ORIGINAL ARTICLE

Evaluation of Knowledge on Clinical Pharmacokinetics: A Cross-sectional Study among Pharmacists in Hospital Raja Perempuan Zainab II, Kelantan.

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Abstract

Clinical pharmacokinetics is the application of pharmacokinetics of drugs, especially drugs with small therapeutic window, to optimize the drug treatment in a patient. The aim of this study was to evaluate the knowledge of clinical pharmacokinetics among pharmacists in a tertiary hospital in Kelantan. A cross-sectional study was conducted using a self-developed research instrument. Following a thorough review of the literature, a multiple-choice questionnaire comprising of 28 questions on gentamicin/amikacin, vancomycin, valproic acid and phenytoin was created. It yielded a Cronbach alpha coefficient of 0.807 after being pilot tested on ten pharmacists. It was then distributed to all pharmacists working at Hospital Raja Perempuan Zainab II. Those who were on long leave or not available during the data collection period were excluded. All data were analysed using descriptive statistics, Chi-square test/Fisher's exact test and independent t-test in Statistical Package for Social Sciences (SPSS) version 20. A total of 116 respondents was recruited into the study. The mean (SD) knowledge of clinical pharmacokinetics was 19.4 (4.8) with minimum score was 5.0 and maximum score was 28.0. It was observed that more pharmacists had poor knowledge (55.2%, n=64). In terms of responses to the questionnaire, four out of 28 questions had the most incorrect answers of $\geq$50%. They were question 7 (50.0%, n=58) regarding amikacin, question 17 (60.3%, n=70) pertaining to valproic acid as well as question 25 (51.7%, n=60) and question 28 (57.8%, n=67) which were about phenytoin. When further tested, it was noted that the knowledge of clinical pharmacokinetics was significantly associated with position (p=0.018), age (p=0.019) and working experience (p=0.016). The hospital pharmacists had a general poor knowledge in clinical pharmacokinetics especially the fully registered pharmacists who were older and had worked for a longer period of time. Therefore, an educational intervention is urgently needed to improve the knowledge in clinical pharmacokinetics among pharmacists working in Hospital Raja Perempuan Zainab II.

Keywords: *clinical pharmacokinetics, knowledge, therapeutic drug monitoring.*

Introduction

Pharmacokinetics is the aspect of pharmacology that describes how the body handles and responds to drugs [1]. The concept explains the relationship between the administered drug dose and its concentration over a period of time. It is characterized by the systemic input which is the drug movement from the site of administration to the systemic circulation and the disposition processes which are the drug distribution and elimination from the systemic circulation [2]. Often time it elucidates the four principle processes which are absorption, distribution, metabolism and excretion of a drug [3]. Each drug is unique and has its own set of pharmacokinetic profile in the body, which ultimately determines the exposure of the body to the drug. It highly depends on other covariates such as age or presence of renal disease which can influence the efficacy of the drug therapy [4]. The pharmacokinetic of drugs can also be altered in critically ill patients as major pathophysiological changes causes abnormalities and disruption [5].

Knowledge of drug metabolism and pharmacokinetics are the fundamentals of therapeutic drug monitoring (TDM) services [6]. TDM is generally defined as the clinical laboratory measurement of a drug that, with appropriate medical interpretation, will directly influence drug prescribing procedures. Otherwise, TDM refers to the individualization of drug dosage by maintaining the serum plasma concentration of a drug within a targeted therapeutic range or therapeutic window [7]. It has been recognized as a useful clinical tool in drug therapy as it enables the assessment of the efficacy and safety of a particular medication in a variety of clinical settings [6].

TDM is of the utmost importance in drugs with narrow therapeutic margins, where there is a small margin between the desired therapeutic benefit and the adverse effects. Therapeutic benefit is attained when a drug achieved a given range for efficacy, yet remain below the toxicity threshold [5]. Examples of drugs with narrow therapeutic window include gentamicin, amikacin, vancomycin, valproic acid, and phenytoin which are commonly encountered in the hospital setting [8]. When a patient is prescribed with these drugs, it is necessary for the drug concentration to be measured and the individual patient's pharmacokinetic data to be calculated, such as elimination rate constant (Ke), half-life (t½), volume of distribution (Vd), as well as clearance (CL) [6]. Pharmacists performing TDM use these data, incorporating with the patient's clinical conditions, to provide interpretations and recommendations in optimizing patient's drug therapy [7]. In addition to analysing the obtained serum drug concentration, their other role is to advise the optimal timing of TDM sampling [9].

Nowadays, multidisciplinary team approaches are progressively used to determine patients' treatment plans [10]. As a result, hospital pharmacists are increasingly incorporated into these multidisciplinary teams, with active engagement for both inpatient and outpatient treatment [11]. Therefore, applying the principles of clinical pharmacokinetics is among the main responsibilities of hospital pharmacists who provide pharmaceutical care services and it extends to those who are working outside of TDM services [12].

Knowledge of clinical pharmacokinetics is indispensable to pharmacists, but the subject is difficult and challenging for some, probably due to its abstract and mathematical nature [4]. According to literature, acquiring the skills and applying the principles of pharmacokinetics in clinical practice require high engagement and thus, can be demanding. However, those studies were mostly conducted among pharmacy students [4], [13], [14] with only a couple were carried out among pharmacists abroad [12], [15].

With the expansion of pharmacy services to 24 hours, pharmacists on duty after office hours are also required to handle TDM cases that are monitored after office hour [16]. Although there are passive callers for TDM on standby, they nonetheless need to know about the basics of pharmacokinetics, do TDM calculations, make

interpretations as well as give recommendations based on the values and patient's clinical condition. In view of the foregoing, we aimed to evaluate the knowledge of clinical pharmacokinetics among hospital pharmacists in a tertiary hospital in Kelantan, Malaysia. We also sought to determine whether there was any association between respondents' characteristics and the level of knowledge of clinical pharmacokinetics.

To the best of our knowledge, no such study has been conducted in Malaysia. Thus, the evaluation is crucial and is expected to gain an intriguing insight on the topic. It is hope that the findings can help to address the gaps in practice to further advance the pharmacy services.

Materials and methods

Study design

This was a cross-sectional study conducted from January to June 2021, using a self-developed multiple-choice questionnaire. All pharmacists working at Hospital Raja Perempuan Zainab II were involved in the study. Those who were on long leave or not available during the data collection period were excluded.

Questionnaire development and scoring method

The questionnaire was constructed following a comprehensive review of literature [5] and was based on the clinical experience of the researchers. It had a close-ended question type in which a respondent has to select one (single-select multiple-choice question) correct response from a given list of options. The content was evaluated by the senior TDM pharmacists and approved by the Head of Pharmacy Department. It was then pilot tested on ten pharmacists and yielded a Cronbach alpha coefficient of 0.807, a value greater than 0.7 which indicated good reliability.

The questionnaire consisted of five parts:

i. Respondents' background (five questions);

ii. Antibiotic: gentamicin/amikacin (eight questions) which had three cases and multiple-choice options;

iii. Antibiotic: vancomycin (seven questions) which were based on two cases with multiple-choice options;

iv. Antiepileptic: valproic acid (eight questions) which consisted of four cases and multiple-choice options;

v. Antiepileptic: phenytoin (five questions) which comprised of two cases with multiple-choice options

The total score for knowledge of clinical pharmacokinetics was calculated from part ii, iii, iv and v of the questionnaire by giving one point (1) for each correct answer and zero (0) for incorrect answers. With a total of 28 questions, the possible score could range from a minimum of 0 to a maximum of 28. Based on the median split [17], respondents who scored ≤20 were grouped as poor knowledge whereas those with a score of >20 were described as having good knowledge.

Questionnaire distribution

During the data collection period, copies of the questionnaire were distributed by the investigators to the pharmacists at each unit. They were explained regarding the study and were given adequate time to read the information sheet. Those who voluntarily consented could complete the questionnaires that the investigators collected, which took about one hour to complete.

Data analysis

Data was entered into the Statistical Package for the Social Sciences (SPSS) version 20 for analysis [18]. Frequencies and percentages (%) were produced for the respondents' characteristics. Chi-square test/Fisher's exact test and independent t-test were used to determine the association between respondents' characteristics

(gender, ethnicity, position, age and working experience) and knowledge of clinical pharmacokinetics (poor knowledge or good knowledge). A value of $p<0.05$ was considered to be statistically significant.

Ethics approval

The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. It was registered with Ministry of Health Malaysia with National Medical Research Register (NMRR) identification number of NMRR-21-100-58244 and ethical approved by the Medical Research and Ethics Committee (MREC), with reference number KKM/NIHSEC/P21-773 (4). Permission was also obtained from the Head of Pharmacy Department and the Hospital Director. All subjects were kept anonymous to ensure their confidentiality.

Results

Respondents' characteristics

A total of 116 respondents was recruited into the study. They were mainly female (n=91, 78.4%), Malay (n=107, 92.2%), fully registered pharmacists (n=84, 72.4%) with mean (SD) age of 30.2 (5.2) years old and mean (SD) working experience of 6.8 (5.4) years (Table 1).

Knowledge of clinical pharmacokinetics

Mean (SD) knowledge of clinical pharmacokinetics was 19.4 (4.8) with minimum score was 5.0 and maximum score was 28.0. It was found that more pharmacists had poor knowledge with the total score of $\leq$20 (n=64, 55.2%). In terms of responses to the questionnaire, four out of 28 questions had the most incorrect answers of $\geq$50%. They were question 7 (n=58, 50.0%) regarding amikacin, question 17 (n=70, 60.3%) pertaining to valproic acid as well as question 25 (n=60, 51.7%) and question 28 (n=67, 57.8%) which were about phenytoin (Table 2).

Question 7 was regarding the interpretation and dose suggestion for amikacin. The last dose was not completely administered as the patient had an asystole and IV amikacin 600mg stat was given after random sample taken with the level of 3.85mg/L. Based on the level measured after 1 hour (25.37mg/L) and 21 hours (11.82mg/L) upon completion of infusion, the respondent was required to interpret and suggest the next dose of amikacin.

Question 17 was pertaining to the nearest dose of valproic acid that was required to achieve the target trough concentration of 90mg/L using the patient's CL. As for question 25, the respondent is required to calculate the Cpss (serum drug concentration obtained at steady state) and Km (Michaelis-Menten constant) for the patient using Vm (estimation of the maximum rate of metabolism) population with result Cpre of 1.68mcg/ml.

The last question with the most incorrect answers was question 28. It was about giving recommendation for the loading dose of IV phenytoin based on Cpre (serum drug concentration obtained at specific time before the drug is served) (5.74mg/L). It was noted that the patient was still having seizures despite given IV Phenytoin 100mg TDS.

Association between respondents' characteristics and knowledge of clinical pharmacokinetics

When further tested, it was noted that the knowledge of clinical pharmacokinetics was significantly associated with position, age and working experience. The results from the Chi-square test showed that more fully registered pharmacists had poor knowledge when compared to provisionally registered pharmacists (p=0.018). Using independent t-test, it was observed that those who were older and had more working experience were also associated with poor knowledge (p=0.019 and p=0.016; respectively) (Table 3).

Discussion

The use of individualized dosage regimens is becoming increasingly common in healthcare settings. Because of this, hospital pharmacists often apply the principles of pharmacokinetics to design appropriate drug regimens for best efficacy and minimal toxicity, [12] as well as to avoid medication errors [4], [19]. This is especially important when it comes to the drugs with narrow therapeutic windows, such as gentamicin/amikacin, vancomycin, phenytoin and valproic acid, which require TDM to obtain the desired therapeutic response [20].

The questionnaire was developed based on the respective drugs, whereby examples of patient cases were used. The respondents were asked regarding Ke, CL, area under the curve (AUC) of the drug in question, the interpretation of the calculations and the dosage recommendations. Data of Cpre, Cpost (serum drug concentration obtained at specific time after the drug is served), Cmax (peak serum concentration) and serum creatinine were given to assist the calculation [5]. These are the basis of pharmacokinetics applications whereby calculations of individualized drug doses and adjusting drug doses as appropriate are necessary to achieve therapeutic drug concentrations [20].

Only a few studies were conducted regarding the knowledge of pharmacokinetics. Even though limited, we found the results of our study were similar with their findings. Our study revealed that more than half of the respondents had poor knowledge and obtained low score of $\leq$20. This was consistent with the findings from Pandit et al. (2021) whereby they found a significantly higher number of medical students failed in pharmacokinetics compared to other disciplines [n=69, 23.8% versus n=31 (10.7%), p<0.001) and had a significantly lower mean score [70.9 (14.2) versus 74.1 (7.7), p<0.001] [4]. A qualitative study among the final semester students from the medical program found that the participants seemed to experience pharmacokinetics tougher than pharmacodynamics and even harder to apply in a clinical situation [19]. Second-year students of the bachelor of health and life sciences also demonstrated lower success rate for the pharmacokinetics questions than other domains [21].

The low score in knowledge of pharmacokinetics could be due to the elements of the topic itself. Pharmacokinetics is a difficult subject which requires knowledge and understanding of chemistry and physiology to comprehend the underlying mechanisms of absorption, distribution, metabolism and elimination of drugs [4]. It is possible that many of the pharmacists are interested in biology and can relate more with biology rather than chemistry making pharmacokinetics to be harder to grasp [21]. The higher failure rates in pharmacokinetics could depend on other factors such as the mathematical nature of pharmacokinetics [22]. The complex pharmacokinetics equations which utilize calculus [23] can be intimidating and lack of thereof can severely hamper the calculation of pharmacokinetics profile [24].

The previous studies regarding pharmacokinetics among pharmacists, however, did not explore in depths regarding calculations and understanding but rather more on the views and perceptions of teaching and applications. The authors agreed that pharmacokinetics courses were important and relevant to their current practice. [12], [15]. Interestingly, Shawahna et. al (2022) reported that hospital pharmacists rated poor understanding of pharmacokinetics by pharmacists as an important barrier limiting the application of pharmacokinetics in optimizing pharmaceutical care services [12]. This statement implicates and highlights the possibility of hospital pharmacists having inadequate knowledge and understanding of pharmacokinetics as an issue to be addressed urgently.

As for the questions, the high percentage with $\geq$50% of incorrect answers were seen in all parts except for vancomycin. One of the pharmacokinetic parameters of the drug is the calculation of area under the curve 24 hours (AUC_{24}). It is illustrated

in the Clinical Pharmacokinetics Pharmacy Handbook Second Edition which is the main reference for TDM service in Malaysia [5]. The distinctive formula can be a possible reason as to why the respondents were proned to give their focus and memorize. This is because individuals tend to remember best what is unique about a particular occasion [25].

Our study also tried to determine whether there was any relationship between respondents' characteristics and the level of knowledge of clinical pharmacokinetics. We observed that fully registered pharmacists who were older and had worked longer had significantly poor knowledge in clinical pharmacokinetics. This was expected as one of the requirements during the training of a provisionally registered pharmacist is a four-week attachment in clinical pharmacokinetic services. Upon completion, he/she must have knowledge of blood sampling time, evaluation of patient parameters, analysis of serum drug concentration, calculations of dosage estimation, result interpretation and make recommendations [26]. On the other hand, fully registered pharmacists who work at other units than TDM services such as dispensing and inventory placement for a long time were less likely to encounter cases requiring pharmacokinetic skills [15]. Knowledge without practice, if not revised, can be lost over time. This is well-known as forgetting curve, whereby there is a declining memory retention if no effort is made to remember it [27].

Our study had several limitations. It involved pharmacists only from a single centre, and hence, the findings could not be generalized to all pharmacists in Malaysia. Furthermore, we did not investigate whether the respondents had previous training in clinical pharmacokinetics or there was preparation prior to answering the questionnaire. There was no monitoring of whether the respondents formed study groups or performed any discussions while answering the questionnaire. Also, the units in which the hospital pharmacists practiced were not included in the analysis. Pharmacists who were directly involved in clinical practice might have applied pharmacokinetics knowledge more often than others.

Conclusion

Pharmacists had a general poor knowledge in clinical pharmacokinetics, especially the fully registered pharmacists who were older and had worked for a longer period of time (senior pharmacists). The findings captured the discernment in pharmacy practice that needs to be addressed. Therefore, an educational intervention is urgently needed to improve knowledge of clinical pharmacokinetics among pharmacists working in Hospital Raja Perempuan Zainab II. A regular continuing professional education (CPE) with actual patient cases and/or bedside ward rounds with case discussions are examples of educational interventions.

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Conflict of interest

The authors declare that there is no conflict of interest that may arise from the research publication.

Author contributions

SM, SLMN and TKM came out with the research concept and design. SHS and SM performed the literature search and data acquisition. SHS and NLA was involved in the statistical analysis and manuscript preparation. All authors agreed and approved the manuscript for publication.

Table 1. Respondents' characteristics (n=116)

Characteristics	**n (%)**	**Mean (SD)**
Gender		
Male	25 (21.6)	
Female	91 (78.4)	
Ethnicity		
Malay	107 (92.2)	
Non-Malay	9 (7.8)	
Position		
Fully registered pharmacist	84 (72.4)	
Provisionally registered pharmacist	32 (27.6)	
Age (years)		30.2 (5.2)
Working experience (years)		6.8 (5.4)

Table 2. Evaluation of respondent's knowledge on clinical pharmacokinetics

Questions	**Correct n (%)**	**Incorrect n (%)**
Antibiotic: gentamicin/amikacin		
Case 1		
Question 1	89 (76.7)	27 (23.3
Question 2	102 (87.9)	14 (12.1)
Question 3	95 (81.9)	21 (18.1)
Case 2		
Question 4	93 (80.2)	23 (19.8)
Question 5	61 (62.6)	55 (47.4)
Case 3		
Question 6	67 (57.8)	49 (42.2)
Question 7	58 (50.0)	**58 (50.0)**
Question 8	86 (74.1)	30 (25.9)
Antibiotic: vancomycin		
Case 1		
Question 9	110 (94.8)	6 (5.2)
Question 10	88 (75.9)	28 (24.1)
Question 11	91 (78.4)	25 (21.6)
Question 12	89 (76.7)	27 (23.3)
Case 2		
Question 13	68 (58.6)	48 (41.4)
Question 14	88 (75.9)	28 (24.1)
Question 15	80 (69.0)	36 (31.0)
Antiepileptic: valproic acid		
Case 1		
Question 16	99 (85.3)	17 (14.7)
Question 17	46 (39.7)	**70 (60.3)**
Case 2		
Question 18	100 (86.2)	16 (13.8)
Case 3		
Question 19	101 (87.1)	15 (12.9)
Question 20	72 (61.2)	45 (38.8)
Case 4		
Question 21	72 (61.2)	45 (38.8)
Question 22	79 (68.1)	37 (31.9)
Question 23	92 (79.3)	24 (20.7)
Antiepileptic: phenytoin		
Case 1		
Question 24	75 (64.7)	41 (35.3)
Question 25	56 (48.3)	**60 (51.7)**
Question 26	69 (59.5)	47 (40.5)
Case 2		
Question 27	73 (72.9)	43 (37.1)
Question 28	49 (42.2)	**67 (57.8)**

Table 3. Association between respondents' characteristics and knowledge of clinical pharmacokinetics

Characteristics	Poor knowledge	Good knowledge	p-value
Gender			
Male	17 (68.0)	8 (32.0)	0.145[a]
Female	47 (51.6)	44 (48.4)	
Ethnicity			
Malay	58 (54.2)	49 (45.8)	0.729[b]
Non-Malay	6 (66.7)	3 (33.3)	
Position			
Fully registered pharmacist	52 (61.9)	32 (38.1)	**0.018[a]**
Provisionally registered pharmacist	12 (37.5)	20 (62.5)	
Age (years)	31.1 (5.6)	28.9 (4.3)	**0.019[c]**
Working experience (years)	7.9 (5.7)	5.5 (4.7)	**0.016[c]**

Data were normally distributed, based histogram and stem-and-leaf plot
Skewness and kurtosis were within $\pm$1.96
[a]Chi-square test, [b]Fisher's exact test, [c]Independent t-test

References

[1] D. G. Waller and A. P. Sampson, *Pharmacokinetics*, 5th ed. Elsevier, 2018.
[2] K. Patel and C. M.J. Kirkpatrick, "Pharmacokinetic concepts revisited - Basic and applied," *Curr. Pharm. Biotechnol.*, vol. 12, no. 12, pp. 1983–1990, 2011, doi: 10.2174/138920111798808400.
[3] J. Fan and I. A. M. De Lannoy, "Pharmacokinetics," *Biochem. Pharmacol.*, vol. 87, no. 1, pp. 93–120, 2014, doi: 10.1016/j.bcp.2013.09.007.
[4] R. Pandit, M. A. F. M. Gerrits, and E. J. F. M. Custers, "Assessing knowledge of pharmacokinetics in an integrated medical curriculum," *Med. Sci. Educ.*, vol. 31, no. 6, pp. 1967–1973, 2021, doi: 10.1007/s40670-021-01442-4.
[5] Clinical Pharmacy Working Committee (Clinical Pharmacokinetics Subspecialty), *Clinical pharmacokinetics pharmacy handbook second edition*. Pharmacy Practice and Development Division, Ministry of Health Malaysia, 2019.
[6] R. J. Flanagan, N. W. Brown, and R. Whelpton, "Therapeutic drug monitoring," *CPD Clin. Biochem.*, vol. 9, no. 1, pp. 3–21, 2008.
[7] J. S. Kang and M. H. Lee, "Overview of therapeutic drug monitoring," *Korean J. Intern. Med.*, vol. 24, no. 1, pp. 1–10, 2009, doi: 10.3904/kjim.2009.24.1.1.
[8] R. R. Yadav, Y. R., and B. S. Reddy, "Narrow therapeutic index drugs - A critical study on prescription trends in South Indian tertiary care hospital," *World J. Pharm. Res.*, vol. 7, no. 19, pp. 834–860, 2018, doi: 10.20959/wjpr201819-13691.
[9] S. Almohammde, H. Alhodian, S. Almofareh, S. Alshehri, D. M. Almasri, and R. H. Ghoneim, "A survey of therapeutic drug monitoring in a teaching hospital," *Saudi J. Biol. Sci.*, vol. 28, no. 1, pp. 744–747, 2021, doi: 10.1016/j.sjbs.2020.11.002.
[10] M. Taberna *et al.*, "The multidisciplinary team (MDT) approach and quality of care," *Front. Oncol.*, vol. 10, no. March, pp. 1–16, 2020, doi: 10.3389/fonc.2020.00085.
[11] M. M. Thurston, T. V. Liao, T. Lim, T. Pounds, and P. M. Moye-Dickerson, "Utilization of a multidisciplinary team to reduce the rate of hospital readmissions in high-risk heart

failure patients at a community teaching hospital: The pharmacist's role in transitions of care," *J. Am. Coll. Clin. Pharm.*, vol. 2, no. 3, pp. 281–287, 2019, doi: 10.1002/jac5.1072.
[12] R. Shawahna, N. Shraim, and R. Aqel, "Views, knowledge, and practices of hospital pharmacists about using clinical pharmacokinetics to optimize pharmaceutical care services: a cross-sectional study," *BMC Health Serv. Res.*, vol. 22, no. 1, p. 411, 2022, doi: 10.1186/s12913-022-07940-4.
[13] A. M. Persky, J. Stegall-Zanation, and R. E. Dupuis, "Students perceptions of the incorporation of games into classroom instruction for basic and clinical pharmacokinetics," *Am. J. Pharm. Educ.*, vol. 71, no. 2, pp. 1–9, 2007, doi: 10.5688/aj710221.
[14] A. M. Persky, "The impact of team-based learning on a foundational pharmacokinetics course," *Am. J. Pharm. Educ.*, vol. 76, no. 2, pp. 1–10, 2012, doi: 10.5688/ajpe76231.
[15] N. Kheir, A. Awaisu, H. Gad, S. Elazzazy, F. Jibril, and M. Gajam, "Clinical pharmacokinetics: perceptions of hospital pharmacists in Qatar about how it was taught and how it is applied," *Int. J. Clin. Pharm.*, vol. 37, no. 6, pp. 1180–1187, 2015, doi: 10.1007/s11096-015-0183-3.
[16] Pharmaceutical Services Programme, "24 hours pharmacy services," *Ministry of Health Malaysia*, 2015. https://www.pharmacy.gov.my/v2/en/content/24-hours-pharmacy-services.html.
[17] D. Iacobucci, S. S. Posavac, F. R. Kardes, M. J. Schneider, and D. L. Popovich, "Toward a more nuanced understanding of the statistical properties of a median split," *J. Consum. Psychol.*, vol. 25, no. 4, pp. 652–665, 2015, doi: 10.1016/j.jcps.2014.12.002.
[18] IBM Corp., "IBM SPSS Statistics for Windows, version 20.0." 2011.
[19] P. Aronsson *et al.*, "The understanding of core pharmacological concepts among health care students in their final semester Assessment and evaluation of admissions, knowledge, skills and attitudes," *BMC Med. Educ.*, vol. 15, no. 1, pp. 1–8, 2015, doi: 10.1186/s12909-015-0522-z.
[20] M. Jain, A. Prakash, and B. Medhi, "Narrow therapeutic index drugs and role of therapeutic drug monitoring," *Drug Bull.*, vol. 46, no. 1, pp. 1–5, 2021.
[21] M. M. M. Wilhelmus and B. Drukarch, "Lower scores in pharmacokinetics than in pharmacodynamics assessment among students in a health and life sciences curriculum," *Eur. J. Pharmacol.*, vol. 876, no. 2020, p. 173074, 2020, doi: 10.1016/j.ejphar.2020.173074.
[22] R. W. Seabury and C. M. Stork, *Pharmacokinetic and toxicokinetic modeling*. Academic Press, 2014.
[23] J. Jain, A. Haque, R. Prajapati, and S. Singh, "Application of mathematics to certain pharmacokinetic equations," *Int. J. Eng. Res. Sci.*, vol. 6, no. 3, pp. 483–490, 2020.
[24] K. Skagerlund, R. Östergren, D. Västfjäll, and U. Träff, "How does mathematics anxiety impair mathematical abilities? Investigating the link between math anxiety, working memory, and number processing," *PLoS One*, vol. 14, no. 1, pp. 1–17, 2019, doi: 10.1371/journal.pone.0211283.
[25] W. A. Bainbridge, *Memorability: How what we see influences what we remember*, vol. 70. Academic Press, 2019.
[26] Pharmacy Board Malaysia, *Record of training and experience for provisionally registered pharmacist - clinical pharmacokinetic services*. Ministry of Health Malaysia, 2017.
[27] J. M. J. Murre and J. Dros, "Replication and analysis of Ebbinghaus' forgetting curve," *PLoS One*, vol. 10, no. 7, pp. 1–23, 2015, doi: 10.1371/journal.pone.0120644.