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Original article

The effects of co-medications on lamotrigine clearance in Japanese children with epilepsy

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Abstract

Purpose: Although it has been reported that some antiepileptic drugs have inducing or inhibiting effects on lamotrigine (LTG) clearance, whether they have the same effects in Asian epilepsy patients as in those in other countries has not been clarified, especially in children. The aim of this study was to determine the effects of co-medications on LTG clearance in Japanese children with epilepsy.

Methods: A total of 342 routine serum concentration measurements of LTG in 102 Japanese epilepsy patients under 20 years of age were reviewed. The dose-corrected concentration (DCC) of LTG was calculated as [concentration]/[dose/(body weight)], and the DCC of LTG was compared by co-medication. The difference in the DCC of LTG was compared between patients with and without valproic acid (VPA) and between those with and without drugs inducing glucuronic acid conjugation (phenytoin (PHT), carbamazepine (CBZ), and phenobarbital (PB)).

Results: The DCC of LTG was significantly higher in patients on VPA and significantly lower in patients on drugs inducing glucuronic acid conjugation than in patients on LTG monotherapy. The DCC of LTG was significantly higher in patients on CBZ than in patients on PHT or PB. There was no correlation between the DCC of LTG and the concentration of VPA or metabolic inducers within the therapeutic range. Other antiepileptic drugs including clobazam, clonazepam, zonisamide, and levetiracetam had little effect on LTG concentration.

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Conclusion: LTG concentration changes dramatically with concomitant antiepileptic drugs in Japanese children, as previously reported from other countries, and special attention is required. Although the dose of LTG should be adjusted when starting or discontinuing VPA or metabolic inducers, no adjustment is needed when changing the dose of VPA or metabolic inducers in the therapeutic range.

Keywords: Lamotrigine; Co-medication; Child; Epilepsy; Drug interaction; Drug concentration

1. Introduction

Lamotrigine (LTG) is one of the newer antiepileptic drugs. It has a broad range of efficacy for diverse types of epilepsy in children, such as idiopathic or refractory focal epilepsy, idiopathic generalized epilepsy, infantile spasms, and Lennox–Gastaut syndrome [1–4]. One of the pharmacological characteristics of LTG is drug interaction. Enzyme-inducing drugs (inducers) such as phenytoin (PHT), carbamazepine (CBZ), and phenobarbital (PB) enhance LTG clearance and lead to reduced concentrations of LTG [5,6]. On the other hand, combined use of valproic acid (VPA) results in a 200% increase in the concentration of LTG [7], because LTG is mainly metabolized to an inactive metabolite by three uridine-5′-diphosphate-glucuronosyltransferases (*UGT*) *1A4*, *2B7*, and *1A1*, and VPA is a potent inhibitor of *UGT1A4* [8,9]. Dose adjustment of LTG is often needed when these drugs are used concomitantly.

In Japan, LTG was approved in 2008 as an adjunctive treatment for focal seizures with or without secondary generalization, tonic–clonic seizures, and generalized seizures of Lennox–Gastaut syndrome in children and adults. LTG was then approved as monotherapy in adults in 2014, and monotherapy for typical absence seizures of children in 2015 in Japan. Although the dose of LTG has been adjusted for these concomitant drugs based on studies in North America and Europe, the pharmacokinetics of LTG might differ in Japanese patients. Yamamoto et al. studied the effects of concomitant drugs on LTG concentration in Japanese adult patients and reported that clearance of LTG may be slower in non-Caucasians than in Caucasians [10]. On the other hand, LTG clearance is higher in children than in young adults [6], and little is known about the effects of concomitant drugs on LTG concentrations in Japanese children. Thus, blood concentrations of LTG were studied in Japanese children with epilepsy to determine the effects of concomitant antiepileptic drugs on LTG concentrations, with a special focus on the correlations between LTG concentrations and blood concentrations of the concomitant drugs to determine the optimal approach to LTG dose adjustment during multidrug therapy for refractory epilepsy.

2. Patients and methods

The blood concentrations of LTG (Lamictal, tablets, GlaxoSmithKline K.K., Tokyo, Japan) were analyzed in children with epilepsy in 9 affiliated hospitals of Nagoya University Graduate School of Medicine. The blood concentrations of LTG were studied for clinical purposes between January 2009 and April 2014. Information was obtained about the time of the last dose, time of blood sampling, daily LTG dose, number of daily intakes, co-medications, body weight, types of epilepsy, underlying disorders, effectiveness of LTG, and adverse effects from medical charts. The patients' data were collected anonymously. In the affiliated hospitals, blood samples were basically obtained 2–5 h after the last intake of antiepileptic drugs. Samples taken less than 2 h or more than 5 h after intake were excluded. The effectiveness of LTG was classified according to the reduction in seizure frequency from 2 months before starting LTG to the last blood test. Effectiveness was classified as effective when seizure reduction was $\geqslant 50\%$ compared with baseline and ineffective when seizure reduction was $<50\%$ of baseline.

The plasma LTG concentration was analyzed using the high performance liquid chromatography method with a reversed-phase column. The dose-corrected concentration (DCC) of LTG was calculated as [LTG concentration]/[dose/(body weight)] (μg/mL/(mg/kg)). The correlations of DCC of LTG with seizure control and adverse effects were evaluated. According to the concomitant antiepileptic drugs, patients were classified into 5 groups: Group 1, samples with VPA co-medication; Group 2, samples with LTG metabolic inducers (inducers) (CBZ, PHT, or PB); Group 3, samples with antiepileptic drugs other than VPA and inducers (CBZ, PHT, or PB); Group 4, samples with VPA and inducers (CBZ, PHT, or PB); and Group 5, samples with LTG monotherapy. Samples with VPA and other drugs without inducers were included in Group 1, and samples with inducers and other drugs without VPA were included in Group 2, because the effects of the other drugs were expected to be much smaller than of VPA or inducers. In Group 2, samples with two or more inducers were excluded. In Group 3, samples with two or more other drugs were excluded. The DCC of LTG