

Assessment of Prescribing Pattern and Safety Profile of Drugs Used in Intranasal Route in Paediatric Age Group of Patients in a Tertiary Care Hospital

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ABSTRACT

Background

Recently there has been an increased preference for intranasal delivery of drugs due to highly vascular nasal mucosa, bypassing first pass metabolism and the blood brain barrier (BBB) lead in quick drug absorption to the systemic circulation and direct access to brain from olfactory region. For pediatric patients this route offers significant benefits over injections or oral routes, like increased compliance, easy administration, and minimal side effects.

Objective

Assessment of prescription pattern of drugs and safety profile of drugs used by intranasal route in paediatric age group.

Method

Our study was a prospective observational study paediatric age group of patients conducted in the departments of Pharmacology, Paediatrics and Otorhinolaryngology of Burdwan Medical College and Hospital, Burdwan. Data were collected in CRF and frequency distribution of collected data done. Microsoft Excel 2010 was used for analysis.

Result

Common age group was infants. Males were more in number. Most common indication was epistaxis. Intranasal drugs per prescription were 1.05. Most commonly prescribed intranasal drug was nasal saline. Nasal decongestant was the most common prescribed medication. Nasal drops were the most common dose formulation.

Conclusion

Intranasal drug prescribing in our study was mainly aimed for treating local problems, very few being for systemic action. Some prescribing indicators like prescribing by generic name and prescribing from national essential drug lists were acceptable with scope for improvement. Average number of drugs per prescription and antibiotic use was high. Adverse events after intranasal drug use were primarily local and nose related.

KEY WORDS

Drug delivery, Intranasal, Paediatric, Prescription, Safety

INTRODUCTION

The administration of target medications in paediatric patients is never an easy task. Barriers are poor palatability or difficulty in swallowing oral pills. Rectal administration is often socially undesirable. Invasive routes of drug delivery often cause severe pain and anxiety. In certain situations, intranasal delivery system is preferred for systemic drugs, as it provides a suitable alternative.

Intranasal drug transport drugs directly into the brain, bypassing the blood-brain barrier (BBB). Clinical Trials.gov registry shows that 18% of the trials aim at local treatment of the nasal cavity or the nasal mucosa. The remaining 82% focus on systemic delivery of vaccines, hormones, peptides, proteins and small molecules and new devices.¹ Assessment of drug prescribing patterns by the WHO/INRUD drug use indicators provide very significant information to the health-care system, also helps in promoting rational drug use.^{2,3} Irrational drug use in the developing countries is attributed to irrational prescribing, dispensing, and also administration of medications.⁴ Medication use indicators including prescription indicators (WHO) ascertain the therapeutic services and identify the prescription profile and quality of different health services.⁵

There are paucities regarding prescription pattern studies involving drugs delivered by a specific delivery route in specific population groups. To know the utility of intranasal route for drug delivery in developing countries, prescription pattern studies involving intranasal drugs can be done. Intranasal route is sometimes utilized for systemic action. However, there remains some concern about it. There is a paucity of data regarding prescribing patterns for several classes of intranasal drugs in this age group. Studies on the safety profile of intranasal drugs given among children are less. Therefore, we planned this study to cover these gaps.

METHODS

Our study was a prospective observational study conducted in the Departments of Pharmacology, Paediatrics and Otorhinolaryngology of Burdwan Medical College and Hospital, Burdwan on patients of newborn to 18 years receiving intranasal drugs in Paediatrics and Otorhinolaryngology department. Permission from the institutional ethics committee was taken prior to the study. Total period of study was 21 months in total from March 2017 to November 2018. Data were collected once a week in both Paediatrics and Otorhinolaryngology departments within the study period according to the study design. Study flow chart depicted in (image 1).

Consecutive sampling method was used. Number of study participants was determined by the availability of patients giving valid consent and fulfilling the inclusion, exclusion criteria during study visits in the specified time period. Patients attending outdoor clinics were studied in 2 visits.

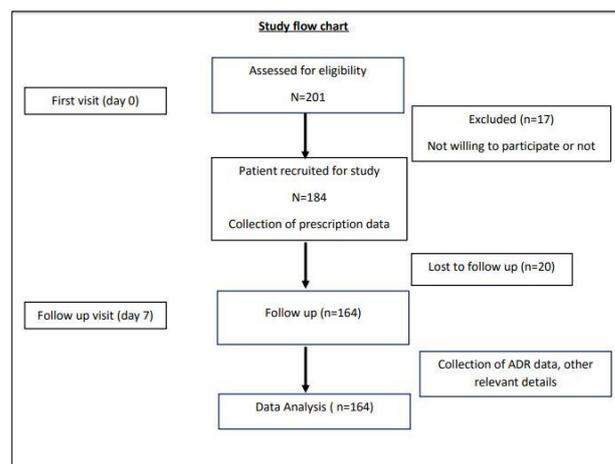


Image 1. Study flow chart

In the 1st visit (0 week), patients were selected according to study protocol. Collection of information from prescriptions of selected patients was done in case report form (CRF). In 2nd visit (1 week) – Data regarding adverse drug reactions following intranasal drug use were collected. A total of 184 patients received intranasal drugs following stipulated inclusion and exclusion criteria within the field study period. Among them 20 participants were lost to follow up. Final analysis was done on 164 participants. All data were entered in Microsoft Excel 2010 and analysis was done with the help of Excel statistical tools. We evaluate rational drug use w, analyzed the parameters like percentage of drugs prescribed by generic name, percentage of prescriptions with an antibiotic, percentage of prescriptions with an injection, percentage of drugs prescribed from an Essential Drug List of India, percentage of drugs prescribed from hospital drug formulary. All relevant information regarding treatment-emergent adverse events including those spontaneously reported by the participant himself, those elicited as clinical signs by investigator during the scheduled visits and adverse laboratory test results. We also analyzed patient's socio-demographic profile, types and quantity of intranasal drug use, dosage forms of intranasal drugs, relevant information regarding co-drugs, percentage of patients receiving monotherapy, percentage of prescriptions with fixed dose combination drugs.

RESULTS

In our study we included the patients of the paediatric age group (up to 18 years) who were prescribed at least one intranasal drug in any dosage form. The most common age group was infants up to 1 year covering 31.1% patient population followed by 13-18 years (28%). Males (51.2%) were more in number than females (48.8%). Age and gender distribution of target population has been presented in Table 1 and common indications for intranasal drug use in figure 1. In total, 547 drugs were prescribed in 164 prescriptions including 173 intranasal drugs and 374 co-drugs. Number of intranasal drugs per prescription was

Table 1. Age and gender distribution

Category	Groups	Percentage (%)
Age (years)	<1	31.1
	1-6	18.3
	7-12	20.7
	13-18	28.0
Gender	Male	51.2
	Female	48.8

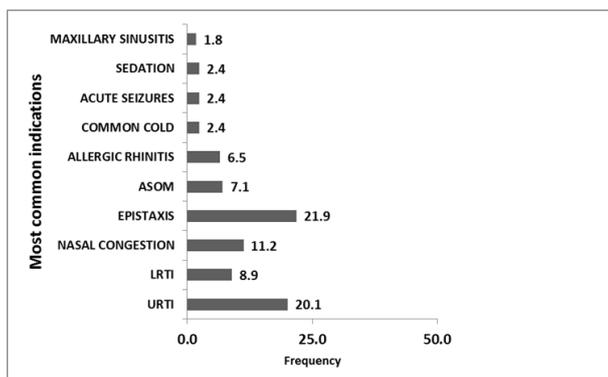


Figure 1. Location of abscesses in patients with Deep Neck Infections

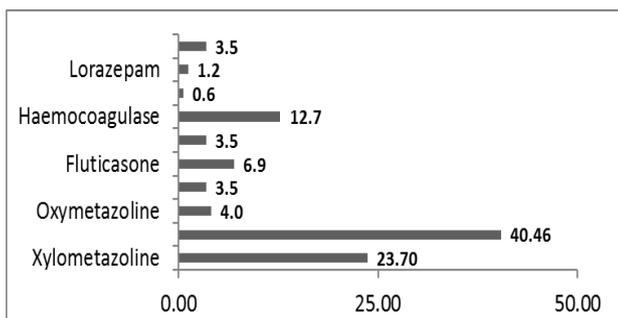


Figure 2. Different classes of intranasal drugs prescribed

Table 2. Drug usage in different age categories

Age group (years)	Intranasal drugs	Frequency (n)
< 1	Nasal saline (0.65%)	48
	Xylometazoline hydrochloride (0.025%)	1
1-6	Nasal saline (0.65%)	18
	Xylometazoline (0.05%)	5
	Midazolam	2
7-12	Xylometazoline hydrochloride (0.05%)	15
	Hemocoagulase	7
	Fluticasone propionate (0.05%)	7
13-18	Hemocoagulase	14
	Mometasone furoate (0.05%)	5
	Fluticasone propionate (0.05%)	5

1.05. Figure 2 shows different classes of intranasal drugs prescribed. In terms of dosage form nasal drops, 138 (79.8%) was most common. Intranasal drug usage in different age

Table 3. The values of core prescribing indicators along with WHO recommended value

WHO core prescribing indicators	WHO reference Values	Study prescription value
Average number of drugs per prescription	1.6-1.8	3.34
Percentage of encounters with an antibiotic prescribed	20.0-26.8%	58.5%
Percentage of encounters with an injection prescribed	13.4-24.1%	22%
Percentage of drugs prescribed by generic name	100%	78.2%
Percentage of drugs prescribed from national essential drug list	100%	73.7%

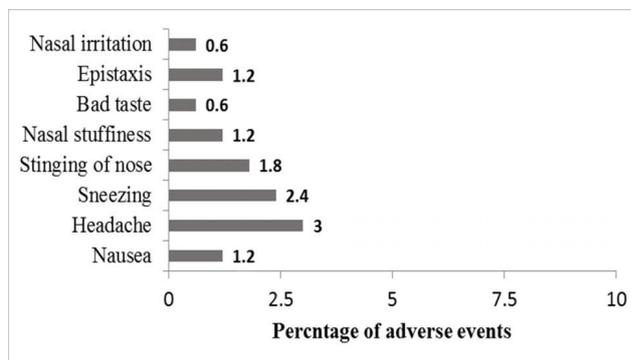


Figure 3. Total adverse events

Table 4. ADR of specific intranasal drugs

Drug	Number of prescriptions	Adverse event	Frequency		
Normal saline	70	Sneezing	2 (2.9%)		
		Xylometazoline	41	Headache	2 (4.9%)
		Stinging of nose		2 (4.9%)	
		Nasal stuffiness		2 (4.9%)	
Epistaxis	1 (2.4%)				
Hemocoagulase	22	Nausea	1 (2.4%)		
		Headache	1 (4.5%)		
		Sneezing	1 (4.5%)		
Fluticasone	12	Nausea	1 (8.3%)		
		Epistaxis	1 (8.3%)		
		Nasal irritation	1 (8.3%)		
Mometasone	6	Headache	1 (16.7%)		
Azelastine + Fluticasone	6	Sneezing	1 (16.7%)		
		Bad taste	1 (16.7%)		
Oxymetazoline	7	Headache	1 (16.7%)		
		Stinging of nose	(14.3%)		

categories depicted in table 2. The values of core prescribing indicators in our study along with WHO recommended values illustrated in table 3. The 9.8% prescriptions showed monotherapy, percentage of polypharmacy was 19.5%, fixed dose combination drugs were 45.7% per prescription, 63% of drugs were prescribed from hospital formulary, we

also found out 37.5 % prescriptions showed percentage of off-label drug use. Analysis of co-drugs revealed the most commonly prescribed antibiotics were Co-amoxiclav (50.5%), Ceftriaxone (25.7%), Ofloxacin (7.9%). The common groups of co-drugs prescribed were mainly Antibiotics (26.2%), followed by antiallergics (16.3%) and vitamins and minerals (14.2%). In consideration of dosage forms, tablets (29.4%) were most common followed by injections (28.1%) and syrups (17.9%). The Ceftriaxone (25.2%) were most commonly prescribed injections followed by Tranexemic acid (19.4%) and Pantoprazole (18.4%).

DISCUSSION

Our idea was to get an idea about intranasal drug usage in our hospital and to check the prescribing pattern of such drugs in paediatric age group of patients along with their safety profile. Nasal saline was the most intranasal drug in two age groups – newborn to 1 year and 1-6 years, whereas xylometazoline and hemocoagulase were the most common intranasal drugs in age groups of 7-12 years and 13-18 years respectively. In our study nasal saline was maximally used for upper respiratory tract infection and nasal congestion. Several studies have reported efficacy of nasal saline solution as an individual or adjunctive drug therapy for allergic rhinitis and nasal congestions.⁷ Intranasal xylometazoline, oxymetazoline has been used for treatment of nasal congestion, rhinitis, sinusitis.^{8,9} Most common use of xylometazoline was epistaxis in our study. Several other studies also prove efficacy of xylometazoline in nasal bleeding due to vasoconstrictor action.^{9,10}

Intranasal corticosteroids used were fluticasone propionate nasal spray with most common indication being allergic rhinitis and mometasone furoate nasal spray with most common indication of use being maxillary sinusitis. Rizzo et al. and several other studies have reported use of intranasal corticosteroids in different nasal disease like allergic rhinitis, sinusitis and nasal congestion or obstruction due to several nasal pathologies.¹¹⁻¹²

Topical coagulant hemocoagulase was used in significant almost 13% of patients as nasal drops and only indication for its use was epistaxis. Hemocoagulase is an enzyme complex, based on the coagulative and anti-hemorrhagic properties of fractions isolated from the poison of *Bothrops atrox* or *Bothrops Jararaca*. Hussain et al. also shows use of local hemostatic agent hemocoagulase in epistaxis.¹³ Antihistamine nasal spray azelastine hydrochloride was used in combination with nasal corticosteroid fluticasone for allergic rhinitis in our study. Other intranasal drugs we found in our study were antimigraine drug zolmitriptan nasal spray prescribed for acute migraine. Several studies had reported efficacy of zolmitriptan nasal spray in controlling acute migraine episodes in adolescent age group.^{14,15}

Administration of anti epileptic medications midazolam and lorazepam via intranasal route in the pediatric population has a proven efficacy in controlling seizures. Due to lack of atomiser device, lorazepam was directly instilled into any one nostril of drop by drop over 30-60s. The formulation and dosage of IN lorazepam were the same as the IV formulation containing lorazepam. When asked to demonstrate steps of intranasal drug administration as per guidelines, it was correct in only 11.6% cases.¹⁶ Following proper procedure for drug administration is vital for desired drug effects, which was certainly lacking. This may be due to low literacy status of the patients or their LARs. Also not demonstrating the proper drug delivery procedure in such busy OPDs like ours, may have some contributions too. In our study intranasal drugs have been used locally, for treating nasal diseases only. Systemic use of intranasal drugs is very sparse in our hospital. No banned drugs were prescribed by prescribers. The reason may be, many such drugs are yet to be labelled and their dose recommendations and therapeutic guidelines are not so well established.

Now coming to the WHO prescribing indicators, average number of drugs per encounter was 3.34 that is higher compared to values of 2.06, 2.75, 2.9 and lesser compared to 3.6, 3.6, 3.62 in some other Indian studies and the closest being 3.2 in Hazra et al.¹⁷⁻²³ Some international studies have reported values as high as 4.51 in Pakistan by Das et al. and as low as 1.3 in Zimbabwe by Hogerzeil et al. whereas studies in Nigeria and Nepal reported values of 2.6 and 2.79 both lie between those extreme values.²⁴⁻²⁷ As per WHO recommendations, the average number of drugs per encounter should be between 1.6-1.8, so the value of 3.34 for this indicator is quite high compared to standard.²⁸ This can be an indicator of polypharmacy and subsequently increased number of drug interactions and adverse events. Although this high value may be due to the fact that our study included inpatients also, who generally have more severe illnesses and need more medications to treat.

We found drugs prescribed by generic name which is higher than results of 51.8%, 51%, 21.5%, 46.2% and 36.2% obtained in different Indian studies and outside India also (Nepal 0% and Nigeria 68.9%).^{18,20,21,23,26,27,35} An Indian study reported of 100% generic prescriptions.²² Although percentage of generic prescription is quite high in our study compared to some similar studies done in past, it is quite below the WHO recommendations of 100% generic prescriptions.²⁸ In our study percentage of prescriptions with at least one antibiotic was close to the value of 55% by Parveen et al.¹⁸ Our value is lower compared to values of 66.7, 72.8, 77.2 and higher compared to 39.6%, 46.2 found in similar studies across India.¹⁹⁻²³ In the neighboring countries like Pakistan and Nepal different studies have revealed higher percentages of antibiotics prescribing 78% Pakistan, 79.9% Nepal.^{24,27} WHO recommended value for this indicator is 20.0-26.8%.²⁸ So, 58.5% prescriptions with an antibiotic is quite higher than WHO standard values.

Rational use of antibiotics also can reduce emerging problems of drug resistance. Prescriptions included at least one injection is comparatively much higher than some previous figures like 0%, 0.2%, 7.0%, 0.17% and 3.9% from similar studies in India and also higher than figures of 13.5% and 0.12% outside India.^{17,19,20,22,23,26,27} Our data is well within the range of WHO recommendations. Limiting the number of injections in prescriptions in an appropriate manner not only reduces cost of treatment but also increases patient's compliance to treatment regimen.

Drugs prescribed from national essential drug list in our study were more or less comparable to other studies 40.9%, 90.3%, 78.4%, 81.6%, 45.7%, 66.9% and 94.5%, although it is lesser if compared to the WHO recommended value of 100%.^{18,19,21,22,23,29,30} Drugs prescribed were available in local hospital formulary, is lesser compared to 82.3% in Siddhartha et al.¹⁷ Percentage of prescriptions with monotherapy is lower than recommended though Parveen et al. reported even lower value (6.2%).¹⁸ The numerical definition of polypharmacy ranges from 2 or more drugs to 11 or more drugs prescribed daily but in a systematic review done by Mansoon et al. five or more medications was defined as polypharmacy in 46.4% articles.³¹ So we categorised polypharmacy as 5 or more drugs per prescription which showed the rate of 25% in our study. This value is lower than 62.4%, 56.8%, 60%, 23.8 and 40% and higher than 7.5% obtained from similar studies in our country.^{19,22,29,32,33} One study by Junius et al. had 53.6% prescriptions with 5 or more medications.³⁴ Though the rate of polypharmacy in our study was much lesser than the studies we discussed here but that may be due to those studies included fewer number of medications for defining polypharmacy. Still our values are not satisfactory regarding rational drug use. Polypharmacy increases the total health care costs and also can lead to poor patient compliance, also there are chances of higher incidences of different adverse events with increased drug-drug interactions. Hence, there is a continuous and urgent need to identify the predictors that leads to polypharmacy. Percentage of fixed dose combinations per prescription in our study was more or less comparable to values of 59%, 46.7% and 47% in other studies.^{20,22,35}

Among the injectables used in our study, ceftriaxone was the commonest followed by tranexamic acid and pantoprazole. Antibiotics were the most common group among the injectables used. Most common antibiotics used in our study were co-amoxyclav, followed by ceftriaxone and ofloxacin. Bhat et al. also reported amoxicillin- clavulanic acid as the most commonly used (53%) antibiotic in a prescription pattern study in the ENT department.³⁶ Off-label use in our study that is comparatively lesser than 50.62% reported by Jain et al. in a study regarding off-label drug use in children.⁶ Most of the adverse events were moderate degrees, resolved spontaneously. Nasal saline therapy was well tolerated in our study. Several other studies also have reported almost no adverse events.³⁷

Xylometazoline is reported safe in most studies causing mainly some mild to moderate side effects e.g. epistaxis, blood-tinged mucus, headache and period pain.³⁸ We also had the same results. Fixed dose combinations of azelastine and fluticasone have reported mild adverse events like dysgeusia, nasal discomfort, nausea, rhinorrhoea and sneezing (n=2, for each event). We also found sneezing, bad taste and headache (n=1, for each event) in patients prescribed such combination drugs.³⁹

Reported adverse events from intranasal steroid use (e.g. MF and FP) have been primarily local (eg, epistaxis, nasal burning, nasal irritation and headache. Based upon the results of several clinical studies, administration of MP, FP even when used in high doses for long term basis show no strong evidence of HPA-axis suppression, growth retardation, disturbed bone metabolism or other systemic side effects. Our study also revealed the same results. Studies involving intranasal zolmitriptan also did not report any serious adverse events, dysgeusia being one common adverse event. We also didn't find any adverse events in a patient who was prescribed zolmitriptan. Intranasal use of hemocoagulase in our study showed some mild adverse events like headache (n=1), sneezing (n=1).

Limitations of our study include study population was lesser compared to other prescription pattern studies. Short term follow up period. Only two departments were included. More attention was needed toward demographic variables. The possible confounders in our study were demographic characteristics of patients, a busy outpatient department. Prescribing habit, knowledge attitude and practice of prescriber toward essential medicine lists and rational drug use is also an important confounder.

CONCLUSION

Intranasal drug prescribing in our study was mainly aimed for treating nose related problems, exploration of this delivery route for systemic action were very few. Some prescribing indicators, such as prescribing by generic name and prescribing from national essential drug list were not bad but there is obvious scope for improvement. Parameters like average number of drugs per prescription and antibiotic use was quite higher than the recommended values while the percentage of injections was as per WHO recommendations.

Intranasal drug use for different systemic illnesses may be considered more often if found beneficial enough as it has a huge prospect in drug therapy. CME's regarding rational drug prescribing should be done on a regular basis to improve the drug prescribing habits of the prescribers. Multidisciplinary approach to be undertaken in future for further exploration.

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