred out of paediatric intensive care unit. Neuroimaging (Magnetic Resonance Imaging - Brain) and electroencephalogram both were normal. Child was discharged after seven days without any neurological deficit or complications.

DISCUSSION

Role of ranolazine in children is under investigation for genetic epilepsy. Mutation involving brain voltage-gated sodium channel NaV-1.1 is a cause of genetic epilepsies like febrile seizures plus (GEFS+), severe myoclonic epilepsy of infancy (SMEI) and familial hemiplegic migraine type 3. Neuronal excitability in these genetic epilepsies is due to increased persistent current due to mutant Na V 1.1 channel. [3] Ranolazine proposed as new antiepileptic drug in such subset of patients through its action on these isoforms of Na channels. Similar effect of ranolazine on other sodium channel isoforms, like on peripheral nerve NaV1.7 and NaV1.8 was shown in study by Rajamani et al [4] and Wang et al. [5] On the contrary, neurological adverse effects have been reported with ranolazine when administered alone or in combination with other drugs. A 71 year old female developed myoclonus within two days of starting ranolazine. The myoclonus resolved completely on discontinuation of ranolazine. She was not on any other drugs which had known interaction with Ranolazine. [6] While Mishra et al [7] reported dysarthria, dysmetria and severe ataxia, but had no seizure activity when ranolazine was administered with clarithromycin in an adult patient. Ranolazine and clarithromycin interact with each other through CYP 3A metabolic pathway. In recent case report by Akil et al [2] a 15 year old boy with attention deficit/hyperactivity disorder, who was on risperidone, clonidine and venlafaxine, developed recurrent seizures after ranolazine overdose. Similar to our case this patient also presented with status epileticus and required ventilator support. Ranolazine and risperidone both are metabolized by CYP2D6 and CYP 3A4 metabolic pathway. [8] Ranolazine competes for these enzymes and increases risperidone level. The risperidone is known to have low seizure activity. Ranolazine overdose might have lowered seizure threshold in this patient. In first two cases the neurological side effects were probably due to ranolazine. In our case patient was not on any other drug, he was not a known epileptic and the history was not pointing to any other CNS insult except the drug ranolazine. Ranolazine though is proposed antiepileptic it may cause neurological adverse effects. Increased neural excitability may be the result of ranolazine interaction with other Na channels as well as persistent resurgent sodium currents. [6] Condition like severe myoclonic epilepsy of infancy (SMEI) may aggravate with selective suppression of persistent sodium current, which are caused by non-functional alleles (e.g. nonsense, frame shift mutations), so antiepileptic action of ranolazine cannot be generalised for all patients with sodium channel mutations. [9, 10] According to Kahlig et al, this action more is beneficial in epilepsy prophylaxis rather than terminating active seizures. [10] On the other hand Kristopher et al in their study reported antiepileptic activity of ranolazine through reduction of hippocampal neuronal excitability. [11] Lyndsey et al found that ranolazine was able to decrease frequency of seizures in mouse model. [12]

CONCLUSION

When we applied Naranjo adverse drug reaction probability scale, it indicated a `probable` relationship between patient's neurologic adverse effect and ranolazine as the causal drug. We therefore conclude that further research is required to know ranolazine related adverse neurologic effects and its role as an antiepileptic in certain types of seizures.

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