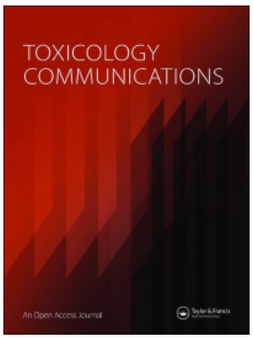

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CASE REPORT

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Ampicillin-induced seizures in a 4-month-old with bacterial meningitis: a case report

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ABSTRACT

Seizure is a rare but documented adverse event associated with ampicillin, which is one of the most commonly used antibiotics used in pediatrics. We report a case of a 4-month-old male infant with *Haemophilus influenzae* type A meningitis that experienced recurrent tonic-clonic seizures, possibly secondary to ampicillin treatment. After ampicillin administration was withdrawn and antiepileptic agents were administered, the seizures resolved, improving the patient's clinical status rapidly. This case report adds to the growing body of literature on ampicillin-induced seizures.

KEYWORDS

Ampicillin; antibiotic; seizures; meningitis; pediatric

Introduction

Childhood seizures are a frightening experience for any parent, yet seizures in pediatric populations are quite common, affecting as many as one in 10 children [1,2]. Ampicillin-induced seizures are a rare side effect whose entity needs better awareness as ampicillin is one of the top five most prescribed childhood antibiotics [3,4]. The most often reported mechanism of antibiotic seizures is via GABA antagonism, causing a lowered threshold for epileptic activity [5]. When new onset or worsening seizure activity cannot be adequately explained by other means, considering the choice of our antibiotic as a mechanism is an important consideration.

We report, in accordance with the CARE guidelines [6], a case of a 4-month-old male infant with *Haemophilus influenzae* type A meningitis who developed seizures after treatment with ampicillin.

Case report

A 4-month-old, fully immunized and previously well male transferred from an outside hospital and was transferred to the pediatric intensive care unit (PICU) with a 14 hour history of bulging anterior fontanelle, inconsolable fussiness, increased somnolence, non-bilious non-bloody emesis, and fever. The patient was born at 34 weeks gestation and had a previous medical history of gastroschisis with repair. We made a presumptive diagnosis of meningitis and started empiric treatment with acyclovir, vancomycin, and ceftriaxone. We performed a lumbar puncture and collected cerebrospinal fluid (CSF) for culture and analysis. Blood cultures were drawn simultaneously. The patient's fever abated, and the patient demonstrated both clinical and laboratory improvement as response to empiric therapy, and he moved from the PICU to the pediatric ward on hospital day 2.

CSF cultures and serum PCR revealed *Haemophilus influenzae* beta lactamase negative, and serotyping further demonstrated *H. influenzae* type A. We discontinued acyclovir and vancomycin on day 3 due to sensitivity testing. As renal function was normal, we switched ceftriaxone to ampicillin at 75 mg/kg every six hours. Each dose of ampicillin was administered over the course of one hour. Several hours after we administered the third dose of ampicillin on day 4,

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the patient had a witnessed tonic-clonic seizure that resolved spontaneously in less than 5 min. Ampicillin was continued on schedule following cessation of the seizure, with a second witnessed tonic-clonic seizure an hour after initiation of the fourth dose of ampicillin. We used lorazepam 0.1 mg/kg to resolve the second seizure. We again administered ampicillin, although halted halfway through the fifth dose as a third tonic-clonic seizure was witnessed, again resolving with use of lorazepam 0.1 mg/kg. Seizures resolved with lorazepam, levetiracetam, and discontinuation of ampicillin. Antibacterial treatment was resumed with ceftriaxone monotherapy at 50 mg/kg IV every 12 h. We performed an MRI which revealed leptomeningeal enhancement consistent with meningitis, while ruling out ventriculitis, intracranial hemorrhage, subdural abscess, and empyema.

No further seizures occurred, and the patient was discharged after 14 days in the hospital. At follow up in an outpatient setting in subsequent months, the child was doing well.

Seizures were charted using the estimated concentration of ampicillin, according to its half-life for clearance and dosing in our patient, Figure 1. We calculated the concentration using half-life data from a previous pharmacokinetic (PK) study [7]. The graph is a simplification of complex pharmacokinetics.

Discussion

The most commonly accepted mechanism for ampicillin to cause seizures is via GABA antagonism, in both direct and indirect pathways. Wanleenuwat et al. offer a comprehensive review of these pathways – direct binding to the $GABA_A$ receptor complex, indirect binding to sites within the $GABA_A$ receptor complex, and additional benzodiazepine receptor binding. These effects lower the seizure threshold[5].

Seizures are listed as a neurological adverse event on the 2017 package insert for intramuscular/intravenous administration (IM/IV) of ampicillin, [8]. Several risk factors are known to increase the risk of seizures in neonates exposed to ampicillin: pre-existing epilepsy, history of CNS damage, renal failure, and sepsis have been correlated with higher incidence of seizures [9]. Although there is an increased relative risk with presence of one or more risk factors, a study by Clark et al. found that incidence of seizures in neonates exposed to ampicillin in combination antibiotic therapies for the treatment of sepsis is low, affecting around 2% of exposed neonates [9]. Management of ampicillin-induced seizures includes cessation of the offending drug, consideration for antiepileptic medication and treatment of underlying causes; for example, electrolyte abnormalities and infection.

The Naranjo Adverse Drug Reaction Probability Scale is a scale with high reliability and validity that assesses whether there is a causal relationship between an adverse event and use of a drug by using a simple questionnaire [10] that assigns probability scores. In our patient's case, the Naranjo score of 5, scored as seen in Tables 1 and 2, suggests that the patient's seizures were possibly related to ampicillin administration. [10].

The limitations of this case report are that it is possible that the seizures were a direct result of the patient's underlying meningitis disease progression. However, the patient had an improved clinical status, was no longer febrile and had down-trending inflammatory markers prior to his seizure activity. It is also possible that further incidence of seizure activity was halted, separate from the cessation of ampicillin, secondary to the administration of levetiracetam. Lastly,

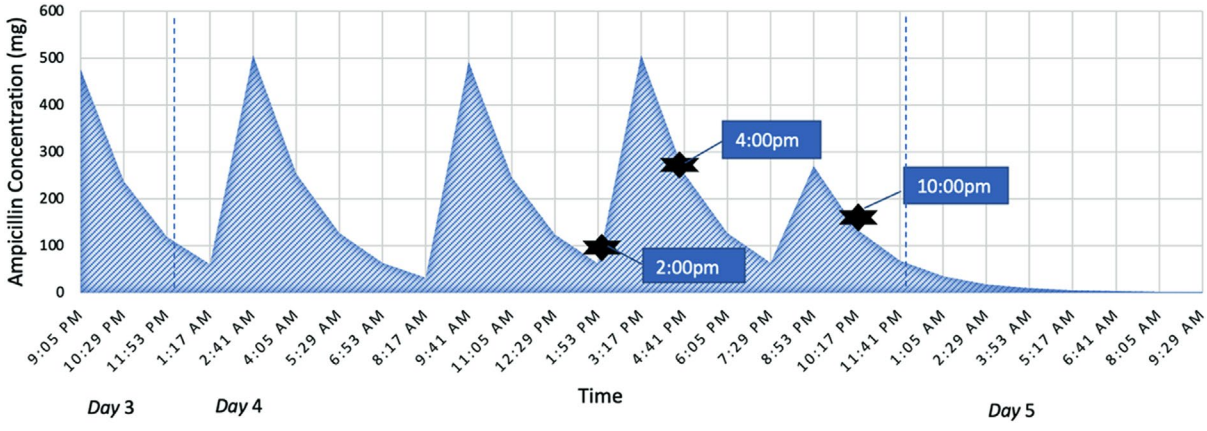

Figure 1. Occurrence of seizures (stars) with estimated ampicillin concentration.

Table 1. Scoring of the Naranjo Adverse Drug Reaction Probability Scale.

1	Are there previous conclusive reports on this action?	**Yes +1**	No	Not known or not done
2	Did adverse event appear after the suspected drug was given?	**Yes +2**	No −1	Not known or not done
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	**Yes +1**	No	Not known or not done
4	Did the adverse reaction appear when the drug was readministered?	**Yes +2**	No −1	Not known or not done
5	Are there alternative causes that could have caused the reaction?	**Yes −1**	No +2	Not known or not done
6	Did the reaction reappear when a placebo was given?	Yes −1	No +1	**Not known or not done**
7	Was the drug detected in any body fluid in toxic concentrations?	Yes +1	No	**Not known or not done**
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Yes +1	No	**Not known or not done**
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes +1	No	**Not known or not done**
10	Was the adverse event confirmed by any objective evidence?	Yes +1	No	**Not known or not done**
	Total Score:	**5**		

Table 2. Probability stratification of the Naranjo Adverse Drug Reaction Probability Scale.

Doubtful ADR (<2): The reaction was likely related to factors other than a drug).

Possible ADR (2 to 4): The reaction followed a temporal sequence after a drug, possibly followed a recognized pattern to the suspected drug and could be explained by characteristics of the patient's disease.

Probable ADR (5 to 8): The reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state.

Definite ADR (≥9): The reaction followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, followed a recognized response to the suspected drug and was confirmed by improvement on withdrawing the drug and reappeared on reexposure.

we have no measured ampicillin concentrations to confirm the estimated pharmacokinetics.

Conclusion

While uncommon, seizures are a potential adverse effect of ampicillin use. Due to its frequent use in the pediatric population in the case of severe infection, ampicillin-induced seizures must be considered where ill patients present with new-onset seizures or otherwise unexplained worsening of pre-existing seizure disorders.

Informed consent

The patient's parents provided informed consent prior to collection of history for purposes of publishing. A copy of the informed consent form can be provided upon request.

Disclosure statement

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