

A Phase 1, Single-center, Double-blind, Placebo-controlled Study in Healthy Subjects to Assess the Safety, Tolerability, Clinical Effects, and Pharmacokinetics–Pharmacodynamics of Intravenous Cyclopropyl-methoxycarbonylmetomidate (ABP-700) after a Single Ascending Bolus Dose

Michel M. R. F. Struys, M.D., Ph.D., F.R.C.A., Beatrijs I. Valk, B.Sc., Douglas J. Eleveld, Ph.D., Anthony R. Absalom, M.B.Ch.B., F.R.C.A., M.D., Peter Meyer, M.D., Ph.D., Sascha Meier, M.D., Ph.D., Izaak den Daas, Ph.D., Thomas Chou, Ph.D., Kai van Amsterdam, M.Sc., Jason A. Campagna, M.D., Ph.D., Steven P. Sweeney, B.Sc.

ABSTRACT

Background: Cyclopropyl-methoxycarbonylmetomidate (ABP-700) is a new “soft” etomidate analog. The primary objectives of this first-in-human study were to describe the safety and efficacy of ABP-700 and to determine its maximum tolerated dose. Secondary objectives were to characterize the pharmacokinetics of ABP-700 and its primary metabolite (cyclopropyl-methoxycarbonyl acid), to assess the clinical effects of ABP-700, and to investigate the dose–response and pharmacokinetic/pharmacodynamic relationships.

Methods: Sixty subjects were divided into 10 cohorts and received an increasing, single bolus of either ABP-700 or placebo. Safety was assessed by clinical laboratory evaluations, infusion-site reactions, continuous monitoring of vital signs, physical examination, adverse event monitoring, and adrenocorticotrophic hormone stimulation testing. Clinical effects were assessed with modified observer’s assessment of alertness/sedation and Bispectral Index monitoring. Pharmacokinetic parameters were calculated.

Results: Stopping criteria were met at 1.00 mg/kg dose. No serious adverse events were reported. Adverse events were dose-dependent and comprised involuntary muscle movement, tachycardia, and ventilatory effects. Adrenocorticotrophic hormone stimulation evoked a physiologic cortisol response in all subjects, no different from placebo. Pharmacokinetics were dose-proportional. A three-compartment pharmacokinetic model described the data well. A rapid onset of anesthesia/sedation after bolus administration and also a rapid recovery were observed. A quantitative concentration–effect relationship was described for the modified observer’s assessment of alertness/sedation and Bispectral Index.

Conclusions: This first-in-human study of ABP-700 shows that ABP-700 was safe and well tolerated after single-bolus injections up to 1.00 mg/kg. Bolus doses of 0.25 and 0.35 mg/kg were found to provide the most beneficial clinical effect *versus* side-effect profile. (**ANESTHESIOLOGY 2017; 127:20–35**)

CYCLOPROPYL-METHOXYCARBONYLMETOMIDATE (CPMM, now ABP-700; The Medicines Company, USA) is a new intravenous anesthetic agent that currently is being developed for the induction and/or maintenance of general anesthesia and sedation in patients undergoing diagnostic or therapeutic procedures. ABP-700 is a second-generation analog of etomidate, a γ -aminobutyric acid (GABA) type A receptor agonist.¹ It contains an ester bond that is subject to rapid hydrolysis by nonspecific tissue esterases, a property that should result in a predictable dose–response relationship. The *in vivo* ester hydrolysis of the methoxycarbonyl moiety in ABP-700 generates a principle active metabolite, cyclopropyl-methoxycarbonyl acid (CPM acid), which is a 1,000-fold less potent activator of the GABA type A receptor compared to ABP-700.² This chemical approach to modulation of pharmacology has been used previously in approved drugs such as remifentanyl, esmolol, and clevidipine to cause rapid inactivation of

What We Already Know about This Topic

- The clinical use of etomidate is limited by variability in recovery times and inhibition of adrenocortical steroid synthesis
- Cyclopropyl-methoxycarbonylmetomidate (ABP-700) is an etomidate analog that undergoes rapid hydrolysis by nonspecific tissue esterases and does not produce prolonged inhibition of steroid synthesis in animal models

What This Article Tells Us That Is New

- In a first-in-human study, cyclopropyl-methoxy-carbonyl-metomidate (ABP-700) was safe and well tolerated up to a maximum tolerated bolus dose of 1.0 mg/kg
- Onset of hypnosis after bolus administration was rapid as was recovery
- APB-700 did not cause cardiovascular depression, centrally induced respiratory depression, or suppression of the physiologic response of the adrenal axis to adrenocorticotrophic hormone stimulation
- Involuntary muscle movements were observed at doses of 0.175 mg/kg and greater

the compound. This approach also is being applied to sedative-hypnotics to create so-called “soft analogs” that show faster pharmacokinetics and a high therapeutic index.^{3,4}

Etomidate was introduced into clinical practice to induce and maintain the hypnotic component of anesthesia while preserving hemodynamic and respiratory stability.⁵ However, large population variability in recovery times and significant suppression of adrenocortical steroid synthesis has limited its clinical use.⁶ In an attempt to eliminate these side effects while retaining its beneficial cardiovascular and respiratory profile, various new analogs of etomidate have been synthesized and tested in preclinical and animal settings.² Of these, ABP-700 showed promising pharmacology in rats.⁷ When tested in beagle dogs, it was observed that recovery after ABP-700 was rapid both after single-bolus and continuous infusion.¹ Also, adrenocortical recovery occurred within approximately 90 min, which is not significantly different from propofol.¹

In this article, results from a first-in-human, Phase 1, single-center, double-blind, placebo-controlled study of ABP-700 after a single ascending bolus dose are reported. The primary objectives were to describe the safety and efficacy of ABP-700 and to determine its maximum tolerated dose (MTD). Secondary objectives were to characterize the pharmacokinetics of ABP-700 and its primary metabolite (CPM acid), to assess the clinical effects of ABP-700, and to investigate the pharmacokinetic–pharmacodynamic relationships. We also tested the influence of a single-dose fentanyl pretreatment on the clinical and side effect profile with two of the most promising ABP-700 dosages.

Materials and Methods

Study Management and Registration

This trial was conducted at the QPS early Phase 1 unit, Groningen, The Netherlands, in cooperation with the Department of Anesthesiology at the University Medical Center Groningen, University of Groningen, The Netherlands, in accordance with the Declaration of Helsinki, in compliance with good clinical practice and applicable regulatory requirements. Ethics committee approval was obtained (Medische Ethische Toetsings Commissie Stichting Bebo, Assen, The Netherlands,

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NL48312.056.14, being the responsible ethics committee for QPS), and the study was registered at a public registry (Dutch Trial Register, NTR4545) before the start of the study. All volunteers provided written informed consent before participation.

Subjects

Healthy nonsmoking men and women aged between 18 and 45 yr with a body mass index (BMI) between 17.5 and 30 kg/m², American Society of Anesthesiologists physical status of I or II, and without risk of a difficult airway (modified Mallampati score I or II) were eligible for this study. Women were included if they were of nonchildbearing potential, *i.e.*, had to have undergone one of the following sterilization procedures at least 6 months before the first dose: hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy, hysterectomy, bilateral oophorectomy, or be postmenopausal with amenorrhea for at least 1 yr before the first dose and have follicle-stimulating hormone serum levels consistent with postmenopausal status (follicle-stimulating hormone levels of less than 30 IU/l). Subjects were excluded in case of a history or presence of significant disease or disease risk. In addition, volunteers must have refrained from, or not anticipate, the use of any medication, alcohol, or (illicit) drug abuse. Participants should not have had surgery within 90 days before drug dosing, a history of febrile illness within 5 days before dosing, not have participated in another clinical trial within 90 days before dosing, and not be pregnant or lactating. Subjects with a history or presence of adrenal insufficiency as defined by serum cortisol level less than 6 µg/dl at screening also were excluded from participation.

Study Execution

This study was set up as a Phase 1, single-center, double-blind, placebo-controlled, single ascending-dose study of ABP-700. In total, 60 volunteers were divided into 10 cohorts. In each cohort, six subjects received a single IV bolus dose of ABP-700 or placebo in a 5:1 ratio. The actual dosages of ABP-700 were 0.03, 0.10, 0.25, 0.35, 0.50, 0.75, and 1 mg/kg. The starting dose of 0.03 mg/kg was chosen as a conservative starting point based on preclinical efficacy and toxicology data and following guidelines from the European Medicines Agency (London, United Kingdom). Two cohorts of six volunteers received a single IV bolus dose of 0.25 or 0.35 mg/kg ABP-700 or placebo preceded by 1 µg/kg fentanyl in a 5:1 ratio. An additional cohort (cohort 10) of six volunteers was added, receiving a single IV bolus dose of ABP-700, 0.175 mg/kg or placebo in a 5:1 ratio to fine-tune the dose–response relationship.

Subjects were admitted to the clinical pharmacology unit 1 day before study drug administration. Subjects were required to fast for a minimum of 8 h overnight before study drug administration and continued to fast for at least 4 h thereafter. Water was not permitted from 2 h before until 1 h after dosing. Consumption of foods and beverages containing caffeine, alcohol, or grapefruit was prohibited 24 h, 48 h, and 10 days before

dosing, respectively, and throughout subjects' admission to the study facility. Before dosing, all subjects were transported to a dedicated treatment room equipped similarly to an operating room used in the University Medical Center Groningen that included monitoring equipment as well as respiratory support, including a tracheal intubation kit, anesthesia machine (Primus®; Dräger, Germany), and a fully equipped emergency "crash" cart immediately available. Subjects breathed room air before, during, and postdosing of ABP-700. In the event that an oxygen saturation (SpO₂) level less than 90% was not resolved by stimulation or jaw thrust, additional oxygen (5 l/min) was delivered *via* nasal prongs (Microstream®; Medtronic, Ireland). If required, brief manual ventilatory support was allowed with the use of a tight-fitting face mask. Before drug administration, two intravenous cannulas were inserted. The intravenous cannula for study drug administration was placed downstream of the arterial sampling and monitoring cannula, which was inserted into the radial artery after local anesthesia. The second intravenous cannula was placed in the opposite arm to draw the venous blood samples. All subjects received minimal crystalloid intravenous fluids during the drug administration period *via* the cannula for drug administration.

Because ABP-700 is derived from etomidate, a drug associated with involuntary muscle movements (IMMs), and because of the preclinical findings that ABP-700 also is associated with IMM, including myoclonic jerking,¹ midazolam was made available as safety medication at an initial 1-mg bolus dose for amelioration of severe myoclonus if observed. Additional midazolam doses of 1 mg could be administered at the discretion of the anesthesiologist-investigator. During the conduct of the study, a board-certified anesthesiologist was present throughout the dosing period until full recovery of the subject.

Subjects remained supine until recovery and were supine or semirecumbent in bed until the removal of the arterial line. When supine or semirecumbent, subjects were allowed to rise for brief periods under supervision. Subjects did not engage in strenuous activity at any time during the confinement period. Subjects were asked to avoid exercise 72 h before clinical laboratory tests at screening, check-in (1 day before dosing), and follow-up. Subjects remained in the clinic through completion of all scheduled postdose procedures on day 2 and returned for a follow-up visit 4 to 6 days after dosing.

After each cohort, the principal investigator (PI), sponsor, and ethics committee evaluated all available data relevant to the safety, tolerability, pharmacokinetics, and clinical effects of ABP-700 to proceed to the next dose level. Once an MTD was identified, no further dose escalation occurred. Stopping criteria for dose escalation were a grade 3 or higher dose-limiting toxicity event as defined in the September 2007 Food and Drug Administration Guidance*; SpO₂ less than 90% not

resolved by simple stimulation, jaw thrust, or supplemental oxygen administered *via* nasal prongs; any serious adverse events (AEs) that were considered by the PI to be related to study drug; and any clinically significant AEs that the sponsor and PI considered a safety concern. Because methanol is a byproduct of the ABP-700 metabolism and was detected during animal studies (data on file), it was indicated to search for significant changes in clinical or laboratory parameters indicative of methanol exposure with the potential for toxicity including, but not limited to, evidence of metabolic acidosis.

Primary Study Endpoints

Safety and tolerability of ABP-700 were assessed by evaluation of AEs, physical examination, safety laboratory tests (serum chemistry, hematology, arterial blood gas, urinalysis, and coagulation), serum methanol concentration, intermittent 12-lead electrocardiograms, temperature, and infusion-site reaction monitoring. Electrocardiograms were evaluated for PR interval, QRS interval, and QTcF interval. AEs were defined as the incidences of treatment-emergent adverse experiences per system organ class according to MedDRA (version 16.1; MedDRA MSSO, USA) from the period of arrival at the clinic up to the follow-up visit.

All volunteers were monitored continuously with a Philips MP50 monitor (Philips, The Netherlands) measuring continuous three-lead electrocardiogram and for heart rate, continuous pulse oximetry, noninvasive blood pressure every minute (at lower limb level), continuous invasive blood pressure *via* the radial artery cannula, respiration rate, respiration pattern, and end-tidal carbon dioxide (Microstream; Medtronic). High-frequency electronic data were captured from 1 min predose until 15 min after full recovery.

An adrenocorticotrophic hormone (ACTH) stimulation test was performed to evaluate the effect of ABP-700 on adrenal function. Screening and baseline cortisol levels were attained before 9:00 AM after 1-h rest in the supine position and after at least an 8-h fast. Adrenocortical stimulation commenced with an IV bolus administration of 250 µg synthetic ACTH 60 min after ABP-700 administration. Cortisol levels were measured at 1 and 2 h after ACTH administration. The MTD was reached when two or more volunteers met stopping criteria in any particular dosing cohort.

Secondary Study Endpoints

The clinical hypnotic-anesthetic drug effect of ABP-700 was evaluated by means of the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score, as shown in table 1. Clinical effect was defined as a MOAA/S less than 5. Onset of deep sedation/anesthesia was defined as the first postdose transition to a MOAA/S value less than 3 and offset of deep sedation/anesthesia as the transition to a MOAA/S value greater than 2. Duration of sedation/anesthesia was defined as the time between onset and offset. MOAA/S scoring was performed 1 min before dosing and at approximately 15 s, 30 s, 1 min postdose, and every minute thereafter for a

*Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials with the following exceptions: local injection-site reactions that are grade 2 or higher, bradycardia must be considered clinically significant, and QTcF change from baseline greater than 100 ms or total QTcF greater than 500 ms.

Table 1. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

minimum of 15 min after full recovery. Subjects were considered recovered when three consecutive MOAA/S scores of 5 were obtained. In addition, a processed electroencephalographic measure, the Bispectral Index (BIS), was applied as a continuous measure of cerebral drug effect. BIS (software revision 1.13; Medtronic) was derived from two-channel frontal electroencephalogram using an Fpz-F7 and Fpz-F8 referential montage and calculated with the BIS-VISTA monitor (Medtronic) using the bilateral electrodes BIS® Sensor electrodes (Medtronic). An average BIS value was calculated by use of data from the left and right BIS values. Electrode impedance was less than 5 kOhm. The smoothing interval of the BIS® monitor (Medtronic) was set at 15 s. BIS values range from 100 to 0, with lower values denoting more drug effect.

Pharmacokinetic–Pharmacodynamic and Clinical Effect Evaluation

The pharmacokinetics of ABP-700 and its metabolite (CPM acid) were studied. Arterial and venous blood samples were collected. Arterial samples were drawn before ABP-700 injection and at 0.5, 1, 2, 3, 4, 8, 12, 20, 30, 45, 60, 90, 120, and 180 min after ABP-700 injection. Venous samples were drawn predose, 1.5, 3.5, 7, 13, 21, 35, 75, 125, 185, 240 min and 6, 8, and 12 h postdosing. Blood samples were collected in prechilled Vacutainers (Becton Dickinson, USA) containing NaF/Na₂EDTA to inhibit nonspecific esterase activity (BD cat. No. 367587; Becton Dickinson). Samples were stored on wet ice for no longer than 30 min until centrifuged at 5°C for 7 min at 1,800g to separate the plasma. Plasma was transferred by the use of disposable pipettes into cryovials and placed immediately on dry ice until transferred to a –80°C freezer within a total allotted time of 60 min.

Plasma concentrations of ABP-700 and metabolite CPM acid were measured by high-performance liquid chromatography with tandem mass spectrometric detection using the SCIEX API 4000 LC/MS/MS System with a TurboIonSpray® interface (AB SCIEX, Canada) in positive mode at QPS.

Deuterium-labeled D5-ABP-700 and D5-CPM-acid were used as internal standards. To 0.05 ml plasma, the internal standard solution and acetonitrile were added. After mixing and centrifuging, part of the supernatant was transferred onto the Ostro Protein Precipitation and Phospholipid Removal Plate, 25 mg (Waters Chromatography B.V.,

The Netherlands). By the use of positive pressure, the supernatant was eluted and collected in a 96-well plate. Before analysis, a dilution step with Milli-Q ultrapure water (Merck Millipore, The Netherlands) and acetonitrile was applied. Liquid chromatography was performed on a C18 column (50 × 3.0 mm, 5 µm; Advanced Chromatography Technologies Ltd, UK) mounted in line with a 4 × 3.0-mm C18 guard column (Advanced Chromatography Technologies Ltd) on an Agilent 1100/1200 LC system (Agilent Technologies, USA). The column temperature was maintained at 50°C. The mobile phase A was 0.1% formic acid in water, and the mobile phase B was 0.1% formic acid in 50% acetonitrile. For sample elution, a gradient of 30 to 95% B was applied over a period of 1 min at a flow rate of 1 ml/min. The approximate elution times for ABP-700 and CPM acid were 2.1 and 1.7 min, respectively. The nominal mass transitions monitored were 315.2 to 211.1 and 301.3 to 197.0 *m/z* for ABP-700 and CPM acid, respectively. The method was validated over a concentration range of 5.00 to 1,250 ng/ml for ABP-700 and 25.0 to 6,250 ng/ml for CPM acid. Precision and accuracy were demonstrated for the validation samples within a single run of six aliquots (within-run for repeatability) and between different runs (between-run for reproducibility) distributed over at least 2 days. Validation samples were prepared in blank human NaF/Na₂EDTA plasma by spiking known concentrations of ABP-700 and CPM acid. For precision, acceptance criteria of coefficient of variation (CV%) not to exceed 20.0% at lower limit of quantification (LLOQ) or 15% at all other levels was met for all samples. For accuracy, acceptance criteria of percentage of relative error not to exceed 20.0% at LLOQ or 15% at all other levels was met for all samples. LLOQ for ABP-700 and CPM acid was determined at 5 and 25 ng/ml, respectively.

Noncompartmental pharmacokinetic analyses of concentration–time data of both arterial and venous plasma ABP-700 and its primary metabolite (CPM acid) were conducted with Phoenix® WinNonlin®, version 6.3 (Pharsight Corporation, USA). Only plasma pharmacokinetic profiles that contained more than five consecutive data points with a quantifiable concentration value were considered evaluable. Actual elapsed times from dosing were used to estimate all individual plasma pharmacokinetic parameters for evaluable subjects. Observed predose concentrations were set as missing to generate *C*₀ values, which were calculated as the extrapolated concentration at time 0 (computed for parent only). Systematic exposure was calculated with the area under the drug concentration–time curve. More detailed information on the applied methods to analyze the noncompartmental pharmacokinetics of the concentration–time data of plasma ABP-700 (both arterial and venous) and its primary metabolite can be found in Supplemental Digital Content 1 (<http://links.lww.com/ALN/B437>).

In addition, compartmental pharmacokinetic and pharmacodynamic models were developed with NONMEM (Icon Development Solutions, USA). The time course of ABP-700

was modeled with a three-compartmental pharmacokinetic model with volumes $V1$, $V2$, $V3$; elimination clearance CL ; and intercompartmental clearances $Q2$ and $Q3$. Arterial observations were related to the central compartment. Venous and metabolite concentrations were not used. All parameters were scaled linearly with total body weight. Mixing delay for the pharmacokinetic was set to 15 s. Residual error in pharmacokinetic observations was assumed to be proportional to the predicted concentration. Pharmacokinetic observations reported as lower than the LLOQ were ignored.

We modeled BIS using a sigmoidal E_{max} model driven by an effect compartment concentration (C_e) connected to the plasma compartment by a first-order rate constant ($ke_{0,BIS}$). The equation of the pharmacodynamic model was as follows:

$$\frac{dC_e}{dt} = ke_{0,BIS} \cdot (C - C_e)$$

$$Effect = E_0 + (E_{max} - E_0) \cdot \frac{C_e^\gamma}{C_{e_{50}}^\gamma + C_e^\gamma} + \varepsilon$$

Where C and C_e are the concentrations in the central ($V1$) and effect compartments, E_0 is the baseline pharmacodynamic measure when no drug is present, E_{max} is the maximum possible drug effect, $C_{e_{50}}$ is the C_e associated with 50% of the maximum effect, γ is the steepness of the concentration *versus* response relation, and ε represents additive residual error to the pharmacodynamic observations. Signal delay in the BIS due to epoch generation and smoothing also was set to 15 s.

MOAA/S observations were treated as ordered categorical responses and modeled with a proportional-odds method. The model estimates the cumulative probabilities of MOAA/S scores. Let S denote an observed score, the logits l_x , of the probabilities that $S = 0$, $S \leq 1$, $S \leq 2$, $S \leq 3$, $S \leq 4$, are:

$$l_{S=0} = b_0 + DEFF \cdot C_e$$

$$l_{S \leq 1} = b_0 + b_1 + DEFF \cdot C_e$$

$$l_{S \leq 2} = b_0 + b_1 + b_2 + DEFF \cdot C_e$$

$$l_{S \leq 3} = b_0 + b_1 + b_2 + b_3 + DEFF \cdot C_e$$

$$l_{S \leq 4} = b_0 + b_1 + b_2 + b_3 + b_4 + DEFF \cdot C_e$$

Where the b_0 is a fixed-effect parameter representing the logit of the probability for score 0 and b_i though b_4 represent the difference in logits between the scores. $DEFF$ is also a fixed-effect parameter for the model, and C_e represents the effect-site concentration of ABP-700, calculated with a first-order rate constant ($ke_{0,MOAA/S}$) in a similar manner as done for BIS. The corresponding probabilities are given by:

$$PC_x = \frac{e^{l_x}}{1 + e^{l_x}}$$

The actual probabilities, p_x , of observing a particular score are: $P_{S=0} = PC_{S=0}$, $P_{S=1} = PC_{S \leq 1} - PC_{S=0}$, $P_{S=2} = PC_{S \leq 2} - PC_{S \leq 1}$, $P_{S=3} = PC_{S \leq 3} - PC_{S \leq 2}$, $P_{S=4} = PC_{S \leq 4} - PC_{S \leq 3}$, $P_{S=5} = 1 - PC_{S \leq 4}$.

For BIS and MOAA/S PD model estimation, the individual predicted plasma concentrations were used as the

driving force for the effect compartment. This is known as the sequential method,^{8,9} also known as the Individual Pharmacokinetic Parameters (IPP) method. Covariate search was not performed due to the limited variability in age, weight, sex, and BMI in the studied individuals.

Model parameters were assumed to be log-normally distributed or constant across the population. For estimates of logarithmic interindividual variability, we report the estimated variance and the coefficient of variation.

Uncertainty in estimated model parameters was evaluated by estimating the upper and lower 95% confidence limits by spline-interpolation of the likelihood profiles. We determined what increase/decrease in each parameter is required to increase NONMEM objective function by 3.84.

To quantify the pharmacokinetic predictive performance for an observation, we calculated the performance error¹⁰ (PE_{PK}) and absolute performance error (APE_{PK}) as follows:

$$PE_{PK} = \frac{C_{observed} - C_{predicted}}{C_{predicted}} \times 100\%$$

$$APE_{PK} = |PE_{PK}|$$

For these measures, the median values are reported. The median PE_{PK} ($MdPE_{PK}$) indicated bias, and median APE_{PK} ($MdAPE_{PK}$) indicates precision.

Clinical Observations

This study was intended to define a MTD for ABP-700. However, it was reasoned that well-tolerated doses would need to be assessed for potential further clinical testing. Therefore, to evaluate the potential clinical utility of every specific dose, we analyzed various relevant clinical observations described by the attending anesthesiologist during the dosing together with a visual inspection of the individual vital signs trends.

IMMs were anticipated with clinical testing of ABP-700 based both on preclinical observations¹ and also by virtue of the parent compound etomidate's known effects on muscle movement in humans.^{11,12} No standardized nomenclature or scoring system was implemented to characterize IMM, as it has not been done for etomidate in the past. Instead, we described the extensiveness of the observed IMMs, rather than their nature. As such, "extensive movements" are movements defined as IMMs that involve the whole body or a considerable part of it. "Few movements" are movements that occur in few body parts, such as both arms or the face.

Breathing was monitored by means of capnography (end-tidal carbon dioxide) and capnography-derived respiratory rate monitoring. Apnea was defined as an absence of breathing for 20 s or more. Tachypnea was defined as a breathing frequency of 20 breaths/min or more. Sinus tachycardia was defined as a heart rate of 100 beats/min or more and if this meant a significant change from baseline (due to possible volunteer stress). Increased blood pressure was defined as a mean arterial pressure greater than 110 mmHg¹³ if this meant a significant change from baseline. Desaturation was defined as a decrease of SpO_2 less than 95%.

Data Recording and Statistics

All vital signs data, MOAA/S, BIS, respiratory function, comments, and a subset of pharmacokinetic sampling time were stored electronically with a dedicated and validated electronic data capturing device (Rugloop II; DEMED, Belgium). Visual and computerized methods of data validation were applied to ensure accurate, consistent, and reliable data for the subsequent statistical analysis.

The sample size was based on previous investigations adequately studying safety, efficacy, clinical effect, and pharmacokinetic–pharmacodynamic behavior of new compounds while minimizing the exposure of volunteers to the compound. Descriptive statistics are displayed as mean \pm SD or geometrical mean \pm 95% CI unless indicated otherwise.

Results

Subjects

In total, 154 subjects were screened by the contract research organization (QPS, The Netherlands). Of these, 60 subjects were admitted to the study, of whom 50 received ABP-700 and 10 received a placebo. All subjects who were enrolled completed the study; no subject withdrew from the study. Mean height, weight, BMI, and age were similar among the groups, as shown in table 2.

Safety and Tolerability

Treatment-emergent adverse experiences were reported in 41 subjects, with 94 AEs reported in total (table 3). Of these, three subjects (30%) in the placebo group reported at least one AE. The majority of AEs were of mild intensity

Table 2. Demographics

Characteristics	Placebo (N = 10)	ABP-700 (N = 50)
Sex, n (%)		
Male	10 (100)	49 (98)
Female	0 (0)	1 (2)
Age, yr, mean (SD)	23 (3.7)	25 (3.0)
Ethnicity, n (%)		
Not Hispanic or Latino	10 (100)	49 (98.0)
Hispanic	0 (0)	1 (2.0)
Race, n (%)		
Asian	1 (10)	2 (4)
Black or African American	0 (0)	1 (2)
White	9 (90)	47 (94)
Smoking status, n (%)		
Never	10 (100)	58 (96.7)
Stopped	0 (0)	2 (3.3)
If yes, subject quit smoking >6 months ago? Yes	0 (0)	2 (100)
Height, cm, mean (SD)	182 (6)	182 (7)
Weight, kg, mean (SD)	74 (7)	76 (7)
Body mass index, kg/m ² , mean (SD)	22 (1.8)	23 (1.8)
Alcohol consumption, units/week, median (range)	4.5 (0–12)	7 (0–14)

ABP-700 = cyclopropyl-methoxycarbonylmetomidate.

Table 3. Adverse Events

Event	ABP-700 (N = 50)	Placebo (N = 10)
Muscle twitching	15	0
Apnea	13	0
Hyperventilation*	10	0
Sinus tachycardia	9	0
Catheter site–related reaction	6	1
Eye disorder†	5	1
Blood pressure increased	4	0
Restlessness	4	0
Nausea/vomiting	2	0
Abnormal respiration‡	3	0
Decreased oxygen saturation	3	0
Neurologic anesthetic complication§	3	0
Hiccups	3	0
Injection-site pain	2	0
Myoclonus	2	0
Headache	2	0
Presyncope	2	0
Fatigue	2	0
Euphoric mood	2	0

Listing of adverse events occurring in two or more ABP-700–treated subjects: *verbatim term: breathing disorder and paradoxical chest wall movements; †verbatim terms: rhythmic movement of eyes, eye lid fluttering, and eye lid twitching; ‡verbatim term: sigh; §verbatim term: emergence delirium; and ||verbatim term: vasovagal reaction (during placement of arterial line).

ABP-700 = cyclopropyl-methoxycarbonylmetomidate.

(93.7%). The number and severity of reported AEs increased with ascending doses of ABP-700. No volunteers withdrew from the study due to AEs. Of the 41 subjects experiencing at least one AE, all had at least one AE of mild intensity. Three subjects also experienced at least one AE of moderate intensity. No AEs of severe intensity were reported. AEs that were “possibly” related to the study treatment were reported for 37 subjects. Four subjects had AEs that were unlikely related, and 15 subjects experienced AEs that were unrelated to the study medication.

For each cohort, figure 1 presents the hemodynamic and respiratory data. More information on vital signs data can be found in Supplemental Digital Content 2 (<http://links.lww.com/ALN/B438>), which are figures plotting the individual data on heart rate, SpO₂, mean arterial blood pressure measured using a noninvasive blood pressure cuff, mean arterial blood pressure using an invasive blood pressure method, respiratory rate, frontal muscles electromyographic activity and BIS measured by the Vista Monitor (Medtronic, Ireland), and end-tidal carbon dioxide for each volunteer receiving ABP-700 or placebo.

Table 4 lists the various tolerability parameters. The occurrence and severity of IMM was reported as dose-dependent. IMM was characterized primarily as muscle twitching or myoclonic activity, but movements including clonic, dystonic, and other variants of IMM also were included and reported as IMM. Figure 1 and table 4 show stable hemodynamics without any occurrence of bradycardia

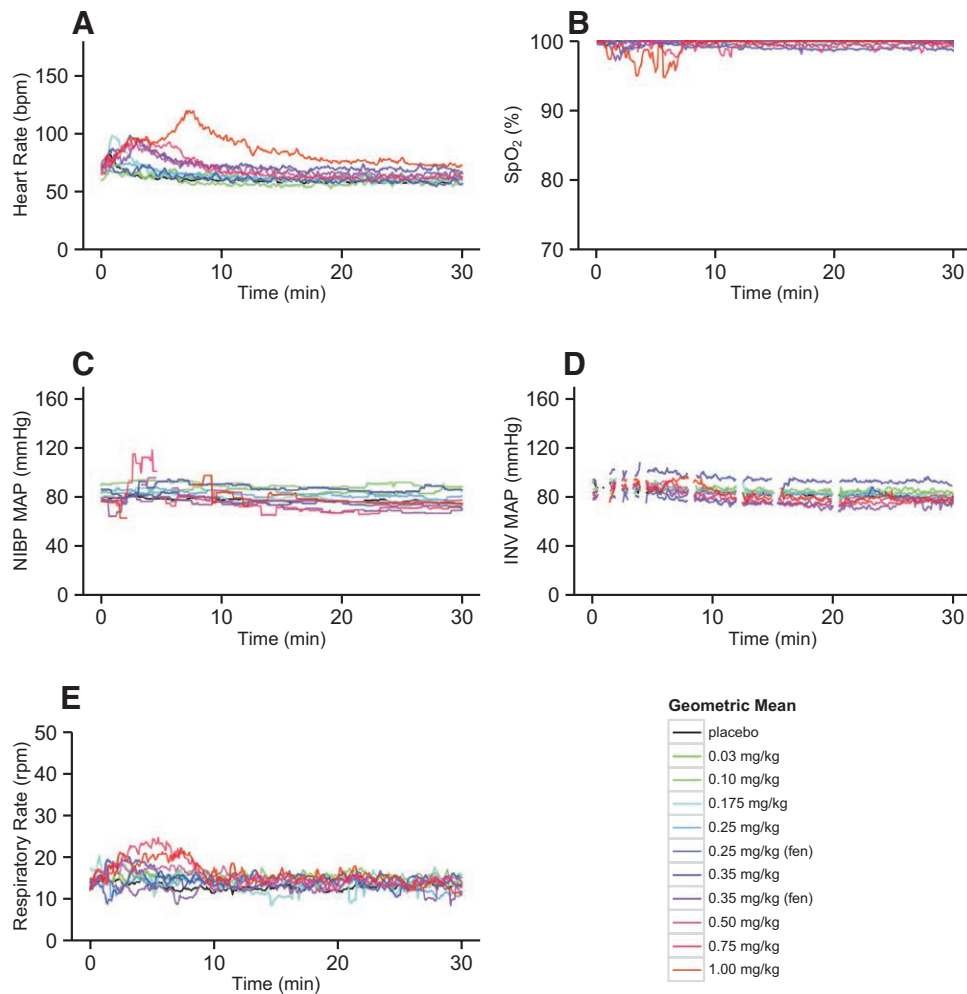


Fig. 1. Vital signs. (A) Heart rate. (B) Oxygen saturation (SpO_2). (C) Mean arterial pressure as measured by no-invasive blood pressure monitoring (NIBP MAP). (D) Mean arterial blood pressure as measured by invasive arterial blood pressure monitoring (INV MAP). (E) Respiration rate. Data are presented as geometrical means per cohort. Fen = fentanyl.

or hypotension after bolus injection. In the higher dosing cohorts, an increase in heart rate and mean arterial blood pressure was observed after similar time course as the cerebral drug effect of ABP-700.

Decreased SpO_2 was reported by seven subjects in the highest dose cohorts and was considered mild and self-limiting (fig. 1). Depression in respiratory rate as measured by capnography, mostly related to IMM resulting in short-lasting and self-limiting upper airway obstruction, was found in 13 volunteers and was dose-related (table 4). Short-lasting chin lift was required in four of these higher dose volunteers to maintain a patent airway. Except in the two highest dosages, where tachypnea was seen, overall respiration rate did not change during the study period, as shown in figure 1.

ABP-700 was not tolerated by three subjects because of the occurrence of severe IMM accompanied by hemodynamic disturbances. One of these subjects had received 0.75 mg/kg ABP-700, and the other two subjects had received 1.00 mg/kg ABP-700. Per protocol, midazolam was given in these three subjects. Total dosages of midazolam ranged from

2 to 5 mg. As such, in the group of 1.00 mg/kg ABP-700 the stopping criteria of the study were met, and it was concluded that 1.00 mg/kg of ABP-700 was the MTD.

Serum chemistry, hematology, urinalysis, coagulation, serum methanol concentration, and temperature did not change during the study period (data not shown). In particular, serum methanol levels were not detectable at all doses tested. Arterial blood gas parameters (pH , PaCO_2 , PaO_2 , HCO_3^- , Na^+ , Cl^- , anion gap) did not change significantly between baseline and 15 min postdose (see Supplemental Digital Content 3, <http://links.lww.com/ALN/B439>, a table with the arterial blood gas sampling values at baseline and 15 min postdose for each ABP-700 dosing cohort and placebo).

On the 12-lead electrocardiogram, a small decrease in the PR interval and QRS interval was observed after bolus injection of ABP-700 of all dosing groups. The changes are not dose-dependent and not clinically significant. A minor increase in the QTcF interval can be seen after bolus injection of ABP-700 (all dosing groups) without dose

Table 4. Evaluation of Tolerability of ABP-700 Given to Healthy Volunteers

	Placebo	0.03 mg/kg	0.10 mg/kg	0.175 mg/kg	0.25 mg/kg	0.25 mg/kg + fen	0.35 mg/kg	0.35 mg/kg + fen	0.50 mg/kg	0.75 mg/kg	1.00 mg/kg	Total
Involuntary muscle movements												
No movements	10	5	5	1	0	1	0	1	0	0	1	24
Few movements	0	0	0	3	5	3	2	4	0	0	0	17
Extensive movement	0	0	0	1	0	1	3	0	5	5	4	19
Ventilation												
Respiratory depression	0	0	0	1	1	1	0	3	1	2	4	13
Tachypnea	0	0	0	1	0	1	0	1	2	5	3	13
Desaturation	0	0	0	0	1	0	0	2	0	1	3	7
Vital signs												
Hypertension	0	0	0	2	0	0	2	0	0	1	3	8
Hypotension	0	0	0	0	0	0	0	0	0	0	0	0
Tachycardia	0	0	0	2	0	0	2	1	1	3	4	13
Bradycardia	0	0	0	0	0	0	0	0	0	0	0	0
Catheter site-related reactions	1	1	0	1	1	0	0	1	0	1	1	7
Nausea/vomiting	0	0	0	0	0	0	0	1	0	1	1	3

Values are number of volunteers. ABP-700 = cyclopropyl-methoxycarbonylmetomidate; fen = fentanyl.

dependency or clinical significance. ACTH stimulation evoked an adrenal cortisol response in all subjects treated with ABP-700. Plasma cortisol concentrations increased by at least 200 nM/l at 60 or 120 min post-ACTH stimulation, indicating no adrenal suppression (fig. 2). There was no difference observed between placebo and the ABP-700 dose levels, other than differences that would be considered with the normal variability of the test.

ACTH testing was not performed for the cohorts that received fentanyl as a pretreatment, because these cohorts were repeats of previous dose levels. Cortisol levels of cohort 10, which received 0.175 mg/kg ABP-700, were not analyzed because an ACTH-stimulation test in previous cohorts that received a higher dose of ABP-700 (0.25, 0.35, 0.50, 0.75, and 1.00 mg/kg) did not reveal any adrenocortical suppression.

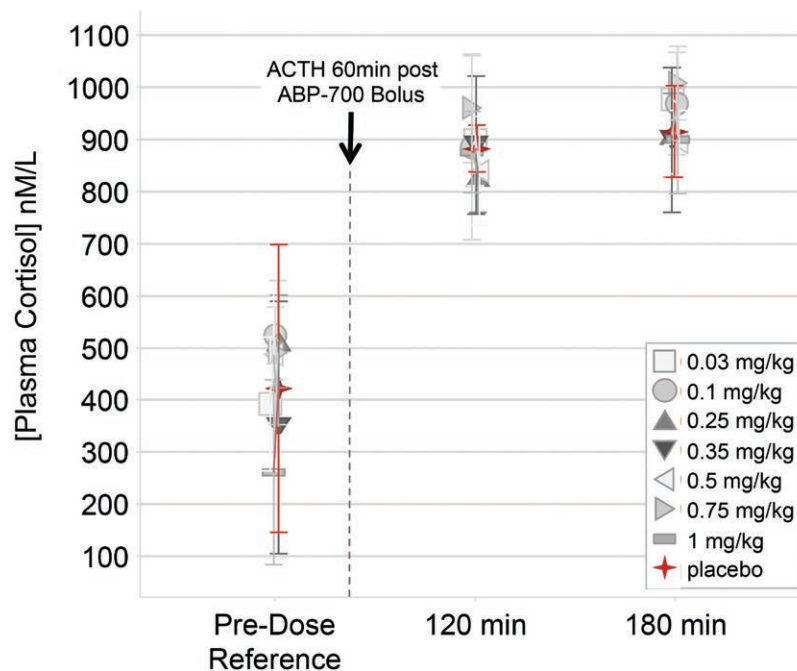


Fig. 2. Human adrenocortical response to adrenocorticotrophic hormone (ACTH) stimulation after bolus administration of cyclopropyl-methoxycarbonylmetomidate (ABP-700) (0.03 to 1.0 mg/kg) or placebo. Adrenocortical response before and after administration of 250 µg synthetic ACTH 1 h after bolus ABP-700. Predose cortisol reference levels were obtained before 9 AM on the day of ABP-700 administration. Values are mean cortisol levels (\pm SD) for ABP-700 and placebo groups. $n = 5$ by ABP-700 dose and $n = 7$ for placebo.

Noncompartmental Pharmacokinetics

For each cohort, the time courses of the arterial and venous concentrations of ABP-700 and of the arterial of CPM acid are displayed in figure 3. The most important noncompartmental pharmacokinetic parameter values for ABP-700 (both arterial and venous) and its metabolite CPM acid are shown as tables in Supplemental Digital Content 1 (<http://links.lww.com/ALN/B437>). Overall, pharmacokinetics were dose-proportional. Clear differences between arterial and venous concentrations and pharmacokinetic parameters were observed.

Compartmental Pharmacokinetics

No significant covariate relationships with age, weight, height, or sex were found. The weight linear scaled model achieved an Akaike information criterion of $-2,700.61$ with a median absolute percentage error of 1.98 (24.5%). The

summarized equations of the final pharmacokinetic model are as follows:

$$SIZE = WGT / 70kg$$

$$V1(L) = V1_{ref} \cdot SIZE \cdot \exp(\eta_1)$$

$$V2(L) = V2_{ref} \cdot SIZE \cdot \exp(\eta_2)$$

$$V3(L) = V3_{ref} \cdot SIZE \cdot \exp(\eta_3)$$

$$CL(L \cdot \min^{-1}) = CL_{ref} \cdot SIZE \cdot \exp(\eta_4)$$

$$Q2(L \cdot \min^{-1}) = Q2_{ref} \cdot SIZE \cdot \exp(\eta_5)$$

$$Q3(L \cdot \min^{-1}) = Q3_{ref} \cdot SIZE \cdot \exp(\eta_6)$$

Symbols $V1_{ref}$, $V2_{ref}$, $V3_{ref}$, CL_{ref} , $Q2_{ref}$, and $Q3_{ref}$ are the estimated compartmental volumes and clearances for a 70-kg individual, and symbols η_1 to η_6 represent random variances. Estimated parameters are shown in table 5. The population and individual predictions *versus* time and observed

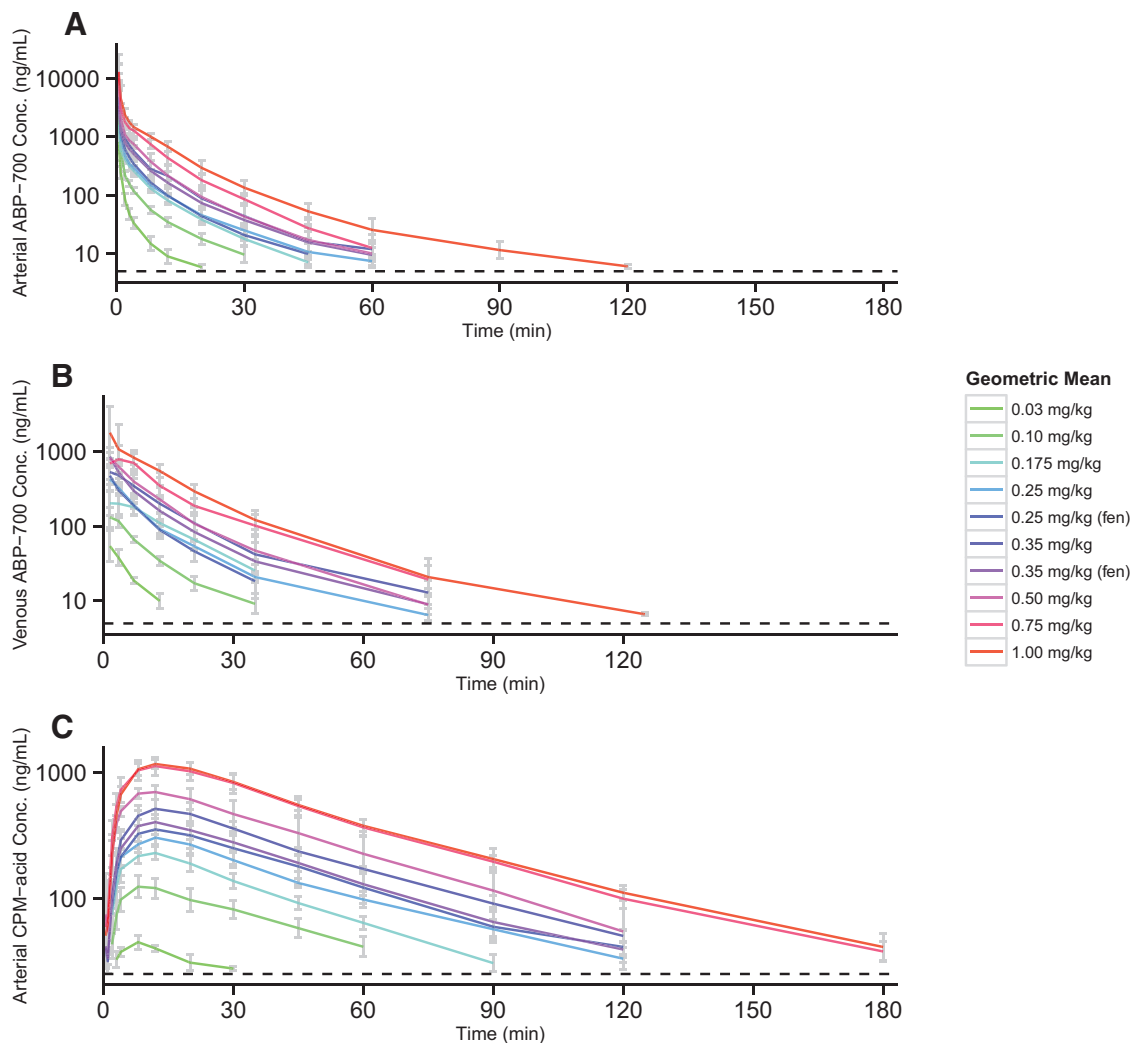


Fig. 3. Pharmacokinetics of cyclopropyl-methoxycarbonylmetomidate (ABP-700) and its primary metabolite cyclopropyl-methoxycarbonyl acid (CPM acid). (A) Arterial plasma concentrations of ABP-700. (B) Venous plasma concentrations of ABP-700. (C) Arterial plasma concentrations of the ABP-700 metabolite, CPM acid. Data are presented as geometrical means \pm 95% CI per cohort. The bolus of ABP-700 was administered at time 0 min.

Table 5. Estimated Model Parameters and Population Variances in the Final Pharmacokinetic Model

		95% Confidence Limits	
Parameters	Estimated Value	Lower	Upper
$V1_{ref}$ l	0.527	0.427	0.649
$V2_{ref}$ l	3.02	2.47	3.71
$V3_{ref}$ l	5.18	4.59	5.85
CL_{ref} l/min	1.66	1.57	1.77
$Q2_{ref}$ l/min	1.14	0.951	1.41
$Q3_{ref}$ l/min	0.336	0.297	0.382
	Variance, ω^2	CV, %	
$\eta 1$	0.323	61.8	
$\eta 2$	0.352	64.9	
$\eta 3$	0.106	33.5	
$\eta 4$	0.0178	13.4	
$\eta 5$	0.249	53.2	
$\eta 6$	0.0804	28.9	
Residual error (SD)			
Arterial observations	0.103		

$V1_{ref}$, $V2_{ref}$, $V3_{ref}$, CL_{ref} , $Q2_{ref}$, and $Q3_{ref}$ are the estimated compartmental volumes and clearances for a 70-kg individual, and symbols $\eta 1$ to $\eta 6$ represent random variances.

CV = coefficient of variation.

ABP-700 arterial concentrations and the likelihood profiles are documented as figures in Supplemental Digital Content 4 (<http://links.lww.com/ALN/B440>) and 5 (<http://links.lww.com/ALN/B441>), respectively.

Clinical Effects and Pharmacodynamics

For each cohort, the time course of the BIS and frontal electromyographic activity are plotted in figure 4. At the lowest dose of ABP-700 administered (0.03 mg/kg), there was no observed effect on BIS. Subjects receiving dose levels of 0.1 mg/kg ABP-700 or greater showed a dose-dependent response to the treatment, as indicated by the rapidly decreasing BIS values (within 1 to 2 min). Duration of cerebral drug effect was longer in higher dosing cohorts. Due to increased electromyographic activity,¹⁴ as shown in figure 4, the decrease in BIS in the 0.75 mg/kg cohort paradoxically was delayed. For BIS model development, Ce_{50} and $ke_{0,BIS}$ were assumed and log-normally distributed across the population. Estimating baseline BIS resulted in numerical instability, and its value was fixed to 90. The summarized equations of the final models are as follows:

$$Ce_{50} = Ce_{50,TYP} \cdot \exp(\eta 1)$$

$$ke_{0,BIS} = ke_{0,BIS,TYP} \cdot \exp(\eta 2)$$

Symbols Ce_{50} and $ke_{0,BIS}$ represent estimated model parameters in the individual; $Ce_{50,TYP}$ and $ke_{0,BIS,TYP}$ represent the typical population model parameters; and $\eta 1$ and $\eta 2$ represent population variances. Estimated parameters are shown in table 6. The population and individual predictions *versus* time and BIS and

the likelihood profiles for the model parameters are shown as figures in Supplemental Digital Content 6 (<http://links.lww.com/ALN/B442>) and 7 (<http://links.lww.com/ALN/B443>).

Figure 5 shows the individual MOAA/S scores. In the placebo and 0.03-mg/kg dose groups, no signs of clinical effect were observed in any subjects. Onset of clinical effect was observed starting with the 0.10 mg/kg dose group. In the 0.175-mg/kg dose group, four subjects (80%) reached clinical effect, and two subjects (40%) reached deep sedation/anesthesia. In the cohorts with a dose of 0.25 mg/kg and higher, both clinical effect and deep sedation/anesthesia was reached in 100% of the subjects. The duration of both the clinical effect and sedation increased with escalating dose. Neither the time to onset of clinical effect nor the time to onset of deep sedation/anesthesia was dose-related.

For MOAA/S PD model development, we assumed log-normally distributed population variability in drug effect.

$$DEFF = DEFF_{TYP} \cdot \exp(\eta 1)$$

$$ke_{0,MOAA/S} = ke_{0,MOAA/S,TYP}$$

Symbols $DEFF$ and $ke_{0,MOAA/S}$ represent estimated model parameters in the individual, $DEFF_{TYP}$ and $ke_{0,MOAA/S,TYP}$ represent the typical population model parameters, and $\eta 1$ represents population variance. For the final model, the estimated parameters are shown in table 7. The population and individual predictions *versus* time and MOAA/S and the likelihood profiles for the model parameters are shown as figures in Supplemental Digital Content 8 (<http://links.lww.com/ALN/B444>) and 9 (<http://links.lww.com/ALN/B445>).

Influence of Fentanyl

After completion of the preplanned cohorts and evaluation for tolerability and potential clinical utility, the 0.25- and 0.35-mg/kg doses of ABP-700 were considered as the two most promising doses and were repeated in the presence of fentanyl pretreatment (1 μ g/kg). The administration of fentanyl resulted in decrease in the incidence and extent of IMM and also in less tachycardia when compared with the ABP-700 dose without fentanyl (table 4). Fentanyl pretreatment did not alter the time to onset of clinical effect or onset of sedation, nor did it alter the duration of sedation or clinical effect (data not shown). As shown in figure 4, a more pronounced clinical effect of ABP-700 as measured by BIS was observed with fentanyl pretreatment than without, although this did not result in a significant covariate in the pharmacodynamic model parameters. Fentanyl did result in somewhat higher frequency of respiratory depression and desaturation events. The administration of fentanyl did not result in a substantial alteration of the pharmacokinetics of either ABP-700 or its metabolite CPM acid, as shown by both noncompartmental and compartmental modeling (analysis not shown).

Discussion

Cyclopropyl-methoxycarbonylmetomidate, or ABP-700, is a short-acting, soft analog of etomidate and was developed to avoid the adrenocortical suppression while preserving

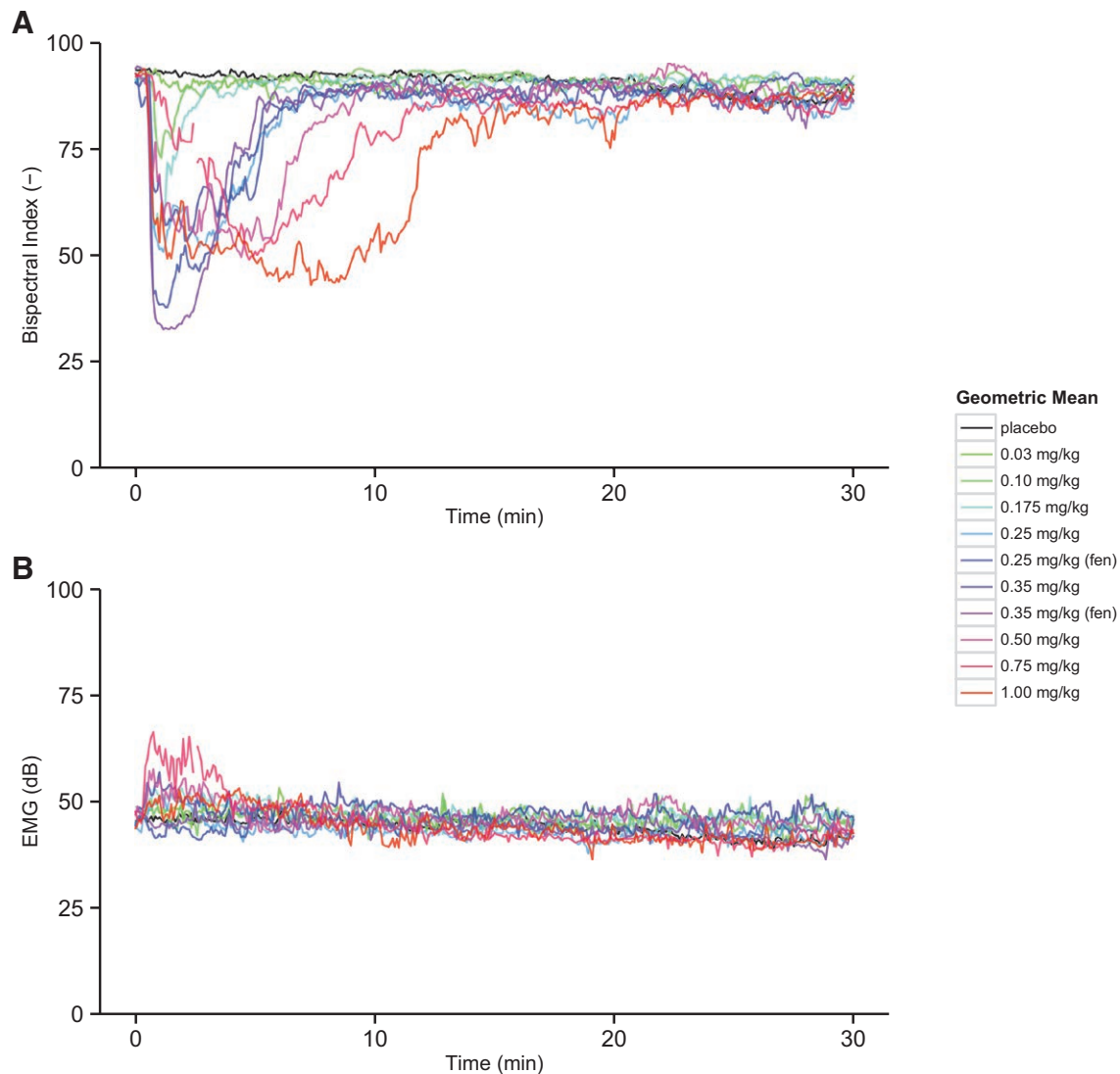


Fig. 4. Hypnotic effect of cyclopropyl-methoxycarbonylmetomidate. (A) Depth of sedation and anesthesia, as measured by the Bispectral Index and (B) frontal electromyographic activity (EMG). Fen = fentanyl.

the beneficial dose–response profile of etomidate.⁵ In this first-in-human study, we found that ABP-700 was safe and well-tolerated after single-bolus injections of up to a maximum of 1.0 mg/kg. The two most promising dosages for potential clinical utility as a bolus induction agent were thought to be 0.25 and 0.35 mg/kg.

As expected, based on the preclinical studies,^{2,7,15} ABP-700 demonstrated hypnotic–anesthetic properties. Clinical effect was first seen after a bolus dose of 0.175 mg/kg of ABP-700 (in four of five volunteers). At doses of 0.25 mg/kg and greater, a decrease in MOAA/S score to 0 was observed in all subjects. The time to onset of deep sedation/anesthesia was found to be dose-independent and extremely short, around 30 s after bolus injection, which is somewhat shorter than etomidate and thiopental¹⁶ and significantly shorter than propofol.¹⁷ Duration of deep sedation/anesthesia was dose-dependent. Offset of deep sedation/anesthesia was characterized by an abrupt and rapid return to a MOAA/S score of 5 in most of the volunteers.

There were very few recorded instances of MOAA/S 2 or 3 during either induction or emergence from deep sedation/anesthesia. BIS profiles showed a similar time course of drug effect to MOAA/S scores, characterized by a rapid, dose-independent decline, with lowest value between 45 and 55, except for the cohort that received a bolus of 0.75 mg/kg ABP-700, due to possible electromyographic artifacts (fig. 4).¹⁴

Pharmacodynamic modeling for both MOAA/S and BIS illustrate the steep relation between the ABP-700 effect-site concentration and the cerebral drug effect. Although possibly influenced by the intermittent nature of MOAA/S scores in this study, figure 6 clearly shows the small range in effect-site concentrations between the probabilities for different MOAA/S scores. It is remarkable that the difference in ABP-700 effect-site concentration between 50% probability of MOAA/S score 5 and 0 is only around 500 ng/ml. The steepness also is evident in the large γ found in the BIS sigmoid pharmacodynamic model. The effect-site

Table 6. Estimated Model Parameters and Population Variances in the Final BIS Pharmacodynamic Model

Parameters	Estimated Value	95% Confidence Limits	
		Lower	Upper
E_0	90	—	—
E_{max}	0	—	—
$Ce_{50, TYP}$ ng/ml	1,200	1,060	1,350
γ	7.24	6.83	7.66
$ke_{0, BIS, TYP}$ l/min	0.156	0.132	0.179
Variance, ω^2		CV, %	
η_1	0.139	38.6	
η_2	0.742	105	
Residual error (SD)			
BIS observations	6.35		

E_0 is the baseline pharmacodynamic measure when no drug is present; E_{max} is the maximum possible drug effect; $Ce_{50, TYP}$ is the typical population model parameter for the effect-site concentration of ABP-700 associated with 50% of the maximum effect; γ is the steepness of the concentration versus response relation; $ke_{0, BIS, TYP}$ is the typical population model parameter for the first-order rate constant between plasma and effect-site compartment; and η_1 and η_2 represent population variances.

BIS = Bispectral Index; CV = coefficient of variation; TYP = population typical value.

concentration reaching 50% of drug effect as measured by BIS is found around 1,200 ng/ml and validates the effect-site concentration range found when using MOAA/S score to quantify cerebral drug effect. A small hysteresis effect between plasma and effect site is observed and is characterized by a fast $ke_{0, MOAA/S}$ of 0.488/min. A smaller $ke_{0, BIS}$ was found; however, this value might be biased because of the delay in the BIS monitor during very fast changes in cerebral drug effect.¹⁸

Clinical observations related to IMM, ventilation, and vital signs were dose-dependent and consistent with the mechanism of action of ABP-700 and its structurally related analog, etomidate.^{5,16} From a dosage of 0.175 mg/kg of ABP-700 upwards, IMM were observed in most of the volunteers. These IMM varied from few muscle movements of a more twitching character to more extensive muscle movements that appeared to be of an intermittent myoclonic nature. In various volunteers, these muscle twitches and myoclonic movements were considered mild and not always considered as an AE by the attending anesthesiologist. In three cases of severe IMM in the highest two dose cohorts, midazolam was administered, which successfully attenuated these movements, consistent with what was seen during preclinical studies.¹ The occurrence of IMM is a common observation among anesthetic agents, such as etomidate,¹⁹ propofol,²⁰ and the novel anesthetic agent AZD-3043.²¹ The etiology of these IMM is not entirely clear. They are not thought to be associated with electroencephalographically measured epileptiform discharges^{16,22} and have been hypothesized to be a subcortically mediated or triggered process.¹¹

ABP-700 did not cause cardiovascular depression, as seen in figure 1 and table 4. However, increases in heart rate and blood pressure were observed in the higher dosing groups and followed a similar time course as the clinical effect. Increases in heart rate with stable blood pressure have been reported previously for etomidate²³ and also with the inhaled agent desflurane.²⁴ Some short-lasting episodes of increased blood pressures (mean arterial blood pressure greater than 110 mmHg) were found, but without any requirement for treatment.

ABP-700 has a remarkably stable respiratory profile. No centrally induced respiratory depression was recorded. Decreases in amplitude and frequency of respiration rate were induced mostly by the IMM, resulting in a brief and self-limiting upper airway obstruction. Per protocol, brief chin lift was applied in four volunteers after 20 s of airway obstruction to maintain a patent airway. Two of these volunteers had received 0.75 mg/kg ABP-700, and two had received 1.00 mg/kg. Tachypnea was observed in parallel with the hypnotic-anesthetic effect in the two highest dosing groups, receiving 0.75 and 1.00 mg/kg AB-700 boluses. Self-limiting changes in SpO_2 were only recorded occasionally. The notion that deep sedation/anesthesia is possible without any appreciable respiratory depression is obviously of potential clinical importance. Etomidate is associated with less respiratory depression than propofol but at deep sedation/anesthesia doses, both decrease medullary respiratory drive and right-shift the hypercarbic ventilator response.^{25,26} Although the stable respiratory rate and arterial carbon dioxide levels seen with ABP-700 are suggestive of preservation of respiratory drive, this MTD dose study was not intended to thoroughly evaluate ABP-700 effects on respiratory function.

Consistent with preclinical findings,^{1,15} ABP-700 did not suppress the physiologic response of the adrenal axis to ACTH stimulation in human volunteers. A significant increase of at least 200 nM at 60 or 120 min poststimulation occurred and was not different from subjects who received a placebo. Although not directly compared in this study, adrenal responsiveness after single-bolus exposure to ABP-700 is superior to the substantial adrenal suppression caused by bolus dosing of etomidate.⁶

Noncompartmental pharmacokinetics were studied for both ABP-700 (arterial and venous) and its metabolite CPM acid (arterial). The results showed rapid elimination of ABP-700 across all dose regimens. The mean clearance values observed in this study were relatively high compared with hepatic blood flow. Clearance and volume of distribution estimated for the venous blood samples were all higher than those estimated for the arterial blood samples, reflecting the rapid metabolism of ABP-700 by esterases during the arterial to venous transport. ABP-700 plasma exposure increased dose proportionally as the dose increased from 0.03 to 1.00 mg/kg for both arterial and venous blood samples. Dose-proportional arterial plasma exposures of CPM acid also were observed.

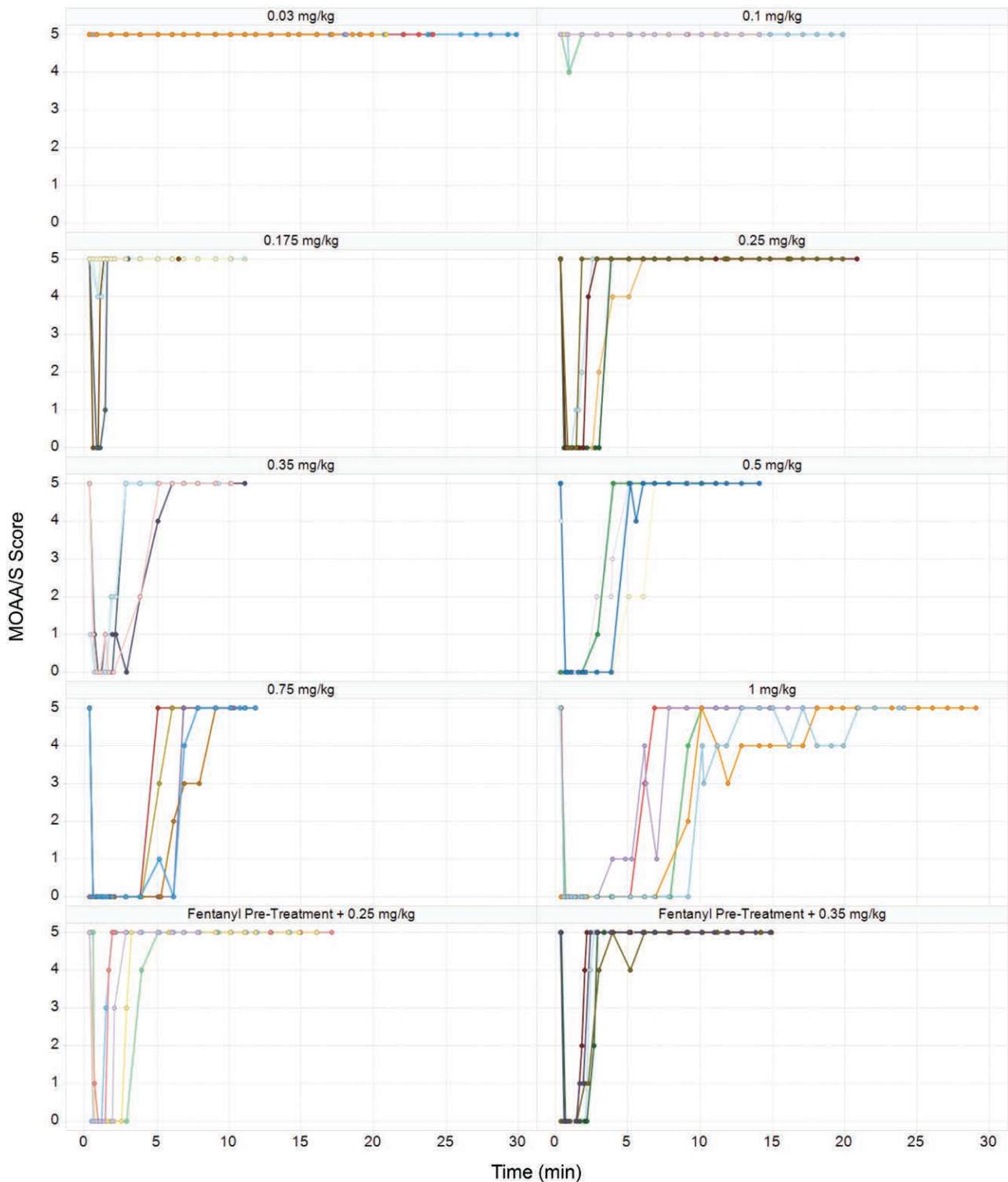


Fig. 5. Modified Observers Assessment of Alertness and Sedation (MOAA/S) scores by subject. The data are displayed by individual subject who received cyclopropyl-methoxycarbonylmetomidate ($n = 50$) and per cohort (10 cohorts in total). Data for placebo were omitted because no subject was scored less than 5.

A three-compartment pharmacokinetic model was developed to describe the time course of arterial drug concentration. The final model accurately predicts the arterial concentrations of ABP-700 after a single-bolus injection in

the central compartment. Venous samples were not used for model estimation. For soft drugs, it is well known that venous samples are potentially very misleading in describing the clinical behavior of a drug through modeling.²⁷ The

Table 7. Estimated Model Parameters and Population Variances in the Final MOAA/S Pharmacodynamic Model

Parameters	Estimated Value	95% Confidence Limits	
		Lower	Upper
$DEFF_{TYP}$	5.25	4.41	6.23
$ke_{0, MOAA/S, TYP}$	0.488	0.443	0.537
b_0	-10.1	-11.7	-8.77
b_1	0.713	0.459	1.02
b_2	0.518	0.307	0.817
b_3	0.407	0.222	0.670
b_4	1.02	0.735	1.36
	Variance, ω^2	CV, %	
η_1	0.0472	22.0	

b_0 is a fixed-effect parameter representing the logit of the probability for score 0; b_1 through b_4 represent the difference in logits between the scores; $DEFF$ is also a fixed-effect parameter for the model; $ke_{0, MOAA/S, TYP}$ is the typical population model parameter for the first-order rate constant between plasma and effect-site compartment; and η_1 represents the population variance.

CV = coefficient of variation; MOAA/S = Modified Observers Assessment of Alertness and Sedation; $DEFF_{TYP}$ = typical population parameter for a fixed-effect parameter for the model.

values for volumes of distribution and clearance echoes the noncompartmental kinetics, although one should be aware that a compartmental model based on single-bolus data only is very biased and often characterized by a misspecified central compartmental volume.²⁸ A more realistic model has to be developed, adding data from continuous-infusion investigations, hereby also exploring other than linear models, more accurate size descriptors than weight, and more covariates.

The use of fentanyl as a premedication to dosages of 0.25 mg/kg ABP-700 and 0.35 mg/kg ABP-700 did not alter the onset, duration, and recovery profile of ABP-700 as measured by MOAA/S. Nevertheless, a more pronounced decrease in BIS was seen. Less extensive IMM were observed with the addition of fentanyl. It is well known IMM due to etomidate can be attenuated by pretreatment with low doses

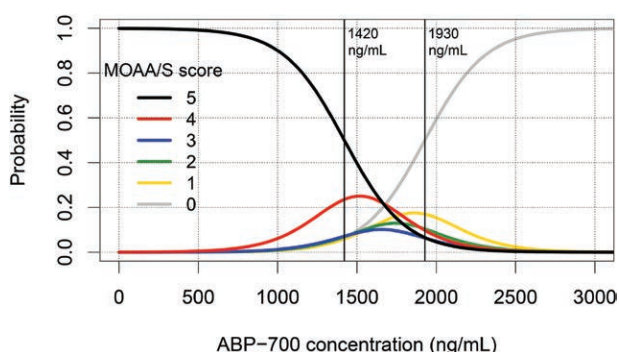


Fig. 6. Population predictions of Modified Observers Assessment of Alertness and Sedation (MOAA/S) scores versus cyclopropyl-methoxycarbonylmetomidate (ABP-700) effect-site concentrations. The vertical lines to the x-axis denote the effect-site concentration at a 50% probability for having an MOAA/S score of 5 and 0, respectively.

of commonly used drugs during procedural care, such as opioids and benzodiazepines.^{11,12} Although speculative, given the chemical derivation of ABP-700 as an etomidate analog, the origin of IMM seen with ABP-700 may be mechanistically similar to that seen with etomidate.

Consistent with known effects, some respiratory and hemodynamic changes were associated with fentanyl administration before ABP-700. This study was not designed to assess these changes, so it is not possible to comment on their clinical significance. Because ABP-700 is not expected to have any analgesic properties, its use in procedural sedation or anesthesia will require concomitant dosing of opioids.

In general, there were no substantial differences in both noncompartmental and compartmental pharmacokinetic parameters for ABP-700 and CPM acid after a bolus dose of 0.25 and 0.35 mg/kg of ABP-700 without and with 1 µg/kg fentanyl pretreatment, respectively. However, these comparisons on pharmacokinetics of ABP-700 or CPM acid between the subjects that have been administered ABP-700 alone or coadministered with fentanyl might be biased and were performed for exploratory purposes. The influence of fentanyl on the pharmacokinetics of ABP-700 and CPM acid should be studied in greater detail within a properly designed drug–drug interaction study.

As always, studies of this type have limitations. One is that the clinical hypnotic–anesthetic drug effect of ABP-700 was assessed by the MOAA/S scale. A problem with using the MOAA/S scale is that the volunteer is stimulated, which might result in an arousal poststimulus and biasing the hypnotic–anesthetic continuum. Furthermore, clinical observations are made by clinicians and are therefore prone to subjectivity. As there were three attending anesthesiologists involved in this study, some variability in MOAA/S assessments is possible.

Another limitation of this study is that BIS monitoring is not validated for monitoring the depth of anesthesia achieved with ABP-700. However, BIS is an established form of monitoring for other GABA-acting drugs,²⁹ and the BIS pattern follows the MOAA/S pattern closely. Therefore, it can be assumed that the BIS data are valid for ABP-700. In addition, as this is a safety and tolerability Phase 1 study, findings should not be extrapolated to any clinical practice guidelines yet.

We can conclude that ABP-700 was safe and well tolerated after single-bolus injections of up to a maximum tolerated bolus dose of 1.0 mg/kg. A bolus dose of 0.25 and 0.35 mg/kg was found to have a sufficiently favorable clinical effect versus side-effect profile to be explored in future studies. These dosages of ABP-700 showed dose responsive hypnotic–anesthetic characteristics and a safety and tolerability profile that warrants further investigation and development.

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Competing Interests

Dr. Struys: his research group/department received grants and funding from The Medicines Company (Parsippany, New Jersey), Masimo (Irvine, California), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, The Netherlands), Medtronic (Dublin, Ireland), and honoraria from The Medicines Company, Masimo, Fresenius, Baxter (Deerfield, Illinois), Medtronic, and Demed Medical (Temse, Belgium). Dr. Absalom: his research group/department received grants and funding from The Medicines Company, Masimo, Fresenius, Acacia Design, Medtronic, and he has received honoraria from The Medicines Company and Janssen Pharmaceutica NV (Beerse, Belgium). Dr. Meyer attended one advisory board from The Medicines Company, for which his department received an honorarium. Dr. Meier received honoraria from Abbott Vascular (Hoofddorp, The Netherlands). He also attended one advisory board from The Medicines Company, for which his department received an honorarium. Dr. Daas is an employee of QPS Netherlands, BV, Groningen, The Netherlands. Dr. Chou is an employee of QPS LLC, Newark, Delaware. Dr. Campagna is an employee of The Medicines Company. Mr. Sweeney is an employee of The Medicines Company and former employee of Annovation Biopharma (Cambridge, Massachusetts). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: m.m.r.f.struys@umcg.nl. Raw data available at: m.m.r.f.struys@umcg.nl.

Correspondence

Address correspondence to Dr. Struys: Department of Anesthesiology, University of Groningen, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands. m.m.r.f.struys@umcg.nl. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Clean Analgesia? A Civil War Tin for Pills of Opium...and Soap



For small-scale production of opium pills during America's Civil War, a drachm (3.89 g) of the powdered drug was mixed with 12 grains (0.72 g) of hard dry soap and molded with a dash of water into a cylindrical mass for division into 60 pills. However, the Union Army required a much more industrial scale of pill rolling. At its Medical Purveying Depot in Astoria, Long Island, New York, the Union Army employed 12 women to roll out an average totaling 60,000 opium pills daily. Men working the nearby printing press generated paper labels (right) for the japanned tins (left) that were corked after being filled with *Pilulae Opii* (Latin: little balls or pills of opium). The soap was considered an “excipient” or inert filler for the analgesic opium. Remarkably, soap was so routinely compounded with opium that, to conceal from patients that they were receiving opium, a physician could simply prescribe opium as *Pilulae Saponis Compositae* or “Compound Pills of Soap.” (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., *Honorary Curator and Laureate of the History of Anesthesia*, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.