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ORIGINAL ARTICLE

Correlation of Serum and Urine Midazolam Levels with Consciousness Tests after Discontinuation of Sedation in the Intensive Care Unit

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ABBREVIATION LIST:
LOC: level of consciousness
GCS: Glasgow Coma Scale
FOUR score: Full Outline of UnResponsiveness Score
SOFA: Sequential Organ Failure Assessment
RASS: RichmondAgitation-Sedation Scale
CVVHDF: Continuous Veno-Venous Haemodiafiltration

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ABSTRACT

BACKROUND: Continuous infusion of midazolam is related to prolonged activity and delayed awakening in the critically ill. Serum midazolam levels can be helpful in differentiating residual benzodiazepine activity from other causes of impaired level of consciousness (LOC). Although drug levels can also be measured in the urine, the relationship between serum and urine levels with the observed LOC has not been studied in clinical practice.

OBJECTIVES: To investigate the correlation between serum and urine midazolam levels in the critically ill and their correlation with the observed level of consciousness estimated with the Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness Score (FOUR score).

PATIENTS AND METHODS: This is a prospective observational study involving patients admitted to a 30 bed General Intensive Care Unit (ICU), who were intubated and mechanically ventilated, with GCS prior to intubation >8. Midazolam infusion was discontinued for at least 12 hours before sampling. Serum and urine sampling to measure midazolam levels and clinical evaluation to calculate the GCS and FOUR score were done simultaneously

RESULTS: Twenty patients fulfilled the inclusion criteria and participated in the study. Serum midazolam levels correlated moderately with the GCS (R =-0.496, p=0.026) and better with the FOUR score (R =-0.685, p=0.001), but did not correlate with measured levels in the urine (R =-0.029 p=0.904).

CONCLUSIONS: After discontinuation of midazolam sedation, the LOC correlate significantly with the drug levels in the serum. Urine midazolam levels do not correlate with those measured in the serum or with the observed LOC.

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INTRODUCTION

Midazolam Hydrochloride was first synthesised by Fryer and Walser in 1976. It is a short-acting water-soluble benzodiazepine drug with an elimination half life of 2.3 - 2.5 hours that acts on GABA- (γ-amino butyric acid) associated benzodiazepine receptors. It has hypnotic, anticonvulsant, muscle-relaxant and anxiolytic properties and anterograde amnesic effects.[1] In clinical practice, it is used for the induction of anesthesia, sedation and the treatment of generalised seizures or status epilepticus.[2,3] Due to its chemical structure it has rapid absorption, distribution rate and metabolism. Following intravenous injection the plasma concentration of the drug decreases to 10% within 2 hours. Midazolam is bound extensively to plasma proteins and only the unbound drug is pharmacologically active. Once administered, it becomes highly lipophilic and has enhanced penetration into the central nervous system (CNS). It is oxidised by the liver faster than other benzodiazepines and, consequently, has a shorter duration of action. Its hepatic metabolites, 1′-hydroxymidazolam (1′-OHMDZ) and, to a smaller extent, 4-hydroxymidazolam (4-OHMDZ) and 1,4-dihydroxymidazolam, are pharmacologically active and are conjugated and then excreted as glucuronides in the urine.[4,5]

Midazolam is the benzodiazepine of choice for sedation in the critically ill[6] because of its fast onset and short duration of action, its minimal cardiovascular and respiratory effects and the induction of retrograde amnesia. Nevertheless, it has significant side effects, the most notable of which is residual sedation after cessation of the drug following prolonged continuous infusion.[7] Residual sedation mechanisms include fat absorption and redistribution of the drug from the fat tissue to the circulation, delayed metabolism and excretion in case of renal and hepatic failure and P450 inhibition by other co-administered drugs. In the critically ill, residual sedation may be difficult to differentiate clinically from other causes of decreased level of consciousness (LOC) such as non-convulsive status epilepticus, encephalopathy, CNS infections, cerebrovascular disease and post anoxic injury.[8,9] The need to rule out these entities may result in overuse of imaging and neurophysiological studies.

Serum benzodiazepine levels can be helpful in differentiating residual drug activity from other causes of impaired LOC.[10] Urine samples have also been used mainly in the emergency and in the palliative care setting.[11] This study aims at identifying if urine midazolam levels are correlated with serum midazolam levels and with the level of consciousness in critically ill patients. Based on the drug's complex pharmacokinetics we hypothesize that serum levels have a better correlation with the LOC as measured by the GCS and the FOUR score than the urine levels, and that there is a weak or no correlation between the serum and the urine levels of the drug.

METHODS

SETTING

A 30 bed University General Intensive Care Unit. The unit admits unselected medical and surgical patients including trauma.

PATIENTS

The inclusion criteria for the study were patient age >18, prior sedation and mechanical ventilation with Glasgow Coma Scale (GCS) prior to intubation >8. Exclusion criteria were admission to ICU with coma, a diagnosis relevant to acute neurological injury, pregnancy and any contraindication to the cessation of sedation, including severe respiratory failure and evidence or suspicion of increased intracranial pressure. Patients that received fentanyl for analgesia were also excluded from the study because this drug can have prolonged action in ICU patients.[12]

CLINICAL ASSESSMENT

After the initial assessment for inclusion in the study, midazolam infusion was discontinued for at least 12 hours. The level of consciousness was subsequently assessed with the GCS and the Full Outline of UnResponsiveness (FOUR) score.[13,14] In cases were other sedatives were used after the discontinuation of midazolam, i.e. propofol or remifentanyl, all sedatives were discontinued for at least 3 hours prior to the clinical assessment. Other data gathered were: age, sex, weight and height, reason for admission to intensive care, renal function tests and the application of renal replacement therapy. The Sequential Organ Failure Assessment (SOFA) score was also calculated for all patients.[15]

MIDAZOLAM MEASUREMENTS

Serum midazolam measurements were performed on the Cobas Integra 400 system (Roche), which is suitable for semiquantitative detection of benzodiazepines in the serum. Urine midazolam levels were measured with the Cobas C501 system (Roche), which is suitable for semiquantitative detection of benzodiazepines in human urine.

ETHICS

The Scientific and Ethics committee of Evangelismos hospital approved the study protocol. Informed consent from the patient's next of kin was obtained for all study participants.

STATISTICS

The maximum, minimum and median values were used for descriptive statistics. Correlation between serum and urine midazolam values, as well as correlation with the LOC scales was measured with the Pearson's coefficient.

RESULTS

During the study period 28 patients were evaluated for participation. Eight of these were excluded. Two did not receive benzodiazepines, two did not produce urine and a consent form could not be obtained in 4 cases. Twenty patients were finally included in the study. The demographics and the clinical characteristics of the study population are presented in Table 1. Six patients were on CVVHDF (Continuous Veno-Venous Haemodiafiltration) during the study period and three of them were on CVVHD at sampling time. Two additional patients fulfilled the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria for acute kidney injury.[16] None of the patients had hepatic failure. All patients received midazolam infusion for a median time of 14 hours (8-27 hours). Midazolam was stopped for at least 12 hours before the clinical assesment and the serum and urine sampling (median 36 hours, minimum time 12 hours, maximum 76 hours) and all concommitant sedation was interrupted for at least 3 hours. Serum and urine midazolam levels are shown in Table 1.

Serum midazolam levels correlated moderately with the GCS (R = -0.496, p = 0.026) and better with the FOUR score (R = -0.685, p = 0.001) but did not correlate with measured levels in the urine (R = -0.029, p = 0.904) even when patients without AKI were analysed separately (n = 12, R = 0.173, p = 0.572). Figure 1 presents the scatter plot of measured urine and serum drug levels in our population.

TABLE 1. Patient demographics, clinical characteristics and measured midazolam levels

Number of patients	20
Male / Female	10 / 10
Age (Years)	66 (20 - 90)[#]
Weight (Kg)	77.5 (45 - 160)[#]
SOFA score	8 (4 - 15)[#]
GCS	7 (3 - 14)[#]
FOUR score	10 (3 - 15)[#]
Reasons for ICU admission n (%)	
Septic shock	7 (35%)
Respiratory failure/ARDS	7 (35%)
Acute surgery and trauma	6 (30%)
Serum midazolam levels (ng/mL)	513 (2200 - 106)[#]
Urine midazolam levels (ng/mL)	571 (938 - 83)[#]

[#] Median (Minimum – Maximum)

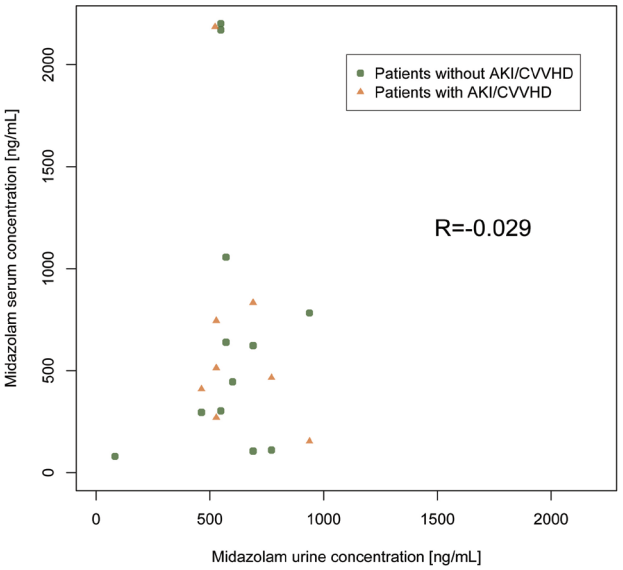

FIGURE 1: Scatter plot showing the correlation between serum and urine levels of midazolam (R = - 0.029, p = 0.904).

DISCUSSION

Our results show that serum midazolam levels correlate with the observed LOC in critically ill patients after discontinuation of sedation, while the urine levels do not. These findings are in accordance with previously published work reporting a reasonable correlation of serum midazolam levels with the depth of anesthesia.[5] There are also in accordance with the findings of Rosich Andreu et al that showed that the serum but not the urine benzodiazepine levels correlated moderately with the time to awakening, estimated as time to eye opening, after discontinuation of sedation in a critically ill population.[17]

The phenomenon of residual sedative action is the main reason for avoiding benzodiazepines in modern ICUs.[18] Residual sedation is related to prolonged mechanical ventilation and ICU length of stay. Other side effects of benzodiazepines include delirium, agitation and withdrawal symptoms when the drug is discontinued. Other sedatives commonly used in in ICU include propofol, remifentanyl and dexmedetomidine. These drugs have a more attractive pharmacokinetic profile and their dosage can be easily titrated to the desired sedative effect. Nevertheless, intravenous benzodiazepines have a favourable hemodynamic profile and provide an acceptable option for sedation in patients that are hemodynamically compromised.[18]

When midazolam is deemed to be the sedative of choice, a number of strategies can be applied to avoid a prolonged sedative effect, such as, careful titration of dosage to the minimum achieving the desired depth of sedation, a lighter level of sedation, combinations of midazolam with other medications and daily sedation vacation. Drug level monitoring and

electrophysiological assessment of the depth of anaesthesia by continuous electroencephalography or with the bispectral index also play a supportive role.[19]

We showed that serum midazolam levels correlated moderately with the GCS (R = -0.496, p = 0.026) and better with the FOUR score (R = -0.685, p = 0.001). In order to understand this finding we need to take a better look at the two methods for assesing the LOC in the critically ill. The GCS (Table 2) was originally designed for assessing head trauma severity[13] and has become the most widely used scoring system for all patients with an altered level of consciousness in the ICU. Important limitations of the GCS are the inconsistent inter-observer reliability, the impossibility of assessing the verbal score in intubated patients, and the exclusion of brainstem reflexes. The FOUR score (Table 3) incorporates important information that is not assessed by the GCS, such as the presence of brainstem reflexes, eye movement (blinking and tracking), a broad spectrum of motor responses and the pattern and rate of respiration, therefore, it is more suitable by design for the critically ill.[14]

We chose to evaluate our patients by using a LOC scale rather than a sedation scale such as the Richmond Agitation–Sedation Scale (RASS).[20] Sedation scales are designed to provide a tool for sedative titration to patient comfort and not for the assesment of wakefulness as a component of consciousness. However, our results show that residual sedation effects were present in many of our patients who had high serum midazolam levels.

TABLE 2. The Glasgow Coma Scale

Behaviour	Response
Eye Opening	4. Spontaneously
	3. To speech
	2. To pain
	1. No response
Verbal	5. Oriented to time, person and place
	4. Confused
	3. Inappropriate words
	2. Incomprehensible sounds
	1. No response
Motor	6. Obeys commands
	5. Moves to localized pain
	4. Flexion to withdraw from pain
	3. Abnormal flexion
	2. Abnormal extension
	1. No response

TABLE 3. The Full Outline of UnResponsiveness Score

Eye Response	
Action	**Score**
Opens eyes spontaneously, tracks, blinks to command	4
Opens eyes, does not track or blink to command	3
Eyes closed, open to loud voice	2
Eyes closed, open to painful stimulation	1
Eyes remain closed following painful stimulation	0
Motor Response	
Action	**Score**
Obeys, makes sign e.g. “thumbs up”	4
Localises painful stimulus	3
Flexes to painful stimulus	2
Extends to painful stimulus	1
No response	0
Myoclonic Status Epilepticus	0
Brainstem Reflexes	
Action	**Score**
Pupils +, corneals +, cough +	4
One pupil unreactive, corneals+, cough+	3
Pupils -, corneals +, cough NA	2
Pupils +, corneals -, cough NA	2
Pupils -, corneals -, cough +	1
Pupils -, corneals -, cough -	0
Intubation	
Action	**Score**
Not intubated, normal respiration	4
Not intubated, Cheyne Stokes respiration	3
Not intubated, irregular respiration	2
Not intubated, apnoeic	0
Intubated, breathes above ventilator settings	1
Intubated, breathes below ventilator settings	0

+ = present, - = absent

The lack of correlation between urine and serum midazolam levels is not surprising given the pharmacokinetics of the drug. Midazolam has a two compartment model of distribution and elimination that can become a three compartment model when the drug is administered by continuous infusion for a prolonged period of time.[21] Pharmacokinetic two-compartment models divide the body into a central and a peripheral compartment. The central compartment consists of the plasma and tissues where the distribution of the drug is practically instantaneous. The peripheral compartment consists of tissues where the distribution of the drug is slower. A third compartment is relevant when highly and poorly perfused tissues participate in the model. In multiple compartment pharmacokinetics, phenomena of redistribution take place.[22] These may interfere with the serum levels of the drug and its rate of elimination and explain why urine levels do not correlate with serum levels even when the former are corrected for the creatinine clearance, the serum albumin or the liver function.

Our study has some limitations that need to be taken into account when interpreting the results. Firstly, the sample size is small. Limited resources did not allow us to have a sample large enough to identify a subpopulation in which urine levels could possibly correlate better with the serum levels and the LOC. Such a subpopulation could theoretically be the healthier patients who received a smaller total dose of the drug. A larger sample would also allow us to obtain measurements from patients with prolonged infusions. Another limitation is that the biochemical methods for midazolam estimation in the serum and in the urine were both semiquantitative rather than quantitative, and this means lower precision.[23,24] One may argue that the lack of precision is a reason for not identifying a correlation between urine levels and the LOC, however we think that this is unlikely, based on both previous work and on the models of benzodiazepine pharmacokinetics.[17,21] In the present study we did not perform serial measurements of midazolam levels and did not observe the patients long enough to identify a correlation of drug levels with the awakening process and the disease severity. Estimating the effect of disease severity to the awakening time is difficult to assess since the GCS is inherent to the SOFA score. Although finding a correlation between disease severity and time to awaken was not the aim of our study, it would definitely be of clinical value. Another limitation is that some patients were on CVVHDF for renal failure. There is a known effect of kidney injury on the pharmacokinetics of midazolam that may affect drug levels. However, when samples from patients without kidney injury are examined seperately (Figure 1) there is still no significant correlation between serum and urine midazolam levels. Lastly, a number of patients received propofol for sedation. The drug was discontinued for at least three hours before the sampling and due to its short time of action we believe that it had little or no effect in the measured LOC.

In conclusion, serum midazolam levels correlate with the LOC particularly as estimated by the FOUR score in the critically ill , and can therefore provide a useful tool for the differential diagnosis in patients who are slow to wake following discontinuation of sedation. Urine midazolam levels, at least as a single measurement are not correlated with the LOC and can not help in the discrimination of residual sedation from other causes of coma. Intensivists need to take into account a possible unwanted prolonged sedative action when choosing midazolam to sedate their patients, should titrate midazolam infusion with caution and reside in this drug when newer sedatives with faster elimination are contraindicated.

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