Comfortable Breathing Duration (CBD) of Fentanyl Using a Three-Compartment Model

Ashley O'Neill

Paul Schreiber High School

Port Washington, New York

Abstract:

Opioid pharmacokinetics is important for the understanding of pain control and the opioid epidemic. This research project started with an overview using a one-compartment model of several opioids given published pharmacokinetic parameters. The apnea time (t_1), analgesia time (t_2), and the comfortable breathing duration (CBD) were estimated for fentanyl, sufentanil, remifentanil, and alfentanil using Excel and Python. This formed the foundation for the development of my three-compartment model to estimate CBD. Unlike the one compartment model which had a fixed CBD for given half-time which did not vary with dose, the three-compartment model demonstrated that increasing dose not only prolonged apnea time, and analgesic time, but also the comfortable breathing duration. This concept is more consistent with published clinical experience.

Introduction:

Fentanyl, a phenylpiperidine opioid, is used to prevent pain during surgery and to manage pain for both inpatients and outpatients. The higher dose fentanyl used in the operating room associated with higher plasma and tissue concentrations (Cp = 2 to 10 ng/mL) [Miller] can lead to respiratory depression or apnea (stopped breathing). In this setting, the patient is protected by endotracheal intubation and mechanical positive pressure ventilation until the return of spontaneous, unsupported ventilation occurs. Unfortunately, when individuals have opioid induced apnea in the outpatient setting, the lack of breathing and airway support frequently leads to cardiac arrest and death from opioid overdose. Therefore, an understanding of opioid pharmacokinetics is important for the understanding of the management of pain, as well as, the opioid related deaths which are occurring in epidemic rates.

Opioids are used for the treatment of pain. They can be classified based on naturally occurring/synthetic, chemical structure, or duration of action. The common routes of opioid administration include intravenous, oral, intramuscular, transdermal, and neuroaxial. In large doses, the blood concentrations are high leading to high tissue concentrations. This defines the dose-response relationship, a sigmoid cumulative probability distribution as a function of dose. The higher the tissue concentration of opioid, the higher the probability of apnea. As the concentration of opioid decreases due to distribution and elimination, there is return of spontaneous, unsupported ventilation. There is a duration of comfort in this therapeutic window. When the opioid concentration continues below a threshold level, there will be the return of pain which will trigger a need for opioid re-dose. Based on the superposition effect, the re-dose may be associated with a higher probability of apnea compared to the original, initial dose, if the re-doses are not adjusted accordingly.

The first and second portions of the opioid research project, the pharmacokinetic parameters were reviewed for various opioids and developed one compartment models to estimate duration of apnea (t_1) and duration of analgesia (t_2) based on published C_{50} values to determine the comfortable breathing duration (CBD), the difference in durations.

Initially, a one-compartment models for opioids given the published pharmacokinetic parameters was considered. The one compartment model is based a first order ordinary differential equation defined by a constant fraction.

$$\frac{dY}{dt} = kt$$

The solution to the one-compartment constant proportion model is an exponential decay function.

$$Y = A\, e^{-kt}$$

This model was used to calculate the duration of apnea, duration of analgesia, and the comfortable breathing duration (CBD). According to the original researchers who had direct access to patient data, the three-compartment model fits the clinical data better than the one-compartment model.

The three-compartment model assumes that the intravenous drug administration enters a central compartment. This theoretical space could be imagined to be like the blood with binding proteins and interstitial fluid which bathes the cells. The central compartment communicates with a rapidly equilibrating compartment and a slowly equilibrating compartment. These theoretical spaces are inactive reservoirs and could be imagined to be like muscle and fat. The central compartment also communicates with the effect compartment. In the case of opioids, the drug needs to pass into the central nervous system to act on opioid receptors to trigger the dose-response relationship. Based on the conservation of mass in the three compartments (x_1, x_2, x_3) one can develop a system of coupled linear differential equations seen below. The rate of change of concentration in each compartment would be the sum of each transfer into and out of the compartment.

The rate constant, k, has subscripts which denote the direction of mass transfer. For example, k_{12} represents the rate constant for transfer from compartment 1 to compartment 2; whereas k_{21} represents the rate constant for transfer from compartment 2 to compartment 1.

$$\frac{dx_1}{dt} = I + x_2k_{21} + x_3k_{31} - x_1k_{10} - x_1\text{-}k_{12} - x_1k_{13}$$

$$\frac{dx_2}{dt} = x_1k_{12} - x_2k_{21}$$

$$\frac{dx_3}{dt} = x_1k_{13} - x_3k_{31}$$

The solution to these differential equations in three-compartment model is a tri-exponential function.

$$Y = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

Al-Rifai, Z. 2015.

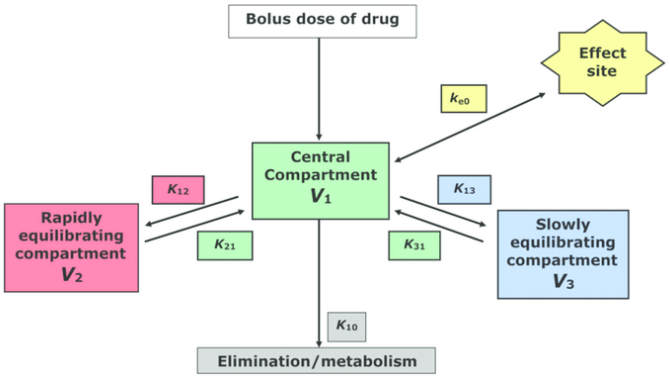

Figure 1: Three compartment model
Al-Rifai, Z. 2015.

Methods:

In the literature, published pharmacokinetic data for opioids including fentanyl was discovered. Given this data, one-compartment and three-compartment models using Excel and Python. A nested loop was used to estimate multiple output variables given the set of input values.

Using published pharmacokinetic data of opioids, the probability of apnea and probability of analgesia were determined as a function of time. Comfortable breathing duration was calculated for commonly used intravenous doses based on half-times and volumes of distribution. A nested loop program in Python generated a set of trial simulations. Confidence intervals for CBD were calculated.

Development of my Three-Compartment Model

The one compartment formed the foundation of developing a three-compartment model using the same published pharmacokinetic parameters. The tri-exponential model was a piece-wise model of the three curves (alpha, beta, and gamma) which were separated by two points: the alpha-beta intersection and the beta-gamma intersection. The initial concentration (C_0 alpha) was determined by dividing the initial opioid dose by the volume of distribution (central). The alpha decay continued for a multiple (Nalpha) of alpha-half times until it intersects the beta decay curve at the alpha-beta intersection (t abi, C abi). The beta decay curve was defined by the beta half time and the alpha-beta intersection. The initial beta concentration (C_0 beta) was extrapolated to the vertical axis as a line after doing a log transformation. Given the initial beta concentration, the alpha-beta intersection, and the beta half time, the beta decay advanced through time a multiple (Nbeta) beta half times until it reached the beta-gamma intersection

(t bgi, C bgi). The initial gamma concentration (C_0 gamma) was extrapolated to the vertical axis as a line after doing a log transformation. Given the initial gamma concentration, the beta-gamma intersection, and the gamma half-time, the gamma decay proceeded indefinitely.
Attached is a summary of the first trial done with the three-compartment model. Confidence intervals were calculated for the estimated parameters. A nested loop program in Python yielded 104,976 simulated trials. The results were sorted to select the largest comfortable breathing durations (CBD) yielding 2592 trials. Descriptive statistics were calculated and analyzed for initial concentrations and intercepts. The pattern suggests that the alpha decay was excessively weighted. Therefore, additional simulations in Python which were performed with modification of input values.

The natural logs of concentrations were plotted as a function of time given the values of initial concentrations and half-times. The family of curves (lines) were plotted to visualize the slopes. Next, the three-compartment model was rewritten in Excel to demonstrate the time dependent composite function using a conditional statement for the time domain and the time of intersections. The Ln (C (t)) and the C (t) were plotted and labeled for comparison with the C_{50} for apnea and the C_{50} for analgesia. The comfortable breathing duration (CBD) can be seen on the chart.

The number of alpha half-times seems to determine how the alpha beta intersection relates to the C_{50} for apnea. The greater the number of alpha half times, the earlier breathing returns and the briefer the duration of analgesia. When both the number of alpha half times and beta half times are fewer, the gamma half time dominates and analgesia is prolonged. Intuitively, it seems as though the optimal model would demonstrate a beta-gamma intersection near C50 for apnea to slowly transition through the comfortable breathing zone. It is not clear what factors determine the number of half-times for a given phase. The number of half-times may be determined by the variation in the central and steady state volumes of distribution and their relationship with clearance.

Table 1: Input Values for Set of Simulated Trials

Trial	**8.6**	**8.21**	**8.25**	**9.4**	**9.17**
N	104,976	104,976	104,976	139, 968	174,960
Dose	2, 4, 8, 16	2, 4, 8, 16	2, 4, 8, 16	2, 4, 8, 16	2, 4, 8, 16
Vd	0.4, 0.6, 0.8, 1	0.4, 0.6, 0.8, 1	0.4, 0.6, 0.8, 1	0.4, 0.7, 1	0.4, 0.6, 0.8, 1
$T_{1/2}$ alpha	1, 1.5, 2	1, 1.5, 2	1, 1.5, 2	1, 1.5, 2	1, 1.5, 2
T ½ beta	10, 20, 30	10, 20, 30	10, 20, 30	10, 20, 30	10, 20, 30
T ½ gamma	120, 180, 240	120, 180, 240	120, 180, 240	120, 180, 240	120, 180, 240
C_{50} apnea	2, 2.5, 3	2, 2.5, 3	2, 2.5, 3	2, 2.5, 3	2, 2.5, 3
C_{50} analgesia	0.5, 0.75, 1	0.5, 0.75, 1	0.5, 0.75, 1	0.5, 0.75, 1	0.5, 0.75, 1
N alpha	3, 4, 5	3, 4, 5	3, 4, 5	0.5, 1, 1.5, 2	0.5, 1, 1.5, 2
N beta	3, 4, 5	3, 4, 5	3, 4, 5	0.5, 1, 1.5, 2	0.5, 1, 1.5, 2

Trial	**10.6**	**10.9**	**10.12**	**10.16**	**10.18**
N	240	240	240	5	135
Dose	16	16	2	2, 4, 8, 12, 16	2, 4, 8, 12, 16
Vd	1	1	1	1	1
$T_{1/2}$ alpha	1, 1.5, 2	1, 1.5, 2	1, 1.5, 2	1.5	1, 1.5, 2
T ½ beta	10, 30	10, 30	10, 30	20	10, 20, 30
T ½ gamma	120, 240	120, 240	120, 240	180	120, 180, 240
C_{50} apnea	2.5	2.5	2.5	2.5	2.5
C_{50} analgesia	0.75	0.75	0.75	0.75	0.75
N alpha	0.5, 1, 1.5, 2	0.5, 1, 1.5, 2	0.5, 1, 1.5, 2	2	2
N beta	0.5, 1, 1.5, 2	0.5, 1, 1.5, 2	0.5, 1, 1.5, 2	2	2

Results:

The one compartment models can be expressed as a linear function after using the natural logarithm transformation. Assuming an initial concentration of fentanyl of 16 ng/mL, alpha decay, beta decay, and gamma decay are displayed for the reported half-times.

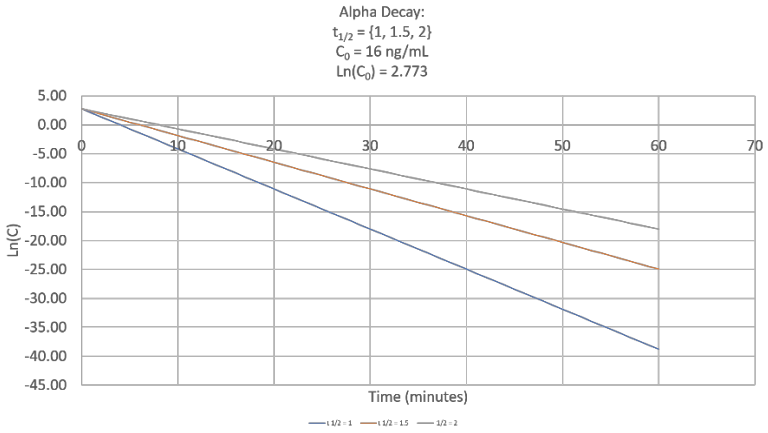

Figure 2: Alpha Decay from Initial Concentration of 16 ng/mL

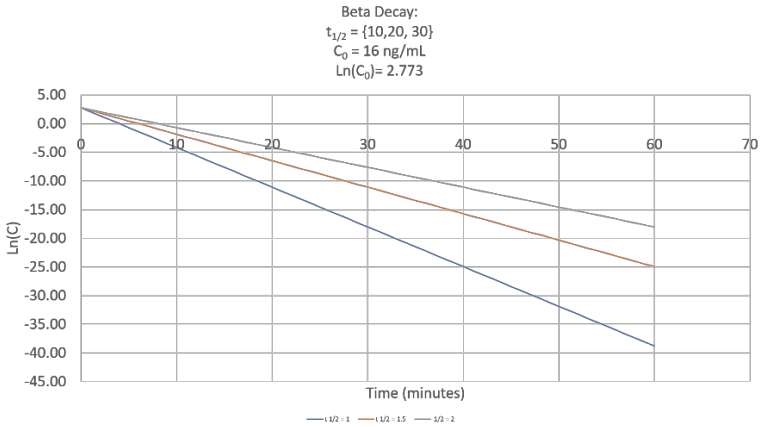

Figure 3: Beta Decay from Initial Concentration = 16 ng/mL

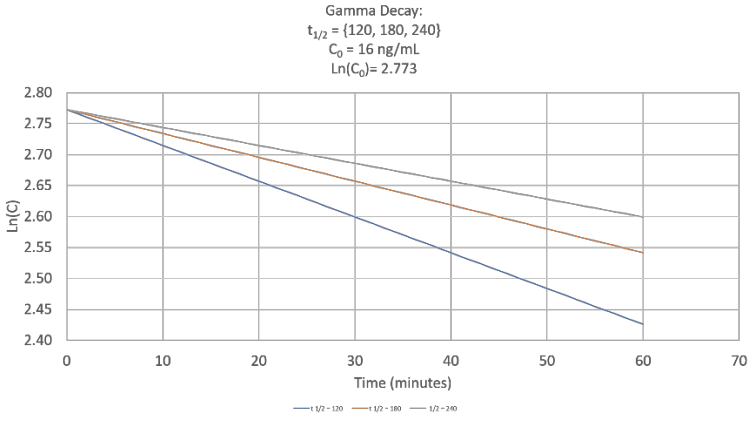

Figure 4: Gamma Decay from Initial Concentration = 16 ng/mL

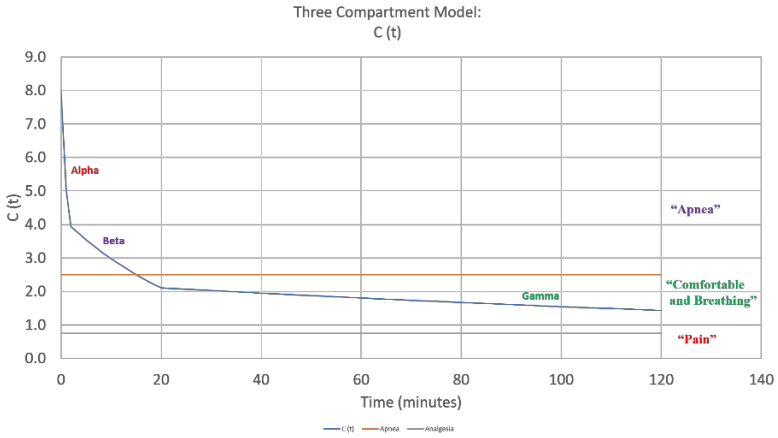

Figure 5: Three-Compartment Model with Initial Concentration = 8 ng/mL demonstrates Beta decay portion intersecting C_{50} apnea

The three functions for the one compartment models were pieced together to form the three-compartment model. The C_{50} for apnea and C_{50} for analgesia were plotted to demonstrate how the C(t) curve could intersect the apnea line at different points depending upon the input values for the parameters.

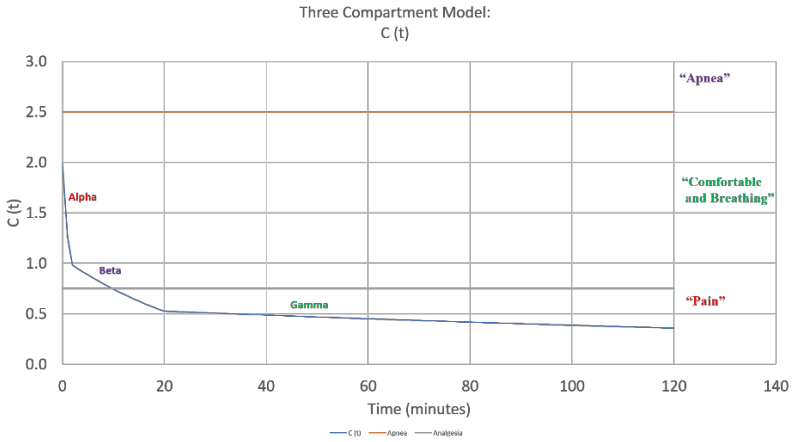

Figure 6: Three-Compartment Model with Initial Concentration = 2 ng/mL which is below the C_{50} apnea

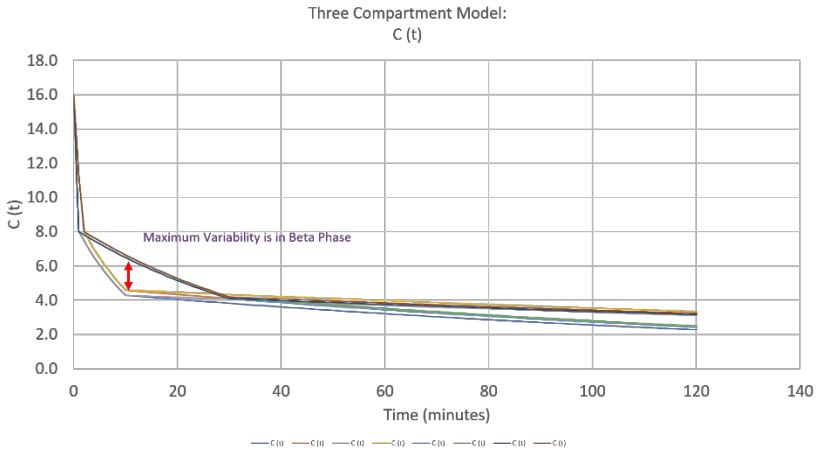

Figure 7: Initial Concentration = 16 ng/mL

In this simulation of 8 cases starting with initial concentration C_0 = 16 ng/mL, the graph suggests that the maximum variability in concentration occurs in the beta phase.

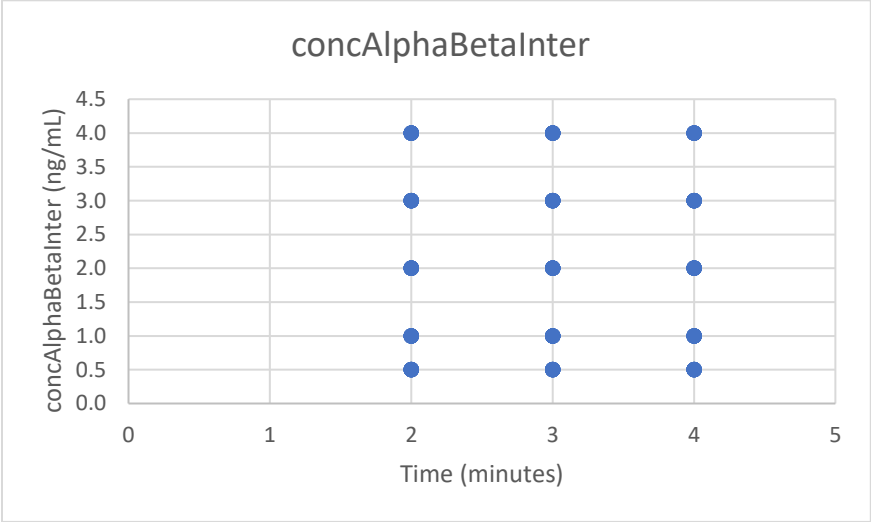

Figure 8: Concentration of Alpha-Beta Intersection

The concentration of the alpha-beta intersection (concAlphaBetaInter) would be determined by evaluating the alpha decay function at the time at which a given number of half-times have elapsed. In this example, two (2), three (3), and four (4) minutes were selected yielding concentrations varying from 0.5 to 4.0 ng/mL.

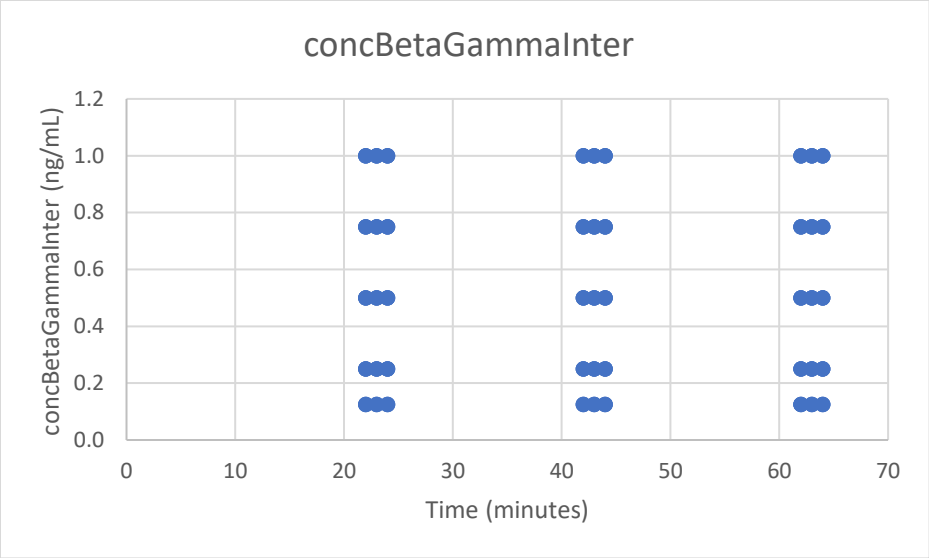

Figure 9: Concentration of Beta-Gamma Intersection

The concentration of the beta-gamma intersection (concBetaGammaInter) was determined by evaluating the beta decay curve at times corresponding to the number of beta half times plus the time of the alpha-beta intersection. In this example, the times range from 22 to 64 minutes yielding concentrations ranging from 0.125 to 1 ng/mL.

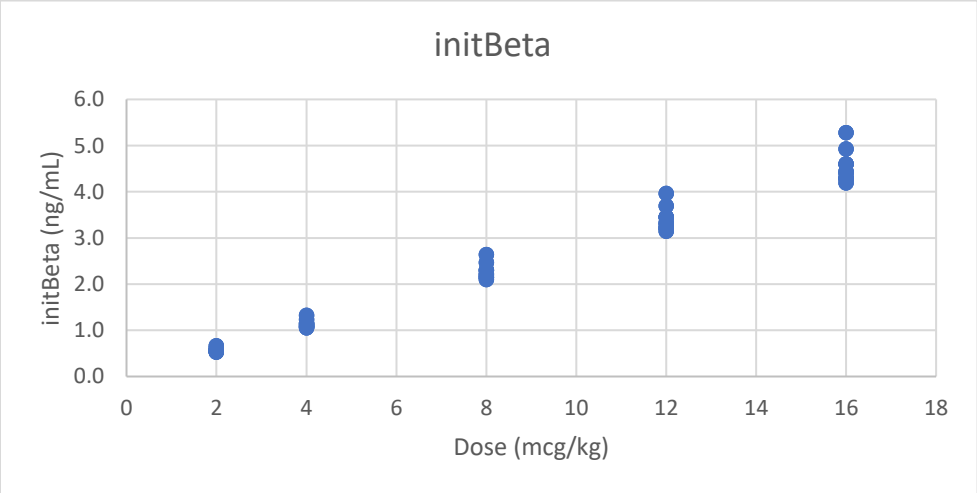

Figure 10: Initial Concentration of Beta Decay

The initial beta concentration (initBeta) is a function of initial opioid dose and is extrapolated from the alpha-beta intercept to the vertical axis using the natural logarithm transformation of the beta-decay function.

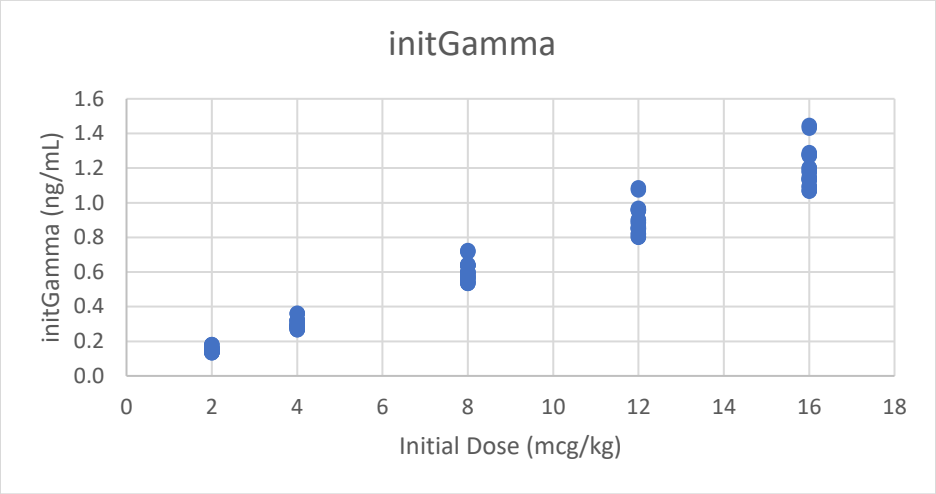

Figure 11: Initial Concentration of Gamma Decay

The initial gamma concentration (initGamma) is a function of initial opioid dose and is extrapolated from the beta-gamma intercept to the vertical axis using the natural logarithm transformation of the gamma-decay function.

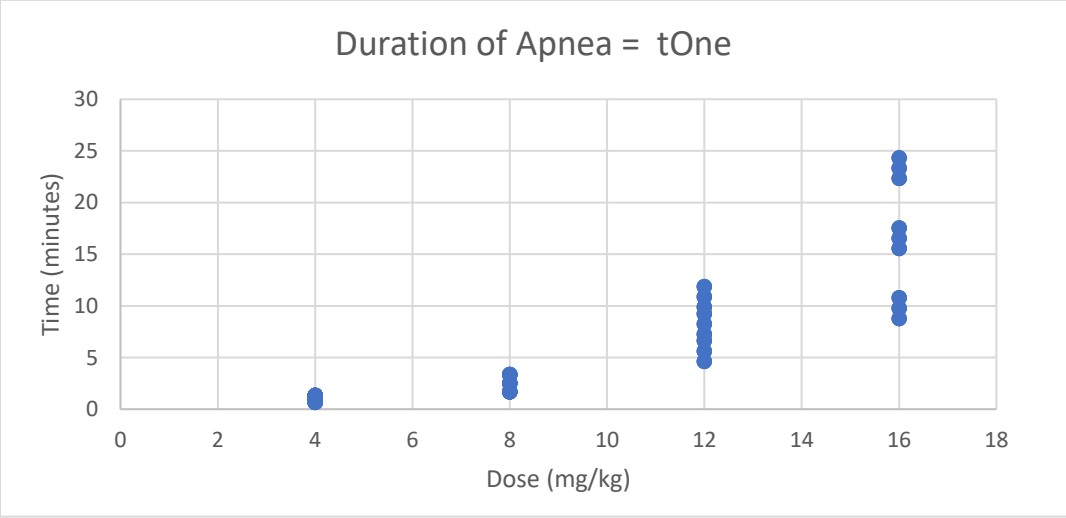

Figure 12: Apnea Time (t1) as a Function of Dose

The duration of apnea would be determined by calculating the time associated with the intersection of the C(t) curve with the C_{50} for apnea (horizontal line). Since each of the three decay curves would intersect the C_{50} line, a conditional decision algorithm was used to select the tOne from the set including AlphaTOne, BetaTOne, and GammaTOne. This chart demonstrates that apnea time (tOne) increases with increasing initial dose.

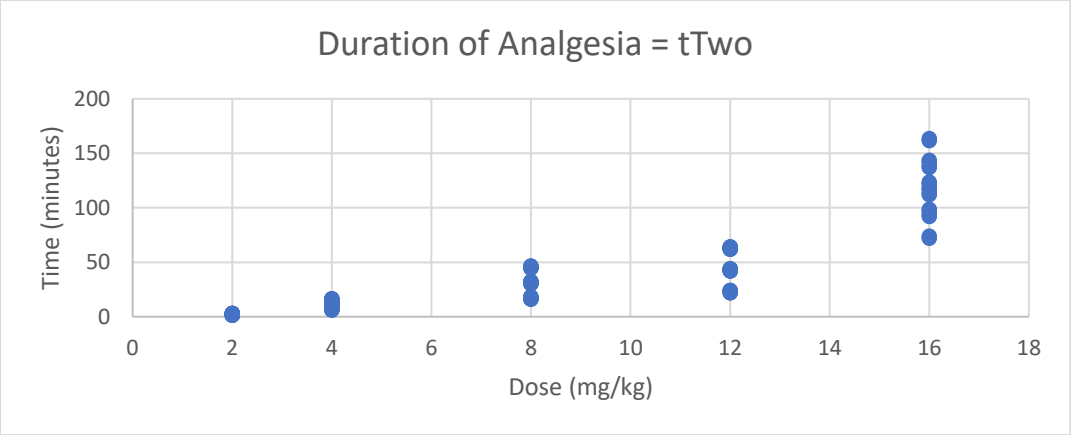

Figure 13: Analgesia Time (t2) as a Function of Dose

The duration of analgesia would be determined by calculating the time associated with the intersection of the C(t) curve with the C_{50} for analgesia (horizontal line). Since each of the three decay curves would intersect the C_{50} line, a conditional decision algorithm was used to select the tTwo from the set including AlphaTTwo, BetaTTwo, and GammaTTwo. This chart demonstrates that analgesia time (tTwo) increases with increasing initial dose.

Table 2: Comfortable Breathing Duration (CBD) as Function of Dose

Dose (mg/kg)	**2**	**4**	**8**	**12**	**16**
UCL	2.88	11.60	33.22	40.19	109.99
Mean	2.61	10.28	28.78	34.74	101.15
LCL	2.33	8.96	24.34	29.29	92.30
N	27	27	27	27	27
STD	0.723	3.497	11.775	14.452	23.458
Conf	0.273	1.319	4.441	5.451	8.848
CV	0.28	0.34	0.41	0.42	0.23

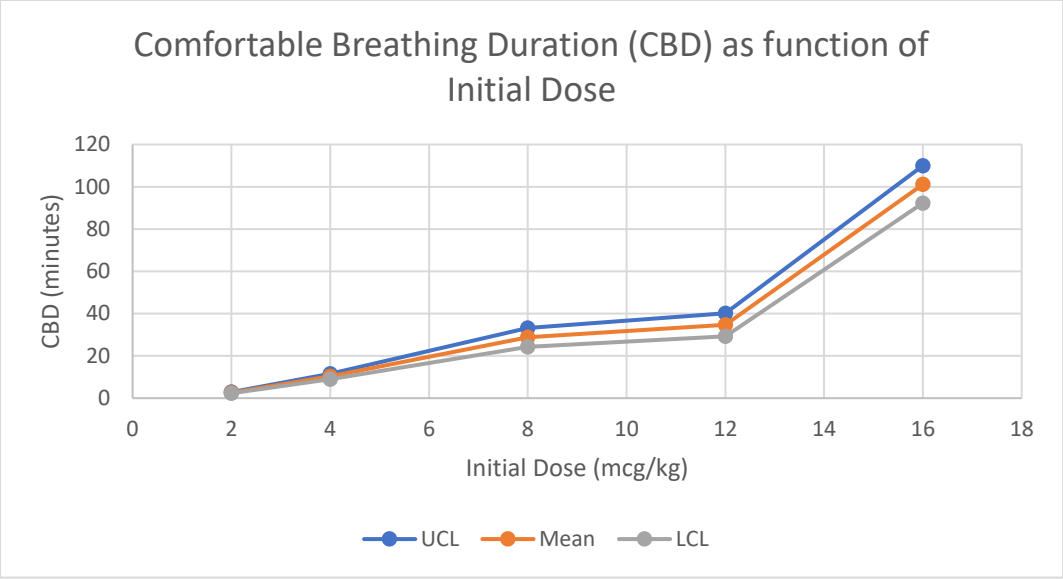

Figure 14: Comfortable Breathing Duration (CBD) as Function of Initial Dose

CBD increases with increasing dose.

Table 3: Frequency Distribution of C_{50} Apnea and C_{50} Analgesia intersecting Phase Time

	t1			t2		
	alpha	**beta**	**gamma**	**alpha**	**beta**	**gamma**
2	27	0	0	0	27	0
4	27	0	0	0	27	0
8	27	0	0	0	27	0
12	0	27	0	0	7	20
16	0	27	0	0	0	27

At lower doses, apnea time is determined more by alpha decay and analgesia time is determined more by beta decay. At higher doses, apnea time is determined more by beta decay and analgesia time is determined more by gamma decay. If you do not want a long apnea time, use a smaller dose, but it will need to be repeated more frequently to maintain analgesia. If an apneic person can be mechanically ventilated for the duration of apnea, like in the operating room, a larger dose would provide a longer duration of analgesia without the need for redosing and selecting the risk of apnea during a particularly risking time, like patient transport from the operating room to the PACU.

Discussion:

Traditionally, opioids have been utilized intraoperatively for anesthesia and postoperatively for analgesia, despite the known risk of respiratory depression and apnea. One critical time period in the perioperative process is the post-extubation transfer from the operating room to the post-anesthesia care unit (PACU). During this time, anesthetic drug levels are declining which increase the risk of pain and risk potential apnea from redosing of opioid without airway protection with an endotracheal tube, especially in combination with other agents which cause respiratory depression or in high risk patients. Ideally, patients would be transferred to the PACU during the comfortable breathing duration of opioid action.

In part one of this opioid research, a one compartment model of concentrations of various opioids and the probability of analgesia and respiratory depression were explored. The opioid epidemic was described with some supporting statistics including numbers of deaths from opioid induced respiratory depression. A three-compartment model was described which foreshadowed this third part of the research. Clearly, there were various plasma concentrations of fentanyl associated with coma, apnea, and analgesia. The various probabilities of apnea and analgesia using Z-scores, C(t), C_{50}, and the cumulative probability distribution.

The premise of the one-compartment model is that the rate of change of concentration is proportional to the concentration. This first order, ordinary differential equation yield an exponential decay curve when solved by integration. The rate constant, k, can be described in terms of half-time or ratio of volume of distribution (Vd) over clearance (Cl). The loading doses divided by the volume of distribution will give the initial concentration.

In the one-compartment model, the Miller textbook provided three-half times, alpha, beta, and gamma, Given the small alpha half-time, only beta half-times and gamma-half-times were analyzed independently for a single volume of distribution, either central or steady-state. The results for estimates of comfortable breathing duration where very divergent for the same doses.

In part two, the option of adding a second dose into the model was included. This feature incorporated into the Python coded demonstrated the superposition effect and the risk of apnea associated with "stacking" of doses. The first part of the one compartment model defined as "Model A". This model featured inputs of loading dose, volume of distribution, and half-time to estimate apnea time (t_1), analgesia time (t_2), and their difference (t_2-t_1), the comfortable breathing duration (CBD).

With some mathematical derivation, Model B was developed to estimate the comfortable breathing duration (CBD) using C_{50} analgesia, C_{50} apnea, and half-time. Interestingly, there is no increase in CBD based on increasing dose. This result is not likely to be consistent with what is seen clinically. This is thought to be because the one-compartment model fails to include the effects of fast and slow

distribution compartments and both the central volume of distribution and the steady-state volume of distribution.

The tri-exponential three-compartment model incorporates alpha, beta, and gamma decay using the three half-times published in Miller. This is derived by the system of differential equations defining the rates of change in each compartment with respect to time based on the conservation of mass and sum of each rate constant*concentration product. The initial concentration would be determined by the loading dose divided by the central volume of distribution. The net effect of all of the inter-compartment rate constants and the steady state volume of distribution can be summarized by the determination of the alpha-beta intersection and the beta-gamma intersection in the three-compartment model.

Conclusion:

Comfortable breathing duration (CBD) is the pharmacokinetic "sweet spot" or therapeutic window for opioid dosing. Unlike the one-compartment model, the three-compartment model has the capacity to demonstrate an increasing CBD for increasing dose, a relationship observed clinically. Mathematical models of opioid dosing could improve patient safety, especially during transport from the operating room to the PACU. The use of the three- compartment model for fentanyl could be applied using computer assisted intravenous delivery systems in the operating room setting.

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Appendix:

Appendix 1: Physiochemical and Pharmacokinetic Data for Commonly Used Opioid Agonists

Table 27-5 Physicochemical and Pharmacokinetic Data for Commonly Used Opioid Agonists

	Morphine	Meperidine	Fentanyl	Sufentanil	Alfentanil	Remifentanil
pK_a	8.0	8.5	8.4	8.0	6.5	7.1
% Un-ionized at pH 7.4	23	<10	<10	20	90	67?
Octanol-H_2O partition coefficient	1.4	39	813	1778	145	17.9
% Bound to plasma protein	20-40	39	84	93	92	80?
Diffusible fraction (%)	16.8	2.2	1.5	1.6	8.0	13.3?
$t_{½\alpha}$ (min)	1-2.5	—	1-2	1-2	1-3	0.5-1.5
$t_{½\beta}$ (min)	10-20	5-15	10-30	15-20	4-17	5-8
$t_{½\gamma}$ (hr)	2-4	3-5	2-4	2-3	1-2	0.7-1.2
Vd_c (L/kg)	0.1-0.4	1-2	0.4-1.0	0.2	0.1-0.3	0.06-0.08
Vd_{ss} (L/kg)	3-5	3-5	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min/kg)	15-30	8.18	10-20	10-15	4-9	30-40
Hepatic extraction ratio	0.6-0.8	0.5-0.7	0.8-1.0	0.7-0.9	0.3-0.5	NA

$t_{½}$ α, β, γ are the half-lives of a three-compartment model; Vd_c, volume of distribution of the central compartment; Vd_{ss}, volume of distribution at steady state.
From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 312.

Source: Miller

Appendix 2: Steady-State Concentrations for Predefined Effects

Table 28-2 Steady-State Concentrations for Predefined Effects*

Drug	C_{50} for EEG Depression†	C_{50} for Incision or Painful Stimulus‡	C_{50} for Loss of Consciousness§	C_{50} for Spontaneous Ventilation¶	C_{50} for Isoflurane MAC Reduction	MEAC
Propofol (µg/mL)	3-4	4-8	2-3	1.33	Not studied	—
Thiopental (µg/mL)	15-20	35-40	8-16	—	—	—
Midazolam (ng/mL)	250-350	—	125-250	—	—	—
Alfentanil (ng/mL)	500-600	200-300	—	170-230	50	10-30
Fentanyl (ng/mL)	6-10	4-6	—	2-3	1.7	0.5-1
Sufentanil (ng/mL)	0.5-0.75	(0.3-0.4)	—	(0.15-0.2)	0.15	0.025-0.05
Remifentanil (ng/mL)	10-15	4-6	—	2-3	1.2	0.5-1

*Values in parentheses are estimated by scaling to the alfentanil C_{50} (see text for details).
†The C_{50} for depression of the electroencephalogram (EEG) is the steady-state serum concentration that causes a 50% slowing of the maximal EEG, except for midazolam, where the C_{50} is associated with 50% activation of the EEG.
‡The C_{50} for skin incision is the steady-state plasma concentration that prevents a somatic or autonomic response in 50% of patients.
§The C_{50} for loss of consciousness is the steady-state plasma concentration for absence of a response to a verbal command in 50% of patients.
¶The C_{50} for spontaneous ventilation is the steady-state plasma concentration associated with adequate spontaneous ventilation in 50% of patients.
MEAC, minimum effective plasma concentration providing postoperative analgesia.

Source: Miller

Appendix 3: Approximate Opioid Doses

Table 27-7 Approximate Opioid Loading (Bolus) Doses, Maintenance Infusion Rates, and Additional Maintenance Doses for Total Intravenous Anesthesia

	Loading Dose (µg/kg)	Maintenance Infusion Rate	Additional Boluses
Alfentanil	25-100	0.5-2 µg/kg/min	5-10 µg/kg
Sufentanil	0.25-2	0.5-1.5 µg/kg/hr	2.5-10 µg
Fentanyl	4-20	2-10 µg/kg/hr	25-100 µg
Remifentanil	1-2	0.1-1.0 µg/kg/min	0.1-1.0 µg/kg

From Bailey PL, Egan TD, Stanley TH: Intravenous opioid anesthetics. *In* Miller RD (ed): Anesthesia, 5th ed. New York, Churchill Livingstone, 2000, p 335.

ApSource: Miller

Appendix 4: Python Codes

Three Compartment Model

```
import math
i = 0
for dose in fDoseArray:
    for centralVD in fCentralVDArray:
        for ssVD in fSteadyStateVDArray:
            for alphaHalfTime in fAlphaHalfArray:
                for betaHalfTime in fBetaHalfArray:
                    for gammaHalfTime in fGammaHalfArray:
                        for c50Apnea in fC50ApneaArray:
                            for c50Analgesia in fC50AnalgesiaArray:
                                for nAlpha in fNAlphaArray:
                                    for nBeta in fNBetaArray:
                                        i = i + 1
                                        duo = 2
                                        natC50Apnea = math.log (c50Apnea)
                                        natC50Analgesia = math.log (c50Analgesia)
                                        initAlpha = dose/centralVD
```

```
                    natInitAlpha = math.log (initAlpha)
                    tAlphaBetaInter = ((alphaHalfTime) * (nAlpha))
                    concAlphaBetaInter = ((initAlpha) * math.exp ((math.log(0.5)) *
(tAlphaBetaInter)/(alphaHalfTime)))
                    natConcAlphaBetaInter = math.log (concAlphaBetaInter)
                    natInitBeta = ((natConcAlphaBetaInter) - ((math.log (0.5)) *
(tAlphaBetaInter)/(betaHalfTime)))
                    initBeta = math.exp (natInitBeta)
                    tBetaGammaInter = (((betaHalfTime) * (nBeta)) + (tAlphaBetaInter))
                    concBetaGammaInter = ((initBeta) * math.exp ((math.log(0.5)) *
(tBetaGammaInter)/(betaHalfTime)))
                    natConcBetaGammaInter = math.log (concBetaGammaInter)
                    natInitGamma = ((natConcBetaGammaInter) - ((math.log(0.5)) *
(tBetaGammaInter)/(gammaHalfTime)))
                    initGamma = math.exp (natInitGamma)
                    alphaTOne = ((natC50Apnea) - (natInitAlpha))*(alphaHalfTime) / (math.log
(0.5))
                    betaTOne = ((natC50Apnea) - (natInitBeta))*(betaHalfTime) / (math.log (0.5))
                    gammaTOne = ((natC50Apnea) - (natInitGamma))*(gammaHalfTime) /
(math.log (0.5))
                    alphaTTwo = ((natC50Analgesia) - (natInitAlpha))*(alphaHalfTime) / (math.log
(0.5))
                    betaTTwo = ((natC50Analgesia) - (natInitBeta))*(betaHalfTime) / (math.log
(0.5))
                    gammaTTwo = ((natC50Analgesia) - (natInitGamma))*(gammaHalfTime) /
(math.log (0.5))
                    concAlphaTOne =
((initAlpha)*math.exp((math.log(0.5))*(alphaTOne)/(alphaHalfTime)))
                    concBetaTOne = ((initBeta)*math.exp ((math.log(0.5))*
(betaTOne)/(betaHalfTime)))
                    concGammaTOne =
((initGamma)*math.exp((math.log(0.5))*(gammaTOne)/(gammaHalfTime)))
                    concAlphaTTwo =
((initAlpha)*math.exp((math.log(0.5))*(alphaTTwo)/(alphaHalfTime)))
```

```
                concBetaTTwo = ((initBeta)*math.exp ((math.log(0.5))*
(betaTTwo)/(betaHalfTime)))
                concGammaTTwo =
((initGamma)*math.exp((math.log(0.5))*(gammaTTwo)/(gammaHalfTime)))
                cOneAlphaTOne = ((natC50Apnea -
natInitAlpha)*(alphaHalfTime))/(math.log(0.5))
                cOneBetaTOne = ((natC50Apnea -
natInitAlpha)*(betaHalfTime))/(math.log(0.5))
                cOneGammaTOne = ((natC50Apnea -
natInitAlpha)*(gammaHalfTime))/(math.log(0.5))
                cOneAlphaTTwo = ((natC50Analgesia -
natInitAlpha)*(alphaHalfTime))/(math.log(0.5))
                cOneBetaTTwo = ((natC50Analgesia -
natInitAlpha)*(betaHalfTime))/(math.log(0.5))
                cOneGammaTTwo = ((natC50Analgesia -
natInitAlpha)*(gammaHalfTime))/(math.log(0.5))
                if ((concAlphaTOne)>(concAlphaBetaInter)):
                   tOne=(alphaTOne)
                   typeOne = "alpha"
                elif ((concGammaTOne)<(concBetaGammaInter)):
                   tOne=(gammaTOne)
                   typeOne = "gamma"
                else:
                   tOne=(betaTOne)
                   typeOne = "beta"
                if ((concAlphaTTwo)>(concAlphaBetaInter)):
                   tTwo=(alphaTTwo)
                   typeTwo="alpha"
                elif ((concGammaTTwo)<(concBetaGammaInter)):
                   tTwo=(gammaTTwo)
                   typeTwo= "gamma"
                else:
                   tTwo=(betaTTwo)
                   typeTwo= "beta"
```

CBD = tTwo - tOne

Appendix 5: Legend for Abbreviations:

Cp	Plasma concentration
C_{50}	Median concentration associated with particular response
ng	nanogram
mL	milliliter
T_1	Time until return of breathing or Duration of Apnea
T_2	Time until return of pain or Duration of Analgesia
CBD	Comfortable Breathing Duration = (T2-T1)
t	time
Y	Dependent variable (concentration)
dY/dt	Rate of change of Y with respect to time
K	Constant (rate constant)
I	Infusion rate
A, B, C	Arbitrary constants
C0 alpha	Initial concentration of alpha decay curve
Vd	Volume of distribution
t ½ alpha	Half-time of alpha decay
NAlpha	Number of alpha half times
Tabi	Time of Alpha-Beta Intersection
Cabi	Concentration of Alpha-Beta Intersection
T bgi	Time of Beta-Gamma Intersection
C bgi	Concentration of Beta-Gamma Intersection
UCL	Upper Confidence Limit (95%)
Mean	Arithmetic Mean (Average)
LCL	Lower Confidence Limit (95%)
N	Number
STD	Standard Deviation
Conf	Confidence Interval
CV	Coefficient of Variation = STD/Mean