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Ibudilast attenuates peripheral inflammatory effects of methamphetamine in patients with methamphetamine use disorder

Michael J. Li^{1,2}, Marisa S. Briones¹, Keith G. Heinzlerling¹, Mariah Kalmin¹, Steven J. Shoptaw¹

¹Center for Behavioral and Addiction Medicine, Department of Family Medicine, University of California, Los Angeles

²Division of Infectious Diseases, University of California, Los Angeles

Abstract

Background: Preclinical studies suggest that the non-selective phosphodiesterase inhibitor, Ibudilast (IBUD) may contribute to the treatment of METH use disorder through the attenuation of METH-induced inflammatory markers such as adhesion molecules, sICAM-1 and sVCAM-1, and cytokines, IL-6 and TNF- α .

Objective: The present study aimed to test whether treatment with IBUD can attenuate peripheral markers of inflammation during a METH challenge in an inpatient clinical trial of 11 patients.

Methods: This trial followed a randomized, within-subjects crossover design where participants received a METH challenge, during which five participants were treated with placebo then with IBUD, while the remaining six participants were treated with IBUD prior to placebo. Mixed effects regression modeled changes in peripheral markers of inflammation—sICAM-1, sVCAM-1, TNF- α , IL-6, MIF, and cathepsin D—by treatment condition, with measurements at baseline, 60 minutes post-METH infusion, and 360 minutes post-METH infusion.

Results: While on placebo, sICAM-1, sVCAM-1, and cathepsin D significantly increased by 60 minutes post-METH infusion, while IL-6 significantly increased 360 minutes post-METH infusion. Treatment with IBUD significantly reduced METH-induced levels of sICAM-1, sVCAM-1, and cathepsin D at 60 minutes post-METH infusion.

Correspondence: Michael Li, Ph.D., M.P.H., Department of Family Medicine, University of California, Los Angeles, 10880 Wilshire Blvd., Ste. 1800, Los Angeles, CA 90024, mjli@mednet.ucla.edu, 310-825-2557.

Contributors

M.J.L. was responsible for the study concept and analytic approach. S.J.S. developed the study concept and supervised the study. M.S.B. and K.G.H. supervised experimental procedures and contributed to the study concept. M.M.K. contributed to statistical interpretation, reporting of findings, and writing/revision of Results and Discussion.

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Conflict of Interest

No conflict declared.

Conflict of Interest

The authors declare no conflict of interest with this manuscript.

Conclusions: Our findings demonstrate that IBUD attenuated acute pro-inflammatory effects of METH administration, which may have implications for treatment of METH use disorder.

Keywords

phosphodiesterase inhibitor; Ibudilast; methamphetamine; inflammation; cytokine; anti-inflammatory

1. Background

Methamphetamine (METH) use disorder (MUD) poses risk of serious medical and psychiatric problems, yet in the U.S., there are currently no approved medications with demonstrated efficacy for the treatment of MUD (Ballester et al., 2017). However, accumulating evidence from both preclinical and human subjects research suggest that targeting factors involved in METH-induced neuroinflammation may be a strategy for developing a potential therapy for MUD (Beardsley et al., 2010; Birath et al., 2017; DeYoung et al., 2016; Loftis and Janowsky, 2014; Snider et al., 2013; Worley et al., 2016).

METH-induced inflammatory signaling involving cytokines (Loftis et al., 2011; Loftis and Janowsky, 2014; Snider et al., 2013) and adhesion molecules (Loftis et al., 2011; Loftis and Janowsky, 2014), as well as changes in neuroplasticity due to dysregulation of cell death factors (Kanthasamy et al., 2006) may be among the factors driving METH neurotoxicity. Acute inflammation vital to protecting the central nervous system from acute tissue damage or infection. For example, acute inflammatory responses to lipopolysaccharide and METH have been shown to protect dopaminergic neurons and play a role in reestablishing homeostasis following METH-induced vascular and neuronal injury (Czeh et al., 2011; Shaerzadeh et al., 2018). However, based on experimental research, chronic inflammation has recently been considered an underlying risk factor in the development of depression, anxiety, and impaired neurocognition (Bollen et al., 2017; Michopoulos et al., 2017; Miller and Raison, 2016), problems often associated with MUD (Zweben et al., 2004). In response to persistent or high doses of METH use, chronic inflammation is associated with impaired memory loss, depression, anxiety, and other psychiatric problems, and may contribute to MUD (Huckans et al., 2015; Loftis et al., 2011; Loftis and Janowsky, 2014; McAfoose and Baune, 2009). In preclinical models, high METH doses and repeated METH exposure have been shown to be associated with activation of microglia, and in turn, increased expression of cytokines (e.g., IL-6, TNF- α , and MIF), adhesion molecules (e.g., ICAM-1), and the lysosomal protease (e.g., cathepsin D) (Kanthasamy et al., 2006; Loftis et al., 2011; Loftis and Janowsky, 2014; McAfoose and Baune, 2009; Snider et al., 2013). Although the mechanisms by which chronic METH-induced inflammation may impair cognitive functioning is not fully understood, it has been suggested that that these effects may be explained by prolonged, inflammatory-mediated damage to the dopaminergic, serotonergic, and vascular systems, as well as to the blood-brain barrier (Blaker et al., 2016; Ghanbari et al., 2019; Loftis et al., 2011). For these reasons, examining inflammatory marker expression in response to METH challenges in humans may help to evaluate new pharmacological treatments for MUD, particularly those that target neuroinflammation (Beardsley et al., 2010; Worley et al., 2016).

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IBudilast (IBUD) is a non-selective phosphodiesterase (PDE) inhibitor and glial activation inhibitor that has shown potential to reduce METH self-administration and reinstatement in rodents (Brensilver et al., 2013; Worley et al., 2016). IBUD potently inhibits a range of phosphodiesterase families, primarily PDE4, as well as PDEs 3, 10, and PDE11 with IC50s ranging from approximately 1 – 10 μ M (Gibson et al., 2006; Huang et al., 2006; Rolan et al., 2009). The inhibition of PDEs is considered to be the principle mode of action by which IBUD bestows its anti-inflammatory effects in both the peripheral immune system and central nervous system (Huang et al., 2006; Kishi et al., 2001; Mizuno et al., 2004; Rolan et al., 2009). As such, IBUD has been tested for its clinical utility in attenuating inflammatory-related diseases such as neurodegenerative disorders, asthma, allergies, and neuropathic pain (Barkhof et al., 2010; Fox et al., 2018; Kishi et al., 2001; Mizuno et al., 2004; Rolan et al., 2009). Given these pharmacologic properties, IBUD has recently been studied for its potential to reduce the symptoms of substance use disorders and substance use withdrawals—such as with alcohol, opioids, and METH. In preclinical research, IBUD has been shown to suppress expression of adhesion molecules and cytokines in rat brains, suggesting that IBUD may have the potential to inhibit the inflammatory response induced by METH use (Kitazato et al., 2010; Lee et al., 2012). Preliminary research has indicated that treatment with IBUD during METH infusion was associated with reduced subjective effects of METH (e.g., discomfort, sadness, nervousness) (DeYoung et al., 2016; Worley et al., 2016) and improved sustained attention during early abstinence from METH (Birath et al., 2017). However, further research is needed to determine whether IBUD can attenuate inflammatory responses to METH use (Beardsley et al., 2010; Worley et al., 2016).

The purpose of this study is to determine whether IBUD can attenuate METH-induced production of peripheral markers of inflammation, including soluble cellular adhesion molecules (sICAM-1 and sVCAM-1), cytokines (TNF- α , IL-6, and MIF), and the lysosomal aspartyl protease cathepsin D.

2. Methods

2.1. Participants

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Participants were 11 people with METH use disorder (MUD) who completed a placebo-controlled, planned crossover trial of IBUD treatment during METH infusion (Birath et al., 2017; DeYoung et al., 2016; Worley et al., 2016). The mean age of the sample was 42 years (SD = 6.7), 82% (n = 9) were male, and 63.6% (n = 7) identified as white. Participants were eligible for the study if they were aged 18–55, met the DSM-IV-TR criteria for METH use disorder (MUD) as verified by the Structured Clinical Interview for DSM-IV Disorders (First and Gibbon, 2004), were not seeking MUD treatment, urine-tested positive for METH at least once prior to admission, and had normal vital signs for cardiovascular, hepatic, and renal functioning. Participants were excluded if they had current alcohol use or other substance use disorder, seizure disorder, history of head trauma, current psychotropic treatment, recent suicide attempt, or major medical or psychiatric illness, including infections such as HIV and Hepatitis C that could induce inflammatory marker expression. The institutional review boards of LA Biomed and UCLA oversaw all study procedures.

2.2. Study design

The present study tests an a priori stated hypothesis using secondary data analysis of a within-subjects, planned crossover trial with repeated measurements within each treatment period. The 11 participants were randomized to two treatment sequences where five participants received placebo followed by steady state of 50 mg IBUD BID, while the remaining six participants received 50 mg IBUD BID followed by placebo. Participants received each treatment for seven consecutive days with a five-day washout period between each treatment. After five days at each dose (steady state), participants received a 30 mg METH intravenous (IV) challenge delivered over two minutes. Immunoassays were performed on blood samples taken during both 50 mg IBUD treatment and placebo at the following time points: baseline prior to METH infusion, 60 minutes post-METH-infusion, and 360 minutes post-METH-infusion. As such, analyses encompass six data points across 11 participants, for a total of 66 participant-observations. More information on the clinical trial's methods and primary findings are described in prior publication (DeYoung et al., 2016).

2.3. Inflammatory Marker Assay and Analysis

Whole blood was collected in EDTA vacutainers and plasma was extracted, aliquotted, and stored at -80°C until analyzed. Peripheral levels of cytokines, chemokines, and cellular adhesion molecules were measured in duplicate by commercial assay services (Eve Technologies, Calgary AB, Canada) using multiplex immunoassays analyzed with a BioPlex 200. Mixed effects linear regression was used to model within-subject effects of METH-infusion (30 mg) on inflammatory marker levels across three time points within treatment period (baseline, 60 minutes post-METH, and 360 minutes post-METH), as well as within-subject effects of IBUD (50 mg BID) compared to placebo (0 mg BID). Use of mixed effects linear regression allowed us to model treatment (IBUD vs. placebo) as varying within-participant (as all participants received both IBUD and placebo), and this approach accounts for random intercepts between-participants and constant correlation within-participant. Therefore, all participants served as their own controls. The fixed effects parameters included time (to estimate temporal effects of METH infusion), IBUD (to estimate baseline differences by treatment), and time x IBUD interaction term (to test whether IBUD attenuates temporal effects of METH). Treatment sequence was included as a covariate to adjust for possible carryover effects among the six participants who received placebo after completing both IBUD dose phases of the design, though carryover effects are minimized with the five-day washout period prior to blood draw. Based on the fitted models, we computed post hoc predicted means of these inflammatory markers for both IBUD and placebo across time, and then tested for significant changes in these predicted means within each treatment condition. Random intercepts adjusted for within-participant correlations. Power analysis indicated that the 66 participant-observations would meet the minimum threshold of 60 observations for this mixed effects regression, with an anticipated medium effect size of 0.15 and a power of 0.80.

3. Results

Table 1 displays the regression estimates for the mixed models of IBUD on peripheral inflammatory markers sICAM-1, sVCAM-1, cathepsin D, IL-6, TNF- α , and MIF over 360 minutes following METH infusion. Post hoc predicted means of these inflammatory markers are reported over time for both IBUD and placebo at the bottom of Table 1, along with p-values corresponding to changes from the prior time point. Figure 1 illustrates these trajectories for sICAM-1, sVCAM-1, cathepsin D, and IL-6 over the 360-minute period, by treatment condition (note that the illustrated confidence intervals correspond to individual point estimates).

3.1. Inflammatory marker expression following methamphetamine infusion

In the absence of IBUD, 60 minutes following METH infusion sICAM-1 increased by 17.80 ng/mL (95 % CI [6.49, 29.11], $p=.002$), sVCAM-1 increased by 93.70 ng/mL (95% CI [13.06, 174.34], $p = .023$), and cathepsin D increased by 27.93 ng/mL (95% CI [7.19, 48.66], $p = .008$) (Table 1). After this increase, levels of sICAM-1, sVCAM-1, and cathepsin D levels gradually decreased from 60 to 360 minutes in the absence of IBUD, albeit not significantly (see predicted means in Table 1 and Figure 1). IL-6, TNF- α , and MIF did not significantly increase 60 minutes post-METH. At 360 minutes post-METH infusion, IL-6 significantly increased compared to baseline by 24.50 pg/mL (95% CI [3.24, 45.75], $p = .024$). There were no statistically significant increases in other inflammatory markers following METH-infusion.

3.2. IBUD treatment and inflammatory marker expression following methamphetamine infusion

From baseline to 60 minutes post-METH infusion, treatment with IBUD attenuated METH-induced pro-inflammatory response of sICAM-1 by -17.29 ng/mL (95% CI [-34.50 , -0.07] $p = .049$, sVCAM-1 by -113 ng/mL (95% CI [-224.00 , -2.42], $p = 0.045$) and cathepsin D by -30.32 ng/mL (95% CI [-60.36 , -0.29], $p = 0.048$) compared to the placebo condition (Table 1). With IBUD, levels of sICAM-1, sVCAM-1, and cathepsin D remained steady during the entire 360-minute period following MA infusion, and did not significantly change from baseline levels (see predicted means in Table 1 and Figure 1). By 360 minutes post-METH, treatment with IBUD attenuated the METH-induced response of IL-6 by -16.39 pg/mL but did not meet the threshold for significance (95% CI [-34.53 , 1.76], $p = .077$). IBUD was not associated with reduced METH-related changes in other pro-inflammatory markers at 60 or 360 minutes.

4. Discussion

Within-subjects analysis of this randomized, escalation trial of steady state 50 mg IBUD BID versus placebo show significant reductions in specific peripheral inflammatory markers observed at 60 minutes following 30 mg METH infusion. As predicted, in the absence of IBUD, METH administration increased several peripheral markers of inflammation, specifically adhesion molecules sVCAM-1 and sICAM-1, and the protease cathepsin D, which then decreased gradually from 60 to 360 minutes post-METH infusion. These

inflammatory patterns are consistent with the pharmacokinetics of METH, where METH levels peak at one hour following intravenous administration before gradually decreasing via metabolism (Cook et al., 1993). Treatment with IBUD reduced the acute effects of METH on sICAM-1, sVCAM-1, and cathepsin D levels 60 minutes after METH infusion. It is also worth noting that with IBUD, sICAM-1, sVCAM-1, and cathepsin D levels remained steady during the entire 360-minute observation period as shown in the predicted means in Table 1 and Figure 1. Therefore, it also is possible that IBUD played a role in sustaining these lower levels even after 60 minutes. Together, these findings suggest that IBUD may have protective utility against the acute inflammatory responses that would otherwise occur soon after METH administration.

Our findings are consistent with prior experimental research showing that administration of METH in both humans and mice induces expression of sICAM-1 and sVCAM-1 (Gonçalves et al., 2017; Loftis et al., 2011). IBUD's reductions of METH-induced sICAM-1 and sVCAM-1 may have important implications for METH treatment. In multiple studies, elevated ICAM-1 and VCAM-1 has shown to mediate anxiety, depression, and memory problems in adults with METH use disorder (MUD) (Huckans et al., 2015; Loftis et al., 2011), psychiatric problems commonly comorbid with chronic METH use (Loftis and Janowsky, 2014; Vearrier et al., 2012) and recently theorized to be rooted in inflammation (Michopoulos et al., 2017; Miller and Raison, 2016). Furthermore, prior IBUD research has shown that IBUD buffered the subjective effects of METH and improved attention in people with MUD (Birath et al., 2017; Worley et al., 2016). The protective effects of IBUD against inflammation, as demonstrated in this study, may provide a biological explanation for these cognitive and self-reported improvements.

Limited inferences can be made about IBUD's direct impact on METH-induced inflammation in the brain because this study solely measured peripheral levels of inflammatory markers. However, multiple studies have shown that peripheral markers of inflammation coincide with neuroinflammation (McCull et al., 2014), especially in the presence of METH, which increases blood brain barrier permeability (Northrop and Yamamoto, 2012, 2015). Therefore, it is quite possible that the effects of IBUD on peripheral inflammation are linked with reductions in neuroinflammation. Although our findings show a direct effect of dampening inflammatory marker expression relevant to active use of methamphetamine in humans with METH addiction, it is difficult to ascertain the degree to which these differences in inflammation by IBUD are clinically meaningful without longitudinally assessing these inflammatory markers alongside long-term health outcomes among human subjects using METH. Furthermore, this pilot analysis of peripheral inflammatory markers was limited to 360 minutes after infusion of 30 mg METH. It is uncertain whether IBUD would continue to maintain baseline levels of inflammatory markers beyond 360 minutes after METH administration, or by extension, during an extended period of abstinence. Lastly, due to the small sample size of our pilot analysis, our study may not be fully powered to detect other anti-inflammatory effects.

Our findings provide insight into possible protective effects of IBUD against inflammation in METH use, which may be an important component of METH treatment and management of inflammation-related symptomatology. Future research in larger studies is needed to

conduct tests of mediation to determine whether reductions in inflammation mediate the association between IBUD treatment and improved subjective effects, as well as whether these effects might have bearing on the use of IBUD in the context of METH abstinence.

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No role declared.

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Highlights

- Without Ibutilast, 30 mg methamphetamine infusion elevated sICAM-1, sVCAM-1, and cathepsin D in 60 minutes.
- Without Ibutilast, 30 mg methamphetamine infusion elevated IL-6 in 360 minutes.
- Treatment with Ibutilast decreased methamphetamine-induced responses of sICAM-1, sVCAM-1, and cathepsin D compared to the placebo condition.

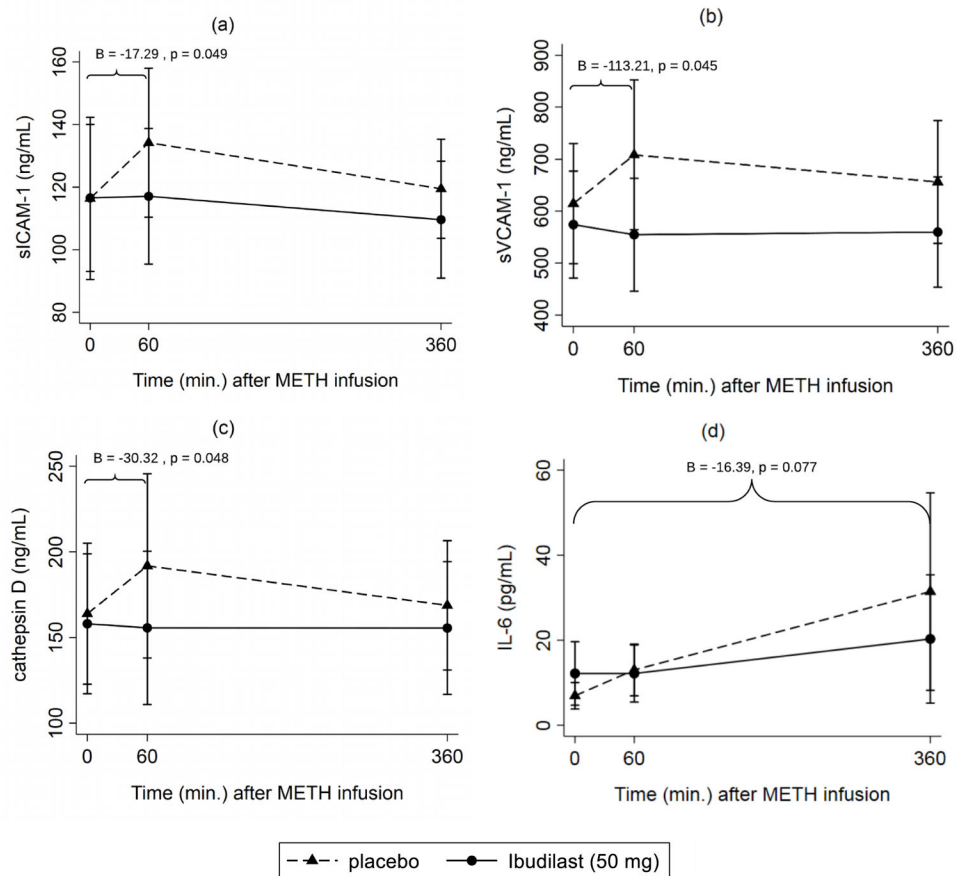


Figure 1.

Predicted means of (a) sICAM-1, (b) sVCAM-1, (c) cathepsin D, and (d) IL-6 by treatment condition (50 mg IBUD vs. placebo) over time. Regression estimates (B) correspond to time intervals in which METH-induced biomarker changes (slopes) are significantly lower with IBUD compared to placebo.

Note: Illustrated confidence intervals correspond to individual point estimates rather than regression estimates of treatment effects.

Table 1.

Mixed effects regression estimates (B) and post-hoc predicted means (M) of peripheral inflammatory markers by IBUD (vs. placebo) after METH infusion

	sICAM-1 (ng)		sVCAM-1 (ng)		cathepsin D (ng)		IL-6 (pg)		TNF- α (pg)		MIF (ng)	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Regression estimates												
IBUD	0.16 (-13.30, 13.63)	0.981	-40.36 (-108.09, 27.37)	0.243	-5.86 (-31.62, 19.89)	0.655	5.25 (0.61, 9.89)	0.027	11.55 (-12.93, 36.03)	0.355	2.08 (-0.18, 4.35)	0.071
Time												
60 min.	17.80 (6.49, 29.11)	0.002	93.70 (13.06, 174.34)	0.023	27.93 (7.19, 48.66)	0.008	6.07 (-1.75, 13.89)	0.128	-8.89 (-32.78, 14.99)	0.466	0.08 (-0.25, 0.42)	0.626
360 min.	3.09 (-15.43, 21.61)	0.744	41.56 (-61.25, 144.37)	0.428	4.89 (-17.62, 27.40)	0.670	24.50 (3.24, 45.75)	0.024	41.76 (-41.75, 125.27)	0.327	0.93 (-0.31, 2.17)	0.143
IBUD x time												
60 min.	-17.29 (-34.50, -0.07)	0.049	-113.21 (-224.00, -2.42)	0.045	-30.32 (-60.36, -0.29)	0.048	-6.08 (-13.69, 1.54)	0.118	11.79 (-15.13, 38.70)	0.391	-1.93 (-4.11, 0.25)	0.082
360 min.	-10.04 (-24.77, 4.70)	0.182	-55.94 (-163.53, 51.65)	0.308	-7.38 (-43.15, 28.39)	0.686	-16.39 (-34.53, 1.76)	0.077	-17.50 (-56.83, 21.83)	0.383	-1.38 (-4.68, 1.93)	0.414
Sequence	18.15 (-18.61, 54.91)	0.333	-8.76 (-207.11, 189.59)	0.931	50.24 (-24.62, 125.10)	0.188	4.36 (-10.67, 19.39)	0.144	53.94 (-49.10, 156.98)	0.305	0.18 (-1.35, 1.71)	0.820
Predicted means	M (95% CI)	p[†]	M (95% CI)	p[†]	M (95% CI)	p[†]	M (95% CI)	p[†]	M (95% CI)	p[†]	M (95% CI)	p[†]
Placebo												
0 min.	116.39 (90.47, 142.30)		614.50 (498.84, 730.15)		163.91 (122.74, 205.07)		6.94 (4.06, 9.81)		28.23 (-0.44, 56.90)		0.57 (0.18, 0.97)	
60 min.	134.19 (110.38, 157.99)	0.002	708.19 (564.11, 852.27)	0.023	191.83 (138.08, 245.59)	0.008	13.00 (6.26, 19.75)	0.128	19.34 (2.46, 36.22)	0.466	0.66 (0.37, 0.94)	0.626
360 min.	119.47 (103.64, 135.31)	0.076	656.06 (538.02, 774.09)	0.193	168.79 (131.06, 206.53)	0.069	31.43 (8.15, 54.72)	0.106	69.99 (-38.43, 178.41)	0.354	1.50 (0.30, 2.70)	0.105
IBUD												
0 min.	116.55 (93.07, 140.03)		574.14 (471.13, 677.15)		158.04 (117.19, 198.90)		12.18 (5.35, 19.02)		39.78 (-11.09, 90.65)		2.66 (0.44, 4.87)	
60 min.	117.06 (95.38, 138.74)	0.911	554.63 (446.04, 663.22)	0.420	155.65 (110.92, 200.37)	0.828	12.18 (5.71, 18.65)	0.997	42.67 (-10.99, 96.33)	0.218	0.81 (0.30, 1.32)	0.069
360 min.	109.60 (90.92, 128.28)	0.169	559.76 (453.48, 666.03)	0.873	155.55 (116.79, 194.31)	0.987	20.29 (5.52, 35.06)	0.152	64.04 (-29.79, 157.87)	0.310	2.21 (0.93, 3.49)	0.066

⁷ p-value corresponds to change in the predicted mean since the prior time point (e.g., 360 min. compared to 60 min.)

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