嘉南藥理科技大學專題研究計畫成果報告

長效 Theophylline 製劑評估及血中濃度監測

計畫類別：個別型計畫

計畫編號：90-PH-02

執行期間：90 年 1 月 1 日至 90 年 12 月 31 日

計畫主持人：宋國峻 教授

執行單位：嘉南藥理科技大學藥學系

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BACKGROUND

Theophylline , the 1,3-Dimethylxanthine, is often used as bronchodilators in the symptomatic treatment of mild bronchial asthma and reversible bronchospasm as well as other obstructive pulmonary diseases. It relieves the primary manifestations of asthma, including shortness of breath, wheezing and dyspnea and improves pulmonary function as measured by increased flow rates and vital capacity. The drug also suppresses exercise-induced asthma and prevents symptoms of chronic asthma [1-3].

Theophylline is well absorbed after oral administration. Food has little effect on theophylline availability; however, absorption may be slower in the presence of high-fat food and more rapid in the presence of large volume of liquid [1,3]. Theophylline plasma or serum levels of about 10 to 20 μg/ml usually are needed to produce optimum bronchodilator response [1-4]. With plasma levels ranging from 8 to 20 μg/ml, a linear relationship exists between improvement in pulmonary function and the logarithm of theophylline plasma concentration [1-3]. Theophylline is excreted by the kidneys and less than 15 % of the drug is excreted unchanged in the urine. The average volume of distribution is about 0.5 L/kg. The elimination half-life of theophylline are approximately 6.9±2.5 hours for healthy adult [1-3, 5, 6].

Theophylline was usually well tolerated in controlled clinical trials. The majority of adverse events were mild, reversible in nature. The most common gastrointestinal side effects include nausea, vomiting, epigastric pain, abdominal cramps, anorexia and diarrhea. Cardiovascular side effects of theophylline include palpitation, sinus tachycardia and increased pulse rate. Theophylline also may produce trasiently increased urinary frequency, dehydration, twitching of fingers and hand and elevated SGOT levels [1-3].

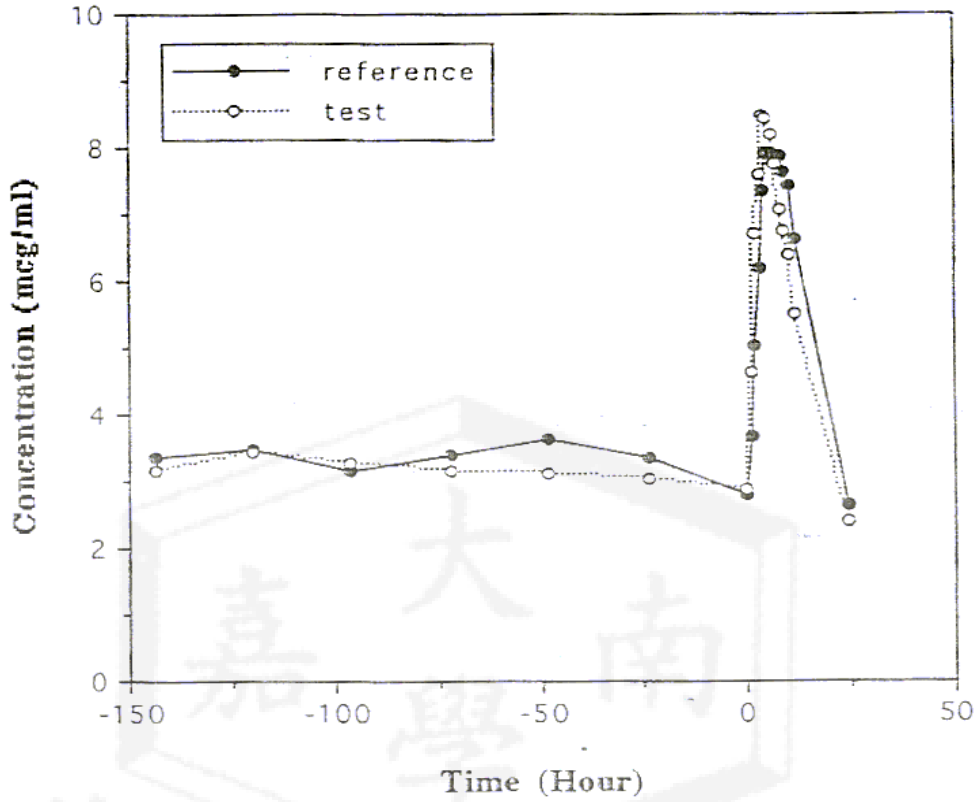
OBJECTIVES

The purpose of this study is to assess the bioequivalence between two formulations of theophylline SR tablets (400 mg of theophylline per tablet) following oral administration. This comparison will be performed using various pharmacokinetic parameters derived from the plasma drug concentration-time curves.

CONCLUSION

According to the results of statistical analysis for the pharmacokinetic parameters, these two products are so similar with respect to the peak drug concentration in a dosing interval at steady state (C_{maxss}) as well as area under the plasma concentration-time curve of a dosing interval at steady state (AUC_{ss}). Therefore, the results of the study support the bioequivalence between the test drug Telin SR Tablet manufactured by SCP and the reference drug Uniphylline Tablet manufactured by Napp Pharmaceutical Co. Ltd..

Mean plasma theophylline concentration vs. time profiles for reference and test drugs in 12 volunteers



Summary of pharmacokinetic parameters (mean±s.d.) and the ratios of test and reference drug

parameter	reference drug	test drug	ratio (test/reference)
C_{maxss} (μg/ml)	8.62±2.06	8.83±2.15	1.04±0.20
AUC_{ss} (μg*hr/ml)	136.61±37.04	129.48±37.33	0.96±0.16
C_{avss} (μg/ml)	5.69±1.54	5.40±1.56	0.96±0.16
F_{ss}	1.10±0.36	1.26±0.45	1.16±0.31

statistical results of C_{maxss} and AUC_{ss} for theophylline bioequivalence study

Parameter	ANOVA α=0.05 (F value)	90% Confidence interval of ratio	Power of test
C_{maxss} (μg/ml)	n.s. (0.25)	93.40-111.47 %	0.95
AUC_{ss} (μg*hr/ml)	n.s. (1.29)	86.45-103.11 %	0.97