ANESTHESIOLOGY

Functional Profile of Systemic and Intrathecal Cebranopadol in Nonhuman Primates

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Anesthesiology 2021; 135:482–93

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Cebranopadol is a compound that serves as an agonist at nociceptin and opioid receptors
- Although cebranopadol is known to have analgesic properties, our understanding of the receptors involved and the ability of the compound to produce side effects is limited

What This Article Tells Us That Is New

- In rhesus monkeys, it was observed that the analgesic activity of cebranopadol is mediated primarily through the μ-opioid receptor
- While cebranopadol caused less scratching behavior and respiratory depression than morphine and fentanyl, it evinced clear reinforcing effects

ABSTRACT

Background: Cebranopadol, a mixed nociceptin/opioid receptor full agonist, can effectively relieve pain in rodents and humans. However, it is unclear to what degree different opioid receptor subtypes contribute to its antinociception and whether cebranopadol lacks acute opioid-associated side effects in primates. The authors hypothesized that coactivation of nociceptin receptors and μ receptors produces analgesia with reduced side effects in nonhuman primates.

Methods: The antinociceptive, reinforcing, respiratory-depressant, and pruritic effects of cebranopadol in adult rhesus monkeys (n = 22) were compared with μ receptor agonists fentanyl and morphine using assays, including acute thermal nociception, IV drug self-administration, telemetric measurement of respiratory function, and itch-scratching responses.

Results: Subcutaneous cebranopadol (ED_{50}, 2.9 [95% CI, 1.8 to 4.6] μg/kg) potently produced antinociception compared to fentanyl (15.8 [14.6 to 17.1] μg/kg). Pretreatment with antagonists selective for nociceptin and μ receptors, but not δ and κ receptor antagonists, caused rightward shifts of the antinociceptive dose–response curve of cebranopadol with dose ratios of 2 and 9, respectively. Cebranopadol produced reinforcing effects comparable to fentanyl, but with decreased reinforcing strength, *i.e.*, cebranopadol (mean ± SD, 7 ± 3 injections) *versus* fentanyl (12 ± 3 injections) determined by a progressive-ratio schedule of reinforcement. Unlike fentanyl (8 ± 2 breaths/min), systemic cebranopadol at higher doses did not decrease the respiratory rate (17 ± 2 breaths/min). Intrathecal cebranopadol (1 μg) exerted full antinociception with minimal scratching responses (231 ± 137 scratches) in contrast to intrathecal morphine (30 μg; 3,009 ± 1,474 scratches).

Conclusions: In nonhuman primates, the μ receptor mainly contributed to cebranopadol-induced antinociception. Similar to nociceptin/μ receptor partial agonists, cebranopadol displayed reduced side effects, such as a lack of respiratory depression and pruritus. Although cebranopadol showed reduced reinforcing strength, its detectable reinforcing effects and strength warrant caution, which is critical for the development and clinical use of cebranopadol.

(Anesthesiology 2021; 135:482–93)

μ receptor agonists are the most widely used analgesics in clinics.[1] However, the side effects associated with these drugs, including abuse liability, respiratory depression, constipation, and itch (pruritus), have resulted in a clear need for safe yet efficacious analgesics with better side effect profiles.[2,3] Several scientific approaches have been proposed to ameliorate μ receptor–mediated side effects while preserving analgesic efficacy.[4] Based on the pharmacologic studies of the functional interactions between nociceptin receptors and μ receptors, the development of mixed nociceptin/μ receptor agonists is of particular interest.[5] Mounting evidence strongly suggests that the coactivation of the nociceptin and μ receptors might provide synergistic analgesic effects and simultaneously counteract μ receptor–mediated side effects.[6–10] Mixed nociceptin/μ receptor agonists are currently being pursued as promising novel analgesics.

Several mixed nociceptin/μ receptor agonists have been reported. BU08028 and BU10038 bind with reasonable

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Submitted for publication December 14, 2020. Accepted for publication May 7, 2021. Published online first on June 11, 2021. From the Department of Physiology and Pharmacology (H.D., M.-C.K.) and the Department of Biostatistics and Data Science (F-C.H.), Wake Forest School of Medicine, Winston-Salem, North Carolina; the Department of Chemical and Pharmaceutical Sciences and the Laboratory for Technologies of Advanced Therapies, University of Ferrara, Ferrara, Italy (C.T.); the Department of Physiological Sciences, School of Pharmaceutical Sciences, Wakayama Medical University, Wakayama, Japan (N.K.); the Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy (G.C.); and W.G. Hefner Veterans Affairs Medical Center, Salisbury, North Carolina (M.-C.K.).

 Anesthesiology 2021; 135:482–93. DOI: 10.1097/ALN.0000000000003848

affinity to all opioid receptor subtypes; however, both show only partial efficacy at nociceptin and μ receptors.[8,11] Similarly, AT-121 displays a high affinity to nociceptin and μ receptors but only partial agonistic efficacy at both receptors.[7] In preclinical pain models, these compounds showed potent antinociceptive effects with favorable side effect profiles, including reduced or lack of respiratory depression, reinforcing effects, physical dependence, and tolerance development.[6–8] In comparison with these nociceptin/μ receptor partial agonists, cebranopadol stands out as a unique mixed nociceptin/opioid receptor agonist which displays full efficacy at μ, nociception, and δ receptors, and partial efficacy at κ receptors.[12,13] The antinociceptive effects of cebranopadol have been demonstrated in various rodent pain models.[14,15] This phenomenon has been translated to human clinical trials, showing promising efficacy in patients with acute or chronic pain.[14,15] However, the receptor components contributing to cebranopadol-induced antinociception in primates remain unknown. Given that nociceptin receptor activation counters μ receptor–mediated antinociception in rodents,[5,10] it is worth investigating the antinociceptive effects of cebranopadol with receptor-selective antagonists in nonhuman primates.

In addition to evaluating the effectiveness of cebranopadol in relieving pain, the side effects typically associated with opioids have also been examined in rodents and humans.[14,15] The absence of respiratory depression[12,16] and a low potential to produce physical dependence[17,18] have been reported in rodent models and human clinical trials. However, there are equivocal reports of rewarding effects in the conditioned place preference paradigm in rodents.[19,20] Given that abuse liability is one of the foremost drawbacks of opioid analgesics in clinical use and cebranopadol displays full efficacy at μ receptors, it is critical to evaluate the abuse potential of cebranopadol in nonhuman primate models with high translational relevance. IV drug self-administration in nonhuman primates is the definitive standard for assessing the abuse potential of drugs.[21,22] Data obtained from this experimental paradigm would be valuable for evaluating the abuse liability of cebranopadol. In addition, pruritus is a common side effect of spinal opioid analgesics that significantly compromises their pain relief values.[23] Considering the full efficacy of cebranopadol at μ receptors, it is important to determine whether cebranopadol could elicit itch sensation.

Given the species differences in the functional and pharmacologic profiles of nociceptin and μ receptor activation between rodents and nonhuman primates and the practicality of simulating the side effect profiles of μ receptor agonists in nonhuman primates,[5,24,25] we used nonhuman primate models in this study to compare the functional profiles of cebranopadol with μ receptor agonists fentanyl and morphine in four aspects: (1) antinociceptive potency; (2) reinforcing effects and strength; (3) respiratory depressant effects; and (4) pruritic effects.

Materials and Methods

Animals

Adult rhesus monkeys (*Macaca mulatta;* n = 22 [14 males, 8 females]), with body weight of 6.4 to 12.1 kg and age of 10 to 18 yr, were used in the current study. The monkeys were housed individually in cages with 0.56 to 1.11 m^2 of floor space and 0.82- to 1.65-m high ceilings that were located in an environmentally-controlled room (21° to 25°C; 40 to 60% relative humidity) with a 12-h light/dark cycle (lights on: 6:30 to 18:30) at an indoor facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (Frederick, Maryland). The monkeys were provided with water and monkey chow (LabDiet, USA) and fresh fruit *ad libitum*. Primate enrichment devices and treats were provided daily. The animals were not subjected to any experiments or given opioid compounds for 1 month before the start of the study. The animals were assigned to each experiment based on the tasks they were trained to perform. All experiments followed a within-subject design (*i.e.*, each group of animals served as its own control and all dosing conditions were randomized by a counterbalanced design). All experiments were conducted during weekday late mornings until the time courses or testing sessions were completed. All animal care and experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Wake Forest University (Winston-Salem, North Carolina). The current study was reported in accordance with the Animal Research: Reporting of *In Vivo* Experiments[26] and designed in settings similar to those reported previously.[27]

Acute Thermal Nociception

μ Receptor agonists change nociceptive thresholds and produce antinociception in both nonhuman primates and humans. Warm water tail-withdrawal assays[27,28] were conducted to examine the thermal antinociceptive effects of cebranopadol and fentanyl. Monkeys were seated in primate restraint chairs, and the lower parts of their shaved tails (~15 cm) were immersed in water maintained at 42°, 46°, or 50°C. Water at 42° or 46°C was used as a non-noxious stimulus (*i.e.*, no tail-withdrawal expected), and water at 50°C was used as an acute noxious stimulus (*i.e.*, 2- to 3-s tail-withdrawal latency), but did not cause thermal injury. The primary outcome was tail-withdrawal latency. Monkeys were randomly assigned to the dosing condition. Experimenters unaware of the dosing conditions measured the tail-withdrawal latencies at each temperature randomly using a computerized timer. A maximum time of 20 s (the cutoff) was recorded if the monkey did not withdraw its tail within 20 s. The latencies were measured before and at multiple time points after subcutaneous or intrathecal

administration of a single dose of the test compound. Tail-withdrawal latencies at 42° and 46°C after exposure to 50°C water remained at 20 s. For dose–response curves, cebranopadol was subcutaneously administered by a cumulative dosing procedure with a 30-min interinjection interval. Tail-withdrawal latencies were measured 20 min after each injection. To determine the involvement of the four opioid receptors in cebranopadol-induced antinociception, monkeys were subcutaneously given selective μ receptor antagonist naltrexone (0.03 mg/kg), selective nociceptin receptor antagonist J-113397 (0.1 mg/kg), or δ receptor antagonist naltrindole (1 mg/kg) 15 min before cebranopadol administration, whereas the κ receptor antagonist 5′-guanidinonaltrindole (1 mg/kg) was given 24 h before cebranopadol administration. The doses and pretreatment time for these antagonists were chosen to show their selective receptor antagonism in rhesus macaques based on previous studies.[29–32]

Itch-scratching Responses

The scratching behavior[31] of monkeys in their home cages was recorded to assess itching sensation caused by the test compounds. Each 15-min recording session was conducted after subcutaneous or intrathecal administration of cebranopadol, fentanyl, or morphine. The primary outcome measure was the number of scratches. A scratch was defined as one brief (less than 1 s) scraping on the skin surface of other body parts using the forepaw or hind paw. The total number of scratches was counted and summed for each 15-min period by experimenters blinded to the dosing conditions.

Drug Self-administration

Six monkeys implanted with IV catheters were used in the drug self-administration procedure in the operant chamber under two different schedules of reinforcement. The primary outcome was the number of drug injections that animals received during the test session. The fixed-ratio 30 schedule of reinforcement[33,34] was used to determine whether cebranopadol had a reinforcing effect. The progressive ratio schedule of reinforcement was used to compare the reinforcing strengths of cebranopadol and fentanyl, which can differentiate reinforcing strengths of abused drugs that function as positive reinforcers.[6,35,36] The ratio progression of the progressive-ratio schedule was from 20 (first injection) to 25, then to 32, 40, 50, 62, 77, 95, 117, 144, 177, 218, 267, 328, and finally 402 (15th injection). The operant response was maintained at 3 μg/kg per injection of oxycodone until the response was stable (mean ± three injections for three consecutive sessions). Dose–effect curves were determined by substituting saline or various doses of cebranopadol (0.01 to 0.06 μg/kg per injection) or fentanyl (0.03 to 0.3 μg/kg per injection) for the maintenance dose in a random order under the fixed-ratio 30 schedule. The dose range for the progressive-ratio schedule was cebranopadol (0.03 to 0.3 μg/kg per injection) and fentanyl (0.1 to 0.6 μg/kg per injection). Doses were available for at least five consecutive sessions until the response was considered stable. On average, the animals were tested for four to five sessions. The blinding method was not used when collecting drug self-administration data, as these data were generated directly from the animals.

Respiratory Responses

The acute effects of cebranopadol and fentanyl on respiratory function were evaluated in four freely moving monkeys implanted with the D70-PCTR telemetry transmitter[6] (Data Sciences International, USA). Respiration data from 30 min before and 60 min after intramuscular administration of cebranopadol (0, 5.6, 10, and 18 μg/kg) or fentanyl (0, 30, and 56 μg/kg) were continuously collected and analyzed using Ponemah software v5.2. The primary outcomes were respiration rate and minute volume. The mean value of each 5-min time block was generated from each animal to represent the measured outcome for each data point. The blinding method was not used when collecting telemetry data, as these data were generated directly from the telemetry device.

Surgical Implantation

The surgical details regarding the implantation of telemetry devices and intrathecal catheterization have been reported previously.[6,37] For preoperative care, animals were administered atropine (0.04 mg/kg, intramuscular), buprenorphine (0.01 to 0.03 mg/kg, intramuscular), dexamethasone (2 mg/kg, IV), and cefotaxime (500 mg, IV) before surgery for pain relief and infection prevention. Animals were then anesthetized with ketamine (10 mg/kg, intramuscular) and intubated, and anesthesia was maintained *via* isoflurane inhalation (1 to 2% in 1 l/min O_2). Intraoperative monitoring was conducted to determine the depth of anesthesia and physiologic status. Monkeys were administered postoperative buprenorphine (0.003 to 0.02 mg/kg, intramuscular) and meloxicam (0.15 mg/kg, subcutaneous) to alleviate pain and inflammation, and ceftiofur (2.2 mg/kg, intramuscular) to prevent infection. Postoperative care was performed daily until the veterinarians confirmed that healing was complete. All animals were monitored daily by veterinarians and laboratory staff to ensure that they remained healthy throughout the study.

For intrathecal catheterization, hemilaminectomy was performed in the lateral aspect of the L4 or L5 vertebral body to expose the dura mater. The intrathecal catheter (3.0 Fr) was then inserted into the intrathecal space and advanced rostrally to place the catheter tip in the lumbar region L1 to L2. Confirmation of catheter placement within the intrathecal space was determined by observing the cerebrospinal fluid flow from the tip of the catheter. The

catheter was routed subcutaneously from the hemilaminectomy site to the vascular access port site and attached to the port. The patency of the intrathecal catheter was confirmed using fluoroscopy after surgery. During the study period, the functionality of the catheter was evaluated based on the fluency of the injection and the response of the implanted monkey to intrathecal morphine. The longevity of the catheter varied from 2 to 4 yr. The suspected malfunction of the catheter was investigated using fluoroscopy.

Drugs

Cebranopadol (Chemical Abstracts Service No. 863513-91-1; molecular weight, 378.5; logP, 4.7) was purchased from MedChemExpress (USA). A concentrated stock solution of cebranopadol was formulated in dimethyl sulfoxide/Tween 80/5% glucose at a ratio of 1:1:18. The stock was diluted with sterile water to obtain the target working solution. The vehicle diluted by the same fold as the test compound was used as a control for both systemic and intrathecal administration. Fentanyl hydrochloride, morphine sulfate, oxycodone hydrochloride, naltrexone hydrochloride, and naltrindole (National Institute on Drug Abuse, USA) were dissolved in sterile water. 5′-Guanidinonaltrindole (National Institute on Drug Abuse) was dissolved in sterile saline. J-113397 was dissolved in dimethyl sulfoxide/Tween 80/sterile water at a ratio of 1:1:8. An injection volume of 0.1 ml/kg was used for systemic drug administration. For intrathecal administration,[37] a total volume of 1 ml test compound or the control vehicle was administered through the subcutaneous access port, followed by 0.35 ml of saline to flush the dead volume of the port and catheter. For all systemic and intrathecal single-dosing procedures, drugs were administered at 1- to 2-week intervals.

Statistical Analysis

The dose–response curves were analyzed using a previously reported method.[38] Individual tail-withdrawal latencies were converted to the percent of maximum possible effect using the following formula: % maximum possible effect = [(test latency − control latency)/(cutoff latency − control latency)] × 100. The mean ED_{50} values were obtained after the log transformation of individual ED_{50} values, which were calculated by linear regression using the portion of the dose–effect curves spanning the 50% maximum possible effect, and 95% CIs were also determined. In addition, dose ratios were calculated by dividing the mean ED_{50} values in the presence of the antagonist by the baseline ED_{50} values. Significant shifts in dose–effect curves were defined when their 95% CI of ED_{50} values did not overlap.

GraphPad Prism v9 software (GraphPad Software, USA) was used for statistical analysis. Blinding was not used to analyze the data. No statistical power calculations were performed before the study. The sample size was determined based on our previous experience with this design.[7,37] Data are presented as mean values ± SD calculated by treatment and time using individual data from all studies. Comparisons were made for the same monkeys across all test sessions for the same experiment. For figures 1, 3, and 4, the repeated measures ANOVA was used to compare the outcome measure (*i.e.*, tail-withdrawal latency and number of scratches) between two factors: dose and time (a two-tailed test). The interactions between the dose and time were also evaluated. For figure 2, the mixed-effects model with random intercept was used to examine the association between the outcome measure (*i.e.*, number of drug injections) and dose. Each monkey was subjected to different treatments; a mixed-effects model was used to handle the correlated structure. A Dunnett multiple comparison test was used to correct for multiple tests. The significance level was set at $P < 0.05$. The assumptions of the ANOVA were verified by D'Agostino–Pearson omnibus (K2) tests for normality and Brown–Forsythe tests for homogeneity of variance. There were no missing data except for the drug self-administration experiment, in which one monkey missed some dosing conditions (saline; cebranopadol, 0.06 μg/kg per injection; fentanyl, 0.03 and 0.3 μg/kg per injection [fig. 2A]; saline; oxycodone; and cebranopadol, 0.03 and 0.3 μg/kg per injection [fig. 2B]) due to malfunction of its IV catheter that was not related to the testing drugs. A few potential outliers were identified based on scatter plots. Since these values represented real data, potential outliers were included in the evaluation with unremarkable findings. Scatter plots showing the raw data from individual monkeys with the mean and SD imposed are presented in Supplemental Digital Content (http://links.lww.com/ALN/C640).

Results

Systemic Cebranopadol Produces Potent Antinociceptive Effects, but not Itch-scratching Response

Subcutaneous cebranopadol (1 to 5.6 μg/kg) produced antinociceptive effects in the acute thermal nociception assay in a dose-dependent ($F_{3,15} = 22$; $P < 0.001$) and time-dependent ($F_{4,20} = 101.9$; $P < 0.001$) manner with significant interaction between dose and time ($F_{12,60} = 23.1$; $P < 0.001$) (fig. 1A). In comparison, fentanyl (10 to 30 μg/kg) displayed antinociception in the same group of animals (dose [$F_{2,6} = 18.6$; $P = 0.003$]; time [$F_{4,12} = 176.7$; $P < 0.001$]; dose × time interaction [$F_{8,24} = 23.6$; $P < 0.001$]) (fig. 1B). The minimum effective dose of cebranopadol to produce full antinociception was 5.6 μg/kg (ED_{50}, 2.9 [95% CI, 1.8 to 4.6] μg/kg) (fig. 1A), which was approximately five-fold more potent than fentanyl, producing near full antinociception at 30 μg/kg (ED_{50}, 15.8 [95% CI, 14.6 to 17.1] μg/kg) (fig. 1B). The duration of the antinociceptive action of cebranopadol (3 h) was slightly longer than that of fentanyl (2 h) (fig. 1, A and B). For the antinociceptive

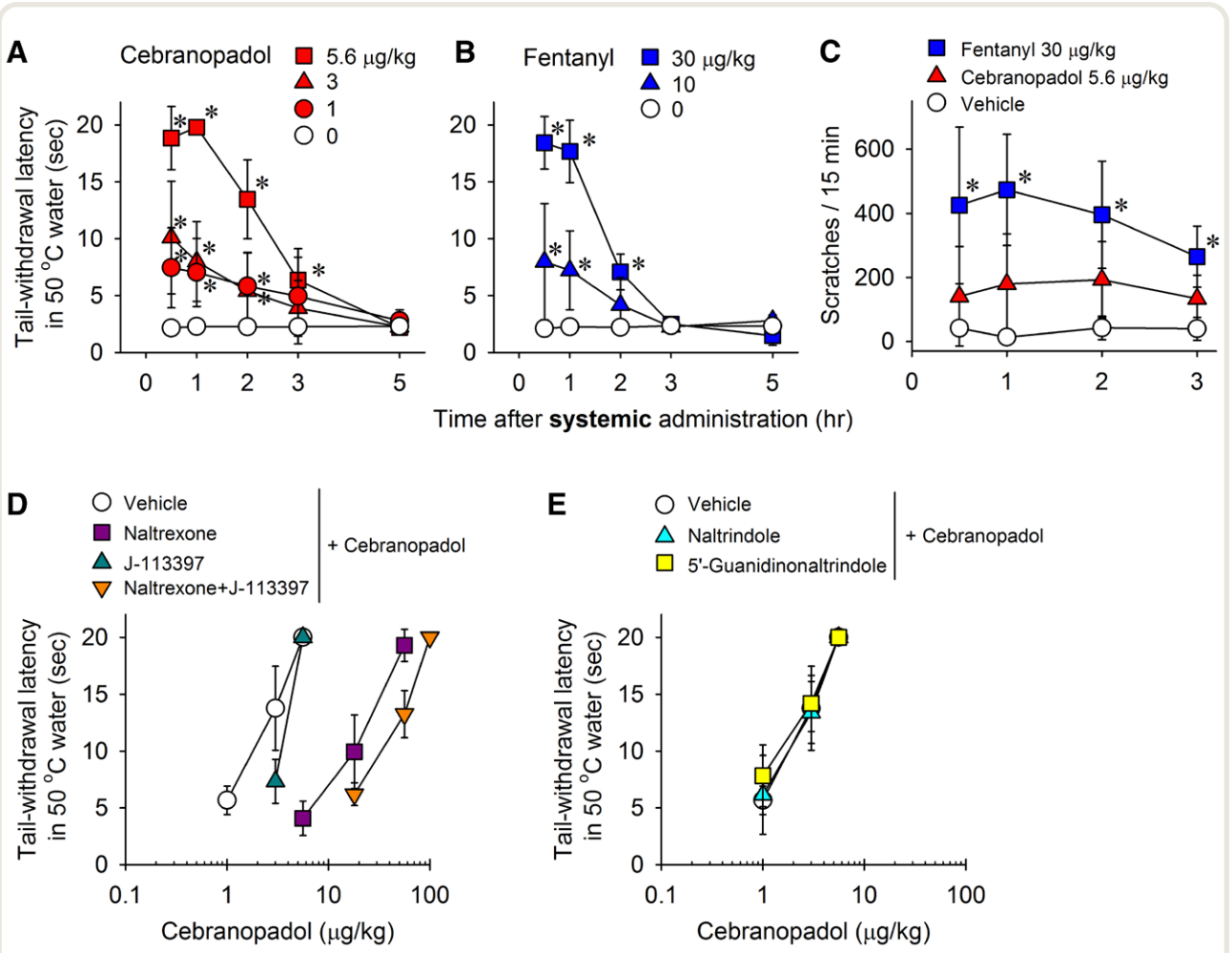

Fig. 1. Effects of systemic administration of cebranopadol on thermal nociception and itch-scratching responses in monkeys. Time courses of cebranopadol-induced (*A*) and fentanyl-induced (*B*) antinociception against an acute noxious stimulus (50°C water). (*C*) Time courses of itch scratching responses elicited by cebranopadol (5.6 μg/kg) and fentanyl (30 μg/kg) at antinociceptive doses. (*D*) Effects of μ receptor antagonist naltrexone (0.03 mg/kg) and nociceptin receptor antagonist J-113397 (0.1 mg/kg) on cebranopadol-induced antinociception. (*E*) Effects of δ receptor antagonist naltrindole (1 mg/kg) and κ receptor antagonist 5′-guanidinonaltrindole (1 mg/kg) on cebranopadol-induced antinociception. All drugs were delivered subcutaneously. Data represent the mean ± SD (n = 6 [*A, C*]; n = 4 [*B, D, E*]) and were analyzed by two-way repeated measures ANOVA followed by the Dunnett multiple comparison test. **P* < 0.05, significantly different from the vehicle condition.

doses, cebranopadol 5.6 μg/kg did not significantly increase scratching responses, whereas fentanyl 30 μg/kg markedly increased the number of scratches in the same group of monkeys ($F_{2,10}$ = 45.1; *P* < 0.001) (fig. 1C).

Dose–response curves were generated for cebranopadol-induced thermal antinociception with vehicle pretreatment (ED_{50}, 2.1 [95% CI, 1.2 to 3.8] μg/kg). In the antagonist studies, pretreatment with μ receptor antagonist naltrexone 0.03 mg/kg and nociceptin receptor antagonist J-113397 0.1 mg/kg resulted in ED_{50} of 19 (95% CI, 11.1 to 32.5) and 3.6 (3.2 to 4) μg/kg, respectively, corresponding to approximately nine- and two-fold rightward shifts of the dose–response curves. Additionally, combined pretreatment with naltrexone and J-113397 revealed a larger rightward shift (30-fold) with an ED_{50} of 41.8 (95% CI, 27.4 to 63.7) μg/kg for the cebranopadol dose–response curve (fig. 1D). In contrast, pretreatment with δ receptor antagonist naltrindole 1 mg/kg (ED_{50}, 2 [95% CI, 0.9 to 4.3] μg/kg) or κ receptor antagonist 5′-guanidinonaltrindole 1 mg/kg (ED_{50}, 1.7 [95% CI, 0.9 to 3.3] μg/kg) did not affect the dose–response curve. Therefore, μ and nociceptin receptors, but not δ and κ receptors, contributed to the antinociceptive effects of cebranopadol. These findings suggest that systemic cebranopadol has a promising analgesic profile in primates that is pharmacologically distinct from classical μ-opioid analgesics such as fentanyl.

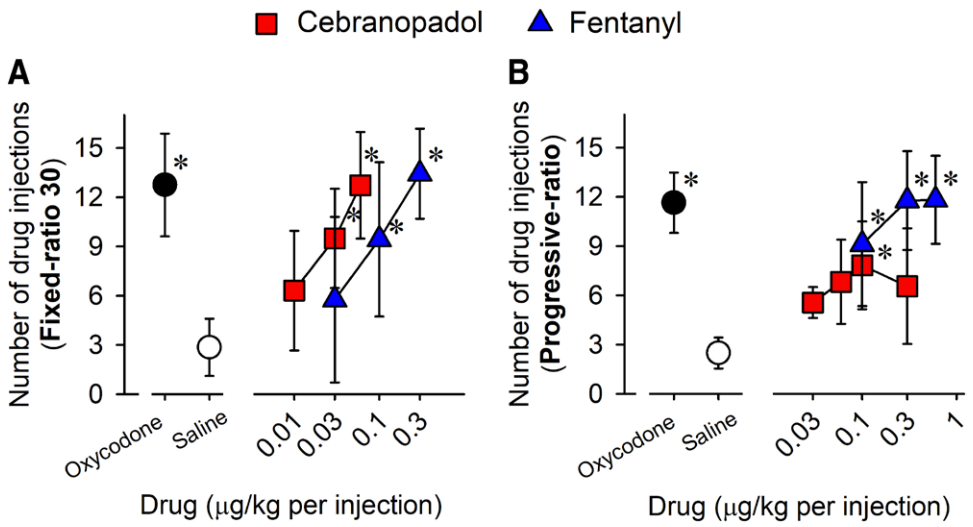

Fig. 2. Reinforcing effects and strength of cebranopadol compared with fentanyl measured by intravenous drug self-administration in monkeys. (*A*) Number of injections received as a function of dose in monkeys responding to oxycodone (3 μg/kg per injection; n = 6), saline (~0.14 ml/kg per injection; n = 5), cebranopadol (0.01 [n = 6]; 0.03 [n = 6]; and 0.06 [n = 5] μg/kg per injection), or fentanyl (0.03 [n = 5]; 0.1 [n = 6]; and 0.3 [n = 5] μg/kg per injection) under a fixed-ratio 30 schedule of reinforcement. (*B*) Number of injections received as a function of dose in monkeys responding to oxycodone (3 μg/kg per injection; n = 5), saline (~0.14 ml/kg per injection; n = 5), cebranopadol (0.03 [n = 5]; 0.06 [n = 6]; 0.1 [n = 6]; and 0.3 [n = 5] μg/kg per injection), or fentanyl (0.1, 0.3, and 0.6 μg/kg per injection; n = 6) under a progressive-ratio schedule of reinforcement. Data represent the mean ± SD and were analyzed by the mixed-effects model. **P* < 0.05, significantly different from saline.

Cebranopadol Produces Reinforcing Effects with Reduced Reinforcing Strength

In the IV drug self-administration paradigm, substitution of saline for the maintenance dose of oxycodone (3 μg/kg per injection) resulted in a much lower number of injections under both fixed-ratio 30 ($P < 0.001$) and progressive-ratio ($P < 0.001$) schedules. Under the fixed-ratio 30 schedule, both cebranopadol (0.03 [$P = 0.021$] and 0.06 [$P < 0.001$] μg/kg per injection) and fentanyl (0.1 [$P = 0.023$] and 0.3 [$P < 0.001$] μg/kg per injection) functioned as reinforcers, showing a main effect of dose for both cebranopadol and fentanyl (fig. 2A). Similar to the more potent antinociceptive effect previously described, cebranopadol showed higher potency in producing reinforcing effects when compared to fentanyl (fig. 2A). Under the progressive-ratio schedule, both cebranopadol (0.1 μg/kg per injection; $P = 0.011$) and fentanyl (0.1 [$P = 0.001$], 0.3 [$P < 0.001$], and 0.6 [$P < 0.001$] μg/kg per injection) showed a significantly higher reinforcing strength than saline; however, the reinforcing strength of cebranopadol was relatively lower than that of fentanyl (fig. 2B). At the highest dose tested, monkeys earned 12 ± 3 injections (mean ± SD) of fentanyl (0.6 μg/kg per injection), but only 7 ± 3 injections of cebranopadol (0.3 μg/kg per injection) (fig. 2B). These data demonstrated that cebranopadol produced a reinforcing effect and a relatively lower reinforcing strength than the selective μ receptor agonist fentanyl.

Higher Doses of Cebranopadol Do Not Compromise Respiratory Function

Fentanyl at a dose of 30 μg/kg produced full antinociception but did not significantly change the respiratory parameters (fig. 3, A and B). However, as an opioid known to cause respiratory depression in humans, fentanyl caused drastic reductions in the respiration rate ($F_{2,6} = 9.7$; $P = 0.013$) and minute volume ($F_{2,6} = 6.6$; $P = 0.031$) in monkeys at a dose of 56 μg/kg, approximately two-fold of its antinociceptive dose, showing a respiration rate of 8 ± 2 breaths/min (mean ± SD) at 15 min after fentanyl administration (fig. 3, A and B). In contrast, when given to the same group of monkeys at the antinociceptive dose 5.6 μg/kg or doses approximately two- to three-fold of its antinociceptive dose (10 and 18 μg/kg), cebranopadol did not significantly change the respiratory rate ($F_{3,9} = 3.8$; $P = 0.053$) or minute volume ($F_{3,9} = 2.6$; $P = 0.115$), and showed a respiration rate of 17 ± 2 breaths/min (mean ± SD) at 15 min after the administration of cebranopadol (10 μg/kg) (fig. 3, C and D). Therefore, cebranopadol may function as a safer analgesic than fentanyl.

Intrathecal Cebranopadol Produces Potent Antinociception but Not Itch Sensation

Intrathecal cebranopadol (0.18 to 1 μg) produced antinociceptive effects in the acute thermal nociception assay in a dose-dependent ($F_{3,15} = 33.7$; $P < 0.001$) and time-dependent

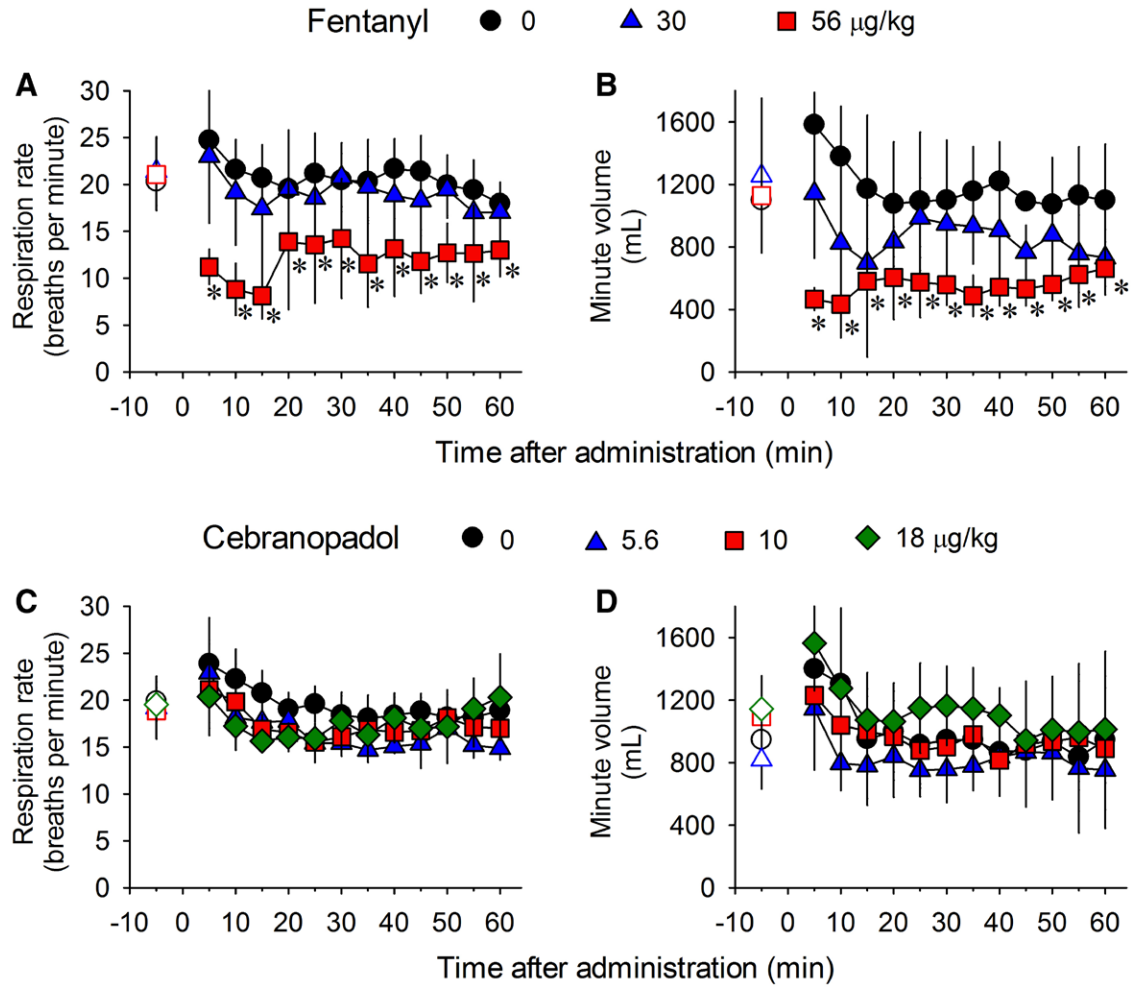

Fig. 3. Comparison of systemic cebranopadol- and fentanyl-induced changes of respiratory parameters in freely moving monkeys implanted with telemetric probes. (*A, C*) Respiration rate; (*B, D*) minute volume. Data represent the mean ± SD (n = 4) from each individual data averaged from a 5-min time block. Both drugs were delivered intramuscularly. *Open symbols* represent the baseline data of the different dosing conditions from the same monkeys before drug administration. Data were analyzed by two-way repeated measures ANOVA followed by the Dunnett multiple comparison test. **P* < 0.05, significantly different from the vehicle condition.

($F_{4,20}$ = 160.4; $P < 0.001$) manner, with significant interaction between dose and time ($F_{12,60}$ = 26.7; $P < 0.001$) (fig. 4A). The minimum effective dose of cebranopadol to produce full antinociception was 1 μg. The antinociceptive action lasted approximately 3 h and subsided after 5 h (fig. 4A). Additionally, this dose of intrathecal cebranopadol (1 μg) did not significantly increase scratching responses. In contrast, intrathecal morphine (30 μg), an antinociceptive dose shown in a previous study,[8] elicited robust scratching responses in the same group of monkeys ($F_{2,10}$ = 19.3; $P < 0.001$) (fig. 4, B and C). The total number of scratches summed from the four 15-min recording sessions was 231 ± 137 (mean ± SD) for 1 μg of cebranopadol, in contrast to 3,009 ± 1,474 for 30 μg of morphine (fig. 4C). These data suggest that cebranopadol could serve as a promising spinal analgesic.

Discussion

Here, we documented the acute effects of cebranopadol after systemic and intrathecal administration. Although cebranopadol has been demonstrated to have analgesic efficacy in human studies,[14,15] this nonhuman primate study provides additional information. Systemic cebranopadol produced antinociception, mainly mediated by μ receptors. It was safe and did not compromise respiratory functions at a dose approximately tenfold of its analgesic ED_{50} value. No pruritic effect was observed after either systemic or intrathecal administration of cebranopadol. Cebranopadol produced reduced reinforcing strength relative to fentanyl; however, it retained a certain degree of reinforcing effects and strength, implying its potential abuse liability. Overall,

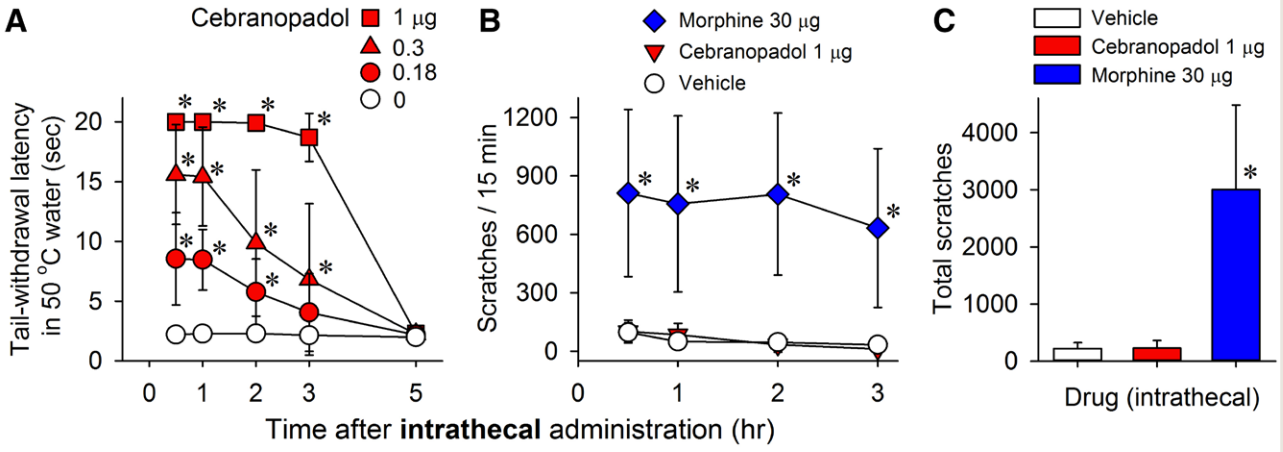

Fig. 4. Effects of intrathecal administration of cebranopadol on thermal nociception and itch scratching responses in monkeys. (*A*) Time courses of cebranopadol-induced antinociception against an acute noxious stimulus (50°C water). (*B*) Time courses of itch-scratching responses elicited by cebranopadol (1 μg) and morphine (30 μg) at antinociceptive doses. (*C*) Total number of scratches summed from the four time points shown in *B*. Data represent the mean ± SD (n = 6) and were analyzed by two-way (*A* and *B*) or one-way (*C*) repeated measures ANOVA followed by the Dunnett multiple comparison test. **P* < 0.05, significantly different from the vehicle condition.

cebranopadol displayed analgesic efficacy similar to that of clinically used μ receptor agonists such as fentanyl and morphine, but with an improved side effect profile.

Subcutaneous cebranopadol more potently produced acute antinociception with a similar duration of action compared to fentanyl, yet without the accompanying itch-scratching responses. The full efficacy and high potency of cebranopadol in the nonhuman primate model of acute pain were consistent with its analgesic efficacy in rodents and humans, whereas the duration of antinociceptive action (3 h) in nonhuman primates was shorter than that in the rat/mouse tail-flick assay.[12,15] The antagonist studies revealed a larger μ receptor contribution than the nociceptin receptor, and no involvement of δ and κ receptors in cebranopadol-induced antinociception in the nonhuman primate model of acute pain. δ and κ Receptor agonists are known to cause convulsions or sedation in nonhuman primates[24]; therefore, the absence of convulsive and sedative behaviors after cebranopadol administration in our study is consistent with the lack of involvement of δ and κ receptors. The nociceptin receptor antagonist had a weak influence on the antinociceptive effect of cebranopadol. This is different from the stronger nociceptin receptor antagonist effect toward AT-121–induced antinociception.[7] This difference may imply that μ receptor full agonists are more efficacious than agonists selective for other opioid receptor subtypes to suppress this nociceptive response in primates. Dual μ and nociceptin receptor agonism has been reported in a rat model of arthritis pain.[39] In contrast, in a rat model of spinal nerve ligation, pretreatment with antagonists for μ, nociceptin, δ, and κ receptors all attenuated the effect of cebranopadol to a similar degree and revealed a synergistic interaction of nociceptin receptor with μ/δ/κ receptors.[40,41] This difference might be attributed to differences in species (nonhuman primate *vs.* rodent) and pain modalities (acute pain, inflammatory pain, and neuropathic pain). The plasticity of the nociceptin ligand–receptor system in different pain states largely influences the functional expression and regulation of nociceptin receptors and their interaction with μ receptors.[42] Nonetheless, the current study indicated that the μ receptor was the main driving force for the antinociceptive effect of cebranopadol in nonhuman primates. Thus, caution should be used when utilizing cebranopadol for acute pain management. It would be interesting to examine whether the effect of a nociceptin receptor antagonist on cebranopadol-induced analgesia changes in nonhuman primates in different pain states.

In addition to demonstrating efficacious analgesic effects, another critical aspect in developing novel analgesics is to evaluate whether they display favorable side effect profiles (*e.g.*, devoid of abuse potential). Knowing that both fentanyl and cebranopadol are lipophilic[13] and highly potent relative to other opioids, we conducted a side-by-side comparison between fentanyl and cebranopadol, using an IV drug self-administration assay under two different schedules of reinforcement. Our results showed that cebranopadol produced fentanyl-comparable reinforcing effects under the fixed-ratio 30 schedule; nevertheless, its reinforcing strength was lower than that of fentanyl under the progressive-ratio schedule. This was different from rodent studies that showed ambiguous rewarding effects in the conditioned place preference paradigm.[19,20] Although a human study showed that oral cebranopadol produced lower drug-liking effects than μ receptor agonist hydromorphone,[43] the reinforcing effects of

cebranopadol were not observed with other reported nociceptin/μ receptor partial agonists, such as AT-121, BU08028, and BU10038, in the same experimental paradigm.[6–8] It is difficult to conceive the potential use of IV cebranopadol for the management of pain compared to other nociceptin/μ receptor partial agonists that have no reinforcing strength. Considering that cebranopadol shows full efficacy, whereas the other three mixed agonists show only partial efficacy at both nociceptin and μ receptors, it is reasonable to conclude that although the reinforcing strength of cebranopadol was attenuated, nociceptin receptor activation might not be sufficient to completely block full μ receptor agonist–associated abuse potential. The balance between nociceptin and μ receptor efficacy could determine different pharmacologic profiles of mixed nociceptin/μ receptor agonists, particularly in terms of their abuse potential. Given that the highly potent opioid fentanyl is widely abused in the United States, the detectable reinforcing effect and strength of IV cebranopadol indicate its potential abuse liability and warrant caution for its clinical use.

Another side effect of classical opioid drugs is respiratory depression, which limits the therapeutic window of opioids and raises safety concerns. This is a major problem leading to increased opioid overdose deaths during the opioid epidemic. We found that cebranopadol did not affect respiratory function at a dose three-fold of the full analgesic dose, in clear contrast to fentanyl, which caused significant decreases in respiration rate and minute volume by doubling the full analgesic dose, thus demonstrating a wider safety window for cebranopadol. The lack of a respiratory depressant effect of cebranopadol in nonhuman primates is consistent with observations in rodent and human studies,[12,16] which could be attributed to the counterbalancing effect of nociceptin receptor agonist activity against μ receptor–dependent respiratory depression. Similar widened therapeutic windows have also been demonstrated with AT-121, BU08028, and BU10038.[6–8] These findings support the research strategy to develop nociceptin/μ receptor agonists as innovative analgesics with improved safety profiles.

The spinal delivery of opioids, such as morphine, is a standard procedure for perioperative analgesia and is effectively used in different clinical contexts.[44,45] However, its effectiveness in pain management is compromised by an intense itching sensation.[23,46] The nonhuman primate model of spinal morphine–induced itch has proven useful for evaluating the pruritic effects of drug candidates.[31,37,47] In this model, intrathecal cebranopadol was more potent than morphine but did not elicit itch-scratching responses. Spinal cebranopadol also showed high potency in producing antinociception and antihyperalgesia in rodents.[48] These observations further strengthen the notion that simultaneous activation of nociceptin and μ receptors enhances the potency of analgesia without eliciting any common side effects. Delayed respiratory depression is associated with hydrophilic morphine rather than lipophilic neuraxial opioids.[49] Although cebranopadol is lipophilic and systemic cebranopadol does not cause respiratory depression, it is important to further investigate whether this potential side effect is associated with spinal delivery of morphine *versus* cebranopadol. Systemic cebranopadol has been associated with several side effects (*e.g.*, dizziness, vomiting, nausea, and constipation) in clinical studies,[17,43] making its use by a systemic route questionable. Given that intrathecal cebranopadol potently produced antinociception with good tolerability in nonhuman primates, intrathecal delivery of cebranopadol for pain management may limit the classical side effects observed with μ receptor agonists. These findings provide a pharmacologic basis for the development of cebranopadol as a promising spinal analgesic.

In summary, our study demonstrated that cebranopadol displayed analgesic efficacy with an improved side effect profile compared with the clinically used μ receptor agonists fentanyl and morphine. It further supports nociceptin and μ receptor coactivation as a viable strategy to develop mixed nociceptin/μ receptor agonists as innovative analgesics with fewer side effects. However, cebranopadol (nociceptin/μ receptor full agonist) has higher abuse liability than AT-121 or other nociceptin/μ receptor partial agonists in nonhuman primate models[6–8]—that is, nociceptin receptor activation suppresses the reinforcing strength mediated by partial, not full, μ receptor agonists. These findings indicate that nociceptin/μ receptor partial agonists might have a favorable side effect profile. In clinical studies, cebranopadol has shown encouraging efficacy in treating patients with chronic pain.[17,50] Several rodent studies have suggested a slower tolerance development and lower potential to produce physical dependence after cebranopadol treatment.[12,15,17] It is essential to further evaluate these outcome measures in nonhuman primates with chronic administration of cebranopadol. Nonetheless, these pharmacologic studies in nonhuman primates document a major difference (*i.e.*, abuse potential) between cebranopadol and nociceptin/μ receptor partial agonists and warrant caution on the clinical use of cebranopadol.

Acknowledgments

The authors thank Kelsey Mabry, B.S., and Brittany Kelly (Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, North Carolina) for their technical assistance with animal training and data collection, Heather DeLoid, D.V.M. (Department of Comparative Medicine, Wake Forest School of Medicine), for performing intrathecal catheterization and telemetry device implantation, and Nicole Bacarella, D.V.M., and Erin Jackson, D.V.M. (Animal Resources Program, Wake Forest School of Medicine), and the Animal Resources Program of Wake Forest University for veterinary care, as well as Editage (Memphis, Tennessee) for editing the manuscript.

Research Support

The work was supported by grants from the National Institutes of Health and the National Institute on Drug Abuse (Bethesda, Maryland; grant Nos. DA-053343, DA-049580, and DA-044450). The content is solely the responsibility of the authors and does not necessarily represent the official views of the U.S. federal agencies.

Competing Interests

The authors declare no competing interests.

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The Heidbrink Anesthetizers: Model A to Z?

The dawn of the twentieth century was a dynamic time for anesthesia machine development, and Jay A. Heidbrink's anesthetizing equipment was among the most successful on either side of the Atlantic. With an alphabet of innovation from the Anesthetizer Model A (*not shown*) in 1912 to the Model T (*left*) in the late 1930s, Dr. Heidbrink refined precise flowmeters and pressure-reducing valves for compressed gas cylinders. As a testament to the Heidbrink Model T's timeless construction, veterinary medical teams repurposed it for field research well into the twilight of the twentieth century. Rather than transport massive marine mammals such as sea lions to the continental United States, veterinary field researchers like Robert B. Heath, D.V.M., M.Sc., opted to modify existing human anesthesia machines with custom circuits and tripods (*upper right*) to withstand his ponderous patients and the unforgiving Alaskan shoreline (*lower right*). Were he alive today, would Dr. Heidbrink have considered renaming Dr. Heath's machine "Model Z" for "Zoological"? (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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