Theophylline-associated status epilepticus in an infant: pharmacokinetics and the risk of suppository use

Zenichiro Kato, Atsushi Yamagishi, Mitsuhiro Nakamura, Naomi Kondo
Gifu, Japan

Background: **Theophylline has been widely used to treat asthma, but recent studies have revealed that the possible risks for seizure may result in the revision of the therapeutic guidelines.**

Methods: **An 8-month-old boy who had been treated with oral sustained-release theophylline and additional aminophylline suppository was hospitalized. A combination of diazepam, lidocaine and thiopental was required to stop his convulsion.**

Results: **The pharmacokinetic study indicated that the usage of a sustained-release formula should not usually be over 15 mg/ml, but the additional use of an aminophylline suppository elevated the concentration to over 20 mg/ml and resulted in the severe adverse effects.**

Conclusion: **The parents of children and also physicians should be educated to ensure the proper use of the suppository formula.**

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pharmacokinetics;
suppository;
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Introduction

Adverse neurological symptoms such as seizure during theophylline therapy are associated with the serum level of theophylline, a significant factor for increased morbidity.[1,2] We present a case of intoxication caused by add-on use of an aminophylline suppository during daily use of a sustained-release formulation. The pharmacokinetic study of this case suggests that the use of suppositories should be revised to avoid the possible adverse effects.

Case report

An 8-month-old boy who had been neurologically normal prior to this episode was transferred to our hospital due to status epilepticus. Before admission he was diagnosed as having bronchitis without fever and was treated with oral sustained-release theophylline (40 mg/day, 5.7 mg/kg per day) but without any antihistamines or antiallergic drugs at a local clinic. On the second day of illness, his mother gave him an aminophylline suppository (50 mg, 7 mg/kg), which had been previously provided by another clinic as a "cough stopper" to attenuate his coughing.

On admission, he was drowsy and his eyes were deviated and fixed to the left side, and he would respond only to painful stimuli. He had tachycardia (180/min) and tachypnea (50/min) without fever. He was diagnosed with a tonic convulsion, but not in a non-convulsive status epilepticus, and the initial dose of diazepam injection (2.5 mg, 0.35 mg/kg) slightly improved his tonic state. However, he developed a massive tonic seizure on the right arm and leg, which required three times of injections of diazepam (2.5 mg, 0.35 mg/kg), lidocaine (20 mg, 3.0 mg/kg) and thiopental (25 mg, 3.5 mg/kg) to cease the seizures. He showed right-sided paresis after the seizure, but the paresis diminished after several hours, suggesting Todd's paresis. No paroxysmal discharge was shown on electroencephalography, but there were periodic high voltage delta waves predominantly on the left hemisphere. Head computed tomography showed no abnormal lesion and he was discharged after three days of hospitalization without any neurological sequelae.

Laboratory tests showed the elevation of muscle related enzymes (aspartate amino transferase 66 mg/ml, lactate dehydrogenase 614 mg/ml, and creatine kinase 410 mg/ml) and abnormalities in a blood gas analysis

Author Affiliations: Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan (Kato Z, Yamagishi A, Kondo N); Department of Pharmacy, Gifu University Hospital, Yanagido 1-1, Gifu 501-1194, Japan (Nakamura M)

Corresponding Author: Zenichiro Kato, MD, PhD, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan (Tel: +81 (58) 230 6386; Fax: +81 (58) 230 6387; Email: zen-k@gifu-u.ac.jp)

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(pH 7.113 and base excess –9.0), which would have been due to the status epilepticus. Routine examination of his cerebrospinal fluid (CSF) was normal. The theophylline concentrations of serum and CSF were 18.2 mg/ml (at 1 hour after the last dose) and 5.2 mg/ml (at 8 hours after last dose), respectively.

Discussion

The theophylline concentration in this case was analyzed according to a pharmacokinetic study of the suppository and sustained-release formulae.[3,4] The results showed that the use of a sustained-release formula should not usually be over 15 mg/ml, but the additional use of an aminophylline suppository elevated the concentration to over 20 mg/ml and resulted in the severe adverse effects (Fig.).

Theophylline associated seizures have a tendency to have more severe outcomes than those without theophylline, possibly due to its pharmacological impairments on the energy metabolisms in cells.[1,2] We previously reported a 2-year-old girl with severe theophylline associated seizure that resulted in quadriparesis, who now at 15 years of age remains a bed-ridden life without any ability for meaningful communication.[5] Our studies of that case and the present case clearly indicate the risk of suppository use of theophylline especially for infants. Our other study about unbound free theophylline in serum also showed a potent risk for neurological complications in infants due to their significant higher ratios of unbound theophylline compared to adults (65%-80% in neonates or early infants; 45%-50% in adults).[6] Moreover, our study showed that the ratio could easily change depending on several intrinsic factors such as albumin concentration.[7]

As suggested by the previous studies, theophylline associated seizures seem to be intractable and it is difficult to stop it by standard treatments with diazepam.[8] Theophylline is known to antagonize the effect of benzodiazepines, and this may explain why drugs such as diazepam are relatively ineffective in treating theophylline-associated seizures. The prompt use of barbiturates is recommended when diazepam is not effective as seen in our case, in which a combination of diazepam, lidocaine, and thiopental was required to stop his convulsion. In addition, cautions also should be taken in using histamine H1 antagonists in young infants because such drugs could potentially disturb the anticonvulsive central histaminergic system.[9]

Aminophylline suppositories are commercially available and widely used for treatment of coughing and wheezing in children, although such use is not recommended mainly because of the unreliable absorption.[10] Pharmacokinetic analysis in the present case showed that the serum theophylline concentration increased more rapidly and to a much greater extent than the concentration predicted by the use of the same dose of an oral sustained-release formulation[5] (Fig.). According to the results and previously described data,[3-7] suppository dosing at home is equivalent to drip infusion without an adequate medical supervision and assessment, thus exposing the user to an increased risk of intoxication.

We previously recommended that aminophylline suppositories should be used only for short-term management with just a single dosing, and not given as maintenance therapy.[5] However, the recommendation should be revised with a caution issued for its additional use with daily sustained-release theophylline treatment. The parents of pediatric patients and also physicians should be educated to ensure the proper use of the formula, not as a "cough stopper".

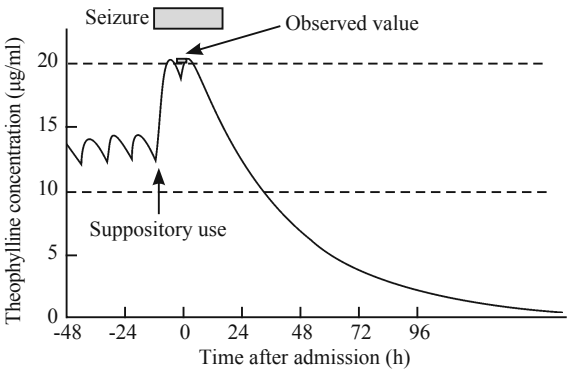

Fig. Time course of serum theophylline concentration predicted by a one-compartment model for sustained-release or suppository formulation.[4,5]

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