Bioavailability of Elixir Theophylline (Siriraj Formula) in Thai Asthmatic Children

Suprida Habanananda, M.D.*
Montri Tuchinda, M.D.*
Renu Koysooko, Ph.D.**

Abstract: **The bioavailability of Elixir Theophylline (Siriraj Hospital Formula) and Tablet Aminophylline (The Government Pharmaceutical Association) was compared with Elixir Quibron in Thai asthmatic children. The mean rate of absorption and the extent of drug absorption were not significantly different for local made drugs, compared with that of an imported one. With regards to the mean maximum serum levels (Cmax) and time to maximum serum level (Tmax) values, there were also no significant differences between two local preparations and an innovative one. Thus, the results suggest that the local made theophylline drugs possess the same efficacy as the imported drug.**

เรื่องย่อ : การเอื้อประโยชน์ของ อีลิกเซอร์ ธีออฟีย์ลลีน (สูตรศิริราช) ในร่างกายเด็กไทยที่เป็นหืด

สุปรีดา ทัพนานนท์ พ.บ.*, มนตรี ตู้จินดา พ.บ.*, เรณู โกยสุขโข ปร.ด.**

* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, ** กรมวิทยาศาสตร์การแพทย์, กระทรวงสาธารณสุข, กรุงเทพฯ 10100.

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ได้ศึกษาการเอื้อประโยชน์ในร่างกาย (bioavailability) ของ Elixir Theophylline (ที่ผลิตโดยโรงพยาบาลศิริราช) เทียบกับ อะมิโน ฟิย์ลลิน ชนิดเม็ด (ผลิตโดยกรมวิทยาศาสตร์การแพทย์ กระทรวงสาธารณสุข) และ Elixir Quibron (ผลิตโดยบริษัทบริสตอลไมเยอร์ สหรัฐอเมริกา) ในเด็กไทยที่เป็นหืด 12 ราย อายุระหว่าง 10-14 ปี โดยผู้ป่วยแต่ละรายต้องได้รับยาแต่ละชนิดทางปากในขนาด 5 มก. ของ ธีโอฟีย์ลลีน/น้ำหนักตัว 1 กก. สลับกันไปโดยห่างกัน 1 สัปดาห์ ได้เจาะเลือดผู้ป่วยก่อนได้รับยา และเมื่อ 10 นาที, 30 นาที, 1 ชั่วโมง, 2 ชั่วโมง, 4 ชั่วโมง, 6 ชั่วโมง, และ 8 ชั่วโมงภายหลังได้รับยา, นำมาวัดค่า ธีออฟีย์ลลีนใน สีรั่มโดยวิธีทางเคมีและวัดด้วย สเปคโตรโฟโตมิเตอร์ และหาค่าทางเภสัชจลนศาสตร์ ภายหลังการใช้ยาแต่ละชนิดแล้วนำมาเปรียบเทียบกัน.

จากการศึกษาพบว่าค่าต่าง ๆ ด้านเภสัชจลนศาสตร์ ไม่แตกต่างกันในยาทั้ง 3 ชนิดที่ทำการศึกษา แสดงว่า Elixir Theophylline ที่ผลิตโดยโรงพยาบาลศิริราชมีประสิทธิภาพเช่นเดียวกับ Elixir Quibron ที่ผลิตในสหรัฐอเมริกา และ อะมิโนฟิย์ลลินชนิดเม็ด ที่ผลิตโดยองค์การเภสัชกรรม กระทรวงสาธารณสุข.

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* *Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700.*
** *Division of Medical Research, Department of Medical Sciences, Ministry of Public Health, Bangkok.*

Theophylline has been widely used in acute attacks and long term treatment of asthma. The minimum effective plasma concentration of theophylline is considered to be about 5 μg/ml and the average concentration is about 10 μg/ml. [1] The concentration in excess of 20 μg/ml may produce nausea and adverse effects. [2] To achieve maximum therapeutic benefit with minimum adverse effects, plasma theophylline should be maintained within the therapeutic range. Incomplete bioavailability of theophylline preparations is one of the major drawbacks to achieve and maintain theophylline concentrations in the therapeutic range, hence it may cause therapeutic failure. [3] Efficacy of oral theophylline preparations were often suspected by physicians because of their apparent ineffectiveness or patient intolerance. The in house preparation of Elixir Theophylline (Siriraj Hospital Formula) was not popular and physicians prefered to prescribe the proprietary drug. Therefore, it appeared beneficial to perform bioavailability studies of Elixir Theophylline (Siriraj Hospital Formula) and Elixir Quibron, an imported drug from U.S.A.. Tablet Aminophylline, manufactured by the Government Pharmaceutical Organization, was also included in this study as the representative for local made tablet form. Plasma theophylline concentrations were determined after oral administration of these three preparations. Pharmacokinetic parameters were used to evaluate the bioequivalence of the two local made drug products as compared to the imported drug.

MATERIALS AND METHODS

The study was carried out on 12 asthmatic children between 10 and 14 years of age, weighing between 25.1 and 44 kg., who attended the Allergy Clinic at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, between 1985-1986. All patients and parents gave verbal consent for the study. The patients had been off medication for at least one week.

Each subject received three preparations of theophylline, one hour after a light breakfast, in a cross over design with a one week wash out period. The three preparations were Elixir Theophylline*, Tablet Aminophylline** and Elixir Quibron*** The dose administered was 5 mg theophylline/kg body weight.

Five milliliter blood samples were collected immediately before and at 10 mins, 30 mins, 1, 2, 4, 6 and 8 hours after dosing. Serum was separated and kept frozen pending assay. Theophylline concentration was determined by ultraviolet Spectrophotometer method [4].

Pharmacokinetic Analysis

The data were analyzed using a simple linear one-compartment open model to determine the pharmacokinetic parameters, comprising absorption rate constant, elimination rate constant, elimination half-life, peak serum concentration, and time to peak concentration. The area under the serum concentration-time curve from the time of drug administration to 8 hours was determined using the linear trapezoidal method. The area from 8 hours to infinity was estimated by dividing the serum concentration at 8 hours by the slope of the terminal log-linear phase of the semilogarithmic plots of concentrations versus time.

Statistical Analysis

The results were expressed as mean ± standard error. ANOVA for randomized block design and Duncan New Multiple Range Test were used to determine the difference. The level of Statistical significance of $p<0.05$ was used.

RESULTS

The mean serum theophylline concentration time profiles following oral administration of single doses of 5 mg theophylline/kg body weight of Elixir

*Elixir Theophylline (Siriraj Hospital Formula) containing 50 mg theophylline/5ml
**Tablet Aminophylline (The Government Pharmaceutical Organization, GPO) containing 85% theophylline
***Elixir Quibron (Bristol-Myers LTD.) containing 50 mg theophylline/5ml

Theophylline, Tablet Aminophylline and Elixir Quibron are shown in Figure 1, 2 and 3 respectively. The pharmacokinetic parameters were calculated for each individual subject by fitting to a one compartment open model. The mean values and standard errors of the means for the parameters obtained from 12 asthmatic children who received elixir or tablet form of theophylline are summarized in Table 1. Elixir Quibron was used as a reference drug in assessing relative bioavailability of the local made drug products. Analysis of variance showed no significant difference in any pharmacokinetic parameter between either Elixir Theophylline or Tablet Aminophylline and Elixir Quibron ($p > 0.05$).

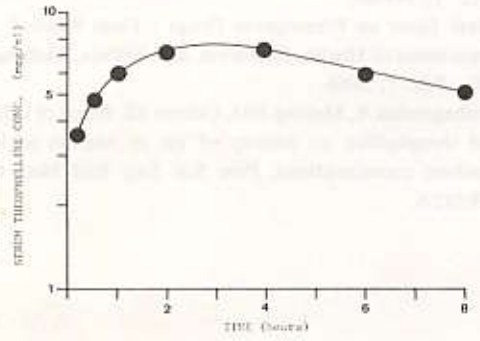

Figure 1. Mean serum theophylline concentrations in 12 asthmatic children as a function of time after a 5 mg/kg single oral administration of Elixir Theophylline (Siriraj Formula)

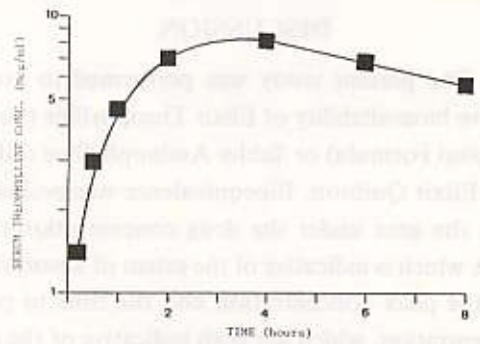

Figure 2. Mean serum theophylline concentrations in 12 asthmatic children as a function of time after a 5 mg/kg single oral administration of Tablet Aminophylline (The Government Pharmaceutical Association)

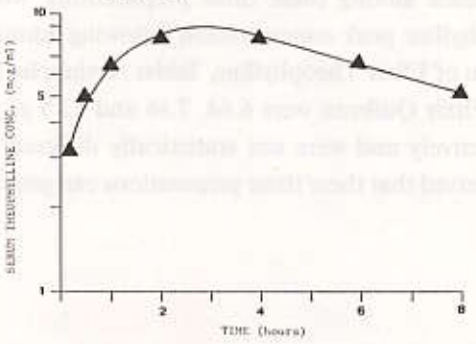

Figure 3. Mean serum theophylline concentrations in 12 asthmatic children as a function of time after a 5 mg/kg single oral administration of Elixir Quibron (Bristol-Myers Ltd.)

Table 1. Pharmacokinetic constants of Theophylline in 12 Thai asthmatic children administered Elixir Theophylline, Tablet Aminophylline and Elixir Quibron

Constant	Mean (SE)		
	Elix. Theophylline	Tab. Aminophylline	Elix. Quibron
Absorption rate const. (Ka), hr^{-1}	0.7757 (0.1135)	0.8292 (0.1250)	0.9536 (0.1176)
Abrorption half-life (T ½ a), hr	1.02 (0.09)	1.20 (0.28)	0.87 (0.11)
Elimination rate const. (K), hr^{-1}	0.0980 (0.0098)	0.0956 (0.0076)	0.1136 (0.0084)
Elimination half-life (T ½ e), hr	7.84 (0.72)	7.84 (0.72)	6.57 (0.62)
Time to maximum conc. (Tmax), hr	3.33 (0.22)	3.55 (0.49)	2.77 (0.21)
Maximum conc. (Cmax), µg/ml	6.64 (0.34)	7.16 (0.52)	7.75 (0.47)
Area under curve (AUC) $0-\infty$ µg-hr/ml	110.20 (11.23)	115.96 (11.59)	104.11 (9.56)

DISCUSSION

The present study was performed to assess relative bioavailability of Elixir Theophylline (Siriraj Hospital Formula) or Tablet Aminophylline (GPO) with Elixir Quibron. Bioequivalence was evaluated from the area under the drug concentration-time curve, which is indicative of the extent of absorption, and the peak concentration and the time to peak concentration, which are both indicative of the rate of absorption. No significant difference between the two local made preparations and the imported one was observed in either speed or extent of drug absorption ($p>0.05$). Absorption rate constant and elimination rate constant also showed no significant difference among these three preparations. Mean theophylline peak concentration following administration of Elixir Theophylline, Tablet Aminophylline and Elixir Quibron were 6.64, 7.16 and 7.75 μg/ml respectively and were not statistically different. It is observed that these three preparations can produce plasma level over the minimum effective concentration of theophylline. The results from this study suggest that the local made drug preparations of theophylline either in the elixir or tablet form are as effective as the imported drug.

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