RESEARCH PAPER

Intranasal Drug Delivery of Sedatives and Anaesthetic Agents

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ABSTRACT

Background: Intranasal drug delivery has emerged as one of the clinically significant non-invasive route for the administration of sedatives and the anaesthetic agents, offering rapid onset, improved patient compliance, and avoidance of the first-pass metabolism. This research paper has addressed critical review, Pharmacokinetics, Pharmacodynamics and Clinical use of three common intranasal agents which are used in midazolam, dexmedetomidine and ketamine. Nares mucosa happens to be a highly vascularized mucosa and thus is efficient in its absorption of systems and is also likely to bypass to the central nervous system either through olfactory and trigeminal pathways.

Methodology: It is a literature review article that is concerned with the comparison of bioavailability of such agents, duration of action, time of onset, and safety profile of such agents in children and in adults. The methodology is assessed on a comparative basis, which is based on their effectiveness as a therapeutic tool in multiple clinical scenarios as premedication, procedural sedation, emergency care, and pain management.

Results: It is demonstrated that intranasal midazolam acts fast on the anxiolytic and anticonvulsant effect, dexmedetomidine is the best in the sedation with the least respiratory depression, and ketamine is good in analgesic or dissociative effect of sedation and excellent safety profile. Nevertheless, intranasal with a parameter of dosing and delivering it has been clinically effective. These limitations comprise mucosal irritation, absorption variability and non-standardized formulations.

Conclusion: The article concludes that this type of streamlining delivery procedures and now gigantic size randomized controlled trials is an imperative that would, in turn, be necessary to further implement the accuracy and safety of the dose in the long-term. Anaesthetic Intranasal drug delivery is a revolutionary product in the practice of anaesthetic especially when there is scarce resource and emergency is the topic of discussion.

Keywords: Intranasal drug delivery, midazolam, dexmedetomidine, ketamine, pharmacokinetics, procedural sedation, non-invasive anaesthesia, nasal mucosa, bioavailability, clinical applications

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1. Introduction

1.1 Background and Significance

The administration of sedatives and anaesthetic agents has well traditionally relied on oral, intravenous, or intramuscular routes, each associated with the limitations such as delayed onset, invasiveness, or the patient discomfort.. Among the other alternative approaches that have been popularized as an augmented approach to treatment is intranasal drug delivery technique that is coupled with rapid absorption in addition to easiness of administration. Vacation of nasal cavity and relatively high surface area are the factors which contribute the enhanced absorption of drugs to the systemic circulation (Parida *et al*., 2023). The pathway also avoids the hepatic first pass metabolism therefore improving bioavailability and drug effect.

This is supported by the increased need of the minimum invasive procedures especially in the geriatric and pediatric segment that have encouraged the relative increase in the intranasal delivery systems. Intranasal is effective and quick in providing administration in case of an emergency and pre hospital in case the individuals might need intravenous administration but it is not possible to make the same. This increment of the utilization of this pathway signifies the accomplishment of the formulation science, the delivery gadgets and pharmacological data.

1.2 Anatomical and Physiological Basis

These areas are named so because of the various functions they serve in drug absorption, Nares, including the parts of the resting area, respiratory, and olfactory. It mainly leads to systemic absorption at the respiratory region where the lining of the ciliated epithelium and cross-pulmonary massively filled vessels (López-Ramis *et al*., 2022). Introduction of auto drugs into the brain does not go through the blood-brain barrier and the process is facilitated by the olfactory which helps to circumvent the blood-brain barrier and as such, be able to administer the drugs straight into the brain. This reciprocal process is what increases the action of the central acting drugs of confidence, including tranquilisers and anaesthetics.

The residence time of the drug and its absorption capacity depend on the mucosal clearance, enzymes and nasal secretions. Others like pH, viscosity and molecular weight embraced in formulations are also very important to pharmacokinetic outcome.

1.3 Scope and Objectives

This research focuses on three key intranasal agents: midazolam, dexmedetomidine, and ketamine (Ingielewicz *et al*., 2024). These are to subject their parabolises values, the clinical use of the multiple types of medical practice or the absence of the same as well as the restriction and the future of the intranasal drug delivery systems.

2. Literature Review

Perri (2025) states intranasal analgesia is the new wind of change in treating pain in children, especially in neonates, both term and preterm, because invasive pathways are dangerous in the case of neonates. The paper highlights the fact that the pain in neonates has both physiological and behavioural outcomes, but its management has not been properly addressed because of the focus on safety and drug metabolism. The author shows that intranasal intake offers a non-invasive, fast and useful approach, which avoids hepatic first-pass metabolism saving time, facilitating analgesia. The review highlights the application of intranasal agent like fentanyl and midazolam in the neonatal intensive care unit and reveals its better suitability in improving the comfort of the procedure like venipuncture and intubation. The issue of pharmacokinetics in neonates is essential because the organ systems are not fully formed, and the author explains how intranasal administration ensures predictable absorption in spite of these constraints. Issues in safety that have been reported in the research show that there were slight incidents of respiratory depression as well as tolerability; nevertheless, close dosing is vital. The research also reveals a lack in standard protocols and recommends the need to investigate further clinical trials that can determine the best dosage regimens. In general, the study can be regarded as a part of the developing literature that advocates the use of intranasal routes as an effective and less harmful method of neonatal analgesia and finds the application in enhancing the effectiveness of clinical procedures and minimizing the levels of stress of the procedure in immunodeficient patients.

Due to the comparative analysis of intramuscular and intranasal dexmedetomidine administration in a cat during total intravenous anesthesia (propofol), Hommuang (2022) informs about the relevance of conducting a comparative study that determines the quality of sedation and physiological stability. The paper illustrates that intranasal delivery also has similar sedative effects to intramuscular delivery and has the benefit of being less invasive. According to the author, dexmedetomidine, being an alpha- 2 adrenergic agonist, has the result of sedation, analgesia, and muscle relaxation, without causing severe respiratory depression. Intranasal delivery had been linked to easier induction and recovery stages proving it as an appropriate method of veterinary anesthesia. Cardiopulmonary parameters such as heart rate and blood pressure were analysed and showed mild bradycardia with no clinically significant complications with regard to the pharmacological effect of the drug. These results indicate that intranasal dexmedetomidine has a potential of alleviating stress related to injections, hence enhancing animal welfare. The inconsistency in the absorption based on nasal mucosal condition is also explained as well as it is essential to address the essential importance of appropriate methods of administration that should be applied. Based on the conclusions made by the author, intranasal dexmedetomidine proves to be a good substitute to intramuscular infections, especially when minimal distress and handling are in the agenda.

Keller (2022) states that the intranasal method of drug delivery has significant potential in contemporary pharmacotherapy and poses significant toxicological issues during drug development. The author presents a detailed discussion of the nasal route as an entry point to the systemic and central nervous system drugs, indicating the benefits of the route to be speedy onset, non-invasive, and lack of first-pass metabolism. The paper examines the formulation methods such as nanoparticles, mucoadhesive systems and permeation enhancers that enhance drug absorption and stability. Nevertheless, the author reiterates that the nasal

mucosa is a delicate and complicated biological barrier and chronic exposure to particular formulae can result in irritation of the mucosal lining, inflammation or chronic toxicity. The regulatory considerations as well are mentioned, in particular, the necessity of strict safety testing and standard testing procedures. The research paper cites issues in the laboratory to clinical scaling up of injectable formulations, such as inconsistent dosing and injection devices. The author emphasizes the necessity of achieving effectiveness and safety, especially in chronic treatment. In general, the review contains important details of the perspectives of intranasal drug development that should be innovational and toxicological considerations should be taken seriously.

Yanmaz (2022) states that the combined application of midazolam and dexmedetomidine through intranasal and intramuscular injections was used in rabbits to offer valuable data concerning the quality of sedation and the cardiopulmonary outcomes. The clinical trial proves that intranasal delivery has equal effectiveness to intramuscular injection and the added advantage that is less intrusive. The author notes that benzodiazepine and alpha-2 syntactically formed agonists work effectively to increase the degree of sedation without negatively affecting physiological stability. The cardiopulmonary monitoring demonstrated little signs of a drop in heart rate and respiratory rate, which is expected in terms of the pharmacological implications of the medications, although there were no serious adverse effects. Its intranasal route showed easier administration and less stress on animals, which serves to suggest broader use of the intranasal route of delivery in veterinary practice. Another issue dealt with in the study is the significance of optimizing dosage and the method of administration as a means of administering drugs in a constant manner. The results Favor the application of intranasal mixes as a feasible option to the conventional injection procedures especially in contexts where it is preferable to keep the insects as small as possible.

Gao (2024) states that the emergence of a new nasal spray of dexmedetomidine is one of the most important innovations in pre-operative pediatric sedation. The randomized, double-blind, placebo controlled trial indicates that the nasal spray formulation is an effective method of sedation that has a good safety profile. According to the author, the children who were exposed to intranasal dexmedetomidine had a lower anxiety, enhanced cooperation and stable hemodynamic parameters than those who were exposed to the placebo group. The paper demonstrates the significance of formulation design in improving the absorption and acceptability of the drugs by the patient. The nasal sprayer will provide proper dosing and equal distribution of the vitrine, which is a limitation to the drop-based method of administering the substance. The safety results show that there were few respiratory depression cases, and the cardiovascular effects of this drug were mild and transient (bradycardia). The author points to the fact that intranasal dexmedetomidine is especially appropriate in the context of pediatric patients because it is non-invasive and easy to use. This research paper has concluded that the new nasal spray preparation can become a standard premedication technique in the field of pediatric anesthesia, awaiting further massive confirmation.

Breitenlechner (2024) asserted that the intramuscular and intranasal injection of sedative medications in piglet castration is an important study of animal welfare and efficiency of the procedure. Its analysis confirms that intranasal injection represents a more comfortable method of delivery as compared to intramuscular injection and it lowers the costs caused by handling piglets, which can be a little traumatic. According to the author, the intranasal method of sedation has reached the same effect as intramuscular delivery, and the degree of immobilization and pain during the procedure is sufficient. The results reveal the importance of intranasal delivery in enhancing the ethics of veterinary practice, especially in practices that involve the occurrence of much suffering. Both routes did not have any significant difference in terms of physiological parameters, so intranasal initiation does not harm the safety. Other issues of concern that are talked about in the study are ease of administration, cost-effectiveness, and scalability in farm environments. The author implies that intranasal sedation may be an effective method of improving animal welfare and simultaneously preserving effective procedures and that it can be applied in a broad spectrum of veterinary procedures.

3. Methodology

3.1 Research Design

The present study adopts as one of the systematic review-based analytical research design aimed at synthesizing and well critically evaluating existing scientific evidence on the intranasal drug delivery of sedatives and anaesthetic agents, specifically midazolam, dexmedetomidine, and ketamine. The construction of the same included qualitative and quantitative components to offer a comprehensive

study of the pharmacokinetics, pharmacodynamics and its clinical functioning (Perri *et al*., 2025). The systematic review methodology represents a type of transparency, minimization and bias oriented, reproducible identification, selection, and analysis of the literature in question.

The accepted systematic review in the form of protocols will be the research design and Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA). It will be conducted in a series of procedures that involve identification and screening of the studies against the set eligibility criterion, the research methodology and consequently synthesis of the results. The specified methodology allows conducting the factual assessment of the evidence base under consideration and is employed to assure the consistency in case of various types of research.Multi database search strategy would be applied because literature would be covered as much as possible (Hommuang *et al*., 2022). Electronic databases, such as PubMed, Scopus, and Web of Science, were used as the selection criteria due to the fact that the databases boasts of a high indexing rate of biomedical and pharmacological research. Peer-reviewed journal articles and all such databases can be accessed and thus assure the quality science evidence. The limit of search has been set at 2000- 2025 so as to obtain the latest tendencies in the intranasal drug delivery systems and in the aspect of pharmacology.

The search instrument included a Medical Subject Headings (MeSH) word, and the free-text key-words. It was done using keywords (intranasal drug delivery, midazolam, dexmedetomidine, ketamine, pharmacokinetics, bioavailability, procedural sedation and nasal absorption). Getting more precise, the AND, OR and NOT operators were applied to narrow the down the results of the search. As a demonstration, the following and relevant search terms were used to obtain the relevant studies: intranasal AND midazolam AND pharmacokinetics and dexmedetomidine OR ketamine AND intranasal sedation.In the study design, the descriptive and analytical factors come in play. The latter is the descriptive part that is connected with the summary of the key pharmacokinetic parameters and clinical results, and the latter implies the comparative analysis of the three chosen agents in various aspects (Keller *et al*., 2022). The whole process makes it possible to determine the patterns, trends, and variations in the performance of the drug in the environment of the existence of various conditions in a clinical set-up.Methodological rigor was assessed with the assistance of standardized means, through quality assessment of the included studies. Trials requested were considered and analysed by Cochrane Risk of Bias and trials that were observational analysed by Newcastle-Ottawa Scale. These tools might be embraced to assess the design of the study in a systematic manner and sample size, data collection procedure, and bias regions. Any doubt about Research papers of low methodological standards or high risk of bias were filtered.

The elements of the pharmacological modelling and comparative analysis are also represented in the research design. The pharmacokinetic properties, e.g. absorption rate, maximal plasma concentration, half-life, et cetera, were compared with the clinical data. It is due to such combination of clinical assistance and the pharmacological information that the interpretative worth of the study is created.Other than this, the study design recognises heterogeneity as far as the study population, dose and mode of delivery is involved. They were compared with their sensitiveness to the demographics of the patients (age, comorbidities and clinical settings) so that the situation is also pertinent. They have been conducted in the sub group analysis which has sufficient evidence especially in the pediatric versus the adult population.It already been considering the ethical requirement through the assistance of the already released information hence, such data do not involve a real involvement of a patient. The paper fulfils the principles of academic ethics and represents and cites the sources correctly.In general, the study design is a good example of assessing the intranasal sedative and anaesthetic agents, in which the analytical power, along with the systematization of the literature analysis, supplies the researcher with the data pertinent to the clinical practice.

3.2 Inclusion and Exclusion Criteria

These inclusion criterion were also narrowed down to give option on the studies, which would be taken in this study because it requires that the study be relevant, reliable and consistent (Vajdi*et al*., 2023). The identification criteria upon which the literature search was founded on were determined in advance to make the selection bias as minimal as possible and increase the effectiveness of the methods.

The inclusion criteria included that the research article contained the direct project on intranasal midazolam, dexmedetomidine, or ketamine in a human being. Randomized controlled trials, quasi experiments, cohort studies, case controls and pharmacokinetic studies could be offered. Others were systematic

reviews and meta-analyses that could be used to give a cumulative data and the general opinion of the clinical outcomes.

The following parameters were mandated to be reported in order to be incorporated in the studies i. e. bioavailability, onset of action, duration of sedation or analgesia, clinical efficacy or adverse effects. This requirement was applied to guard that included research studies found significant information to the research targets (Breitenlechner *et al*., 2024). The research performed was also done in both hospital and pre-hospital ensuring that no application of the research was overlooked in terms of its use in the clinic.

The language restrictions were applied to reduce the number of studies to interpret the research results and analyze them properly because only English was utilized in the research. It omitted the overly antique publication date with the most recent publication date of 2025 that encompasses the most recent trends in the compositions of drug developments, the delivery method, as well as the clinical practice.

The exclusion criteria as well were not liberal enough as to make the analysis sound. The lack of use of the non-human subjects in research was based on the variations in anatomy of the nose, speed of drugs and generalizability (Fan *et al*., 2025). Other types of studies in which different routes could not be taken like oral, intravenous and intramuscular route were deleted unless comparative figures were also given with that of intranasal route.

The researchworks that were omitting the adequate pharmacokinetic/clinical outcome data were jettisoned as it could not permit the objective of the test. Another added filter was also the case reports whose sample was very small, that were further off-puttable except when there is something novel or in clinical interest. Through critic strictness the overlaps of the publication and other related studies were brought out to avoid making mistakes.

Only when experimental preparations of the studies were yet not approved that discrimination of proceeding to clinical practice did not form any part unless it contained pharmacokinetic information that could prove of any usefulness to that practice of the kind meant (Okur *et al*., 2023). Moreover, the reviews in which the formulation of drugs had been assessed in isolation with no clinical examination or pharmacokinetic analysis had been examined were omitted.

The sampling plan consisted of a two-step screening so that there were fewer options. The screening of titles and the abstracts through which potential relevant studies were determined was carried out. The second step featured Collision of the entire text articles with the inclusion and exclusion criteria. Consensus assessment was done to remove disagreements in the selection of the studies.

These criteria led to a pool of quality researches which generated a whole picture of intranasal delivery of sedatives and anaesthetic drugs. Through such stringent and rigorous form of selection, the results of the study in progress will be based on sound and clinically applicable evidence.

3.3 Data Extraction and Analysis

The process of data extraction and analysis was to get, compile and interpret data in an organized way with regard to the information of interest in identity of the chosen studies. A general data extraction framework was created in order to have the possibility to standardize and be accurate in all the studies that had been included (Cinar *et al*., 2024).

The extraction of the data was performed through the use of a structured template, which included significant variables including the research design, size of the study, demographic variables of the patients, the pharmaceutical, dosage, drug formulation, drug delivery vehicle, pharmacokinetic parameters of the research, clinical outcomes, and the adverse effects. Each and every study was carefully browsed and tabulated information related to the research was made in the table in order to make them easy to compare and synthesize.

One of the important analysis elements was pharmacokinetic parameters. The determination of bioavailability was done to establish what percentage of the drug was taken to the systemic circulation. The period during which the administration had been performed and onset of the clinical action and duration of action have been put into consideration in order to determine the persistence of the therapeutic action of the medications (Mauthe von Degerfeld *et al*., 2023). Peak plasma concentration had also been taken into account and time to peak concentration had also been taken in the case available.

The chart based evaluation approach was used to evaluate clinical efficacy of the study based on the result indexes (sedation score, pain reliever, successful success of the procedure and patient satisfaction). The most of the studies also used the standardized tools of assessment such as the sedation scales and the pain scoring system drafted during the analysis. The effects were classified depending upon the severity and prevalence particularly regarding

respiratory depression, the effects hemodynamic and irritation of local nasal.

The method of analysis was qualitative synthesis and quantitative comparison analysis. The qualitative analysis of the data was synthesized with the aim of determining the common themes, tactics, and inconsistencies of the studies. The comparative analysis involved likelihood of summing the numerical information and enabled the comparative discourse of the pharmacokinetic and clinical variables.

Also a comparative analysis was done to explore the comparative performance of the Midazolam, dexmedetomidine, and ketamine in various clinical scenarios. Comparison of onset time, duration of action and safety profile parameters or measures were done in order to determine what agent is the most suitable to be used. The subgroup analysis was conducted on the method of studying the differences in results depending on the age of the patient, medical setting, and pharmaceutical treatment.

The analysis had provided the required attention to the study diversity. The difference in the styles of study, sample size and measurement methods was considered and the influence of the factors was determined in the results obtained (Tahmasbi *et al*., 2023). Great caution was exercised in the results on the occasions where high degree of heterogeneity was observed and no extra priority was given to the objective of finding consistent trends and not some absolute values.

This also was done alongside data synthesis to improve reliability through cross-referencing the outcome of different researches. The consistency was also seen as high in the sense that the outcomes of the various types of study designs and population were comparable. The analysis of the conflicting results was conducted regarding the differences in the process and the possible bias.

The statistical analysis has been applied at a time when there were adequate data to be conducted with it like determining the mean values, SDs and CI. The fact that there was, however, lack of time to do a complete meta-analysis was not unfortunate as different reporting forms and outcome measures were used. Rather, it has used a method of synthesis of the findings which utilizes a narrative way of integrating the findings in a significant and integrated way.

It also played a role in the course of analytical process where analytical relevance of findings was formulated. The interpretation of the pharmacokinetic parameters was performed according to practicability in the real life scenario (administration and adherence) and safety in administration (Abusinna *et al*., 2022). Through this, the study will not only be a mere provision of theoretical information, but will have some contribution towards the clinical decision making.

To conclude, data extraction and analysis can be defined as a systematization of data, full assessment and comparative interpretation of evidence. The specified methodology will allow the assessment of intranasal sedative agents, and anaesthetics in comprehensive key that will become the strong point of the further argumentation and conclusions.

4. Results and Analysis

4.1 Pharmacokinetic Profiles

The pharmacokinetic evaluation of intranasal midazolam, dexmedetomidine, and ketamine reveals distinct absorption patterns, onset times, and also the duration profiles that significantly influence their actual clinical applicability.. The absorption tendency is also augmented as intranasal midazolam is very lipophilic and this implies that it is well absorbed and diffused to the nasal mucosa. It is fast acting and gets the highest plasma concentrations normally in a range of 8-12minutes. Intranasal delivery of midazolam is bioavailable with varying ways of delivery formation 55-83 percent. Its half-life is not quite long (in general: 1.5 to 3 hours), and it may be applied to short-duration procedures.

The dexmedetomidine, in its turn, possesses slow absorption profile and its absorption is slower when it is used via a nasal route. The highest plasma concentration occurs at an average time of 25-45 minutes of administration (Jain *et al*., 2023). It has a decent absorption and derivation to bioavailability of 60 to 70 percent. Although it takes a longer time to induce sedation, dexmedetomidine offers a longer duration of sedation since this agent has a long elimination half of 2-3 hours. The agonism effect was the alpha -2 adrenergic receptor which has a long-term history of sedation and anxiolysis with restricted respiratory decompensation.

Median level of pharmacokinetics of ketamine is represented. It is reported that the highest plasma level of ketamine using the intranasal route is reached in the shortest possible time, ranging between 10 to 20 minutes. Its intermediate bioavailability between midazolam and dexmedetomidine (45 to 50 percent) is caused by an imprecise bioavailability through the first-pass metabolism and unreliable through the intestinal mucosa absorption (Dwivedi *et al*., 2022). Its effectiveness provides a lesser time than

dexmedetomidine and protracted duration than midazolam in a small number of cases and the half period of eradication is around 2-4 hours. The use of the Ketamine also results to its extreme usefulness in analgesia and dissociation as it penetrates the central nervous system in a high rate.

The difference between the pharmacokinetic properties of such agents justifies the effect of molecular design, receptor-affinity, and formulation properties. Oral route circumvents orally without significant hepatic first-pass metabolism and this characteristic increases the surrogate bioavailability and decreases variability compared to intranasal administration. The Natal congestion, mucocele clearance, and effectiveness of the delivery device are some of the factors that increase inter-individual variation in absorption in a better way.

4.2 Clinical Effectiveness

The clinical effectiveness of intranasal sedatives and anaesthetic agents is well determined by their ability to achieve desired sedation or the analgesia within an particular appropriate timeframe while maintaining patient safety. It is also a well-known fact that midazolam is absorbed intranasally much faster and, thus, is most often used in situations when the goal is to provide the patients with the state of full sedation. It is at this point that it finds its application specifically on the short activity where there is major operations, dental operations as well as imagological tests. It influences its anxiolytic and amnestic effects leading to an increase in compliance among the patients particularly in case of a paediatric population.

Dexmedetomidine has been proved to be more ideal in the procedures which include lengthy and continuous sedation (Preethy *et al*., 2022). It has a strong natural sleep effect of sedation that allows the patient to be easily aroused and be in acceptable level of sedation. This property is more convenient to the investigative process like the magnetic resonance imaging and scans computer tomography whereby the patient is expected to remain motionless over a long period of time. Moreover, dexmedetomidine produces minimal reaction on the breathing systems thus be utilized on patients with poor respiratory functions.

The ketamine can be characterized by the strong clinical efficacy regarding the cases when the conditions involved are not only the sedation but also the analgesia. Its dissociative effect correlates with good analgesia and sedation at the same time hence its applicability during the emergencies, which come in the form of trauma, fracture reduction and burn care. Other possible applications are huge cases of intranasal ketamine in cases that occur in pre-hospital settings where speedy painkilling is necessary, but entry to the intravenous system is not key (Abdelraheem *et al*., 2023). It is also added that the drug can preserve the airways reflex which also contributes to the application in the emergency medicine.

The comparative analysis of the mentioned cases shows that midazolam is the most suitable in the scenario when the speedy and temporary mode of action needs to be used, dexmedetomidine needs to be used when the process should take more than a couple of hours and the constant sedation needs to be ensured, and ketamine should be used when both supreme analgesics and stabilizing effects are important. The evaluations of agent as such are closely connected with procedural demands and with the aspect of patient.

4.3 Safety and Adverse Effects

The utility of intra nasal anaesthetic agents is highly determined by their safety profile which is very severe; a critical determinant. Midazolam nasal can also result in low respiratory depression especially when the patients are on high doses of the drug or using it alongside other drugs with an ability to cause CNS deprecations (Srivastava *et al*., 2024). The pH and excipients in the formulation normally cause irritation, burning and sneezing at very few occasions. These are the effects with the least prevalence of right dose instructions are the severe complications.

When used as an alternative to other sedatives, dexmedetomidine is an adequate sedative with a tolerable safety level minimum respiratory depression. The way it reacts on the cardiovascular system however can cause bradycardia and hypotension especially in people who have a heart disease. These are dose-related and they are in most aspects dysfunctional and clear independent of any considerable intervention.

Ketamine has a catalo of the side effects in specific and had been linked to the central nervous system. Among the transient psychotropic effects in the adults are hallucination, vivid dreams, emergence reaction and others. Other things that are common on the list include the enhancement in salivation and mild tachycardia. Nevertheless, ketamine is not linked to respiratory depression but it does not inhibit airflow reflexes hence, it is a drug of choice where there is need to administer in emergency and pre-hospital setting.

The adverse effects of intranasal usage (iritis, discomfort of the mucosa) are topical, and are

administered to all three of the agents, though are normally mild and self-limiting (Lepel tier *et al*., 2022). The nature of the safety of the two agents indicates that both of the agents have their respective side effects but both may be utilized in the clinical practice with a recommendation on the therapy and dosage of the drug taken.

4.4 Comparative Outcomes

The comparative analysis of the intranasal midazolam, dexmedetomidine and ketamine represents that each agent has a distinct pharmacological feature that would qualify the agent to a given clinical case. The parameters of an agent are never ideal on any side of the agent, which is a factor that promotes the concept of selective operation with regards to circumstances.

The fastest in onset of action thus highly effective in case there is need of immediate sedation is midazolam. It also has a negative aspect in it in the fact that it has less duration and can result into respiratory depression hence constraining its use in the long running operations (Mauthe von Degerfeld *et al*., 2023). The one is dexmedetomidine, which offers both long-term and constant sedation and has minimal effects on respiration, but the slow development of its effect is the one that did not succeed as the best option in the state of emergency. Ketamine has a good balance profile with a rapid onset and a high analgesic but its psychotropic component would not allow its usage on some selective patients.

Regarding the combination of pharmacokinetic and clinical evidences, the most successful results were obtained when the selection of an agent was assigned to the specifications of a particular procedure, information about a particular person, and safety concerns (Tahmasbi *et al*., 2023). The combination therapy may as well be applied to leverage the strengths of a combination agent despite limiting the drawbacks of a particular instance in order to overcome its weakness.

Table 1: Comparative Pharmacokinetic and Clinical Parameters of Intranasal Agents

Parameter	Midazolam	Dexmedetomidine	Ketamine
Bioavailability (%)	55–83	60–70	45–50
Onset Time (minutes)	8–12	25–45	10–20
Peak Plasma Time (minutes)	10–15	30–45	15–20
Duration of Action (hours)	1.5–3	2–4	1–3
Elimination Half-life (hours)	1.5–3	2–3	2–4
Primary Clinical Use	Short sedation	Prolonged sedation	Analgesia + sedation
Respiratory Depression Risk	Mild	Minimal	Minimal
Cardiovascular Effects	Minimal	Bradycardia, hypotension	Mild tachycardia
CNS Effects	Sedation, amnesia	Sedation	Dissociation, hallucination
Local Nasal Effects	Irritation	Mild irritation	Mild irritation

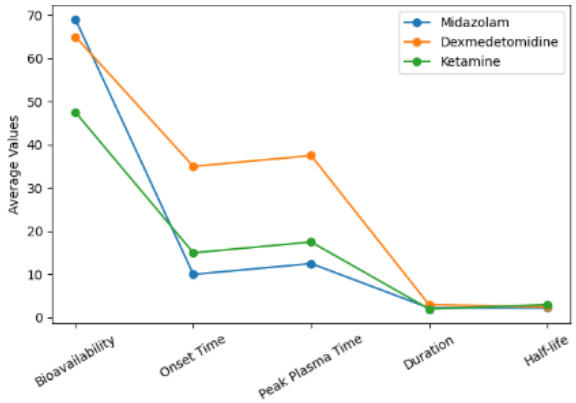

Figure: Comparative Pharmacokinetic and Clinical Parameters of Intranasal Agents

5. Discussion

5.1 Clinical Implications

Intranasal delivery of drugs has some attractive strengths as far as patient comfort level, rapid cameo and direct delivery levels are concerned (Abusinna *et al*., 2022). The opportunity of administering sedatives without access and by an intravenous method of administration gives the app the justifiable domain to the outpatient and emergency backdrop.

5.2 Limitations of Current Practice

Problems of variability in the absorption of the various nasal pathology also exist, lack of homogenous dosing systems and inconsistency in the formulation. The efficiency of spraying and particle size make also such issues of devices, which depend on drug delivery.

5.3 Technological Advancements

Stability and absorption increase of the drugs has been enhanced by the development of the nanoparticles based preparations, mucoadhesive gels, aerosol equipment in form of metered dose. The inventions will make intranasal delivery systems more reliable (Jain *et al*., 2023).

5.4 Future Research Directions

More studies should be conducted to formulate such universal dosing schedules, formulations and the long term safety as well (Dwivedi *et al*., 2022). To proof the widespread use, it is reported to need massive clinical trials and pharmacoeconomical research due to its broad use.

6. Conclusion

Intranasal drug delivery represents a significant advancement in the administration of sedatives and anaesthetic agents. The pharmacokinetic and clinical strengths all midazolam, dexmedetomidine, and ketamine possess could be applied to the various clinical requirements. The fact that it is non-invasive, quick acting, and offers the user better response makes its use as an alternative route acceptable in comparison to the standard routes, rendering the consideration of its usage as an alternative route over conventional one a valid possibility. Nevertheless, this application is not unlikely to receive improvements in the clinic, regardless of its inefficiency at present, due to the current research and technological development. Intranasal drug delivery as a practice that has been introduced can be applied to improve patient outcomes in scenarios where the practice is practiced in the environment of emergency and resource strained.

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