Original Article

Developing mathematical models to compare and analyse the pharmacokinetics of morphine and fentanyl

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Quick response code

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ABSTRACT

Background and Aims: The two-compartment model is generally used in pharmacokinetics to illustrate the distribution and excretion of drugs. In this study, we evaluated the distribution patterns of morphine and fentanyl by using a two-compartment model. **Methods:** Using numeric analysis techniques, non-linear ordinary differential equations were used to mathematically analyse drug distribution, transition, and concentration in the body compartments. Math Works, Inc., MATLAB, version 2023a, a programming tool, was used to characterise the impact of initial concentration and rate constants on the kinetics of the drug. For a definite therapeutic concentration of morphine and fentanyl in blood, pharmacokinetic characteristics were plotted. **Results:** The study results showed the time taken by morphine and fentanyl to reach a target concentration in the blood that is sufficient to generate the preferred therapeutic effects. The mathematical models comparing morphine and fentanyl pharmacokinetics showed that fentanyl reached the target therapeutic concentration 125 minutes earlier than morphine and was metabolised and removed from the body more rapidly (44 minutes earlier than morphine). **Conclusion:** These comparative mathematical models on morphine and fentanyl enable the determination of drug dosages and understanding of drug efficacy that facilitates optimising dosing regimens. The right choice between them can be made based on the time to reach the target therapeutic concentration in the blood, elimination time, severity of pain, and patient characteristics.

Key words: Drug, fentanyl, mathematical model, morphine, pharmacokinetics

INTRODUCTION

Pain is a negative sensation that combines both physical and emotional experiences. It can be linked to injury or the possibility of injury.[1,2] Alternatively, analgesia refers to alleviating pain that may be achieved via various pharmacological and non-pharmacological methods, which rely on the nature and intensity of the pain.[3-6] Pharmacokinetics entails evaluating the processes involved in its transitions through the human body, from its administration to elimination.[7-9] Mathematical modelling uses mathematical equations and can take many forms, such as differential and difference equations, stochastic models, and network models.[10] Compartmental modelling is a frequent approach used in pharmacokinetics to explain the movement and elimination of drugs inside the human body.[11,12]

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The two-compartment model includes a central and peripheral compartment.[13,14] Three-compartment modelling segregates the human body into central (highly perfused organs, such as the heart, liver, and kidneys, where the drug distributes relatively quickly) and peripheral compartments (lesser perfused tissues, such as fat and muscle, where the drug distributes slowly).[15] The movement of the drug between the compartments is explained by the differential equations that incorporate the drug's pharmacokinetic parameters, such as clearance, the volume of distribution, and absorption rate. Morphine is a potent analgesic that binds to specific brain and spinal cord receptors, decreasing pain perception.[16,17] Fentanyl is considered to be 50–100 times more potent than morphine and is available in various forms, including parenteral, transdermal patches, lozenges, and nasal sprays.[18,19]

This study compared different types of mathematical models to understand drug pharmacokinetics. The effect of rate constants and initial concentration on the drug kinetics was studied. Models specific to morphine and fentanyl were developed to study their efficacy and long-term behaviour in the human body.

METHODS

This study is a system pharmacokinetic modelling that describes the relationships between different variables in a system. This study does not involve any animal or human participants, and the detailed mathematical simulation process is described in this section. The behaviour of drugs inside the human body is described using these models when administered via oral and intravenous routes using Math Works, Inc., MATLAB, version 2023a, as the simulation platform. These models are then extended to capture the pharmacokinetic behaviour of morphine and fentanyl in particular. This mathematical analysis provides optimised solutions for complex problem statements, making it crucial to establish mathematical models for estimating drug concentration at various places and in the blood.[20-22] When administered orally, the drug dissolves and releases the medication in the gastrointestinal (GI) tract. The drug then reaches the blood and sends it to the site where therapeutic effects occur.[23] The excretory organs gradually clear the drug from the blood. The different body parts are treated as compartments to characterise the flow of drugs within the body, and the movement of drugs into and out of each compartment is tracked. The rate at which the drug travels between the compartments is described using first-order kinetic expressions.[12] Suppose x(t) is the drug concentration at time *t* seconds.

$$\frac{dx}{dt} = \text{input rate of the drug} - \text{output rate of the drug} \quad (1)$$

If the drug is administered orally, it diffuses into the blood via the GI tract, forming the first and second compartments. Suppose x_0 is the initial concentration of the drug, and $x_1(t)$ and $x_2(t)$ are the concentration in the GI tract and bloodstream compartments, respectively,[12] then,

$$\frac{dx_1(t)}{dt} = -k_1 x_1(t) \quad (2)$$

$$\frac{dx_2(t)}{dt} = k_1 x_1(t) - k_e x_2(t) \quad (3)$$

where k_1 and k_e are the rate constants at which the drug travels from one compartment to another. Solving Equations (2) and (3), we obtain,

$$x_1(t) = x_0 e^{-k_1 t} \quad (4)$$

$$x_2(t) = \frac{x_0 k_1}{k_1 - k_e}\left(e^{-k_e t} - e^{-k_1 t}\right) \quad (5)$$

In clincial situtations, where administration of drug via oral route is not feasible, intravenous administration is preferred, where medication is directly administered into the bloodstream. Blood is treated as the first compartment to which the drug is administered, and the tissue is the second compartment with a therapeutic effect. The drug reaches tissue at a rate constant k_b from the blood and is excreted with a rate constant of k_e. Redistribution of drugs happens to blood from tissue with a rate constant of k_t. If the concentration of the drug in the blood is $x_b(t)$ and that in tissue is $x_t(t)$, the mathematical model for the drug is described using the following set of equations: [12]

$$\frac{dx_b(t)}{dt} = -(k_b + k_e)x_b(t) + k_t x_t(t) \quad (6)$$

$$\frac{dx_t(t)}{dt} = k_b x_b(t) - k_t x_t(t) \quad (7)$$

The three-compartment model describes the characteristics of a drug after the intravenous administration in the three compartments: the central compartment (depicting plasma), the highly perfused peripheral compartment indicating well-perfused organs and tissues, and the scarcely perfused peripheral compartment representing poorly perfused organs and tissues. If $x_1(t)$, $x_2(t)$, and $x_3(t)$ are concentrations in the central and peripheral compartments, the

following equations define the characteristics of drug concentration in all three compartments:[24]

$$\frac{dx_1(t)}{dt} = -(k_{10} + k_{12} + k_{13})x_1(t) + k_{21}x_2(t) + k_{31}x_3(t) \quad (8)$$

$$\frac{dx_2(t)}{dt} = k_{12}x_1(t) + k_{21}x_2(t) \quad (9)$$

$$\frac{dx_3(t)}{dt} = k_{13}x_1(t) + k_{31}x_3(t) \quad (10)$$

Intravenous bolus injections are commonly used for short-term drug administration, providing rapid effects within 1–30 minutes. Suppose we specifically focus on intravenous bolus of morphine. It can potentially affect the central nervous system rapidly; thus, appropriate dosing is crucial.[25] The usual dosage of morphine ranges from 0.1 to 0.2 mg/kg.[26,27] Suppose an adult weighing 50 kg with a normal physiological state is administered morphine intravenous bolus of 5 mg (0.1 mg/kg). In that case, it is essential to know the drug kinetics in the body, which will also help to decide the interval for the next dosage.

Molecular weight of morphine = 285.34 g/mol[28]

$$\text{Concentration of bolus} = \frac{\text{Amount of morphine in the bolus}}{\text{Volume of bolus}}$$

For reaching a minimum of 50 ng/mL of morphine in the blood,

$$\text{Therapeutic concentration} = \frac{\text{Minimum concentration in the blood}}{\text{molecular weight}}$$

$$= 1.7523 \times 10^{-10}\, mM$$

Fentanyl dosage varies between 1 and 2 μg/kg.[26] Suppose the same person is treated with a fentanyl intravenous bolus of 0.1 mg (2 μg/kg).

Molecular weight of fentanyl = 336.471 g/mol[28]

For setting a minimum of 50 ng/mL of fentanyl in the blood:

$$\text{Therapeutic concentration} = \frac{\text{Minimum concentration in the blood}}{\text{molecular weight}}$$

$$= 1.486 \times 10^{-10}\, mM$$

The fourth-order Runge–Kutta method, a numerical analysis technique, is used to solve these ordinary differential equations for parameter estimation.[29] For the given ordinary differential equation, which is in the form of $\frac{dx}{dt} = f(x,t)$, the new value of x can be computed as follows:

$$x_1 = x_0 + (D_1 + 2D_2 + 2D_3 + D_4)/6 \quad (11)$$

For a particular step size h and initial values x_0 and t_0:

$$D_1 = h \times f(x_0, t_0), D_2 = h \times f(x_0 + h/2,\ t_0 + D_1/2), D_3 = h \times f(x_0 + h/2,\ t_0 + D_2/2), D_4 = h \times f(x_0 + h,\ t_0 + D_3).$$

RESULTS

Based on the first-order kinetics, Figure 1 illustrates the drug kinetics considering the whole body to be a single compartment for various rate concentrations with the oral drug dosage. It also illustrates the drug kinetics with varying dosages. Drug concentration gradually decreases with time. A more significant rate of constant results in quicker absorption, preventing the residues of the drug in the body and minimising its adverse effects.

The central compartment includes plasma and tissues, where drug distribution occurs rapidly. The peripheral compartments comprise tissues in which the distribution of the drug is relatively slower compared to compartment 1 [Figure 2].

Morphine bolus injection is modelled for the central (blood) and peripheral compartments (tissue) [ANNEXURE 1]. The characteristics give a time of 4570 minutes for morphine to leave the blood and tissues [Figure 3]. Approximately 220 minutes are taken by the human body to achieve the therapeutic concentration of 50 ng/mL (1.7523×10^{-10} mM).

Fentanyl bolus injection is modelled for central (blood) and peripheral compartments (tissue) [ANNEXURE 2]. As per the characteristics, fentanyl takes 4526 minutes to leave the blood and tissues [Figure 3]. Approximately 95 minutes are needed for the human body to achieve the therapeutic concentration of 50 ng/mL (1.486×10^{-10} mM). Figure 4 provides a comparative analysis of morphine and fentanyl characteristics in the plasma and tissues.

DISCUSSION

Opioids are highly effective in relieving pain; they are usually reserved for severe pain or if any other

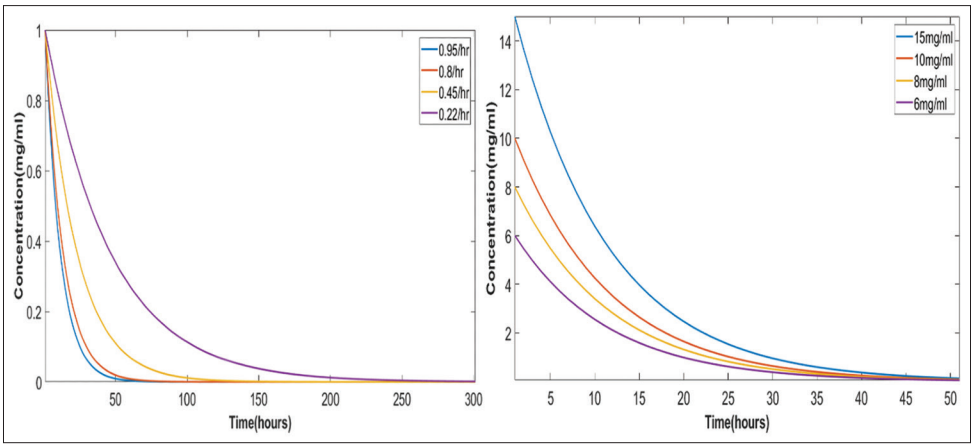

Figure 1: Variation of drug concentration at different rate constants and dosages

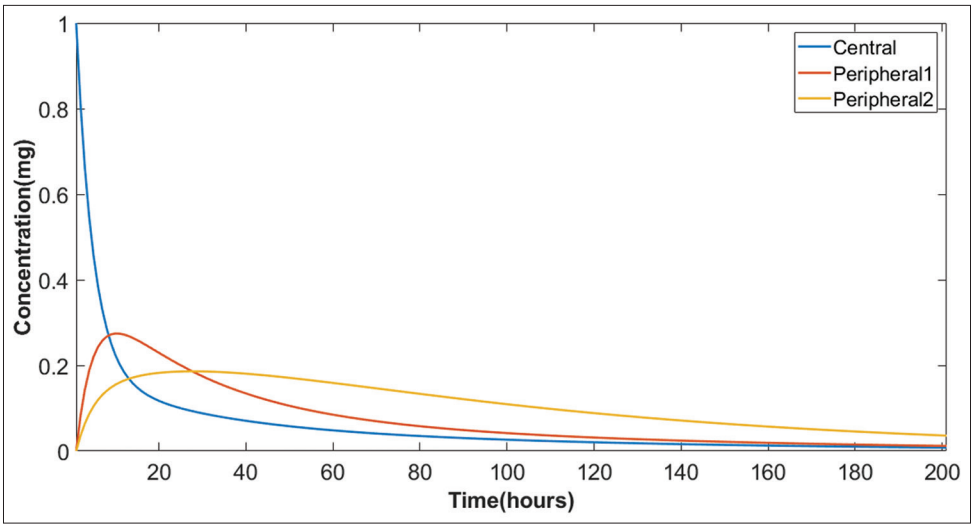

Figure 2: Drug distribution with intravenous administration in the three compartments

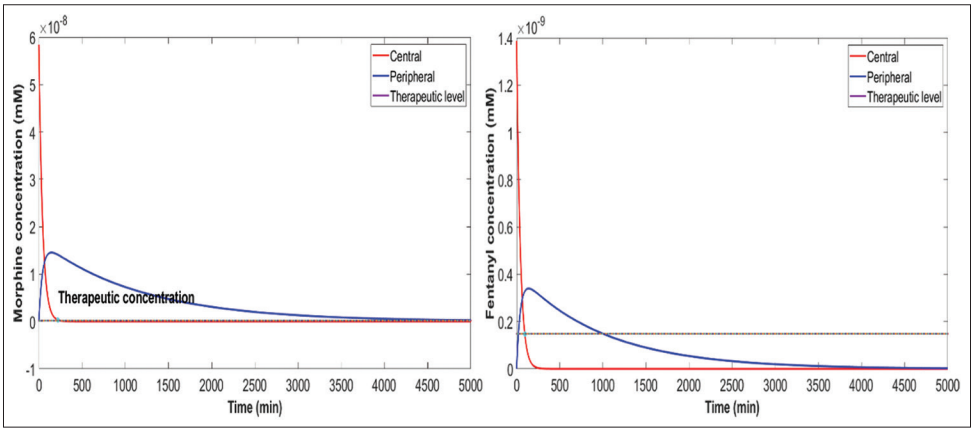

Figure 3: Morphine and fentanyl clearance from tissue after a bolus injection of 5 mg and 0.14 mg, respectively

non-opioid treatments fail.[30] They could lead to significant adverse effects, including the potential for abuse, addiction, and overdose.[31,32] Frequent dependence on these opioids might result in tolerance and physical dependence.[33,34] Morphine is known as a first-line opioid used to manage pain due to surgery, trauma, or some serious injuries.[35,36] Fentanyl has shown more potency than morphine and hence

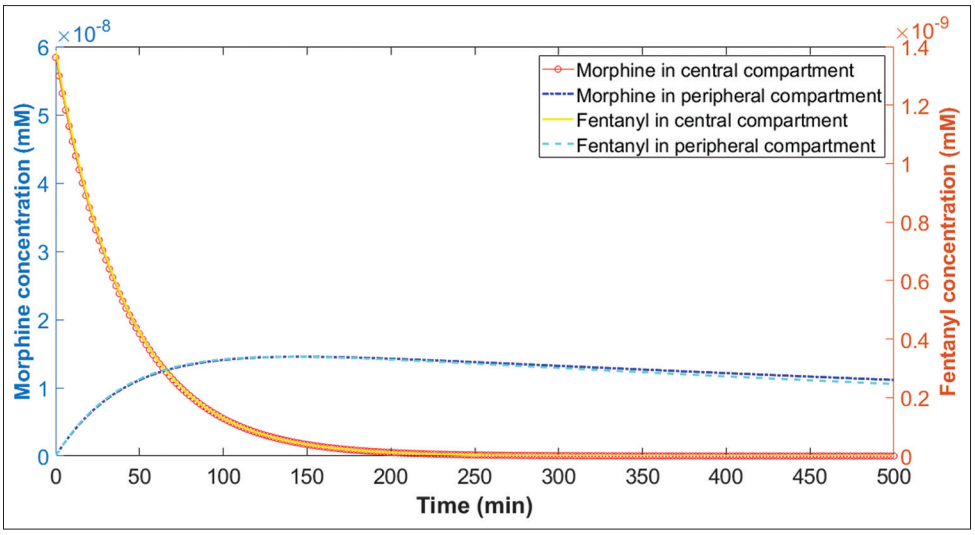

Figure 4: Comparison of morphine and fentanyl characteristics

requires monitored dosing and administration to avoid overdosage and respiratory depression.[37-39]

In this study, various mathematical models were used to characterise the drug behaviour inside the human body. With the aid of compartment modelling, morphine and fentanyl pharmacokinetics were plotted, and fentanyl was found to take less time to reach the target therapeutic threshold set in the blood. Compared to morphine, fentanyl left the body earlier. Pharmacokinetic models are crucial in defining drug interactions inside the human body, optimising dosing regimens, predicting drug effects, and designing clinical trials.[40] These mathematical models predict and quantify drug–drug interactions due to one drug altering the effects of another and enhancing the understanding of drugs' effects on multiple targets and pathways. However, these models apply only to the bolus injection of the drug by splitting the human body into two compartments. These models consider definite volume in the compartments and reaction rates to be constant. These models also treat every patient similarly reacting to the drug. More complex models can be developed by increasing the compartments in the models to achieve better accuracy in the results.

Although many researchers have focussed on investigating the synergistic pharmacokinetic effects resulting from the administration of both drugs, there have been no studies to compare the kinetics of morphine and fentanyl.[41-45] In a study, Feizabadi *et al*.[46] explained a two-compartment model for anti-cancer agents. Cherruault and Sarin explained the three-compartment model with a time lag.[47] Khanday *et al*.[48] developed a mathematical model characterising the drug diffusion process within the transdermal drug delivery system. These models focus on drug delivery dynamics within the body and quantify the absorption rates in different layers of the skin and subcutaneous tissues. Performing data analysis from many individuals enables one to estimate the variation in drug responses due to age, gender, genetics, and medical condition. Using this information, drug dosing for specific patient populations can be determined. Determination of drug efficacy reduces the number of clinical trials and thus accelerates drug development.

These models aid in knowing the safety of a particular drug to predict the possible adverse effects and guide drug developers. Hence, this is an efficient drug development and pharmacology strategy, enabling researchers and clinicians to gain information about drug behaviour-optimised therapies and improved patient outcomes. By comparing the drug kinetics and distribution of morphine and fentanyl, clinicians can make informed decisions about the dosing patterns, ensuring effective treatment while considering individual patient characteristics and minimising potential adverse effects.

CONCLUSION

In this study, different mathematical models were discussed to expand the knowledge of the kinetics of morphine and fentanyl within the human body. The non-linear ordinary differential equations helped determine the time required for the drugs to reach the minimum effective concentration in the blood and the time it takes to leave the body altogether. Future

studies are needed on routes of administration of analgesics to improve pain relief and minimise the side effects.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Cohen M, Quintner J, van Rysewyk S. Reconsidering the international association for the study of pain definition of pain. PAIN Rep 2018;3:e634. Doi: 10.1097/PR9.0000000000000634.
2. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, *et al*. The revised international association for the study of pain definition of pain: Concepts, challenges, and compromises. Pain 2020;161:1976-82.
3. Oertel BG, Lötsch J. Clinical pharmacology of analgesics assessed with human experimental pain models: Bridging basic and clinical research. Br J Pharmacol 2013;168:534-53.
4. Maciel HI, Costa MF, Costa AC, Marcatto J de, Manzo BF, Bueno M. Pharmacological and nonpharmacological pain management and treatment measures among neonates. Revista Brasileira de Terapia Intensiva 2019;31:21-6.
5. El Geziry A, Toble Y, Al Kadhi F, Pervaiz and Mohammad Al Nobani M. Non-pharmacological pain management. Pain Management in Special Circumstances 2018;1-4.
6. Milani DA, Davis DD. Pain management medications. InStatPearl 2023; StatPearls Publishing.
7. Turfus SC, Delgoda R, Picking D, Gurley BJ. Pharmacokinetics. Pharmacognosy 2017. Boston: Academic P. 495-512.
8. Alagga AA, Gupta V. Drug absorption. InStatPearls 2022; StatPearls Publishing.
9. Mansoor A, Mahabadi N. Volume of distribution. InStatPearls 2023; StatPearls Publishing.
10. Siepmann J, Siepmann F. Mathematical odelling of drug delivery. Int J Pharm 2008;364:328-43.
11. Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn 2007;34:711-26.
12. Khanday MA, Rafiq A, Nazir K. Mathematical models for drug diffusion through the compartments of blood and tissue medium. Alexandria J Med 2017;53:245-9.
13. Iga K, Kiriyama A. Usefulness of two-compartment model-assisted and static overall inhibitory-activity method for prediction of drug-drug interaction. Biol Pharm Bull 2017;40:2024-37.
14. Yen P, Finley SD, Engel-Stefanini MO, Popel AS. A two-compartment model of VEGF distribution in the mouse. PloS One 2011;6:e27514. Doi: 10.1371/journal.pone. 0027514.
15. Tingle M, Park B. The use of a three compartment *in vitro* model to investigate the role of hepatic drug metabolism in drug-induced blood dyscrasias. Br J Clin Pharmacol 1993;36:31-8.
16. Pathan H, Williams J. Basic Opioid pharmacology: An update. Br J Pain 2012;6:11-6.
17. Chahl LA. Experimental and clinical pharmacology: Opioids – mechanisms of action. Aust Prescr 1996;19:63-5.
18. Fentanyl – StatPearls – NCBI Bookshelf – National Center for …. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459275/[Last accessed on 2023 Dec 20].
19. Poklis A. Fentanyl: A review for clinical and analytical toxicologists. J Toxicol Clin Toxicol 1995;33:439-47.
20. Bruschi ML. Strategies to Modify the Drug Release from Pharmaceutical Systems. Woodhead Publishing. United Kingdom; 2015. p. 63-86.
21. Trucillo P. Drug carriers: A review on the most used mathematical models for drug release. Processes 2022;10:1094.
22. Arifin DY, Lee LY, Wang C-H. Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems. Adv Drug Delivery Rev 2006;58:1274-325.
23. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. Front Pharmacol 2021;12:618411. doi: 10.3389/fphar. 2021.618411.
24. Cascone S, Lamberti G, Piazza O, Abbiati RA, Manca D. A physiologically-based model to predict individual pharmacokinetics and pharmacodynamics of remifentanil. Eur J Pharm Sci 2018;111:20-8.
25. Hoskin P, Hanks G. Morphine: Pharmacokinetics and clinical practice. Br J Cancer 1990;62:705-7.
26. Katzung BG. Basic and Clinical Pharmacology. 2012. McGraw Hill Medical, San Francisco; p. 513-23, 2001.
27. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg 2003;789-95.
28. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, *et al*. PubChem 2019 update: Improved access to chemical data. Nucleic Acids Res 2018;47:D1102-9. doi: 10.1093/nar/gky1033.
29. Dormand JR, Prince PJ. A family of embedded Runge-Kutta formulae. J Comput Appl Math 1980;6:19-26.
30. National Institute of Diabetes and Digestive and Kidney Diseases (US). LiverTox: clinical and research information on drug-induced liver injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
31. Volkow N, Benveniste H, McLellan AT. Use and misuse of opioids in Chronic pain. Ann Rev Med 2018;69:451-65.
32. Nadeau SE, Wu JK, Lawhern RA. Opioids and chronic pain: An analytic review of the clinical evidence. Front Pain Res 2021;2:721357. doi: 10.3389/fpain. 2021.721357.
33. Adriaensen H, Vissers K, Noorduin H, Meert T. Opioid tolerance and dependence: An inevitable consequence of chronic treatment? Acta Anaesthesiologica Belgica 2003;54:37-48.
34. Kosten T, George T. The neurobiology of opioid dependence: Implications for treatment. Sci Pract Perspect 2002;1:13-20.
35. Abdolrazaghnejad A, Banaie M, Tavakoli N, Safdari M, Rajabpour-Sanati A. Pain management in the emergency department: A review article on options and methods. Adv J Emerg Med 2018;2:e45. doi: 10.22114/AJEM.v0i0.93.
36. Ahmadi A, Bazargan-Hejazi S, Zadie ZH, Euasobhon P, Ketumarn P, Karbasfrushan A, *et al*. Pain

management in trauma: A review study. J Injury Violence Res 2016;8:89-98.
37. Hill R, Santhakumar R, Dewey W, Kelly E, Henderson G. Fentanyl depression of respiration: Comparison with heroin and morphine. Br J Pharmacol 2019;177:254-65.
38. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. MMWR Recomm Rep 2016;65:1-49. doi: 10.15585/mmwr.rr6501e1.
39. Preuss CV, Kalava A, King KC. Prescription of Controlled Substances: Benefits and Risks. StatPearls Publishing; 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537318/. [Last accessed on 2023 Apr 29].
40. Li Y, Meng Q, Yang M, Liu D, Hou X, Tang L, *et al*. Current trends in drug metabolism and pharmacokinetics. Acta Pharmaceutica Sinica B 2019;9:1113-44.
41. Stuart-Harris R, Joel SP, McDonald P, Currow D, Slevin ML. The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine. Br J Clin Pharmacol 2000;49:207-14.
42. Manara AR, Shelly MP, Quinn KG, Park GR. Pharmacokinetics of morphine following administration by the Buccal Route. Br J Anaesth 1989;62:498-502.
43. Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Shephard B, *et al*. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: Secondary results from the neopain trial. Br J Anaesth 2008;101:680-9.
44. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. J Pain Palliative Care Pharmacother 2002;16:5-18.
45. Lötsch J, Walter C, Parnham MJ, Oertel BG, Geisslinger G. Pharmacokinetics of non-intravenous formulations of fentanyl. Clin Pharmacokinet 2012;52:23-36.
46. Feizabadi MS, Volk C, Hirschbeck S. A two-compartment model interacting with dynamic drugs. Appl Math Lett 2009;22:1205-9.
47. Cherruault Y, Sarin VB. A three compartment open model with two time lags. Int J Biomed Comput 1993;32:269-77.
48. Khanday MA, Rafiq A. Variational finite element method to study the absorption rate of drug at various compartments through transdermal drug delivery system. Alexandria J Med. 2015;51:219-23.

ANNEXURE 1

MATLAB code for morphine pharmacokinetic characteristics

```
mg_bolus = 5;
V_bolus = 10;
mw_morphine = 285.34;
mmol_bolus = mg_bolus / mw_morphine;
C_bolus = mmol_bolus / V_bolus;
kg_patient = 50;
V_per_kg = 6000;
V_1 = V_per_kg*kg_patient;
V_2 = V_per_kg*kg_patient;
C1i = mmol_bolus / V_1;
C3i = (10/mw_morphine)/V_1;
C5i = (5/mw_morphine)/V_1;
C_therapeutic = 5E-8/mw_morphine;
renal_clearance = 2;
to_peripheral = 40;
k1 = 1E-6 * mw_morphine;
kd = 3E-6 * mw_morphine;
kt = to_peripheral/V_per_kg;
ke = kg_patient*renal_clearance/V_per_kg;
t_end = 72*60;
t=0:2:5000;
C1 = C1i * exp(-(k1+kt+ke)*t);
C2 = (kt*mmol_bolus/V_2)*(exp(-(k1+kt+ke)*t) - exp(-kd*t))/(-k1-kt-ke+kd);
t_therapeutic = 220;
hold on
plot(t,C1,'r',t,C2,'b','LineWidth',2)
box on
yi = interp1(t,C1,t_therapeutic);
plot(t_therapeutic, yi,'c','LineWidth',2);
 xlabel(['Time (min)'],'FontWeight', 'bold');
ylim( [-1E-8 6E-8])
ylabel('Morphine concentration (mM)','FontWeight', 'bold')
text(t_therapeutic,yi+.5E-8,'Therapeutic concentration','FontWeight', 'bold')
tnew=0:10:5000;
plot(tnew,C_therapeutic,'.-','LineWidth',2)
hold off
legend( 'Central','Peripheral','','Therapeutic level')
fontsize(gca, 20,'points')
```

ANNEXURE 2

MATLAB code for fentanyl pharmacokinetic characteristics

```
mg_bolus = 0.14;
V_bolus = 10;
mw_fenta = 336.471;
mmol_bolus = mg_bolus / mw_fenta;
C_bolus = mmol_bolus / V_bolus;
kg_patient = 50;
V_per_kg = 6000;
V_1 = V_per_kg*kg_patient;
V_2 = V_per_kg*kg_patient;
C1i = mmol_bolus / V_1;
C3i = (10/mw_fenta)/V_1;
C5i = (5/mw_fenta)/V_1;
C_therapeutic = 5E-8/mw_fenta;
renal_clearance = 2;
to_peripheral = 40;
k1 = 1E-6 * mw_fenta;
kd = 3E-6 * mw_fenta;
kt = to_peripheral/V_per_kg;
ke = kg_patient*renal_clearance/V_per_kg;
t=0:2:5000;
C1 = C1i * exp(-(k1+kt+ke)*t);
C2 = (kt*mmol_bolus/V_2)*(exp(-(k1+kt+ke)*t) - exp(-kd*t))/(-k1-kt-ke+kd);
t_therapeutic = 95;
box on
hold on
plot(t,C1,'r',t,C2,'b','LineWidth',2)
yi = interp1(t,C1,t_therapeutic);
text(t_therapeutic,yi+.5E-8,'Therapeutic concentration','FontSize',↙
40,'Units','normalized')
plot(t_therapeutic, yi,'c*','LineWidth',2);
tnew=0:10:5000;
plot(tnew,C_therapeutic,'.-','LineWidth',2)
hold off
legend( 'Central','Peripheral','','Therapeutic level')
xlabel('Time (min)','FontWeight', 'bold');
ylabel('Fentanyl concentration (mM)','FontWeight', 'bold')
ylim([0 1.4E-9])
fontsize(gca, 20,'points')
```