พารามิเตอร์ทางเภสัชจลนศาสตร์ของวอริโคนาโซลแบ่งตามฟีโนไทป์ของ CYP2C19
Voriconazole Pharmacokinetic Parameters Based on CYP2C19 Phenotype

นิพนธ์ต้นฉบับ

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2563;15(1):43-48.

บทคัดย่อ

วัตถุประสงค์: เพื่อหาค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของวอริโคนาโซลซึ่งจะนำไปสู่ขนาดวอริโคนาโซลที่เหมาะสมโดยแบ่งตามฟีโนไทป์ของ CYP2C19 เพื่อให้ได้ระดับยาต่ำสุดในเลือดอยู่ในช่วงการรักษาที่ 1-5 มก./ลิตร **วิธีการศึกษา:** การวิจัยเชิงสำรวจโดยการเก็บข้อมูลย้อนหลังจากเวชระเบียนของผู้ป่วยผู้ใหญ่ที่ได้รับการรักษาด้วยวอริโคนาโซลระหว่างเดือนมกราคม 2555 ถึงมีนาคม 2559 ณ โรงพยาบาลรามาธิบดี ข้อมูลดังกล่าว ได้แก่ อายุ เพศ น้ำหนัก จีโนไทป์และฟีโนไทป์ของ CYP2C19 แบบแผนการให้ยาวอริโคนาโซลและระดับยาต่ำสุดในเลือด แล้วคำนวณค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของวอริโคนาโซลโดยใช้สมการ Michaelis-Menten จากนั้นคำนวณขนาดวอริโคนาโซลเพื่อให้ระดับยาอยู่ในช่วงการรักษาแบ่งตามฟีโนไทป์ของ 2C19 **ผลการศึกษา:** จากผู้ป่วยทั้งหมด 53 ราย เป็นเพศชาย 29 ราย (54.7%) อายุและน้ำหนักเฉลี่ย 52.98 ปี และ 57.97 กิโลกรัม ตามลำดับ ค่ามัธยฐานของค่าคงที่ Michaelis-Menten (K_m) สำหรับผู้ที่มีฟีโนไทป์ของ CYP2C19 แบบ extensive metabolizer (EM) และแบบ non-extensive metabolizer (non-EM) เท่ากับ 0.262 มก./ลิตร และ 0.666 มก./ลิตร ตามลำดับ (*P*-value = 0.008) ค่ามัธยฐานของอัตราการเมทาบอลิสมยาสูงสุด (V_{max}) สำหรับ EM และ non-EM เท่ากับ 0.425 มก./กก./ชม. และ 0.483 มก./กก./ชม. ตามลำดับ (*P*-value = 0.262) ขนาดวอริโคนาโซลที่แนะนำเพื่อให้ได้ระดับยาต่ำสุดในเลือดอยู่ในช่วง 1 - 5 มก./ลิตร เท่ากับ 8.9 - 10.7 มก./กก./วัน และ 6.7 - 9.9 มก./กก./วัน สำหรับ EM และ non-EM ตามลำดับ และเพื่อให้สะดวกในทางปฏิบัติ ขนาดวอริโคนาโซลที่แนะนำสำหรับ EM และ non-EM เท่ากับ 10 มก./กก./วัน และ 8.5 มก./กก./วัน ตามลำดับ เพื่อให้ได้ระดับยาต่ำสุดในเลือดประมาณ 2 มก./ลิตร **สรุป:** การศึกษานี้ให้ข้อมูล K_m,V_{max} และขนาดยาวอริโคนาโซลสำหรับผู้ป่วยผู้ใหญ่ไทยแบ่งตามฟีโนไทป์ของ CYP2C19 แต่จากค่า K_m และ V_{max} ที่มีความแปรปรวนค่อนข้างมากพิจารณาจากช่วงที่กว้าง จึงยังไม่แนะนำให้ใช้ขนาดยาที่คำนวณได้จากการศึกษานี้จนกว่าจะได้ทดสอบความเหมาะสมของขนาดยาดังกล่าว การติดตามตรวจวัดระดับยาในเลือดจึงยังจำเป็น

คำสำคัญ: วอริโคนาโซล, ฟีโนไทป์ของ CYP2C19, เภสัชจลนศาสตร์แบบไม่เป็นเส้นตรง, ขนาดยาแนะนำ

Editorial note
Manuscript received in original form on January 10, 2018;
revised December 5, 2019;
and accepted in final form on December 18, 2019

Original Article

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Thai Pharmaceutical and Health Science Journal 2020;15(1):43-48.

Abstract

Objective: To determine pharmacokinetic parameters of voriconazole (VRZ) that will lead to finding appropriate VRZ dose to maintain trough concentration (C_{tr}) within target therapeutic range of 1-5 mg/L based on CYP2C19 phenotype. **Methods:** The medical records of adult patients who received VRZ treatment between January 2012 and March 2016 at Ramathibodi Hospital were retrospectively reviewed. Patient's data including gender, age, body weight, CYP2C19 genotype and phenotype, VRZ dosing regimen, and VRZ C_{tr} were collected. The pharmacokinetic parameters of VRZ were calculated using conventional nonlinear pharmacokinetic study, i.e., Michaelis-Menten equation. Proper dose for keeping VRZ C_{tr} within therapeutic range were then determined for each CYP2C19 phenotype. **Results:** A total of 53 patients were included into this study. Twenty-nine (54.7%) were male with mean age and body weight of 52.98 yrs and 57.97 kg, respectively. Median Michaelis-Menten constant (K_m) for CYP2C19 extensive metabolizers (EM) and non-extensive metabolizers (non-EM) were 0.262 mg/L and 0.666 mg/L, respectively (*P*-value = 0.008). Median maximum rate of metabolism (V_{max}) for EM and non-EM were 0.425 mg/kg/h and 0.483 mg/kg/h, respectively (*P*-value = 0.262). The doses to achieve therapeutic C_{tr} (1 - 5 mg/L) were 8.9 - 10.7 mg/kg/day and 6.7 - 9.9 mg/kg/day for EM and non-EM, respectively. For more applicable in real world practice, the rounded dose of 10 mg/kg/day and 8.5 mg/kg/day for EM and non-EM, respectively, were recommended to provide VRZ C_{tr} around 2 mg/L. **Conclusion:** This present study provided Michaelis-Menten constant (K_m and V_{max}) of VRZ for Thai adult patients and the dose recommendation for this patient group based on CYP2C19 phenotype. The K_m and V_{max} of VRZ in this study show high variability judged from their wide range, therefore our recommended doses still cannot be used in practice unless its appropriate would be validated. Therapeutic drug monitoring of VRZ is still warranted.

Keywords: voriconazole, CYP2C19 phenotype, nonlinear pharmacokinetic, dose recommendation

Journal website: http://ejournals.swu.ac.th/index.php/pharm/index

Introduction

Voriconazole (VRZ) is a synthetic triazole antifungal derived from fluconazole. VRZ has a broad spectrum and is recommended in the treatment of invasive fungal infections (IFIs) caused by common pathogens such as *Aspergillus, Candida, Cryptococcus neoformans*, as well as less common pathogens such as *Fusarium* and *Pseudallescheria*.[1] IFIs caused by these species resulted in significant mortality and morbidity, especially in immunocompromised patients such as

those receiving chemotherapy and immunosuppressive therapy (e.g., solid organ or bone marrow transplant patients, and systemic lupus erythematous (SLE) patients), or those infected with human immunodeficiency virus (HIV).[2] VRZ pharmacokinetics exhibit high inter- and intra-individual variability because it has nonlinear pharmacokinetics associated with its saturated hepatic metabolism and with diverse patient characteristics. VRZ is metabolized mainly by CYP2C19 isozyme, and to the lesser extent by CYP3A4 and CYP2C9.[3,4] Therefore, CYP2C19 polymorphisms may explain inter-individual variability in voriconazole exposure.[4] *CYP2C19*2* and *CYP2C19*3* are the variant alleles associated with a decreased activity of CYP2C19; on the contrary, *CYP2C19*17* is the variant allele associated with an increased activity of CYP2C19.[5,6] On the basis of CYP2C19 metabolizing activity, individuals could be classified into four CYP2C19 phenotypes, specifically (i) ultra-rapid metabolizers (UM), e.g., **17/*17, *1/*17*, (ii) extensive metabolizers (EM), e.g., **1/*1*, (iii) intermediate metabolizers (IM), e.g., **1/*2, *1/*3, *2/*17, *3/*17*, and (iv) poor metabolizers (PM), e.g., **2/*2, *3/*3, *2/*3*.[7] Many studies have shown that the frequency of CYP2C19 polymorphisms varies among different ethnic groups.[8,9] A number of studies have documented that patients with a PM phenotype have VRZ plasma concentrations 2 - 4 times higher than those with an EM phenotype; while patients with a UM phenotype (**1/ *17, *17/*17*) have voriconazole plasma levels lower than EM (**1/*1*) patients.[9-11] In addition to CYP2C19 polymorphism, various factors have been reported to influence the VRZ plasma concentrations such as age[3,12], drug interactions[3,12], albumin level[13], C-reactive protein level[13] and body weight[3]; whereas some studies reported no significant relationship between the plasma concentration and genotype[14], age[14], sex[12,14] or use of concomitant proton pump inhibitors.[14,15] Unpredictability of VRZ plasma concentrations complicated its usefulness in clinical practice. This study aimed to determine pharmacokinetic parameters of VRZ based on CYP2C19 phenotype which will lead to finding a dose that will optimize the invasive aspergillosis treatment.

Methods

Patient enrollment and data collection

Thai patients aged 18 years or older who were being treated with voriconazole at least two different doses and had at least one plasma trough concentration (C_{tr}) of each dose at Ramathibodi Hospital, Thailand between January 2013 and March 2016 were eligible for participation. Patients' medical records were reviewed and patients-specific characteristics were retrospectively collected. Voriconazole dosage regimen, administration time, blood sampling time, steady state voriconazole trough concentration, and duration of voriconazole treatment were collected. VRZ was considered to be at steady state after 24 hrs of administration following two loading doses or after 5 days without loading dose and blood samples were drawn before the next dose would be considered a trough concentration.[16] Patients were excluded if they had severe hepatic disease which was defined as the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of grade $\geq$ 4, or were pregnant. Voriconazole concentrations were analyzed by toxicology laboratory of Ramathibodi Hospital, Thailand where validated liquid chromatography mass spectrometry (LC-MS/MS) assay was used.

DNA extraction and CYP2C19 genotyping

Genomic DNA was extracted from venous blood specimens with the use of a purifier kit (QIAamp DNA Blood mini kit; Qiagen NV, Venlo, Netherlands) according to the manufacturer's instructions. The association of genetic variants in the *CYP2C19* gene encoding enzyme was tested in this study to assess the effect of *CYP2C19*2* (splicing defect G681A SNP), *CYP2C19*3* (stop codon G636A SNP) and *CYP2C19*17* (increased enzyme activity g.−806 C > T) allelic variation in response to clopidogrel. A microarray-based technique (AmpliChip CYP450 test; Roche, Basel, Switzerland) was performed to genotype the *CYP2C19* gene *(*1/*2/*3)*. Regarding the predicted metabolic phenotypes related to CYP2C19 polymorphisms, an extensive metabolizer was defined as a patient who had a homozygous wild-type genotype *(CYP2C19*1/*1)* and an ultra-rapid metabolizer was defined as a patient who had a heterozygous genotype with at least one *CYP2C19*17* allele (*CYP2C19*1/*17* or *CYP2C19*17/*17*). An intermediate metabolizer was defined as a patient who had a heterozygous genotype with at least one *CYP2C19*1* allele (*CYP2C19*1/*2* or **1/*3*), and a poor metabolizer was classified as a patient who had a homozygous (*CYP2C19*2/*2* or **3/*3*) or heterozygous (*CYP 2C19*2/*3*) genotype with a mutant allele.

This study was performed in accordance with the Declaration of Helsinki, 1996 good clinical practice. The study protocol was approved by the Ethics Committee of Ramathibodi Hospital, Thailand (Protocol number 07-57-21).

Analysis of voriconazole pharmacokinetics

Voriconazole exhibits nonlinear pharmacokinetic profiles which could be described by Michaelis-Menten equation (1)

$$R = \frac{V_{max} \cdot C}{K_m + C} \quad (1)$$

R specifies a voriconazole dosing rate which is expressed in milligram per kilogram per hour (mg/kg/h). With an initial dosing rate of 8 mg/kg/day, dosing rate would be adjusted according to the measured concentration. V_{max} represents the maximum rate of metabolism at saturating substrate concentration (mg/kg/h). K_m or Michaelis constant is voriconazole concentration at which the metabolism rate is half of V_{max} which is expressed in milligram per liter (mg/L). Finally, C is the steady state voriconazole trough concentration (mg/L). To determine patient-specific pharmacokinetic parameters, K_m and V_{max}, we need two dosing rates (R_1 and R_2) and one trough concentration from each dosing rate (C_1 and C_2) using the equations (2) and (3). Then the recommended dose will be calculated (R) using previously determined K_m and V_{max} for this patient group to keep voriconazole concentration within therapeutic range (i.e., 1.0 - 5.0 mg/L).

$$K_m = \frac{R_1 - R_2}{\frac{R_2}{C_2} - \frac{R_1}{C_1}} \quad (2)$$

$$V_{max} = Km\frac{R}{C} + R \quad (3)$$

Statistical analysis

Statistical analysis was performed using SPSS, version 21 (SPSS Inc., Chicago, IL, USA). Continuous data (i.e., K_m and V_{max}) were presented as mean with standard deviation and median with interquartile range (IQR); while categorical data as proportions. Analyses of continuous data were performed using Mann-Whitney U test due to the nonnormality of voriconazole concentrations. Statistical significance was set at a type I error of 5%, or *P*-value of less than 0.05.

Results

Subjects and clinical characteristics

A total of 53 adult patients with invasive aspergillosis (IA) who were receiving voriconazole and whose submitted blood samples were analyzed for voriconazole trough plasma concentrations were included in this study. Demographic and clinical characteristics of the patient population are summarized in Table 1. Mean (SD) age of patients in this study was 52.98 (15.64) years. Slightly more than half (n = 29, or 54.7%) of the patients were male. Mean (SD) body weight is 57.97 (9.99) kg.

The number and frequencies of variant alleles of CYP2C19 in our population are shown in Table 1. Of these patients, **1/*1* was the majority (n = 26, or 49.1%) followed by **1/*2* (n = 19, or 35.8%). When patients were classified according to CYP2C19 phenotypes, there were 26 (49.1%) extensive metabolizers (EM), 22 (41.5%) intermediate metabolizers (IM), and 5 (9.4%) poor metabolizers (PM).

Pharmacokinetic analysis

Median (IQR) K_m of VRZ was 0.262 (0.29) mg/L for EM and 0.666 (1.78) mg/L for non-EM (*P*-value = 0.008). Median (IQR) V_{max} of VRZ was 0.425 (0.14) mg/kg/h and 0.483 (0.25) mg/kg/h for EM and non-EM, respectively. Median (IQR) plasma VRZ trough concentration (C_{tr}) after initiation of same maintenance dose of 8 mg/kg/day, divided into 2 doses, were 1.870 mg/L (3.20) and 2.060 mg/L (4.69), for EM and non-EM, respectively (Table2). No significant differences were observed for V_{max} and C_{tr} between CYP2C19 EM and non-EM.

Table 1 Demographic and clinical characteristics of participants (N = 53).

Characteristics	Number of patients (%)
Gender	
Male	29 (54.7)
Female	24 (45.3)
Age (yrs), mean ± SD (range)	52.98 ± 15.64 (18.09 - 82.48)
Body weight (kg), mean ± SD (range)	57.97 ± 9.99 (38.80 - 84.00)
CYP2C19 genotype	
**1/*1*	26 (49.1)
**1/*2*	19 (35.8)
**1/*3*	3 (5.7)
**2/*2*	2 (3.8)
**3/*3*	1 (1.9)
**2/*3*	2 (3.8)
CYP2C19 phenotype	
Extemsive metabolizer (EM)	26 (49.1)
Non-EM	
Intermediate metabolizer	22 (41.5)
Poor metabolizer	5 (9.4)

Table 2 Pharmacokinetic parameters of voriconazole classified by CYP2C19 phenotype (N = 53).

CYP2C19 phenotype	median ± IQR					
	K_m (mg/L)	*P*-value	V_{max} (mg/kg/h)	*P*-value	C_{trough} (mg/L)	*P*-value
EM (n = 26)	0.262 ± 0.29	0.008**	0.425 ± 0.14	0.262	1.870 ± 3.20	0.845
Non-EM (n = 27)	0.666 ± 1.78		0.483 ± 0.25		2.060 ± 4.69	

* Statistically significant at *P*-value < 0.01, Median Km and Vmax for all patients were 0.391 mg/L and 0.467 mg/kg/h, respectively.

Based on calculated pharmacokinetics parameters, median K_m of 0.262 mg/L for EM and 0.666 mg/L for non-EM, and median V_{max} of 0.467 mg/kg/h for all patients, optimal dose of VRZ were then be estimated using Michaelis-Menten equation (eq.1) to keep C_{tr} within a therapeutic range of 1.0 - 5.0 mg/L. The recommend doses were 8.9 – 10.7 mg/kg/day and 6.7 – 9.9 mg/kg/day divided into 2 equal doses and given every 12 hrs, for EM and non-EM, respectively (Table 3).

To be more applicable in clinical practice, we recommend VRZ daily dose of 10 mg/kg/day and 8.5 mg/kg/day for EM and non-EM, respectively, to keep plasma VRZ C_{trough} approximately 2 mg/L.

Table 3 Recommended VRZ dose for IA treatment according to CYP2C19 phenotype (N = 53).

Target Trough Concentration (mg/L)	Dose (mg/kg/day)	
	Extensive metabolizer (N = 26)	Non-extensive metabolizer (N = 27)
1	8.9	6.7
1.5	9.5	7.8
2	9.9	8.4
2.5	10.2	8.9
3	10.3	9.2
3.5	10.4	9.4
4	10.5	9.6
4.5	10.6	9.8
5	10.7	9.9
Recommended dose* (mg/kg/day)	10.0	8.5

* To keep C_{tr} of approximately 2 mg/L.

Discussions and Conclusion

Calculated K_m for EM was lower than that in non-EM which was reasonable because the lower K_m the higher metabolizing activity. The median K_m for all of our patients was 0.391 mg/L which was lower than K_m reported by Masumoto K et al. of 1.32 mg/L.[17] It was possibly since there was a higher frequency of CYP2C19 EM in our study when compared to that frequency reported in Japanese population.[7] Other factor that might explain the low value of our patient's K_m was there was no *CYP2C19*17* genotype which is a functioning allele, in our study. However, the frequency of this variant in Thai population was relatively low. Other than CYP2C19, CYP3A4 is also responsible for VRZ metabolism and CYP3A4 is a polymorphism as well; but the effects of CYP3A4 variants were not examined in this study. Regarding calculated V_{max}, it was not much different between the value of our patients and previous studies[4,17,18], that means the maximum rate of VRZ metabolism was not different among ethnic groups.

Conventional pharmacokinetic study can be used even in the setting that CYP2C19 genotyping was not available, dose adjustment can be performed by K_m and V_{max} calculation. Nonetheless, population pharmacokinetic was also be performed and reported in our other study (unpublished data).

Doses recommended by the present study was not equal to those in VRZ package insert which recommend daily dose of 12 mg/kg/day, divided into 2 equal doses for 1 day as loading dose followed by 8 mg/kg/day given every 12 hrs as maintenance doses for adult patient.[19] Based on our calculation, if EM individuals received VRZ dose as recommended in the package insert, VRZ plasma C_{tr} will lower than 1 mg/L which was insufficient while those with IM or PM can maintain VRZ plasma C_{tr} within therapeutic range. CYP2C19 EM was the majority of Thai population as well as Asian population. Therefore, CYP2C19 polymorphisms should get more attention for VRZ dosing to optimize VRZ plasma C_{tr}. Based on our calculation, we recommend a maintenance dose of 10 mg/kg/day for CYP2C19 EM and 8.5 mg/kg/day for non-EM to maintain the steady state VRZ C_{tr} around 2 mg/L.

It can be seen that the calculated K_m and V_{max} value had a high uncertainty, considering a fairly wide range compared to the median value. Alhough the median C_{tr} levels after receiving the same maintenance dose were not different between EM and non-EM, these values were presented with wide ranges. However, they showed the reasonably trend of a higher median C_{tr} for non-EM. Acoordingly, the recommended dose in this study is still not recommended for practical use, unless its propriety would be validated because of the high inter-individual variation.

Our study had several limitations. This retrospective study enrolled a relatively small number of patients with a limited number of PMs (9.4%, 5/53). We did not exclude patients who received medications that may interact with voriconazole. Most frequently co-administered VRZ with possible drug interactions were proton pump inhibitors and glucocorticoids. The study of Zvyaga et al. revealed that proton pump inhibitors

are mostly weak inhibitors of cytochrome P450 *in vivo*; however, two members (esomeprazole and omeprazole) are more likely to serve as clinically relevant inhibitors of CYP2C19.[20] Nonetheless, another study showed that receiving proton pump inhibitors together with VRZ had no effect on VRZ levels and only patients who received higher dose of omeprazole (> 20 mg/d) were more likely to have higher concentrations of VRZ.[15] In addition, there was a study showing that omeprazole was the most potent CYP2C19 inhibitor, whereas rabeprazole had no influence on VRZ (omeprazole > esomeprazole > lansoprazole > rabeprazole). However, in consideration of the therapeutic concentration range, dosage adjustment of VRZ is unnecessary regardless of which proton pump inhibitor was co-administered.[21] There were three patients in this present study receiving omeprazole before initiating VRZ but had been changed to lansoprazole once VRZ was introduced.

When considering the induction of CYP2C19, there were no co-administrations of VRZ and CYP2C19 inducers, such as rifampicin, phenobarbital, phenytoin, or carbamazepine. However, co-administration of glucocorticoids was found. Glucocorticoids may increase or decrease VRZ level via CYP3A4 and CYP2C19 interactions.[22] Recent study reported an inverse correlation between VRZ concentration and corticosteroid dose.[23] The results from a systematic review by Li et al. showed that glucocorticoids had inconclusive effect on VRZ pharmacokinetics.[24] From six cohorts, one showed that treatment with glucocorticoids had no impact on VRZ C_{tr}, three studies reported that glucocorticoids slightly elevated the metabolism of VRZ but with no significance, and it did not affect the plasma exposure of VRZ. Two studies included in the review found that co-administration of VRZ with glucocorticoids led to a significant decrease in normalized VRZ C_{tr}.[24] However, one recent physiology-based pharmacokinetic model study showed that the predicted maximum concentration and the area under the plasma concentration-time curve from 0 hrs to infinity ($AUC_{0\rightarrow inf}$) of VRZ remained unchanged when in combination with dexamethasone.[25] It suggested that dexamethasone had no influence on the pharmacokinetics of VRZ.[25]

In addition, results from a population pharmacokinetic analysis showed that both proton pump inhibitors and glucocorticoids were not a significant covariate of VRZ clearance.[26] In our present study, many patients were on glucocorticoids and proton pump inhibitors concomitantly.Co-administration of a CYP450 enzyme inducer and inhibitor simultaneously could potentially decrease the potential effects of these medications. However, physicians should continue to pay attention when prescribing enzyme inducers and inhibitors together with voriconazole.

Furthermore, since there were only five PMs included in this study, we could not calculate the recommended dose for each phenotypic group, i.e. EM, IM, and PM. The study of Kim et al. could offer CYP2C19 phenotype-guided initial dosing regimen for EM, IM, and PM individuals.[26] Unfortunately, optimal recommendation corresponding to individual phenotype differences could be made but with some cautions. Therefore, further studies with a relatively large number of patients with each CYP2C19 phenotype are needed.

In conclusion, K_m and V_{max} of VRZ in EM and non-EM were 0.262 mg/L and 0.425 mg/kg/h, and 0.666 mg/L and 0.483 mg/kg/h, respectively. Our recommended maintenance dose of VRZ directed by CYP2C19 phenotype of 10 mg/kg/day and 8.5 mg/kg/day for CYP2C19 EM and non-EM have not been validated, therefore it is not recommended for practical use. In addition, we recommended therapeutic drug monitoring should be performed concurrently with VRZ treatment due to high intra- and inter-individual variation of VRZ's pharmacokinetics.

Acknowledgement

This study was funded by the National Science and Technology Development Agency (NSTDA), Ministry of Higher Education, Science, Research, and Innovation, Thailand.

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