

## **KetaDex 12.5/25 Nasal Spray: A New Sedative-Analgesic Formulation**

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### **Abstract**

Intranasal administration offers an alternative route for systemically acting drugs, especially low molecular weight, lipophilic and potent drugs with high first-pass metabolism. It's well recognized that nasal bioavailability is optimum with atomized volumes less than 100 microlitres (0.1 ml), available ampoule content therefore has limited nasal residence time, absorption and bioavailability due to excess volume that drains into the throat and is swallowed. Ketadex nasal spray offers additive effects of sedation, analgesia, bronchodilation with nasal decongestion and dilation of cutaneous veins for cannulation. Opposing side effects produce dry mouth, reduced secretions and cardiovascular stability. A wide margin of safety is predicted because both ketamine and dexmedetomidine are devoid of respiratory depressant effects. We present an easy to administer nasal spray, concentrated (3.75x) ketamine and dexmedetomidine solution to produce reliable sedation and analgesia with minimal adverse effects due to favourable pharmacokinetic and pharmacodynamic interactions.

**Keywords:** *Ketadex Nasal Spray; Ketamine; Dexmedetomidine*

### **Introduction**

The quest for an ideal procedural sedative with predictable onset, reliable effects, low adverse event profile and fast track recovery continues [1]. Sting of injection, unpleasant taste, inadequate sedation, agitation, delirium, movement, airway events, including saliva/mucus aspiration, coughing, laryngospasm, over-sedation with dynamic airway collapse, respiratory depression, nausea and poor quality recovery are some of the collective hazards of procedural sedation induced with benzodiazepines, opioids, ketamine and/or propofol. Psychodysleptic effects associated with ketamine can generally be avoided by co-administration of propofol and meticulous technique [2].

Clonidine was developed as a nasal decongestant in the early 1960s and noted to have unexpected side effects of sedation and sympatholysis. Another  $\alpha_2$ -adrenoceptor agonist was first registered in 1999 for short term ICU sedation, dexmedetomidine also has unique properties that render it suitable for sedation and analgesia during the perioperative period. It has applications as a premedication, as an anaesthetic adjunct for general and regional anaesthesia, and as a postoperative sedative similar to those of the benzodiazepines, but a closer look reveals that this  $\alpha_2$ -adrenoceptor agonist has more beneficial effects [3]. Additionally, procedural sedation with dexmedetomidine was approved by the US Food and Drug Administration (FDA) in 2003 and dexmedetomidine has appeared useful in multiple off-label applications including intranasal and buccal administration [4,5].

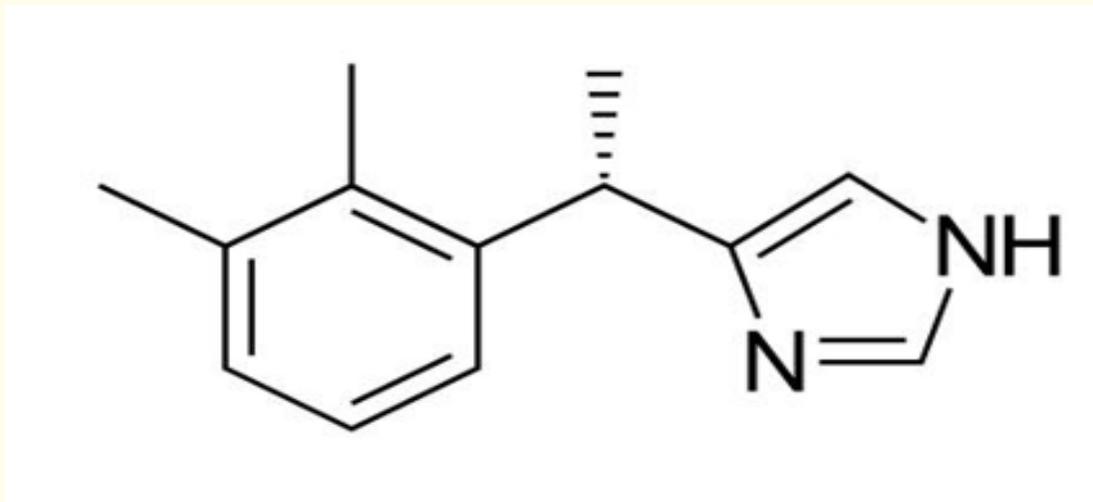
Procedural sedation is being performed more often in modern healthcare settings. There's a larger array of diagnostic and interventional procedures with on-going development of less invasive procedures involving radiologic imaging, endoscopic and catheter-based techniques. Procedures can be associated with significant anxiety and discomfort, particularly for paediatric and special needs patients [6-8].

Fear of medical procedures often has origin with bad memories or imagination related to the anaesthetic face mask, needles, sharp instruments and associated catastrophic thoughts of being hurt. Commencing healthcare procedures by restraining an upset child is not ideal in the 21<sup>st</sup> century. A better way is safe and effective premedication to minimize alertness, discomfort and distress and avoid unfavourable experiences. Pre-emptive sedation and analgesia mean procedures like mask induction, intravenous cannulation, local anaesthetic injection, burn, wound and fracture management are less stress for patients and caregivers.

Some advantages of intranasal premedication compared with oral administration are, no swallowing and limited cooperation needed, minimal taste disturbance, independent of fasting guidelines or gastro-intestinal tract function. Intranasal bioavailability is optimum with atomized volumes less than 100 microlitres (0.1 ml) [9-11]. Therefore existing ampoule concentrations administered intranasally mostly runoff into the throat and are subjected to first-pass metabolism. KetaDex intranasal provides a concentrated solution with minimal atomized volume that enhances nasal residence time, absorption and bioavailability.

### Dexmedetomidine

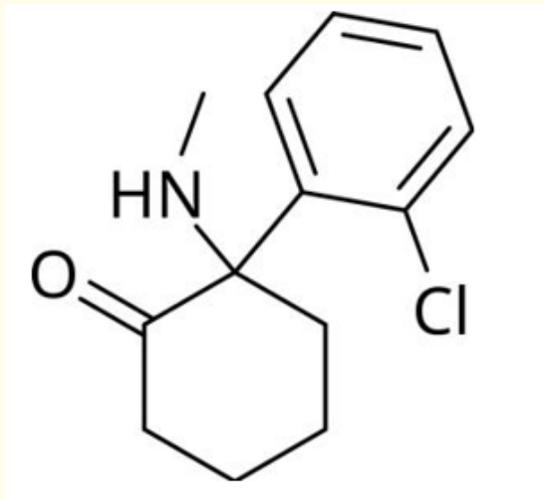
Dexmedetomidine is an  $\alpha_2$ -adrenoceptor agonist with sedative, anxiolytic, sympatholytic, and analgesic sparing effects, and minimal depression of respiratory function. It is potent and highly selective for  $\alpha_2$ -receptors with an  $\alpha_2$ : $\alpha_1$  ratio of 1620:1. Haemodynamic effects, which include transient hypertension (with intravenous administration), bradycardia, and hypotension, result from the drug's peripheral vasoconstrictive and sympatholytic properties. Dexmedetomidine exerts its hypnotic action through activation of central pre- and post-synaptic  $\alpha_2$ -receptors in the locus coeruleus, thereby inducing a state of unconsciousness similar to natural sleep, with the unique aspect that patients can remain rousable and cooperative [3-5].



**Figure 1:**  $C_{13}H_{16}N_2$  Molecular Weight 200 g/mol log Poct/wat: 2.8.

## Ketamine

Having been in use for more than 50 years, racemic ketamine has proven to be a safe dissociative anaesthetic drug with potent analgesic properties even at much lower doses. It has been widely used to induce sedation and hypnosis, because of the preservation of cardiovascular and respiratory functions, and in the context of an emergency, because it allows the preservation of airway tone and reflexes [2,12,13].



**Figure 2:**  $C_{13}H_{16}ClNO$  Molecular Weight 237 g/mol log *Poct/wat*: 2.9.

The psychodysleptic effects explain a fall in ketamine use during the 1980s. But during the 90s, its peculiar anti-hyperalgesic properties renewed the interest for this agent, which reduces acute opioid tolerance and opioid induced hyperalgesia [14] in the context of postoperative pain. More recently, a rapidly acting anti-depressive activity has been demonstrated that may participate in the recovery from acute injury and chronic pain syndromes [12,13].

### The ketamine and dexmedetomidine combination

The favourable properties of these two drugs are additive, whereas adverse effects tend to antagonize each other. The effect of sedation and analgesia is additive, both of the drugs preserve spontaneous respiration, airway tone and patency. On the other hand, cardiovascular stimulatory effects of ketamine counterbalance the hypotension and bradycardia that may occur with dexmedetomidine. Dexmedetomidine prevents ketamine induced salivation, psychodysleptic effects and emergence complications [15]. The recovery profile of this drug combination is good, calm and comfortable without undue delay.

The combination of ketamine and dexmedetomidine has a predicted wide margin of safety because both drugs support spontaneous respiratory drive. Moreover, intranasal administration results in a smooth rise in plasma concentrations without high peaks as with intravenous infusion that would be associated with adverse effects such as transient hypertension and hallucinations (Figure 5). Intranasal dexmedetomidine acts as a nasal vasoconstrictor/decongestant for several hours which slows the absorption of both drugs, improves the nasal airway and reduces airway secretions.

### Clinical use of unregistered and off-label medicines

Therapeutic Goods Administration (TGA) registration is based on the results of extensive clinical trials and a lengthy drug development and approval process for detailed assessment of quality, safety and efficacy. Because of the huge cost and time involved, pharmaceutical companies do not attempt to gain approval for less common uses and routes of administration. Fortunately, the TGA recognizes that clinicians are permitted to use their professional judgment as to the use and administration of an unregistered medicine when equivalent registered alternatives are not available. Examples of unregistered medicines in frequent clinical use in the operating theatre are pharmacy compounded oral midazolam 2 mg/ml, compounded local anaesthetic infusion solution, amethocaine gel 4% (Local AnGel® RCH), and cocaine 10% 1ml with adrenaline 1 ml 1:1000 (Moffett's solution).

Off-label medicine use, most drugs used for sedation in children do not carry paediatric information that has been reviewed and approved by government authorities and as such, these drugs are used off-label. An audit has found that out of 106 drugs administered during anaesthesia to paediatric patients from an operating room pharmacy, drugs were administered off-label in about 73% of cases [16]. FDA guidelines for off-label use state that if clinicians use a product for an indication not in the approved labelling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects [16].

Off-label use also includes the use of routes of administration that are not contained in current drug information [16]. Clinicians often trial innovative off-label use of medicine in order to benefit their patients, and this has led to the development of a concentrated formulation (a multiple of 3.75x compared to available ampoule supply) of ketamine and dexmedetomidine nasal spray to effectively reduce pain and distress associated with patient's healthcare procedures.

### Intranasal drug delivery [9-11]

The nasal mucosa provides a practical entrance portal for systemically acting molecules. The nasal route is especially useful for the administration of low molecular weight, lipophilic drugs with high potency. Intranasal administration offers relatively rapid onset of therapeutic effects, avoids the first-pass metabolism and gastro-intestinal degradation of drugs, is non-invasive, essentially painless and easily administered by patients, nurses or physicians.

Nasal atomizers will deposit most of a spray into the anterior region of the nasal cavity. Surface tension of the droplets on the mucus layer will cause the immediate spread of the deposited drug solution. Afterwards muco-ciliary clearance will distribute the liquid layer within the nasal cavity. The nasal mucus layer is continuously renewed and discarded into the throat, the nasal residence time of an administered drug will depend on any initial runoff of excessive volume, how fast it dissolves within the mucus layer and penetration into the mucosa.

The optimal properties of a nasally delivered drug are:

- Drug characteristics: Molecular weight < 500 g/mol, log P<sub>oct/wat</sub> < 5.
- Dose per spray: Potency < 5 mg/dose; volume maximally 100 microlitres/spray.
- Drug in solution: pH approximately 5.5, osmolality 300 - 700 mosm/kg.

KetaDex nasal solution resembles these physico-chemical and pharmacological properties.

### KetaDex nasal spray: The new formulation

KetaDex nasal spray (ketamine 125mg/ml and dexmedetomidine 250 mcg/ml nasal solution) is manufactured through a series of proprietary steps which have been validated and performed in accordance with TGA regulations [17]. KetaDex nasal is supplied as a clear, colourless, hypertonic solution with a pH of 4.5 to 5.5. Each mL contains 144.175 mg of ketamine hydrochloride equivalent to 125 mg of



**Figure 3 and 4:** KetaDex nasal spray actuator.

ketamine, 295 mcg of dexmedetomidine hydrochloride equivalent to 250 mcg (0.25 mg) of dexmedetomidine, sodium citrate dihydrate and edetate disodium dihydrate in water. The solution is preservative-free.

The primary packaging consists of 1ml glass syringes (highly resistant borosilicate) sealed with a tip cap (a synthetic polyisoprene rubber) and a plunger. The dispensing actuator device is a proprietary 0.1 ml meter dose sprayer.

Stability studies according to International Council for Harmonisation (ICH) guidelines have commenced at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and  $65\% \text{ RH} \pm 5\%$  with an anticipated shelf life of 24 months. The drug syringe cartridge is stored at room temperature ( $25^{\circ}\text{C}$ ) until use. Once the nasal actuator is attached, the product should be used as soon as practical because of microbial risk. Once primed, the device is ready for use and the spray can be actuated in any direction depending on patient positioning.

Eight full sprays are deliverable, each directed spray delivers ketamine 12.5 mg and dexmedetomidine 25 mcg to the nasal mucosal surfaces. In monitored clinical settings, the nasal spray will have intrinsic safety due to a relatively slow rise to moderate therapeutic plasma concentrations with minimal respiratory depression. KetaDex nasal will have pharmacokinetic interaction with any co-administered intranasal drug, e.g. Fentanyl. Nasal mucosal vasoconstriction effects of dexmedetomidine will slow absorption, diminish peak plasma concentrations and extend drug effects.

The plasma concentration-time curve of administration of KetaDex nasal plus co-administered intranasal drug would be comparable to that of an intravenous infusion over 60 minutes duration (Figure 5). It is postulated that the nasal mucosa acts like a drug reservoir, and plasma uptake rate is limited by reduced nasal blood flow due to dexmedetomidine's nasal mucosal vasoconstriction.

#### **KetaDex nasal spray dose: recommended range**

Clinical factors to consider for prescription of maximum dose (up to ketamine 2 mg/kg and dexmedetomidine 4 mcg/kg) include:

- Very high anxiety and sympathetic activity.

- Previous failure of sedation or bad experience.
- High analgesic requirements of procedure.

13 - 19 kg	1 - 2* sprays
20 - 29 kg	2 sprays
30 - 39 kg	3 sprays
40 - 49 kg	4 sprays
> 50 kg	Ketamine 1 - 2 mg/kg
	Dexmedetomidine 2 - 4 mcg/kg

\*: 0.2 - 0.5 ml saline spray can be used to dilute dose and washout if required.

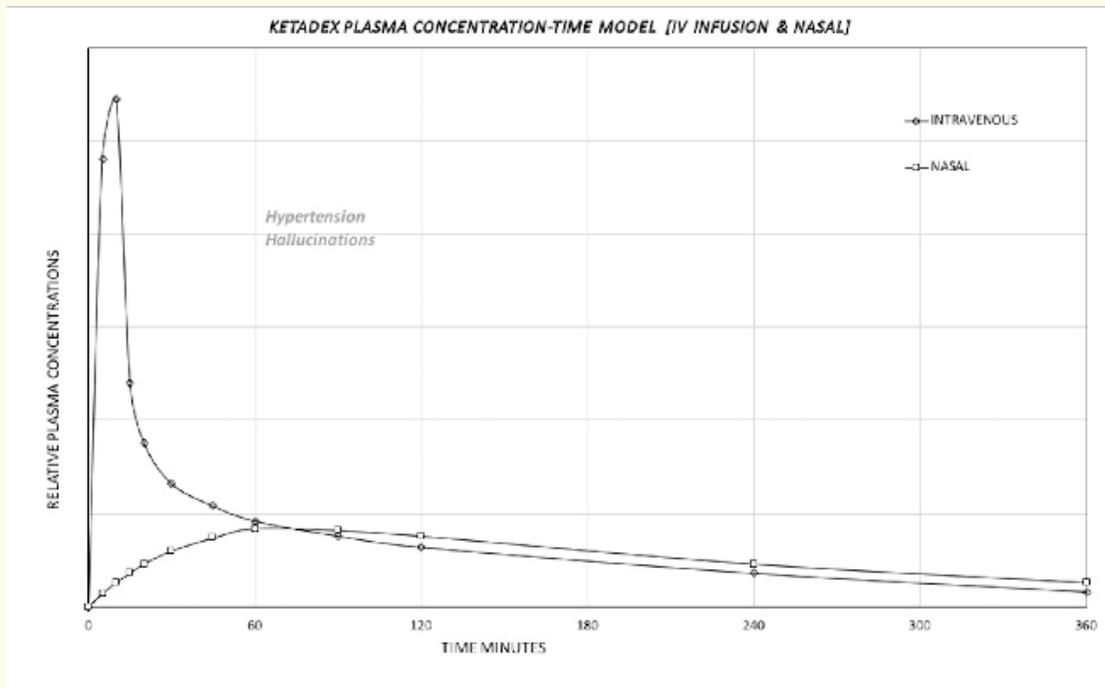
Allow 1 - 2 minutes between ipsilateral sprays for normal nasal breathing and mucosal evaporative loss to optimize bioavailability.

**KetaDex nasal drug combination: pharmacokinetics [4,12]**

80% of ketamine’s hepatic biotransformation produces an active metabolite, norketamine which contribute to analgesic effects [12].

	Bioavailability		Peak conc.	Vd l/kg	Protein	Elimination
	Nasal#	(Oral)	minutes#		binding	t1/2 hours
Ketamine	50%	(17%)	60 - 90	2 - 3	30%	2 - 3
Dexmedetomidine	75%	(16%)	60 - 90	2	94%	2 - 3

#: Predicted value.



**Figure 5:** Comparative plasma concentration-time model of ketamine and dexmedetomidine administered by intravenous infusion over 10 minutes versus equivalent dose of KetaDex nasal spray (Single line representation of the drug combination’s congruent pharmacokinetics).

### KetaDex nasal spray: Potential clinical uses

- **Premedication for procedural sedation:** KetaDex nasal is indicated for patients with needle phobia and distress level fear of medical, surgical, diagnostic, dental and anaesthetic induction procedures. It has the advantages of no needle, non-opioid sedation and analgesia with minimal respiratory depression, reduced airway resistance and secretions. Cutaneous veno-dilation may assist intravenous cannulation. KetaDex nasal will have an opioid and anaesthetic sparing effect.
- **Opioid-sparing duo for acute pain presentations:** KetaDex nasal spray is an easy to administer, incremental and titratable drug combination. Opioid related adverse drug effects (ORADEs) and the recent opioid epidemic have rallied efforts to develop new balanced analgesia strategies, which reduce reliance on opioids [18-20]. Multi-modal suppression of nociceptive transmission has the significant added benefit during general anaesthesia of decreasing arousal, which appreciably reduces the need for hypnotic drugs. This may facilitate a smoother recovery and help prevent emergence delirium and agitation postoperatively.

Precautions include obstructive sleep apnoea, pre-existing hypotension, bradycardia, ECG abnormalities, conditions that rely on high sympathetic tone e.g. hypovolaemia, congestive cardiac failure. Use with renin-angiotensin antagonists and other antihypertensives. Caution is required with concomitant use of other sedatives, hypnotics, opioids and general anaesthetics. Depth of anaesthesia monitoring is recommended e.g. BIS, frontalis EMG [2]. Decreases in heart rate and blood pressure below acceptable limits may be easily treated with oral or intramuscular ephedrine at a dose of 0.2 - 0.4 mg/kg. Oral bioavailability of ephedrine is excellent and will add to ketamine's antagonism of the cardiovascular effects of dexmedetomidine.

### Future Research

KetaDex nasal spray is available now for clinical use, so on request of a clinician, this unregistered medicine can be supplied under contract to your hospital pharmacy [21]. Preliminary pharmacokinetic and safety data is to be determined by upcoming clinical trial. However, more clinical trials are strongly encouraged of this novel no needle, non-opioid sedative-analgesic drug combination. Other potential clinical roles of this nasal spray are for acute agitation, obstetric analgesia, complex regional pain syndrome, opioid withdrawal in chronic pain conditions, opioid induced hyperalgesia, migraine, polymyalgia rheumatica, depressive disorders and palliative care.

### Conclusion

We present an easy to administer KetaDex 12.5/25 nasal spray, concentrated for bioavailability to produce reliable sedation and analgesia with minimal adverse effects due to favourable pharmacokinetic and pharmacodynamic interactions.

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