Pharmacokinetics and Bioavailability Studies of Generic Ondansetron, and the Innovator Preparation, in Healthy Thai Male Volunteers

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Abstract

The pharmacokinetics and bioequivalence of two oral formulations of ondansetron were evaluated; Zetron® (Biolab Pharmaceutical, Bangkok, Thailand), as the test formulation and Zofran® (Glaxo Wellcome Operations, Greenford, UK), as the reference formulation. The two products were administered as a single oral dose of 8 mg according to a randomized two-way crossover design to 12 healthy Thai male volunteers. The washout period between treatment was 1 week. Ondansetron plasma concentrations were measured using HPLC. The oral bioavailability of ondansetron averaged 67 per cent and the elimination half-life after oral administration was 5.6 hours. The means and parametric 90 per cent CI of the ratios of C_{max} and AUC $_{0-\alpha}$ [μ Zetron® (Test) / μ Zofran® (Reference)] were 0.95 (0.84-1.07) and 0.94 (0.80-1.10), respectively. These values were well within the bioequivalence range of 0.8-1.25 as established by the US-FDA. The mean difference of T_{max} (Test-Reference) was approximately 20 per cent. Thus, our study demonstrated bioequivalence of the two products (Zetron® and Zofran®) regarding the rate and extent of absorption.

Key word : Ondansetron, Generic, Innovator Preparation, Pharmacokinetics, Bioavailability, Healthy Thai

Ondansetron is a selective 5-HT_3 receptor antagonist with antiemetic properties[1-5]. Previous studies revealed that this drug significantly decreased the number of episodes of emesis and delayed the first episode of emesis in patients receiving chemotherapy and/or radiation therapy[6,7]. In comparative trials, the drug has proven to be more effective than placebo or metoclopramide and had less toxicity than metoclopramide (e.g. extrapyramidal side effects)[8]. Therefore, it is clinically useful for patients who develop chemotherapy-induced nausea and vomiting who may refuse further

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treatment because of this adverse effect[9]. Ondansetron is now approved for use in the prevention of nausea and vomiting associated with cancer chemotherapy, available as tablets for oral administration and as a solution for intravenous injection. In healthy volunteers, the drug was well absorbed from the gut and underwent limited first-pass metabolism. The drug was first detected in plasma 30 minutes after a single 8 mg oral administration. The average time to reach peak concentration (T_{max}) was 1.0-3.0 hours and the peak concentrations (C_{max}) ranged between 20-40 μg/L[10-13]. Its oral bioavailability was approximately 56-70 per cent [11,13]. In patients with cancer, the T_{max} and C_{max} values were in the same range as those for healthy individuals of similar age. However, its bioavailability varied and ranged from 60-165 per cent due to the change of ondansetron metabolism[14]. The C_{max} values obtained after slow intravenous administration of a single 8 mg dose ranged from 68-120 μg/L. The disposition of ondansetron following both oral and intravenous dosing was similar with a terminal elimination half-life ($t_{1/2}$) of 3-5 hours[10,12,13]. The drug was extensively metabolized by the liver and the hepatic oxidative metabolism accounting for more than 95 per cent ondansetron clearance from the body[12]. In patients with mild to moderate hepatic impairment, the mean half-life increased to 10-13 hours and may be prolonged to 15-32 hours in patients with severe hepatic insufficiency[15,16]. In such patients a total daily dose of 8 mg should not be exceeded. A reduction in clearance and an increase in half-life were also seen in patients over 75 years old, however, no dosage adjustment was required[17]. The extent and rate of ondansetron's absorption were greater in women than in men. Slower clearance, smaller apparent volume of distribution and higher absolute bioavailability resulted in higher plasma ondansetron levels in women. Nonetheless, clinical significance of gender-related differences of its disposition is not known. Ondansetron is generally well tolerated. Toxicity is mild and transient, including headache, dizziness, constipation and rarely, anaphylaxis and hypotension[12,18]. Ondansetron in the range of 8-32 mg/day is generally recommended for prevention and/or treatment of nausea and vomiting associated with cancer chemotherapy and postoperation. For most patients receiving chemotherapy, it can be administered at a dose of 8 mg with slow intravenous injection immediately before treatment or 8 mg orally 1-2 hours before treatment. Thereafter, 8 mg orally or slow intravenous every 12 hours or constant infusion of 1 mg/h for 24 hours should be followed during the course of cancer chemotherapy. Moreover, to protect against delayed emesis, it should be continued orally, 8 mg twice daily for up to 5 days after a course of treatment. For highly emetogenic (e.g. high-dose cisplatin), a single dose of 32 mg diluted in 50-100 ml of saline and infused over 15 minutes immediately before chemotherapy can be given. The dose regimen should be chosen depending on the severity of the symptoms[17]. Since the cost of the innovator preparation (Zofran®, the Glaxo Wellcome Operations, Greenford, UK) is rather high, a local drug company (the Biolab Company, Bangkok, Thailand) has a tentative plan to manufacture generic oral preparations of 8 mg ondansetron (Zetron®) for clinical use with a significantly lower cost. Since any difference in the manufacturing process at different in the manufacturers may affect their drug preparations, and thus, their pharmacokinetics and their bioequivalence, we, therefore, investigated the pharmacokinetics and bioequi-valence of an 8 mg oral formulations of the generic drug Zetron® and the innovator product Zofran®, in healthy Thai male volunteers.

METHOD AND STUDY DESIGN

Subjects

Since gender is a factor affecting ondansetron pharmacokinetics, only male volunteers were enrolled in this study[18]. A total of 12 healthy Thai volunteers who ranged in age from 18-48 years (average 30.3 ± 10.5 years) participated. Weight and height of the subjects ranged from 51-72 kg (64 ± 7.4) and 158-182 cm (167.1 ± 7.7), respectively. All were in good health on the basis of medical history, physical examination, blood chemistry and urinalysis. None had a history or evidence of disease especially kidney, liver, and hematological diseases. The laboratory tests included complete blood count with differentials, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and bilirubin. Subjects were told to refrain from taking any medication for 1 week before, during and 1 week after the study period. Cigarette smokers and alcoholic subjects were excluded from the study. Subjects were enrolled to the study after giving written informed consent. The protocol of the study was reviewed and approved by the Ethical Committee of Chiang Mai University, Thailand.

Study Drugs

The formulations tested were :

1. Reference product : Zofran® (Glaxo Wellcome Operations, Greenford, UK)
   - 8 mg intravenous solution (lot No. L/C 1B2117DD, Mfd. 05.03.1997)
   - 8mg oral tablet (lot No. L/C 1W0737CC, Mfd.12.12.1996, Exp.12.12.1999)
2. Test product : Zetron® (Biolab Company, Bangkok, Thailand)
   - 8 mg oral tablet (lot No. ZET8/E2, Mfd. 17.02.1998)

Study Design

Subjects received each treatment in an open two period crossover design. The sequence of the assigned treatments was obtained from a computer-generated list of the randomization. A single dose of ondansetron 8 mg, the most frequent dosage used clinically was chosen. All subjects also received 8 mg Zofran® intravenous bolus dose on the last study visit. Since the elimination half-life of ondansetron following both oral and intravenous dosing has been reported to be about 3-5 hours in healthy volunteers[18], the wash out period between each treatment was at least 1 week to ensure the total clearance of the drug.

On the study day, subjects were admitted to the Clinical Pharmacology Unit of the Department of Pharmacology, the Faculty of Medicine, Chiang Mai University after an overnight fast. Base line vital signs were measured at the beginning of the visit. A peripheral intravenous catheter for blood sample collection was placed into a forearm vein using aseptic technique. Thereafter, subjects were randomized to receive a single oral dose of 8 mg ondansetron either test (Zetron®) or reference (Zofran®) product. The oral preparations were administered with 200 ml water. Thirteen 10 ml aliquots of blood samples were drawn in sodium heparin tubes just before oral dosing and at 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15 and 24 hours after dosing. Blood samples were centrifuged within 30 minutes, then the plasma was kept immediately at -20°C until analysis. All subjects remained fasted for 4 hours post dose. Water and juice were served 2 hours after dosing. Lunch was served after the 4 hours blood drawn was completed. No drug, alcohol or caffeine containing beverages were allowed during the study period. The following study visits were at least 1 week apart from the previous visit. The same procedure was performed except that a different oral preparation of the other drug company was administered to the same patient. To investigate intravenous pharmacokinetics of ondansetron, all subjects received a single intravenous dose of 8 mg on the last study visit. An intravenous preparation (2 mg/ml) was diluted to 50 ml with normal saline solution and administered slowly over 5 minutes. For the slow intravenous administration, blood samples were taken before dosing and at 5, 10, 15, 30 minutes and 1, 1.5, 2, 4, 8, 12 and 15 hours after dosing. Meals and fluid intake were identical for all study visit.

Quantitative Measurement of Ondansetron Concentration

Ondansetron in plasma was determined by the use of a high performance liquid chromatography (HPLC) after CN solid-phase extraction [Accubond, SPE 1ml, 100 mg CYANO (J&W Scientific, Calif. U.S.A.)] and separation on an Inertsil silica column (Sil 150-5, 4.6 x 150 mm., GL Sciences Inc.). The HPLC system consisted of an DUG-3A degasser and LC-10 AS pump connected to a SPD-10A UV/VIS detector. Separation was performed at 40°C on an Inertsil Silica HPLC column with ultraviolet detection at 305 nm. The mobile phase was a mixture of 0.025 M sodium acetate buffer adjusted to pH 4.2 with glacial acetic acid, and acetonitrile at the ratio 6:4 (v/v). Samples and standards were prepared with the use of CN solid-phase extraction. The extraction and evaporation procedures were carried out on a J&W SPE Vacuum Manifold and Savant Speed Vac Concentrator, respectively. This method was modified from the method successfully employed in previous studies [11,13]. Calibration standard (0.5-20.0 ng/ml) and control plasma were analyzed in duplicate. Linear regression analysis of peak-height *vs* ondansetron concentrations, consistently gave coefficients of determinant (R^2) of 0.999 or better. Ondansetron concentrations in quality control and study samples were quantified by comparison of the peak height with these standard lines using the external standard method. Samples containing drug concentrations in excess of 20 ng/ml were analyzed after dilution with

control plasma to within the calibration range of the assay. Method validation was determined by carrying out 5 sets of control samples at 4 different drug concentrations, evaluated with a single calibration curve run concurrently for within-run accuracy and precision. For between-run assay precision, 5 sets of control samples at 4 different drug concentrations were assayed on 6 different days with 6 standard curves. The mean coefficient of variation of the calculated concentration values were consistently less than 15 per cent.

Pharmacokinetics Analysis

Model-independent pharmacokinetic method was used to derive the pharmacokinetic parameters with the use of TopFit 2.0, a pharmacokinetic and pharmacodynamic data analysis program for PC. The following parameters were derived : time to reach the maximal plasma concentration (T_{max}, hour), the maximal plasma concentration (C_{max}, ng/ml), area under the plasma concentration-time curve (AUC, ng.hour/ml), mean residence time (MRT, hour), plasma elimination half-life ($t_{1/2}$, hour), plasma clearance (Cl, ml/hour) and volume of distribution (Vd, L)

Statistics Analysis of Bioequivalence

The differences in the pharmacokinetic parameters of the generic and the innovator ondansetron oral preparations given at the same 8 mg dosage were investigated. Bioequivalence testing comprised of assessment with respect to the rate (C_{max}, T_{max}) and extent (AUC) of ondansetron absorption. The C_{max} and AUC were analyzed using the parametric method (the data was logarithmically transformed and ANOVA was performed). Only AUC extrapolated to infinity (AUC $_{0-\alpha}$), a characteristic of the extent of absorption in the single dose study was used for the calculation. It is important that the extrapolation fraction should not exceed 20 per cent of the total AUC. In our study, the average AUC-extrapolated portion was less than 10 per cent of the total AUC since our blood sampling time was long enough (4 times the terminal elimination half-life) and our assay was fairly sensitive. Thereafter, using the variance estimate (VAR) obtained from the analysis of variance, the 90per cent confidence intervals (90% CI) of AUC and C_{max} were calculated from the formulation

$$(\mu_A - \mu_B) = (\bar{X}_A - \bar{X}_B) \pm t^{v}0.1 \sqrt{\frac{2VAR}{n}}$$

Where $\bar{X}_A$, $\bar{X}_B$ were the observed means of the (ln) transformed parameters (either C_{max} or AUC) for the test product (A) and the references (B), VAR was the error variance obtained from the three-way ANOVA (the residual mean square of a three-way crossover study), n was the number of subjects and $t^{v}0.1$ was the tabulated two-tail *t* value for 90 per cent CI and v was the number of degree of freedom of the mean square from the analysis of variance. The antilogarithm of the confidence interval would express the bioequivalence as a ratio of the test and the reference products. The US-FDA and the Canadian Health Protection Branch accept the bioequivalence ranges of 0.8-1.25 for the 90 per cent CI of AUC and C_{max}. The time to reach the maximal plasma concentrations (T_{max}) was statistically analyzed as an absolute difference. The stipulated bioequivalence range of difference of T_{max} (Test-Reference) is ± 20 per cent. of the reference T_{max}[19, 20].

RESULTS

Twelve healthy Thai volunteers completed this study without any serious adverse effect. The mean plasma concentration-times curves following a single oral dose of 8 mg Zofran® (Reference) and Zetron® (Test) were compared and presented in Fig. 1. The plasma concentration-time profiles of each preparation were relatively consistent with little variation in plasma ondansetron levels at each point of time. The calculated pharmacokinetic parameters following a single oral dose of 8 mg Zofran® (Reference) and Zetron® (Test) were then summarized and presented as mean ± SD to compare between the two preparations (Table 1). The average C_{max} value (ng/ml) observed after a single oral dose of 8 mg Zofran® (Reference) and Zetron® (Test) were 39.33 ± 12.11 and 36.66 ± 8.95, respectively. The average areas under the plasma concentration ($AUC_{0-\alpha}$, ng.h./ml) were 253.95 ± 127.54 and 227.10 ± 77.73 for Zofran® (Reference) and Zetron® (Test), respectively. The mean resident times (MRT, hour) of Zofran® (Reference) and Zetron® (Test) were 7.23 ± 1.65 and 6.96 ± 1.31, respectively. The average half-life ($t_{1/2}$) of Zofran® (Reference) and Zetron® (Test) were 5.57 ± 1.01 and 5.00 ± 1.13, respectively.

Table 2 illustrates the calculated pharmacokinetic parameters following an intravenous administration of 8 mg Zofran® (Reference). The elimination half-life, the plasma clearance, and the volume of distribution of intravenous ondansetron

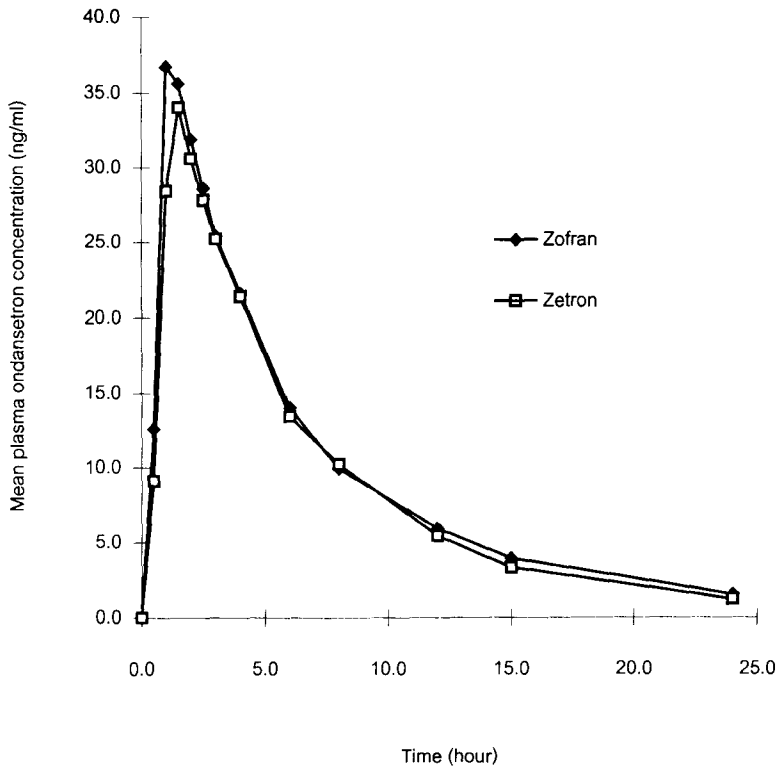

Fig. 1. Mean plasma concentration-time curves following a single oral dose of 8 mg Zetron® (Test) and Zofran® (reference)

Table 1. Pharmacokinetic parameters following single oral administrations of 8 mg ondansetron [Zofran® (Reference) and Zetron® (Test)] in 12 healthy subjects.

Parameters	Zofran® (Reference)	Zetron® (Test)
C_{max} (ng/ml)	39.33 ± 12.11	36.66 ± 8.95
T_{max} (h)	1.21 ± 0.26	1.54 ± 0.54
$AUC_{0-\alpha}$ (ng.h/ml)	253.95 ± 127.54	227.10 ± 77.73
MRT (h)	7.23 ± 1.65	6.96 ± 1.31
$t_{1/2}$ (h)	5.57 ± 1.01	5.00 ± 1.13
F (%)	67 ± 20	

Data expressed as mean ± SD.

Table 2. Pharmacokinetic parameters following intravenous asministrations of 8 mg Zofran® (Reference) in 12 healthy subjects.

Parameters	Zofran® (Reference)
C_{max} (ng/ml)	278.20 ± 206.93
$AUC_{0-\alpha}$ (ng.h/ml)	360.78 ± 103.63
MRT (h)	5.58 ± 1.51
$t_{1/2}$ (h)	4.50 ± 0.95
Cl (ml/min)	398.50 ± 117.72
Vd (L)	130.17 ± 15.09

Data expressed as mean ± SD.

were 4.5 ± 0.95 hours, 398.50 ± 117.72 ml/min, and 130.17 ± 15.09 L, respectively.

Table 3 illustrates the mean and 90 per cent CI of the ratio [Test/Reference] of the C_{max}, and $AUC_{0-\alpha}$ as well as the differences of T_{max} between the test and reference preparations. The mean and 90 per cent CI of the ratio of the C_{max} and $AUC_{0-\alpha}$ for Zetron® (Test)/Zofran® (Reference) were 0.95 (0.84-1.07) and 0.94 (0.80-1.10), respectively. These values were well within the acceptable

Table 3. Parametric 90% confidence intervals (90% CI) for the mean pharmacokinetic parameters of 8 mg Zetron® (Test) and Zofran® (Reference).

Parameters	[Zetron® (Test) /Zofran® (Reference)] ratio	
	Mean	90% CI
C_{max}	0.95	0.84 - 1.07
$AUC_{0-\alpha}$	0.94	0.80 - 1.10
	T_{max} Zetron® (Test) - T_{max} Zofran® (Reference)	
$\%T_{max}$ difference	21%	

bioequivalence ranges of 0.8-1.25, proposed by the US-FDA. The per cent T_{max} differences [T_{max} Zetron® (Test) - T_{max} Zofran® (Reference)] was 21 per cent.

DISCUSSION

Following the oral administration of 8 mg of Zofran® (Reference) or Zetron® (Test) the absorption was rapid with maximal plasma concentration (C_{max}, ng/ml) of 39.33 ± 12.11 (range 21.70-58.40) and 33.66 ± 8.95 (range 27.40-53.80), respectively. The maximal plasma concentration values compared favorably well with values reported in the literature (20-40 ng/ml) and there was no statistical difference between the two preparations. It can also be seen from Table 1 that both preparations were rapidly absorbed with average time to peak plasma concentration (T_{max}, hour) of 1.21 ± 0.26 (range 1.0-1.5) and 1.54 ± 0.54 (range 1.0-3.0), respectively. Again, these values were similar to those reported in the literature (1-3 hours) and there was no statistical difference between the two preparations. The mean residence times (MRT, hour) of the two preparations were nearly identical (7.23 ± 1.65 *vs* 6.96 ± 1.31) and there was no statistical difference between these preparations. The average area under the plasma-concentration time curves ($AUC_{0-\alpha}$, ng.h/ml) were 253.95 ± 127.54 *vs* 227.10 ± 77.73), the mean elimination half-lives ($t_{1/2}$, hour) were 5.57 ± 1.01 *vs* 5.00 ± 1.13, for Zofran® (Reference) and Zetron®(Test) , respectively. Similar to results reported in the literature, a large variation in the clearance values in subjects receiving ondansetron was observed. This is probably due to variation in hepatic ondansetron metabolism. The average half-life of ondansetron in healthy male volunteers was consistent with the values reported in the literature (3-5 hours). The oral bioavailability (F) of ondansetron in our study was 67 ± 20 per cent.

The means (parametric 90 per cent confidence intervals) of the ratios of C_{max} and $AUC_{0-\alpha}$ [(μ Zetron® (Test) / μ Zofran® (Reference)] were 0.95 (0.84-1.07 and) 0.94 (0.80-1.10), respectively. These values were well within the bioequivalence range of 0.8-1.25 for the ratios $(\frac{\text{Test}}{\text{Reference}})$ C_{max} and AUC as established by the US-FDA. A small range of confidence intervals observed in this study verified that an adequate number of subjects were enrolled. The mean difference of T_{max} (Test-Reference) was approximately 20 per cent, an US-FDA acceptable value. Thus, our study demonstrated bioequivalence regarding rate and extent of ondansetron absorption in healthy Thai male volunteers and Zetron® (Test) possessed as high a probability of demonstrating practical equivalence as Zofran® (Reference).

SUMMARY

We conducted pharmacokinetics and bioequivalence testing of 8 mg oral formulations of ondansetron (Zetron® *vs* Zofran®) in 12 healthy male volunteers. The results showed that both formulations were well tolerated and there was no difference in the pharmacokinetic parameters. We also demonstrated bioequivalence of the two products concerning the rate (C_{max}, T_{max}) and extent ($AUC_{0-\alpha}$) of absorption. The parametric 90 per cent confidence intervals and point estimates of the mean difference of these parameters were well within the acceptable range based on standard bioequivalence guidelines. Ondansetron pharmacokinetic parameters obtained from this study were also comparable to those values reported in the literature. Therefore, the oral preparation of a generic drug ondansetron (Zetron®) can be used interchangeably with the innovative product (Zofran®) when cost-effectiveness is concerned.

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การศึกษาเปรียบเทียบเภสัชจลศาสตร์และไบโออะเวลบิลิตีย์ของยาออนแดนซีทรอนที่ผลิตจากบริษัทต้นตำรับกับบริษัทอื่นในอาสาสมัครชาวไทยสุขภาพดี

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การศึกษาเปรียบเทียบเภสัชจลนศาสตร์และ bioavailability ของยาออนแดนซีทรอนชนิดเม็ดที่ผลิตจากบริษัทภายในประเทศ (Zetron®) กับที่ผลิตจากบริษัทต้นตำรับ (Zofran®) ในอาสาสมัครชาวไทยสุขภาพดีจำนวน 12 คน การศึกษาเป็นแบบ randomized, two-way cross over design การวัดระดับออนแดนซีทรอนในพลาสมาใช้วิธี high performance liquid chromatography การศึกษาพบว่าไบโออะไวลาบิลิตีของยาออนแดนซีทรอนมีค่าเฉลี่ยร้อยละ 67 ค่าทางเภสัชจลนศาสตร์ของยาออนแดนซีทรอนทั้ง 2 ตำรับไม่มีความแตกต่างกัน มีค่าเฉลี่ยและช่วงระยะความเชื่อมั่นร้อยละ 90 ของอัตราส่วนระหว่าง Zetron®/Zofran® ของความเข้มข้นสูงสุดของยาในเลือดและพื้นที่ใต้กราฟที่เวลา 0-อนันต์ มีค่าเท่ากับ 0.95 (0.84-1.07) และ 0.94 (0.80-1.10) ตามลำดับ ค่าต่างๆเหล่านี้อยู่ในช่วงของชีวสมมูลที่ยอมรับได้คือ 0.8-1.25 จากการศึกษาครั้งนี้ สรุปได้ว่ายาออนแดนซีทรอนจากทั้งสองบริษัทนี้มีชีวสมมูลกัน

คำสำคัญ : ออนแดนซีทรอน, ผลิตจากบริษัทอื่น, ต้นตำรับ, เภสัชจลศาสตร์, คนไทยสุขภาพดี

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