

## LITERATURE REVIEW

# Drug Dose Calculator Application to Prevent Medication Errors

Mayang Indah Lestari<sup>✉</sup>, Zulkifli, Rizal Zainal, Muhammad Imam Mulia

Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sriwijaya/  
Mohammad Hoesin Hospital, Palembang, Indonesia

<sup>✉</sup>Correspondence: [mayangindah@fk.unsri.ac.id](mailto:mayangindah@fk.unsri.ac.id)

### ABSTRACT

As a part of the essentials in achieving patient safety, medication errors are one of the most financially detrimental problems in the treatment process faced by health institutions. This article firstly debriefs the definition of medication error and its general classification based on the treatment process. Wrong dose calculation has become one of the most frequent medication errors, especially among anesthesiology-care providers. This article then concisely defines the side effects of commonly-used anesthesia drugs in critical and perioperative care. This article examines medication errors prevalence among anesthesiologists and investigates the line between several risk factors and wrong dosage calculation. Finally, this article concludes with the elucidation of current trends of drug dosage calculators and several studies that aim to validate and prove the efficacy of those applications.

**Keywords:** anesthetics; calculator application; drug dosage; medication error; patient safety

### INTRODUCTION

The healthcare paradigm is increasingly shifting from physician-centered to patient-centered to ensure the accommodation of patient safety. One of the predicaments in patient safety is medication error. Medication errors can potentially prolong the length of stay in the hospital, increase the cost of treatment, and increase the risk of morbidity and mortality. A review in the United States ascertained that medication errors occurred in 8 of 1000 patients, often as wrong doses and wrong drugs, and accounted for a loss of \$8,439 medical expenses.<sup>1</sup> A survey in Finland

in 2017 found that of 9269 reported hospital incidents, 5,692 (61 %) of them were medication errors, and the two most frequent errors in the administration were low-molecular heparin (34 %), opioid drugs (13 %).<sup>2</sup> Heparin and opioids are two of the many high-alert drugs commonly used in critical or intensive care circumstances.<sup>3</sup>

Anesthesiologists are particularly synonymous with the utilization of high-alert drugs. High alert drugs are a class of drugs that have a higher risk of inducing significant harm in patients if incorrectly administered. These include intravenous

adrenergic agents, beta-blockers, intravenous sedation, anticoagulants, opioid drugs, muscle relaxants, and inhalation anesthetic agents, all of which are the bedrocks of anesthesiology.<sup>4</sup> In addition, anesthesiologists also have an understandably heavy workload, such as a time-critical work environment and demanding long working hours, so medication error events are likely to transpire. A study in the United States revealed that the administration of anesthesia drugs contributed to 19 % of all medication error events. However, the figures were expected to be more eminent due to low reporting.<sup>5</sup> Similarly, a study in Japan reported about 27 % of all medication error incidents in all hospitals involved anesthesia drugs.<sup>6</sup>

Medication error is a preventable problem. Medication errors can be alleviated by reviewing aspects called "five corrects", which consists of the correct indication, the correct patient, the correct time, the correct drug selection, and the correct dose.<sup>7</sup> Technological advancements allow the mitigation of errors in drug dose calculations. Programming experts have developed applications<sup>8-10</sup> that aims to simplify the calculation of doses for health workers, especially anesthesiologists and nurse anesthetists who are very dependent on the accuracy of drug doses. National surveys in the US<sup>8,10,11</sup> and the UK<sup>12</sup> found that all healthcare providers working in the anesthesiology field, including nurse anesthetists, resident anesthetists, and consultant anesthesiologists, relished using a dose calculator installed in their smartphones, and found it helpful in their work when administering anesthetic drugs, whether inhalation, local or general. This literature review will synthesize the types of medication errors, trends of aforementioned errors in the world of

anesthesia, and the benefits of drug dose calculators in patient safety in anesthesia practice.

## **MEDICATION ERROR**

### **Definition**

Medication error is a failure in the treatment process that leads to or has the potential to cause harm to the patients. The treatment process is all efforts prepared for managing a disease that aims to investigate or prevent the disease or physiological change caused by the disease. It may consist of therapeutic drugs and non-therapeutic interventions. Therefore, when it comes to pharmacology, it revolves around compounding, prescribing, transcription (wherever relevant), dispensing, administering the drugs, and subsequently monitoring its effect.<sup>13</sup>

### **Classification**

Arronson broadly divides medication error into two large groups, namely:

a. Mistakes / Planning-related errors  
There are two planning-related errors, namely, knowledge-based errors and rule-based errors. Knowledge-based errors can be associated with any degree of knowledge, such as basic, specialized, or expert. For example, it is basic knowledge that penicillin can provoke allergic reactions; knowing that a patient is allergic to penicillin is specialized-level knowledge; knowing that amoxicillin contains penicillin is expert-level knowledge. Nescience of any of these facts can lead to knowledge-based errors that lead to medication errors. Not knowing the rationale or the maximum dose of one drug is another frequent example of knowledge-based error. Healthcare providers may prevent knowledge-based errors by increasing knowledge, such as ensuring that students are taught basic therapeutic principles and tested on their clinical

application. Another method such as constantly updating the knowledge of medicine in every institution. In addition, the use of computerized decision support systems, such as dosage calculator applications or formulary applications, further allows physicians as prescribers to conceive fewer errors.<sup>13-15</sup>

On the other hand, rule-based errors consist of (a) errors resulting from a failure to obey respected rules; or (b) errors caused by a poor application of the rules. Errors caused by the application of poorly formulated standard operating procedures, incorrectly applying the standard operating procedures, or failing to apply respected rules can be overcome jointly with the medical committee reviewing and revising the existing operational standards for a better future.<sup>13-15</sup>

b. Skill-based / Implementation-related errors

There are two implementation-related errors, namely action-based errors and memory-based errors. Action-based errors are defined as the inappropriate performance of actions or are familiarly known as technical errors. For example, a spelling error occurs when the doctor intends to write diltiazem but writes diazepam. This error is defined to occur when physicians get a failed outcome, or the imperfect execution of the action delivered unexpected results. Another example that often occurs is the calculation of doses that are wrong or inaccurate. Technical errors can be mitigated by continuing to train relevant medical personnel.<sup>13-15</sup>

Memory-based errors occur when healthcare providers fail to execute actions because of forgetfulness. For example, a clinician intends to give penicillin but he/she forgets that the

patient is allergic to it. This type of error is the most difficult to prevent. The best way is to provide a system to detect these errors and allow corrective action either by computerization or assistance personnel to re-examine all medical decisions related to drugs, usually pharmacy staff.<sup>16-18</sup>

Based on the treatment process, a medication error can occur in all four stages of treatment, namely:

a. Prescribing error

A prescription is a written order which includes detailed drug instructions that must meet the "5 rights" rules, namely the right type of drug, the right patient, the right dose, the right route of administration, the right time of administration, and the frequency. Errors in the prescribing process or prescription writing, according to Aronson, include (1) irrational prescriptions, (2) unreadable writing, and (3) over-dosing and under-dosing. This type of error exists abundantly among clinicians. Apart from the wrong dose, polypharmacy or the large number of drugs given are some of the examples of prescribing errors that also often occur.<sup>7,13,19</sup> Writing a complete prescription requires extensive knowledge and a deep understanding of the pathophysiology of the disease. Furthermore, the physician needs to understand the relevant pharmacological properties of the drug.<sup>14</sup> A survey in Iran found that individual factors, with "inadequate medical knowledge" as the most frequent reason, were the most widely reported source of prescribing-type medication error. Fear of being reprimanded or dismissed caused by whistle-blowing other colleagues is a blunder clinician often make.<sup>20</sup> Anzan et al. found that the most human-related cause of prescribing errors was lack of

knowledge (40.9 %), followed by inappropriate drug selection (31.8 %).<sup>21</sup>

b. Transcribing error

Transcribing errors include changes in drug names, drug formulations, routes, doses, dosing regimens against prescription orders. This mistake is commonly made by pharmacists and doctors. The types of transcribing errors are as follows:<sup>22-24</sup> (1) Patient identification error includes name, age, gender, registration that is not written or are incorrectly written on the receipt; (2) negligence is when a physician has prescribed a drug but the receipt is not delivered to the apothecary; (3) errors in the timing of administration, namely when the prescribed drug dose is not given to the patient at a specific time; (4) dosage error; For instance, when the prescription says 0.05 mg when it should have been 0.5 mg on the copy of the prescription; (5) error in the route of administration, for example in the prescription was ordered oral paracetamol over paracetamol infusion; (6) unreported substitution happens when a pharmacist substitutes the prescribed drug using a second-line drug without the knowledge of the prescribing doctor.

c. Dispensing error

Errors in the dispensing stage consist of omissions in dosage compounding, wrong doses, or wrong drug formulations. Dispensing errors can be medication errors given to patients, errors on labels, and when patients do not receive drug information. Pharmacists often make this kind of error. Sard et al. state that errors in the dispensing stage mostly happen when drug preparation is not appropriate and incomplete, nor there is no drug information (about 3.6 % of all dispensing errors). A high number of prescriptions can cause all of those

problems and must be processed with the limited number of pharmacists. Incomplete or non-existent patient drug information can cause discrepancies between what the doctor means in the prescription and what the patient does.<sup>7,24,25</sup>

d. Administering error

Administering errors are the difference between what the patient received and what the prescribing author intended in the initial order. Medication administration errors are one of the risky areas of nursing practice, which the main perpetrators are nurse medical personnel.<sup>24</sup>

The distribution of administering errors indicates that most of these errors involved omissions in dosing (42 %) or errors in the timing of administration (50 %). The Patient Safety Agency in the UK found that medication administration errors occur in 50 % of all drug administration in hospitals.<sup>26,27</sup> One way to overcome this is by asking nurses to re-check drugs at the pharmacy and sign a re-checking form. This intervention reduces missing sequences and emphasizes double-checking. Another reason for skipping doses, especially intravenous drugs, is the late mixing of drugs. Another way to solve the problem is to ask nurses working in the intensive care unit (ICU) to notify the satellite pharmacy half an hour before drug administration. Hence, late mixed drugs can be prepared before the time of administration.

## **MEDICATION ERROR IN ANESTHESIA**

### **Anesthesia drugs' side effects**

Anesthesiologists work in a field that demands critical care and emergency management. Therefore, they often use drugs that alter the function of vital

organs, such as the brain, heart, and blood vessels, or chemical agents that involve acute pain management. The administration of intravenous adrenergic agents, beta-blockers, local anesthetics, intravenous anesthetics, volatile anesthetics, opioid drugs, anticoagulants, and muscle relaxants are all conventional.

a. Local anesthetics

Generally speaking, local anesthesia agents block the Na<sup>+</sup>/K<sup>+</sup> ATPase channels and prevent sodium efflux, interfering with the stimulation of nerve fibers by inhibiting depolarization. Nociceptors, the receptors of pain stimuli, are more prone to this mechanism than tactile, such as pressure and vibration. There are two types of local anesthesia, injectable and topical. The popular combination of injectable anesthesia with epinephrine enhances the anesthesia effect by constricting capillary vessels around the site and limiting the absorption. Topical anesthetics employ a similar mechanism of action as injectable anesthetics and must be absorbed cutaneously to affect dermal nerve endings. Local anesthetics that are often used range from the fastest such as lidocaine to the slower but longer duration of action such as bupivacaine. The more lipophilic the agent is, the more effective and longer its duration of action will be. Consequently, it will contribute to a greater risk of clinical toxicity. Hence, bupivacaine is more likely to cause arrhythmias than lidocaine, whereas the latter may cause diminished cardiac contractility, but without arrhythmias.<sup>28</sup>

Local anesthetic systemic toxicity, or LAST, is the most knowledgeable complication of local anesthesia which revolves around the central nervous system and cardiovascular function. A

thirty-year-long prospective review starting from 1979 defined that LAST transpired in 60 % of cases of local anesthesia. The symptoms began in less than 5 minutes, and 18 % of the cases started with prodromal symptoms such as dizziness, drowsiness, tinnitus, confusion, dysarthria, perioral paresthesia, and auditory disturbances. Central nervous symptoms occurred more often in lidocaine rather than bupivacaine and included seizures, agitation, and loss of consciousness. However, cardiovascular effects are more common in bupivacaine, such as heart rate instability, hypotension, chest pain, dyspnea, hypertension, ventricular tachycardia, ventricular fibrillation, and even asystole.<sup>29,30</sup>

On the other hand, local toxicity mainly consists of ischemic necrosis on the applied site. The condition possibly occurs due to vasoconstriction and is exacerbated by the irritation from the injected solution and volume pressures. A study revealed that the adverse event is more prominent when anesthetizing mucosal surfaces, such as the hard palate or buccal surface.<sup>28</sup>

Allergy side effect in local anesthetics was also recorded. To, Kossintseva, and de Gannes found that the prevalence of contact dermatitis to local anesthetics is significant at 2.4 % among 1819 patients in British Columbia, Canada. The most common drug is benzocaine which occurred in 45 % of subjects, followed by lidocaine (32 %) and dibucaine (23 %). Patients who are patch test-positive should undergo intradermal drug challenge to a local anesthetic. However, contact dermatitis is a delayed Type IV hypersensitivity reaction, so the risk of anaphylaxis is not concerning.<sup>31</sup>

b. Intravenous anesthetics

One systematic review and meta-analysis revealed that the most common adverse event of intravenous sedatives was hypoxia, with an incidence of 40.2 per 1,000 sedations, followed by post-operative nausea and vomiting (PONV) with 16.4 per 1,000 sedation and hypotension with 15 per 1,000 sedations. Severe adverse events requiring emergent medical intervention were rare, with only a single case of aspiration in 2370 sedations (0,42 per 1000), one case of laryngospasm in 883 sedations (4.2 per 1000), and only two intubations in 3,636 sedations (0,5 per 1000). The incidence of agitation (164 per 1000) and vomiting (170 per 1000). Apnea was more common with midazolam (51 per 1000). The case of laryngospasm was in a patient who received ketamine, and the aspiration and intubations were in patients who received propofol.<sup>32</sup> Moreover, except for propofol, intravenous sedatives are also known to depress all aspects of the immunity system, which further increases the surgically-induced immunosuppression.<sup>33</sup>

Intravenous regional anesthetics (IVRA) has been popular in recent times, mainly due to its some important advantages: easily performed, cost-effective and relatively safe, fast onset of effect (5-10 min), high success rates, good muscle relaxation, and fast return of sensation. In some clinical constellations, it might represent a preferable low-risk technique for multimorbid patients with a high-risk profile for general anesthesia (GA). Most of the observed minor side effects are associated with symptoms of the central nervous system (CNS): dizziness, blurred vision, facial tingling, facial numbness, metallic taste, tinnitus, difficulty in speaking, and dysphoria. Dunbar and Mazze described a

probability of 2.1 % for mild CNS reactions. Major adverse events such as seizures, myoclonia, cardiac depression, and death (as it was reported for bupivacaine) have been reported in the context of IVRA. The cardiac arrest was also recorded after the use of bupivacaine for IVRA.<sup>34</sup>

c. Intravenous opioid

One systematic review on 34 randomized controlled trials (RCTs) found that among 4212 non-cancer patients, dry mouth (25 %), nausea (21 %), and constipation (15 %) were the most common adverse events in opioid use.<sup>35</sup> In the perioperative setting, another systematic review and meta-analysis found that in 23 RCTs, including 1304 subjects, the most common adverse effects of intravenous opioid is nausea and vomiting (PONV). Meanwhile, according to one systematic review, the most feared respiratory depression in opioids was found in just four out of 1064 patients and only one needed temporary respiratory support for breathlessness.<sup>36</sup> The presence of these stressful side effects is responsible for post-operative complications such as prolonged length of stay, delayed recovery, unanticipated re-admission, and, economically, increased costs of health service.<sup>37</sup>

d. Adrenergic agents

The side effects observed with adrenergic agonists are widespread and depend on the type of the receptors. Generally, all four often affect the changes in blood pressure and heart rate. Selective agonists that bind to the alpha-1 receptor can cause hypertension. Certain drugs that bind to alpha-1 receptors, such as phenylephrine, can cause reflex bradycardia. Alpha-2 drugs that selectively bind to the receptor can cause hypotension, dry mouth, and

sedation. High doses can cause respiratory depression and drowsiness. These effects are most common in clonidine and dexmedetomidine. Dexmedetomidine, however, has protective factors against hypertension and tachycardia in perioperative settings. The alpha-2 agonists with a dose higher than 5 ug/kg body weight and administered by bolus have a higher risk of causing adverse events.<sup>38</sup>

Selective binding to the beta-1 receptor often causes tachycardia, palpitations, and hypertension. Tachyarrhythmias and anxiety are also common. High doses may cause dangerous arrhythmias. An example of a selective  $\beta_1$  receptor agonist is dobutamine. Finally, beta-2 receptor agonists can cause tremors, tachycardia, palpitations, and anxiety. Frequent examples are various bronchodilators such as albuterol and salmeterol. A large, multinational, RCT called Peri-operative ISchemic Evaluation (POISE), revealed that beta-adrenergic antagonism given to patients having non-cardiac surgery reduced the incidence of post-operative myocardial infarction but at the cost of post-operative hypotension, cerebral infarction, and even death. Two meta-analyses supported the finding, concluding that perioperative beta-blocker agents before non-cardiac surgeries had preventive traits against nonfatal MI but increased risks of stroke, hypotension, bradycardia, and death.<sup>39,40</sup>

Non-selective binding to the adrenergic receptor can cause a variety of side effects, depending on the active ingredient and dosage. Common non-selective agonists are noradrenaline, adrenaline, and isoproterenol (isoprenaline). Common side effects are tachycardia, hypertension, arrhythmia, palpitation, and anxiety. Norepinephrine

is probably more selective for the alpha 1 receptor compared to the beta 1 receptor, so it is less likely to cause arrhythmias than some other antihypertensive drugs.<sup>41</sup>

#### e. Muscle relaxants

What makes muscle relaxants' side effects dangerous is not solely on their status as breathlessness potential, but their interaction with other two drugs in anesthesia triads. Most local anesthetics when given in large doses potentiate neuromuscular blockers. Antidysrhythmic drugs, such as quinidine, also potentiate neuromuscular blockers. Inhalational anesthetics potentiate the neuromuscular blocking effect of nondepolarizing neuromuscular blockers. This potentiation results mainly in a decrease in the required dosage of neuromuscular blocker and prolongation of both the duration of action of the relaxant and recovery from neuromuscular block. The magnitude of this potentiation depends on several factors, including the duration of inhalational anesthesia, the specific inhalational anesthetic used, and the concentration of inhalational agent used.<sup>42</sup>

Life-threatening anaphylactic (immune-mediated) or anaphylactoid reactions caused by neuromuscular blockers during anesthesia occurred in as often as 1 in 1000 administrations and were associated with a mortality rate of about 5 %. A study in France by Laxeanire et al. showed the most common causes of anaphylaxis in patients who experienced allergic reactions were reported to be neuromuscular blocking drugs (58.2 %) and considered muscle relaxants responsible for 61.6 % of the 692 cases of anaphylaxis. In that study, the muscle relaxants most implicated in anaphylaxis were vecuronium (n = 130) and atracurium (n = 107).<sup>43</sup>

### **Incidence**

Statistically, based on a limited number of prospective studies, the incidence of medication error during anesthesia practice in hospitals worldwide ranges from 0.33 % to 0.73 %, and surprisingly, this figure has not changed over the last 15 years. This data may happen due to a poor reporting system. Research in the US found that anesthesiologists performed one out of twenty perioperative drug administrations as medication error with or without significant drug side effects. Furthermore, the risk of medication error events experienced by anesthesiologists increased exponentially since the second surgery on the same day.<sup>44</sup> Research in Brazil found that, on average, an anesthesiologist experienced five medication errors while on duty every day.<sup>45</sup> The most common type of medication errors found, according to several studies in the Middle East, United Kingdom, and Indonesia is the administration of the wrong drug and the wrong dose.<sup>46-51</sup> In summary, there is a twofold increased risk of medication error in anesthesia in resident anesthesia compared to established consultants, with the most frequent type of medication error being the wrong drug and the wrong dose.

According to two systematic reviews, internal medicine and anesthesia departments were the most frequently reported hospital departments performing medication errors in all hospitals in the Middle East.<sup>47,48</sup> Macfie et al. found that in an intensive care setting, polypharmacy is often performed by anesthetists, causing medication error up to 96 per 1000 patients, and this occurs in conjunction with prescription drugs that have not previously been exposed to patients.<sup>16,52,53</sup> Dosage errors are very frequent in anesthetized patients

and children, both of whom depend on expected body weight for potent dosing. The failures that often occur are obtaining an accurate weight for the patient and lack of knowledge by the providers of the pharmacokinetics and pharmacodynamics of the drug given.<sup>54</sup>

As mentioned earlier, the high-stress level, the high level of complexity of the work, and the complex nature of perioperative care and intensive care, which race against time, create a higher risk of medication error scenarios in anesthesiologists.<sup>16,48,49</sup> Nanji et al. found, in 277 operations observed, there were a total of 3671 drugs administration. From that study, medication errors and adverse drug events characterize in 1 out of every 20 drug administrations conducted by an anesthesiologist. In other words, there were a total of 153 (79.3 %) medication errors done by an anesthesiologist, all of which were preventable.<sup>44,55</sup>

A study by Webster, which recruited nearly 7800 anesthesiologists, found that the frequency of medication error (of all types) per anesthetic case was 0.75 % (1 per 133 anesthetic procedures) with the two most frequent forms involving the wrong dose (20 %) and the wrong drug (20 %). This finding explains that the drug side effects during anesthetic treatment were much more prevalent than those reported in other drugs.<sup>5,56</sup> A survey in Brazil among 91.8 % of anesthesiologists found that there had been an average of 5-7 errors per respondent. The most frequent errors were medication errors (68.4 %), followed by dose errors (49.1 %).<sup>45</sup> Yamamoto found that over eight years period, the most frequent medication error experienced by anesthesiologists in Japan was overdosing (25 %), followed by wrong medication administration (23



%).<sup>6</sup> Research by Gabriel in France found that 2.6 % of 1925 anesthesiologists performed medication errors. The drugs most frequently experienced errors in administration, including the dose or route of administration, were opioids and antibiotics.<sup>57</sup> Meanwhile, incorrect doses represent two-thirds of medication errors. The study of Woo reported that accidental overdose was eight times higher in anesthetized pediatric patients than in adult patients.<sup>58</sup>

### **Risk factors**

Several systematic reviews formulate some of the causes of medication error in the perioperative setting in anesthesiologists. The highest incidence of medication error reported was due to lack of knowledge about drugs (45 %), followed by distraction during prescribing (48 %), pharmacist-nurse-doctor axis miscommunication (22 %), haste (23 %), and inattention (17 %). Lack of knowledge was reported as a cause of error in the perioperative area. Systematic reviews show that poor communication contributes to errors in the intraoperative and post-operative settings. Incorrect labeling and sharing of needles are the most common causes of administering errors. Drug labeling, double-checking manually, and the use of technology (e.g., label printers, barcode scanners) can be implemented to assist in the labeling of syringes and to reduce administrative errors.<sup>59-61</sup>

## **DRUG DOSAGE CALCULATOR APPLICATION**

### **Background**

In the perioperative setting, particularly anesthesia, most drugs are administered invasively to the patient, either intravenously, spinal, or a combination of both. The situation urges the provision of accurate calculation and decent

preparation of specific, individualized, body-weight-based drug doses for each individual, which varies widely across age groups. This error-prone process and the high-risk nature of anesthetic drugs put the anesthesiologist at high risk for developing life-threatening medication errors.<sup>62</sup> One way to mitigate dose calculation errors is the use of technology. Programmers have developed several dose calculators which can be downloaded on doctors' phones to assist them in calculating doses. Hence, dose calculators is quite popular among attending pediatricians and physicians who use high-risk drugs.<sup>63,64</sup> In fact, the pediatric department was the pioneer of the dose calculator's implementation, as its department is associated heavily with accurate dose prescribing based on children's body weight.<sup>65</sup> Stretching back in 2003, a prospective cohort study found that dosing errors were issued the most among pediatricians and the utilization of a computerized dosing calculator mitigated the rate of errors.<sup>66</sup>

### **Examples**

Many smart apps related to drug dose calculators are available for download in several online software stores. These drug dose calculators are available as a stand-alone or as a part of the hospital medical application or website. Only some are trademarked while the majority often integrate with their own affiliated hospital computer database. For example, there is QxMD™, which provides medical calculators and drug dosage features, is also primarily a vehicle for reading medical articles and journals.<sup>67</sup> In addition, there is PedAMINES™ which is a unique dose calculator application for children in emergency settings.<sup>62</sup> E-Calculator™ is an anesthetic dose calculator designed exclusively for nursing students anesthesiologists in teaching hospitals in

Mississippi, USA.<sup>68</sup> One app developed in Indonesia is AnesthCalc™, an anesthetic and adjuvant dose calculator developed in Mohammad Hoesin General Hospital.

### Effectiveness

As mentioned earlier, the pediatric department has popularly utilized the dosing calculator programs. In 2003, Kirk et al. revealed that hospitals that utilized a computerized dose calculator found a decreased medication error rate from 28,2 % cases to 12,6 % among 4281 prescriptions.<sup>66</sup> Recently documented review by Zanden et al. in the Netherlands explained that they have created, validated, and implemented a dosing calculator based on their pediatric formulary, used more than 65,000 times monthly.<sup>69</sup> A study on 100 pediatricians in Texas found that an electronic dosing calculator created by Brian Murray may reduce the number of medication errors per patient visit. Before implementing the app, there were ten errors in 28,400 visits, compared to after implementation which was only a single error occurred in 17,900 visits.<sup>70</sup>

In the anesthesiology, similar breakthroughs have been groundbreaking. Research in Mississippi, USA, found that nurse anesthetists who used a dose calculation application E-Calutron™ found a benefit to the accuracy of administering drugs according to the dose.<sup>68</sup> A survey held at a teaching hospital in Philadelphia, USA, found that 60 % of residency anesthetists, consultants, and nurse anesthetists enjoyed using a mobile application Epocrates™ to calculate anesthetic drug doses every week while on duty.<sup>64</sup> Another survey in Chicago, USA, found that anesthetic dose calculators QxMD™ were used more frequently for regional anesthetics and

antithrombotic drugs among anesthetic consultants.<sup>67</sup> Whereas in the U.K., a smartphone application called Anaesthetic Impact Calculator by Kevin Scott to calculate doses is preferred to calculate inhaled anesthetic agents over the intravenous one.<sup>71</sup> A study in Germany found that the dose calculation application was valid and well-applied in an emergency department setting, with a dosing accuracy of 98 % among 74 attending anesthesiologists.<sup>72</sup> The recent revelation was a quasi-experiment in Brazil by Jara et al. It found that the implementation of a dosing calculator smartphone app can greatly diminish anesthetic-related deaths upon using doses of ketamine and xylazine (an analog of clonidine) among mice, with astonishing total mortality of 8 in 773 subjects (1,03 %) compared to 17 deaths in 166 (10,3 %).<sup>73</sup>

### CONCLUSION

This literature review's objective is to assist the reader to underline many perspectives modeled by several pieces of reviews, postulates and studies on medication errors and drug dosage calculator applications. It is paramount because the utilization of applications has the potential to be implemented as a standard of care in the anesthesiology field around the world. There have been discussions conducted on this topic of the implementation of technology in preventing wrong dose calculation. Most of the research was promising, as the dosage calculators' applications were proven to increase the dose accuracy. However, we still lack more research at present to gain better evidence of whether a more diverse population also shows similar positive results of increasing performance or not. It is crucial to conduct more studies on the results and identify side factors that may hamper the implementation of the drug

dosage calculator applications, such as level of education, work experience, and many more.

### ACKNOWLEDGEMENT

We acknowledge Universitas Sriwijaya for supporting our research with grant number 0010/UN9/SK.LP2M.PT/2021.

### CONFLICT OF INTEREST

There is no conflict of interest.

### REFERENCES

1. Choi I, Lee SM, Flynn L, et al. Incidence and treatment costs attributable to medication errors in hospitalized patients. *Research in Social and Administrative Pharmacy*. 2016;12(3):428-437. doi:10.1016/j.sapharm.2015.08.006
2. Laatikainen O, Sneek S, Turpeinen M. The risks and outcomes resulting from medication errors reported in the Finnish tertiary care units: A cross-sectional retrospective register study. *Frontiers in Pharmacology*. 2020;10(January):1-11. doi:10.3389/fphar.2019.01571
3. Zhou S, Skaar DJ, Jacobson PA, Huang RS. Pharmacogenomics of Medications Commonly Used in the Intensive Care Unit. *Frontiers in Pharmacology*. 2018;9. doi:10.3389/fphar.2018.01436
4. Golembiewski J, Wheeler PJ. High-Alert Medications in the Perioperative Setting. *Journal of Perianesthesia Nursing*. 2007;22(6):435-437. doi:10.1016/j.jopan.2007.09.002
5. Cooper L, Nossaman B. Medication errors in anesthesia: A review. *International Anesthesiology Clinics*. 2013;51(1):1-12. doi:10.1097/AIA.0b013e31827d6486
6. Yamamoto M, Ishikawa S, Makita K. Medication errors in anesthesia: An 8-year retrospective analysis at an urban university hospital. *Journal of Anesthesia*. 2008;22(3):248-252. doi:10.1007/s00540-008-0624-4
7. Ulfah SS, Mita SR. Medication Errors Pada Tahap Prescribing, Transcribing, Dispensing Dan Administering. *Farmaka*. 2017;15(2):233-240.
8. Wuenstel A, Cheng P, Clebone A. New Applications for Your Mobile Device. *Anesthesia & Analgesia*. 2017;124(1):364. doi:10.1213/ane.0000000000001694
9. Siebert JN, Bloudeau L, Ehrler F, et al. A mobile device app to reduce prehospital medication errors and time to drug preparation and delivery by emergency medical services during simulated pediatric cardiopulmonary resuscitation: Study protocol of a multicenter, prospective, randomized controlled. *Trials*. 2019;20(1):1-12. doi:10.1186/s13063-019-3726-4
10. James E. Integrating E-Calculator into the Anesthesia Clinical Settings to Reduce Potential Medical Calculation Errors Among Student Registered Nurse Anesthetists. Published online 2020.
11. Green MS, Mathew JJ, Gundigi Venkatesh A, Green P, Tariq R. Utilization of Smartphone Applications by Anesthesia Providers. *Anesthesiology Research and Practice*. 2018;2018:5-9. doi:10.1155/2018/8694357
12. Pierce JMT, Taylor R. Validation of the mathematics in the anaesthetic impact calculator, a smartphone app for the calculation the CO<sub>2</sub>e of inhalational anaesthesia. *Anaesthesia*. 2020;75(1):136-138. doi:10.1111/anae.14896
13. Aronson JK. Medication errors: Definitions and classification.

- British Journal of Clinical Pharmacology*. 2009;67(6):599-604. doi:10.1111/j.1365-2125.2009.03415.x
14. MacFie CC, Baudouin S V., Messer PB. An integrative review of drug errors in critical care. *Journal of the Intensive Care Society*. 2016;17(1):63-72. doi:10.1177/1751143715605119
  15. Mackay E, Jennings J, Webber S. Medicines safety in anaesthetic practice. *BJA Education*. 2019;19(5):151-157. doi:10.1016/j.bjae.2019.01.001
  16. Aronson JK. Medication errors: Definitions and classification. *British Journal of Clinical Pharmacology*. 2009;67(6):599-604. doi:10.1111/j.1365-2125.2009.03415.x
  17. MacFie CC, Baudouin S V., Messer PB. An integrative review of drug errors in critical care. *J Intensive Care Soc*. 2016;17(1):63-72. doi:10.1177/1751143715605119
  18. Mackay E, Jennings J, Webber S. Medicines safety in anaesthetic practice. *BJA Education*. 2019;19(5):151-157. doi:10.1016/j.bjae.2019.01.001
  19. Beng yi S, Chan Pei Shan J, Lay Hong G. Medication reconciliation service in Tan Tock Seng Hospital. *International Journal of Health Care Quality Assurance*. 2013;26(1):31-36. doi:10.1108/09526861311288622
  20. Ava Mansouria, Alireza Ahmadvandb, Molouk Hadjibabaiec, et al. A Review of Medication Errors in Iran: Sources, Underreporting Reasons and Preventive Measures. *Iranian Journal of Pharmaceutical Research*. 2014;13(1):3-17.
  21. Anzan M, Alwhaibi M, Almetwazi M, Alhawassi TM. Prescribing errors and associated factors in discharge prescriptions in the emergency department: A prospective cross-sectional study. *PLoS ONE*. 2021;16(1 January). doi:10.1371/journal.pone.0245321
  22. Sari DD, Oktarlina RZ. Peresepan Obat Rasional dalam Mencegah Kejadian Medication Error. *Jurnal Kedokteran Universitas Lampung*. 2017;7(5):100-105.
  23. Kabra A, Kabra R. Study of medication errors and compliances for inclusion of new drugs in hospital formulary International Journal of Fundamental & Applied Sciences Study of medication errors and compliances for inclusion of new drugs in hospital formulary. 2020;(May):13-16.
  24. Khairurrijal MAW, Putriana NA. Review: Medication Error Pada Tahap Prescribing, Transcribing, Dispensing, dan Administration. *Farmasetika.com (Online)*. 2018;2(4):8. doi:10.24198/farmasetika.v2i4.15020
  25. Gloria L, Yuwono, Ngudiantoro. Analisis Faktor Yang Mempengaruhi Medication Error Pada Pasien Kemoterapi Di RSUP DR . Mohammad Hoesin Palembang. *Majalah Kedokteran Sriwijaya*. 2017;4(49):178-184.
  26. Alomar M, Ahmad S, Moustafa Y, Alharbi L. Reducing missed medication doses in intensive care units: A pharmacist-led intervention. *Journal of Research in Pharmacy Practice*. 2020;9(1):36. doi:10.4103/jrpp.jrpp\_19\_95
  27. Tsegaye D, Alem G, Tessema Z, Alebachew W. Medication administration errors and associated factors among nurses. *International Journal of General Medicine*.

- 2020;13:1621-1632.  
doi:10.2147/IJGM.S289452
28. Park KK, Sharon VR. A Review of Local Anesthetics: Minimizing Risk and Side Effects in Cutaneous Surgery. Published online 2017;173-187.  
doi:10.1097/DSS.0000000000000887
  29. El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: Current perspectives. *Local and Regional Anesthesia*. 2018;11:35-44. doi:10.2147/LRA.S154512
  30. Di Gregorio G, Neal JM, Rosenquist RW, Weinberg GL. Clinical presentation of local anesthetic systemic toxicity: A review of published cases, 1979 to 2009. *Regional Anesthesia and Pain Medicine*. 2010;35(2):181-187. doi:10.1097/AAP.0b013e3181d2310b
  31. To D, Gannes G De. Lidocaine Contact Allergy Is Becoming More Prevalent. Published online 2014:1367-1372.  
doi:10.1097/DSS.0000000000000190
  32. Erwin PJ, Anderson JR, Miner JR, Hess EP. Incidence of Adverse Events in Adults Undergoing Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis. *Academic Emergency Medicine*. 2016;23(0):119-134. doi:10.1111/acem.12875
  33. Yaacoub S. *General Anesthesia : A Literature Review - Induction , Mechanism , Agents , and Effects*. 2015.
  34. Löser B, Petzoldt M, Löser A, Douglas R. Intravenous Regional Anesthesia: A historical overview and clinical review. *Journal of Anesthesia History*. 2018;7(10):1-32. doi:10.1016/j.janh.2018.10.007
  35. Moore RA, Mcquay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: Systematic review of randomised trials of oral opioids. *Arthritis Research & Therapy*. 2005;7(5):1046-1051. doi:10.1186/ar1782
  36. Verberkt CA, Everdingen MHJVDB van, Schols JMGA, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J*. 2017;50(1153):1-15.  
doi:10.1183/13993003.01153-2017
  37. Frauenknecht J, Kirkham KR, Albrecht E. Analgesic impact of intra-operative opioids vs . opioid-free anaesthesia: A systematic review and meta-analysis. Published online 2019.  
doi:10.1111/anae.14582
  38. Demiri M, Antunes T, Fletcher D, Martinez V. Perioperative adverse events attributed to a 2-adrenoceptor agonists in patients not at risk of cardiovascular events: systematic review and meta-analysis. *British Journal of Anaesthesia*. 2019;123(6):795-807.  
doi:10.1016/j.bja.2019.07.029
  39. Bouri S, Shun-shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of  $\beta$  -blockade to prevent perioperative death in non-cardiac surgery. Published online 2014:456-464. doi:10.1136/heartjnl-2013-304262
  40. Wijeyesundera DN, Committee ER, Duncan D, et al. Perioperative Beta Blockade in Noncardiac Surgery : A Systematic Review for the 2014 ACC / AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac

- Surgery. 2014;64(22). doi:10.1016/j.jacc.2014.07.939
41. Farzam; K, Kidron; A, Lakhkar. AD. Adrenergic Drugs. *StatPearls*. 2021;1(1).
  42. Clar D, Liu M. Non-depolarizing Neuromuscular Blockers. In: *StatPearls*. StatPearls Publishing; 2021:1-6.
  43. Vilardi V, Sanfilippo M, Crarlone A. Muscle Relaxants : Side Effects and Complications. Published online 2001.
  44. Nanji KC, Patel A, Shaikh S, Seger DL, Bates DW. Evaluation of Perioperative Medication Errors and Adverse Drug Events. *Anesthesiology*. 2016;124(1):25-34. doi:10.1097/ALN.0000000000000904
  45. Erdmann TR, Garcia JHS, Loureiro ML, Monteiro MP, Brunharo GM. Profile of drug administration errors in anesthesia among anesthesiologists from Santa Catarina. *Brazilian Journal of Anesthesiology (English Edition)*. 2016;66(1):105-110. doi:10.1016/j.bjane.2014.06.011
  46. Anzan M, Alwhaibi M, Almetwazi M, Alhawassi TM. Prescribing errors and associated factors in discharge prescriptions in the emergency department: A prospective cross-sectional study. *PLoS ONE*. 2021;16(1 January). doi:10.1371/journal.pone.0245321
  47. Vaziri S, Fakouri F, Mirzaei M, Afsharian M, Azizi M, Arab-Zozani M. Prevalence of medical errors in Iran: A systematic review and meta-Analysis. *BMC Health Services Research*. 2019;19(1):1-11. doi:10.1186/s12913-019-4464-8
  48. Thomas B, Paudyal V, MacLure K, et al. Medication errors in hospitals in the Middle East: a systematic review of prevalence, nature, severity and contributory factors. *European Journal of Clinical Pharmacology*. 2019;75(9):1269-1282. doi:10.1007/s00228-019-02689-y
  49. Swinton P, Corfield AR, Moultrie C, et al. Impact of drug and equipment preparation on pre-hospital emergency Anaesthesia (PHEA) procedural time, error rate and cognitive load. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*. 2018;26(1):1-10. doi:10.1186/s13049-018-0549-3
  50. Gloria L, Yuwono, Ngudiantoro. Analisis Faktor Yang Mempengaruhi Medication Error Pada Pasien Kemoterapi Di RSUP DR . Mohammad Hoesin Palembang. *Majalah Kedokteran Sriwijaya*. 2017;4(49):178-184.
  51. Hartati, Lolok NH, Fudholi A. Analisis Kejadian Medication Error Pada Pasien ICU. *Journal of Management and Pharmacy Practice*. 2014;4(2):125-132. doi:10.22146/jmpf.277
  52. Ulfah SS, Mita SR. Medication Errors Pada Tahap Prescribing, Transcribing, Dispensing Dan Administering. *Farmaka*. 2017;15(2):233-240.
  53. Oktarlina RZ, Wafiyatunisa Z. Kejadian Medication Error pada Fase Prescribing di Poliklinik Pasein Rawat Jalan Rumah Sakit Daerah Mayjend HM Ryacudu Kota Bumi. *Fakultas Kedokteran Universitas Lampung*. 2017;1(3):540-545.
  54. Merry AF, Anderson BJ. Medication errors - New approaches to prevention. *Paediatric Anaesthesia*. 2011;21(7):743-753. doi:10.1111/j.1460-9592.2011.03589.x

55. Cohen MR, Orser B. Perioperative Medication Errors; Building Safer Systems. 2016;(1):1-3.
56. Dhawan I, Tewari A, Sehgal S, Sinha AC. Medication errors in anesthesia: unacceptable or unavoidable? *Brazilian Journal of Anesthesiology (English Edition)*. 2017;67(2):184-192. doi:10.1016/j.bjane.2015.09.006
57. Gariel C, Cogniat B, Desgranges FP, Chassard D, Bouvet L. Incidence, characteristics, and predictive factors for medication errors in paediatric anaesthesia: a prospective incident monitoring study. *British Journal of Anaesthesia*. 2018;120(3):563-570. doi:10.1016/j.bja.2017.12.014
58. Woo Y, Kim HE, Chung S, Park BJ. Pediatric medication error reports in Korea adverse event reporting system database, 1989-2012: Comparing with adult reports. *Journal of Korean Medical Science*. 2015;30(4):371-377. doi:10.3346/jkms.2015.30.4.371
59. Boytim J, Ulrich B. Factors contributing to perioperative medication errors: A systematic literature review. *AORN Journal*. 2018;107(1):91-107. doi:10.1002/aorn.12005
60. Alomar M, Ahmad S, Moustafa Y, Alharbi L. Reducing missed medication doses in intensive care units: A pharmacist-led intervention. *Journal of Research in Pharmacy Practice*. 2020;9(1):36. doi:10.4103/jrpp.jrpp\_19\_95
61. Ariyaratnam R, Palmqvist CL, Hider P, et al. Toward a standard approach to measurement and reporting of perioperative mortality rate as a global indicator for surgery. *Surgery (United States)*. 2015;158(1):17-26. doi:10.1016/j.surg.2015.03.024
62. Siebert JN, Bloudeau L, Ehrler F, et al. A mobile device app to reduce prehospital medication errors and time to drug preparation and delivery by emergency medical services during simulated pediatric cardiopulmonary resuscitation: Study protocol of a multicenter, prospective, randomized controlled. *Trials*. 2019;20(1):1-12. doi:10.1186/s13063-019-3726-4
63. Carvalho H, Verdonck M, Forget P, Poelaert J. Acceptance of mHealth among health professionals: A case study on anesthesia practitioners. *BMC Anesthesiology*. 2020;20(1):1-10. doi:10.1186/s12871-020-00958-3
64. Green MS, Mathew JJ, Gundigi Venkatesh A, Green P, Tariq R. Utilization of Smartphone Applications by Anesthesia Providers. *Anesthesiology Research and Practice*. 2018;2018:5-9. doi:10.1155/2018/8694357
65. Wong I. Ways to reduce drug dose calculation errors in children. 2010;15(January):2009-2011.
66. Kirk RC, Goh DL meng, Packia J, Kam HM, Ong BKC. Computer Calculated Dose in Paediatric Prescribing. *Drug Safety*. 2005;28(9):817-824.
67. Wuenstel A, Cheng P, Clebone A. New Applications for Your Mobile Device. *Anesthesia & Analgesia*. 2017;124(1):364. doi:10.1213/ane.0000000000001694
68. James E. Integrating E-Calculator into the Anesthesia Clinical Settings to Reduce Potential Medical Calculation Errors Among Student Registered Nurse Anesthetists. Published online 2020.
69. Zanden TM Van Der, Goedknecht L, Hoog M De, Mooij MG, Wildt SN De. Development and

- implementation of a paediatric dosing calculator integrated in the Dutch Paediatric Formulary. *Drugs & Therapy Perspectives*. 2020;36(6):253-262. doi:10.1007/s40267-020-00724-y
70. Murray B, Streit MJ, Hilliard M, Maddry JK. Evaluation of an Electronic Dosing Calculator to Reduce Pediatric Medication Errors. *Clinical Pediatrics*. 2019;58(4):413-416. doi:10.1177/0009922818821871
71. Pierce JMT, Taylor R. Validation of the mathematics in the anaesthetic impact calculator, a smartphone app for the calculation the CO<sub>2</sub>e of inhalational anaesthesia. *Anaesthesia*. 2020;75(1):136-138. doi:10.1111/anae.14896
72. Baumann D, Dibbern N, Sehner S, Zöllner C, Reip W, Kubitz JC. Validation of a mobile app for reducing errors of administration of medications in an emergency. *Journal of Clinical Monitoring and Computing*. 2019;33(3):531-539. doi:10.1007/s10877-018-0187-3
73. Jara CP, Carraro RS, Zanesco A, et al. A Smartphone App for Individual Xylazine / Ketamine Calculation Decreased Anesthesia-Related Mortality in Mice. 2021;8(July):1-7. doi:10.3389/fvets.2021.651202