ผลของการใช้แอปพลิเคชันในโทรศัพท์มือถือตรวจสอบขนาดยาความเสี่ยงสูง เทียบกับการคำนวณด้วยมือ
Effects of A Mobile Phone Application in Examining Dosage of High Alert Drugs Compared with Manual Calculation

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบคะแนนที่ได้และเวลาที่ใช้ตรวจสอบขนาดยาความเสี่ยงสูงในใบสั่งยาสมมติระหว่างการใช้แอปพลิเคชันบนโทรศัพท์มือถือและการคำนวณด้วยมือ **วิธีการศึกษา:** การวิจัยแบบ cross-over design ที่มี two-period (ก่อนและหลัง washout period), two-sequence (ใช้แอปพลิเคชันตามด้วยการคำนวณด้วยมือ กับการคำนวณด้วยมือตามด้วยแอปพลิเคชัน), two-method (วิธีที่ใช้แอปพลิเคชันและวิธีคำนวณด้วยมือ) กลุ่มตัวอย่างเป็นเภสัชกร 31 คน ที่ทำงานในโรงพยาบาลทั่วไปและโรงพยาบาลศูนย์ 5 แห่ง ดำเนินการวิจัยในช่วงธันวาคม พ.ศ. 2558 ถึงมีนาคม พ.ศ. 2559 โดยสร้างแอปพลิเคชันสำหรับโทรศัพท์มือถือระบบแอนดรอยด์ โดยแอปพลิเคชันแสดงขั้นตอนการคำนวณอย่างละเอียด แล้วสร้างคำสั่งใช้ยาในใบสั่งยาสมมติพร้อมคำถามประกบใบสั่งยาให้เภสัชกรตรวจสอบขนาดยาว่าเหมาะสมหรือไม่ โดยทดสอบยาความเสี่ยงสูง 6 ชนิด คือ dobutamine, dopamine, potassium chloride, nicardipine, nitroglycerine และ norepinephrine โดยแสดงการคำนวณเป็น (1) อัตราการให้ยา (ml/hr) (2) ขนาดยาที่ผู้ป่วยควรได้รับ (µg/kg/min) และ (3) ขนาดยาที่ใช้กับผู้ป่วยรายนั้น ๆ (mg) โดยใช้ใบสั่งยา 7 ใบที่มีความยากง่ายใกล้เคียงกันสำหรับแต่ละวิธีตรวจสอบขนาดยา ให้เภสัชกรตรวจสอบขนาดยาทั้ง 7 ใบแล้วจับเวลาและให้คะแนนผลการตรวจสอบ เปรียบเทียบคะแนนที่ทำได้ถูกต้อง (เต็ม 7 คะแนน) และเวลาเป็นวินาทีโดย ANOVA **ผลการศึกษา:** คะแนนตรวจสอบขนาดยาส่วนมากมีค่า 6 คะแนนขึ้นไป และไม่ต่างกันทั้งในแง่ period, sequence หรือ method แต่เวลาที่ใช้ต่างกัน คือ ช่วงแรก (1,014.65 วินาที) ใช้เวลามากกว่าช่วงที่สอง (852.90 วินาที) อย่างมีนัยสำคัญทางสถิติ (*P*-value = 0.002) และแอปพลิเคชัน (649.06 วินาที) น้อยกว่าการคำนวณด้วยมือ (1,218.48 วินาที) อย่างมีนัยสำคัญทางสถิติ (*P*-value < 0.001) **สรุป:** แอปพลิเคชันบนโทรศัพท์มือถือช่วยให้การตรวจสอบขนาดยาความเสี่ยงสูงได้ดีพอ ๆ กับการคำนวณด้วยมือ แต่ลดเวลาการทำงานได้มาก

คำสำคัญ: แอปพลิเคชัน, โทรศัพท์มือถือ, ตรวจสอบขนาดยา, ยาความเสี่ยงสูง

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Abstract

Objectives: To compare scores and times in examining prescribed doses of high-alert drugs (HADs) in prescriptions between mobile phone application and manual calculation. **Methods:** This cross-over study tested two-period, two-sequence (application use followed by manual calculation and vice versa) and two-method (application and manual calculation) effects on scores and time in examining prescribed doses of 6 HADs (dobutamine, dopamine, potassium chloride, nicardipine, nitroglycerine and norepinephrine). Sample was 31 pharmacists working in 5 general hospitals and medical centers. The study was conducted from December 2015 to March 2016. The developed android application displayed all calculation steps. With each method, pharmacists examined (1) rate of administration (ml/hr) (2) dose per kg per min and (3) total dose (mg) in 7 prescriptions along with questions with comparable difficulty. Scores (total of 7 points) and time (in seconds) were recorded and statistically tested using ANOVA. Questionnaire on desirable characteristics the application was filled at the end of the experiment and presented as percentage. **Results:** Total scores on examining the prescribed doses were mostly more than 6 points with no statistical difference regarding differences in period, sequence or method. Time used in the first period (1,014.65 seconds) was longer than that in the second period (852.90 seconds) with statistical significance (*P*-value = 0.002), and that with application use (649.06 seconds) was shorter than that with manual calculation (1,218.48 seconds) with statistical significance (*P*-value < 0.001). **Conclusion:** Mobile phone application offered performance in examining prescribed doses of HADs comparable to that of manual calculation but with a shorter time.

Keywords: application, mobile phone, dose examination, high alert drug

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Introduction

High-alert drugs (HADs) are those with a high potential to cause harms if not used properly. Pharmacists are responsible for checking prescribed HAD dosage in an accurate and fast manner since HADs are usually used in critical situations. Many efforts have been put to enhance understanding HAD prescritptions, preparations and administration of HADs; yet errors have continuously occurred. Mobile phone application with steps of dose calculations detailed could have aided pharmacists to examine HAD prescribed dosage.

HADs usually have a narrow therapeutic window with serious or life-threatening adverse effects if medications errors occur. These included adrenergic agonists (e.g., adrenaline,

dopamine, dobutamine, and norepinephrine), drugs for critical cardiovascular disorders (eg., alteplase injection, nicardipine injection, and nitroglycerine injection), unfractionated and low molecular weight heparin (LMWH) (eg., enoxaparin, fondaparinux and tinzaparin).[1-3] Medication errors (MEs) have been prevalent globally. Specifically, in 11 countries in southeast Asia, the most found MEs were administration errors accounting for 15.2% - 88.6% of all MEs.[4] Of these administration errors, early or delayed dosing and dose omission were the most frequently found, followed by wrong dose. Among intravenous (IV) drugs, which many of them are HADs, the most found administration errors were wrong injection technique and faster infusion rate.[4] Unfortunately, more than 50% of ME-associated adverse events are preventable.[5] A medical center in Thailand reported that prescribing errors increased by 1.97 and 2.34 times for out-patient and in-patient departments, respectively, from 2015 to 2016; while dispensing errors increased by 8 and 2 times.[6] With MEs of certain HADs, in 2015, 6 MEs with severity levels of D or higher were found. Specifically, there were 3 D-level event (adverse events that cause close and prolonged monitoring), 2 F-level event (hospitalized or prolonged hospitalization) and one I-level event (death).[6]

A study on understanding and preparation steps of HAD prescriptions including dopamine, dobutamine, adrenaline and norepinephrine revealed that 66.97% and 52.6% of nurses understood the prescriptions and preparation steps, respectively; while 86.11% and 69.44% of pharmacists understood the prescriptions and dispensing steps, respectively.[7] This suggests that nurses and pharmacists had misunderstanding with prescriptions of HADs and associated dispensing, preparations, and administrations.[7] There have been various aides for drug information and drug dose calculation in texts and electronic calculation aides both online and offline formats.

Mobile phone or smartphone has been highly developed for Android™, iOS™ and Windows™ operating systems. Mobile phone has been used to provide drug information including indication, dosage, adverse effects, and drug interactions. Application for dosage calculation for HADs for specific patients on mobile phone has been limited. Only applications on website to calculate dosage of general drugs, pediatric dosing, and few HADs have been available on websites. Unfortunately, these websites have some limitations such as the need for online Internet, inability to convert units, calculation limited to rate of administration, no display of calculation steps for users to follow the cognitive process, and display of only the final calculation result. In 2013, a study in the US showed that there were 27 applications for pharmacy practice and medical practice on mobile phone providing drug information, clinical data, clinical tools, laboratory reference, and continuing educations.[8] These applications did not provide the calculation for HADs or the calculation steps. Applications showing all calculation steps with all units could help users examine the prescribed doses in a accurate and fast fashion and maintain the users' cognitive function.

With a concern that HAD prescriptions should be checked with effective tools, this present study aimed to develop a mobile phone application for calculating doses of HADs in an accurate and fast fashion with the display of all steps to help maintain the user's cognitive process. In addition to the fast checking of HAD doses before dispensing, the application was designed to provide drug information for fast referencing for given patients, i.e., doses of HADs adjusted according to age and body weight. This application offered dose calculation and information of common and complicate dosing HADs including dobutamine, dopamine, potassium chloride, nicardipine, nitroglycerine and norepinephrine. The application consisted of two parts, namely calculation and drug information modules.

In dose calculation, dosing based on age and body weight of given patients to assure safe and effective use is a task that uses cognitive function than traditional dispensary. Based on pharmaceutical care concept, all tasks are based on more cognitive function than traditional pharmacy tasks. These new tasks could be viewed as medicine therapy management which are carried out in various settings including hospital out-patient and in-patient departments, primary care unit, and community pharmacy.[9] As an calculation aide, the application was expected to ease the calculation process, but not to deter cognitive function of the pharmacist. If possible, the detailed steps were expected to strengthen cognitive function of the users even though not evaluated in this study. The application was expected to display dosage in the format of total dose (mg), volume of parenteral solution (ml), body weight (kg), rate of administration (ml/hr) and the dose delivered (µg/kg/min). All steps and results could be checked by the pharmacist to help inspect their thinking process. This aimed at reducing chance of human error.

The **objectives** of this study were to determine accuracy, time used, and desirable characteristics of mobile phone

application compared with manual calculation in examining the prescribed dose of HADs among hospital pharmacists. **Specific objectives** were to determine whether the use of mobile phone application and manual calculation resulted in difference in scores (points) of correctly identifying whether the HAD prescribed dose was correct or incorrect, and time used (in seconds) between the use of application and manual calculation. The study also determined frequency of each of desirable characteristics of the two methods.

The prescribed doses to be examined included total dose (mg), volume of parenteral solution (ml), body weight (kg), rate of administration (ml/hr), the dose given (µg/kg/min). HADs referred to dopamine dobutamine, norepinephrine, nitroglycerine, nicardipine and KCl. These HADs were commonly prescribed and with complicate calculations that make them susceptible for errors such as the need for conversion of amount and concentration, and the ratio order.[1] The application was defined as a software program developed by the researchers and a programmer for mobile phone and tablet computer with Android operating system. The Android system was chosen because it was more feasible to develop the application for.[10] Manual examination on the prescribed doses of HADs allowed the use of basic calculator but not instruments with pre-programmed calculation formula either online or offline.

Methods

The components of the study's crossover design included two-method (i.e., the use of application and manual calculation), two-sequence (i.e., th use of application followed by manual calculation or sequence App-Manual, and manual calculation followed by application or Manual-App), and two- period (i.e., the periods before and after 1-week washout period). [11] This cross-over design reduces inter-person variability in calculation capability and other characteristics of individual pharmacists.

Population and sample

Study population was pharmacists at HRH Princess Maha Chakri Sirindhorn Medical Center, Mahawajiralongkorn Thanyaburi Hospital, Siriraj Hospital, Ramathibodi Hospital, and Burapha University Hospital. They could be working in out-patient and/or in-patient department. Sample was those pharmacists who were working from December 2015 to March 2016 who met the inclusion and exclusion criteria and willing to participate in the study. To be eligible, pharmacists had to be working at one of the five hospitals at out-patient and/or in-patient departments. Since pharmacists sometimes have to allocate between these units, dose calculation for HADs is needed as a basic performance regardless of service unit. They also had to be able to use mobile phone or tablet with Android system and willing to participate. However, those who could not complete the two periods or who requested discontinuation were excluded. For participants in difficulty testing of the prescriptions of HADs, they were 40 6th year pharmacy students of Srinakharinwirot University recruited by convenience sampling and were willing to participate.

Sample size justification

Since there had been no studies on testing effectiveness of applications for dose calculation, a small-to-moderate 25% intrasubject coefficient of variation (CV) in cross-over design was chosen.[12] With a type I error of 5% and a power of 80%, a sample size of 28 subjects or 14 subjects per group (i.e., per sequence) was needed.[13] To compensate for a probably underestimated % intrasubject CV, a total of 34 subjects or 17 subjects per sequence were needed for a 20% compensation rate. Subjects were randomized to the two sequences using a random number table.

Research instruments

The instruments included mobile phone application for dose calculation, prescriptions of HADs, questionnaire on desirable characteristics of the use of application compared with manual calculation, data collection forms for time used in calculation and demographic characteristics of the participants.

Mobile phone application for dose calculation

The application consisted of dose calculation module and drug information module. The calculation module helped examine whether the dose was appropriate for the given patient. The pharmacist was expected to fill the dosing information relating to the prescription including total dose (mg), volume of parenteral solution (ml), body weight (kg), rate of administration (ml/hr), or the dose given (µg/kg/min). The application calculated each of the missing dosing information which was suitable for each HAD and physician's order. The

calculated results could be compared with the physician's dosing order whether it was appropriate or correct or not. Pre-programmed calculation formula of dobutamine, dopamine, potassium chloride, nicardipine, nitroglycerine and norepinephrine were developed. This list of HADs was approved by 3 pharmacists experienced in in-patient department for at least 3 years.

Application design was based on the basis that it would examine the dose order and present the results as (1) total dose (mg), (2) administration rate (mL/hr) and (3) the dose given (μg/kg/min). The application requested the user to fill information such as age, body weight, dose (mg), administration rate (mL/hr), volume of parenteral solution, and the dose given (μg/kg/min) in the numeric field.

Example of dose examination on dobutamine injection prescription in the application

The application requested the patient age. If not over 18 years old, the application displayed the recommended dose of 2 – 20 μg/kg/min with the recommended maximum given dose of 40 μg/kg/min; if older than 18 years, 2 – 40 μg/kg/min. The application then displayed the ratios prescribed by physician for the pharmacist to choose (i.e., the ratio of 1:1, 2:1, and 4:1 referring to the concentrations of 1, 2, and 4 mg/ml, respectively). The pharmacist was then asked to fill the volume of parenteral solution for dilution (mL). Finally, the pharmacist was asked to fill the dose of dobutamine (mg), administration rate (mL/hr) and the given dose (μg/kg/min). For any unknown information, it could be left unfilled, and the application will show the unknown calculated information at the end. The details of calculation formulas of all scenarios are shown in Figure 1.

Scenario 1: Examining dose (mg)

$$\frac{\text{body weight } (kg) \times 60 \times \text{dose given } (\mu g/kg/min) \times \text{volume of paenteral solution } (ml)}{\text{administration rate } (ml/hr) \times 1000}$$

Scenario 2: Examining administration rate (mL/hr)

$$\frac{\text{body weight } (kg) \times 60 \times \text{dose given } (\mu g/kg/min)}{[\text{dose } (mg) \div \text{volume of parenteral solution } (ml)] \times 1000}$$

Scenario 3: Examining dose given (μg/kg/min)

$$\frac{[\text{dose } (mg) \div \text{volume of parenteral solution } (ml)] \times 1000 \times \text{administration rate } (ml/hr)}{\text{body weight } (kg) \times 60}$$

Figure 1 Formulas for examining dose of dobutamine injection for various scenarios displayed by the application.

The application then displayed details of calculation results for each scenario as shown in Figure 2.

Result display	
What to know	**Details**
Dose (mg)	= dose given (μg/kg/min) x body weight (kg) = result (μg/min) x 60 = result (μg/hr) / administration rate (ml/hr) = result (μg /mL) x volume of parenteal solution (mL) = result (μg)/1000 = dose (mg)
Administration rate (mL/hr)	= dose given (μg/kg/min) x body weight (kg) = result (μg/min) x 60 = result (μg/hr) / 1000 = result (mg/hr) x dose (mg) / volume of parenteral solution (mL) = administration rate (mL/hr)
Dose given (μg/kg/min)	= dose (mg) / volume of parenteral solution (mL) = result (mg/mL) x 1000 = result (μg/mL) x administration rate (mL/hr) = result (μg/hr) / body weight (kg) = result (μg/kg/hr) / 60 = dose given (μg/kg/min)
	If any, dose (mg), administration rate (mL/hr) or dose given (μg/kg/min), was not in the recommended range, the application displayed the warning. The application then re-calculated and showed the appropriate dose.

Figure 2 Details of calculation results for each scenario displayed by the application.

Prescriptions for dose examination by the use of application and manual calculation

Prescriptions were created based on well-known drug information databases and manuals[14-17] with a report of problems of HADs of Siriraj Hospital.[1] The participants were expected to correctly identify whether the dose was correct/appropriate or not, and to show the correct dose if the prescribed dose was incorrect. The researchers created 30 prescriptions, i.e., 5 prescriptions for each of the 6 HADs with a unique question accompanying each prescription. The question was, for example, for a female patient aged 58 years old, weighed 41 kg, the physician prescribed dopamine 250 mg in D5W 250 mL to be given at a rate of 10 microdrop/min. What is the dose given to this patient (mcg/kg/min) and whether it was within the recommended dose or not (recommended dose: 2 - 10 mcg/kg/min). Half of 30 prescriptions contained correct doses.

Difficulty was tested in 40 6th year pharmacy students of Srinakharinwirot University. Each student examined the 30 prescriptions with manual calculation within 90 minutes. A score of 1 point was given for an answer within ±10% of the correct dose, and 0 points otherwise. With a possible total score of 40 points for each prescription, mean score for each prescription and the grand mean were calculated. Prescriptions with the mean closest to the grand mean were

selected so their difficulties were comparable.[18] For each sequence, two prescriptions for each of the three dose formats (i.e., administration rate (mL/hr), dose given (μg/kg/min), and dose (mg)) were selected. Since KCl prescription was not represented based on mean score, one prescription of KCl was additionally selected for each sequence. As a result, there were 14 prescriptions, i.e., 7 for each sequence. All 6 HADs were distributed evenly in the two sequences.

Application development

The researchers designed the application algorithm and interface based on relevant websites found in the year 2014, and guidelines on interface design.[19,20] Two modules, dose calculation and drug information, were readily available for pharmacists to choose. In the dose calculation module, the steps of calculation were arranged as shown above. The programmer developed the application accordingly. For the drug information module, necessary data were extracted from well-known databases, textbooks, and report[1,14-17] and displayed in two discrete parts, i.e., warnings and monitoring/evaluation, to choose from.

Once version 1 was developed, the researchers tested the application with 2 prescriptions and provided the programmer opinions for revision. Version 2 was tested with the 14 selected prescriptions in 6 6th year pharmacy students of Srinakharinwirot University. This test was based on usability testing.[20,21] Some pitfalls were detected and corrected in the last version.

Time data collection form

The researcher used a stopwatch to record the time used in examining 7 prescriptions. Time in seconds were recorded in the time data collection form.

Collection form of demographic characteristics of the participants

The researcher recorded gender, age, number of years working as a hospital pharmacist, and service unit (out-patient and/or in-patient departments) in the data collection form.

Questionnaire on desirable characteristics of the use of application compared with manual calculation

Characteristics that were desirable were partly guided by strength and drawbacks suggested in previous studies[8,20] and experiences of the researchers. Twelve characteristics of the three domains included (1) cognitive function (2 items), (2) access to information of HADs (5 items), and (3) facilitations in identifying dose related medication errors (5 items). The response was a 5-point Likert-type scale ranging from 5-application helps much more, to 4-application helps more, 3-about the same, 2-manual calculation helps more, and 1-manual calculation helps much more. Since it was not a psychometric scale, psychometric properties were not tested, except the basic content validity test.

Content validity testing on the instruments

Three hospital pharmacists experienced in in-patient department were asked to evaluate content validity of each instrument and the correctness of the 30 prescriptions. Content validity the instruments was evaluated using the index of item-objective congruence (IOC).[22,23] A score of +1, -1, and 0 point was given for the content that was consistent, inconsistent, and neither, respectively, with the study objectives. Each aspect should be averagely rated wit an IOC of 0.5 or higher to be consistent with the study objectives. There were 2 items for the time used in examining the prescription, 30 items/prescriptions for dose examination by the application and manual calculation, 13 items for the desirable characteristics of the application compared with manual calculation. Based on the IOC, it was found that 31 of 35 No items/prescriptions/questions were rated as 1.0, and the rest 4 items as 0.66. No items/prescriptions/questions were deleted but slightly revised as suggested by the raters. In addition to the IOC, 30 prescriptions were also reviewed for accuracy of the physician orders, questions and answers. The 30 prescriptions/questions/answers were found to be accurate, with some wording revision needed.

After revision, the researchers had 5 6th year pharmacy students of Srinakharinwirot University review 14 prescriptions (after selection process as mentioned previously) and questions of desirable characteristics of the application compared with manual calculation for understanding. Slight wording revision was made.

Ethical protections on participants

This research was approved by the Ethics Committee for Human Study of Faculty of Pharmacy, Srinakharinwirot University (approval number: 007/2559, for Jan. 13, 2013, to Jan. 12, 2017). All participants voluntarily participated with signed informed consent form. They were allowed for

withdrawal with no reasons needed at any time. Data were presented as a summary.

The experiment and data collection procedure

The researcher contacted the director of each hospital for experiment permission. Once permitted, head of the pharmacy department was contacted to recruit participants and conduct the experiment. With permission, the potential participants were contacted and screened for eligibility. Once the written informed consent from was obtained, those eligible were randomized into sequence App-Manual (use of application in the first period followed by manual calculation in the second period) or sequence Manual-App which was the opposite of the former one. With a 1-week washout period, the participants were tested with 7 prescriptions for each of the two periods (Figure 3).

The researcher recorded the time used for examining dose of the 7 prescriptions (in seconds). The answer on each prescription was graded and scored with a possible total score of 7 points. The criterion for scoring was mentioned previously. Once the experiment was over, each participant was asked to complete the questionnaire of desirable characteristics of the use of the application compared with manual calculation.

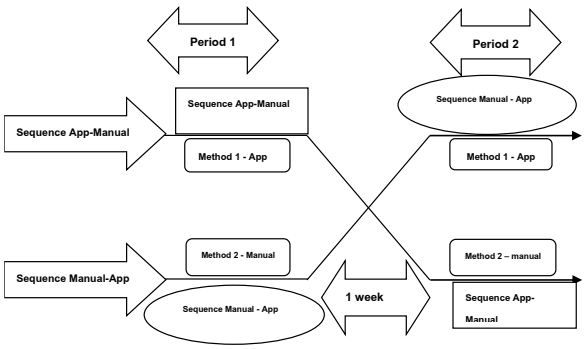

Figure 3 Study profile of the cross-over study design.

Method 1 App = Use of application.

Method 2 Manual = Use of manual calculation.

Sequence App-Manual = use of application in the 1st period followed by manual calculation in the 2nd period.

Sequence Manual-App = use of manual calculation in the 1st period followed by application in the 2nd period.

Period 1 = Before 1-week washout period.

Period 2 = After 1-week washout period.

Data analysis

Demographic characteristics were presented by frequency with percentage and mean with standard deviation. Scores and time (in seconds) were summarized as mean with standard deviation. Differences in demographic characteristics with sequences were tested by chi-squared test or Fisher's exact test, as appropriate, for categorical variables, and independent t test or Mann-Whitney U test, as appropriate, for continuous variables. Differences in score and time regarding differences in method, period, and sequence were tested using ANOVA. Since data of score and time were not normally distributed, log transformation was applied. Any differences in demographic characteristics regarding the sequence, if any, were also tested in ANOVA. Statistical significance was set at a type I error of 5%. All statistical analyses were conducted using the free software program PSPP.[24] Each of the desirable characteristics was presented as frequency and percentage.

Results

Of the 34 participants, one withdrew from the study and two were lost to follow-up resulting in a total of 31 participants. Most were female (70.29%). No differences of demographic characteristics were found between the two sequences except number of years working as hospital pharmacist as a categorical variable (*P*-value = 0.049). Majority in sequence App-Manual had worked less than 1 year (37.50%) and 1 – 5 years (31.25%); while most in sequence Manual-App had worked for 1 – 5 years (80.00%) (Table 1).

Table 1 Demographic characteristics of the participants (N = 31).

Characteristics	Total N (%)	N (%) by Sequence§		P-value*
		Sequence App-Manual (n = 16)	Sequence Manual-App (n = 15)	
Gender				
Female	22 (70.97)	14 (87.5)	8 (53.33)	0.054[a]
Male	9 (29.03)	2 (12.50)	7 (46.67)	
Age (years)				
Mean ± SD	27.90 ± 3.73	28.50 ± 4.62	27.27 ± 2.46	0.855[†]
21 - 30	25 (80.65)	11 (68.75)	14 (93.33)	0.209[b]
31 – 40	5 (16.13)	4 (25.00)	1 (6.67)	
> 40	1 (3.23)	1 (6.25)	0	
Number of years working as hospital pharmacist				
Mean ± SD	3.91 ± 3.88	4.73 ± 5.01	3.04 ± 1.94	0.952[†]
< 1	8 (25.81)	6 (37.50)	2 (13.33)	0.049[b]
1 – 5.99	17 (54.84)	5 (31.25)	12 (80.00)	
6 – 10.00	3 (9.68)	3 (18.75)	1 (6.67)	
> 10	7 (22.58)	2 (12.50)	0	
Hospital				
Ramathibodi Hospital	12 (38.71)	6 (37.50)	6 (40.00)	0.865[b]
Siriraj Hospital	9 (29.03)	5 (31.25)	4 (26.67)	
Mahavajiralongkorn Thanyaburi Hospital	5 (16.13)	3 (18.75)	2 (13.33)	
Burapha University Hospital	1 (3.23)	0	1 (6.67)	
HRH Princess Maha Chakri Sirindhorn Medical Center	4 (12.90)	2 (12.5)	2 (13.33)	
Service unit				
Out-patient department	14 (45.16%)	6 (37.50)	8 (53.33)	0.674 [a]
In-patient department	12 (38.71%)	7 (43.75)	5 (33.33)	
Out- and in-patient department	5 (16.13%)	3 (18.75)	2 (13.33)	

[a] Fisher's exact test.

[b] Pearson chi-square test.

[†] Mann-Whitney U test.

§ Sequence App-Manual = use of application in the 1st period followed by manual calculation in the 2nd period.
Sequence Manual-App = use of manual calculation in the 1st period followed by application in the 2nd period.

Since number of years working as hospital pharmacist as a categorical variable was significantly associated with sequence (*P*-value = 0.049), score and time were tested for associations with methods. It was found that in manual calculation, score was positively associated with number of years of working without statistical significance (Spearman's rho = 0.280, *P*-value = 0.129); while in the use of application, score was negatively associated with number of years of working without statistical significance (Spearman's rho = -0.050, *P*-value = 0.804). For time used, it was found that in manual calculation, time was positively associated with number of years of working without statistical significance (Spearman's rho = 0.040, *P*-value = 0.820); while in the use of application, score was positively associated with number of years of working without statistical significance (Spearman's rho = 0.300, *P*-value = 0.103). Therefore, number of years working as hospital pharmacist was not included in the following ANOVA.

Scores of correctly identifying the prescribed dose

The mean scores were higher than 6 out of 7 points in most aspects of cross-overdesign (Table 2). No differences of score regarding periods or sequences (*P*-value = 0.380 and 1.000, respectively). Regarding methods, score with the use o application was slightly higher than that with manual calculation (6.32 and 6.23 points, respectively) but with no statistical significance (*P*-value = 0.761).

Table 2 Comparisons of scores of correctly identifying the prescribed dose (N = 31).

Variables	Score (mean ± SD)	$F^{\S}$	*P*-value
Period 1 (N = 31)	6.35 ± 0.16	0.80	0.380
Period 2 (N = 31)	6.19 ± 0.20		
Sequence App-Manual (N = 16)	6.65 ± 1.19	0.00	1.00
Sequence Manual-App (N = 15)	5.90 ± 1.13		
Method 1 App (N = 31)	6.32 ± 0.19	0.09	0.761
Method 2 Manual (N = 31)	6.23 ± 0.17		
Subjects (N = 31)	6.27 ± 0.99	2.11	0.025

§ F = 2.03, df = 33, 28, *P*-value = 0.030, by one-way ANOVA on score data which were log transformed.

Note:

Method 1 App = Use of application

Method 2 Manual = Use of manual calculation

Sequence App-Manual = use of application in the first period followed by manual calculation in the second period

Sequence Manual-App = use of manual calculation in the first period followed by application in the second period

Period 1 = Before 1-week washout period

Period 2 = After 1-week washout period

Time used in examining the prescribed dose

Time used in examining the prescribed dose was with a large range (Table 3). In period 1, participants spent 1,014.65 seconds, but in period 2, they spent only 852.90 seconds, with a statistical significance (*P*-value = 0.002). Such change could be an effect of learning bias which remained even with a one-week washout period. Time used in sequence Manual-App (1,995.67 seconds) was slightly higher than that in sequence App-Manual (1,747.44 seconds) with no statistical significance. Most importantly, time with the use of application (649.06 seconds) was significantly less than that with manual calculation (1,218.48 วินาที) (*P*-value < 0.001) (Table 3).

Table 3 Comparisons of time used in examining the prescribed dose (N = 31).

Variables	Score (mean ± SD)	$F^{\S}$	*P*-value
Period 1 (N = 31)	1,014.65 ± 83.63	11.44	0.002
Period 2 (N = 31)	852.90 ± 77.11		
Sequence App-Manual (N = 16)	1,747.44 ± 631.41	0.00	1.000
Sequence Manual-App (N = 15)	1,995.67 ± 481.90		
Method 1 App (N = 31)	649.06 ± 28.41	97.04	< 0.001
Method 2 Manual (N = 31)	1,218.48 ± 84.64		
Subjects (N = 31)	933.77 ± 451.57	2.98	0.002

§ F = 6.07, df = 33, 28, *P*-value < 0.001, by one-way ANOVA on time data which were log transformed.

Note:

Method 1 App = Use of application.

Method 2 Manual = Use of manual calculation.

Sequence App-Manual = use of application in the 1st period followed by manual calculation in the 2nd period.

Sequence Manual-App = use of manual calculation in the 1st period followed by application in the 2nd period.

Period 1 = Before 1-week washout period.

Period 2 = After 1-week washout period.

Desirable characteristics of the use of application compared with manual calculation

Overall, participants agreed that the application offers more help than the manual calculation (Table 4). Most participants agreed that application helps them think step by step better in dose calculation (71%) with 35.5% each indicating that application helps more and much more. For the access to the information, 41.9% thought that application helps them access to information with various aspects more while 22.6% agreed that manual calculation was better which was different from other aspects. Regarding the search for many sources of information, 58.1% thought that the application help limit the search much more. For identifying errors in prescriptions, 100% of participants agreed that the application helps limit the time identifying errors more (51.6%) and much more (48.4%). It was worth noting that the application helps them focus on identifying medication errors more (45.2%) and much more (35.5%) (Table 4).

Table 4 Desirable characteristics of the use of application compared with manual calculation (N = 31).

Characteristics	Opinion level									
	5-Application helps much more		4 Application helps more		3-about the same		2-Manual calculation helps more		1- Manual calculation helps much more	
	N	%	N	%	N	%	N	%	N	%
1. think step by step better in dose calculation.	11	35.5	11	35.5	5	16.1	3	9.7	1	3.2
2. identify medication error better.	14	45.2	10	32.3	6	19.4	1	3.2		
3. access to information better.	17	54.8	11	35.3	3	9.7				
4. access reliable information better.	11	35.5	8	25.8	10	32.3	2	6.5		
5. access information with various aspects better.	8	25.8	13	41.9	3	9.7	7	22.6		
6. avoid the search for many sources of information	18	58.1	11	35.5	1	3.2	1	3.2		
7. limit the time to search for information of HADs	22	71.0	7	22.6	2	6.5				
8. limit tools to use in calculation better	17	54.8	10	32.3	4	12.9				
9. limit the time identifying errors better	15	48.4	16	51.6						
10. carry the tool more practically	21	67.7	7	22.6	3	9.7				
11. identify medication errors easier	11	35.5	15	48.4	5	16.1				
12. to have convenience in identifying medication errors better	21	67.7	9	29.0	1	3.2				
13. focus on identifying medication errors better	11	35.5	14	45.2	2	6.5	3	9.7	1	3.2

Discussions and Conclusion

In this cross-over experiment to compare scores and time used in the use of an Android application compared with manual calculation in examining prescribed doses of high-alert drugs, the scores of correctly identifying the doses were not different between the two methods, two periods, or two sequences. However, timed used was significantly shorter with the application (649 seconds) compared with that with manual calculation (1,218 seconds) (*P*-value < 0.001). In addition, time used in the first period (1,014 seconds) was significantly longer than that in the second period (853 seconds) (*P*-value = 0.0021).

With no differences of the scores between the two periods, most participants reported that they could not remember the details of the prescriptions in the first period. For the sequence effect, using manual calculation or application first did not affect the scores. This could be due to fact that the ability to dose examination and calculation does not depend solely on the tool but largely on knowledge and skills accumulated over time. Therefore, the use of the application before or after the wash-out period resulted in no differences in scores.

No differences in score between the use of application and manual calculation could be controversial. However, this could be because the application could not foster or facilitate the thinking process in a very short time or the difficulty of the prescriptions was at a low level as indicated by very high mean scores obtained. This could also mean that most participating pharmacists had a high level of knowledge and skill in dose calculation for HADs. With unlimited time allowed, they therefore could identify the dose errors correctly.

With the time used in the first period (i.e., before the wash-out) (1,014 seconds) that was significantly longer than that in the second period (853 seconds), this could be because the participants were more familiar with the prescriptions and questions and the experiment process even though the critical thinking performance was similar as shown by comparable scores. In addition, the application helped significantly reduce the time by half (649 and 1,218 seconds) (*P*-value < 0.001). This could be because the application clearly led the pharmacist step by step and that allowed for a shorter time to complete. The application also required fewer data inputting than the traditional manual calculation. The application could also save time because it converses units automatically for the users. Certain pharmacists rarely rotated to the in-patient department, therefore their unit conversion task could be slower. The unit conversion and other features of the application could be of great help.

No differences in the time used regarding sequences could be due to the averaging effect of the two periods. In addition, it could because certain pharmacists were highly skilled in dose calculation since they had been working in the in-patient department for a relatively long time, hence the strong skills. Drug information offered by the application could also help save the time used.

The effect of experience in the use of mobile phone o smart phone could not be proved in this study since we did not put a strict criterion in the inclusion criteria. We only

expected that the participants were adequately familiar with smart phone with the Android system to use the application.

Regarding the desirable characteristics of the use of application compared with manual calculation, most pharmacists agreed with the concept that the application helped lead the thinking process of the calculation and identify medication errors. They provided additional opinion that the displayed pre-programmed formulas helped them proceed the calculation and identify the errors with ease in a timely fashion with no need to remember the formula.

Most pharmacists agreed that the application allowed a better access to the information in various aspects. This could be because we selected only warnings, monitoring and evaluation information highly necessary for the use of HADs. The easy and fast access and use of the information could be achieved.

The convenience of the application was evident. The participants agreed that the application reduced the need for tools simply to a single instrument. It was easy to carry and practical and convenient for use with various necessary features combined in one tool. The detailed display of calculation steps helped ease the process. The calculation and drug information combined helped reduce the need to access additional information sources. Previous studies indicated that applications should offer a comprehensive set of necessary features.[25-27] The application that could help conserve units is needed since unit conversion capability has been an obstacle to certain healthcare providers which is in part based on their basic mathematic skill.[28]

This present study had certain limitations. The application was far from perfect when running. This was the programmer was not highly experienced in programming calculation applications and pharmacy practice. The researchers might not be able to communicate the needs well with the programmer. In the future, programmers with more experience and better communication by the researchers should be sought. The use of the application was not free of problems or inconvenience. This was because of many participating pharmacists used iPhone (iOS system) in daily life but they were required to use the phone with Android system. The inconvenience based on unfamiliarity of the navigation system could be expected. In future studies, applications with both Android and iOS systems could allow for less biased results. With a total of 31 participants which was fewer than the expected 34 participants, the result could be of less power. However, with the original sample size of 28 participants with no compensation, the power was hopefully adequately maintained. The loss of a few participants was due to a high workload and unavailable time. Future studies should allow longer time for the experiment to obtain the sample size needed. The number of the prescriptions (7 prescriptions per test) was relatively small. In addition, the prescriptions could be relatively easy to identify the errors. These resulted in high mean scores of correctly identifying the errors by both methods. In future studies, more prescriptions with higher difficulty level could be tested. This could distinguish the performance using the application and manual calculation. Lastly, it was hoped that the application could help maintain or enhance cognitive function in calculation. However, we could not evaluate the cognitive function since it was highly complicate to do. Therefore, we could not directly and objectively prove that the application could maintain or enhance cognitive function. Future studies could also incorporate methods to prove cognitive functions objectively. If possible, it would further demonstrate that cognitive function basis is highly necessary in pharmaceutical care concept which deserves financial compensation.[9]

In conclusion, the Android application on mobile phone reduced the time used in identifying dose errors in the prescriptions of high-alert drugs when compared with manual calculation. No difference in scores of correctly identifying errors was not found. The application offered most desirable characteristics for the use.

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