The Effect of Fentanyl Administration on Plasma Agmatine Concentration In Critically Ill Patients

Abstract

Background: Agmatine, a product of L-arginine metabolism, has been shown to influence opioid tolerance, dependence and withdrawal in animal studies. The purpose of this study was to characterize the plasma agmatine concentration of critically ill, mechanically ventilated patients receiving continuous fentanyl infusion as part of their sedation/analgesia regimen. We hypothesized that these patients would demonstrate lower plasma agmatine levels.

Methods: All admissions to our pediatric intensive care unit (PICU) who received mechanical ventilation and fentanyl infusions as part of their sedation/analgesia regimen were eligible. Plasma agmatine concentrations were correlated with patient demographics and medication administration data.

Results: Twenty two mechanically ventilated children were enrolled and showed a negative correlation between Δ plasma agmatine concentration and the COMFORT score ($r=-0.42$, $p<0.01$), Δ cumulative fentanyl dose ($r=-0.48$, $p<0.01$), Δ fentanyl infusion rate ($r=-46$, $p<0.01$), and fentanyl infusion duration ($r=-37$, $p<0.01$).

Conclusions: Mechanically ventilated, critically ill patients receiving prolonged opioid infusions and meeting the definition of tolerance demonstrated lower plasma agmatine concentrations relative to baseline.

Keywords: Agmatine; Opioid; Intensive care; Critical illness; Drug tolerance

Research Article

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Introduction

An integral part of critical care medicine is ensuring that critically ill patients supported by mechanical ventilation are comfortable and pain-free while in the unfamiliar and often stressful environment of the intensive care unit (ICU). The use of opioids to assist in sedation and analgesia has been a common and long-standing practice in ICUs [1,2]. This intervention, however, comes with unfavorable effects such as the development of opioid tolerance, dependence, and withdrawal.

Agmatine is an endogenous mammalian polyamine that is formed from the metabolism of L-arginine. Numerous animal studies demonstrated that administration of exogenous agmatine prevents the occurence of opioid tolerance and dependence and abates the occurrence of withdrawal [3-6]. In animal studies, endogenous agmatine levels are influenced by chronic morphine exposure and induction of withdrawal, suggesting an important role in the regulation of opioid tolerance, dependence, and withdrawal [7].

To our knowledge no studies have attempted to assess the relationship of agmatine and opioid administration in humans. Therefore, the purpose of this study was to observe the effects of continuous fentanyl infusion on plasma agmatine concentration in critically ill, mechanically ventilated patients in a Pediatric ICU (PICU). We hypothesized that ventilated, critically ill patients receiving a continuous fentanyl infusion would demonstrate lower plasma agmatine levels.

Materials and Methods

All critically ill patients admitted to our PICU were considered for inclusion into this study. The Baylor College of Medicine Institutional Review Board approved the study protocol, H-22143, on July 15th, 2008. Written informed consent was obtained from the subjects parents or legal guardians. This prospective, observational study was conducted from August 2008 to April 2009 at a single-center, tertiary medical-surgical PICU.

Eligible critically ill patients underwent immediate baseline blood sampling after they were entered into the study and consent was obtained. Repeated blood samplings were taken at 3 days and at termination of the opiate infusion (irrespective of opiate infusion day).

Additional blood sampling was performed on no more than two separate occasions if patients met our definition of tolerance or required an increase in their opiate infusion dose. Tolerance was defined as a worsening COMFORT score at the same dose of opiate infusion from that given during the previous 24 hours and was determined by the medical staff caring for the patient. Plasma concentrations of agmatine and related amino acids, fentanyl and

midazolam were measured in the study patients. Patients were stratified by age, PRISM, and COMFORT scores. Cumulative dose from fentanyl boluses, peak fentanyl infusion rate, and cumulative fentanyl dose (infusion and boluses) were recorded on each day of blood sampling. Data on duration of fentanyl infusion were also collected.

Many of the patients had received a variety of analgesics/sedatives, such as fentanyl, morphine, ketamine and/or midazolam, during the intubation period and/or during surgery (i.e., before our baseline samples [T=0] were drawn). Therefore, Δ of all time points from baseline (Δ=Tn-T0) were calculated for plasma agmatine levels, drug concentrations, and dosages. Consequently, we were able to "zero" baseline values and estimate the Δ trends over time analyzing the Δ at subsequent time points.

A longitudinal time series analysis was performed between the different sampling time periods. A non-parametric test, Kruskal-Wallis, of plasma concentrations between groups was performed because fentanyl, midazolam, and plasma agmatine concentrations did not follow a Gaussian distribution. Linear regression analysis (ANOVA "least squares") was performed to correlate baseline plasma agmatine concentration with the patients' gender, ethnicity, disease category, ages and weights. Generalized Linear Model of repeated generalized estimating equations was used to compare the time series differences (Δ) of plasma agmatine levels from baseline with the COMFORT scale, fentanyl infusion duration in days, Δ of cumulative fentanyl dose, and Δ of fentanyl infusion rate.

Finally, the Univariate Regression Analysis, General Linear Model, was used to examine which variables were independently associated with changes of Δ in plasma agmatine levels from baseline when our definition of tolerance was met. Statistical asymptomatic significance was defined as 2-sided $p < 0.05$. SPSS version 17.0 (SPSS Inc, Chicago, IL) was used for data entry and statistical procedures.

Results

Of 99 critically ill patients screened, 51 met exclusion criteria and 48 were found to be eligible. Of the 48 eligible critically ill patients, 22 were enrolled into the study after consent was obtained (Figure 1). Demographic and recorded data is shown in Table 1.

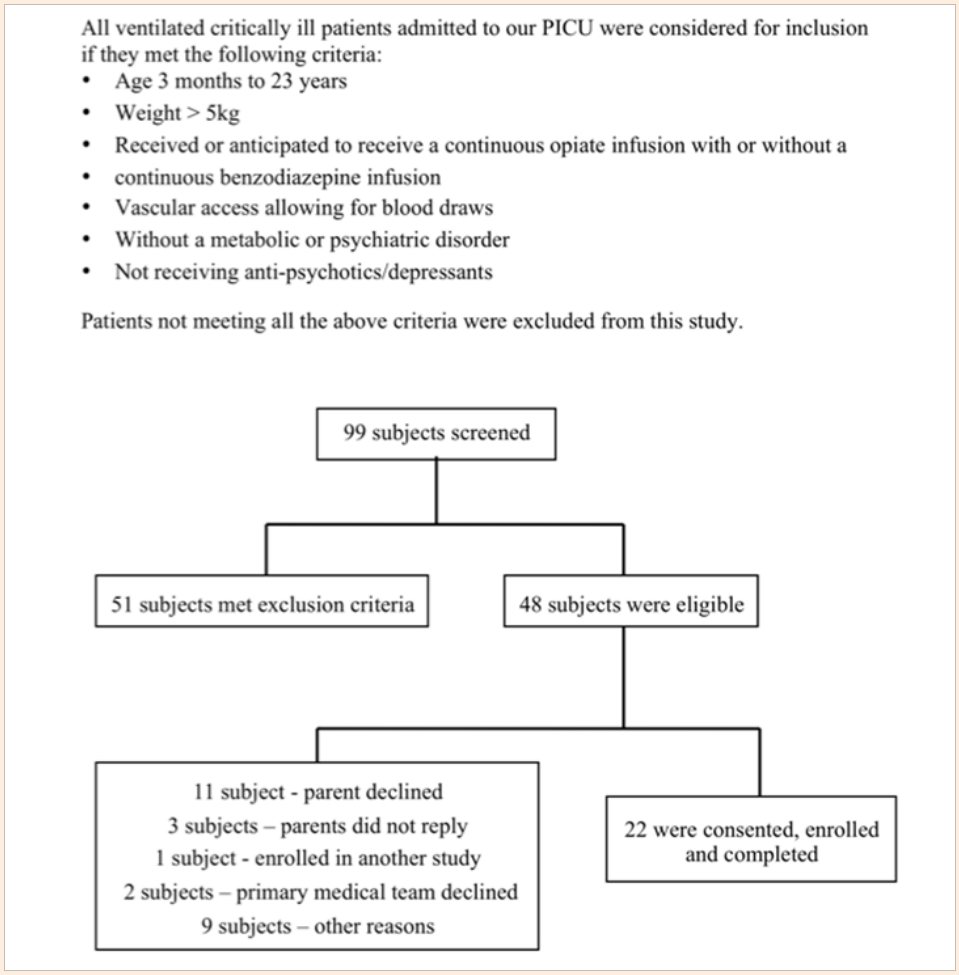

Figure 1: Patient Enrollment Flow Diagram.

Table 1: Clinical characteristics and demographics of the critically ill pediatric patients.

Patients	n = 22
Age (median in years [range])	5 (0.5-23)
Weight (median in kg [range])	20.6 (7.1-64.5)
Gender	**n (%)**
Male	16 (73)
Female	6 (27)
Ethnicity	
Caucasian	7 (32)
Hispanic	10 (45)
Other	5 (23)
Primary Diagnosis	
Pulmonary	11 (50)
Sepsis	2 (9)
Transplant	2 (9)
Trauma	2 (9)
Other	5 (23)
PRISM III score (median [range])	9.5 (0-22)
Length of PICU Stay (median in days [range])	3 (0-35)
Cumulative Dose From Fentanyl Boluses [median in mcg/day [range]) [a]	200 (0-2400)
Peak Fentanyl Infusion Rate (median in mcg/kg/hr) [a]	2.5 (0-8)
Cumulative Fentanyl Dose (infusion and boluses) (median in mcg/kg/day) [a]	13.5 (0-156)
Duration of Fentanyl Infusion (median in days)	6 (0-6)
COMFORT score (median)	25 (7-40)

[a]Values are those obtained on the day of blood sample measurement.

The median (range) PICU day at study enrollment was 3 days (1-35); 60% (13 of 22) of the patients were enrolled within 3 days of PICU admission. The median (range) number of ventilator days at study enrollment was 3 days (1-24); 55% (12 of 22) of the patients were mechanically ventilated for 3 days or less at the time of study enrollment. The median (range) number of hospital days at study enrollment was 4 days (1-72).

Fifty-eight blood sample measurements were done in the 22 critically ill patients. The median (range) number of samples per patient was 2 (1-5). Plasma agmatine concentration had a positive correlation with age ($r=0.49$, $p<0.001$), with higher values in the older children, but they did not correlate with gender, ethnicity, or disease category.

A longitudinal time series analysis of simultaneous plasma agmatine and drug concentrations did not differ significantly between the different sampling time periods. All other amino acid concentrations also did not differ in this analysis. The Δ plasma fentanyl and midazolam concentrations did not correlate with Δ plasma agmatine concentration, COMFORT scale, or Δ fentanyl dosage.

Time series analyses of the Δ plasma agmatine levels did show a negative correlation with the COMFORT score ($r=-0.42$, $p<0.01$), Δ cumulative fentanyl dose ($r=-0.48$, $p<0.01$), Δ fentanyl infusion rate ($r=-46$, $p<0.01$), and fentanyl infusion duration ($r=-37$, $p<0.01$), (Figures 2a-d).

At the time points when our definition of tolerance was met, the Δ plasma agmatine concentration were negatively independently associated with COMFORT score ($F=11.7$, $p<0.007$), fentanyl cumulative dose ($F=21.7$, $p<0.001$), fentanyl infusion rate ($F=5.7$, $p<0.04$), and fentanyl infusion duration ($F=20.4$, $p<0.001$) (Univariate Regression Analysis, General Linear Model, corrected model $F=11.4$, $p=0.001$).

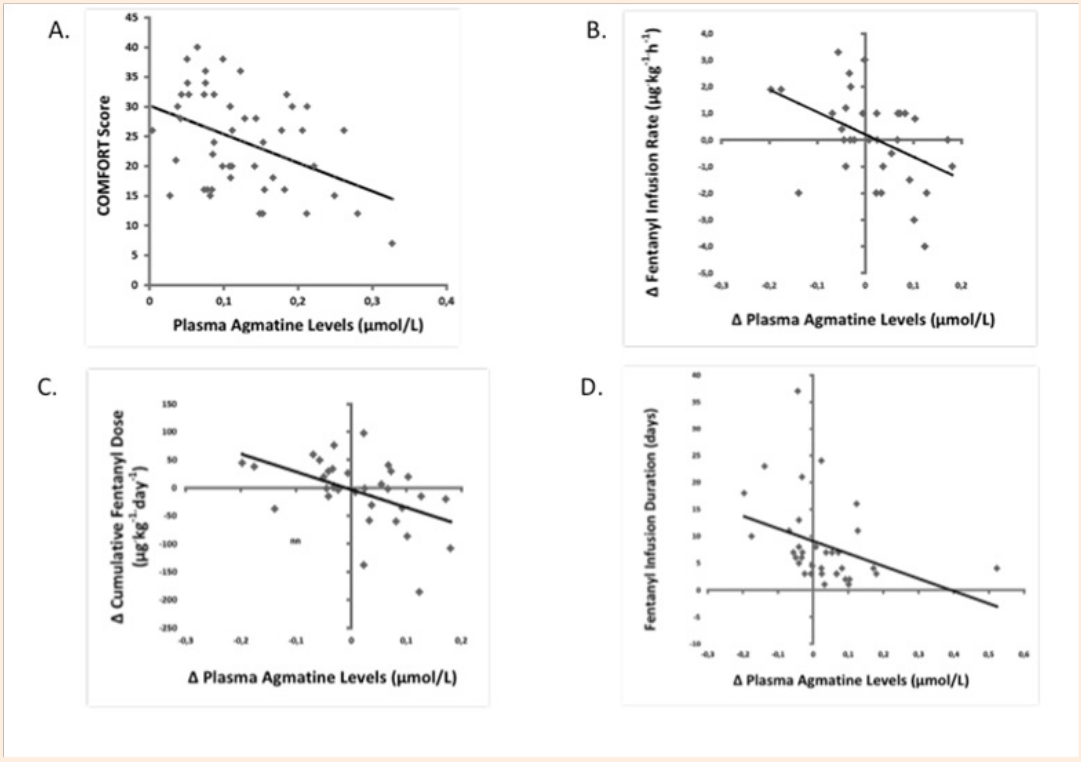

Figure 2a: Line fit scatterplot showing the negative correlation between COMFORT scores and simultaneously measured plasma agmatine levels. (r=-0.42, p<0.01);
Figure 2b: Scatterplot showing a negative correlation between the Δ plasma agmatine level and the Δ fentanyl infusion rate on the day of sampling (r=-46, p<0.01);
Figure 2c: Scatterplot showing a negative correlation between Δ plasma agmatine level and the Δ cumulative fentanyl dose (infusion and bolus doses) on the day of sampling (r=-0.48, p<0.01);
Figure 2d: Scatterplot showing a negative correlation between Δ plasma agmatine levels and duration of fentanyl infusion in days (r=-37, p<0.01).

Discussion

The present study aimed at examining the plasma concentration of agmatine in relation to opioid administration in mechanically ventilated, critically ill patients in a PICU. Agmatine is a cationic amine formed by the decarboxylation of L-arginine by the enzyme arginine decarboxylase (ADC). Agmatine appears to fit the criteria for a neurotransmitter and may exert neuromodulatory effects, leading some researchers to consider this as its primary role and function in the CNS [8]. Of particular interest is its potential role in the modulation of opioid analgesia, tolerance, and dependence.

Several studies have explored agmatine's role in the modulation of opioid functions through the adminsitration of exogenous agmatine [3-6,9-12]. Aricioglu-Kartal F and Regunathan S [7,8] were among the first to demonstrate the effects of opioid administration on endogenous agmatine metabolism. They examined the effects of agmatine metabolism in rats where they had an animal control group, a group with "chronic" (3 days) exposure to morphine and a group with chronic morphine exposure who were then induced to withdrawal. Aricioglu-Kartal et al. found that, compared to controls, the rats exposed to chronic morphine treatment expressed reduced ADC activity in brain tissue. Agmatine levels in most tissues, including plasma, also were significantly reduced whereas agmatine degradation was unchanged. Additionally, compared to both the morphine-treated and control groups, similar findings occurred in the rats that were induced to withdraw. Thus, their data suggest that morphine affects tissue and plasma levels of endogenous agmatine by reducing agmatine synthesis [7].

Similarly, our results suggest that endogenous agmatine in humans is also influenced by the administration of opioid infusions, based on the negative correlation we found between the changes from baseline in plasma agmatine levels and fentanyl infusion rate and cumulative dose. Thus, increased infusion rates and cumulative doses from baseline, at study entry, were associated with decreased levels of plasma agmatine from baseline. Longer duration of continuous fentanyl infusion was also associated with decreasing levels of plasma agmatine from baseline. Lastly, higher COMFORT scores were associated with lower plasma agmatine concentration and help to define mechanically ventilated patients

who are inadequately sedated, possibly due to a decreased drug effect, implying drug tolerance. Therefore, this finding could suggest an association with opiod tolerance.

Despite our interesting observations, there are several limitations to our study. First, there exists a gap in knowledge regarding fluctuations in agmatine synthesis and degradation and resultant plasma agmatine concentrations, especially with respect to various disease entities, time and/or age. To the best of our knowledge, the variation of plasma agmatine concentrations over time are unknown in both animals and humans. Agmatine is found to have multiple roles in mammals but the majority of studies have primarily involved animals and focused on the distribution of agmatine in the various tissues of the body and its potential role in these tissues [3-7,13-19]. The brain has been a major area of interest as agmatine's role is believed to be that of a neurotransmitter based on its concentration, distribution, presence and function in the CNS [8]. There is a paucity of studies investigating the role of agmatine in humans and the few studies that exist are mainly those associating lower plasma agmatine levels with depression [17]. Raasch et al. [13] discovered agmatine to be unevenly distributed in mammalian tissue but also demonstrated the presence of significant variability in tissue concentrations within animals of the same strain as well as animals of different strains. Raasch et al. also did not find an influence of aging on tissue agmatine concentration within a singular animal strain except in the cerebral cortex where agmatine concentration were reduced by about half compared to older animals. Again, Raasch et al.'s [13] study only examined these animals at one point in time. Our study found a positive correlation between plasma agmatine levels and age in our critically ill patients, with higher values in the older children, but we did not find any correlations with gender, ethnicity, or disease category. Therefore, with such intra- and inter- species variation, animal studies may not povide the answers to this question.

Another limitation of our study is the limited sample size. Analysis of simultaneous plasma agmatine and drug concentrations in a longitudinal time series analysis did not find a significant difference between the samples grouped into different time periods. The Δ plasma fentanyl concentration also did not correlate with Δ plasma agmatine concentration or Δ fentanyl dosage. These findings challenge the conventional, and our operational, definition of tolerance. Although lacking statistical significance, arguably, our longitudinal time series analysis did demonstrate a trend for decreasing plasma agmatine concentrations noted with the fourth and fifth samples obtained and increasing plasma fentanyl concentrations with the fourth sample. The authors hypothesize that the limited sample size, especially with the attrition of samples over time, is a likely contributor to the lack of statistical significance. Another potential confounder could be the lack of differentiating agmatine concentrations into age groups as we found a correlation in plasma agmatine levels with age.

To our knowedge, this study is the first attempt at examining the plasma concentration of agmatine in relation to opioid administration in humans. Further studies, of larger size, are warranted to better assess this relationship as this can have profound effects on a common practice in ICUs and beyond. Future studies should also address the normal variation in concentrations in both health and disease.

Conclusions

We have demonstrated a negative association between continuous fentanyl administration and plasma agmatine levels in critically ill pediatric patients supported by mechanical ventilation. To our knowledge, this is the first attempt to establish this relationship in humans. Inadequate levels of sedation, longer duration of fentanyl infusions, and increasing cumulative fentanyl doses and infusion rates from baseline were related to lower plasma agmatine levels relative to baseline. The same was determined when tolerance was appreciated clinically. Animal, and now human, studies show similar trends that open up numerous possibilities and opportunities for research in the prevention and management of opioid tolerance, dependence, and withdrawal.

Notes

This paper was orally presented at the Society of Critical Care Medicine's 39th Annual Critical Care Congress in Miami, FL on January 2010.

Potential Conflicts of Interest

Leticia D. Castillo received funding from the USDA and the Ajinomoto Research Program.

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