THERAPEUTIC DRUG MONITORING TO ASSESS CLINICAL RESPONSE TO SEDATIVE MEDICATIONS IN THE INTENSIVE CARE UNIT: A CASE REPORT AND DISCUSSION

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ABSTRACT

We describe the pharmacological evaluation of a 60 year old female admitted to the intensive care unit with severe necrotizing fasciitis not responding to excessive dosages of intravenous sedatives and analgesics. This evaluation revealed the first to be reported midazolam-ketamine drug interaction in the medical literature and explains how we were able to answer a relevant clinical question using pharmacokinetics and pharmacodynamics analysis of serum drug levels.

Key Words: *Shock, hypotension, bacterial infections, midazolam, interactions*

Case Report

A 60-year-old female was admitted to the general medical ward of a tertiary care hospital with generalized weakness, decreased level of consciousness, progressive weight loss, hypoglycemia and extensive cellulitis involving her right lower limb and part of her abdominal wall, which rapidly progressed to necrotizing fasciitis affecting her entire thorax, abdomen, and bilateral lower limbs.

Her past medical history included chronic hypertension, gastroesophageal reflux disease, previous Roux-en-Y surgery for peptic ulcer disease, un-explained iron deficiency anemia, hepatitis C virus infection, previous liver abscess, chronic obstructive pulmonary disease and narcotic addiction, for which she was enrolled in a methadone maintenance program with her most recent dose dispensed two weeks prior to admission and was not continued in the hospital. The patients' medications list documented at the time of admission to the hospital included: salbutamol puffer as needed, fluticasone puffer once daily, rabeprazole 20 mg once daily, ferrous fumerate 300 mg once daily, methadone 40 mg once daily, ramipril 10 mg once daily and domperidone 10 mg before meals. Broad-spectrum antibiotic therapy in the form of pipercillin/tazobactem was initiated and dosed according to weight (75 kg) after blood cultures were withdrawn. On the day following admission, the patient was transferred to the intensive care unit (ICU) with multi-organ failure in the form of coma, hypotension and respiratory failure secondary to septic shock after undergoing airway intubation. The patient had preserved renal function as indicated by a normal creatinine level, however, creatinine clearance was not measured. Intravenous (IV) antibiotics were continued and IVimmunoglobulin therapy was started in addition to IV vasopressors (dopamine) and ventilatory support. On the fourth day of hospitalization, 40% of her body surface area (BSA) was surgically debrided to control overwhelming sepsis. Blood cultures grew group Aβ-hemolytic *streptococcus*. Antimicrobial therapy was switched to intravenous Penicillin G and Clindamycin.

The patients' overall clinical status progressed with multiple vasopressors (norepinephrine, dobutamine and vasopressin) needed for circulatory support in addition to high requirements for oxygen. However, parameters stabilized then improved with gradual weaning off of ventilator and circulatory support. The patient also received total parenteral nutrition for nutritional support. Ongoing care in the ICU required twice daily dressing changes (approximately 1 hour each time), which were associated with severe pain and discomfort despite escalating doses of intravenous fentanyl, midazolam, propofol and ketamine. The ventilator adjusted: motor assessment scoring scale (VAMASS), which is a well-known and validated scale, was used to monitor the need for additional anesthesia and analgesia.[1] (Table 1)

TABLE 1 VAMASS Ventilator Adjusted: Motor Assessment Scoring Scale (if not ventilated, determine MASS only)

MASS Score	Description of MASS	VA Score	Description of VA
0	Unresponsive to pain	A	Minimal coughing; few alarms; tolerates movement
1	Opens eyes and/or moves to pain only	B	Coughing, frequent alarms when stimulated; settles with voice or removal of stimulus
2	Opens eyes and/or moves to voice	C	Distressed, frequent coughing or alarms; high RR with normal/ low PaCO2
3	Calm and cooperative	D	Unable to control ventilation; difficulty delivering volumes; prolonged coughing
4	Restless but cooperative; follows commands		
5	Agitated; attempts to get out of bed; may stop behavior when requested but reverts back		
6	Dangerously agitated; pulling at tubes or lines, thrashing about; does not obey commands		

TABLE 2 Sedatives/Analgesics Used

Medication	Maintenance dose	Dosing for dressing change	Total received (24 hours)
Midazolam	2 mg/hr IV	4 mg IV q3 minutes PRN	96 mg
Fentanyl	450 mcg/hr IV	50-100 mcg q5 min PRN	11,000 mcg
Hydromorphone	8 mg/hr IV	3 mg IV q30 minutes PRN	210 mg
Ketamine		20-40 mg IV q40 minutes PRN	120 mg

The Clinical Pharmacology service was consulted on day 9 of her ICU admission to provide suggestions regarding additional options for effective anesthesia and analgesia, and to determine potential reasons as to why this patient seemingly failed to respond to high doses of multiple analgesic and anesthetic agents. At the time of this consultation, the patient was receiving the sedative and analgesic medications at the doses as depicted in Table 2. In addition, standard therapy according to the institutions ICU protocol was given and included medications such as subcutaneous low molecular weight heparin for DVT prophylaxis, oral peptase (pancreatic enzymes), IV ranitidine for gastric acid suppression and IV albumin (20% albumen

solution 100 cc twice daily). To maintain hydration in the setting of a 40% BSA-wound, intravenous 0.9% saline was administered at 300 mL/hour. The BSA was calculated using our institutes' burn protocol. The patients' fluid balance was carefully monitored and the IV fluid rate was adjusted to maintain an overall positive balance. It is possible that at the time the ranitidine was initiated the ICU team was not aware of this fact and hence the patient received it as per ICU protocol.

A thorough review of the patient's hospital chart demonstrated a progressive and gradual increase in sedative and analgesic requirements; however, the patient continued to be agitated and demonstrated signs of severe pain throughout her dressing changes.

AIM & METHODS

We sought to investigate the pharmacokinetic/pharmacodynamic relation between "midazolam" and the "patients'level of sedation".

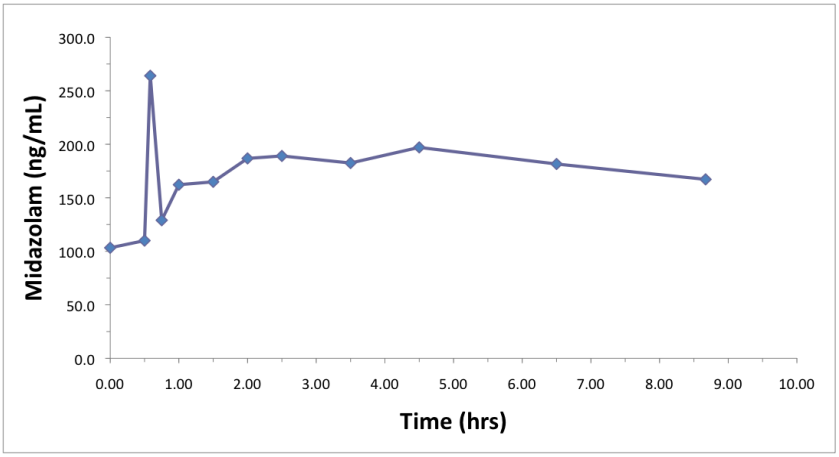
The most recent regimen given to the patient for analgesia and anesthesia prior to our assessment was IV hydromorphone 8 mg/hr, IV fentanyl 100 mic/hr, IV midazolam 4 mg/hr and IV propofol 1-5 mg/kg/hr as needed only at the time of dressing changes. The last dose of IV ketamine was given 5 days prior to our evaluation. From a clinical perspective, the patient appeared to be stable, with similar serum creatinine, albumin, and hemoglobin values for at least 48 hours prior to sampling and 48 hours after sampling. We collected 2 blood samples from the patient; one at baseline and the second prior to a scheduled 4 mg IV bolus of midazolam; then collected samples at 5,15,30,45,60 and 90 minutes and at 2,4,6 and 8 hours after the initial bolus (Figure 1a). The patient continued on basal IV midazolam infusion at 2 mg/hr. Midazolam concentrations were determined using a validated, previously published method.[2-4] On the day of sample collection the patients' albumin level was documented to be 34 g/l and her serum creatinine was 32 mmol/l.

DISCUSSION

Question 1: *Were midazolam concentrations adequate to maintain appropriate sedation?*

Midazolam is a potent benzodiazepine with hypnotic, sedative, anxiolytic, amnestic, anticonvulsant, and muscle relaxant properties. It is frequently used in the ICU setting to facilitate invasive interventions such as mechanical ventilation. In healthy volunteers, the plasma concentration and pharmacokinetics of midazolam are related to its pharmacodynamic response, thus resulting in a predictable PK/PD relationship.[5,6] Drug level analysis in our patient demonstrated an initial (basal) midazolam concentration of approximately 100 ng/mL with a peak concentration of 250 ng/mL, and an increase to 200 ng/mL after an IV bolus of ketamine that was given shortly after a bolus dose of midazolam (figure 1A). The patient was on a prolonged infusion of midazolam (5 days); we therefore assumed that the basal level observed was reflective of the steady state concentration (C_{ss}). From a previous publication by Albrecht et al[5], we hypothesized that the measured concentration in the patient would not be expected to result in adequate or complete sedation, which occurs at levels above300 ng/mL. Based on these results we determined that the patient had inadequate plasma concentrations of midazolam to achieve adequate sedation.

FIG. 1A



Question 2: *Why the increase in plasma concentration at 2 to 5 hours after bolus administration?*

We hypothesized that the increase in midazolam concentration following a bolus of ketamine may have been the result of an interaction between the two drugs via inhibition of CYP3A4 by ketamine, thus preventing the biotransformation of midazolam to 1-OH-midazolam (figure 1B). To our knowledge, this is the first example of inhibition of CYP3A by ketamine in humans, although a modest effect on rat CYP3A isoforms has been reported previously.[7,8]

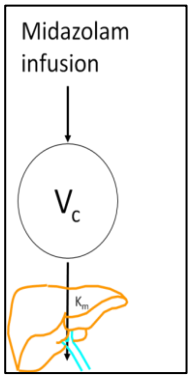
Question 3: *How can we account for the high systemic clearance of midazolam in this critically ill patient?*

As mentioned above, the pharmacokinetics of midazolam are related to its clinical response, and its relatively short elimination half-life (1.5-3hrs in healthy volunteers) makes it an attractive candidate for short and long-term sedation. Midazolam pharmacokinetics has been well characterized.[4,5] Midazolam is highly protein bound (95%), though the unbound fraction is higher in patients with chronic renal failure and/or cirrhosis (neither of which our patient suffered from).[9-11] The volume of distribution (V_d) is 1 to 2.5 L/kg, and likewise can be higher in patients with congestive heart failure, chronic kidney disease, and/or obesity, secondary to its high lipophilicity.[6] Midazolam is exclusively eliminated by biotransformation via CYP3A4 into the biologically active 1-hydroxy-midazolam and relatively inactive 4-hydroxy-midazolam metabolites; which are rapidly inactivated by glucuronidation ($T_{½}$ of 1 hour), but can accumulate in patients with renal failure. The clearance of midazolam in normal subjects is approximately 0.25 to 0.54L/h/kg. However, this can vary with concomitant use of medications known to induce or inhibit CYP3A4.[12,13] While midazolam clearance is relatively preserved in critically ill patients[14], previous studies in this population have demonstrated that recovery times from continuous midazolam infusions can be prolonged, as a result of prolonged elimination half-life and elevated volume of distribution (V_d). There may be a tendency for midazolam to distribute into adipose tissue during prolonged infusions.[15]

Systemic clearance of midazolam was calculated based on the measured plasma concentration and was similar to the values reported in healthy volunteers (~ 27l/h) (figure 2a). In healthy volunteers, midazolam clearance can be modeled using a 1-compartment model in which the primary determinant of systemic clearance is hepatic CYP3A4 activity. However, in our patient, there was the presence of co-administered CYP3A4 substrates and inhibitors, and a large inflamed/resected surface of large amounts of serous exudates through the

wounds. We therefore proposed a 2 compartment model to try to understand the kinetics and distribution of the midazolam (figure 2B). The revised model, accounting for normal systemic clearance of midazolam, may be accounted for by a combination of inadequate metabolic clearance and some degree of loss via her extensive wounds.

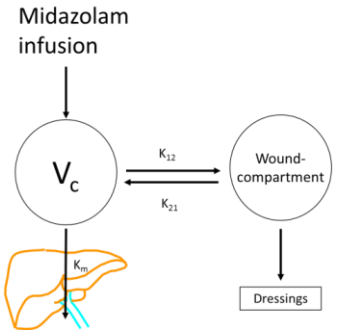
FIG. 2A Normal midazolam clearance



Total systemic clearance
= rate of infusion/C_{ss}
= (2 mg/hr)/(C_{ss})
= (2 x 10^6 ng/hr)/100 ng/mL
= 20 L/hr

Where C_{ss} is the concentration measured at steady state, V_c is the volume of the central compartment, and K_m is the rate constant for hepatic elimination of midazolam.

FIG. 2B Midazolam clearance in a patient with wounds covering 40% BSA



$Cl_T = kV_D = Cl_{liver} + Cl_{wound}$ = 20 L/h
Cl_{wound} = rate of loss from wound/C_{ss}
Rate of loss from wound = 1 ng/ml of wound exudate x 400 ml/h = 400 ng/h
Cl_{wound} = (400 ng/h)/(100 ng/ml) = 4 ml/h = 0.004 L/h
$Cl_{liver} = Cl_T - Cl_{wound}$ = 20 L/h – 0.004 L/h ≈ 20 L/h

To determine the contribution of wound clearance of midazolam to overall systemic clearance, we elected to directly sample wound exudates and dressings. A total of 290 g of wet dressings were extracted in a 250 ml of methanol and the extract volume was reduced to 50 mL with heat. The concentration of midazolam in the resulting extract was 94ng/ml for a total of 4.7 μg of midazolam recovered from wound dressings. The concentration of midazolam in separately collected wound exudates was 1 ng/ml. Even when accounting for exudate losses of up to 400 ml/hour, the loss of midazolam through the wound would only be 0.4 μg/hour, (figure 2b). This would suggest that virtually all drug clearance is dependent on hepatic CYP3A metabolism.

Question 4: *Why does hepatic CYP3A activity appear to be preserved?*

A number of factors presented in this critically ill patient have previously been shown to result in impaired CYP3A activity in both human and rodent models.[16] CYP3A4 is the most abundant hepatic and intestinal CYP and it is responsible for the metabolism of most drugs in clinical use (~50%).[17,18] CYP3A4 is also involved in the metabolism of dietary toxins, and may modulate the systemic exposure to these substances. It is well known that genetic variation in the genes encoding the individual CYPs can account for significant inter-individual variation and have profound implications for clinical drug therapy in normal individuals.[18] Additional alterations in activity in disease states may add further variability in drug response. It is now known that inflammation regulates the expression, activity, and functions of drug metabolizing enzymes and drug transporters.[19,20]

The changes seem to be common throughout the disease states of infection or inflammation; such that, in the face of a global inflammatory stimulus most CYPs, and transporters are down regulated.[19-21] The pathway involves the release of cytokines (particularly IL-6) from inflammatory cells in response to inflammatory stimuli, which modulates transcription factor activity in the liver, ultimately leading to the down-regulation in expression of most CYP genes. In addition, cytokine production also leads to the production of nitric oxide, which directly inhibits CYP enzyme activities.[22] The loss of CYP450 activity has also been observed during inflammatory responses, both in the brain and peripheral tissues, which has subsequently altered drug disposition in the brain, with potentially toxic consequences.[23,24] Given the high likelihood of low CYP450 activity, the paradoxically normal level of activity requires some consideration. Induction of CYP3A enzyme expression is possible, although our patient was not receiving any of the commonly recognized inducing agents. Midazolam is a drug with a high hepatic extraction ratio, thus hemodynamic shifts favoring splanchnic/hepatic blood flow may increase the overall systemic elimination of metabolism. We did not account for renal clearance in our calculations. However, it is unlikely that renal clearance of midazolam contributed in a significant way in that less than 0.5% of the unmetabolized drug is recovered in urine of healthy volunteers. Ideally, creatinine clearance should have been measured simultaneously to help us reach this conclusion.

In conclusion, therapeutic monitoring of midazolam concentrations in this patient allowed for a better understanding of its role in providing this patient with adequate sedation. Recognizing that clearance via the CYP3A pathway was maintained in this patient allowed for the recommendation to simply increase the dosing of the currently used sedatives, most of which are cleared via CYP3A, rather than the alternative approach of adding other sedative agents, which would likely have delayed the achievement of optimal sedation control. This patient appears to have had relatively normal CYP3A metabolic capability despite her acute illness, highlighting the need to assess metabolic capability on an individual basis. Furthermore, we report the first published case of a potential ketamine/midazolam interaction and highlight the need for vigilance when using these agents simultaneously.

Key Points:

- Patients in the ICU have metabolic derangements that could effect the metabolism of certain drugs including sedatives such as midazolam.
- Measuring serum drug levels can be helpful in this setting if they are used to titrate dosages to achieve clinically meaningful endpoints and clearly defined goals of care.
- Drug interactions are fairly common and are commonly unrecognized.

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