PHC721 - CLINICAL PROBLEM SET # 2

Patient

Female, 58 years old

Chief Complaint

"My back teeth hurt and TMJs got worse in the last couple of weeks. The pain does not go away with Aspirin anymore. I used to take two regular Aspirin pills for my TMJ pain and they would take care of the problem."

Background and/or Patient History

Congestive Heart Failure; Dental Phobia;
Liver Cirrhosis; Morbid Obesity;
Peptic Ulcer Disease (recent exacerbation);
Temporomandibular Disorder.

Medications:

- Aspirin 325 mg (2 tablets once daily)
- Bisoprolol
- Furosemide
- Omeprazole (Prilosec® OTC)

Current Findings

Tense facial and jaw muscles; Clicking and locking of the jaw with limited motions; Patient reports ringing in the right ear; Abraded and fractured teeth; Pericoronitis and caries of mandibular third molars.

Temp: 98.8 F; BP: 125/70 mmHg; HR: 65 bpm; Body weight: 286 lb; Height: 5' 10"; BMI: 41

Current treatment involves wisdom tooth extraction with conscious sedation:
The patient initially received 1.0 mg of Midazolam (log P=3.4; pKa=6.6; 97% plasma protein bound) intravenously, infused over 2 minutes. The depression of consciousness was apparent already at the end of the 2-minute infusion (patient responded purposefully to verbal commands accompanied by light tactile stimulation). In order to maintain the same level of sedation, the initial (loading) dose was repeated every 15 minutes until the end of the extraction 50 minutes later. The patient's status was monitored continuously.

1. What is the most likely mechanism of the loss of the analgesic effect of Aspirin?

2. Please calculate the approximate Volumes of Distribution for Midazolam at two time points:
   i) at the end of the first infusion (plasma concentration of Midazolam 200 ng/ml),
   and
   ii) right before the next infusion (plasma concentration of Midazolam 20 ng/mL). Assume no Midazolam elimination during the 15-minute interval between infusions.

3. Since Midazolam elimination half-life (i.e. the time it takes to reduce the drug plasma concentration by 50%) is approximately 3 hours, why was the dentist repeating the initial (loading) dose every 15 minutes?

4. Now let's assume that, after several re-infusions, the dentist did not have to add subsequent doses anymore, and the Midazolam plasma concentration at the steady state was 1.5 ng/mL. What is the apparent Volume of Distribution of Midazolam in this patient?

5. The FDA-recommended loading dose of Midazolam is 0.01-0.05 mg/kg. Why did the dentist choose the lower limit?

6. Which of the patient's health conditions are likely to affect Volume of Distribution of Midazolam? Please explain each mechanism.