

Review of Theophylline-induced Seizures and Serum Theophylline Concentrations.

Mayuko Hashikura*¹⁾, Yuko Watanabe¹⁾, Tomoko Terajima¹⁾, Kayoko Maezawa¹⁾,
Seiji Hori²⁾, Junko Kizu¹⁾

¹⁾ Faculty of Pharmacy, Keio University, 〒105-8512 1-5-30 Shibakoen, Minato-ku, Tokyo

²⁾ Jikei University School of Medicine, 〒105-8461 3-25-8 Nishishinbashi, Minato-ku, Tokyo

(Received July 10, 2008
Accepted October 31, 2008)

Abstract

Objective: Theophylline is widely used as an anti-asthmatic drug. It is well known that the serum theophylline concentration should be controlled within the range of 8–20 $\mu\text{g}/\text{mL}$, or various side effects occur when the serum theophylline concentration exceeds 20 $\mu\text{g}/\text{mL}$. Recently, however, a number of theophylline-induced seizures have been reported, although the serum theophylline concentration was below 20 $\mu\text{g}/\text{mL}$. This paper investigates these cases to evaluate the relationship between theophylline-induced seizures and the serum theophylline concentration based on both domestic and overseas studies.

Methods: We investigated cases which were reported in papers found through MEDLINE and *Igakuchuou-zasshi*, and cases reported to pharmaceutical companies. These cases were sorted by sex, age, and the serum theophylline concentration at the time of seizure.

Results: Overall, 356 cases of theophylline-induced seizures (233 domestic and 123 foreign) were reported from 1978 to 2008. The sex ratio was male:female=65:35 (66:34 domestic and 63:37 foreign), after excluding 22 cases (6 domestic, and 16 foreign) of excessive dose. Their ages ranged from 0 to 95, and infants under five years old comprised 81.8% of all domestic cases whereas only 19.0% of foreign cases. Serum theophylline concentrations were measured in 268 cases (166 domestic, and 102 foreign), and 50.0% (70.5% domestic and 16.7% foreign) produced seizures with a serum theophylline concentration below 20 $\mu\text{g}/\text{mL}$. In addition, a correlation between theophylline dosage and the serum theophylline concentration was seen strongly in adults but weakly in children.

Conclusions: These results indicate that theophylline-induced seizures are more likely to occur among younger patients with lower serum theophylline concentrations in Japan than in foreign countries. It is also shown that many patients suffered seizures even when their serum theophylline concentrations were within the therapeutic range, especially among children under five years old. Since the correlation between theophylline dosage and the serum theophylline concentration is low among children, more attention should be paid in the use of theophylline for children.

Key words: Theophylline, seizures, convulsion, concentration