Using the BIS Monitor to Determine Peak Onset of Sedation

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Introduction

Pharmacokinetic models are used to predict plasma drug concentrations which are considered to be the drug level, for example, of sedation agents in the brain. More recently, a new concept of effect site concentration, now considered a better model, takes into account drug entry and drug action delay effect (receptor, enzymatic, membrane). This constant, Ke0, can be calculated theoretically using complex mathematics or more simply by measuring the time to peak effect from a bolus (Figure 1). The BIS monitor is a multi-processed EEG that displays the depth of hypnosis as a number 1-100 (deep coma to awake).

The aim of this study is to estimate the time to peak effect in children for boluses of midazolam and fentanyl using the BIS monitor to determine the depth and time to peak effect.

Methods

Two age groups of children are being used in this study (G1: 11 to 14 years old and G2: 15-17 years old) who are undergoing a dental procedure under deep sedation. Patients must satisfy research criteria and parental consent must be obtained.

The research criteria include the appropriate procedure, patients age 10-17 years old, able to comprehend consent form in English, willing to participate, and not pregnant. Patients will not qualify for the study if they have any one or more of the following: pregnancy, inability to comprehend consent in English, complex medical history, recent URI, use of alcohol or drugs, use of multiple psychotropic medications, use of ADHD medication, patients with IDD, patients on Autism spectrum, patients on seizure medication, BMI over 25 if patient under 14 years old, BMI over 30 if patient is over 14 years old, patient fall outside of study age range.

The BIS clock and monitor time are synchronized. The patient's forehead is wiped and the BIS monitor applied. After the BIS monitor is applied to the forehead and connected to the monitor, a bolus of sedative (either midazolam or fentanyl) which is part of their scheduled deep sedation regimen, is given. The BIS monitor readings are recorded every 5 seconds as was time of initial dose and initial effect felt by patient.

M-G1 group includes children ages 11 to 14 receiving a bolus midazolam, M-G2 group includes children ages 15-17 receiving midazolam, and F-G2 is 14-17 year olds receiving fentanyl. Once the study sedation drug bolus had reached its nadir, the sedation was continued as planned using additional midazolam or fentanyl as needed and a propofol infusion.

Figure 1. Ke0, Effect Site and Plasma conc.

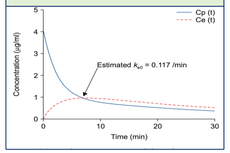


Table 1. DEMOGRAPHICS

GROUPS	NO.	AGE (YRS)	WEIGHT (KG)	BMI	DOSE WT (KG)	ASA
M G1	12	13.1	58.3	21.0	53.9	1.3
M G2	12	16.2	70.2	22.9	66.5	1.4
F G2	12	16.2	63.0	21.8	60.8	1.4

Table 2. STUDY SEDATION DOSING

GROUPS	BOLUS/START MID MG	TOTAL MID MG	BOLUS/START FENT MCG	TOTAL FENT MCG	TOTAL MID MG/KG	TOTAL FENT MCG/KG
M G1	3.8	4.0	45.8	95.8	0.069	1.64
M G2	4.0	5.3	50.0	100.0	0.058	1.46
F G2	2.0	4.3	93.8	97.9	0.033	1.59

Results

After IRB approval and informed consent, 36 patients (3 groups; n=12 each): M-G1, M-G2 and F-G2 have been recruited thus far. Patient demographics are shown in table 1. Sedative doses and procedure times are shown in tables 2 and 3 respectively. In group M-G1 the average time to peak effect is 120s and the average peak effect BIS is 70.9 (Table 4 and Figure 2). In group M-G2 the average time to peak effect is 125s and the average peak effect BIS is 76.7 (Table 4 and Figure 3). In group F- G2, the average time to peak effect is 96s and the average peak effect BIS is 89.1 (Table 4). In all 3 groups, the average BIS at bolus dose was similar (Table 4). Of note, the BIS only fell in 17% of the patients in F-G2 as shown in Table 5 and Figure 4. The initial clinical effect (when the patient first notices a drug effect) BIS is shown in Table 4.

When using a corrected peak onset time (due to analysis delay in the BIS monitor, calculated at about 25s; see poster by *Pernick et. al.*), the effect site conc. for the three groups is shown in Figures 5 through 7. Mathematically the ke0 can now be calculated from this onset time so that a pharmacokinetic model of effect site concentration is possible, rather, than a direct based measurement using clinically measured time to peak effect.

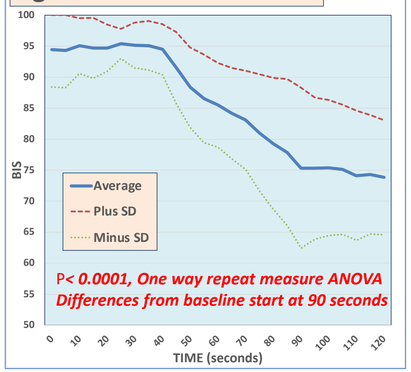
Table 3. TIMING (MINUTES)

GROUPS	SED TIME	PROC TIME	PHASE 1	PHASE 2	DC TIME
M G1	8.4	13.6	22.4	16.1	38.5
M G2	8.6	19.8	19.1	12.4	31.5
F G2	8.5	14.6	18.5	15.8	34.3

Table 4. INITIAL CLINICAL ONSET AND PEAK EFFECT

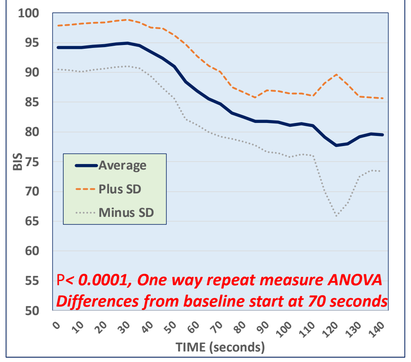
GROUPS	AVERAGE DOSE BIS	AVERGE INITIAL EFFECT BIS	AVERAGE PEAK EFFECT BIS	AVERAGE TIME TO PEAK
M G1	94.5	86.4	70.9	120
M G2	94.2	87.5	76.7	125
F G2	94.2	93.9	89.1	96

Figure 2. M G1: ONSET BIS



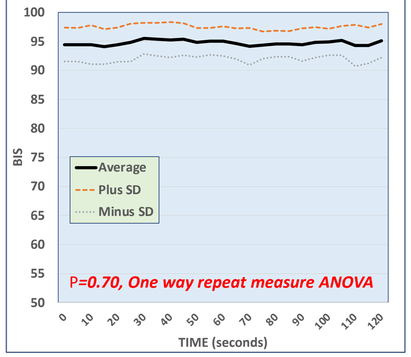
P< 0.0001, One way repeat measure ANOVA
Differences from baseline start at 90 seconds

Figure 3. M G2: ONSET BIS



P< 0.0001, One way repeat measure ANOVA
Differences from baseline start at 70 seconds

Figure 4. F G2: ONSET BIS



P=0.70, One way repeat measure ANOVA

Table 5. PEAK EFFECT RESPONSE **p=0.028 1W ANOVA*

GROUPS	BASELINE BIS (1 MIN PRE)	ONSET_BIS	% SIG from BASELINE
M G1	93.6	84.3	91.7
M G2	94.4	85.6	91.7
F G2	95.1	94.6*	16.7

Discussion

From the data collected thus far, group M-G2 (average age 16.2 years (Table 1.) had an average time to peak effect with a bolus of midazolam that was 5 seconds longer than group M-G1 (average age 13.1 years). Group M-G1 had a greater peak effect BIS score of 70.9 than group M-G2 that had peak effect BIS score of 76.7. The difference in BIS levels over time between the two age groups are illustrated in Figures 2 and 3. This could indicate that as age increases, time to peak effect of midazolam also increases. It also indicates that the depth of sedation greater as age decreases.

From the data gathered from F-G2, the average BIS at bolus dose was 94.2 (Table 3). The average peak effect BIS of the same group was 89.1. Figure 4 demonstrates a relatively constant BIS reading over time. This demonstrates that fentanyl does not have a significant effect on the BIS monitor which limits the effectiveness of this particular evaluation of opiates.

Figure 5. M G1: Case 3

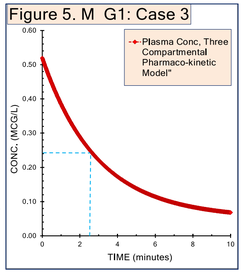


Figure 6. M G2, Case 3

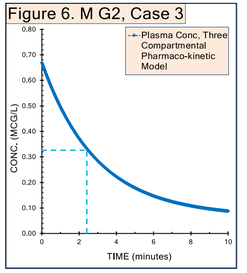
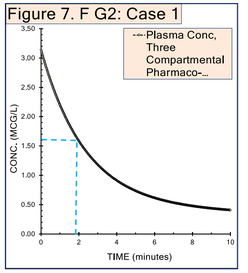


Figure 7. F G2: Case 1



Conclusion

Knowing the sedation peak onset time for sedation agents will facilitate safer sedation titration regimens by allowing improved pharmacokinetic modeling and adjusting dosing intervals. Regiments and dosing intervals should be adjusted based on target depth of sedation, age of patient and the pharmacokinetic properties of the sedation agent.