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Increased Clearance of Morphine in Sick Cell Disease: Implications for Pain Management

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Abstract

Acute vaso-occlusive painful episodes associated with sickle cell disease (SCD) are frequently treated with morphine. Many SCD individuals require relatively higher doses of morphine to achieve optimal analgesia. We studied pharmacokinetics of morphine in SCD to explore if altered disposition could be a factor for increased requirement of morphine in this population. The study subjects were in steady state of health to avoid the effect of hemodynamic changes associated with vaso-occlusion on morphine disposition. The plasma concentrations of morphine and its major metabolites were measured at timed intervals in 21 SCD subjects after they received a single 0.1 mg/ Kg infusion of morphine sulfate. USCPACK software was used to fit candidate pharmacokinetic models. Non-compartmental pharmacokinetic parameters for morphine were calculated. Morphine clearance was 2.4 – 3.6 L/h, half-life was 0.3 – 0.7 hours, $AUC_{0-\infty}$ was 27.7 – 42.5 ng*h/mL, and volume of distribution was 0.96 – 3.38 L/kg. Clearance of morphine in the study population was 3 – 10 folds higher than published estimates in the non-SCD population, with correspondingly lower AUC and half-life. Volume of distribution was similar. This observation suggests that due to increased clearance SCD individuals may require higher dose and frequency of morphine to achieve comparable plasma levels.

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Keywords

Sickle cell disease; morphine; pharmacokinetics; clearance; pain management

Introduction

Individuals with sickle cell disease (SCD) frequently experience recurrent episodes of severe pain commonly referred as vaso-occlusive crises (VOC). These painful episodes can start as early as 6 months of age and continue to occur unpredictably through life. Other causes of pain in SCD include priapism, avascular necrosis of hip and shoulder joints and acute chest syndrome.²⁴⁻⁴⁰ Severe pain associated with SCD frequently requires treatment with opioids.²⁴⁻³⁴ Morphine remains one of the most commonly used opioids in this population due to global availability and widespread experience with its use. However, many individuals with SCD fail to achieve adequate analgesia with standard doses of morphine.³ Postoperative children with SCD who underwent cholecystectomy had an increased requirement of morphine administered via PCA (patient controlled analgesia) pump compared to children without SCD.⁹ The reasons for increased opioid requirement in this population have been elusive. Factors generally considered responsible for poor opioid response such as altered pharmacokinetics and tolerance have not been fully explored in SCD.¹⁻²¹

Morphine is metabolized through conjugation with glucuronic acid by the enzyme uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7) that results in formation of two major metabolites: morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G).⁷ M6G is an active metabolite of morphine which contributes to analgesia by binding to μ -opioid receptors and has been shown to be twice as potent as morphine in some animal and human studies.²⁰⁻²⁷⁻³⁰ In contrast, M3G has little affinity for opioid receptors and it may be responsible for the excitatory effects of morphine.³⁷ M6G, M3G, and a small fraction of unchanged morphine are excreted by glomerular filtration into the urine.¹⁸ Most of the conjugation takes place in the liver, but because morphine clearance exceeds hepatic blood flow, additional glucuronidation may occur elsewhere, for example the kidneys.⁴⁻¹⁶⁻²⁵⁻⁴¹ Individuals with compromised hepatic function are at risk for accumulation of morphine and toxicity due to reduced hepatic clearance of morphine whereas in presence of renal failure morphine metabolites accumulate to a greater extent than morphine itself and contribute to adverse effects.²³⁻³¹⁻³³⁻³⁵

In SCD the hepatic and renal blood flow are increased as a consequence to increased cardiac output associated with chronic hemolytic anemia.¹⁵⁻¹⁷⁻²⁹ Furthermore, the glomerular filtration rate (GFR) is markedly increased in SCD children which gradually decreases during adulthood.¹³⁻¹⁵ Increased clearance of morphine during painful crises reported in SCD children thus could be related to increased GFR and accelerated glucuronidation and elimination caused by changes in hepatic and renal blood flow.¹⁰ Although afore referenced studies demonstrated an increased clearance and increased requirement of morphine in children with SCD, both of these studies were conducted during painful state which itself could alter the disposition of morphine due to hemodynamic and inflammatory changes associated with vaso-occlusion and pain.⁹⁻¹⁰ Therefore, to isolate the effect of sickle cell disease on morphine pharmacokinetics, the present study was performed in steady state of health in young adults with SCD who were not on opioids and did not have vaso-occlusive crises or any other acute complications of SCD.

Methods

This cross-sectional study of morphine pharmacokinetics was approved by the Howard University Institutional Review Board and General Clinical Research Center (GCRC) Advisory Committee. Study subjects were 18 years or older individuals with SCD who were screened and consented during their routine clinic visits. Subjects with serum creatinine or hepatic transaminase values (alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) that were more than 2 times the upper limit of normal, or who had suffered any acute complication of SCD within the two weeks prior to the study were not eligible. Individuals with a history of chronic pain (defined as pain that lasted for more than six months)⁴², chronic opioid use or any opioid use within the two weeks preceding the study were not enrolled. A urine drug screen was performed on all study subjects at admission to detect recent use of opioids and those with positive results were excluded from the study. Eligible subjects were admitted to the GCRC for a 24 hour pharmacokinetic study. Two indwelling venous catheters, one in each arm, were placed. The catheter in one arm was used for morphine infusion while the catheter in the opposite arm was used to obtain blood samples.

Morphine infusion and assays

All participants received a single 30-minute infusion of morphine sulfate (0.1 mg/kg dose, maximum dose 10 mg). Blood samples were obtained from the catheter in the opposite arm before beginning of the infusion, at the end of the infusion, at 15, 30, 45, 60, 90 minutes, and at 3, 4, 5, 6, 12, 18 and 24 hours after the end of the infusion. Morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were measured in the plasma by liquid chromatography with electrospray ionization tandem mass spectrometry at the Center for Human Toxicology, University of Utah, Salt Lake City, UT.³⁶ In this method deuterated analogues (MOR-d₃, M3G-d₃, and M6G-d₃) are added to 50–500 microL of plasma as internal standards. The plasma is extracted by solid phase extraction. The extracted analytes and their internal standards are analyzed by liquid chromatography (LC) with electrospray ionization (ESI) tandem mass spectrometry (MS/MS). The LC system consists of an Agilent 1100 series in-line degasser, binary pump with solvent switching valve, thermostated autosampler, and thermostated column compartment. The LC column is a YMC™ ODS-AQ 2.0 × 150 mm S-3 120 Å reversed phased HPLC column (Waters Corporation, Milford, MA). The MS/MS system consists of a Thermo Finnigan model TSQ@7000 triple-stage quadrupole mass spectrometer equipped with a Gateway GP6450 or equivalent computer running Windows NT operating system and Xcalibur™ (v. 1.2) software. The LC is interfaced to the MS by means of an ESI ionization manifold. The mass spectrometer is operated in the selected reaction monitoring (SRM) mode. Four selected reactions to be monitored (*m/z*) include: 286.1→286.1 for MOR, 289.1→289.1 for MOR-d₃, 462.2→286.1 for M3G and M6G and 465.2→289.1 for M3G-d₃ and M6G-d₃. The concentration of each analyte is determined from the ratio of the peak area of the drug to the peak area of its deuterated internal standard, and comparison of this ratio with the calibration curve that was concurrently generated from the analysis of human plasma fortified with known concentrations of morphine, its metabolites and their internal standards. The limit of quantitation of the assay was 0.25 ng/mL for all analytes.

Pharmacokinetic modeling

The MM-USCPACK software collection, which is available by license from the University of Southern California at <http://www.lapk.org> was used to fit candidate pharmacokinetic models to the time-concentration data for morphine and each of its metabolites. The model building process proceeded from simple to complex until no further improvement in either the model log-likelihood or visual predictive checks (described below) could be obtained.

Body weight, body surface area (calculated using the Mosteller formula)²⁶, age, sex, and creatinine clearance were examined for covariate relationships with pharmacokinetic parameters using a two-stage process. First, model parameters without covariates were fitted to the data; second, linear regression of parameter values and covariates were tested for significance. Those with a significant relationship to a covariate were included in the model, which was refitted to the data. Because of the large number of model parameters and covariates, the entire population was used in model development as opposed to a subset. In the MM-USCPACK software, a portion of the random error in the model is attributed to the drug assay, multiplied by a factor, gamma, to capture additional error associated with measurement of serum concentration such as uncertainty in dose times. This “assay error” was calculated for each compound from the reported variability in their respective assays at given concentrations and the software estimated gamma from the pooled participant concentration data. In the model fitting process, measured concentrations were weighted according to the inverse of the product of assay error and gamma.

To compare results of the present study with published morphine pharmacokinetic parameter values, the following parameters were calculated from estimated model parameter values.

$$CL = \text{dose} / AUC_{0-\infty} \quad [a]$$

$$V_d = CL / K_t \quad [b]$$

$$t_{1/2} = \ln(2) / K_t, \quad [c]$$

where CL is clearance; $AUC_{0-\infty}$ is the area under the time-concentration curve from time 0 extrapolated to infinity, estimated by MM-USCPACK; V_d is volume of distribution; K_t is the total morphine elimination rate constant estimated by MM-USCPACK; and $t_{1/2}$ is elimination half-life in plasma. The healthy adult AUC range was calculated from the range of morphine clearance reported in the Duramorph® (morphine sulfate for injection) package insert (0.9 – 1.2 L/kg/h) using equation [a] with the same dose used as in the current study.

Predictive checks

To assess the ability of the final model to accurately represent the study population, visual predictive checks were made using the simulation module of the pharmacokinetic program ADAPT II.¹² A population of 1000 was simulated from the model, randomly selecting pharmacokinetic parameter values from the probability-weighted distribution of values for each parameter in the model (a technique known as Monte Carlo simulation). Each simulated subject was administered 0.1 mg/kg of morphine over 30 minutes, as was done in this study. The 5th, 25th, 50th, 75th and 95th percentiles of the calculated concentrations of morphine, M3G, and M6G in all 1000 simulated subjects vs. time were plotted. Superimposed upon these plots were the real concentrations of each compound measured in the participants. A visual predictive check was considered good if the distribution of concentrations in the simulated population was similar to that in the real study population. Additionally, the distribution of simulated vs. observed AUCs for morphine, M3G and M6G were compared by the non-parametric Wilcoxon Rank Sum test as a numerical predictive check.

Results

Characteristics of the study population

Twenty-one eligible individuals participated in the study. The data from three participants was excluded from the analysis due to dosing error in one and presence of opiates in the baseline urine sample in two others. Demographic and clinical characteristics of the study subjects are described in Table 1. Recently Smith and colleagues have reported that most adults with SCD are not hospitalized or seek medical care for the majority of days they experience pain including the pain self-identified as crisis.³⁸ We reviewed the medical records of the study subjects to assess the history of severe VOCs that required visits to emergency department (ED) or resulted in hospitalization, a strategy used to define disease severity in the multicenter study of hydroxyurea in SCD although history of daily episodes of pain and opioid use was not collected.⁶ It is therefore possible that the number of hospital admissions and ED visits do not accurately reflect the frequency of pain and opioid use in the study population. In the year preceding the study fourteen subjects (77%) had no inpatient admission, three subjects (16%) had one and one patient (5%) had two admissions for vaso-occlusive episodes. One patient was on monthly red blood cell transfusion for history of stroke. Twelve (66%) subjects were on hydroxyurea. None of the subjects had laboratory parameters suggestive of significant hepatic or renal dysfunction. All subjects reported not receiving any opioids in at least two weeks preceding the study and did not have history of chronic opioid use making tolerance to opioid unlikely.

Pharmacokinetic Modeling

There were 678 possible samples from the 18 participants. Twenty-seven (4.0%) samples were missing and 30 samples (4.4%) were reported as below the assays' limits of detection. All of these samples were treated as missing samples, which was unlikely to bias the results. 2 Two and a half to 6 fold variability was observed in peak plasma concentrations of morphine, M3G and M6G and time to reach peak concentration among the study subjects (Table 2). A 3-compartment model was most appropriate for morphine, with a 2-compartment model for M3G, and a single compartment model for M6G based on the maximal log-likelihood, individual observed vs. predicted plots, and visual and numerical predictive checks, therefore, there were 6 compartments, and 12 parameters to estimate from the population data (Figure 1). The median and inter quartile range of the model parameter estimates are reported in Table 3. The quality of the fit, as measured by observed vs. predicted plots (Figure 2), and visual predictive checks (Figure 3) was good. As a numerical check also, the simulated vs. observed morphine AUCs were not significantly different (median 28.4 vs. 31.9 ng*h/mL, $P=0.15$, Wilcoxon Rank Sum), shown in Figure 4. For M3G, the model slightly under-predicted the AUC relative to the observed AUCs (median 288.8 vs. 347.3 ng*h/mL, $P=0.04$, Wilcoxon Rank Sum). For M6G, the simulated vs. observed AUCs were similar (50.0 vs. 58.3 ng*h/mL, $P=0.08$, Wilcoxon Rank Sum). Altogether, the visual and numerical checks suggested that simulations from the model would represent the study population well.

As shown in Figure 4, the distribution of morphine $AUC_{0-\infty}$ in the 1000 simulated SCD subjects was much lower than the typical range of AUCs for non-SCD adults receiving the same dose (80 – 120 ng*h/mL), which is a direct consequence of higher morphine clearance as observed in our SCD study population. Based on our simulations, only 8% of individual SCD with similar characteristics as our study population would be expected to achieve the minimum typical non-SCD adult morphine AUC of 80 ng*h/mL with similar dosing. The healthy adult AUC range calculated from the range of morphine clearance reported in the Duramorph® (morphine sulfate for injection) package insert described in methods was consistent with the range of AUCs (74.7 – 106.7 ng*h/mL) reported by Hoskin et al in six

healthy volunteers.²² Calculated non-compartmental pharmacokinetic parameters for morphine are presented in Table 4, along with the parameters for the general population as reported in or derived from the Duramorph® package insert and other references.^{5,25,32} Similar parameters could not be calculated for M3G and M6G without a defined “dose” for these compounds. However, the observed median (IQ range) of the $AUC_{0-\infty}$ for M3G was 347.3 (309.5 – 389.2) ng*h/mL and for M6G was 58.3 (48.4 – 76.6) ng*h/mL. None of the estimated or calculated pharmacokinetic parameters were significantly associated with age, sex, hemoglobin concentration, serum bilirubin levels, and creatinine clearance.

Discussion

We describe morphine pharmacokinetics in steady state of health in young adults with SCD. The inter-individual variability of PK parameters was similar to that has been reported in non-SCD populations but the clearance of morphine was about three-fold higher in SCD study population than published parameters in individuals without SCD.⁴³ The half-life of morphine was correspondingly 3- to 10-fold shorter, while the volume of distribution was within the range with the non-SCD individuals. These results suggest that the more rapid clearance of morphine in SCD is due to increased metabolism/elimination of the drug rather than changes in the volume of distribution. We do not believe that past use of opioids and tolerance had played a role in increased clearance based on the fact that these participants had not taken opioids in at least two weeks prior to the study, and were not among the individuals who were frequently admitted or treated for pain. Additionally, the study participants were free of vaso-occlusive and other complications of SCD at the time of the study thus hemodynamic changes associated with acute complications of SCD were not a factor. We did not find an association between clearance of morphine and clinical characteristics including age, sex, hemoglobin concentration, serum bilirubin levels, and creatinine clearance. This observation may be related to narrow range of these parameters observed in our small study population and requirement of normal creatinine for enrollment in the study however these variables may be important in a larger SCD population.

The reasons for accelerated clearance of morphine are not completely clear. The clearance of hepatically metabolized drug such as morphine is dependent on the hepatic blood flow as well as intrinsic clearance determined by the activity of hepatic enzymes. Individuals with SCD have increased cardiac output and thus increased hepatic and renal blood flow.^{8,29} We therefore hypothesize that increased hepatic and renal blood flow and elevated GFR are likely reasons for increased clearance of morphine. Even though the GFR has also been reported to be elevated in a significant proportion of young adults with SCD, significant inter-individual variability of GFR exists and the GFR can be potentially increased, normal or decreased despite apparently normal renal function by serum creatinine.¹⁹ Although not confirmed in human studies, bilirubin mediated induction and increased activity of UGT isoenzymes, the primary enzymes responsible for hepatic clearance of morphine has been described in murine models and could be another mechanism.²⁸ The pharmacokinetic parameters of other drugs that utilize hepatic and renal pathways for metabolism and elimination have been described to differ between individuals with or without SCD.¹⁷ Due to lack of urinary data we cannot confirm if clearance was higher due to increased glucuronidation of morphine, urinary elimination of unchanged morphine or both. Previously we have reported impact of a UGT2B7 genetic variant on hepatic clearance of morphine.¹¹ The clearance of morphine continued to be higher in SCD regardless of their UGT2B7 variant status when compared to non-SCD.

The finding of increased morphine clearance and correspondingly lower plasma exposures in SCD may have implications in selection of appropriate doses and frequency of morphine administration. To achieve exposures of morphine that are similar to those in individuals

without SCD, higher and/or more frequent dosing may be required in SCD individuals. This finding is consistent with the clinical finding of increased morphine requirement in SCD which is often labeled as addiction or drug seeking behavior by many health care providers. 9-14.39-44 The results of present study should be interpreted with a caveat that a significant inter-patient variability of morphine disposition exists which is likely determined by the factors such as history of morphine exposure, organ function, and pharmacogenomics and therefore the therapy should be individualized to achieve optimal analgesia with minimum side effects.

Perspective

Accelerated clearance of morphine likely related to increased hepatic and renal blood flow may be responsible for increased requirement of morphine in SCD. Although SCD individuals may require higher and more frequent doses of morphine, inter-individual variability of morphine disposition highlights the importance of individualization of the therapy.

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Figure 1.

Final structural model for morphine (M) and its two primary metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Boxes represent pharmacokinetic compartments. INF = morphine infusion. Arrows are rate transfer constants (K_{xy}) from compartment x to compartment y , or elimination if $y = 0$. K_t = total morphine elimination rate constant. f_{m3} , f_{m6} = fraction of morphine metabolized to M3G and M6G respectively. = measured morphine, M3G or M6G concentration.

(A)

(B)

Figure 2. Observed vs. Predicted plots for morphine, using (A) population parameter estimates and (B) Bayesian posterior individual parameter estimates.

(A)

(B)

(C)

Figure 3.

Visual predictive checks for (A) morphine, (B) M3G, and (C) M6G. Lines are the concentration percentiles at a given time among the 1000 individuals simulated from the model: dark line is 50%, thin solid lines are 25% and 75%, thin dashed lines are 5% and 95%. For example, in individuals similar to those in this study, the expected median concentration of morphine 1.5 hours after the start of the infusion is approximately 5 ng/mL as shown in (A). The points are the actual measured concentrations for each compound in the real participant population. The relatively similar distributions of lines and points indicate that the model is free from significant bias or misspecification and that conclusions based on the simulated population are likely valid.

Figure 4.

Comparison of $AUC_{0-\infty}$ distribution in 1000 simulated individuals using the model (histogram bars), the measured $AUC_{0-\infty}$ range among current SCD individuals (dark lines), and the typical morphine $AUC_{0-\infty}$ range in adult individuals without SCD derived from the Duramorph® package insert (hatched box, 80 – 120 ng*h/mL). Vertical dashed line is the observed median $AUC_{0-\infty}$ in the SCD individuals (31.9 ng*h/mL), and the dot-dashed line is the median $AUC_{0-\infty}$ in simulated individuals (28.4 ng*h/mL), showing no significant difference ($P=0.15$, Wilcoxon Rank Sum test).

Table 1

Demographic and clinical characteristics of sickle cell subjects (n=18)

Males, number (%)		11(61)
Median age in years		20
Median height/ weight in centimeters/ kilograms	Male	171.7/ 56.8
	Female	163.4/56.8
Hemoglobin phenotype, number (%)	SS (homozygous hemoglobin S) disease	15 (83)
	SC disease	3(17)
On hydroxyurea, number (%)		12(66)
Laboratory data(median)	Creatinine (mg/dL)	0.6
	ALK/ALT/AST ^I (units/L)	117/20/42
	Hemoglobin (g/dL)	8.8
	Bilirubin (mg/dL)	3.5

^I ALK: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase

Table 2

Plasma concentrations of Morphine, M3G and M6G by HPLC MS/MS in SCD population

Parameter	Morphine Median (range)	M3G Median (range)	M6G Median (range)
Peak plasma concentration (ng/ml)	16.0 (9.1–50.7)	65.3 (40.8–99.4)	13.6 (7.9–25.6)
Time to reach peak concentration (minutes from the end of infusion)	Zero (End of infusion)	15 (15–60)	30 (15–90)
Plasma Concentrations at 24 hour (ng/ml)	0.29 (n.d. ¹ –0.32)	4.06 (0.50–6.28)	0.58 (n.d. ² –0.06)

n.d. = not detectable due to concentrations being below the limit of quantitation of the assays which was 0.25 ng/mL for all analytes

¹ Morphine assays: At 24 hours all but two individuals had undetectable levels of morphine

² M6G assays: At 24 hour all but two individuals had detectable levels of M6G

Table 3

Fitted compartmental population model parameter values for the model shown in Figure 1.

Parameter	Units	Median	Interquartile (IQ) Range
Kt	h^{-1}	1.28	0.91 – 2.66
K12	h^{-1}	6.79	5.34 – 8.11
K13	h^{-1}	1.22	0.72 – 1.79
K21	h^{-1}	3.68	2.69 – 5.06
K31	h^{-1}	0.07	0.05 – 0.12
K40	h^{-1}	1.23	1.08 – 1.58
K46	h^{-1}	1.31	0.87 – 2.09
K50	h^{-1}	0.68	0.62 – 1.05
K64	h^{-1}	1.31	1.01 – 2.02
V1	L	106.00	46.58 – 220.05
V4/fm3	L	11.41	10.92 – 14.51
V5/fm6	L	123.53	95.37 – 161.68

Kt = total elimination rate of morphine from V1 compartment; K_{xy} = rate constant of drug transfer from compartment x to compartment y; V_x = volume of compartment x; fm3 = fraction of morphine metabolized to M3G; fm6 = fraction metabolized to M6G.

Table 4

Calculated morphine population pharmacokinetic parameter estimates, derived according to the equations in the text.

Parameter	Units	SCD	Non-SCD*
		Median (IQ Range)	Typical Ranges
AUC _{0-∞}	ng [*] h/mL	31.9 (27.7 – 42.5)	80 – 100
CL	L/kg/h	3.1 (2.4 – 3.6)	0.9 – 1.2
Vd	L/kg	1.92 (0.96 – 3.38)	1.0 – 4.7
t _{1/2}	hours	0.52 (0.3 – 0.70)	1.5 – 2.0

AUC_{0-∞} = area under the time-concentration curve from dose time extrapolated to time infinity; CL = clearance; Vd = volume of distribution; t_{1/2} = half life.

* Non-SCD PK parameters reported or derived from the Duramorph® package insert and references for the same dose as used in the current study^{5,25,32}