A "Smart" Biosensor-Enabled Intravascular Catheter and Platform for Dynamic Delivery of Propofol to "Close the Loop" for Total Intravenous Anesthesia

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ABSTRACT

Background:

Target-controlled infusion anesthesia is used worldwide to provide user-defined, stable, blood concentrations of propofol for sedation and anesthesia. The drug infusion is controlled by a microprocessor that uses population-based pharmacokinetic data and patient biometrics to estimate the required infusion rate to replace losses from the blood compartment due to drug distribution and metabolism. The objective of the research was to develop and validate a method to detect and quantify propofol levels in the blood, to improve the safety of propofol use, and to demonstrate a pathway for regulatory approval for its use in the USA.

Methods:

We conceptualized and prototyped a novel "smart" biosensor-enabled intravenous catheter capable of quantifying propofol at physiologic levels in the blood, in real time. The clinical embodiment of the platform is comprised of a "smart" biosensor-enabled catheter prototype, a signal generation/detection readout display, and a driving electronics software. The biosensor was validated in vitro using a variety of electrochemical methods in both static and flow systems with biofluids, including blood.

Results:

We present data demonstrating the experimental detection and quantification of propofol at sub-micromolar concentrations using this biosensor and method. Detection of the drug is rapid and stable with negligible biofouling due to the sensor coating. It shows a linear correlation with mass spectroscopy methods. An intuitive graphical user interface was developed to: (1) detect and quantify the propofol sensor signal, (2) determine the difference between targeted and actual propofol concentration, (3) communicate the variance in real time, and (4) use the output of the controller to drive drug delivery from an in-line syringe pump. The automated delivery and maintenance of propofol levels was demonstrated in a modeled benchtop "patient" applying the known pharmacokinetics of the drug using published algorithms.

Conclusions:

We present a proof-of-concept and in vitro validation of accurate electrochemical quantification of propofol directly from the blood and the design and prototyping of a "smart," indwelling, biosensor-enabled catheter and demonstrate feedback hardware and software architecture permitting accurate measurement of propofol in blood in real time. The controller platform is shown to permit autonomous, "closed-loop" delivery of the drug and maintenance of user-defined propofol levels in a dynamic flow model.

INTRODUCTION

Target-controlled infusion anesthesia (TCIA) has been used worldwide for decades to provide user-defined, stable, blood concentrations of propofol (2,6-diisopropylphenol) for conscious sedation and general anesthesia.[1–3] The drug infusion rate is set by a microprocessor-controlled syringe pump that uses population-based pharmacokinetic data and the patient's biometrics to estimate (i.e., "target") the required infusion rate to replace losses from the blood compartment due to drug distribution and metabolism.[4–6] To date, the U.S. Food and Drug Administration (FDA) has not permitted the use of autonomous drug delivery by TCIA in part because the

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No animals or human subjects were used in the performance of these studies. Referenced studies and data presented in this manuscript utilized anonymized, pooled human blood samples from a commercial vendor.

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level of the drug in the blood, although targeted by validated algorithms, is not known. There is a relatively narrow therapeutic window for the drug; thus, the risk of hypotension from overdosing, or unrecognized consciousness from underdosing during its intended use as a sedative or general anesthetic, is a safety concern for patient care.

Biosensors are an interface between biological and electronic systems that convert specific chemical information into quantifiable electronic signals (e.g., glucose sensors for diabetes).[7,8] Previously, to detect and quantify propofol in biological samples, liquid/gas chromatography and mass spectroscopy methods were required. We present here the "smart" biosensor and the design of a first-in-class propofol delivery platform technology and delivery method that permits real-time quantification of intravenous propofol levels and the potential for autonomous propofol drug delivery by using only a small footprint device. The biosensor and its feedback control were previously validated using a benchtop flow analytical system that modeled propofol pharmacokinetics and were shown to be capable of fine-tuning the propofol delivery rate to align the concentration to a preset value accurately, in an experimental closed-loop drug delivery model. Our work has shown that the biosensor has, in a wide range, linear dependence on the drug concentration and permits the determination of nanomolar concentrations using electrochemical (EC) methods.[9–11]

The objective of the research was to develop and validate an in vitro method to detect and quantify propofol levels in the blood, in real time, to improve the safety of propofol use and demonstrate a pathway for FDA regulatory approval of TCIA for its use in the USA. Inherent in the development of in vivo sensing technology is a feedback loop and controller method that may permit a "closed-loop" anesthesia method (total intravenous anesthesia, TIVA).[11,12]

METHODS

Reagents

Propofol [2,6-Diisopropylphenol] as a pure chemical was purchased from Sigma-Aldrich (St. Louis, MO) and prepared as a 10 mM stock solution in 0.1 M NaOH. Studies were also performed using a clinical propofol emulsion (Diprivan, 10 mg/mL). Select results of studies using the clinical emulsion are indicated in the figures and are similar to the results using pure drug in vitro. This solution was diluted to a 1 mM secondary stock solution in phosphate buffer saline (PBS) for use in experiments. The PBS buffer (pH 7.2) was prepared as a mixture of 0.1 M KH_2PO_4, 0.1 M K_2HPO_4, 0.1 M KCl and 0.045 M NaOH.

The PVC (polyvinylchloride) membrane solutions were prepared as 250 mg quantities, consisting of ~25 wt% PVC, ~50 wt% plasticizer, ~22 wt% organic electrolyte, and ~3 wt% ion-exchange salt. This mixture was dissolved in 2.5 mL of tetrahydrofuran. The PVC (high molecular weight) and its plasticizers, 2-nitrophenyl octyl ether, bis(2-ethylhexyl) sebacate, and 1-octanol, were selectophore grade. The organic electrolyte, tetradodecylammonium tetrakis(pentafluorophenyl) borate, was prepared in our laboratory and the membrane solution was spin-coated on to the electrode surface.

Human blood used in these studies was obtained from a commercial vendor (Bioreclamation) and comprised pooled samples from anonymous donors. The protocol was approved by the DOD, Human Research Protection Office under the funded research projects listed.

Automated Flow Analytical System

We monitored propofol levels in flowing solutions using an EC flow cell in combination with a home-made Automated Flow Analytical System. The automated flow analytical system (AFAS) managed the sampling, the sample transport, the measurement, and data acquisition through a LabView-based software developed in our laboratory and previously published.[11] In batch experiments, cyclic voltammetry (CV) and chronoamperometric (CA) measurements were performed in a 3-electrode cell, using a CH Instruments model 900 potentiostat. For these measurements, Ag|AgCl|3.0 M KCl) and a platinum wire served as the reference and counter electrodes, respectively. The feedback control and monitoring system consisted of: (1) a dilution chamber with first-order exponential decay characteristics; (2) a flow-through EC cell to monitor the drug concentration in the dilution chamber; (3) a syringe pump for feedback-controlled drug delivery; and (4) a proportional–integral–derivative (PID) controller to drive the syringe pump to maintain the target drug concentration. The dilution rate was set using a programmable peristaltic pump.

For the CA measurement of propofol, 1.2 V was applied to the membrane-coated working electrode. The real-time signal of the biosensor was used as a feedback input for the PID controller to adjust the rate of drug delivered by the syringe pump to approach the preset targeted concentration of the drug in the dilution chamber. Before starting the feedback-controlled monitoring, the sensor was calibrated in propofol solutions by spiking continuously stirred PBS solution with propofol standard solutions. The parameters of the linear relationship between the measured current and the drug concentration were determined by linear regression analysis.

To simulate the concentration decay in a single-compartment model, a dilution chamber was used. A beaker with a known volume of solution acted as a dilution chamber in which the concentration decays exponentially upon constant influx of diluting solution, e.g., PBS. To model different pharmacokinetic decays of the drug, dilution chambers with different volumes and different dilution rates were used. The dilution rate was set by the revolution per minute rate of a programmable peristaltic pump. A constant solution level in the dilution chamber was set by positioning a suction tube to the required depth in the dilution chamber. The flow rate of the suction was always faster than the dilution flow rate, which

prevents the solution level from rising above the suction tube inlet. The content of the chamber is recirculated, transporting the fluid through the EC flow cell for continuous measurement of the drug concentration.

ANALYTICAL METHODS AND RESULTS

Our initial work demonstrated that the propofol molecule can be oxidized (electrons stripped from the molecule) by scanning the applied voltage between 0.8 and 1.6 V (CV), thus establishing the conceptual basis for a propofol biosensor. We showed that the drug concentration can be determined at sub-micromolar concentrations using the biosensor, and that there is a strong, linear, concentration-dependent, propofol signal using CV (Fig. 1) and other EC methods such as CA. We show here cyclic voltammograms recorded in increasing concentrations of propofol. The SD of replicate measurements is indicated as error bars on the individual points in the calibration curve which is constructed from the currents measured at the peak potentials (Fig. 1, inset).

The quantification of propofol was also possible in solutions containing 1% or 5% bovine serum albumin used as model solutions for human serum (Supplemental Figure 1). The detection limit for propofol using the membrane-coated sensor in PBS was $0.03 \pm 0.01 \mu M$. In serum-like electrolyte solutions containing physiologically relevant levels of albumin (5%), including 3 mM ascorbate and 1 mM acetaminophen as potential clinical interferents, the detection limit for propofol was 0.5 ± 0.4 μM. Both values are below the lower limit of the therapeutic concentration range (target concentration) used clinically during anesthesia and sedation.

The key innovation of the biosensor is the addition of a thin (∼1 micron) plasticized PVC membrane coating over the electrodes (Fig. 2). The PVC membrane contains about 66% plasticizer which acts as an organic film. This organic plastic coating is highly hydrophobic and excludes charged hydrophilic ions, hydrophilic small molecules, and proteins from reaching the electrode surface, thus preventing the oxidation of electrochemically active interferents and biofouling by blood components. Conversely, many drugs like propofol are lipophilic in nature and possess a high octanol: water partition coefficient (logP), which is why they are highly protein bound in the blood. For example, the logP of propofol is ∼3.8, thus the bioactive, free drug partitions into the membrane (vs. the aqueous blood) at a ratio of $10^{3.8}$ or ∼6,300:1.

The biosensor actively partitions lipophilic drugs from the blood and other biological fluids into the membrane, permitting EC detection and quantification in real time. The signal is directly proportional to the concentration of propofol at the electrode in the plasticized PVC membrane. The hydrophobic nature of the membrane both enhances the detection of propofol and prevents biofouling. This selective enhancement of the analyte signal related to the chemical structure of the drug is the second key feature of the sensor. Because of the relative equilibria between protein-bound drug and rapid diffusion of the drug from the blood into the membrane, it permits direct measurement of the concentration of the free drug in the blood without any requirement for processing of the biologic specimen before analysis. The direct measurement of free drug in the blood represents a departure from the traditional determination of the total concentration of drug in the blood using mass spectroscopy or other laboratory analytical methods. An analogy is the correlation between total versus ionized calcium levels in clinical practice. It is the ionized calcium (not total calcium) that is the physiologically relevant form of blood calcium. Future clinical validation studies will be required to determine the relationship of the free drug measured by the biosensor to total drug levels, the effect of protein levels, and volume of distribution, and how they correlate with the bispectral index and other physiological readouts during anesthesia.

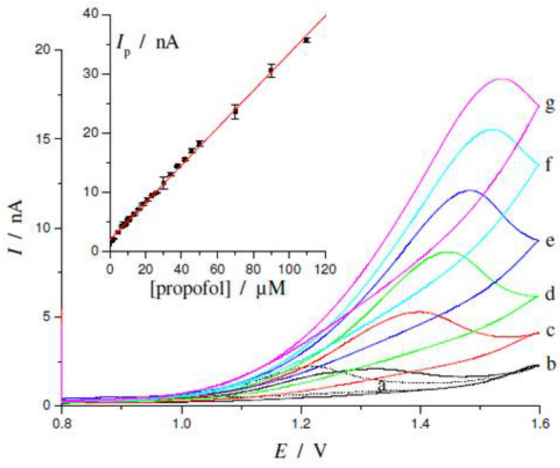

FIGURE 1. Cyclic voltammetric scans recorded with a PVC membrane-coated sensor in propofol solutions of different concentrations. Scan rate 0.1 Vs^{-1}. Concentrated Propofol, (a) 0 μM, (b) 2 μM, (c) 10 μM, (d) 21 μM, (e) 30 μM, (f) 42 μM, and (g) 50 μM in 0.1 M $NaKHPO_4$ + 0.1 M KCL pH 7.2. Inset: Calibration curve constructed from the peak current values.

Quantification of Propofol in Reagents and Biofluids Using a Flow System

The rapid CA response of the membrane-coated electrode in PBS spiked with 1.25 μM propofol is shown in Supplemental Figure 2. The analysis of small volumes of samples by flow injection analysis (FIA) is shown in Fig. 3. In FIA, small volumes of samples are injected into a continuously flowing carrier solution. In the experiment shown, the propofol concentration was semi-continuously monitored in samples prepared using physiological levels of human serum albumin from a commercial provider. The analyzed samples contained 6.0 μM propofol plugs injected in a continuously flowing buffer solution. The response of the biosensor to replicate sample injections in continuous FIA mode was found to be stable and reproducible.

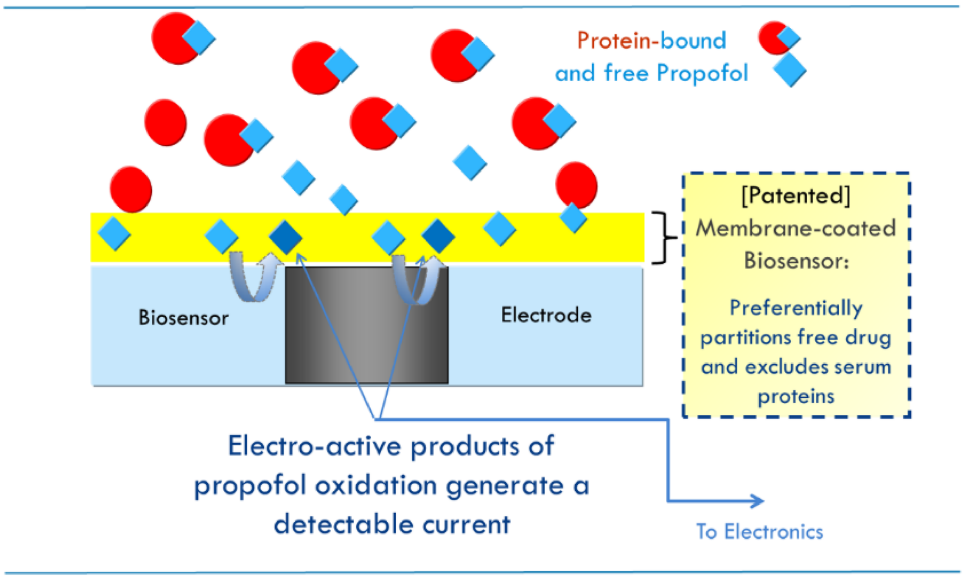

FIGURE 2. Design concept of the propofol biosensor. The plasticized hydrophobic membrane excludes hydrophilic components of the blood (e.g., protiens, other electrolytes, and partitions lipophilic drugs to the electrode surface according to their octanol:water partition and diffusion coeffficients. The drug is oxidized at the electrode to generate a current that is directly propotional to the free drug concentraction in the blood.

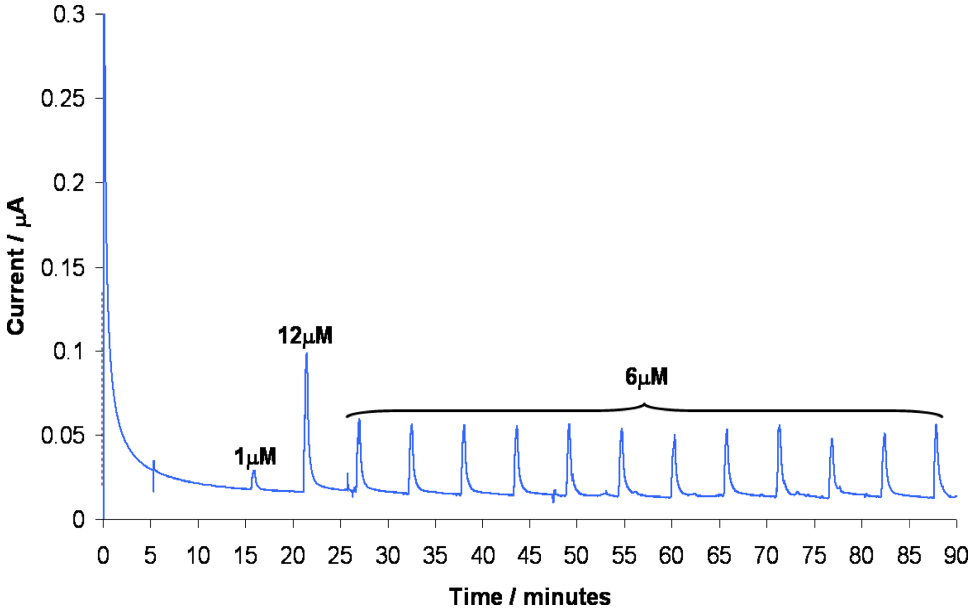

FIGURE 3. Chronoamperometric transients recorded by the membrane-coated biosensor following the injection of 175 μL propofol standards (1.0 μM and 12.0 μM, with 5% bovine serum albumin content). Samples with 6.0 μM propofol concentration in human serum albumin were measured in a continuously flowing buffer solution.

Determination of propofol levels was performed in 3 individual (anonymized) human blood samples containing propofol. Supplemental Table 1 shows a summary for a series of 3 unknowns quantified using either a calibration graph (left), or standard equation method (right). Each unknown was tested in the same manner, using the same biosensor. The actual concentration of these propofol-spiked samples was 4.98 μM. The level of error between the actual and measured/calculated value is low. The 2 methods are equivalent and demonstrate the ability to measure propofol directly in human blood.

Correlation with Mass Spectroscopy

The results of EC analysis is highly correlated with the results of the "gold standard" HPLC/MS (high pressure liquid chromatography/mass spectroscopy) method at all concentrations

of propofol tested in reagents and in complex biological fluids including human serum and blood, using solid-phase extraction methods (Supplemental Figure 3). But the EC method is simpler, faster, and the detection limit for propofol is well below the therapeutic levels of the drug for its clinical use for sedation. In addition, it permits continuous propofol monitoring in blood, whereas quantification using HPLC methods is ex vivo and requires a solid-phase extraction step. We believe that this is because of the relative equilibria between protein-bound drug and the very rapid diffusion of the drug from the blood into the membrane. Our group is investigating this equilibrium between bound and free drug and the levels measured by the biosensor to total HPLC/MS quantification to establish the correlation. In our published studies, there is a strong linear correlation in the range measured between 2.5 and 111.1 μM. The calculated limit of detection of 2 independent methods is between 5.09 and 11.41 μM. More recent data with carbon electrodes are significantly lower, in the nanomolar range.[13]

Quantification of Propofol Using an Intravascular Catheter Biosensor

The biosensor circuit has been prototyped as an intravascular catheter, designed to deliver the propofol drug by continuous infusion (TCIA) using validated algorithms for propofol delivery in use worldwide for over 20 years.[3,4,14] The biosensor is mounted on the external surface of the catheter and measures blood levels after completion of 1 body circulation by the drug. The current functional 3D-printed prototype is shown with a computer-aided design drawing of the integrated propofol biosensor and connector and the circuit on the external surface of the catheter (Fig. 4).

Supplemental Figure 4 demonstrates the CA response of an early catheter prototype to propofol emulsion in PBS. The calibration curves constructed from the corresponding steady-state current and concentration values show a linear response to propofol emulsion levels in the solution and rapid dynamic responses to changes in concentration.

Biosensor Performance in Flowing Systems: A Proof of Concept

Development and maturation of the technology have been performed in collaboration with a commercial design and manufacturing partner to finalize the embodiment of the biosensor. The design process has been divided into 3 verification and validation steps: (1) biosensor catheter design (above), (2) signal detection and readout display, and (3) driving electronics and infusion pump. The circuit design and signal output provided an opportunity to integrate with standard clinical monitors that are designed to collect and display information from diverse medical devices (RJ-45 connector). The biosensor design is a "plug-and-play" device that will work with standard anesthesia monitors in clinical use. This includes a graphical user interface (GUI) managed through an "app" on a tablet (not shown).

To build an integrated potentiostat and controller hardware platform (biosensor control module), we prototyped a microcontroller board. Input controls provide an interface to the microprocessor to set controller target thresholds. The device also features output controls for displaying concentration and modulation of the infusion syringe output. Inputs enable the target concentration to be set and maintained throughout the duration of use. The output of the controller enables the syringe to deliver the propofol infusion at a calculated rate, which is shown together with the real-time drug concentration. It functions to: (1) Read and amplify the signal from the controller, (2) process the drug concentration, (3) calculate the rate needed to maintain the targeted concentration (controller algorithm), and (4) maintain the targeted concentration level. The system features PID controls to set the gain and response of the rate of infusion. The biosensor control module prototype is a standalone device connected to the IV (intravenous) catheter with a shielded 6-stranded thin flexible cable to supply a potential between the working electrodes and the reference electrodes by sourcing current from the counter electrodes to 2 independently addressable biosensors opposite to each other on the catheter (to prevent signal blocking by apposition of 1 sensor pad to the vessel wall). The current is sensed using a simple analog feedback control circuit

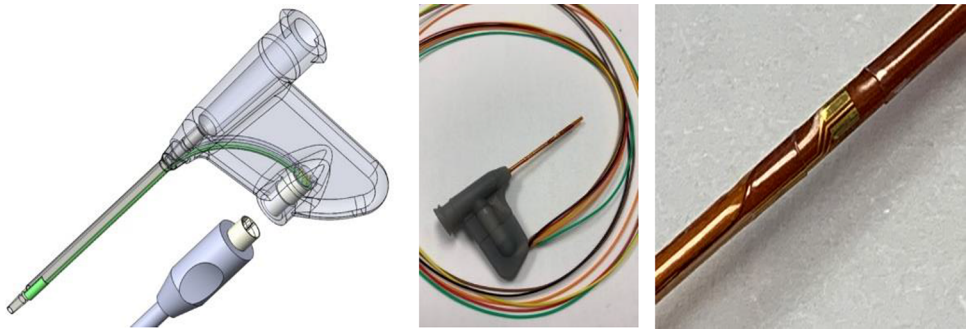

FIGURE 4. Intravascular catheter computer-aided design with integrated propofol biosensor and circuit connector (left). Functional 3D-printed prototype (middle) with higher magnification of the biosensor circuit on the external surface (right).

generating a voltage which is proportional to the propofol concentration. The voltage is digitized using a standard analog to digital converter and interfaced with a microcontroller. The microcontroller interfaces with a standardized monitor RJ-45 connector to show the propofol concentration to the anesthesiologist.

Benchtop Patient Model

The configuration is a 2-component benchtop prototype, a flow system and a measurement/ PID controller system. The flow system moves background material (PBS, serum, and blood) in and out of a beaker and into a waste container. The measurement system involves a detector that captures the different levels of drug (e.g., propofol) within the simulated "patient", (i.e., a beaker with both inflow and outflow to simulate drug delivery and dilution mimics the pharmacokinetic decay), and drives a PID controller to input additional drug to maintain target levels within the beaker.[15] The simulation involves the following steps:

- PBS is extracted from a beaker (a) by a "dilution pump" (b) to dilute a concentration of the organic compound (propofol or other) within a separate beaker (the "patient") (c).
- The dilution pump is set at a specific rate to simulate PK and dilution of the drug through its metabolism.
- A pump (d) extracts drug in solution from the "patient" beaker and passes the material through a detector via the automated flow analytical system (e), to measure the drug concentration in real time. A potential is applied to the working electrode to convert the drug concentration to a measured electric current.
- A potentiostat and a computer (f) enable the current to be measured, and the PID controller (g) determines if the current differs from a targeted threshold. The following formula measures the decay rate of the current as it pertains to concentrations of drug and reagent:
- $$C = C_o - e^{-t\left(\frac{w}{Volume}\right)}$$
- where C_0 equals initial concentration, t is equal to time, and w is equal to flow rate which is divided by volume.
- As the rate decreases exponentially from the diffusion of PBS in the beaker, the controller will add additional drug (i) into the beaker via a syringe pump (h). Fluid from the "patient" is moved into a waste beaker (j). A diagram and image illustrate the flow system and benchtop setup (Supplemental Figure 5).

Software and GUI

The concentration of the drug in the blood (in the "patient") is measured in real time by the sensor. The flow system dilutes the drug concentration according to its known PK. After it reaches a programmed target, the concentration of drug will then decay below the target threshold. Once this deviation is detected, additional drug is added to the "patient," causing the drug level to rise toward the target once again. Target and actual drug values are calculated in real time to maintain drug levels within a programmed error value, which is used as feedback into the controller. The PID controller maintains these concentrations throughout the experiment. The real-time control and reporting of propofol delivery is shown in the simulated "patient". The targeted level (white line, 20 μM) and actual propofol level measured by the biosensor (red line) are shown. The controller modulates propofol concentration by directing drug delivery from the syringe pump according to the measured drug level relative to the target value. A video demonstration of controlled modulation of drug levels can be seen at https://www.youtube.com/watch?v=wb0szheZcfQ.

An intuitive GUI has been developed to: (1) Detect and quantify the biosensor signal, (2) determine the difference from the targeted drug concentration, and (3) communicate the variance with the controller in real time using the modeled 'patient and known PK of propofol (published algorithms). The GUI is designed to enhance the ease of use for an open-loop drug delivery platform and shows a proof of concept for real-time control and reporting of propofol delivery in a closed-loop embodiment. A human factors-focused embodiment was prototyped. The green/yellow/red configured signal lights indicate the difference of the actual drug level from the target in real-time. As the variance increases beyond threshold values, the lights indicate the deviation from target (±<5%—green; ±5%-10%—yellow; ±>10%—red). An auditory signal is also provided. A video of the human factors GUI can be viewed online at https://www.youtube.com/watch?v=9xyUaIYVEBQ.

DISCUSSION

This paper describes this innovative, proof-of-concept intravenous propofol biosensor. Under completed DOD-funded projects, we have designed and prototyped a biosensor capable of detecting propofol at therapeutic levels in blood with high sensitivity and specificity for the drug signal. The biosensor design prevents biofouling and interference. The biosensor can be controlled through a laptop-based control module and data storage platform using prototype software algorithms. The performance characteristics of this propofol biosensor (sensitivity, specificity, accuracy, signal stability, and duration of action) have been published. There is a strong linear correlation between the propofol concentration measured by the biosensor and liquid chromatography analysis of propofol in human blood samples. Pilot studies to validate a closed-loop application of the biosensor and its feedback control software have shown the platform to be capable of directly controlling precise propofol delivery and drug concentration in a dynamic flow experimental closed-loop anesthesia delivery system in an autonomous manner; thus, demonstrating a proof-of-concept for TIVA.

Target-controlled infusion anesthesia systems attain desired plasma drug concentrations using the pharmacokinetics and pharmacodynamics of the drug.[14,16] Algorithms to achieve stable bioactive drug concentrations have been developed and are used to monitor the depth of anesthesia, correlated with the predicted blood and brain concentrations.[17,18] However, previously it has not been possible to quantify propofol in vivo, necessitating the use of algorithms that target drug levels. The technology presented is a proof-of-concept and provides the first method to do so. Numerous studies have compared the safety of TCIA for various forms of anesthesia, including general anesthesia, patient-controlled sedation, and military applications.[19–21] Many studies have documented excellent patient safety profiles for clinical parameters, including hemodynamic stability, apnea, and recovery times. Indirect propofol detection methods use bedside mass spectroscopy methods to measure propofol in breath (Xhale) or in blood (Pelorus) but never been brought to market. Indirect delivery methods such as Sedasys (J&J, now off the market) were protocols to improve the safety of continuous propofol infusions through indirect measures of sedation. Its use was not approved beyond monitored endoscopy and was not applicable to TCIA/TIVA because it did not measure drug levels. Experimental TIVA platforms to close the loop using bispectral index measures of consciousness to assist drug delivery have been proposed for decades but are indirect measures of the drug effect, not a quantification of the drug level in the body.[22–24] TIVA is routinely used by military medical providers for trauma care and sedation in austere environments, but no previous method has been sufficiently accurate or real time to permit TCIA approval by the FDA. A "smart" propofol biosensor may serve to address some of the issues to establish a formal regulatory pathway for FDA approval of TCIA and permit a "closed-loop" approach to the delivery of TIVA.

CONCLUSIONS

Under these projects, we have successfully validated in vitro, the proof-of-concept for a "first-in-class" intravascular biosensor that permits the delivery of propofol sedation in a manner that can meet these objectives. A small mass/cube portable medical device concept is shown (Supplemental Figure 6).

In addition to in-field care, effective sedation management is essential for critically ill patients on ventilators. Inadequate sedation can result in agitation, unstable hemodynamic status, risk for self-extubation, and injury to the patient. Many studies have shown that use of propofol sedation regimens reduce delirium, duration of mechanical ventilation, and length of stay in the ICU (intensive care unit) better than benzodiazepines[25,26] and more recently, similar or equivalent to dexmedetomidine.[27,28] As is being seen with COVID-19 pandemic, there is a critical need for a scalable solution to improving the sedation, management, and comfort of larger cohorts of patients by ICU care teams, to optimize clinical outcomes and survival. Biosensor and telemetry technology to deliver new methods of care in the ICU[29,30] (similar to what is currently being done with vital signs), represents an enabling technology that will also benefit civilian intensive care.

Military Relevance

The objectives of this research funded under the prior Department of Defense (DOD) grants; W81XWH-05-2-0064, W81XWH-10-1-0358, and W81XWH-13-C-0099, were to develop and validate a method to detect, quantify, and monitor propofol levels in the blood, and thus demonstrate the safety of TCIA drug delivery sufficiently to permit a pathway for FDA regulatory approval of its use for sedation and anesthesia. Inherent in the development of this technology is a feedback loop and controller method that may permit approval of the "closed-loop" anesthesia method (TIVA), currently used for trauma care and sedation in austere environments, for broader civilian clinical applications. The previously funded DOD grants supported the development of specific technologies applied to Deployment-Related Research Gaps. This included medical devices for use in-theater seeking "highly portable, autonomous or semi-autonomous systems, including decision-assist and closed-loop algorithms applicable over a wide range of physiological conditions." TIVA has become an integral part of combat anesthesia practice for trauma management and resuscitation for patients in austere environments. It offers significant clinical benefits and logistic advantages in the field, both in the battlespace and more established deployed settings.[31–33] Though in use, its current application may benefit from technology like that presented, that gives the care provider real-time knowledge of propofol drug levels to improve its safety for use in patient care. Like end-tidal drug concentration used with volatile gas anesthesia, measuring the level of propofol in the blood in real time will confirm delivery of the drug to the patient, and provide a measurable blood level useful to the provider, in addition to the physiologic changes in the vital signs that occur during delivery of anesthesia. It may also benefit the use of propofol in the setting of hemorrhage when the drug dosing may need to be reduced to achieve the intended clinical response.[34]

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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CONFLICT OF INTEREST

Dr. Chaum has a declared equity interest in Infusense, a startup company with the license to commercialize the technology presented in this manuscript.

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