Published in final edited form as:

Anesth Analg. 2013 November ; 117(5): . doi:10.1213/ANE.0b013e31829cc6ae.

Liposomal Bupivacaine as a Single-Injection Peripheral Nerve Block: A Dose-Response Study

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DISCLOSURES:

Name: Brian M. Ilfeld, MD, MS (Clinical Investigation)

Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript

Attestation: Brian M. Ilfeld has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files

Conflicts of Interest: Brian M. Ilfeld consulted for Pacira Pharmaceuticals (during protocol and manuscript authorship periods) and received research funding from Pacira Pharmaceuticals for this investigation, including funding for his nonclinical time used working on this project during enrollment.

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Contribution: This author helped conduct the study and write the manuscript

Attestation: Nisha Malhotra approved the final manuscript

Conflicts of Interest: Nisha Malhotra received research funding from Pacira Pharmaceuticals for this investigation used to compensate nursing staff, volunteers, and the clinical research center.

Name: Timothy J. Furnish, MD

Contribution: This author helped conduct the study and write the manuscript

Attestation: Timothy J. Furnish approved the final manuscript

Conflicts of Interest: Timothy J. Furnish received research funding from Pacira Pharmaceuticals for this investigation used to compensate nursing staff, volunteers, and the clinical research center.

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Attestation: Michael C. Donohue approved the final manuscript

Conflicts of Interest: Michael C. Donohue received research funding from Pacira Pharmaceuticals for this investigation used to compensate nursing staff, volunteers, and the clinical research center; as well as funding for the nonclinical time Dr. Donohue used for this project.

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Contribution: This author helped design the study, conduct the study, and write the manuscript

Attestation: Sarah J. Madison has seen the original study data and approved the final manuscript

Conflicts of Interest: Sarah J. Madison received research funding from Pacira Pharmaceuticals for this investigation used to compensate nursing staff, volunteers, and the clinical research center.

This manuscript was handled by: Terese T. Horlocker, MD

Abstract

Background—Currently available local anesthetics approved for single-injection peripheral nerve blocks have a maximum duration less than 24 hours. A liposomal bupivacaine formulation (EXPAREL®, Pacira Pharmaceuticals, Inc., San Diego, California), releasing bupivacaine over 96 hours, recently gained Food and Drug Administration approval exclusively for wound infiltration, but not peripheral nerve blocks.

Methods—Bilateral single-injection femoral nerve blocks were administered in healthy volunteers (n=14). For each block, liposomal bupivacaine (0–80 mg) was mixed with normal saline to produce 30 mL of study fluid. Each subject received two different doses, one on each side, applied randomly in a double-masked fashion. The end points included the maximum voluntary isometric contraction (MVIC) of the quadriceps femoris muscle and tolerance to cutaneous electrical current in the femoral nerve distribution. Measurements were performed from baseline until quadriceps MVIC returned to 80% of baseline bilaterally.

Results—There were statistically significant dose responses in MVIC (0.09% / mg, SE = 0.03, 95% CI 0.04 to 0.14, $p = 0.002$) and tolerance to cutaneous current (−0.03 mA / mg, SE = 0.01, 95% CI −0.04 to 0.02, $p < 0.001$), however, in the opposite direction than expected (the higher the dose, the lower the observed effect). This inverse relationship is biologically implausible, and most likely due to the limited sample size and the subjective nature of the measurement instruments. While peak effects occurred within 24 hours after block administration in 75% of cases (95% CI 43 to 93%), block duration usually lasted much longer: for bupivacaine doses above 40 mg, tolerance to cutaneous current did not return to within 20% above baseline until after 24 h in 100% of subjects (95% CI 56 to 100). MVIC did not consistently return to within 20% of baseline until after 24 hours in 90% of subjects (95% CI 54 to 100%). Motor block duration was not correlated with bupivacaine dose (0.06 h/mg, SE = 0.14, 95% CI −0.27 to 0.39, $p = 0.707$).

Conclusions—The results of this investigation suggest that deposition of a liposomal bupivacaine formulation adjacent to the femoral nerve results in a partial sensory and motor block of more than 24 hours for the highest doses examined. However, the high variability of block magnitude among subjects and inverse relationship of dose and response magnitude attests to the need for a Phase 3 study with a far larger sample size, and these results should be viewed as suggestive, requiring confirmation in a future trial.

Introduction

Single-injection peripheral nerve blocks provide a maximum duration of 8–24 hours with currently available local anesthetics.¹ Multiple additives such as buprenorphine,² naloxone,³ clonidine,⁴ and dexamethasone⁵ have failed to reliably extend action beyond 24 hours. An alternative approach is to encapsulate a long-acting local anesthetic within microspheres or liposomes.^{6–15} Bupivacaine encapsulated microspheres provided intercostal nerve analgesia for 3–5 days in volunteers.¹⁶ Despite this potential for prolonged analgesia, no such ultra-long-acting local anesthetic appropriate and approved for peripheral nerve blockade is available commercially.

Liposome encapsulated morphine (DepoDur, EKR Therapeutics, Bedminster, New Jersey) was approved by the United States Food and Drug Administration (FDA) specifically to treat postoperative pain and has been available for clinical use since 2004.¹⁷ The medication delivery vehicle for this formulation (DepoFoam, Pacira Pharmaceuticals, Parsippany, New Jersey) containing bupivacaine recently became the first encapsulated local anesthetic approved by the FDA and commercially available for clinical use (EXPAREL®, Pacira Pharmaceuticals).^{18–21} However, the encapsulated bupivacaine is FDA-approved

exclusively for surgical site infiltration. Regarding use in peripheral nerve blocks,²¹ two Phase 1 studies were completed and, based on the safety data, the FDA has now approved subsequent Phase 2 and 3 trials.^a

We therefore designed a dose-response cohort study to investigate the onset, magnitude, and duration of the sensory and motor block produced with varying doses of this recently approved formulation after a single bolus adjacent to the femoral nerve at the approximate level of the inguinal crease in volunteers.

Materials and Methods

Enrollment

The local IRB (University of California San Diego, San Diego, CA) approved all study procedures. The FDA prospectively approved an Investigational New Drug submission initiated through Pacira Pharmaceuticals (IND 69–198) and the trial was prospectively registered at clinicaltrials.gov (NCT01144559). Enrollment included a convenience sample of relatively healthy adult (> 18 years) volunteers of both sexes willing to have bilateral femoral nerve blocks placed and repeated motor/sensory testing for 24–120 hours. Exclusion criteria included daily analgesic use within the previous 6 months; any opioid use within the previous 4 weeks; any neuromuscular deficit of either femoral nerve and/or thigh musculature; body mass index more than 30 kg/m²; incarceration; a coagulation disorder; uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the investigators, might have interfered with study assessments or adherence; previous allergic reaction to study medications, including unencapsulated amide local anesthetics; involvement in a previous investigation involving the study medication; illicit drug or alcohol abuse within the previous year; current pregnancy; nursing mothers; and/or plans on becoming pregnant within one month after study participation. Of note, any individual (e.g., medical trainees, study coordinators, etc.) whose non-study performance was potentially evaluated by the Principal Investigator (B.I.) was considered part of a “vulnerable population” and excluded from volunteering as a study subject as mandated by current United States ethical guidelines.²² All participants provided written, informed consent before any study procedures. This study was performed in a Clinical and Translational Research Institute (University of California, San Diego, California).

Dose Determination

Initial doses of the liposomal bupivacaine began at 0 mg (low: exclusively normal saline as the treatment) and 2 mg (high) for the first subject; and 1 mg (low) and 3 mg (high) for the second subject. The volume of fluid injected for each of the two bilateral femoral nerve blocks was 30 mL. Therefore, the first subject's concentrations were 0 mg / 30 mL (0%) and 2 mg / 30 mL (0.007%); while the second subject's concentrations were 1 mg / 30 mL (0.003%) and 3 mg / 30 mL (0.010%). Unmasking of treatments occurred after the completion of data collection for each subject to allow determination of dosing for subsequent subjects. The dose remained between 0–80 mg per side, determined by the Principal Investigator in consultation with representatives of Pacira Pharmaceuticals before randomization of each subsequent subject. The dose was never increased by more than 20 mg between consecutive subjects.

^aWebsite accessed August 7, 2012: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022496Orig1s000TOC.cfm

Treatment group assignment

The dominant side (right or left) was randomized to one of two treatment groups: the higher or lower concentration of the investigational medication. Randomization was based on computer-generated codes in blocks of two. The Investigational Drug Service prepared the randomization list and all study medication, with each dose provided to the investigators in a 30 mL syringe with IV line extension tubing, both wrapped in opaque tape to retain masking since the relative study drug concentration could be inferred by the opacity of the injectate. One syringe was labeled “Dominant” and the other labeled “Other.” In this manner, all investigators, nursing staff, and subjects remained masked to treatment group assignment during all outcome measurements.

Intervention

In the supine position, subjects had an IV line placed in the upper extremity, standard American Society of Anesthesiologists-recommended external monitors applied, and oxygen administered by nasal cannula (3 L/min). Oral diazepam (10 mg) was administered. After sterile preparation (chlorhexidine gluconate and isopropyl alcohol), bilateral femoral peripheral nerve blocks were inserted using the identical insertion protocol. The dominant side (right vs. left) was always inserted first.

With a 13–6 MHz 38 mm linear array transducer (HFL 38x, SonoSite M-Turbo, Bothell, Washington), the femoral nerve was identified in a transverse cross-sectional (short axis) view at the inguinal crease. A local anesthetic skin wheal was raised lateral to the ultrasound transducer. An uninsulated, 8.9 cm, 17 gauge, Tuohy-tip needle (TeleFlex Medical, Research Triangle Park, North Carolina) was inserted through the skin wheal and directed medially in-plane beneath the transducer toward the femoral nerve with an anterior bevel direction. Study solution (30 mL) was injected as the needle tip approached the lateral edge of the femoral nerve to open the space between the nerve and underlying muscle and avoid needle-nerve contact. The needle was then withdrawn and the contralateral femoral nerve block administered using the same protocol. Subjects remained in the Clinical and Translational Research Institute for 23 hours, or until both quadriceps femoris strength had returned to at least 80% of baseline levels, whichever was longer.

Outcome measurements

We selected measures that have established reliability and validity,^{23–27} and minimal inter-rater discordance.²⁶ Measurements were performed at Hour 0 (baseline), and every 10 minutes through the first hour, every 15 minutes during the second hour, every 30 minutes for the following two hours, and then on the hour until Hour 10. Beginning the following day, measurements were performed every three hours for a total of six times/day. In all cases, measurements were taken in the seated position with the dominant side measured first, followed by the nondominant side. Initially, quadriceps femoris strength was evaluated; followed by tolerance of transcutaneous electrical stimulation 2 cm medial to the distal quadriceps tendon.

Muscle strength—We evaluated muscle strength with an isometric force electromechanical dynamometer (MicroFET2, Lafayette Instrument Company, Lafayette, IN) to measure the force produced during a maximum voluntary isometric contraction (MVIC) in a seated position with the knees flexed at 90°. ²⁶ For quadriceps femoris evaluation, the dynamometer was placed on the ipsilateral anterior tibia perpendicular to the tibial crest just proximal to the medial malleolus. ^{25–27} Subjects were asked to take 2 sec to come to maximum effort contracting the ipsilateral quadriceps femoris, maintain this effort for 5 sec, and then relax. ^{23,27} The measurements immediately before study drug administration were designated baseline measurements, and all subsequent measurements

are expressed as a percentage of the preinfusion baseline.²³ Block onset was defined as a decrease of 10% from baseline quadriceps MVIC,^{28,29} and block duration was defined as the time from the end of local anesthetic (saline) injection and a return of 80% of baseline quadriceps MVIC without return to a lower value.

Sensory effect—We evaluated tolerance of transcutaneous electrical stimulation with the same quantitative procedure as described previously.^{24,30,31} Electrocardiogram pads were placed 2 cm medial to the distal quadriceps tendon and attached to a nerve stimulator (EZstimII, Model ES400; Life-Tech, Stafford, Texas). The current was increased from 0 mA until subjects described mild discomfort, at which time the current was recorded as the tolerated level and the nerve stimulator turned off. All sensory measurements are expressed as a percentage of each patient's preinfusion baseline.

Statistical Analysis

A post hoc analysis of the dose response in MVIC and tolerance was conducted using linear mixed-effects models fit³² (Table 1) with the nlme package³³ in R version 2.15.1 (2012).^b The model included fixed effects for dose and each of the observation times, and subject-specific random intercepts. Note that each subject is observed at two doses for up to 99 hours each, which the model accounts for with the random intercepts. The parameter of interest is the dose effect, which provides the estimated effect, averaged across all observations, of one milligram increase in bupivacaine. We report estimates with standard error (SE), 95% confidence interval (CI), and p-value. In addition, we fit a simple linear mixed model with a fixed intercept and slope to test the association between dose and various event times including motor block (MVIC) onset, motor block peak (MVIC nadir), motor block (MVIC) duration, and sensory block (tolerance to cutaneous electrical current) peak. Since some subjects failed to attain sensory block, we used a Cox Proportional Hazards model to assess effects of dose. The linear models also included subject-specific random intercepts to account for repeated observations made at two different doses. Similarly, the Cox model included a subject-specific frailty term. We checked model assumptions by examining residual plots (see Results). We examined the appropriateness of modeling choices by comparing the Akaike Information Criterion from models with alternative mean and covariance structures. Since subjects remained under observation for various durations, where observations were missing after discharge we imputed the baseline observation to compute area under the curve.

Results

Fourteen subjects enrolled during a 2-month period beginning February 2012. All had bilateral femoral nerve blocks administered per protocol (Table 2). In 4 of the initial subjects the research nurse collecting data recorded the wrong information from the pressure transducer used to measure the quadriceps femoris MVIC (Table 3). Therefore, this MVIC data are unavailable for 4 of 14 subjects. However, there were no other protocol deviations, and tolerance to transcutaneous electrical current was measured and recorded correctly for all 14 subjects (Table 3).

Onset

Onset, defined as a decrease of 10% from baseline quadriceps MVIC, occurred within the first 10 and 20 minutes in 80% and 95% of subjects, respectively (one subject exhibited onset between 40 and 50 min). There was no association between bupivacaine dose and

^bR Software Environment for Statistical Computing, R Foundation for Statistical Computing (version 2.15.1), Vienna, Austria. Available at: <http://www.r-project.org>. Accessed September 25, 2012.

onset time for motor (< 0.01 h/mg, SE = 0.01, 95% CI -0.01 to 0.01 , $p = 0.95$) or sensory (hazard ratio = 1.01 per mg, 95% CI 0.99 to 1.03, $p = 0.31$) block.

Magnitude

Peak effects occurred within 24 hours after block administration in 75% of subjects (95% CI 43 to 93%). There was no association between bupivacaine dose and time until maximum motor block (MVIC nadir, Figure 1; 0.04 h/mg, SE = 0.10, 95% CI -0.18 to 0.26 , $p = 0.67$). In contrast, the association between dose and the time until sensory block peak was statistically significant (Table 3, Figure 1). Each milligram increase in bupivacaine increased the time until sensory block peak 13 min (0.22 h/mg, SE = 0.09, 95% CI 0.01 to 0.43, $p = 0.04$). The linear mixed-effects model also found significant dose responses in MVIC (Figure 2) and tolerance to cutaneous current (Figure 3): for each milligram increase in bupivacaine, the MVIC increased an average of 0.09% (SE = 0.03, 95% CI 0.04 to 0.14, $p = 0.002$) and tolerance to cutaneous current changed -0.03 mA per milligram of bupivacaine (SE = 0.01, 95% CI -0.04 to -0.02 , $p < 0.001$). In other words, the magnitude of motor and sensory block as measured by quadriceps MVIC and tolerance to cutaneous electrical current within the femoral nerve distribution both correlated with local anesthetic dose, but in the opposite direction than expected (the higher the dose, the lower the observed effect). The Akaike Information Criterion preferred the model with time treated as a categorical value and random subject-specific intercepts rather than models with time treated as continuous and/or compound symmetric covariance. The MVIC residual plots revealed skewedness and heavy tails; the significant effect of dose on MVIC was robust to log transformation of the outcome and removal of outlier residuals, which yielded reasonable residual plots.

Duration

MVIC did not consistently return to within 20% of baseline until after 24 h in 90% of subjects (95% CI 54 to 100%); and, for bupivacaine doses above 40 mg, tolerance to cutaneous current did not return to within 20% above baseline until after 24 h in 100% of subjects (Table 3, Figure 4; 95% CI 56 to 100). However, motor block duration was not correlated with bupivacaine dose (0.06 h/mg, SE = 0.14, 95% CI -0.27 to 0.39 , $p = 0.707$).

Adverse events

There was one adverse effect that occurred in the 12th subject (27 years of age; 180 cm; 77 kg; body mass index 24 kg/m²). The day after block administration, the subject noted pruritus around the needle entry site on the right side. The following day he complained of worsening pruritus in the same area, and a mild erythematous area of 10 cm diameter to the needle entry point was observed. The area was not contiguous, and there was no erythema within 2 cm of the entry site. There was no exudate or induration, and the site was not tender to palpation. The subject never exhibited fever, chills, rigors, or nausea/vomiting. Within the next two days the rash and pruritus resolved completely without treatment. The subject was discharged home, per study protocol. The side that had developed the rash had received only normal saline within the femoral nerve block, while the opposite side, without any rash or pruritus, had received 80 mg of study medication. Per protocol, both needle sites had been prepared with chlorhexidine gluconate and isopropyl alcohol. The rash and pruritus were deemed unrelated to the study medication, but the etiology remains undetermined.

Discussion

This dose-response study suggests that deposition of a liposomal bupivacaine formulation adjacent to the femoral nerve results in a partial sensory and motor block of over 24 hours for the highest doses examined, with a very high degree of intersubject variability. However,

we emphasize that because the formulation used in our investigation is currently approved by the FDA exclusively for surgical infiltration, our protocol was executed only after an Investigational New Drug application was approved by this regulating body. In addition, its use in peripheral nerve blocks must still be considered experimental. Of relevance, the current study suggests that the interindividual response to the microsomal bupivacaine varies widely even within a narrow dose range, possibly making clinical application/results unpredictable.

Placebo injections

Quadriceps MVIC data are unavailable from 4 of the initial subjects due to inaccurate recording of measurements by a research nurse. Two of these subjects had received placebo injections, and therefore we repeated placebo injections in two subsequent volunteers who received active treatment (80 mg) in their contralateral limb. For these two subjects, there was extraordinary correlation between active treatment and placebo for both quadriceps MVIC and tolerance to cutaneous electrical current (for these subjects, results of the two limbs receiving 80 mg are presented separately from the other subjects to help demonstrate these findings in Figure 4). These findings are both curious and concerning, and we can only speculate on possible etiologies. The first is a placebo effect, in which each subject experienced quadriceps weakness and decreased cutaneous sensation in the limb that had received active treatment, and this carried over to the contralateral limb. Although possible, we believe it improbable given this same model of bilateral femoral nerve blocks in volunteers has resulted in different results for different intrasubject treatments.³⁴ Another conceivable etiology is a previously unreported effect of perineural normal saline upon the femoral nerve. However, we find this explanation unconvincing given the near-perfect correlation of the limb that received placebo with the side receiving active treatment. Finally, while it is unsettling to raise this possibility, we would be remiss to exclude it: subjects were compensated for their time and efforts on a nightly basis, the more time they spent in the research center, the higher their total compensation. Thus, it is possible that these two subjects (who shared a research center room) purposefully and artificially reproduced their active treatment side findings in their contralateral limbs, in an effort to maximize study participation duration and compensation.

Study Limitations

The inclusion of nonsurgical volunteers makes direct extrapolation to clinical practice difficult since the degree of postoperative analgesia correlating with the level of tolerance to cutaneous electrical current remains undetermined. Discerning the effects of liposomal bupivacaine on postoperative analgesia and optimizing dosing for various peripheral nerve blocks requires Phase 2 and 3 clinical trials involving patients undergoing multiple types of surgical procedures. A related limitation of this investigation is the extremely limited number of subjects, common to all early phase studies. The study protocol produced considerable inter and intrasubject variation in measured sensory and motor responses. There are several potential sources of such variability including the "noise" when small numbers of subjects are studied, the subjective nature of the perception of pain and muscle weakness in this experimental setting involving healthy volunteers, and the potential for variability in responses to the study medication, particularly at the lower dose levels.

Tolerance to cutaneous electrical current in 16 limbs (57%) failed to return to baseline because subject discharge was determined by a bilateral return of quadriceps strength, and not sensory deficit resolution. Thus, the maximum duration of sensory effects remains unknown. Additionally, the doses chosen for each subject were not based on a predetermined algorithm, which resulted in some doses being more represented than others.

Lastly, there is a loss of quadriceps MVIC data from four of the initial subjects due to observation error that decreases the available information for doses from 0–20 mg.

Our data also suggest that the study medication resulted in longer sensory block than motor block, and did not produce substantial motor blockade of a prolonged nature greater than placebo. Combined with the relatively rapid onset time (95% of cases within 10–20 min), this liposomal bupivacaine formulation may provide an effect profile at least as favorable as currently available local anesthetic drugs. Nonetheless, the biologically implausible inverse relationship between dose and response magnitude attests to the need for a Phase 3 study with a larger sample size; and, the results should be viewed as suggestive, requiring future confirmation. Finally, we emphasize this bupivacaine formulation is currently approved by the FDA exclusively for infiltration of surgical wounds. Therefore, for use in peripheral nerve blocks, a Phase 3 trial involving surgical patients is the next logical step.

Acknowledgments

Funding: Funding for this project provided by the Department of Anesthesiology, University of California San Diego (San Diego, California); the Clinical and Translational Research Institute, University of California, San Diego, with funding provided by the National Institutes of Health National Center for Research Resources grant UL1RR031980; and Pacira Pharmaceuticals, Inc. (Parsippany, New Jersey) provided a research grant and product (liposomal bupivacaine) used in this investigation. Dr. Ilfeld conceptualized the study and performed the protocol development, data collection and interpretation, and manuscript preparation, with limited input from Pacira Pharmaceuticals. Dr. Ilfeld and the University of California San Diego retained full legal control over the resulting study data and its publication. Pacira Pharmaceuticals had the opportunity to review and comment—but not approve—the data analysis and resulting manuscript. Dr. Ilfeld was compensated as a consultant when writing the study protocol and manuscript (the consulting agreement was suspended during enrollment per University of California San Diego requirements, and Dr. Ilfeld's nonclinical time during enrollment was partially funded by the research contract between Pacira Pharmaceuticals and the University of California San Diego). The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the funding entities.

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Figure 1.

Effects of a liposomal bupivacaine formulation (EXPAREL[®], Pacira Pharmaceuticals) administered as a single-injection femoral nerve block on motor (Panel A) and sensory (Panel B) block peak (h) versus dose (mg). There was no association between bupivacaine dose and time until maximum motor block (maximum voluntary isometric contraction (MVIC), nadir, 0.04 h/mg, SE = 0.10, 95% CI -0.18 to 0.26, $p = 0.70$). In contrast, the association between dose and the time until sensory block peak was statistically significant. Each milligram increase in bupivacaine increased the time until sensory block peak 13 min (0.22 h/mg, SE = 0.09, 95% CI 0.01 to 0.43, $p=0.04$).

Figure 2. Effects of a liposomal bupivacaine formulation (EXPAREL®, Pacira Pharmaceuticals) administered as a single-injection femoral nerve block on quadriceps femoris strength, as measured with maximum voluntary isometric contraction (MVIC), presented as group means (Panel A) and with 95% CI as shaded regions (Panel B).

Figure 3. Effects of a liposomal bupivacaine formulation (EXPAREL®, Pacira Pharmaceuticals) administered as a single-injection femoral nerve block on sensory block within the femoral nerve distribution, as measured with tolerance to cutaneous electrical current (mA), presented as group means (Panel A) and with 95% CI as shaded regions (Panel B).

Figure 4.

Effects of a liposomal bupivacaine formulation (EXPAREL[®], Pacira Pharmaceuticals) administered as a single-injection femoral nerve block on (Panel A) quadriceps femoris strength, as measured with maximum voluntary isometric contraction (MVIC); and (Panel B) sensory block within the femoral nerve distribution, as measured with tolerance to cutaneous electrical current (group means illustrated). For two subjects receiving both 0 mg (normal saline placebo; yellow line) and 80 mg (black line), the limbs receiving active treatment are presented separately from other subjects receiving 60–80 mg to illustrate the extraordinary correlation between the findings for the placebo and active treatment in these two individuals.

Table 1

Parameter estimates from linear mixed-model of the effect of dose and time from administration. The dose effect was significant with $p < 0.001$. The model also included random intercept ($SD=23.6$) and the residual standard deviation was $SD = 14.3$.

Time (h)	Value	Standard Error	t-Value
0.17	56.94	8.48	6.72
0.33	54.04	8.48	6.38
0.50	53.79	8.48	6.35
0.67	58.94	8.48	6.95
0.83	52.84	8.48	6.23
1	55.24	8.48	6.52
1.25	53.39	8.48	6.30
1.5	52.49	8.48	6.19
1.75	52.44	8.48	6.19
2	51.69	8.48	6.10
2.5	51.59	8.48	6.09
3	47.21	8.55	5.52
3.5	53.89	8.48	6.36
4	50.94	8.48	6.01
5	49.84	8.48	5.88
6	48.84	8.48	5.76
7	47.49	8.48	5.60
8	52.79	8.48	6.23
9	50.64	8.48	5.97
10	44.29	8.48	5.22
24	51.39	8.48	6.06
27	56.29	8.48	6.64
30	61.74	8.48	7.28
33	55.11	8.55	6.44
36	51.56	8.55	6.03
48	62.43	8.59	7.26
51	57.21	8.76	6.53
54	60.28	8.76	6.88
57	62.14	8.76	7.09
60	55.78	8.91	6.26
72	68.43	9.00	7.60
75	55.04	9.42	5.84
78	54.29	9.42	5.76
81	62.67	9.42	6.65
84	71.79	9.42	7.62
96	100.67	9.42	10.68
99	182.24	10.80	16.87
Dose	0.09	0.03	3.15

Table 2

Subject characteristics

	N = 14
Age [yr]	35 (20–44)
Sex [female / male]	7 (50%) / 7 (50%)
Height [cm]	168 (160–198)
Weight [kg]	65 (52–110)
Body mass index [kg/m ²]	24 (20–29)
Dominant limb = right [#]	14 (100%)

Values are reported as median (range) or number of subjects (%)

Table 3

Dose-Response for individual subjects

Dose	Limb	MVIC Returned to > 80% of Baseline (h) §	MVIC Nadir % Baseline	Time (h)	Sensory Block Peak % Baseline	Time (h)
0	Nondominant	*	*	*	127	4
0	Nondominant	*	*	*	275	4
0	Nondominant	99	9	10	486	5
0	Dominant	99	13	10	209	4
1	Dominant	36	12	10	400	10
2	Nondominant	*	*	*	‡	‡
3	Dominant	48	8	24	‡	‡
4	Dominant	*	*	*	125	10
7	Nondominant	*	*	*	‡	‡
10	Nondominant	*	*	*	127	3
15	Dominant	*	*	*	300	4
20	Dominant	*	*	*	156	1
25	Dominant	51	31	1	107	30
30	Dominant	30	52	9	‡	‡
35	Nondominant	51	27	3	225	33
40	Nondominant	30	74	5	‡	‡
40	Nondominant	72	49	6	109	3
50	Nondominant	96	31	48	300	81
60	Dominant	48	52	36	150	27
60	Dominant	72	28	1	190	5
60	Dominant	84	39	24	157	1
60	Nondominant	5	60	4	200	5
70	Dominant	84	40	36	229	84
80	Dominant	99	9	2	363	5
80	Dominant		81	4	325	5
80	Nondominant	72	41	33	150	8
80	Nondominant	99	11	10	200	36

Dose	Limb	MVIC Returned to > 80% of Baseline (h) §	MVIC Nadir % Baseline	MVIC Nadir Time (h)	Sensory Block Peak % Baseline	Sensory Block Peak Time (h)
80	Nondominant	81	37	10	138	24

Values are reported as number of subjects (%)

MVIC: maximum voluntary isometric contraction

§ MVIC returning to and remaining above 80% of baseline after MVIC nadir

* Unavailable due to observation error by research nurse

‡ Subject never exhibited a sensory block > 100% of baseline

Subject never exhibited an MVIC < 80% of baseline