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A Review on Novel Progressions in Intravenous (IV) agents for Anesthesia

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors red and approved the final manuscript.

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Review Article

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ABSTRACT

One of the main medical proficiencies involved with the procedure of patient's perioperative care before, during and after operation is anesthesiology. This field of science has made a lot of hopeful progression in detection of new, secure, impressive, and productive procedures for proper management of patients. The most effective sedative–hypnotic agents which categorized in titratable intravenous medication, have highest medicinal effect and the least side effects. Currently a high effort is employed for developing such drugs with central focus on improving the available drugs structures for modifying their pharmacokinetic (PK) and pharmacodynamic (PD) characteristics. Various drugs are investigating for achieving more progression which includes etomidate, midazolam analogues, and diprivan. One of the main approaches for investigating about the development of anesthesia agents is swift screening of related libraries of molecular structure which evaluate phenotypic or structural assays of anesthetic and receptor interactions of agents. Due to the recently high demands of clinical operations for more sufficient anesthesia agents, the progression of anesthetic agents is experiencing a new generation of advanced clinical trials. In this regard, the current study is trying to provide a brief look on the newest anesthetic drugs and novel developed procedures which simplify this objective. This comprehensive study reviews would clarify the novel technology of progression of drugs which do not have physical addiction effects, distinctive system of anesthetic drug delivery, and the novel failures of drugs and their facilities.

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1. INTRODUCTION

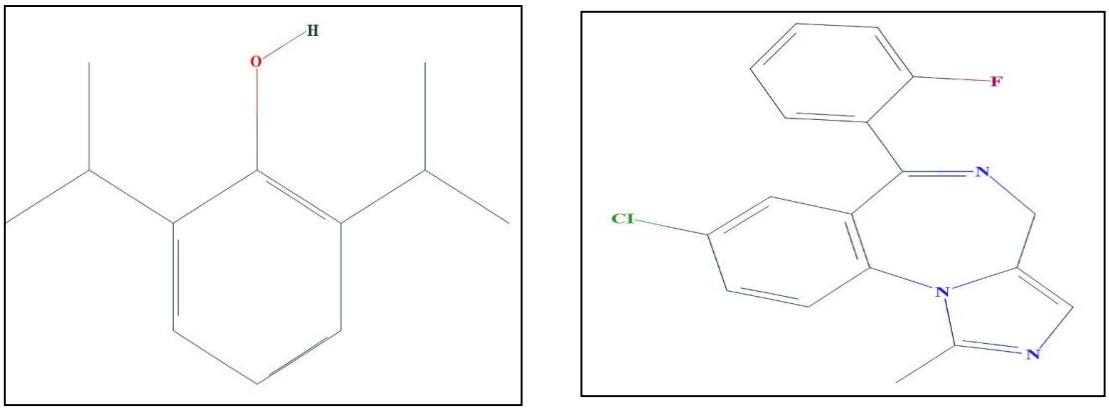
The decade of 1930 was the time when first generation of intravenous (IV) drugs for induction and maintenance of anesthesia were emerged. From that decade, benzodiazepines (benzos), dexmedetomidine, etomidate (amidate), propofol (Diprivan), and ketamine are known as the main productive intravenous sedative or anesthetic agents. On the other hand, researchers are trying to develop new chemical entity (NCE) and formulations of available remedies for improving security, productiveness, profile of recovery, action onset, and also increasing the capability of reduction side effects. The progression of novel agents is full of risk, costly and a bit challenging [1]. However, approximately just 10% of drugs in first step of progression would be able in earning Food and Drug Administration (FDA) acceptance [2]. It is while, some approved agents would be removed from the drug markets, due to unexpected disadvantage, side effects or other restrictions. One of the most productive technology as an investigating tool or a standard agent for anesthesia delivery worldwide is the technology of target controlled infusion (TCI). TCI development could provide the potential of increasing efficacy, dependability, safety, and accuracy of intravenous general anesthesia [3]. The aim of this comprehensive study is pointing out the novel progressions and defeats in innovation of remedies and devices and also introducing new systems of drug delivery.

Recently, due to large demands of clinical operations especially in emergency departments a swift progression has been happened in discovering and creating novel sedative and anesthetic agents. Those procedures which performed previously only in hospital operating theaters are recently applied in outpatient departments ever more in older patients with larger amount of considerable comorbidities. Additionally, the increased number of demands for more affordable and easier usage IV agents have enhanced the expectations for presence of nonspecialists in emergency cases and decreased the requirement for inhalational anesthetic equipment [4].

Hypothetically, these novel agents should be capable of providing swift titratable effects of sedation or/and anesthesia like swift onset of action and recovery and also reduce various side effects such as injection pain, cardiovascular depression, vomiting, and hypoventilation. However, any supposed advanced agents like these would have higher levels of therapeutic index and also be easily dissolved in an aqueous solution. But unfortunately, not any agents with all of aforementioned characteristics are available. Two of the most frequent sedative-hypnotics agents which commonly used by anesthesiologists are propofol and midazolam (Fig. 1). The two are the most sufficient and well approved agent in this regard [5].

Generally, propofol is applied for anesthesia purposes and midazolam for sedation and it should be noted that, the usage of both of them at appropriate doses would gain the most appropriate clinical outcomes. Propofol and midazolam could improve the inhibitory postsynaptic potential (IPSP) of type A gamma-aminobutyric acid (GABAA) receptors within the central nervous system (CNS) through simplifying the chloride ions diffusion to nerve cell and promoting channel opening [6]. The created changes in a cell's membrane potential could diminish the capability of these nerve cells for involving a possible action which would cause the depression of central nervous system. Although there are some similarities in deterministic or physical terms, these two drugs are assumed to stick to different sites on the type A GABA receptor and also modifying the receptor with diverse productivities [7,8].

The dissolving capability of midazolam in water is higher than propofol and also its pharmacological action is reversible. On the other hand, midazolam onset and duration of action is relatively short and slow respectively and also the recovery time would last due to the presence of active drug metabolites [9]. One of the most dangerous side effects of midazolam is hypoventilation which would occur even in doses adequate for causing deep anesthesia or sedation that has induced a lot of fatalities at the first market entry. On the other hand, propofol has a quicker onset and shorter recovery time in comparison with midazolam. Additionally, propofol would cause considerable respiratory and hypotension depression, especially in patients who are too old or severely ill [10]. Unlike midazolam, propofol would not be dissolved well in water and commonly produce an emulsion which provide the proper growth of bacteria and its extended infusion probably induce metabolic acidosis syndrome. However, both of these agents known



Propofol **Midazolam**

Fig. 1. Two-dimensional chemical structure of propofol and midazolam. Derived in accordance with [4]

as effective sedative-hypnotic drug have significant advantages. The presence of the deficiencies which these agents have provided the motivation for novel anesthetic agents' development [11].

2. DEVELOPMENT OF NEW GENERATION OF AGENTS

The process of enhancing the quality of new generation drugs is concentrated mostly on improving the chemical structures of available agents. On the other hand, this procedure has the purpose of modifying agent's pharma-cokinetic, pharmacodynamic characteristics, and also removing all possible side effects. There are two main strategies for investigating around novel drug development that include scientific experimentation method of high-throughput screening (HTS) and rational design strategy. However, the main objective of this comprehensive study is to review available anesthetic agents and methods on discovering novel agents [12]. The present study is trying to review midazolam and propofol derivatives and their alternatives agents that have been prepared for improving their fundamental compounds.

3. RESEARCH STRATEGIES

In field of bimolecular engineering and, the strategy of producing novel molecules with a specific level of functionality, in accordance with their capability of forecasting the effectiveness of molecule's structure in modifying their functional behavior through physical models is known as rational design strategy. This strategy utilizes the biologic target structure information achieved from the technique of mathematical computational modeling studies and X-ray crystallography (XRC) for improving the structural design of available agents or producing novel ones [13]. The main objective of these investigations is to gain the most appropriate pharmacologic action of the drugs through amplifying the dependency to the target responsible. The availability of adequate structural information provides overall comprehend for cognizing the reasons that anesthetic agents stick to relevant protein targets. Unfortunately, due to the lack of accessibility to transparent information about anesthetic agents, these strategies have not been adequately applied. However, one of the main objectives is decreasing the dependency of agents to the target which is responsible for an unpleasant side effect [14].

On the other hand, this strategy has been applied for decreasing the interpolation of etomidate to steroid 11β-hydroxylase, therefore the capability of agent for repressing the synthesis of natural steroid hormones. The strategy of rational design is somehow that would modify an available drug for improving its aqueous solubility or pharmacokinetic characteristic. The strategy of rational design is somehow that would modify an available drug for improving its aqueous solubility or pharmacokinetic characteristic. Herein, the limiting factor would be the lack of adequate information about the structure of drug molecular targets within the body [15]. The usual approach

is to combine a section of unstable ester with an available drug for creating a novel agent, which is sensitive enough for being hydrolyze through activity of plasma esterase. Consequently, the produced agent is capable of being metabolized faster, during intravenous therapy its titration would be done more easily and its action duration would be shorter. The term "soft drugs" comes from the fact that these agents are precisely designed for being metabolized swiftly. Cardioselective beta esmolol and remifentanil are two know drugs which are within the soft drugs category [16].

4. BENZODIAZEPINE (BENZOS)

One of the main agents which are frequently applied for anesthesiological objectives in clinical status is benzodiazepine that could be used as sedative–hypnotics, amnestics, and anxiolytics [6]. Due to the fact that these agents would cause cardiovascular depression and also lengthen the recovery time, at the common dosage needed for yielding anesthesia, they are not used as agents of induction of anesthesia much as before [17]. Midazolam is one of the best known agents from benzos family drugs which are frequently applied by anesthesiologists due to the fact that it has a partly short duration of action. Anyway, there is always a need to for effective shorter-acting agents which could gain deeper levels of sedation during procedures while achieving quick and foreseeable recovery. Anyway, the main agent in this group which is aimed to be investigated is remimazolam [18].

5. REMIMAZOLAM

One of the most frequent derivatives of benzos drugs is remimazolam which is developed by specialty pharmaceutical company of PAION as a sufficient alternative remedy to midazolam for conscious sedation and anaesthesia induction for minimally invasive medical procedures. The most popular facilities of remimazolam in comparison with midazolam are swift action and lasting only a short time. On the other hand, clinical examinations proved that this agent has a predictable and faster recovery time, has more regular pharmacokinetics and also has more advantages than other available related agents (Fig. 2) [19].

Midazolam is broadly applied as sedative and anxiolytic which has played its part as a beloved sedation and also used for patients care in a diversity of inpatient and ambulatory surgery procedures. Several disadvantages of midazolam application are such as extended time of recovery and deficiency of analgesia especially in patients who suffer from hepatic disease. However, this drug is novel, with a swift onset, located within the amino ester class that provides the capability of esterase-mediated metabolism which is independent of enzymes and function of liver or kidneys [20]. Remimazolam is created from combination of two well-known agents of remifentanil and midazolam and has the properties of two of them together. Just alike midazolam, remimazolam could easily act on GABA receptors and also represent pharmacokinetic characteristic joint with the pure μ-opioid receptor agonist of remifentanil.

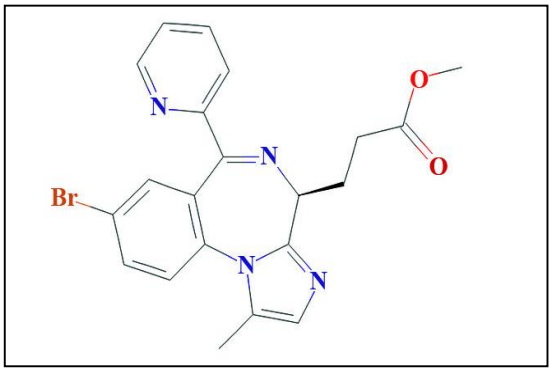


Fig. 2. Two dimensional chemical structure of remimazolam. Derived in accordance with [19]

The combination of benzos and remifentanil create a powerful mixture that is rich of properties of two of them with enhanced quality of anxiolysis and sedation. The tissue hydrolase enzyme esterase (carboxylesterases) immediately clear remimazolam. Carboxylesterases (CESs) are the enzyme of carboxylic-ester hydrolase which catalyzes a chemical reaction of the form a carboxylate + H_2O an alcohol + a carboxylic ester. CESs take part in the metabolic processes of exogenous and endogenous compounds. On the other hand, CESs could considerably affect the esters metabolism of human enzyme of carboxylesterase 1 such as hCE-1 and hCE-2 [21].

It should be noted that happening accumulation after remimazolam injection would be dangerous

due to its immediate removal through special tissue hydrolase enzyme of esterase, that could change it to inactive metabolic of carboxylic acids. This new anesthetic drug could be reserved with selective GABAA antagonist of flumazenil like midazolam, and even after 120 minutes of injection, has a shorter context sensitive half-time of seven minutes [22]. In spite of the fact that the primary application of remimazolam was for procedural sedation, recently a lot of study have concentrated on the usage of this drug for the maintenance and induction of general anesthesia. Bevans *et al* [23] have investigated the possibility of applying remimazolam via inhalation lonely or in combination with remifentanil in a clinical trial. They reported that, remimazolam could notably empower the analgesic effect of remifentanil, diminish irritation of the lungs, decrease various damaging side effects of lungs such as bronchospasm. However, the safest and most effective dosage of remimazolam at a clinical trial of phase I was reported to be 0.075 to 0.2 mg/kg [23].

The most significant clinical applications of remimazolam are including quick onset of action and keeping the dynamics of blood flow stable. Despite the availability of some clinical trials around the advantages and disadvantages of remimazolam, some further information is needed for specifying the way that metabolism would be affected through extended injections [22].

6. ANALOGUES OF ETOMIDATE

Etomidate is one of the strongest imidazole-based anesthetic agents with quick onset with smallest amount of side effects on respiratory system and pressure of circulating blood with a high satisfactory therapeutic index [24,25]. Etomidate through improving the function of Gamma-Aminobutyric acid ($GABA_A$) receptors in the brain could produce adequate hypnosis and dependent [26]. Amongst general anesthesia which are applied clinically, Etomidate is a the most popular one, but unfortunately its application would account for distinguishing pharmacological aspects of etomidate like it is probability for producing myoclonus or keeping the stability of cardiovascular function [27] (Fig. 3).

At the first time of its progression, etomidate introduced as an antifungal drug, with powerful hypnotic capability and also sufficient therapeutic index. From 1970 decade, it was presented to the clinical operations and proved to be an adequate anesthetic agent within the operating theater and also a powerful sedative in the intensive treatment unit (ITU) due to that causing the least cardiovascular depression [28]. Afterwards, it was proved that continuous injection of Etomidate considerably increase the fatality rate in patients who are most seriously ill through terminating the synthesis of adrenocortical hormone and preventing the activity of steroid 11β-hydroxylase [29,30]. Due the presence of this adverse effect, the application of etomidate as a continuous infusion agent has become restricted. It is while before the start of surgical treatment especially amongst old patients, for anesthesia purposes, Etomidate still in use [31]. Some researchers have reported that the application of etomidate even in single doses could cause adrenocortical suppression which would increase the mortality rate. Consequently, there are a lot of recommendations on eliminating the application of Etomidate completely [32].

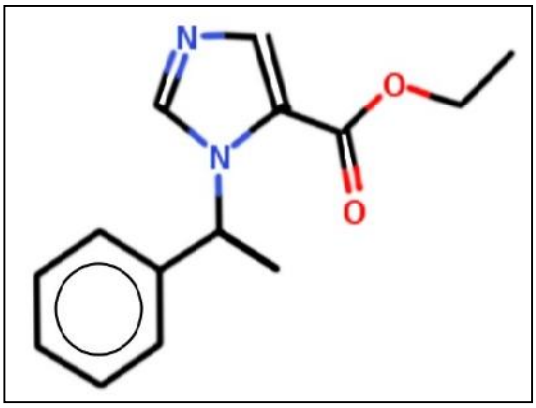


Fig. 3. Two dimensional structure of Etomidate as a derivative of imidazole capable of quick onset, hypnotic and with general anesthesia characteristics. Derived in accordance with [27]

The process of drug progression is aimed to maintain the most appropriate properties of etomidate and also simultaneously keeping any vital adrenocortical function [33].

7. METHOXYCARBONYL ETOMIDATE (MOC-ETOMIDATE)

The initial soft derivative of etomidate is MOC-etomidate which its structure is shown in Fig. 4. MOC-etomidate contains an unstable ester

moiety which swiftly would be hydrolyzed via the hydrolase enzyme of esterase's for creating carboxylic acid metabolite (MOC-ECA) and also preventing prolonged adrenocortical suppression. The gained MOC-ECA has extremely lower soporific drugs, inhibitory potencies of adrenocortical hormone and also lower type A (GABAA) receptors than those of their basic compound have [33,34].

8. CARBOETOMIDATE

One of the pyrrole derivatives of etomidate which is not much powerful a suppressor of *in vitro* synthesis of cortisol in comparison with etomidate and also does not barricade *in vivo* production of steroid hormones is carboetomidate [36] (Fig. 5). The term "MOC-carboetomidate" signify the combination of the minimal carboetomidate adrenocortical suppression and quick MOC-etomidate metabolism. Compared with MOC-etomidate and exactly alike carboetomidate, water solubility of MOC-carboetomidate is low and also its onset of action is slow [36]. One the main advantages of carboetomidate is maintaining the potential minimum level of etomidate effect on function of cardiovascular system. But in contrast to etomidate, carboetomidate could not prevent synthesis of steroid hormones and also is not capable of enhancing production of inflammatory cytokine especially in animal case models of metabolic endotoxemia [37].

9. CYCLOPROPYL-METHOXYCARBONYL METOMIDATE (CPMM)

CPMM is a second-generation soft derivative of etomidate which could be metabolized swiftly and nowadays is applied in clinical trials (Fig. 5). CPMM is a new, strong and GABAA receptor positive allosteric modulators which proved to have favorable pharmacokinetic and pharmacodynamic indices in various clinical trials, somehow CPMM represents higher levels of hypnosis and effectiveness. Pejo et al. [38] demonstrated that infusion of CPMM is not context sensitive due to the failure of its metabolite for reaching adequate concentrations in either cerebrospinal fluid (CSF) or blood which is satisfactory for creating hypnotic effect.

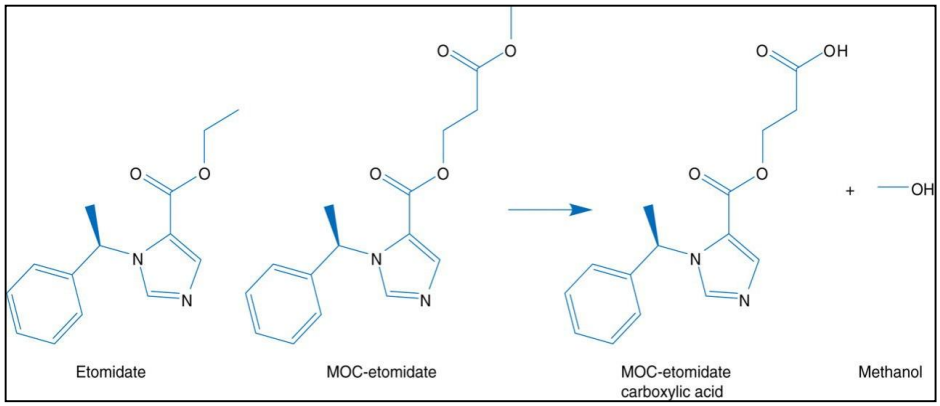


Fig. 4. Etomidate, MOC-etomidate and MOC-etomidate carboxylic acid (with an inactive metabolite).Derived in accordance with [35]

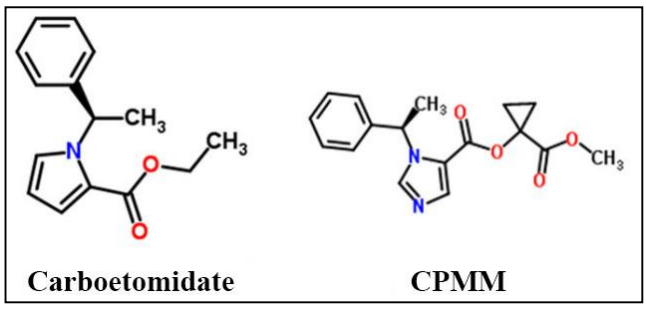


Fig. 5. Two dimensional structures of caeboetomidate and CPMM. Derived in accordance with [39]

10. DERIVATIVES AND MODIFICATION OF PROPOFOL AGENTS

One of the main derivatives of hypnotic alkylphenol as an organic compound is propofol (Fig. 6). It is adjusted for intravenous injection that could provide hypnosis and sedation during anesthesia procedure. On the other hand, propofol through simplifying repressive process of neurotransmission resolved through gamma-aminobutyric acid (GABA). Propofol cause the lowest level of respiratory depression, has a swift onset of action, and benefits from short biological half-life and the least side effects [40].

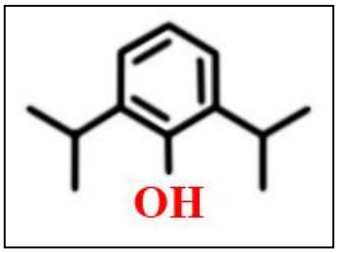


Fig. 6. Two-dimensional structures of propofol agent which aim HCN channels. Derived in accordance with [40]

Anyway, alike any other agents, propofol have several significant disadvantages including; propofol oily suspended emulsion increase risk of hyperlipidemia and bacterial pollution. One other is that, the intravenous injection of propofol agent would cause considerable amount of pain and possibly increase the risk of critical propofol infusion syndrome (PRIS). Due to the presence of aforementioned challenges, there is a great will for expanding previous drugs formulations and also discovering novel alternatives for enhancing the pharmacologic index and also defeating some of these disadvantages [41].

Nowadays, a lot of anesthetic agents are going through clinical progression which is altered for improving the characteristics of propofol. Anyway, there is not any perfect agent which could absolutely satisfy the procedure. 2,6-disubstituted alkylphenols with improved anesthetic indices are one of the most significant instances of novel propofol modification and appears to meet demanded properties of anesthetic agents. However, the sedation assessment of this novel formulation proved that it is more powerful and also have a quicker onset of action and predictable recovery in comparison with propofol [42].

One of the most annoying problems about propofol is, the pain during injection which not a new matter and would be seen in about 60% of cases [43]. It should be noted that, the injection pain is classified as one of the most painful anesthesia procedures in outpatient clinics [33]. But unfortunately, the main pain mechanism of propofol injection is not known exactly. Within their study Wang et al. [44] reported some potential factors which could affect the occurrence and intensity of pain that are including: the age of patient, pretreatment drugs, propofol concentration, injection rate, equipment of Intravenous infusion, temperature, menstrual period and also retinal vein occlusion [44].

In spite of existence of all aforementioned challenges, some modifications could be done on the formulation of propofol emulsion for defeating injection pain and probable risks of infection. Despite of that, propofol microemulsions are stable from thermodynamic point of view and could be produced easily, the injection of these emulsions would induce severe pain. Micro to macro (M2M) as an advanced procedure for destabilizing the propofol microemulsions straightly before intravenous delivery of it has been developed properly. Through this novel procedure more stability could be achieved and simultaneously the injection pain would reduce potentially [45].

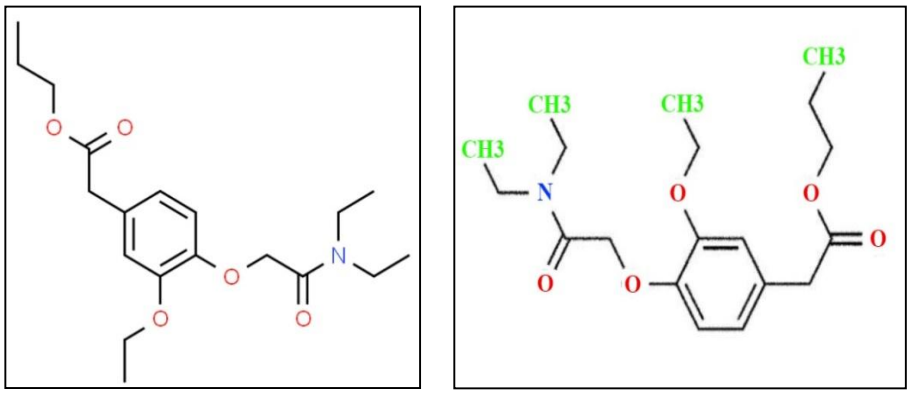
Additionally, by modifying the medium-chain triglycerides (MCTs) proportion within the propofol emulsion, the overall composition of propofol would be modified sufficiently and would be metabolized quicker than long-chain triglycerides (LCTs). The combination of LCT and MCT is a new formulation of propofol with an oily phase which provide the facility of dissolving large amount of propofol and also pain reduction [36]. PD and PK properties of propofol agent would not be affected via the new produced emulsion, the triglyceride would be eliminated in a higher speed and more pain reduction would be achieved during the propofol injection [46].

11. ALTERNATIVES OF PROPOFOL

All propofol alternatives are produced with the purpose of dominating propofol emulsion disadvantages like probable risk of infection and injection pain. Several agents with similar pharmacological properties like propofol are under research which is mentioned in Table 1. One of these derivatives, introduced from 1960

decade which has a close structure to propanidid is AZD-3043 that has a swift onset of action and is a sufficient sedative-hypnotic drug. In comparison with propanidid, AZD-3043 has an extra methylene group with an oily emulsion formulation, just alike propofol (Fig. 7) [41].

AZD-3043 could enhance the currents of $GABA_A$ receptor chloride ion channels and also prevent 35S-t-butylbicyclophosphorothionate (TBPS) binding $GABA_A$ receptors. On the other hand, AZD-3043 could be hydrolyzed swiftly in human liver microsome (HLM) [47]. During the application of AZD-3043 patients would represent the lowest level of injection pain. Additionally, in some cases, chest pain, erythema episodes, and shortness of breath following the injection would be experienced. However, for more accurate assessment of this agent, more clinical trials should be carried out [48].



Propanidid **AZD-3043**

Fig. 7. Two dimensional chemical structure of Propanidid and AZD-3043 as one of the main derivatives and/or alternatives of propofol agent. Derived in accordance with [41] and [47]

Table 1. Characteristics of several derivatives and alternatives of propofol in status of human trials pending. Derived in accordance with [41]

Agent	Chemical mixture	Advantages	Disadvantages
polymeric micelle of propofol [49]	An agent which is produced from formulating propofol in copolymers of Poly(N-vinyl-pyrrolidone)-block-poly(D,L-lactide) and and poly-oxyethylene esters of 12-hydroxystearic acid (Solutol HS 15)	Sterility, improved stability and spontaneous formation of micelles	Not specified (Due to the lack of data)
HX0969w [50]	Propofol phosphate esters prodrug just alike fospropofol (INN) but it release γ-Hydroxybutyric acid instead of formaldehyde	Swift onset of action, sterility and high aqueous solubility	Not specified (Due to the lack of data)
AZD‑3043 [48,51]	Have a chemical structure alike propanidid, sedative-hypnotic drug with short duration of action	Quicker onset of action, predictable recovery, lowest amount of pain during injection	Not soluble in water, with a formulation of oily emulsion, hypersensitivity intolerance
Alfaxalone [52,53]	Alfaxalone formulated in sulfobutyl ether (7)-β-cyclodextrin	PK characteristics is similar to propofol, cause lower amount of cardiovascular depression, eliminate the injection pain	Related safety thresholds have not been determined properly

One other of alternative anesthetic agents is alfaxalone with quick onset of action, short period of anesthesia and also equipped with swift predictable recovery which its first presentation was in clinical trials in 2015 year. The facility of being formulated in the sulfobutyl ether (7)-β-cyclodextrin making it possible to be dissolved in water easily [53]. The peak point of alfaxalone application was as a short-acting intravenous anesthetic agent was from 1970 to 1980 decades. The first human trial of alfaxalone demonstrated that, the anesthetic effects such as its recovery time and hypnosis effects were exactly alike propofol.

It is while, alfaxalone could induce less de-pression of cardiovascular system in comparison with propofol and also its injection produces less pain. But unfortunately, due to the fact that alfaxalone's solvent, Kolliphor EL, would cause hypersensitivity intolerance, the application of this agent was not continued [52]. However, more clinical trials are required for assessment of characteristics of this agent more precisely.

12. DEVELOPMENT OF DRUG DELIVERY SYSTEMS

The potential of being informed about concentration of anesthesia agents in patients who undergo a surgical procedure helps improving the monitoring of patient and also drug administration control. One novel procedure of delivering drugs to the predefined targets through the veins by means of a special pump and controlled by a computer in called target controlled infusion (TCI) which its main objective is to achieve a prespecified concentration of plasma. The main application of computer in this method is to compute the injection rate needed for achieving the demanded concentration as quickly as possible [3]. The technique of TCI is mostly applied for delivering infusing intravenous drugs persistently which is a field of anesthetic science.

This technique is mainly applied for remedial management of opioids agent for sedation and anesthesia purposes for patient satisfaction with procedural care worldwide. The pumps which are used for delivering agents to the specified targets, are updated to the second generation that make user capable of administering a preselected drug (for instance: remifentanil and propofol) through various pharmacokinetic procedures. One of the main things that will occur during each anesthetic drug delivery to the specified tissue is accumulation of agent within that tissue, which confuses the correlation of the injection rate and the concentration of the drug in the patient's body [54].

Consequently, for achieving and maintaining the concentration of drug at a steady state within the prespecified sites or plasma, there should be a device that assess the drug accumulation within body tissues and also control the rate of injection, which is TCI [55]. TCI device could easily adjust a prespecified serum blood level concentration based on some demographic characteristics of patients such as sex, height, weight, age, and PK derived models particular to a specific agent [49,50]. However, this novel technology could assess the concentration of any specified agents in the plasma and at the determined target constantly, and also make it possible for the clinician to adjust changes based on physiological or/and clinical indicators [56].

Recently, the technology of TCI is mainly based on controlling concentrations of plasma instead of concentrations of effect-site. It is while, Rinehart et al. [57] at their PD/PK modeling preferred the effect-site over the concentration of plasma for proving the fact that patient rousability corresponding with dexmedetomidine will indicate a clear response to repeated auditory stimulation.

Nowadays, the concentration anesthesia agents are evaluated in accordance with a model-based open-loop prediction, which could predict the concentration of applied agents through solving the multi-compartmental model of population-based patient PK and PD characteristics (Fig. 8). When there is not the capability of correction any feedbacks, the available variance among the real amount of PK of patients and the PK obtained from population-based model could be the main errors source in the process of assessment of drug concentration. In spite of its apparent disadvantage, the open-loop prediction procedure has been broadly applied, especially because of that there is not any dependable alternative methods [58].

The closed-loop system is enriched with more accurate dosing in comparison with the open-loop system, it could change the drug dosage based on various conditions, enhance the capability of controlling sedation and anesthesia depth, the consumption of drug will be decreased, the stability of dynamics of blood flow will be improved and additionally the fast and predictable recovery after the procedure will be achieved [59,60].

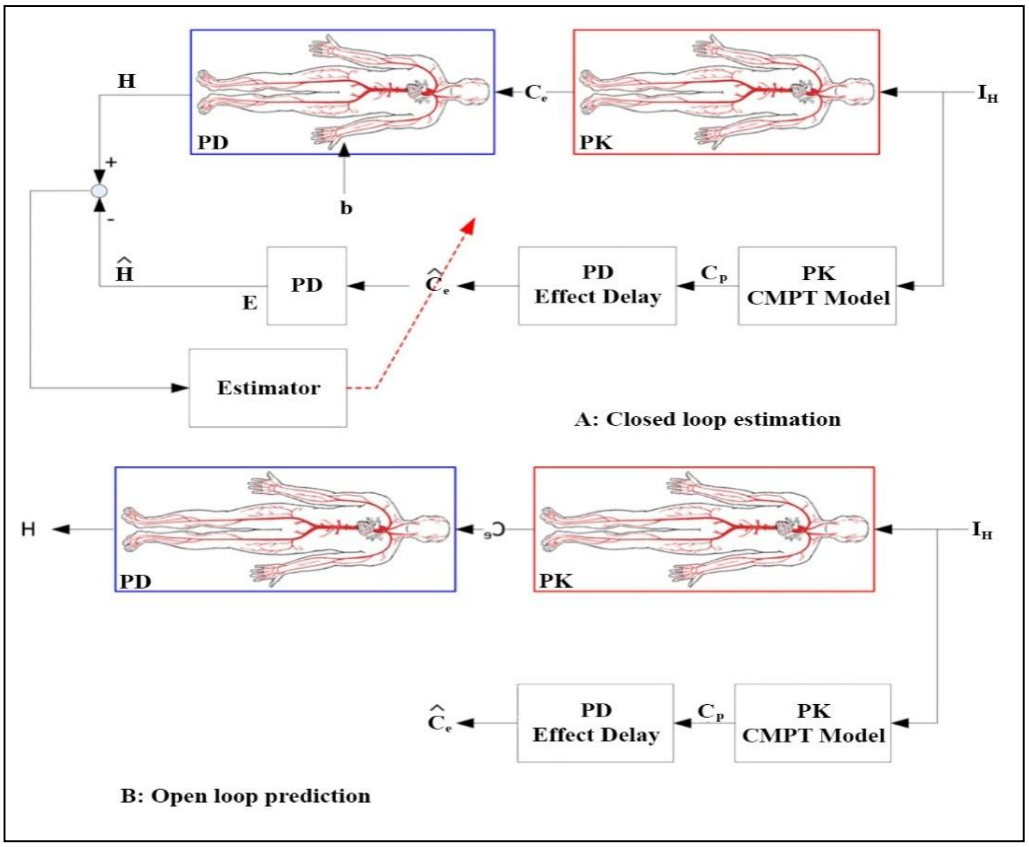


Fig. 8. Concentration of anesthesia drug closed-loop estimation versus open-loop prediction. Derived in accordance with [58]

13. CONCLUSION

The new produced anesthetics agents have been progressed by means of the aimed moderation of available chemical compounds such a way that enhance their quality of PK and PD characteristics. Through adding an ester linkage to the parent chemical compound of available agents, while improving their PK characteristics, some soft drugs could be produced which are more susceptible to the metabolisms of nonspecific esterase within the bloodstream. However, as an instance of prototypical soft drugs is esmolol and remifentanil and examples of novel anesthetic agents are MOC-etomidate and remimazolam which are produced through this method. Additionally, modifying the structure of parent chemical compound for changing its PD characteristics would be administered as an alternative procedure, as applied for derivative carboetomidate agent from its parent's compound. Development of new generation of drugs and drug delivery procedures would improve anesthesia quality during procedural operations. For achieving this aim, comprehensive advanced clinical trials are required for enhancing safety and the most considerable level of evidence prior to performing extensive clinical operations.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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