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Progress in the Clinical Utilization of Subtherapeutic Dosages of Anesthetic Agents

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Abstract

The effective dose at which 50% of the population has a response, known as ED50, is a fundamental notion in pharmacology crucial for evaluating pharmacological efficacy. This metric indicates the dosage level necessary to achieve the intended therapeutic effect in precisely 50% of subjects treated in specific experimental settings. The ED50 is an essential metric widely employed in multiple medical fields, especially in the delivery of anesthetics by intrathecal, intravenous, and inhalation routes. This article intends to deliver a thorough examination of the progress and innovations in the use of ED50 within the field of clinical anesthesiology. This review emphasizes the optimization of drug dosages, strategies for numerous drug combinations, a comparison of drug efficacy, the ED50 experimental design methodology, and the application of artificial intelligence in dosage prediction and optimization. We aim to scrutinize the significance and difficulties in clinical anesthesia, thereby providing direction for managing anesthetics in clinical environments.

Keywords

Suboptimal Effective Dosage, Personalized Dosing, Artificial Intelligence, Anesthetic Safety

1. Introduction

The half-effective dose (ED50) denotes the quantity of medicine that produces 50% of the maximum reaction intensity in a quantitative assessment and induces a positive response in 50% of participants in a qualitative evaluation [1]. The half-effective dose, or ED50, serves as a crucial pharmacological metric that quantitatively underpins the judicious application of anesthetic agents. There are notable variations in the ED50 of diverse anesthetic agents among different surgical inter-

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ventions and patient demographics. Moreover, medication interactions during concurrent use can influence the anesthetic efficacy. Currently, the comprehensive analysis of the ED50 of anesthetics in clinical practice serves as a crucial metric for assessing drug safety. This evaluation aids in determining appropriate dosages of clinical anesthetics, appraising drug efficacy, ensuring safety, facilitating drug development and enhancement, improving anesthesia quality, and mitigating the risk of adverse reactions. Consequently, the examination of its clinical application holds substantial practical value.

2. ED50 in Anesthetic Agents

2.1. Optimized Pharmaceutical Dosage

A smaller ED50 indicates more efficacy or a more favorable response to the medicine at a lower dose, signifying increased potency. Mivacurium chloride is an ultra-short-acting muscle relaxant utilized in therapeutic settings, esteemed for its quick duration of action, efficient muscle relaxation, and absence of accumulation in the body. It provides a considerable benefit during brief surgical procedures when delivered continuously. Fu Yi-Qing *et al.* employed the modified Dixon up-and-down sequential approach to ascertain the ED50 of mivacurium chloride during continuous infusion in laparoscopic cholecystectomy, which was determined to be 7. 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [2]. In recent years, the intravenous anesthetic remimazolam has been extensively employed in adult general anesthesia treatments. This medicine, recognized for its swift onset and brief duration of action, has become essential in the operating room, offering anesthesiologists a crucial instrument for administering anesthesia in adult patients. Pediatric preoperative anxiety is more common than in adults, with children frequently exhibiting heightened worry and apprehension around impending surgical interventions. This increased anxiety can complicate the perioperative phase and may adversely impact the child's recovery. Consequently, the investigation of the judicious application of pharmaceuticals to mitigate this anxiety has emerged as a contemporary research priority. Researchers are rigorously examining the optimal application of current anesthetics, including remimazolam, in pediatric populations to guarantee safe and effective sedation while mitigating unwanted effects and enhancing the surgical experience for young patients. Remazolam was utilized in a study to assess preoperative sedation in pediatric patients and ascertain its ED50. Given the mild respiratory depression linked to preoperative sedation in pediatric patients, its effect on postoperative awakening is negligible, and the medication ensures effective control and safety, thereby presenting an outstanding option for pediatric preoperative sedation and offering further pharmacological alternatives for this application [3]. Ultrasound-guided regional nerve block provides enhanced postoperative analgesia for the elderly, and the ED50 of the local anesthetic ropivacaine for iliopsoas muscle gap block in postoperative analgesia for anesthetized hips in this demographic has been determined [4] to decrease the substantial volume of local anesthetics utilized in the initial study (0.33% ropivacaine 30 ml) [5], significantly

diminishing the occurrence of adverse effects such as local anesthetic toxicity, nausea, and vomiting that may result from an overdose of local anesthetics. The selection of the correct drug dosage is essential for establishing the depth of anesthesia, which significantly influences the patient's hemodynamic stability throughout surgery. The exact dosage of medication supplied significantly impacts the quality of surgical recovery, influencing pain levels, the occurrence of side effects, and the overall healing process.

The ED50 of various medications allows for the comparison of their efficacy; specifically, a lower incidence of adverse events correlates with greater drug safety while maintaining equivalent efficacy. Therefore, the equilibrium between the drug's efficacy and its safety profile is essential, favoring those that ensure high effectiveness while reducing the likelihood of unwanted effects. Ciprofol is a novel intravenous anesthetic independently discovered in China, exhibiting 4 - 5 times the potency of propofol [6], while greatly reducing the occurrence of adverse responses, such as injection discomfort, in comparison to the classic sedative propofol. Liao *et al.* [7] utilized the Dixon up-and-down sequential approach to compare the ED50 for the suppression of cardiovascular responses during tracheal intubation and the occurrence of adverse events between ciprofol and propofol. Equivalent dosages of both medications produced a similar occurrence of hypotension and bradycardia. The reduced likelihood of injection discomfort, enhanced hemodynamic stability, and expedited recovery linked to ciprofol may be attributed to its unique emulsion composition. Thus, ciprofol may serve as a viable alternative to propofol, perhaps providing enhanced safety and efficacy during anesthesia induction. In comparisons between novel and conventional pharmaceuticals, newer medications are frequently favored for their enhanced efficacy and lower occurrence of unwanted effects. These innovative pharmaceuticals are often created to address the shortcomings of previous therapies, which may encompass diminished efficacy, heightened adverse effects, or a restricted therapeutic range. The objective is to deliver therapies to patients that are not only more effective but also safer, therefore improving the overall quality of care and patient outcomes. Norepinephrine serves as a primary vasopressor for managing and prevention hypotension during intrathecal anesthesia in cesarean birth [8], Phenylephrine assesses blood pressure and activates the vagus nerve, potentially resulting in a decreased heart rate. A sequential strategy was utilized to compare the two agents for preventing hypotension during intrathecal anesthesia in cesarean birth, with an ED50 study estimating the relative efficacy of Norepinephrine to be 6:1 compared to Phenylephrine [9].

2.2. Polypharmacy Approach

2.2.1. Medication Mitigates or Amplifies the Side Effects of Another Drug

Drug interaction (DI) includes antagonistic, synergistic, and additive effects. Antagonistic effects arise when multiple medications are administered together, resulting in one drug reducing the effectiveness of another, which may lead to diminished therapeutic efficacy. Synergistic effects refer to interactions between

medications that have a more potent effect than when the treatments are delivered separately. This may be beneficial in specific circumstances but could also lead to heightened medication reactions. Additive effects refer to drug combinations that yield an effect equivalent to the cumulative impact of the individual drugs' effects. In such instances, the overall pharmacological effect is foreseeable; yet, precise dosage adjustments remain essential.

Remazolam, an innovative benzodiazepine sedative, is widely employed for the induction and maintenance of general anesthesia owing to its quick onset and hemodynamic stability. Nevertheless, clinical practice often experiences deleterious effects following intubation, including hypertension and tachycardia. Cyclobenzaprine demonstrates a synergistic sedative effect in conjunction with remazolam. A little dosage of cyclobenzaprine (ED50 0.182 mg/kg) can alleviate reactions generated by tracheal intubation with remazolam, while preserving hemodynamic stability [10]. Pan Yangyang *et al.* demonstrated that [11] the ED50 for respiratory depression caused by sufentanil in the absence of esketamine was 0.152 μg/kg. At a subanesthetic dosage of esketamine at 0.25 mg/kg, the ED50 for respiratory depression caused by sufentanil rose to 0.199 μg/kg. Nonetheless, an anesthetic dosage of esketamine at 0.5 mg/kg resulted in a reduction of the ED50 for respiratory depression caused by sufentanil to 0.109 μg/kg. The ED50 of respiratory depression induced by sufentanil diminished to 0.109 μg/kg with a combination anesthetic dosage of 0.5 mg/kg of esketamine. Consequently, minimal dosages of the non-opioid analgesic esketamine enhance respiration without diminishing the analgesic efficacy of opioids, mitigate the respiratory depression induced by opioids, and elevate the ED50 of the deleterious effects associated with sufentanil. The quest for optimal drug therapy efficacy may result in an increased incidence of undesirable effects associated with most medications. The examination of the dosage-response relationship indicates that efficacy marginally increases beyond half the effective dose, although unfavorable effects persist in escalating [12]. Attaining personalized medicine dosages to optimize benefits while mitigating risks and unwanted effects is indeed a problem.

2.2.2. ED50 of a Medication in Conjunction with Another Substance

The strategic amalgamation of diverse medications can markedly diminish the requisite dosage of individual drugs, thereby leveraging the synergistic advantages of various pharmaceutical agents to attain a result that is twice as efficacious while necessitating only half the effort and potentially mitigating side effects. Lidocaine, an amide local anesthetic, is frequently employed to anesthetize localized tissues. Research indicates that intravenous lidocaine at a dosage of 1 mg/kg can significantly decrease the half-effective concentration of propofol necessary to suppress somatic motility during cervical os dilation in abortions [13], the study utilized a propofol-targeted controlled infusion based on the Schnider model for anesthesia induction. It was categorized into two groups: the lidocaine group and the saline group. The lidocaine group employed a sequential upper and lower technique to ascertain the EC50 of propofol. In comparison to the control group, the admin-

istration of propofol was diminished by 13.3%, and the occurrence of injection pain associated with propofol was markedly reduced. The outcomes were positive with few side consequences. Dexmedetomidine nasal drops serve as a novel preoperative sedative that stimulates *α*2 receptors inside the central nervous system. In contrast to other sedatives, it offers tranquil and cooperative relaxation without inducing deep sedation, enabling patients to remain responsive to vocal instructions while preventing excessive drowsiness or loss of consciousness [14]. Midazolam is a benzodiazepine exhibiting anxiolytic, hypnotic, sedative, and amnesic properties. It alleviates anxiety and promotes sleep, beneficial for unconscious procedures, and soothes patients by diminishing agitation. A study on sedation for children undergoing magnetic resonance imaging utilized a combination of two drugs with sedative and hypnotic properties [15]. The ED50 and ED95 were established through a sequential method and probabilistic regression, allowing for a more efficient evaluation of drug efficacy with fewer cases. This process resulted in suggested dosages for both drugs that were lower than those in previous studies, devoid of respiratory adverse effects, so providing a more precise reference dose for pediatric clinical drug administration. This led to recommended dosages for both medications that were lower than those in earlier studies, without respiratory side effects, so offering a more accurate reference dose for clinical pediatric drug administration. The research conducted by Brendan Carvalho *et al.* [16] found that the ED50 and ED95 values for isobaric intrathecal bupivacaine combined with opioids were comparable to those previously reported for hyperbaric bupivacaine with the same opioid combination in a previous study by the same group. Furthermore, isobaric bupivacaine can effectively provide anesthesia for cesarean sections, yielding outcomes similar to those of hyperbaric bupivacaine, regarding the incidence of adverse effects. In the contemporary framework of multimodal analgesia [17], opioids and NSAIDs are integral to postoperative pain management. A study [18] has demonstrated that the ED50 for acetaminophen in postoperative analgesia is 2.1 grams, whereas for morphine it is 5 milligrams when both are combined. The ED50 for the combination is 1.3 grams of acetaminophen and 2.7 milligrams of morphine. The synergistic interaction between acetaminophen and morphine, resulting in an enhanced overall impact, is particularly advantageous for clinical anesthesiologists. Comprehending this additive effect enables the formulation of a more logical and efficient multimodal analgesic anesthetic strategy. Integrating acetaminophen with morphine may enhance pain management outcomes for patients. This method enhances the analgesic efficacy while concurrently decreasing the dosage of each medication, therefore mitigating the danger of bad effects. Thus, this knowledge enables anesthesiologists to customize anesthetic strategies that are safer and more efficient, thereby enhancing the overall quality of care for patients undergoing surgical operations. In clinical anesthesia, the administration of various pharmacological agents in conjunction can enhance patient comfort during surgical or diagnostic procedures and reduce the likelihood of adverse responses associated with the individual medications.

Furthermore, investigating the ED50 of these pharmaceuticals yields essential reference data for clinical application.

3. Personalized Pharmacotherapy: Clinical Variables Influencing ED50 (Sex, Age, Body Mass, Surgical Technique)

3.1. Patient-Specific Factors

Personal characteristics, such as the patient's age, physical health, body mass index (BMI), and the functionality of their liver and kidneys, are pivotal in establishing the effective dose for 50% of the population (ED50) of anesthetic agents. Drugs exert efficacy via many modes of action, including receptor stimulation, enzyme activity inhibition, and ion channel modulation. The varying mechanisms of action result in differing ED50 values based on the modes and intensities of target interaction, as well as the physical and chemical properties of the drugs. Additionally, drug interactions in combination influence their absorption, distribution, metabolism, and excretion in vivo, subsequently impacting the determination of ED50. A younger, healthier individual with a normal BMI and optimal liver and kidney function may necessitate a different dosage than an elderly patient or one with impaired organ function. Propofol is a highly lipophilic compound, and those with a lower BMI has reduced adipose tissue. Thus, the ED50 (the dose necessary for a 50% effective reaction) will exceed that of normal-weight patients, requiring an increased dosage of propofol to attain the equivalent sedative effect [19]. Sex hormones may have an effect on therapeutic efficacy, and as individuals age, drug distribution volume diminishes, resulting in lower plasma protein concentrations, reduced drug binding, and consequently elevated free drug concentrations, which enhances efficacy in older patients. Research [20] indicates that young and middle-aged women have a higher ED50 for successful sedation with Rimazolam during painless gastrointestinal procedures compared to elderly women and male patients of equivalent age. Moreover, the majority of pharmaceuticals are metabolized via hepatic and renal routes, and any dysfunction in the patient's hepatic or renal systems may influence the drug's metabolism and excretion. Such conditions can modify the drug's concentration and duration of action in the body, hence affecting the ED50.

3.2. Procedural Elements

Various surgical procedures necessitate distinct anesthetic requirements. The duration of the surgery, the extent of trauma, and the site locati0n affect the required dosage of anesthetic agents. Prolonged and very traumatic treatments may require increased dosages of anesthetic agents to sustain anesthesia depth, whereas shorter procedures may require correspondingly lower amounts. The distribution of nerves and sensitivity at the surgical site influence the effectiveness of anesthetic agents, hence affecting the ED50. Thus, the careful selection of anesthetic agents and the dosage determination based on the surgical characteristics are essential for the seamless execution of the procedure.

4. Assessment of ED50 via Sequential Methodology

The experimental design for the clinical measurement of ED50 typically encompasses the fixed dose grouping technique, the up-and-down sequential approach, and the biased coin flip sequential method. The fixed-dose grouping method involves calculating the effective dose range from 0% to 100% based on existing data and preliminary experimental results. It identifies the minimum and maximum doses, typically dividing them into 5 to 8 groups, recording the efficacy rate of each group, and analyzing the dose-response relationship. This method is primarily utilized to assess the toxicity of a drug in pharmacology. The up-and-down sequential approach determines a dose value near ED50 based on reference data to initiate measuring. Commencing with the initial subject recruited in the trial, if the treatment proves helpful, the subsequent subject will be assigned to a dose group one grade lower; conversely, the dose group will be elevated by one grade until a minimum of six negative/positive crossover points are achieved. The sequential rule of coin toss design exhibits greater randomness based on the up-down sequential method. Designate the specific probability as P, and define the probability b as the effective probability odds ratio ($b = P/1 - P$). If the current subject's test result is negative, the subsequent subject will be advanced to the next dose group. If positive, there exists a stochastic probability of b persisting at the present dosage level, and a stochastic probability of $(1 - b)$ transitioning to the lower dosage group [21].

5. Implementation of an Artificial Intelligence Predictive Model

Advancements in precision medicine and artificial intelligence technologies enable the establishment of a more precise model for forecasting anesthetic medication doses through methodologies such as big data analysis and machine learning. This approach facilitates the tailored and accurate adjustment of anesthetic drug dosages, hence progressing clinical anesthesia towards safer, more efficient, and more exact methodologies. The machine learning (ML) method has attained significant success in the domain of personalized drug administration. It can be utilized to forecast plasma drug concentration, drug dosage, pharmacokinetic characteristics, and adverse drug reactions, and to develop a more refined customized drug delivery system. In the context of multi-center studies with large sample sizes, nonlinear correlations, many variables, or intricate interrelations across covariates, machine learning algorithms can attain superior accuracy and precision compared to traditional methods while also addressing the issue of missing data commonly found in clinical practice [22]. Target-controlled infusion (TCI) presently involves dose adjustments according to patient requirements and health conditions; however, artificial intelligence models represent a potentially transformative solution that could supplant TCI's existing functionality. These models can assimilate numerous clinical variables as inputs, facilitating automatic modifications that remain customized to the patient's immediate needs [23]. Nonethe-

less, incomplete, unstable, biased, or erroneous "black boxes" in AI data processing depend only on AI to render inaccurate judgments for the majority of healthcare practitioners lacking computer proficiency.

6. Summary

The half-effective dosage (ED50) of anesthetic agents has considerable therapeutic relevance. Investigating the ED50 of anesthetic agents in many clinical contexts might provide a scientific foundation for their judicious application. This method refines anesthesia procedures, improves anesthesia quality, and diminishes the likelihood of adverse reactions. Furthermore, recognizing the interactions and influencing aspects of medication combinations might enhance the implementation of personalized anesthetics. Nonetheless, the sample sizes in contemporary ED50 studies are limited, and several of these investigations focus on patient populations from particular regions and hospitals, despite the existence of simulation studies [24] indicating that a sequential method with a sample size of 20 - 40 can yield a stable estimation of the target dose, the generalizability of these study results requires further validation. The investigation of the half-effective dose of anesthetic agents presents significant potential for the advancement of clinical anesthesia and enhances patient safety and health.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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