Research Article

Journal of Anesthesia & Pain Medicine

Opioid Analgesic Choices Based On Pharmacokinetics

Tanya Manisha Machado* **and Princy Louis Palatty**

Father Muller Medical College, Mangalore, Karnataka, India

***Corresponding author**
Tanya Manisha Machado, Father Muller Medical College, Mangalore, Karnataka, India, Tel: +91-7411338151; E-mail: Tanya.nicole94@gmail.com.

Submitted: 10 Oct 2016; **Accepted**: 03 Nov 2016; **Published**: 07 Nov 2016

Abstract

Introduction: *This study looks the multiple factors- specifically the pharmacokinetics that are involved while selecting an opioid to ensure its optimum efficacy. Combinations of analgesics are an enticing option, for achieving maximal analgesia with minimal adverse reactions. The choice of analgesic depends on the sub-population it caters to, and the etiology of pain involved.*

Methodology: *112 articles involving an inclusion criteria of "pharmacokinetic aspects in combination of opioid" from a Pubmed search were assessed. Associations among the opioids and suggested guidelines were drawn after thoughtful analysis.*

Discussion: *Single-injection neuraxial; fentanyl and sufentanil are preferred over parenteral opioids. Remifentanil and Dexmedetomidine are preferred for ICU patients. Tramadol can be used for mild to moderate pain, and morphine is the choice for severe and intractable pain. The parenteral routes is commonly used but it is beset with pain and other adverse drug reactions.*

Conclusion: *Combination of analgesics having varied mechanisms of action is advocated for optimizing analgesic therapy. Opioid analgesics are widely used but ferreting out the appropriate dose, route and agent is the crux in effect analgesic. A holistic approach that considers all aspects of an opioid need to be considered before selection, and the pharmacokinetics aspect plays a pivotal role.*

Keywords: Opioids, Differential pharmacokinetics, Background morphine, Opioid induced constipation.

Introduction

"The greatest happiness mankind can gain is not from pleasure,but relief of pain." John Milton, Paradise Lost. Mankind seeks out analgesics for imminent pain relief despite the wide array of analgesics available, opioids are a formidable choice. The greatest limitation of opioid usage is its addiction liability. The defined daily dose for statistical purposes of opioid analgesics was about 110 per million inhabitants/ day in Mexico as compared to 43879 per million inhabitants per day in the USA [1]. Use of opioid painkillers increases fourfold in Australia in 10 years while most of the world lacks access to basic pain relief [2].

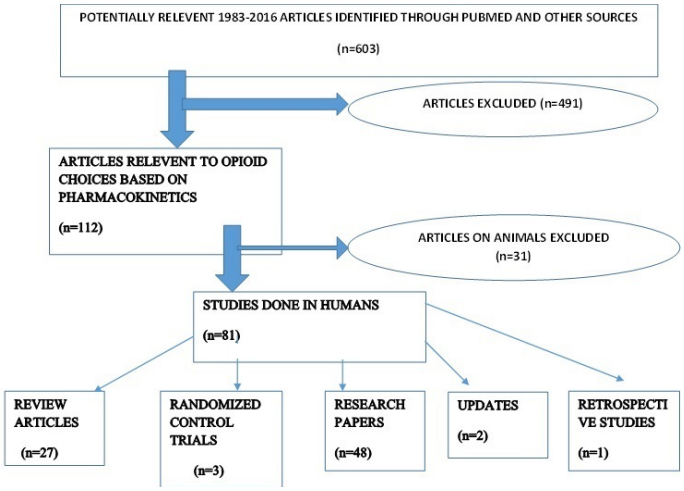
Analgesic choices are difficult due to addiction liability, adverse effects and singular mechanism of action. Combinations of analgesics are an enticing option, for achieving maximal analgesia with minimal adverse reactions. The individual options of analgesics can be enhanced by opting for the route that gives maximal analgesia with minimal adverse reaction. Moreover, subsets of population such as geriatric, pediatric, pregnant, hepatic failure, renal failure, and compromised respiration need special emphasis on the choice of analgesia. The choice of analgesic also varies on the etiology of pain i.e. post operative pain, palliative care oncology patients, neuropathic pain etc. There is a lot of published data on analgesics but, the focus varies among different studies. The available published data do come up with seemingly small insights into analgesic choices based on pharmacokinetics and adverse reactions.

This study forays into the realm of analgesics, based on variations in pharmacokinetics of different opioids, with their doses and their routes.

Methodology

This study delved into the basis of pharmacokinetics for optimizing the choice of the opioid analgesic. A pubmed search using the National Library of Medicine's PubMed website (http://www.ncbi.nlm.nih.gov/PubMed) for Articles published in English over the 30-year period of 1983-2016 was done on the topic. Which showed 603 on 12th October 2016 at 5:30 pm GMT articles using

an inclusion criteria of "pharmacokinetic aspects in combination of opioid" this filtered down to 112 articles. The investigators combed through the 112 and focused on articles, drawing conclusions from these published papers Table 1.



Result

Table 2 [3-27].

All Articles That Involved Humans In Their Study			
Sr. No	**Opioid used In the study**	**Workers and paper reference**	**Year**
1	Combination of various opioids	Ladd LA, et al.. [3]	2005
		Joseph V. Pergolizzi Jr, et al. [4]	2015
		Lawrence Librach, et al. [5]	1995
		Jeffrey A. Gudin, et al. [6]	2013
2	Buprenorphine	Duchar S, et al. [7]	2012
3	Fentanyl	Lewis Nelson, et al. [8]	2009
		Noah D. Syroid, et al. [9]	2010
4	All opioids	Kanwal jeet J. S, et al. [10]	2010
		Vijay Sharma, et al. [11]	2009
		Robert H. Dworkin, et al. [12]	2010
		Nalini Vadivelu, et al. [13]	2010
		Marie Fallon, et al. [14]	2006
		Karel allegaerta, et al. [15]	2013
		Anand KJS, et al. [16]	2006
		Pascal H Vuilleumier, et al. [17]	2012
5	Oxycodone	James P. Zacnya, et al. [18]	2009
		Samer CF, et al. [19]	2012
		Gary Vorsanger, et al. [20]	2011
		Ryan M Frank, et al. [21]	2016
		Krishna Devarakonda, et al. [22]	2014
6	Remifentanil	Wolfram Wilhelm, et al. [23]	2008
7	Sufentanil	Timothy I, et al. [24]	2014
8	Methadone	Amin Rostami-Hodjegan, et al. [25]	1999
	Tramadol	William W Stoops, et al. [26]	2013
		Justin C Stricklanda, et al. [27]	2015

Discussion

In our quest for optimizing analgesic choices our literature review lead us to analyze 112 papers. The pharmacokinetic aspects in determining the choice in analgesics were gleaned from the literature. This study has focused only on the opioid analgesic, singly or in combination with other opioids/ other agents. (i.e. local anesthetics, NSAIDs, GABA analogues). The present day opioid analgesics have been classified to be used as a template in for analgesic choices (Table 3).

Classification of opioid agonists			
Endogenous opioids	Natural opium alkaloids	Semisynthetic opium derivatives	Synthetic opium substitutes
Endorphins	Phenantherine derivatives: Morphine, Codeine, Thebaine	Morphine derivatives: Hydromorphine, Oxymorphine, Heroine	Morphinans: Levorphenol, Dextromethorphan
Enkephalins	Benzylisorquinoline derivatives: Papaverine, Narcotine	Codeine derivetives: Hydrocodone, Oxycodone, Dihydrocodiene, Pholcodine	Diphenylprolylamine series: Methadone, Propoxyphene
Dynorphins		Thebaine derivatives: Buprenorphine (partial agonist at μ opioid receptor)	Benzomorphans: Pentazocine, Phenazocine (opioid agonist-antagonists)
Endomorphins			Phenylpiperidines: Mepridine, Fentanyl, Sufentanil, Alfentanil, Remifentanil, Loperamide, Diphenoxylate
Nociceptin			Miscellneous: Dextromoramide tartarate, Dipipanone HCl

The opioid analgesic pharmacokinetic parameters have been tabulated (Table 4) [28]. The pharmacokinetics of a drug are sectioned into absorption, distribution, metabolism and excretion.

Absorption

Opioids have moderate gastro intestinal absorption from oral morphine and hydromorphone dose. Hence it is also used as a suppository. More lipophilic agents have guaranteed absorption from the buccal and nasal epithelium [29]. Morphine undergoes, first pass metabolism and hence parenteral route is preferred [30]. The liposolubility is inversely proportional to their spinal selectivity, which is higher for morphine, than for other more lipophilic drugs, such as fentanyl and sufentanil [31]. The limited and slow transfer from the CFS, morphine presents a slow onset of action, extensive and prolonged rostral spread resulting in delayed respiratory depression (6-12 hours) and a broad band of analgesia surrounding the site of injection, and a relative long duration

Drug name	Metabolizing enzyme	Metabolites	Site of action	Vol. of Distribution	Equi analgesic oral dose	Equi analgesic parentral dose	Remarks
Fentanyl	CYP3A4	Norfentanyl [I]		++			
Sufentanyl				++			
Afentanyl							Preferred in neonates
Remifentanil	Esterases			++			Preferred in those with liver and kidney failure
Morphine	Glucuronide	Morphine3 glucoronide Morphine6 glucoronide	Histamine liberator	+	30 mg q3-4h (round the clock dosing) 60 mg q3-4 (single dose/ intermittent)	10 mg q3-4	
Hydromorphone	Glucuronide			+	7.5 mg q3-4h	1.5 mg q3-4h	
Meperidine	CYP2B6 CYP3A4				300 mg q2-3h	100 mg q3h	
oxymorphone					-	1 mg q3-4h	
Levorphanol					4 mg q6-8	2 mg q6-8	
Buprenorphine					-	0.3-0.4 mg q6-8h	
Butorphanol					-	2 mg q3-4h	
Pentazocin							
Brenazocin							
Codine	CYP2D6				130 mg q3-4h	75mg q3-4h	
Oxycodone	CYP2D6 CYP3A4				30 mg q3-4h	-	
Hydrocodone	CYP2D6 CYP3A4				30 mg 3-4h	-	
Methadone	CYP2D6 CYP3A4				20 mg q6-8h	10 mg q6-8h	
Tramadol	CYP3A4 CYP2D6 Glucuronide	O-demethy-tramadol [A]	Anti-cholinergic, Opioid receptor, Norepinephrine, Serotonin reuptake inhibitor		100 mg	100 mg	
propoxyphene					130 mg	-	Used in combination with tapentadol for elderly patients

Table 4: Pharmacokinetics. KEY: [I]= Inactive metabolite; [A]= active metabolite; [T]=Toxic metabolite; - = not avalible.

of action (18-24hours) [32]. The qualification stems from data suggesting that lipophilic opioids, particularly sufentanil, produce analgesic plasma concentrations after intrathecal administration [31].

The relatively rapid movement of sufentanil into plasma to produce analgesic concentrations is responsible for the early respiratory arrests reported when this drug was administered intrathecally, occurring within the first 20-30 min after intrathecal injection [31]. Perhaps the best clinical evidence of the limited ability of sufentanil to reach the spinal cord dorsal horn after intrathecal administration is the dose required producing analgesia. A common sufentanil dose is 10μg, which is equivalent to 10mg of morphine based on their relative potency following IV administration. However, a typical intrathecal morphine dose is only 100 μg, thus intrathecal administration results in a 100-fold decrease in the relative potency of morphine and sufentanil [31].

The use of a lipophilic opioid such as fentanyl has been shown to be effective when given by other routes such as the transmucosal route and in formulations such as a buccal tablet, due to the lipophilic nature of the drug and its rapid onset of action [29]. The rapid onset of action of fentanyl can match the rapid onset of action for most forms of breakthrough pain. The rapid onset of action by the intranasal route has been evaluated as another alternative route for the management of breakthrough pain [29].

Remifentanil is an ultra-short acting opioid that gets rapidly metabolized by nonspecific blood and tissue esterases. It is similar to fentanyl, and possesses a high affinity for μ-receptors while a lower affinity for δ- and κ-receptors [33]. Fentanyl rapidly distributes with sequestration in fat and it extensively binds to human plasma proteins [29]. It is metabolized mainly by the liver and is excreted via the kidney. Elimination half-life varies from 6 to 32 hrs. Action starts almost immediately with intravenous administration and after 7-8 min with intramuscular dosing. The peak effect that the drug achieves is observed in 5-15 min following intravenous injection. Duration of the analgesic effect is 1-2 h on intramuscular administration [29]. So it has a faster onset of action but a shorter duration of action than morphine. The opioids are hydrophilic or hydrophobic (Table 5) [29].

Hydrophillic and Hydrophobic Opioids	
Hydrophillic	Hydrophobic
Morphine	Fentanyl
Hydromorphine	Sufentanyl
	Remifentanyl

Opioids have been delivered by varied routes of administration (Table 6).For the neonates, continuous opioid infusion is preferred in the following routes Spinal /intrathecal, Epidural, Caudal routes [6].

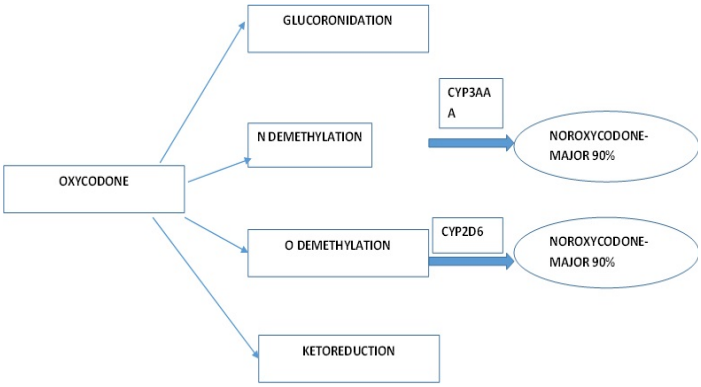
Routes of Administration of Opioids	
Oral route	Parentral
Tablets	Transdermal patch
Buccal tablet	Intravenous
Oral sustained release	Sub cutaneous injection
Lollipop	Intrathecal infusion
Sub lingual	Epidural-
	- Extended release
	- Bolus
	- Continious infusion
	Intradermal
	Via catheter
	Suppository
	Intranasal

Distribution of Opioid Drug

One third of morphine in the blood gets protein bound, and tissue concentration of morphine diminishes after 24 hours. Both metabolites morphine-6-glucuronide and morphine-3-glucuronide can cross the blood brain barrier. Fentanyl and its congeners require a short time to peak their analgesic effect, though they demonstrate a much shorter duration of action when administered intravenously. Propoxyphene on oral administration reach their highest values in the plasma within 1-2 hours [28].

Metabolism

Fentanyl undergoes fast first-pass metabolism that precludes its use orally. Fentanyl has a wide range of dose formulations i.e. Buccal tablet, transdermal patch, oral, transmucosal fentanyl, an intranasal fentanyl spray. The main metabolites of fentanyl are phenyl acetic acid and nor fentanyl [34]. It is still possible that variations in metabolic phenotypes combined with the low training dose used in this study contributed to differential drug effects and variability in discrimination performance The metabolite of oxycodone are: noroxycodone, oxymorphone [30]. Renal dysfunction with oxycodone can occur due to deposition of multiple active metabolites [30,35] (Table 7).



Transdermal Buprenorphine is the choice for renally impaired in those who require opioid therapy [36]. Liver impairment is not a clinically significant outcome, because of the low-activity of its metabolites. Precautions should be taken in patients with asthma or chronic obstructive pulmonary disease (COPD) specially when shifting from full agonist to partial agonist as withdrawal symptoms can ensue. Example: buprenorphine - a partial agonist [14].

Caution should be taken when administering opioids in combination with acetaminophen, in alcoholics/malnourished as CYP2e1 is induced, that could lead to acetaminophen producing its toxic metabolite N-Acetyl-P-Benzoquinone Imine [14,37,38]. Patients with cirrhosis have a high tendency for renal dysfunction with opioids like Meperidine. Most opioids need dose titration according to glomerular filtration rate to preempt adverse drug reactions [14]. In cirrhotic patients with intractable pain Tramadol is a preferred choice as it has additional effect on peripheral pain pathway in low doses with good tolerability. Tramadol can lead to seizures and serotonin syndrome [29]. Interaction of diazepam with methadone causes increased methadone levels in the blood by reducing renal clearance. Methadone kinetics show marked inter individual variability [14,34].

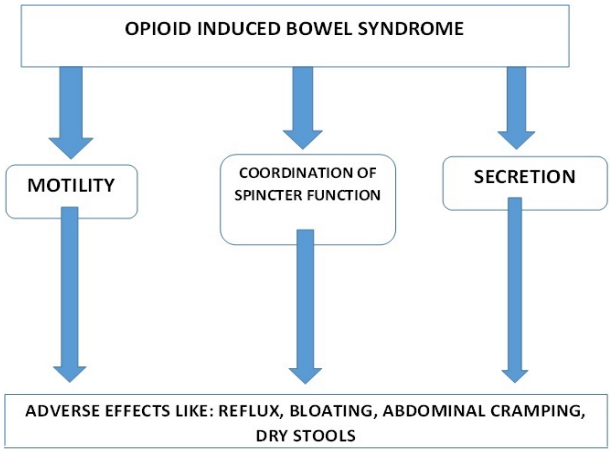
BOLD is a blood oxygen level-dependent- (fMRI) functional magnetic resonance imaging, used to observe different areas of the brain or other organs, which are found to be active at any given time [39]. Morphine and remifentanil have been reported to induce positive changes in (BOLD) signal, reported regional positive increases in blood oxygen level-dependent signal [39]. Remifentanil is the preferred option in renal or liver impairment as they are metabolized by esterases [10,22].

Alcohol increases the maximum plasma concentration (Cmax) of certain opioids-oxymorphone, hydromorphone and morphine.

Caution should be exercised when using long acting opioids in combination with prescription/social use of alcohol [14]. The active metabolites of opioids have varying pharmacodynamics or pharmacokinetic action. Single- and multiple-dose pharmacokinetics of biphasic immediate-release/ extended-release hydrocodone bitartrate/acetaminophen (MNK-155) compared with immediate-release hydrocodone bitartrate/ibuprofen and immediate-release tramadol HCl/acetaminophen showed similar peak concentration, steady state concentration and adverse effects [40]. In neonates it has been noted that there is decreased clearance of opioids [22]. Sufficient data on usage of opioids in pregnant women are unavailable from pub med as only 1.29% clinical trials are indexed in PubMed [41].

Adverse drug Reactions

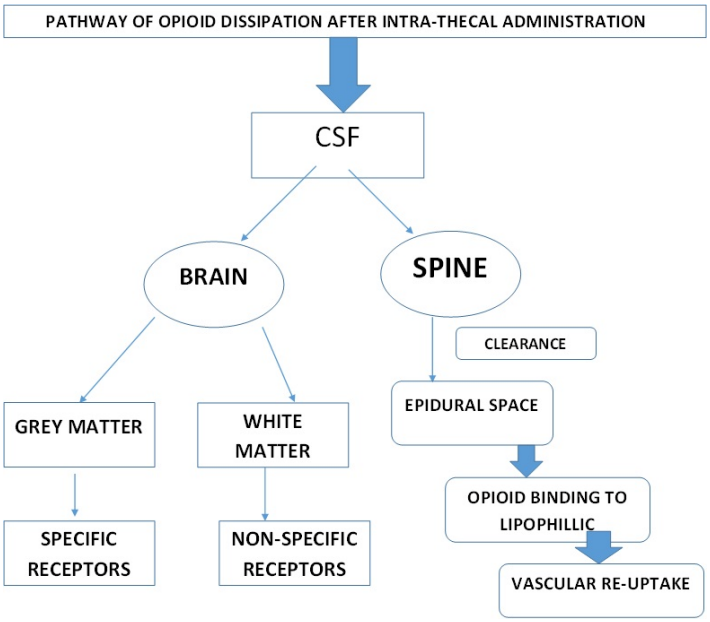
Opioid bowel dysfunction is not only due to their direct action but also could have spinal/supraspinal constipating effect. Opioids that bind to GIT opioid receptors lead to opioid induced bowel dysfunction i.e. opioid induced bowel dysfunction that affects motility, sphincter usage and secretion [42]. The GIT Symptoms with opioids have been characterized in Vide Table 8 [42].The Vide Table 9 [43] gives the entire list of opioid drug reactions. Tramadol interacts with anti-depressant drugs [16].



Opioid Adverse Drug Reaction List
Bowel disease
Chest wall rigidity
Epileptic seizures r myoclonic seizures
Headache
Hypotension
Induced bowel dysfunction
Nausea
Opioid induced constipation
Pruritis
Pyrexia
Respiratory depression
Sedation
Urine retention
Vomiting

Choice of Drug

Single-injection of neuraxial opioids is preferred over parenteral opioids [31]. Single-injection neuraxial; fentanyl and sufentanil are preferred over morphine and hydromorphone. Concomitant administration of sedatives, hypnotics, or magnesium and parenteral opioids, require therapeutic drug monitoring [31]. IV PCA morphine is better than intramuscular morphine [12]. Various modes of analgesia are often equi-analgesic but for the incidence of Adverse drug reactions. It is a preferred strategy to use background morphine when using IV PCA as it minimizes the dosage of analgesic required [12]. In ambulatory patient's morphine is not the preferred post-operative analgesic [5,44]. Use of Fentanyl causes minimal cortical depression, prolonged respiratory alteration with minimal cardiovascular effects [29]. The clinical characteristics of each opioid will be the consequence of the sum of all these types of distribution as they define its bio availability and spinal effect [31]. The dissipation of opioids following intrathecal administration has been characterized in table 10.



Opioids have been combined with cannabinoids but optimal dose combinations have not yet, been determined. Remifentanil can be used in ICU patients for IV sedation [45]. Dexmedetomidine accentuates the action of opioids by its action on the alpha 2 receptors. [41]. It is also used in ICU for sedation with analgesic sparing. [46]. The biosocial nature of pain should be considered when dealing with pediatric age group as they find it difficult to articulate quantum of pain [22]. Tramadol can be used for mild to moderate pain, and morphine is the choice for severe and intractable pain [12,47]. The higher plasma concentration of oxycodone is due to greater clearance of morphine, in the study where analgesics were given in ventilated patients [25]. Such differential pharmacokinetics makes for optimal choice. The parenteral routes are commonly used but it is beset with pain and other adverse drug reactions.

Perioperative analgesics are provided in lower dosages in elderly patients as they are more prone to adverse effects [5]. There are

still lacunae in the optimal analgesic therapy in geriatrics as often times they are undertreated [5].

Combination of Opioids

Better compliance can be fostered by using effective, rational combinations (opioid+ NSAID/ GABA analogs), reducing pill burden, dosing convenience and reduced adverse reactions [30]. Synergistic analgesic benefits have been noted with opioid +NSAID (30-40%). GABA analogs combination, due to opioid sparing effect that allows better analgesia at low doses of opioid [30,48-53]. The investigators have arrived at the recommendations which should be kept in mind in the choice of an optimal analgesic.

The guidelines for optimizing analgesic therapy

- Assessment of pain and therapy of pain should be in tandem.
- The pain assessment tools should correlate with the cognitive abilities of the individual- i.e. Geriatric and paediatric.
- Analgesic dose titration is mandatory to optimise pain relief and reduce adverse drug reactions.
- Pain being subjective, all measures in communication to be set in place to prevent oversight.
- Consideration of comorbid conditions is mandatory in analgesic decision making.
- Combination of analgesics having varied mechanisms of action is advocated for optimising analgesic therapy.
- Vigilance of concomitant drugs with opioids is necessary to wards off unwanted side effects and ensures the ability to tolerate.
- Varying sensitivity of individuals to opioids is also a moot point in analgesic selection.
- Genotyping for CYP2D6 metabolize status would help in accurate dosing
- Clinical usage of opioids requires the right agent, optimization of dose and at times rehabilitation and physiotherapy for effective recovery.
- A multimodal approach to pain allows for lower doses of opioids with risk reduction.
- The perioperative pain management could be achieved by epidural or intrathecal opioids, systemic opioid PCA and regional technique
- The choice of analgesic and its administration hangs on the anesthetists' competency.
- It is not enough to manage pain through pharmacotherapy, but emotional and behavioral component should also be addressed.
- The Concomitant use of alcohol and opioids lead to dumping syndrome which is a pharmacokinetic phenomenon characterized by unintended, rapid release (over a short period of time) of the entire amount or a significant fraction of the drug contained in a modified-release dosage form.
- combination of opioids with NSAIDs require short duration of therapy as deleterious effects of NSAIDs supervene.

Conclusion

A review of the published data focusing on the pharmacokinetics of opioids brought forth pertinent variations that are critical in making optimal analgesic choice. Analgesic dose titration is mandatory to optimize pain relief and reduce adverse drug reactions. Combination of analgesics having varied mechanisms of action is advocated for optimizing analgesic therapy. Opioid analgesics are widely used but ferreting out the appropriate dose, route and agent is the crux in effect analgesic.

Acknowledgements

Special mention of acknowledgement to Mrs. Prathiba Kamble, for her contribution of the classification of opioids- Vide table 3 to this article.

References

1. UN Office on Drugs and Crime. The international drug control conventions. New York: United Nations 2009.
2. Stefano Berterame, Juliana Erthal, Johny Thomas, Sarah Fellner, Benjamin Vosse et al. (2016) Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study 387: 1644-1656.
3. L A Ladd, P C Kam, D B Williams, A W E Wright, M T Smith et al (2005) Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under imposed hypercapnic and hypoxemic conditions. British Journal of Clinical Pharmacology 59: 524-535.
4. Ducharme S, Fraser R, Gill K (2012) Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician 58: 37-41.
5. Lewis Nelson (2009) Transdermal Fentanyl: Pharmacology and Toxicology, Robert Schwaner Journal Of Medical Toxicology 5: 230-241.
6. Kanwaljeet J S Anand, Douglas F Willson, John Berger, Rick Harrison et al. (2010) Tolerance and Withdrawal from Prolonged Opioid Use in Critically Ill Children. J. Michael Dean, and Carol Nicholson; Paediatrics 125:1208-1225.
7. Sharma V, McNeill JH (2009) to scale or not to scale: the principles of dose extrapolation. Br J Pharmacol 157: 907-921.
8. Zacny JP, de Wit H (2009) the prescription opioid, oxycodone, does not alter behavioral measures of impulsivity in healthy volunteers. Pharmacol Biochem Behav 94: 108-113.
9. V. Pergolizzi, Robert Taylor, Robert B. Raffa (2015) the Potential Role of an Extended-Release, Abuse- Deterrent Oxycodone/Acetaminophen Fixed-Dose Combination Product for the Treatment of Acute Pain.Joseph Advances in Therapy 32: 485-495.
10. Wilhelm W, Kreuer S (2008) the place for short-acting opioids: special emphasis on remifentanil. Crit Care 12 Suppl 3: S5.
11. CF Samer, Y Daali1, M Wagner , G Hopfgartner , CB Eap et al. (2010) The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. British Journal of Pharmacology 160: 907-918.
12. Timothy I Melson, David L Boyer, Harold S Minkowitz, Alparslan Turan, Yu-Kun Chiang, et al. (2014) Sufentanil Sublingual Tablet System vs. Intravenous Patient-Controlled Analgesia with Morphine for Postoperative Pain Control: A Randomized, Active-Comparator Trial. Pain Practice 14: 679-

688.
13. Librach SL (1995) Special issues in pain control during terminal illness. Can Fam Physician 41: 415-419.
14. Gudin JA, Mogali S, Jones JD, Comer SD (2013) Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med 125: 115-130.
15. Noah D Syroid, Ken B Johnson, Nathan L Pace, Dwayne R Westenskow, Diane Tyler et al. (2010) Response surface model predictions of emergence and response to pain in the recovery room: an evaluation of patients emerging from an isoflurane and fentanyl anesthetic. Anesthesia Analg 111: 380-386.
16. Robert H Dworkin, Alec B O'Connor, Joseph Audette, Ralf Baron, Geoffrey K Gourlay et al. (2010) Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update. Mayo Clinic proceedings 85: S3-S14.
17. Vadivelu N, Mitra S, Narayan D (2010) recent advances in postoperative pain management. Yale J Biol Med 83: 11-25.
18. Fallon M, Hanks G, Cherny N (2006) Principles of control of cancer pain. BMJ 332: 1022-1024.
19. Vorsanger G, Xiang J, Biondi D, Upmalis D, Delfgaauw J, et al. (2011) Post hoc analyses of data from a 90-day clinical trial evaluating the tolerability and efficacy of tapentadol immediate release and oxycodone immediate release for the relief of moderate to severe pain in elderly and nonelderly patients. Pain Res Manag 16: 245-251.
20. Rostami-Hodjegan A, Wolff K, Hay AW, Raistrick D, Calvert R et al. (1999) Population pharmacokinetics of methadone in opiate users: characterization of time-dependent changes. British Journal of Clinical Pharmacology 48:43-52.
21. Franke RM, Morton T, Devarakonda K (2015) Pooled post hoc analysis of population pharmacokinetics of oxycodone and acetaminophen following a single oral dose of biphasic immediate-release/extended-release oxycodone/acetaminophen tablets. Drug Des Devel Ther 9: 4587-4597.
22. Allegaert K, Tibboel D, van den Anker J (2013) Pharmacological treatment of neonatal pain: in search of a new equipoise. Semin Fetal Neonatal Med 18: 42-47.
23. Anand KJ, Hall RW (2006) Pharmacological therapy for analgesia and sedation in the newborn. Arch Dis Child Fetal Neonatal Ed 91: F448-453.
24. Krishna Devarakonda, Terri Morton, Rachel Margulis, Michael Giuliani, Thomas Barrett (2014) Pharmacokinetics and bioavailability of oxycodone and acetaminophen following single-dose administration of MNK-795, a dual-layer biphasic IR/ER combination formulation, under fed and fasted conditions Drug Design, Development and Therapy 8:1125-1134.
25. Pascal H Vuilleumier, Ulrike M Stamer, Ruth Landau (2012) Pharmacogenomic considerations in opioid analgesia. Pharmacogenomics and Personalized Medicine 5: 73-87.
26. William W Stoops, Michelle R Lofwall, Paul A Nuzzo, Lori B Craig, Anthony J et al. (2013) Pharmacodynamic Profile of Tramadol in Humans: Influence of Naltrexone Pretreatment. psycopharmacology 4: 427-438.
27. Justin C Stricklanda, Craig R Rush, William W. Stoops (2015) Mu Opioid Mediated Discriminative-Stimulus Effects of Tramadol: An Individual Subjects Analysis. J Exp Anal Behave 103: 361-374.
28. Goodman and Gilman's (2007) pharmacological basis of therapeutics 18: 497-509.
29. Prommer E, Thompson L (2011) intranasal fentanyl for pain control: current status with a focus on patient considerations. Patient Prefer Adherence 5: 157-164.
30. Raffa RB, Pergolizzi JV, Segarnick DJ, Tallarida RJ (2010) Oxycodone combinations for pain relief. Drugs Today (Barc) 46: 379-398.
31. Mugabure Bujedo B (2012) A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat 2012: 612145.
32. Kuo A, Wyse BD, Meutermans W, Smith MT (2015) In vivo profiling of seven common opioids for antinociception, constipation and respiratory depression: no two opioids have the same profile. Br J Pharmacol 172: 532-548.
33. Katsuya Tanaka, Judy R Kersten, Matthias L Riess (2014) Opioid-induced Cardio protection. Current pharmaceutical design 20: 5696-5705.
34. Mao J, Gold MS, Backonja MM (2011) Combination drug therapy for chronic pain: a call for more clinical studies. J Pain 12: 157-166.
35. Kahan M , Srivastava A , Wilson L , Mailis-Gagnon A , Midmer D (2006) Opioids for managing chronic non-malignant pain: safe and effective prescribing. Canadian family physician 52: 1091-1096.
36. Andresen T, Staahl C, Oksche A, Mansikka H, Arendt-Nielsen L, et al. (2011) Effect of transdermal opioids in experimentally induced superficial, deep and hyperalgesic pain. Br J Pharmacol 164: 934-945.
37. Pal D1, Kwatra D, Minocha M, Paturi DK, Budda B et al. (2011) Efflux transporters- and cytochrome P-450-mediated interactions between drugs of abuse and antiretroviral" Life Science 88: 959-971.
38. Mark R Hutchinson, Andrew Menelaou, David J R Foster, Janet K Coller, and Andrew A Somogyi (2004) CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. British Journal of Clinical Pharmacology 57: 287-297.
39. Christina H Liu, Doug N Greve, Guangping Dai, John J A Marota, Joseph B Mandeville (2007) Remifentanil administration reveals biphasic phMRI temporal responses in rat consistent with dynamic receptor regulation. Neuroimage 34: 1042-1053.
40. Krishna Devarakonda, Kenneth Kostenbader, Michael J Giuliani, Jim L Young (2015) Single- and multiple-dose pharmacokinetics of biphasic immediate-release/extended- release hydrocodone bitartrate/acetaminophen (MNK-155) compared with immediate-release hydrocodone bitartrate/ibuprofen and immediate- release tramadol HCl/acetaminophen. Journal of Pain Research 8: 647-656.
41. McCormack SA, Best BM (2014) Obstetric Pharmacokinetic

Dosing Studies are Urgently Needed. Front Pediatr 2: 9.
42. Jakob Lykke Poulsen, Christina Brock, Anne Estrup Olesen, Matias Nilsson and Asbjørn Mohr Drewes (2015) Evolving paradigms in the treatment of opioid-induced bowel dysfunction; Therapeutic advances in gastroenterology 8: 360-372.
43. Wesmiller SW, Henker RA, Sereika SM, Donovan HS, Meng L et al. (2013) The association of CYP2D6 genotype and postoperative nausea and vomiting in orthopedic trauma patients. Biol Res Nurs 15: 382-389.
44. Tuttle CB (1985) Drug management of pain in cancer patients. Can Med Assoc J 132: 121-134.
45. Gommers D, Bakker J (2008) Medications for analgesia and sedation in the intensive care unit: an overview. Crit Care 12 Suppl 3: S4.
46. Davis MP1 (2012) Drug management of visceral pain: concepts from basic research. Pain Res Treat 2012: 265605.
47. Raffa RB, Pergolizzi JV Jr (2012) Intracerebroventricular opioids for intractable pain. Br J Clin Pharmacol 74: 34-41.
48. Nalamachu S, Morley-Forster P (2012) Diagnosing and managing postherpetic neuralgia. Drugs Aging 29: 863-869.
49. Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA et al.(2014) Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Research and Management 19:328-335.
50. Brigden ML, Barnett JB (1987) a practical approach to improving pain control in cancer patients. West J Med 146: 580-584.
51. Marier JF, Lor M, Morin J, Roux L, Di Marco M et al. (2007) Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation. British Journal of Clinical Pharmacology 63: 121-124.
52. Ruben S Vardanyan, Victor J Hruby (2014) Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications. Future Med Chem 6: 385-412.
53. Chandok N, Watt KD (2010) Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc 85: 451-458.