



“A Comprehensive Review on Oxymetazoline Hydrochloride as Nasal Spray”

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Abstract:

Oxymetazoline HCL is a nasal decongestant commonly used to relieve nasal congestion caused by colds, allergies, or sinusitis. Oxymetazoline, an alpha-adrenergic agonist, reduces edema and makes breathing easier by narrowing blood vessels in the nasal passages. It acts rapidly to provide temporary relief and is usually applied as a nasal spray. Although it works, using it for longer than three days can cause rebound congestion, also known as rhinitis medicamentosa, in which the congestion gets worse when you stop using it. When taken as directed, it is usually well tolerated, though it may have modest side effects such as transient dryness or irritation of the nose. This selective alpha-adrenergic agonist is frequently applied topically to relieve congestion.

It reduces nasal congestion and edema by narrowing blood vessels in the nasal mucosa. This substance is frequently present in over-the-counter medications used to alleviate sinus and nasal congestion brought on by colds or allergies. Although generally helpful usage over time may result in rebound congestion, also referred to as rhinitis medicamentosa. According to research, oxymetazoline's vasoconstrictive effects are a result of its stimulation of alpha-1 and alpha-2 adrenergic receptors. When used as prescribed, clinical research has shown that it is both safe and effective.

Keywords: Nasal congestion, Adrenergic alpha-1 receptor agonists, adrenergic receptor agonists, adrenoceptors, oxymetazoline

INTRODUCTION:

A common sympathomimetic medication used as a nasal decongestant is oxymetazoline. It primarily functions as an α -adrenergic agonist and is a member of the imidazoline derivative class. When oxymetazoline is administered topically, it reduces blood flow and relieves nasal congestion by narrowing the blood vessels in the nasal mucosa. This impact aids in reducing the symptoms of illnesses like sinusitis, allergic rhinitis, and the common cold. Usually sold as nasal sprays, oxymetazoline relieves nasal congestion quickly and temporarily—often within minutes of treatment. The mechanism of action of oxymetazoline is based on the specific activation of α_1 -adrenergic receptors on smooth muscle cells in the nasal vasculature. This causes vasoconstriction, which widens the nasal airways and lessens mucosal edema. Because of its prolonged duration of effect, oxymetazoline usually lasts for up to 12 hours after a single dose [1].

However, rebound congestion, sometimes referred to as rhinitis medicamentosa, is a major concern associated with the misuse of nasal decongestants such as oxymetazoline [2]. While oxymetazoline is typically seen as safe for short term consumption, it can have adverse effect like burning, stinging, or dry nose. One of the main issue with this group of drug is rebound congestion, which can result from prolonged or excessive use.

Chronic nasal blockage may result from dependence on nasal decongestant, particularly if the medicine is used for prolonged periods of time [3].

Vascular Pathophysiology:

Two highly unique features of the nasal vasculature are both much more noticeable in the respiratory system than in the nose's olfactory regions. The first is the evidence of a subepithelial capillary network below a huge sinusoidal or sinai network of significant capacitance vessels deep within the mucosa. 'Erectile' or 'tumefacient' nasal mucosa are caused by these blood sinuses. The capacitance system's physiological benefit might be that it enhances the nose's air conditioning system [4], despite the fact that the nose is such an effective air conditioner that it may not need to be improved or that it improves its filtering capabilities. The latter benefit is negated in humans if mouth breathing results from nasal obstruction. Regardless of the sinuses' normal function, nasal obstruction in pathological situations must be largely caused by their distension. In some species, including sheep and rabbits, the tracheobronchial circulation also features visible blood sinuses in the submucosa [5].

Causes of nasal congestion:

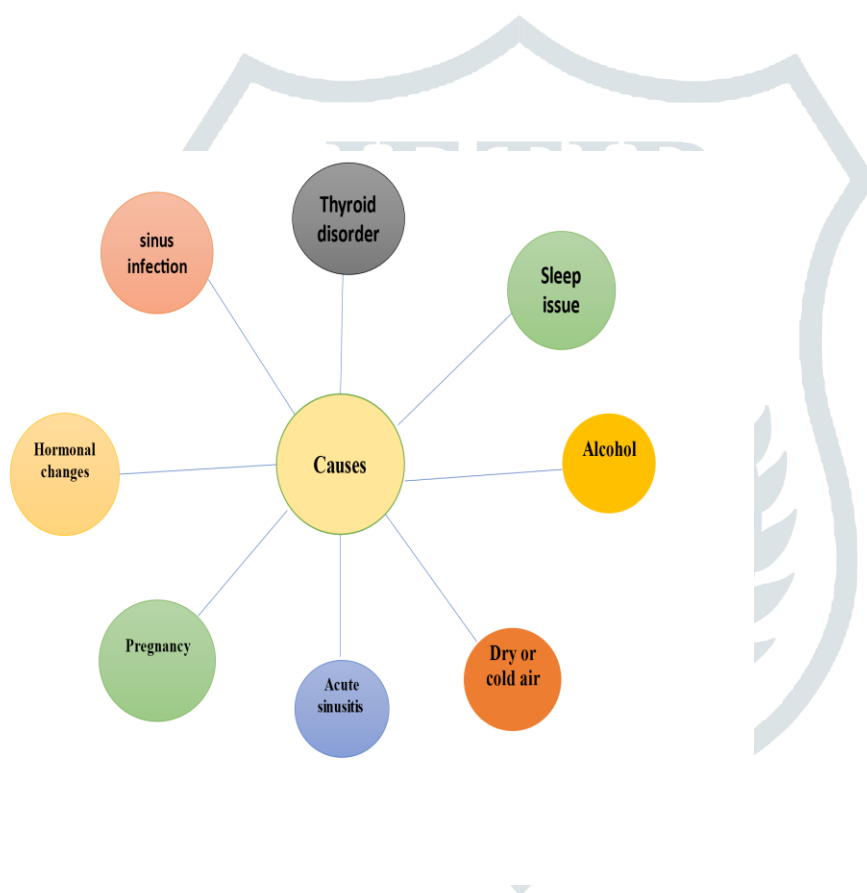


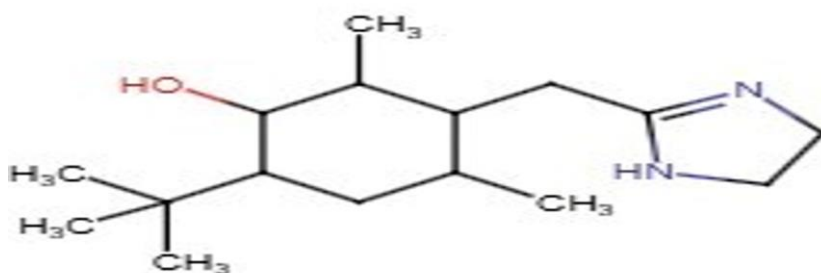
Fig no.1: Causes of nasal congestion

OXYMETAZOLINE HYDROCHLORIDE:

Oxymetazoline hydrochloride is a type of medicine which shows vasoconstriction. It helps to shrink blood vessels in the nose, which makes it easier to breathe. People have been using it as a nasal spray without needing a prescription in the United States for a long time, over 40 years. It's allowed to be used for making it easier to breathe when you have a cold or allergies. This medicine is put directly into the nose and has been used for a while to treat stuffy nose and runny nose [6].

Oxymetazoline is an α -adrenergic agonist with greater activity at the α_2 versus α_1 adrenergic receptor. It's action on peripheral α_2 -adrenergic receptor on the smooth muscle of the vasculature results in Vasoconstriction, thereby defining its clinical utility as both a decongestant and a topical haemostatic agent [7].

Chemical Structure:



6-tert-Butyl-3-(4,5-dihydro -1H-imidazol-2-ylmethyl)-2, 4-dimethylphenal hydrochloride

Fig. no.2: Chemical structure Oxymetazoline hydrochloride

DISCOVERY AND DEVELOPMENT OF OXYMETAZOLINE HYDROCHLORIDE:

Oxymetazoline is an imidazole derivative. It was discovered from xylometazoline at Merck by Wolfgang Fruhstorfer and Helmut Miller-Calgan in 1961. Oxymetazoline is a direct sympathomimetic that mainly binds to and activates α_2 adrenergic receptors. In 1966, the oxymetazoline-containing brand Afrin was first sold as a prescription medication. It had considerable early popularity as a prescription drug before being over-the-counter in 1975. It wasn't widely promoted by Schering-Plough until 1986 [8].

Oxymetazoline is a example of imidazole and serves as a powerful direct-acting alpha (α)-adrenergic agonist, showing affinity for both α_1 - and α_2 -adrenoceptors. This medication has many clinical uses and is available in many forms. Adults with chronic face redness are treated with the topical form of oxymetazoline. Oxymetazoline is a very powerful decongestant that is used in over-the-counter nasal sprays to relieve sinus and nasal congestion caused by a variety of illnesses, such as upper respiratory allergies, hay fever, and the common cold. Intranasal spray containing oxymetazoline and tetracaine (Kovanaze) is used in dentistry to provide regional anaesthetic for both adults and children during dental treatments. In July 2020, the first FDA-approved medication for acquired blepharoptosis was an ocular formulation of oxymetazoline (Upneeq), which was licensed for use in adults with the condition [9].

In the United States, A topical 1% oxymetazoline cream has been approved by the Food and Drug Administration to treat people with rosacea-related persistent facial redness. Oxymetazoline's capacity to narrow blood vessels makes it useful for treating nosebleeds and mild eye redness brought on by irritation [10].

CLINICAL DATA:

Trade names: Afrin

Route of administration: Intranasal, eye drop, topical

Dependence liability: Moderate

Elimination half- life: 5-6 hours

Excretion: Kidney 30%, faeces 10% [11].

Chemical Properties:

Chemical formula: $C_{16}H_{24}N_2O \cdot HCl$

Molecular weight: 296.84

CAS number: 2315-02-8

Solubility: Freely soluble in water and ethanol, slightly soluble in chloroform, and practically insoluble in ether and benzene

Appearance: White or almost white, hygroscopic crystalline powder with a bitter taste

Synthesis: Prepared from (4-tert-butyl-2,6-dimethyl-3-hydroxyphenyl) acetonitrile and ethylenediamine [11].

Synthesis:

Oxymetazoline hydrochloride is made by reacting equimolar amounts of oxymetazoline and hydrogen chloride. Oxymetazoline is synthesized by the following steps:

Chloromethylate 6-tert-butyl-2,4-dimethylphenol

Convert the chloromethyl derivative into a nitrile

React the nitrile with ethylenediamine [11].

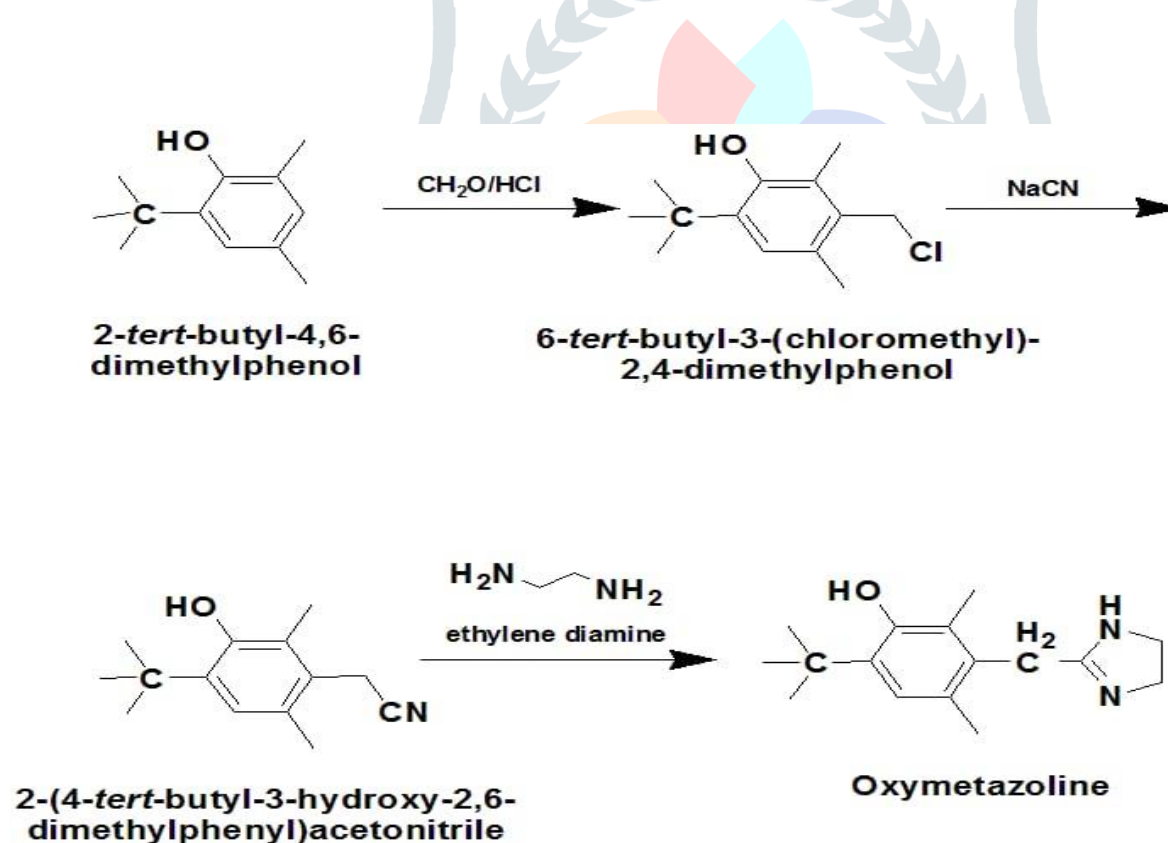


Fig No.3: Synthesis of Oxymetazoline hydrochloride [45].

[<https://images.app.goo.gl/WQqUpARFvX8EmYkh7>]

Structure Activity Relationship:

The high agonist action requires a primary or secondary aliphatic amine that is two carbons away from a substituted benzene ring.

The hydroxyl substituted carbon must be in the R configuration for the maximal direct activity.

R¹ substitution:

- When R¹ is increased in size, activity of alpha receptors decreases and activity of the beta receptors increases
- Activity of both alpha and beta receptors is maximum when R¹ is methyl group.
- Alpha agonist activity decreases when R¹ is larger than methyl, and went negligible when R¹ is isopropyl.
- Large lipophilic groups can afford compounds with alpha blocking activity.
- N-substituent provides selectivity for different receptors.
- Arylalkyl group can provide beta selectivity, increased cell penetration and increased lipophilicity for the longer duration of action.

R² substitution:

- Ethyl group can eliminate the alpha activity of the drug.
- Erythrosteroid isomers have maximal activity.
- The additional methyl group makes the drug more selective for the alpha₂

R³ substitution on the aromatic ring:

- 3',4'-dihydroxy substituted benzene ring has poor oral activity.
- 3', 5'-dihydroxy compounds are orally active.
- At least one of the groups is required which can form hydrogen bonds. And if only one group is present then it is preferred at 4' position to retain the beta₂
- If phenyl group has no phenolic substituent then it may act directly or indirectly [12].

Mechanism of action:

Oxymetazoline binds to α_1 - and α_2 -adrenoceptors, which, respectively, are receptors connected to the Gq and Gi proteins. While α_2 -adrenoceptor agonism, specifically the α_2B -adrenoceptors, can also cause vasoconstriction by inhibiting adenylyl cyclase, α_1 -adrenoceptor agonism increases intracellular calcium levels by activating phospholipase C, which in turn enhances vascular smooth muscle contraction [13,14].

Rosacea is a condition characterized by transient and persistent facial erythema. By generating vasoconstriction and activating α_1A -adrenoceptors, oxymetazoline is thought to reduce erythema symptoms. In blepharoptosis, it is hypothesized that oxymetazoline works by stimulating α -adrenergic receptors on the Müller muscle that elevates the upper eyelid, causing muscle contraction. Oxymetazoline is used in combination with tetracaine for local anaesthesia in dentistry. The use of this combination has additional positive effects: the vasoconstrictor reduces blood flow to the application region by restricting dilated arterioles and preventing the vasodilatory function of the local anaesthetic agent. Oxymetazoline relieves nasal congestion by vasoconstricting the respiratory microvasculature, in the human nasal mucosa's resistance and capacitance blood vessels, resulting in edema, reduced nasal mucosal blood flow, and airflow resistance [15,16,17].

Pharmacodynamics:

Oxymetazoline is an adrenergic $\alpha 1$ - and $\alpha 2$ -agonist and a direct-acting sympathomimetic drug. By stimulating adrenergic receptors, oxymetazoline results vasoconstriction of dilated arterioles and decreases blood flow. In a radio ligand competition study, oxymetazoline displayed higher affinity at $\alpha 1A$ -adrenoceptors compared to $\alpha 2B$ -adrenoceptors, but with higher potency at $\alpha 2B$ -adrenoceptors. When sprayed intranasally, oxymetazoline relieved relief nasal congestion and enhance nasal airflow in patients with acute coryzal rhinitis for up to 12 hours following a single dose [18].

An early in vitro study demonstrated oxymetazoline to exert anti-oxidant actions, where it inhibited microsomal lipid peroxidation and mediated hydroxyl radical scavenging activity. This implies that oxymetazoline has a protective effect against oxidants, which contribute to inflammation-induced tissue damage [19].

Pharmacokinetics:

Since imidazolines are sympathomimetic agents, their primary effects appear on α adrenergic receptors, with little if any effect on β adrenergic receptor. Like other imidazolines, Oxymetazoline is readily absorbed orally. Effects on α receptors from systemically absorbed oxymetazoline hydrochloride may persist for up to 7 hours after a single dose. The elimination half-life in humans is 5–8 hours. It is excreted unchanged both by the kidneys (30%) and in faeces (10%) [20].

FUNCTIONALITY OF NASAL SPRAY SYSTEM:

Nasal spray systems have three main parts: a chamber, a piston, and an actuator. Compared to drops, nasal sprays are more precise, delivering exact doses with consistent plume shape. Formulation properties like thixotropy, surface tension, and viscosity may influence droplet size and accuracy. Factors such as applied force, orifice size, and pump design can also affect droplet size, impacting where the spray reaches in the nasal passage.[21,22,23]

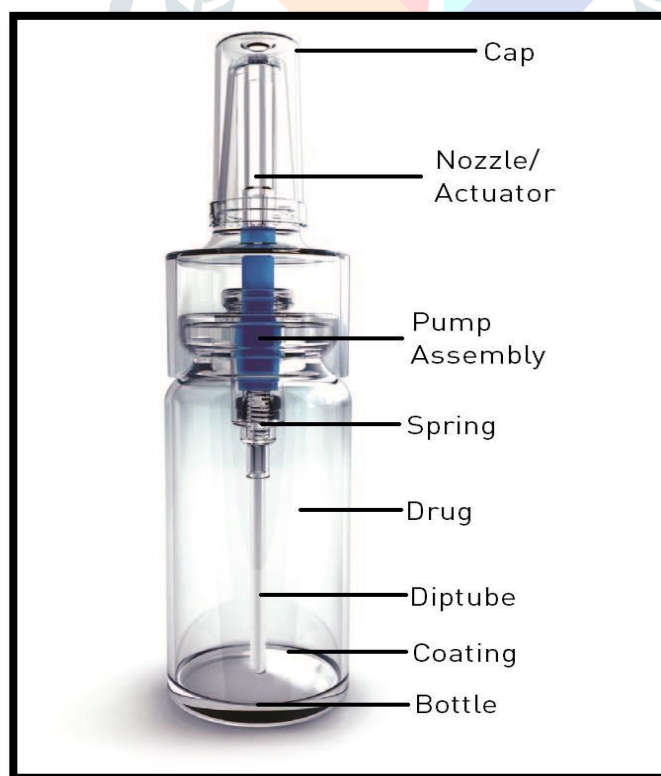


Fig. no 3: Components of nasal spray [46].

[<https://images.app.goo.gl/VAiukoPLcghN2zzSA>]

Overview of Nasal spray Brands, Manufacturer and Formulation Types: [43,44]

Brand Name	Manufacturer	Formulation Type
Afrin	Bayer	Nasal Spray
Zicam	Matrix Initiatives	Nasal Spray
Dristan	Prestium Prarmaceuticals	Nasal Spray
Otrivin	Glaxosmithkline	Nasal Spray
Nasalube	Health Enterprises	Nasal Spray
Sudafed Pe	Johnson & Johnson	Nasal Spray
Zymar	Allergen	Nasal Spray

Spray Pattern Testing Guidelines:

It's essential to accurately assess spray pattern and plume geometry for pump and nozzle evaluation. Multiple factors impact these characteristics, such as nozzle size, pump design, chamber size, and formulation traits. Regular spray pattern testing is crucial for quality control during drug product release. Plume geometry characterization is typically established during product characterization and may not require routine testing.

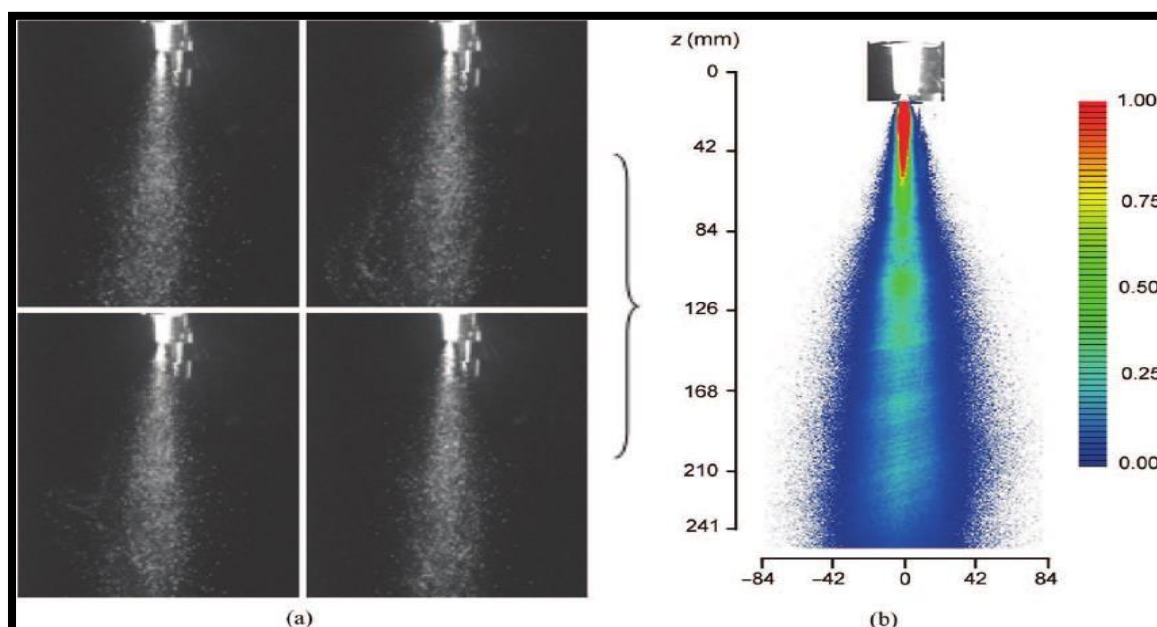


Fig.no. 5: Spray pattern and pump geometry [47].

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Dose And Administration Of Oxymetazoline Hydrochloride Nasal Spray:

In adults and children's -2-5 drops of oxymetazoline hydrochloride solution or spray in every 10 -12 Hours

Pharmacokinetics Of Oxymetazoline Hydrochloride Nasal Spray:

Absorption:

Following nasal spray administration of a 0.6 ml combination product containing tetracaine and Oxymetazoline hydrochloride in adult person, the maximum concentration of Oxymetazoline hydrochloride were raised within ten min. The mean C_{max} was 1.78 nanograms per ml, and the AUC_{0- inf} value was 4.24 nanograms per hour per millilitres, with a median T_{max} of five min.

Protein Binding:

In vitro condition the Oxymetazoline hydrochloride is 56.7 % to 57.5 % bound to human plasma proteins which is administered through the nasal cavity

Metabolism:

In vitro condition, Oxymetazoline hydrochloride which is given through the nasal route is normally metabolized by human liver enzymes limitedly to produced mono-oxygenated and dehydrogenated metabolites.

Route of Elimination:

The comprehensive characterization of Oxymetazoline hydrochloride excretion after nasal, topical, or ophthalmic use in humans remains incomplete. It is currently understood that the primary method of elimination of Oxymetazoline hydrochloride, at concentrations relevant to clinical usage, is through renal excretion.

Half-Life:

The elimination half-life of oxymetazoline hydrochloride after nasal administration of a combination product containing oxymetazoline and tetracaine in adult subjects was around 5.2 hours [24].

Drug Interactions of Oxymetazoline Hydrochloride:

It's important to understand that oxymetazoline hydrochloride, can interact with other drugs you may be taking. Maintaining a comprehensive list of all medications you use, including prescriptions, non-prescriptions, and herbal products, is crucial to avoiding potential interactions and ensuring your safety.

- 1) Tricyclic antidepressants (e.g. amitriptyline) because the effectiveness of oxymetazoline hydrochloride result may be dropped.
- 2) Cocaine, furazolidone, MAO impediments (e.g. phenelzine), or tricyclic antidepressants (e.g., amitriptyline) because side goods, similar as headache, fever, or high blood pressure, may be increased.
- 3) Bromocriptine or cocaine because the conduct and side goods of these drugs may be increased antidepressants (e.g., amitriptyline) because the effectiveness of oxymetazoline hydrochloride result may be dropped.
- 4) Cocaine, furazolidone (FZ), MAO impediments (e.g. phenelzine), or tetracycline antidepressants (e.g., amitriptyline) because side goods, similar as headache, fever, or high blood pressure, may be increased.
- 5) Bromocriptine or cocaine because the conduct and side goods of these drugs may be increased [25].

Advantages Of Nasal Spray:

1. Easy availability and needle free medicine operation without the necessity of trained labour force facilitates tone drug, therefore perfecting patient obediences compared to parenteral routes.
2. Good penetration of lipophilic medicine and low molecular weight of medicines through the nasal mucosa. For case the absolute nasal bioavailability of fentanyl is around 80%.
3. Rapid immersion and fast onset of action due to fairly large immersion face and high vascularization.
4. Avoidance of the various environmental factors in the gastrointestinal tract(chemical and enzymatic declination of medicines).
5. Avoidance of hepatic first pass metabolism and therefore eventuality for cure reduction compared to oral delivery.
6. Implicit for direct delivery of medicine to the central nervous system via the olfactory region, therefore bypassing the blood brain hedge.
7. Direct vaccine delivery through the lymphatic tissue and induction of a secretory vulnerable response at distant mucosal point [26].

Disadvantages Of Nasal Spray:

1. Nasal cavity provides smaller absorption surface area when compared to GIT.
2. Relatively inconvenient to patient when compared to oral delivery system since there is a possibility of irritation.
3. Something it causes irreversible damage of the nasal mucosa which is due to the ingredients added to the formulation.
4. It provide inaccurate dose and insufficient deepness of administration.
5. Some of the nasal spray administration causes nasal irritation [27-30].

Side Effects of Oxymetazoline Hydrochloride Nasal Spray:

Paranoid Psychosis:

Several reports have linked orally ingested sympathomimetic drugs with psychosis. Others have attributed schizophrenic-like psychotic reactions and toxic psychoses to nasal sprays ingested orally or injected intravenously. However, reports of psychoses induced by the inhalation of nasal sprays are rare. There are two reports of psychiatric syndromes associated with the sympathomimetic agent oxymetazoline administered by nasal spray: Soderman reported adverse reactions in the central nervous system such as convulsions, excitation, insomnia, sedation and visual hallucinations in five infants who received regular doses of the drug, and Blackwood's described a delirious state with acute paranoid symptoms in a 41-yearold woman who used oxymetazoline and many other agents, including menthol and camphor.

The case he describe is the first report of psychosis in an adult who used only oxymetazoline administered by nasal spray. The abuse of this drug resulted in paranoid psychosis, with clear consciousness and no delirium. He's report confirms this association because it describes the patient's repeated abuse of the drug, with the same result [31-35].

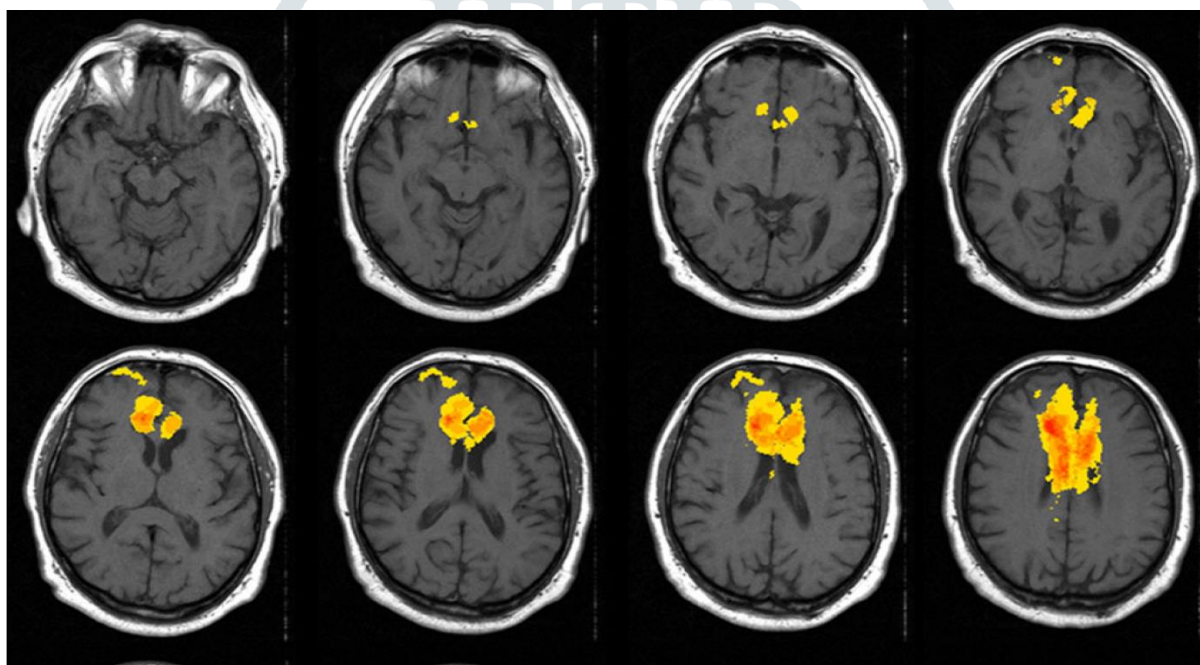


Fig.no:6. Paranoid Psychosis [48].

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Thunderclap headache:

Thunderclap headache (TCH) is a hyperacute, severe headache that is so named because of its unforeseen onset. It frequently ails a serious intracranial vascular event similar as subarachnoid haemorrhage, cerebral venous sinus thrombosis or paedietary apoplexy. Still it may also do spontaneously or in the setting of cerebral vasoconstriction. Duration may be from 1 hour to 10 days. In this case, grounded on angiographic follow- up, the underpinning cause of blast headache was set up to be reversible segmental cerebral vasoconstriction.

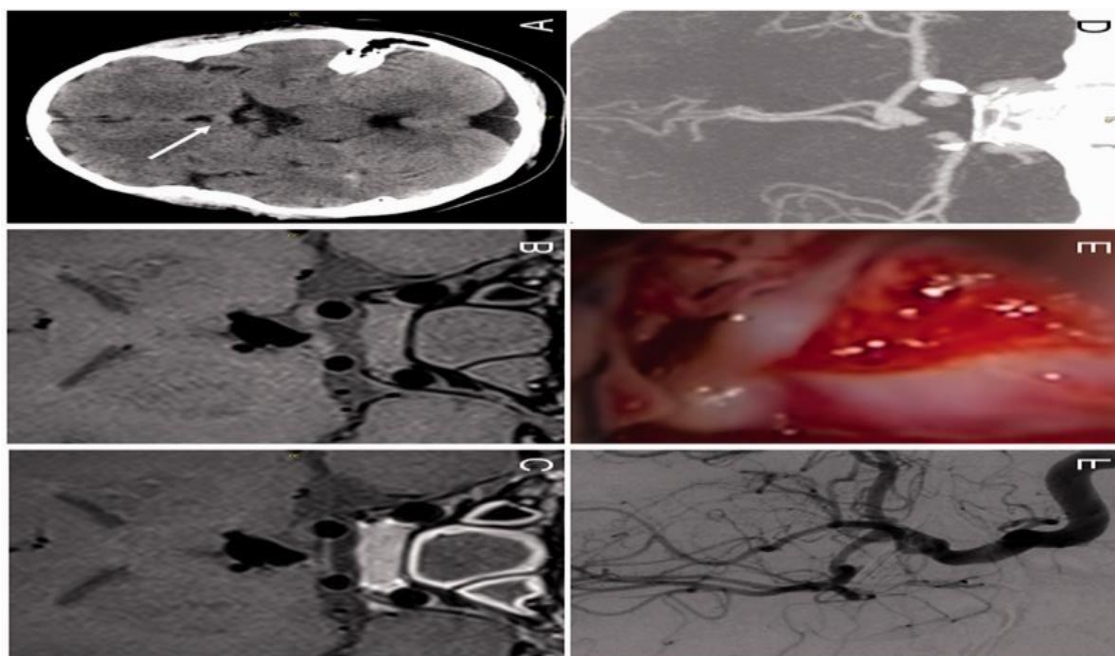


Fig. no :7. Thunderclap headache [49].

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This case highlights an implicit systemic poisonous effect of oxymetazoline nasal spray, with blast headache should be questioned about their use of prepping specifics including specifically reversible segmental cerebral vasoconstriction causing blast headache. Cases presenting untoward nasal decongestants. In addition various cerebral angiography, CT scans and MRI angiography of brain and transcranial Doppler this have been used to diagnosed intracerebral vasoconstriction in other cases. Abstinence from the offending medicine is the main remedy, although calcium channel blockers may also have a remedial part [36-38]

Other side effects:

- Difficulty in breathing or swallowing
- Lump of the face, lips, lingo or throat
- Severe side effects like itching of the skin, and red rashes observed in the skin.

USES OF OXYMETHAZOLINE HYDROCHLORIDE NASAL SPRAY

Oxymetazoline hydrochloride Spray is used in the treatment of nasal congestion

- ★ It treats congestion associated with disinclinations
- ★ High fever.
- ★ Sinus vexation [39].

Comparison to other decongestant:**[40,41,42]**

Property	Oxymetazoline Hydrochloride	Phenylephrine	Pseudoephedrine
Mechanism of Action	Constricts blood vessels in the nasal mucosa, reducing congestion	Constricts blood vessels in the nasal mucosa, reducing congestion	Constricts blood vessels in the nasal mucosa, reducing congestion and improving airflow
Duration of Action	Up to 12 hours	4-6 hours	4-6 hours
Indications	Constricts blood vessels in the nasal mucosa, reducing congestion	Nasal congestion due to colds, sinusitis, allergies	Nasal congestion due to colds, sinusitis, allergies
Efficacy	Highly effective for severe nasal congestion	Less effective, especially in oral form	Highly effective for severe nasal congestion
Side Effects (Local)	Nasal dryness, irritation, rebound congestion	Nasal dryness, irritation	Nasal dryness, irritation (if nasal spray used)
Use Duration Recommendation	Short-term (3 days or less)	Short-term use for nasal congestion, oral form for mild symptoms	Short-term use for nasal congestion, oral form for mild symptoms
Common Brand Names	Afrin, Zicam, Dristan	Sudafed PE, Neo-Synephrine, Little Noses	Sudafed, Claritin-D, Zyrtec-D
Legal Status (U.S.)	Available over-the-counter	Available over-the-counter	Available OTC, but regulated

CONCLUSION:

Oxymetazoline hydrochloride, when used as a nasal spray is essential for clearing congestion in the nose because of its strong vasoconstrictive effects. It reduces edema and congestion in the nasal passages by activating alpha-adrenergic receptors in the smooth muscles of blood vessels in the nasal mucosa, which causes the vessels to constrict. Because of this, it works well as a temporary remedy for sinusitis, colds, and allergies that induce nasal congestion.

However, oxymetazoline nasal sprays must be used carefully because they might cause rebound congestion, also known as rhinitis medicamentosa, if used for longer than three days in a row. Once the medicine is withdrawn, this condition may cause nasal congestion, leading to an ongoing pattern of dependence.

The intranasal route is a reachable alternative route for drug administration. The development of drugs for directly target the brain in order to achieve a good therapeutic effect in CNS with reduced systemic side effects. It has advantages in terms of reduces systemic exposure and hence side effects and avoiding first-pass metabolism. Nasal spray drug products Contain active ingredients dissolved or suspended in Solutions or mixtures of

excipients in non-pressurised dispenser that deliver a spray containing a metered Dose of the active ingredient. Vital characterization Test for nasal spray includes spray pattern, droplet size Distribution, spray content uniformity these depend on Formulation as well as device properties.

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