Effects of Obstructive Sleep Apnea and Obesity on Morphine Pharmacokinetics in Children

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Abstract

BACKGROUND: Obesity increases susceptibility to chronic pain, increases metabolism, and is associated with obstructive sleep apnea syndrome (OSAS), all which can complicate perioperative pain management of patients. In addition, obesity and OSAS can cause elevation of the adipose-derived hormone leptin, which increases metabolism. We hypothesized that obesity along with sleep apnea and leptin independently enhance morphine pharmacokinetics.

METHODS: Children 5–12 years of age who were presenting for surgery were administered a morphine dose of 0.05 mg/kg. Blood was collected at baseline and at subsequent preset times for pharmacokinetic analysis of morphine and its metabolites. Three groups were studied: a nonobese group with severe OSAS, an obese group with severe OSAS, and a control group.

RESULTS: Thirty-four patients consisting of controls (n = 16), nonobese/OSAS (n = 8), and obese/OSAS (n = 10) underwent analysis. The obese/OSAS group had a higher dose-adjusted mean maximum morphine concentration (C_{MAX}) over 540 minutes compared to the controls ($P < .001$) and those with only OSAS ($P = .014$). The obese/OSAS group also had lower volume of distribution (Vd) when compared to OSAS-only patients ($P = .007$). In addition, those in the obese/OSAS group had a higher morphine 3-glucuronide (M3G) maximum concentration ($P = .012$) and a higher ratio of M3G to morphine than did the control group ($P = .011$). Time to maximum morphine 6-glucuronide (M6G) concentration was significantly lower in both nonobese/OSAS and obese/OSAS groups than in the control group ($P < .005$). C-reactive protein (CRP), interleukin (IL)-10, and leptin were all higher in the obese/OSAS group than in controls ($P = .004$, 0.026, and <0.001, respectively), and compared to OSAS-only patients, CRP ($P = .013$) and leptin ($P = .002$) levels were higher in the obese/OSAS group.

CONCLUSIONS: The combination of obesity and OSAS was associated with an increase in morphine metabolism compared with that in normal-weight controls. Our previous study in mice demonstrated that obesity from leptin deficiency decreased morphine metabolism, but that metabolism normalized after leptin replacement. Leptin may be a cause of the increased morphine metabolism observed in obese patients.

Respiratory complications, including hypoxia and upper airway obstruction, remain among the leading causes of postoperative morbidity and mortality in the pediatric surgical population.[1] Patients at highest risk for perioperative respiratory complications include children <3 years of age,[2,3] obese patients,[4] and those with obstructive sleep apnea syndrome (OSAS).[5,6] Because opiate therapy with morphine is commonly administered perioperatively for surgical procedures that cause severe pain, a better understanding of how OSAS and obesity affect opioid metabolism will provide insight into appropriate dose concentrations and dosing frequency. Armed with such knowledge, anesthesiologists may be able to limit complications commonly associated with opioid therapy while still providing adequate postoperative pain management.

OSAS affects approximately 3% of the total pediatric population and is primarily treated by performing an adenotonsillectomy (AT). It has been reported that OSAS patients require less opioid medication than non-OSAS patients to meet equivalent pain scores[7,8] and are more sensitive to the respiratory side effects of opioids.[6] Pediatric patients diagnosed with severe OSAS based on hypoxia during sleep have been reported to have an increased sensitivity to

opiates, and reducing the dose has been reported to reduce the incidence of respiratory complications by ; 50%.[9] These observations may result from hypoxia-related changes to opioid receptor expression. Intermittent hypoxia has been shown to upregulate mu-receptors and decrease pain sensitivity in rats,[10] and studies have shown that children living at high altitude require less opioid for pain.[11]

Sensitivity to opioids may also be explained by hypoxia-induced changes to enzymatic function[10] and thus to metabolism. Uridine diphosphate glucuronosyltransferase (UGT) 2B7 is the phase II enzyme responsible for glucuronidation metabolism of morphine sulfate to morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). Hypoxia has been shown to decrease UGT2B7 expression; however, few studies have evaluated morphine metabolism in patients who experience OSAS-related hypoxic episodes.

Pediatric obesity is reaching epidemic proportions. Approximately 33% of children in the United States are overweight, and 17% are obese. These statistics have shown little improvement since 2006. Obese adults are believed to have a low threshold for pain owing to chronic disease states and poor health. However, obese adults and children are also at a higher risk for postoperative respiratory complications, specifically after AT.[12] Murine studies suggested that obesity decreased morphine metabolism, potentially via leptin.[13,14] Obesity leads to multisystem diseases including a chronic inflammatory state, fatty liver, and defects in metabolism. Though glucuronidation is increased in obesity, studies evaluating the effects of UGT2B7 on morphine metabolism are limited.[15]

Both obesity and OSAS are multisystem, proinflammatory disorders[16–18] that lead to multiorgan dysfunction, insulin and leptin resistance, pulmonary disease, and metabolic dysfunction[18–22] that may play an integral role in altering opioid sensitivity. The mechanism for opioid sensitivity in these patient populations is poorly understood. Therefore, we examined effects of the interplay between obesity and OSAS on morphine pharmacokinetics in children. We hypothesized that morphine metabolism and clearance would be reduced in patients with (1) severe OSAS (diagnosed by polysomnography) and (2) obesity (defined as body weight >95th percentile by age). A better understanding of the interaction between obesity and OSAS-altered opioid metabolism will provide new insight into more effective and safer opioid treatment for these patients.

METHODS

This study was approved by the Johns Hopkins Institutional Review Board (IRB; No. IRB00059675) and was conducted in accordance with its guidelines. The trial was also registered with Clinicaltrials.gov (No. NCT02732795).

Patients selected were scheduled for otolaryngologic (ear/nose/throat [ENT]), orthopedic, genitourinary, and general surgery at the Johns Hopkins Hospital from February 5, 2016, to March 13, 2018. Children 5–12 years of age with a perioperative hospital stay 9 hours and for whom opioid therapy was indicated were eligible for this study. Informed consent/assent was obtained for all subjects in accordance with IRB protocol. Patients were excluded from the study if they were currently taking opioid medications, had an allergy or contraindication

to morphine administration, took medications that altered liver metabolism (including seizure medications), or had end-stage liver or kidney disease. Initially, subjects were grouped into 4 classifications based on their weight and OSAS status as follows: nonobese and no OSAS (control), obese and no OSAS, nonobese and severe OSAS, and obese and severe OSAS. Severe OSAS (respiratory disturbance index 10) was diagnosed by a board-certified sleep physician who evaluated the polysomnogram using criteria established by the American Academy of Sleep Medicine.[23] Obesity was defined as the child's weight being greater than the 95th percentile, as delineated by the Centers for Disease Control.[24] Patients defined to be nonobese were those below the 85th percentile for weight, thus excluding overweight children. Patients who did not have a polysomnogram were screened for exclusion secondary to sleep-disordered breathing with 2 questions: "Does your child snore at night?" and "Have you witnessed your child stop breathing during sleep?" If either question was answered in the affirmative, the child was not enrolled in the study. In addition to OSAS diagnosis and weight, patient demographics, including race, sex, age, comorbid diseases, and prematurity, were recorded.

Intraoperative Management

General anesthesia was induced with sevoflurane and/or N_2O, and the American Society of Anesthesiologists (ASA) standard monitors were placed. After induction, an intravenous (IV) catheter was inserted. At that time, blood was obtained to measure biomarker levels (including interleukin [IL]-1, IL-6, and IL-10, tumor necrosis factor [TNF]-α, C-reactive protein [CRP], glucose, insulin, and leptin) and morphine concentration at time = 0. A second IV line was placed in case the first failed. The duration of anesthesia, surgical procedure, and additional medication types and doses were recorded (Table 1).

After the initial blood draw, a standard dose of 0.05 mg/kg morphine hydrochloride (molecular weight [MW] = 375.9; 10 mg/mL; West-Ward, Eatontown, NJ) was administered. For all obese patients, the morphine dose was based on the patient's ideal body weight (http://nccd.cdc.gov/dnpabmi/Calculator.aspx) as recommended for morphine dosing.[15,25] After this initial dose of morphine, no additional morphine was administered intraoperatively or postoperatively. Other pain medications, including nonopioid analgesics such as acetaminophen and ketorolac, as well as nonmorphine opioids, including fentanyl and hydromorphone, were administered as deemed necessary to ensure that each patient's pain was controlled.

Blood Collection

Blood samples were collected at 10, 30, 45, 60, 90, 120, 180, 220, 360, 400, 480, and 540 minutes after the single morphine dose. After 1–2 mL of blood was aspirated and discarded, approximately 0.5 mL of blood was collected in a green-top Lithium Heparin Vacutainer tube (BD, Franklin Lakes, NJ). The 9-hour sampling duration allowed for 3 metabolic halflives of morphine ($T_{1/2}$ = 3 hours) to elapse, which enabled robust estimation of the critical pharmacokinetic parameters for morphine and morphine metabolites.[25]

Blood Sample Storage and Analysis

Whole blood samples were centrifuged immediately after collection, or the Vacutainer was stored in a 0°C refrigerator for processing the next day. Processing consisted of centrifuging the samples at 3000 rpm at 4°C for 20 minutes. The 0.5–1.0 mL aliquots of plasma were then stored at −80°C. We analyzed the samples in batches by high-performance liquid chromatography-tandem mass spectroscopy[26] to identify concentrations (ng/mL) of morphine, M3G, and M6G. Mass spectrometry was performed in the positive multiple reaction monitoring mode (MRM). Dynamic range of the assay was 0.25–1000 ng/mL ($r^2 > 0.99$) for morphine and 1–1000 ng/mL ($r^2 > 0.99$) for M3G and M6G. Accuracy and precision were within 15% of the nominal values.[26]

Pharmacokinetic Determinations

Morphine, M3G, and M6G concentration data were analyzed by noncompartmental methods (Phoenix WinNonlin version 6.4 software; Pharsight A Certara Company, Cary, NC). Individual maximum concentration (C_{MAX}) and time to reach C_{MAX} (T_{MAX}) values were obtained by visual inspection of the semilogarithmic plots of concentration versus time (Figure 1). We calculated area under the curve (AUC) for plots of morphine, M6G, and M3G concentration versus time over 540 minutes (AUC_{540}) by the log-linear trapezoidal method. [27] We planned for 9-hour duration of blood sampling, approximately 3 $T_{1/2}$ lives of morphine.[28] Studies have shown that only 8% of the morphine AUC is extrapolated beyond the 6-hour observation, and only 6% is extrapolated beyond our planned 9-hour terminal observation making for very robust AUC estimates.[25] Due to the low rate of metabolism during the terminal phase (or third halflife), time between blood draws was extended to minimize patient discomfort. We determined the terminal elimination rate constant (λz) from the slope of the terminal phase of concentration versus time curve. Both AUC_{540} and C_{MAX} were dose adjusted to a 0.05 mg/kg equivalent for comparison across groups by multiplying the ratio of 0.05 mg/kg to the actual individual mg/kg dose received based on the patients' ideal body weight. The elimination $T_{1/2}$ was calculated as ln(2) divided by λz. Standard equations for apparent volume of distribution (Vd) and total clearance adjusting for weight were used, utilizing AUC_{0-inf} to determine clearance.[29] For terminal elimination end points, an adjusted r^2 0.80 was used as a quality metric. This model is fitted to the elimination phase, using elimination rate constant (Kel; terminal phase constant) and fitting a linear model to the time versus log concentration curve. We did not report the M6G and M3G λz, Vd, and clearance because the number of terminal concentration points was insufficient to accurately characterize these pharmacokinetic parameters. M3G-to-morphine and M6G-to-morphine AUC_{540} ratios were calculated based on morphine, M3G, and M6G levels detected.

Statistical Analysis

A sample size calculation was performed based on our previous AUC calculations in obese and wild-type mice. With a sample size of 7 per group, we will have to have 90% power (type 1 error = 0.02). All pharmacokinetic parameters are summarized by descriptive statistics. Initially, univariate linear regression analysis was used to determine significance between pharmacokinetic parameters and demographic covariates, including anesthesia

duration, sex, and race. These variables have been shown to affect liver metabolism and why they were chosen for univariate analysis. Weight was not analyzed because all obese patients had severe OSAS as a comorbid condition. Differences in demographic variables among groups were initially tested by the nonparametric Kruskal-Wallis test. In addition, a Dunn post hoc pairwise comparison with Bonferroni correction between groups was performed. Inflammatory biomarker concentration differences were analyzed using a Kruskal-Wallis test with a Dunn post hoc pairwise comparison test as well as multivariable linear regression models adjusting for weight, sex, and duration of anesthesia. These analyses were repeated for M3G and M6G pharmacokinetics (PK) parameters. Statistical analysis was performed using Stata v15.1 for Mac (StataCorp, College Station, TX), which adjusted *P* values in the results for an experiment-wise error rate of 0.05 for 3 comparison groups. Therefore, Bonferroni-adjusted *P* values <0.05 were considered statistically significant.

Results

A total of 331 patients were prescreened for obesity and OSAS. After those who met exclusion criteria were eliminated, the 2 primary reasons that patients were not enrolled were surgery occurring too late in the day and absence of polysomnogram to diagnose OSAS severity. Only 1 patient was recruited to the obese/no OSAS group because the families of most obese patients reported on the screening questionnaire that their child snored and/or had nocturnal apneas. This patient, and thus the obese/no OSAS group, was not included in the final analysis.

Excluding the 1 obese/no OSAS patient, 40 children were enrolled into the study as follows: nonobese/no OSAS (control, n = 18), OSAS only (n = 9), and obese with severe OSAS (n = 13). Overall, the mean age was 7.4 ± 0.4 years (mean ± standard error of the mean [SEM]), with slightly more males (63.4%) than females with predominantly Caucasians (46.3%) and African American (39%) participants. On average, ideal body weight dosing provided lower doses to the obese/OSAS group (0.04 mg/kg ±0.0005) than the other groups (0.05 ± 0.001; Table 1). Surgical procedures differed significantly between the groups. Patients in the control group primarily underwent genitourinary surgeries (92.9%), which were significantly longer in duration (426.4 ± 253 minutes) than the surgeries of the OSAS-only group (59.4 ± 9.3 minutes; *P* < .001) and obese/OSAS group (80.4 ± 44.5 minutes; *P* < .001). Patients with OSAS only underwent primarily ENT procedures, and those in the obese/OSAS group all underwent ENT procedures.

Pharmacokinetics

Pharmacokinetic analysis could not be completed for 6 patients who had too few data points (3 recorded morphine concentrations) or incomplete data. Data were incomplete if blood was not collected. Reasons for a missing blood draw included the inability to aspirate blood from the IV line, patient refusal, or IV line inaccessible during surgery. These missing data points appeared to be at random. Pharmacokinetic parameters for morphine could not be determined for 2 patients from the control group, 1 from the OSAS-only group, and 3 from the obese/OSAS group, leaving a total of 34 patients for analysis. When performing noncompartmental calculations, 1 subject in the control group and 1 in the OSAS-only

group did not have all 3 analyte (MS, M3G, and M6G) curves fit within the established r^2 0.80 metric. In the control patient, there were several missing data points (due to the angiocatheter not drawing back), leading to a less accurate fit for M3G ($r^2 = 0.78$) and M6G ($r^2 = 0.52$). In the OSAS patient, there was a value at T0 (likely due to a contaminant) leading to a more poorly fit curve for morphine analysis ($r^2 = 0.71$). Both subjects were retained in the analysis because data acquired were not outliers from the data points collected. PK parameters (except for AUC540) were not conducted for the M3G and M6G analytes.

Pharmacokinetic parameters of the control, OSAS only, and obese/OSAS groups are summarized in Table 2. Univariate linear regression analysis revealed no significant differences in morphine pharmacokinetic parameters when we evaluated the individual effects of race, sex, or anesthesia duration.

Morphine Pharmacokinetics

There was evidence that patients with obesity and OSAS have different morphine pharmacokinetics compared to that of controls. PK parameters evaluated include area under curve (AUC), clearance, C_{MAX}, Kel, T_{MAX}, and Vd. The mean morphine AUC_{540} of the obese/OSAS group (1537.9 ng-min/mL) was significantly lower than that of the control group (2505.6 ng·min/mL, $\chi^2 = 9.4$, $P = .004$). However, after dose adjusting for AUC_{540} in the obese/OSAS group (2206.6 ng·min/mL), there was no longer a significant difference in AUC_{540} compared to the controls ($\chi^2 = 2.5$, $P = .72$). After dose adjusting for C_{MAX} calculations, the C_{MAX} for the obese/OSAS group (47.6 ng/mL) was found to be significantly higher than both the control (30.1 ng/mL, $\chi^2 = 12.7$, $P < .001$) and the OSAS-only groups (29.0 ng/mL, $\chi^2 = 12.7$, $P = .01$; Figure 2). The Vd also differed between the groups, with the obese/OSAS group having a significantly lower Vd (0.09 mL/kg) than the OSAS only (0.29 mL/kg, $\chi^2 = 8.5$, $P = .007$).

M3G Pharmacokinetics

Patients with obesity and OSAS also had significant changes in M3G C_{MAX} and M3G-to-morphine sulfate ratio when compared to controls (Table 2). Patients in the obese/OSAS group had a higher C_{MAX} (56.4 ng/mL) than did control patients (41.4, $\chi^2 = 7.1$, $P = .01$). The ratio of M3G to morphine was also higher in the obese/OSAS group (10.1) than in the control group (5.5, $\chi^2 = 7.1$, $P = .01$).

M6G Pharmacokinetics

One patient from the control group was removed for M6G evaluation owing to an extremely high level. T_{MAX} significantly differed among the groups, whereby the median T_{MAX} was significantly lower in both OSAS-only (90 minutes) and obese/OSAS (60 minutes) groups than in the control group (120 minutes, $\chi^2 = 18.6$, $P < .005$). The M6G:morphine ratio was also lower in the obese/OSAS group (0.0009) compared to controls, but was not significant (0.001, $\chi^2 = 4.4$, $P = .053$).

Biomarker Analysis

Insulin was measured in every patient, and leptin levels were measured in all but 2 patients (both in the OSAS-only group). Levels of CRP were not analyzed in 5 patients from the obese/OSAS group, and inflammatory biomarkers, including IL-6, IL-10, and TNF-α, failed to be analyzed in 7 patients (2 in the OSAS-only group and 5 in the obese/OSAS group), and IL-1β failed to be measured in 13 patients (6 in the control group, 2 in the OSAS-only group, and 5 in the obese/OSAS group) owing to sample processing error.

The obese/OSAS group had significantly higher mean values of the inflammatory markers CRP ($\chi^2 = 10.1$, $P = .004$), IL-6, ($\chi^2 = 8.4$, $P = .006$), and IL-10 ($\chi^2 = 6.4$, $P = .03$) than did controls. In addition, the obese/OSAS group had higher CRP ($\chi^2 = 10.1$, $P = .01$), insulin ($\chi^2 = 8.5$, $P = .03$), and leptin ($\chi^2 = 14.4$, $P = .003$) levels than did the OSAS-only group. Insulin levels were significantly lower in the OSAS-only group than in the control group ($\chi^2 = 8.5$, $P = .01$; Table 3 and Figure 3).

Leptin was significantly higher in the obese/OSAS group (28.8 ± 21.3) than in the control (7.4 ± 8.8, $\chi^2 = 18.7$, $P < .001$) or OSAS-only group (4.5 ± 2.1, $\chi^2 = 18.7$, $P < .002$). A multivariable linear regression established that leptin could predict dose-adjusted morphine AUC_{540} ($F(4, 28) = 3.3$; $P = .002$; 95% confidence interval [CI], −64.1 to −16.0) and that leptin accounted for 22.1% of the variability in morphine AUC_{540}. Leptin levels did not predict morphine Vd in this analysis ($P = .66$).

DISCUSSION

Obesity with a comorbid diagnosis of severe OSAS has a pronounced effect on morphine pharmacokinetics. Our findings show that obese patients with severe OSAS have higher peak intravascular morphine concentrations compared to normal-weight patients and those with OSAS. Also, obese patients with severe OSAS had a lower morphine Vd than patients with OSAS alone. In addition, the M3G-to-morphine ratio was significantly higher in the obese/OSAS group than in the control group, providing evidence of a more rapid metabolism.

Reports from previous studies have been conflicting with regard to the effects of obesity on liver enzyme function and morphine pharmacokinetics. Murine and rat studies showed decreases in UGT RNA, and UGT enzyme activity was decreased by as much as 60% in mice fed a high-fat diet as compared to that in lean mice. One study in adult humans showed that clearance of morphine metabolites was delayed in obese patients compared with that in lean controls.[30] Lloret-Linares et al[31] studied the effects of weight change, specifically after gastric bypass, on oral morphine pharmacokinetics and showed that morphine absorption increased drastically after weight loss, increasing AUC and morphine exposure in these patients. Changes to the gut microbiome were suggested as a possible cause for these observations.[32,33] By contrast, several studies in obese humans showed increased UGT activity leading to higher morphine glucuronidation and clearance.[34] Studies comparing obese to nonobese adults and children showed increased clearance of UGT-mediated medications, including paracetamol, oxazepam, and lorazepam.[35,36] Our results are

consistent with these later studies, showing that morphine pharmacokinetics was enhanced in obese subjects compared to normal-weight controls.

The mechanisms by which obesity affects UGT activity are not well known. One potential regulatory element is leptin, an adipokine secreted by adipose tissue. In an obese murine model, Miyamoto et al[37] showed reduction in 5-adenosine monophosphate (AMP)-activated protein kinase and reduced triglyceride levels in the liver. In addition, we previously showed that leptin-deficient obese (ob/ob) mice had decreased morphine metabolism that normalized to that of wild-type lean mice after they received leptin replacement.[13] Diet-induced obese mice did not show substantial changes to morphine metabolism when compared to wild-type mice, suggesting that leptin deficiency and not obesity alone predominantly affected morphine metabolism. UGT activity has been shown to decrease with weight loss.[31] How obesity affects the specific subunits of UGT involved in morphine metabolism, however, remains unclear. In our current study, leptin levels directly predicted morphine AUC_{540} and clearance suggesting that it might activate phase I and/or phase II enzymes, including UGT, as 1 possible mechanism for increasing morphine metabolism.

Our results have several clinical implications for the care of obese children with OSAS who require opioid therapy. We have shown that when dosing obese patients based on the recommended ideal body weight, a significantly lower amount of morphine is present in the vasculature (lower AUC). Patients with obesity have a higher incidence of chronic pain,[38] and murine models of obesity indicate a higher incidence of postoperative pain. However, by dose-adjusting PK parameters, we can compare morphine exposure among groups, mimicking what would happen if an obese child were dosed based on their actual body weight. Our results show that higher morphine concentrations are achieved in obese patients with OSAS, as described by higher C_{MAX} with similar clearance, which is likely caused by the hydrophilic properties of morphine and its metabolites. By dosing on actual body weight, our calculations suggest that a higher morphine concentration will be achieved; however, due to morphine's hydrophilicity, more of the drug will stay within the vasculature, distribute to the brain, and may increase the risk for respiratory depression. Obese patients are at a higher risk of respiratory complications and upper airway obstruction after anesthesia and higher intravascular morphine concentrations may be a significant contributor to this observation.

A higher M3G:morphine ratio also suggests increased morphine metabolism in patients who are obese with OSAS. Because morphine is metabolized more quickly in obese children with OSAS undergoing surgery, multimodal pain therapies should be implemented that include medications with minimal to no respiratory side effects. In addition to a multimodal approach, morphine dose reduction with a more frequent dosing schedule may optimize postoperative pain while minimizing postoperative respiratory events.

Leptin was significantly higher in obese/OSAS patients than in either controls or those with only OSAS, suggesting that it might mediate the increase in morphine metabolism. Because leptin is also a respiratory stimulant, postoperative leptin administration may be an ideal adjunctive medication with morphine for nonobese patients at increased risk for postoperative respiratory complications. In addition, leptin administration could increase

morphine metabolism in patients experiencing an overdose and, unlike naloxone, increase morphine metabolism without causing complete opioid pain blockade that may lead to hyperalgesia. Future studies are necessary to better understand the mechanism by which leptin affects morphine pharmacokinetics as well as the potential role of leptin as a short-term adjunctive therapy.

Our study had several limitations. First, we were only able to recruit 1 patient with obesity but no OSAS due to high frequency of snoring in obese children. To evaluate the effects of obesity alone, 1 possible population to study would be obese patients presenting for AT who have been diagnosed by preoperative polysomnogram with mild OSAS. However, these patients do not have prolonged postoperative hospital stays that would allow for adequate blood sampling time. Second, patients from the control group underwent anesthesia for longer periods of time than those in the other groups. Although having sedated patients facilitated blood draws, inhalational anesthesia can affect hepatic blood flow, primarily reducing portal blood flow,[39] and may affect morphine metabolism. Our findings indicated that morphine metabolism was faster in those undergoing longer surgery durations. Shorter surgeries in otherwise healthy patients often did not warrant hospitalization postoperatively, limiting the pool of available control patients with shorter duration surgeries. Also, we were unable to assess some pharmacokinetic parameters, specifically elimination parameters, for M3G and M6G owing to an insufficient period of postdose sampling.

CONCLUSIONS

Obesity and OSAS increased morphine metabolism compared to that in normal-weight controls. A previous study from our laboratory showed in a murine model that obesity from leptin deficiency decreased morphine metabolism, which normalized after leptin replacement. In the current study, obesity caused elevated leptin levels, suggesting that leptin may be the cause of increased morphine metabolism observed in obese patients with OSAS. Additional studies are required to determine more optimal regimens for opioid administration in obese pediatric patients to avoid the higher risk of respiratory depression with higher peak concentrations and inadequate pain management with altered clearance.

Acknowledgments

GLOSSARY

AMP	adenosine monophosphate
ASA	American Society of Anesthesiologists
AT	adenotonsillectomy
AUC	area under curve
CI	confidence interval

| C_{MAX}	maximum concentration
CRP	C-reactive protein
ENT	ear/nose/throat
IL	interleukin
IRB	institutional review board
IV	intravenous
Kel	elimination rate constant
M3G	morphine 3-glucuronide
M6G	morphine 6-glucuronide
MRM	multiple reaction monitoring mode
MW	molecular weight
OSAS	obstructive sleep apnea syndrome
PK	pharmacokinetics
SEM	standard error of the mean
SML	suspension microlaryngoscopy
$T_{1/2}$	half-life
T_{MAX}	time to maximum concentration
TNF	tumor necrosis factor
UGT	uridine diphosphate glucuronosyltransferase
Vd	volume of distribution

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KEY POINTS

- **Question:** Does obesity and obstructive sleep apnea affect morphine pharmacokinetics in children?

- **Findings:** In obese children with obstructive sleep apnea syndrome (OSAS), lower dosed morphine concentrations reach higher intravascular levels than nonobese, non-OSAS children.

- **Meaning:** Morphine dose adjustments should be made for patients with obstructive sleep apnea and obesity.
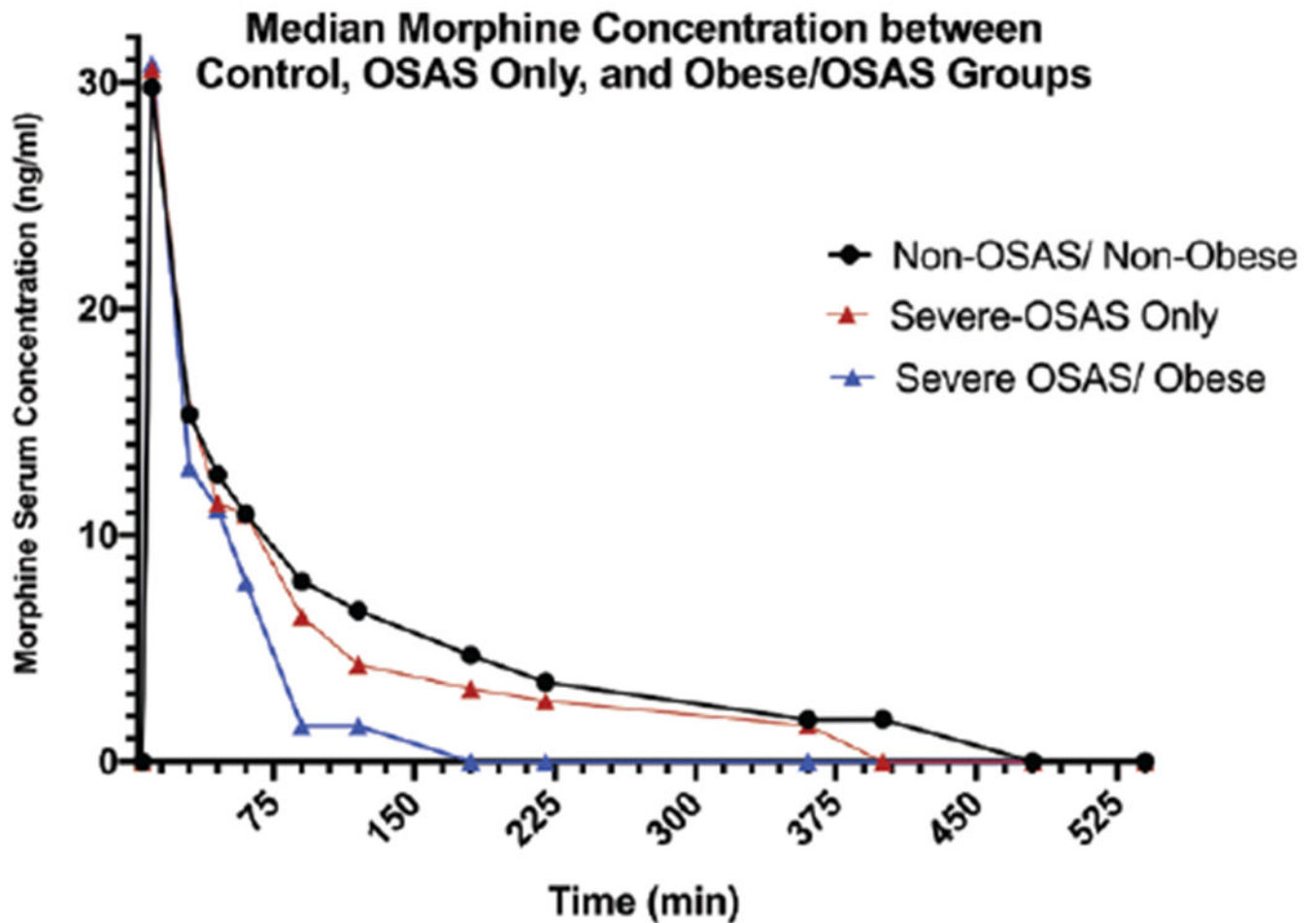
Figure 1.
Comparison of mean serum morphine concentrations measured at preset time points after morphine injection in normal-weight patients without OSAS, patients with severe OSAS only, and obese patients with severe OSAS. OSAS indicates obstructive sleep apnea syndrome.
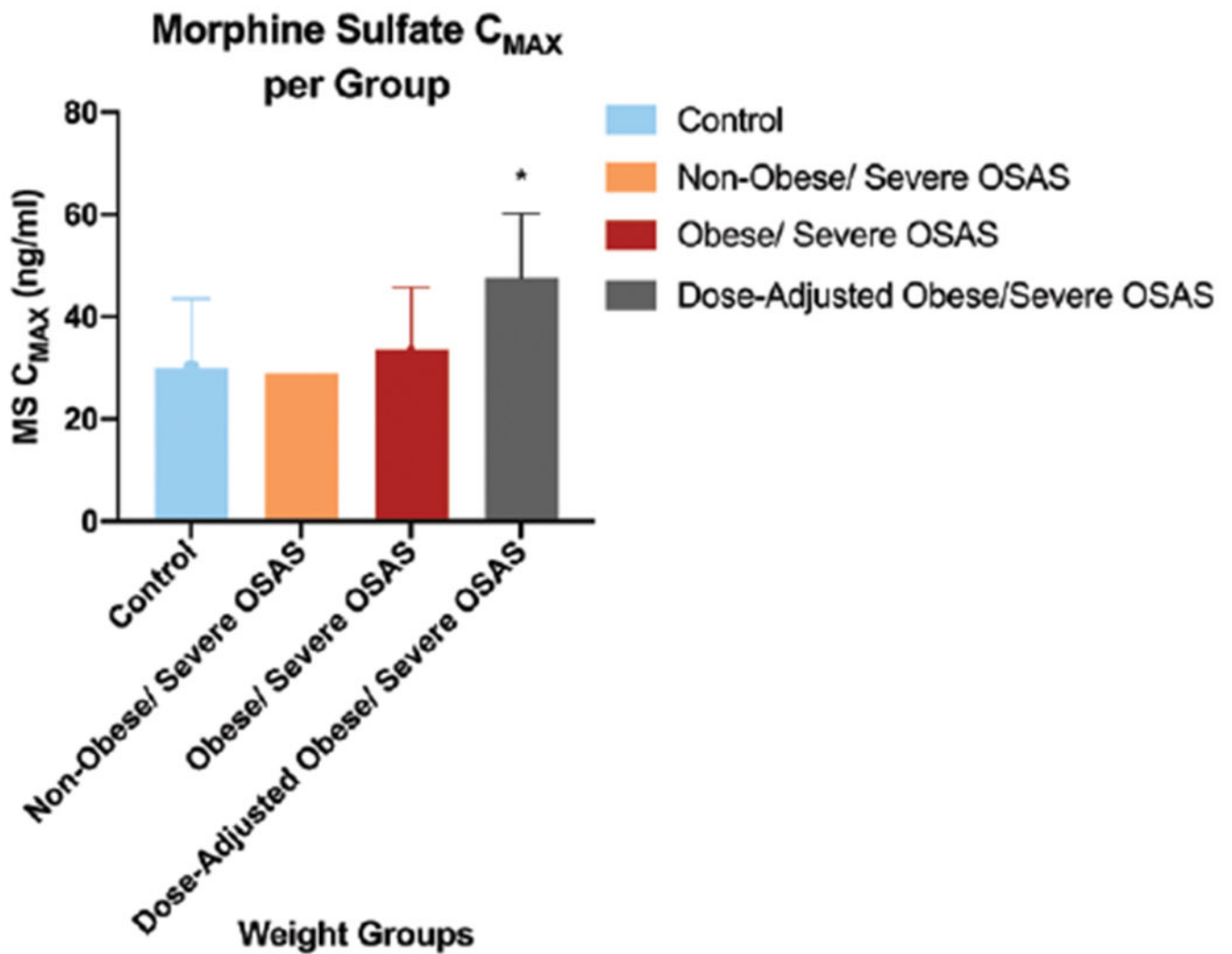
Figure 2.
C_{MAX} of MS. Comparison of mean (±SD) C_{MAX} for plasma morphine during 540 minutes of blood sampling time between normal-weight, non-OSAS controls, nonobese OSAS, and obese patients with OSAS. Dose-adjusted mean C_{MAX} in obese patients with OSAS is also presented. *$P < .05$ versus the nonobese/non-OSAS control group. C_{MAX} indicates maximum concentration; MS, morphine sulfate; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.
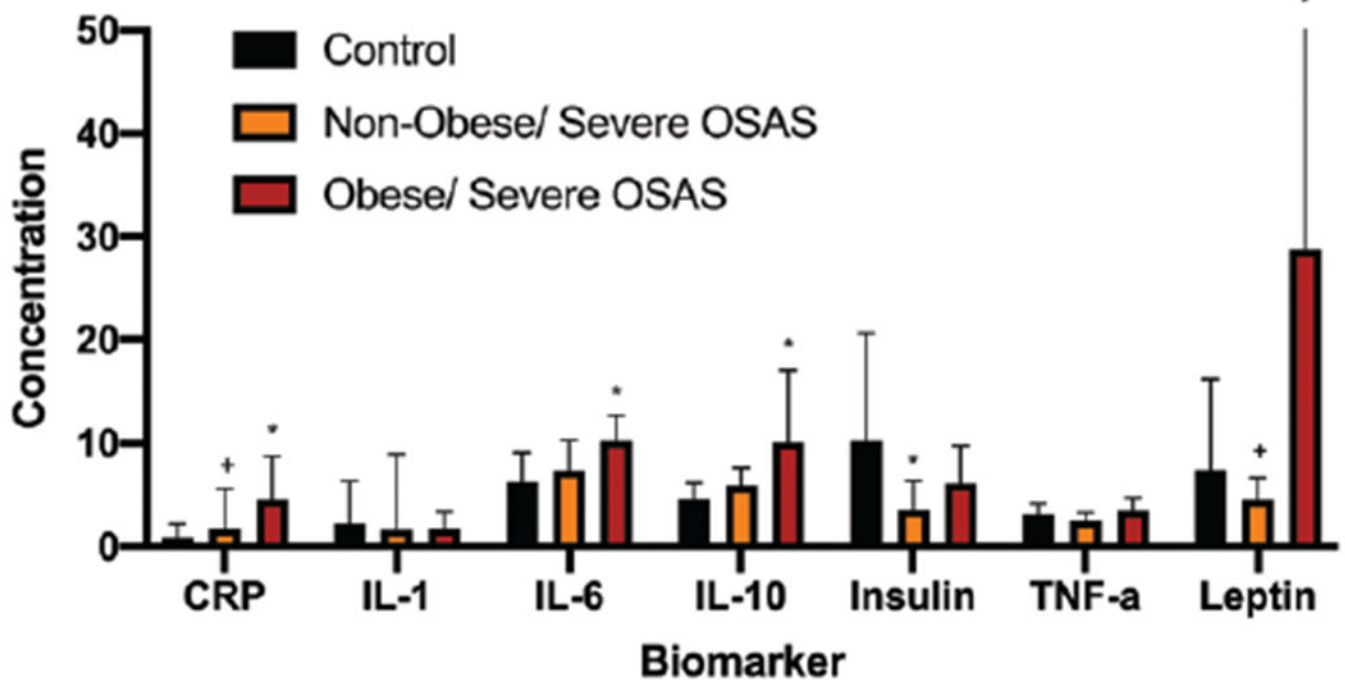
Figure 3.
Comparison of biomarker concentrations between normal-weight and obese patients with and without OSAS. *$P< .05$ versus nonobese/non-OSAS control group. +$P< .05$ versus obese/OSAS group. Units of measurement are as follows: CRP (µg/mL), IL-1β (pg/mL), IL-10 (pg/mL), insulin (µU/mL), leptin (ng/mL), TNF-α (pg/mL). Concentrations of IL-1, IL-6, and IL-10 were multiplied by 10 to optimize visual comparisons on the graph. CRP indicates C-reactive protein; IL, interleukin; OSAS, obstructive sleep apnea syndrome; TNF, tumor necrosis factor.

Table 1.

Demographic Data of Enrolled Patients

	Total (n = 40)	Control (n = 18)	OSAS Only (n = 9)	Obese and OSAS (n = 13)	P Value
Age, mean (SEM) (y)	7.4 (0.4)	8.3 (0.5)	6.0 (0.6)	7.0 (0.7)	.022
Sex (%)					.840
Male	26 (63.4)	11 (61.1)	5 (55.6)	9 (69.2)	
Female	15 (39.6)	7 (38.9)	4 (44.4)	4 (30.7)	
Race (%)					.004
Caucasian	19 (46.3)	13 (72.2)	2 (22.2)	4 (30.8)	
Black/African American	16 (39.0)	3 (16.6)	3 (33.3)	9 (69.2)	
Asian	2 (4.9)	1 (5.6)	1 (11.2)	0	
Other	4 (9.8)	1 (5.6)	3 (33.3)	0	
Weight, mean (SEM) (kg)	30.8 (2.6)	27.3 (2.1)	20.4 (1.1)	42.9 (6.2)	<.001
Morphine dose, mean (SEM), actual (mg/kg) [a]	0.05 (0.002)	0.05 (0.001)	0.05 (0.001)	0.04 (0.005)	.003
Surgical procedure (%)					<.001
ENT (AT, SML/bronchoscopy)	21 (51.2)	0	8 (88.9)	13 (100)	
General surgery (hernia, laparoscopy)	3 (7.3)	3 (16.7)	0	0	
Genitourinary (bladder extrophy)	14 (34.2)	13 (72.2)	1 (11.1)	0	
Orthopedic (arthroscopy) [b]	3 (7.3)	2 (11.1)	0	0	
Anesthesia duration, mean (SD) (min)	230.3 (243)	426.4 (253.0) [c]	59.4 (9.3)	80.5 (44.5)	.001

Measures of association between groups were calculated using Fisher exact test for categorical and binomial variables. Pairwise comparisons were calculated by Kruskal-Wallis χ^2 analysis for continuous variables.

Abbreviations: AT, adenotonsillectomy; ENT, ear/nose/throat; OSAS, obstructive sleep apnea syndrome; SD, standard deviation; SEM, standard error of the mean; SML, suspension microlaryngoscopy.

[a] Actual mg/kg dosing for morphine reflects the dose the patients received if one were to administer morphine on a mg/kg basis based on their actual body weight.

[b] Patients undergoing surgery who required blood product transfusion, including spinal fusion, were not enrolled.

[c] Patients in the control group underwent short procedures including ENT procedures (mean anesthesia duration 73.1 minutes, SD = 36.1), as well as long procedures including bladder extrophy repair (mean anesthesia duration = 458.6 minutes, SD = 259.9).

Table 2.

Pharmacokinetic Analysis for Morphine Sulfate

Parameter	Control (N = 16)	OSAS Only (N = 8)	Obese and OSAS (N = 10)	OSAS Only Versus Control (P Value)	Obese and OSAS Versus Control (P Value)	Obese and OSAS Versus OSAS Only (P Value)
Morphine						
AUC$_{540}$-adjust (ng·min/mL)	2505.6 (±149.7)	2083.0 (±194.6)	2206.6 (±316.0)	.17	.72	.60
C$_{MAX}$-adjust	30.1 (±3.4)	29.0 (±2.6)	47.6 (±4.0)	1.0	<.001	.01
AUC$_{540}$ (ng·min/mL)	2505.6 (±598.6)	2083.0 (±550.5)	1537.9 (±764.6)	.16	.004	.41
C$_{MAX}$ (ng/mL)	30.1 (±13.5)	29.0 (±7.4)	33.5 (±12.3)	.87	.55	1.0
T$_{MAX}$ (min)	10 (10, 60)	10 (10, 45)	10 (10, 10)	.70	.14	.67
T$_{1/2}$ (min)	138.0 (27.1, 780.1)	171.9 (53.3, 898.8)	61.8 (22.9, 392.9)	1.0	.13	.13
Clearance (mL/min/kg)	0.02 (±0.001)	0.02 (±0.003)	0.02 (±0.004)	.70	.28	.96
Vd (mL/kg)	0.18 (±0.03)	0.29 (±0.09)	0.09 (±0.03)	.32	.07	.01
M3G						
C$_{MAX}$ (ng/mL)	41.4 (±4.6)	45.5 (±3.3)	56.4.0 (±4.1)	.52	.01	.27
T$_{MAX}$ (min)	90 (30,220)	90 (45, 180)	60 (30,120)	.82	.03	.30
M6G						
T$_{MAX}$ (min)	120 (90,480)	90 (45, 90)	60 (45, 120)	<.002	<.001	1.0
M3G:MS ratio	5.5 (±0.76)	6.0 (±0.79)	10.1 (±1.83)	.5	.01	.24
M6G:MS ratio	0.001 (±0.0004)	0.0007 (±0.0002)	0.0009 (±0.0002)	.67	.05	.46

Pharmacokinetic data are expressed as mean (±SEM) with exception of T$_{MAX}$ and T$_{1/2}$, which is reported as median (min, max). Comparisons were made by Kruskal-Wallis rank sums test, and family-wise error rate is controlled using Dunn post hoc test with Bonferroni adjustment (STATA SE v15.1). Only statistically significant M3G and M6G PK parameters are shown in the table.

Abbreviations: AUC, area under curve; AUC-adjust, AUC calculation dose adjusted in obese group; CMAX, maximum concentration; CMAX-adjust, CMAX calculation dose adjusted in obese group; M3G, morphine 3-glucuronide; M6G, morphine 6-glucuronide; MS, morphine sulfate; OSAS, obstructive sleep apnea syndrome; PK, pharmacokinetics; SEM, standard error of the mean; T1/2, half-life; TMAX, time to maximum concentration; Vd, volume of distribution.

Table 3.

Comparison of Inflammatory Biomarker Levels Between Patients With Obstructive Sleep Apnea Only and Those With Obesity and Obstructive Sleep Apnea

Biomarker	Control	OSAS Only	Obese and OSAS
CRP (μg/mL)	0.85 (±1.3)	1.78 (±3.8)	4.53 (±4.2)[a,b]
	n = 18	n = 9	n = 8
IL-1β (pg/mL)	0.22 (±0.41)	0.17 (±0.07)	0.18 (±0.16)
	n = 12	n = 7	n = 8
IL-10 (pg/mL)	0.46 (±0.16)	0.59 (±0.17)	1.0 (±0.70)[a]
	n = 18	n = 7	n = 8
IL-6 (pg/mL)	0.59 (±0.26)	0.74 (±0.29)	1.02 (±0.25)[a]
	n = 18	n = 7	n = 8
Insulin (μU/mL)	10.2 (±10.4)	3.6 (±2.8)[c]	7.6 (±3.6)
	n = 18	n = 9	n = 13
Leptin (ng/mL)	7.4 (±8.8)	4.5 (±2.1)	28.8 (±21.3)[a,b]
	n = 18	n = 7	n = 13
TNF-α (pg/mL)	3.0 (±1.2)	2.6 (±0.7)	3.5 (±1.1)
	n = 18	n = 7	n = 8

Results are expressed as mean (SD). A total of 40 participants underwent biomarker analysis; however, due to lab error or insufficient sampling, not all biomarkers were performed on all subjects. The sample size for each biomarker per group is listed below mean (SD). Comparisons were made by Kruskal-Wallis rank sums test and Dunn post hoc method using Bonferroni correction.

Abbreviations: CRP C-reactive protein; IL, interleukin; OSAS, obstructive sleep apnea syndrome; SD, standard deviation; TNF, tumor necrosis factor.

[a] $P < .05$, control versus obese and OSAS.

[b] $P < .05$, OSAS only versus obese and OSAS.

[c] $P < .05$, control versus OSAS only.