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ORIGINAL RESEARCH ARTICLE

Adverse Drug Reactions of Intranasal Corticosteroids in the Netherlands: An Analysis from the Netherlands Pharmacovigilance Center

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Abstract

Background Intranasal corticosteroids are one of the cornerstone treatment options for allergic rhinitis and chronic sinusitis complaints. Safety information in the summary of product characteristics may not be representative for observations in daily clinical practice. The Netherlands Pharmacovigilance Center (Lareb) collects post-marketing safety information, using spontaneous reporting systems.

Objective Our objective was to analyse reports of adverse drug reactions associated with intranasal corticosteroids reported in the Dutch spontaneous reporting database of the Netherlands Pharmacovigilance Center Lareb to obtain insight into real-world safety data.

Methods We retrospectively examined all adverse drug reactions of intranasal corticosteroids reported to the Netherlands Pharmacovigilance Center Lareb, entered into the database from 1991 until 1 July, 2020.

Results In total, 2263 adverse drug reactions after intranasal corticosteroid use were reported in 1258 individuals. Headache (n = 143), epistaxis (n = 124) and anosmia (n = 57) were reported most frequently. Nasal septum perforation (reporting odds ratio 463.2; 95% confidence interval: 186.7–1149.7) had the highest reporting odds ratio, followed by nasal mucosal disorder (reporting odds ratio 104.5; 95% confidence interval 36.3–301.3) and hyposmia (reporting odds ratio 90.8; 95% confidence interval 45.1–182.7). Moreover, 101 (4.5%) reports were classified as serious by Lareb, including reports of Cushing's syndrome, adrenal cortical hypofunction and growth retardation.

Conclusions Many side effects are consistent with the safety information in the summary of product characteristics of intranasal corticosteroids. Several serious (systemic) side effects are reported and it is important to realise that intranasal corticosteroids may contribute to the development. Healthcare providers and patients should be aware of the potential (individual) adverse drug reactions of intranasal corticosteroids. This information could help in discussing treatment options.

Key Points

To our best knowledge, this is the first study to analyse database reports of intranasal corticosteroids in Europe.

Many adverse drug reactions that are reported in the database are consistent with the safety information in summary of product characteristics of intranasal corticosteroids.

Intranasal corticosteroids may be a contributing factor in the development of serious (systemic) or rarer side effects.

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1 Introduction

Allergic rhinitis (AR) is a symptomatic nasal disorder affecting both children and adults, with a worldwide prevalence of 8.5–27.2% depending on age [1–3]. Intranasal corticosteroids (INCs) are one of the cornerstone treatment options for this indication. Intranasal corticosteroids have proven to be effective in preventing allergic symptoms [4, 5]. Intranasal corticosteroids are also prescribed for chronic sinusitis complaints with nasal polyps. In the summary of product characteristics (SmPC) safety data from clinical trials, post-authorisation marketing studies and spontaneous reports (if a causal relationship is at least a reasonable possibility) are summarised [6].

Adverse drug reactions (ADRs) of INCs are classified as local and systemic ADRs. Occurrence of systemic ADRs is partly subject to systemic bioavailability. Systemic ADRs can be type A reactions (are the result of pharmacological properties of the drug) or type B reactions (are not directly linked to systemic bioavailability) [7]. Systemic bioavailability is determined by the small fraction of INCs that diffuses across the nasal mucosa, but is mainly determined by the fraction swallowed and absorbed by the gastrointestinal tract and cleared by first-pass metabolism [8–10]. Intranasal corticosteroids that are now commonly used (including mometasone furoate, fluticasone propionate and fluticasone furoate) have pharmacokinetic properties that minimise systemic bioavailability (<1%) in comparison with other INCs (triamcinolone acetonide, flunisolide, beclomethasone dipropionate and budesonide) [10, 11].

Safety information in the SmPC is at least partly gathered from a carefully selected population that received medication under controlled and monitored conditions in clinical trials. Therefore, the safety information in the SmPC may not be fully representative for observations in daily clinical practice [12]. To our best knowledge, extensive analysis of real-world safety data of INCs is lacking in peer-reviewed literature.

Spontaneous reporting systems are used to collect post-marketing safety information. Patients and healthcare workers are able to report clinical information about ADRs to pharmacovigilance centres. The Netherlands Pharmacovigilance Center (Lareb) collects and analyses ADRs of medicines and vaccines reported by healthcare professionals and patients from clinical practice in the Netherlands, received either directly or via marketing authorisation holders. In this study, we analysed the reports of ADRs possibly associated with INCs in the Dutch spontaneous reporting database of the Netherlands Pharmacovigilance Center Lareb in order to get insight into real-world safety data.

2 Materials and Methods

2.1 Data Source and Selection

We retrospectively observed all ADRs of INCs (Anatomical and Therapeutic Chemical classification code R01AD) reported to the Netherlands Pharmacovigilance Center Lareb. Reported ADRs in the database of the Netherlands Pharmacovigilance Center Lareb were coded using the *Medical Dictionary for Regulatory Activities* structure version 23.0, which has a hierarchical structure [13]. Drugs were coded using the Dutch drug dictionary and were classified using Anatomical and Therapeutic Chemical classification codes [14]. Data included suspect drug, co-medication, patient's sex and age, and the suspected ADR [13].

We included all reports in which an INC was reported as a suspect or interacting drug (a drug potentially causing the ADR) entered into the database from 1991 until 1 July, 2020. Intranasal corticosteroids included were azelastine/fluticasone propionate, beclomethasone dipropionate, budesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate and triamcinolone acetonide. We included spontaneous reports from healthcare professionals and patients. Adverse drug reactions were analysed at the *Medical Dictionary for Regulatory Activities* high-level term and preferred term levels. The dataset was checked for duplicate reports. Duplicate reports may occur if an ADR report includes two different suspect INC products. When counting the reported ADRs, these ADRs are counted twice. In the analysis of the characteristics of the users and the ADRs at the high-level term level, these duplicates were corrected. There might be reports in which an ADR has been reported separately by both the patient and the healthcare provider.

2.2 Data Analysis

We calculated the reporting odds ratio (ROR) for selected associations. The ROR compares the rate of reporting a specific ADR for a drug with the rate of reporting the same ADR for all other drugs. The ROR is calculated by a division: the numerator is the number of cases in which an INC was used and a specific ADR was reported divided by the number of cases using INCs in which this ADR was not reported; the denominator is the number of cases using other suspected drugs reporting a specific ADR divided by the number of cases using other suspected drugs without reporting that specific ADR. It is expressed as a point estimate with corresponding 95% confidence intervals (CIs). At least three reports have to be present in the database to compute a reliable ROR [15]. If the ROR was statistically significant (lower limit of the two-sided 95% CI was ≥1), then the ADR was considered to be significantly associated with the drug

of interest in reference to other reports in the database. The ROR offers insight into the disproportionality of an association and not into its causality [16].

We described the rankings of the most reported ADRs (top 20) and the highest ROR values (top 20) in the overall population, independent of age or INC that was used. Furthermore, we analysed ADRs that were reported only in children (defined as individuals aged between 0 and 18 years) and not in adults (defined as individuals aged 19 years and older) and vice versa. The same analysis was conducted for ADRs that were reported for only one INC and not for other INCs and vice versa. In these two analyses, ADRs were included if the association was statistically significant (the ROR lower limit of the two-sided 95% CI was ≥ 1), the ROR values were ≥ 10 and the number of reports was ≥ 3. In these analyses, we checked whether the ADRs were described in the Dutch SmPCs of the different included INC products.

Reported ADRs were classified as non-serious and serious by Lareb. Serious ADRs include fatal outcome, life-threatening ADRs, ADRs requiring (prolongation of) hospitalisation, ADRs resulting in significant disability/incapacity, ADRs resulting in a congenital anomaly/birth defect and other medically important conditions [17]. All other ADRs were classified as non-serious. We assessed the causality using the Naranjo score for a selection of reported serious ADRs, considered as relevant by the authors (serious and remarkable ADRs). The Naranjo algorithm is a quantitative method to assess whether there is a causal relationship between a drug and an adverse effect [18].

3 Results

3.1 Data Characteristics

We found 2263 reports of ADRs after use of INCs from 1258 individuals. An overview of the characteristics of these individuals and the reported ADRs at a high-level term level is provided in Table 1 and the Electronic Supplementary Material, respectively. Most affected individuals were female adults (n = 784, 62%). Fluticasone propionate (drops or spray) was used by most individuals (n = 451, 36%). Duplicates were corrected. There were 14 ADRs double reported by three individuals using two INC products.

Table 1 Characteristics of the individuals

Characteristic	Includes	Reports, *n* (%)
Sex	Male	456 (36)
	Female	784 (62)
	Unknown	18 (1)
Age	Child	106 (8)
	Adult	1008 (80)
	Unknown	144 (11)
Intranasal corticosteroid	Azelastine/fluticasone propionate	96 (8)
	Beclomethasone dipropionate	88 (7)
	Budesonide	172 (14)
	Nasal inhalation powder	36
	Spray	136
	Flunisolide	14 (1)
	Fluticasone furoate	150 (12)
	Fluticasone propionate	451 (36)
	Drops	118
	Spray	333
	Mometasone furoate	278 (22)
	Triamcinolone acetonide	12 (1)

3.2 Overview of Reports

A ranking of the most reported ADRs (preferred term name) is given in Table 2, and a ranking of the highest ROR values is given in Table 3. Headache (n = 143; 6%), epistaxis (n = 124; 5%) and anosmia (n = 57; 3%) were reported most frequently. The ROR of headache, epistaxis and anosmia was, respectively, 2.1 (n = 143; 95% CI 1.8–2.5), 23.8 (n = 124; 95% CI 19.6–28.8) and 49.1 (n = 57; 95% CI 36.8–65.7). Most ADRs were described in the Dutch SmPCs of INC products. Reports of palpitations (n = 52; ROR 2.0; 95% CI 1.5–2.6), anxiety (n = 21; ROR 2.4; 95% CI 1.5–3.6), tinnitus (n = 19; ROR 2.4; 95% CI 1.5–3.8) and migraine (n = 14; ROR 2.4; 95% CI 1.4–4.0) were considered as ADRs currently not described in the Dutch SmPC of INC products.

Nasal septum perforation (n = 14; ROR 463.2; 95% CI 186.7–1149.7) had the highest ROR value, followed by nasal mucosal disorder (n = 5; ROR 104.5; 95% CI 36.3–301.3) and hyposmia (n = 11; ROR 90.8; 95% CI 45.1–182.7). The majority of ADRs with the highest ROR values were described in the Dutch SmPC of INC products, except for abortion (n = 3; ROR 16.0; 95% CI 5.0–51.7).

We analysed the ADRs reported in children and adults separately. An overview of ADRs that were reported only in children and not in adults, and vice versa, is given in Table 4. In children, growth retardation (n = 4; ROR 26.9; 95% CI 9.5–75.7) is a noteworthy ADR. In adults, local and known ADRs are particularly reported.

There were no ADRs that were reported for only one INC and not for others. Our results did not indicate any

Table 2 Ranking of the most reported adverse drug reactions

ADR (PTName)	Number of reports	ROR	Lower limit ROR	Upper limit ROR	Described in SmPC
Headache	143	2.11	1.77	2.51	Yes
Epistaxis	124	23.76	19.59	28.82	Yes
Anosmia	57	49.14	36.75	65.71	Yes
Dyspnoea	53	1.55	1.18	2.05	Yes
Palpitations	52	1.97	1.49	2.60	No
Therapeutic response unexpected	38	1.53	1.11	2.12	Not applicable
Dysgeusia	30	3.65	2.53	5.26	Yes
Ageusia	28	6.30	4.31	9.20	Yes
Parosmia	27	21.55	14.47	32.09	Yes
Nasal discomfort	24	56.02	35.76	87.77	Yes
Vision blurred	23	2.74	1.81	4.14	Yes
Anxiety	21	2.34	1.51	3.60	No
Nasal congestion	20	12.11	7.70	19.04	Yes
Visual impairment	20	2.13	1.37	3.32	Yes
Tinnitus	19	2.41	1.53	3.81	No
Throat irritation	16	7.61	4.61	12.56	Yes
Nasal septum perforation	14	463.23	186.65	1149.67	Yes
Migraine	14	2.37	1.40	4.03	No
Rhinorrhea	13	6.23	3.58	10.84	Yes
Dysphonia	13	3.30	1.90	5.72	Yes

ADR adverse drug reaction, *PTname* Preferred Term name of Medical Dictionary for Regulatory Activities [12], *ROR* reporting odds ratio, *SmPC* summary of product characteristics

clinically relevant differences between the different INCs (data not shown).

3.3 Serious Reports

Of all reports, 101 (4.5%) reports were catogorised as serious by Lareb. There was one death: a young boy died and was using mometasone furoate, further details were missing but the autopsy revealed that the patient died because of a heart anomaly and was not related to INCs. There were three reports of foetal death. Three women (unknown age, 26-year-old, 30-year-old, respectively) lost their child in different periods in pregnancy (27th week, 11th week, unknown, respectively) after INC use. The relationship between INC use and foetal death in the first case was described as unlikely (baby had Downs' syndrome) and in the other two cases as unknown (further details were missing).

In 33 cases, the ADR led to hospitalisation. At the moment of reporting, 19 patients recovered completely, four patients have not yet recovered and two patients did not recover. None of them died. The recovery status of eight patients was not known.

There were six reports of Cushing's syndrome, five reports of adrenal cortical hypofunction and five reports of growth retardation (Table 5). We assessed causality using the Naranjo algorithm for a selection of reported serious ADRs, considered as relevant by the authors (i.e. aggression, chest discomfort, epilepsy, tendon rupture, tinnitus and vocal cord paralysis). The association between INC use and these serious ADRs was classified as possible. Given the relatively low number of reports and the fact that these associations were classified as possible and not as probable or definite using the Naranjo algorithm, further expansion and explanation of the results of the Naranjo scores were considered as not relevant for further discussion and therefore were not included in detail in this article.

4 Discussion

In this study, we analysed the ADRs after INC administration that were reported in the nationwide spontaneous reporting database of the Netherlands Pharmacovigilance Center Lareb. These safety data from daily clinical practice are of value in addition to the safety data that are already known and described in Dutch SmPCs. Headache, epistaxis and anosmia were reported most frequently in

Table 3 Ranking of the adverse drug reactions with the highest reporting odds ratio values

ADR (PTName)	ROR	Number of reports	Lower limit ROR	Upper limit ROR	Described in SmPC
Nasal septum perforation	463.23	14	186.65	1149.67	Yes
Nasal mucosal disorder	104.52	5	36.26	301.27	Yes
Hyposmia	90.77	11	45.09	182.72	Yes
Nasal discomfort	56.02	24	35.76	87.77	Yes
Anosmia	49.14	57	36.75	65.71	Yes
Nasal disorder	45.92	3	13.28	158.80	Yes
Nasal crusting	45.92	3	13.28	158.80	Yes
Nasal pruritus	38.26	3	11.26	130.06	Yes
Chorioretinopathy	38.26	3	11.26	130.06	Yes
Rhinalgia	31.31	3	9.36	104.73	Yes
Epistaxis	23.76	124	19.59	28.82	Yes
Cushing's syndrome	22.11	5	8.82	55.44	Yes
Hypogeusia	21.90	11	11.77	40.75	Yes
Parosmia	21.55	27	14.47	32.09	Yes
Product odour abnormal	18.75	4	6.76	52.05	Not applicable
Abortion	16.02	3	4.96	51.69	No
Dry throat	14.51	10	7.64	27.56	Yes
Glaucoma	14.26	7	6.63	30.66	Yes
Cataract	14.01	12	7.80	25.15	Yes
Growth retardation	13.68	5	5.54	33.79	Yes
Nasal dryness	13.68	5	5.54	33.79	Yes

ADR adverse drug reaction, *PTname* Preferred Term name of Medical Dictionary for Regulatory Activities [12], *ROR* reporting odds ratio, *SmPC* summary of product characteristics

Table 4 Overview of adverse drug reactions that only are reported in adults and not in children and vice versa

Age group	ADR (PTName)	Number of reports	ROR	Lower limit ROR	Upper limit ROR	Described in SmPC
Child	Enuresis	3	27.50	8.35	90.62	No
	Growth retardation	4	26.85	9.53	75.68	Yes
	Mood swings	3	16.67	5.15	53.99	Yes
Adult	Anosmia	55	48.12	35.66	64.93	Yes
	Chorioretinopathy	3	40.20	11.62	139.07	Yes
	Dry throat	9	13.78	6.99	27.14	Yes
	Eye infection	4	15.47	5.59	42.86	No
	Glaucoma	6	15.91	6.91	36.61	Yes
	Hypogeusia	10	23.26	12.05	44.88	Yes
	Hypomania	3	12.83	3.99	41.28	Yes
	Hyposmia	8	73.45	32.62	165.37	Yes
	Intraocular pressure increased	8	15.38	7.48	31.65	Yes
	Migraine with aura	4	13.19	4.79	36.34	No
	Nasal dryness	5	14.80	5.96	36.79	Yes
	Parosmia	25	20.36	13.44	30.86	Yes
	Pharyngitis	8	10.29	5.04	20.99	Yes
	Wheezing	4	10.73	3.92	29.38	Yes

ADR adverse drug reaction, *PTname* Preferred Term name of Medical Dictionary for Regulatory Activities [12], *ROR* reporting odds ratio, *SmPC* summary of product characteristics

Table 5 Reports of Cushing's syndrome, adrenal cortical hypofunction (including 'adrenal insufficiency'; 'adrenal suppression'; 'secondary adrenocortical insufficiency') and growth retardation after intranasal corticosteroid administration

ADR	Comment
Cushing's syndrome	6-year-old girl using fluticasone furoate. Concomitant use of lamivudin, lopinavir, ritonavir and abacavir.
	7-year-old boy using fluticasone. Concomitant use of montelukast and inhaled salmeterol/fluticasone.
	19-year-old woman using fluticasone. Concomitant use of inhaled fluticasone, mebeverine, amitriptyline, piroxicam, ethinylestradiol/levonorgestrel and morphine.
	40-year-old man using mometasone. Concomitant use of calcium carbonate, rosuvastatin, tenofovir/emtricitabine, darunavir, cetirizine, valsartan, metoprolol, allopurinol and esomeprazole.
	55-year-old man using fluticasone. Concomitant use of amlodipine, tenofovirdisoproxil/emtricitabine, atazanavir and ritonavir.
	70-year-old woman using budesonide. Concomitant use of inhaled formoterol/budesonide and acetylcysteine.
Adrenal cortical hypofunction	10-year-old girl using beclomethasone. Concomitant use of inhaled budesonide and fluticasone.
	11-year-old girl using budesonide. Concomitant use of cetirizine.
	14-year-old girl using budesonide. Concomitant use of inhaled salbutamol.
	41-year-old man using budesonide. Concomitant use of inhaled salmeterol/fluticasone.
	55-year-old man using fluticasone. Concomitant use of amlodipine, tenofovirdisoproxil/emtricitabine, atazanavir and ritonavir.
Growth retardation	6-year-old boy using fluticasone. Concomitant use of inhaled beclomethasone, ciclesonide and salbutamol.
	10-year-old girl using beclomethasone. Concomitant use of inhaled budesonide.
	11-year-old girl using budesonide. Concomitant use of cetirizine.
	5-month-old boy whose mother used fluticasone. No concomitant medication.
	Girl of unknown age whose mother used fluticasone. No concomitant medication.

ADR adverse drug reaction

the database. Nasal septum perforation, nasal mucosal disorder and hyposmia were the ADRs with the highest ROR values.

4.1 Main Findings

The ADRs with a relatively high number of reports and high ROR values are mostly already known and have been extensively observed in research. Occurrence of a number of local ADRs, including nasal discomfort, nasal congestion, nasal mucosal disorder and nasal crusting, may be explained by the local effect of INCs in the nose and throat. After administration, the glucocorticosteroid (GC) and excipients are deposited on the nasal mucosa, and they end up in the throat via the nose. This may lead to mucosal drying and thinning, resulting in irritation and dryness as (very) common side effects [8, 10]. Our results suggest a possible association, but it is also possible that these side effects are symptoms of the underlying pathology. Epistaxis is a more severe and common side effect and nasal septum perforation is a severe and rare side effect, which both could be avoided by using an appropriate administration technique [8]. Glucocorticosteroid particles mainly collide with the anterior septum of the nose. The anterior septum is a vulnerable part in the nose because of the high density of blood vessels (Kiesselbach's plexus), and it contains very thin mucosa [11, 19, 20]. Trauma to this part of the nose may lead to epistaxis. Another explanation is the chemical trauma of the GC itself or the physical trauma caused by the spray tip when it is inserted into the nose [11, 19, 20]. We found relatively high ROR values for these local side effects, which indicates that the use of INCs may be associated with the occurrence of these local side effects.

When interpreting these results, we need to consider the fact that these relatively high ROR values are observed because these local side effects mainly occur after the use of intranasally administered drugs. In comparison with orally administered drugs, intranasally administered drugs were less frequently reported to the Netherlands Pharmacovigilance Center Lareb, which will lead to higher ROR values in proportion.

Adverse drug reactions describing olfactory and gustatory dysfunction were also widely observed in our database, with a relatively high number of reports and high ROR values. These effects are known as side effects of INCs. The mechanism of smell and taste alterations is not fully understood. An explanation may be the direct action of the drug, which includes a drug-receptor interaction, the influence of action potential propagation in cell membranes of neurons, and an effect on neurotransmitter function and intervention in neural networks in brain regions associated with sensory coding and modulation [21, 22]. In addition, INCs can indirectly lead to smell and taste changes by affecting sensory

receptors (e.g. owing to drying of mucus, increased nasal secretion and closed-off taste pores) [21, 22]. Our results suggest an association, but it is also possible that these side effects are symptoms of the underlying pathology. In a review by Muganurmath et al. [21], a weak association was found between INCs and smell and taste alterations.

A number of ADRs include visual disturbances, such as blurred vision, cataract, chorioretinopathy, glaucoma and visual impairment. These ADRs are observed in our database with a relatively high number of reports and ROR values. Cataract, chorioretinopathy and glaucoma were mainly observed in adults (mean age 47 years), but cataract was also reported in one child. All are known side effects of INCs. Glucocorticosteroid administration by any route, including intraocular, topical or systemic, may lead to increased intraocular pressure by accumulation of proteins at the trabecular meshwork in the eye, which prevents normal drainage of ocular fluids. This leads to an increased intraocular pressure, which is a risk factor for developing (corticosteroid-induced) glaucoma [23, 24]. Glucocorticosteroids may boost fibroblastic growth, resulting in capillary fragility in the choroidal vessels and suboptimal choriocapillaris function. Additionally, GCs may also interfere with ion transport across the retinal pigment epithelium. This causes fluid accumulation behind the retina, primarily in the macula, causing chorioretinopathy [25]. Direct action of GCs on lens epithelial cells and indirect action through changes to the levels of intraocular growth factors possibly lead to (steroid-induced) cataracts [26]. All these effects may include symptoms of blurred vision or visual impairment.

Considering the ROR values, our findings indicate an association between INCs and cataracts, chorioretinopathy and glaucoma. A meta-analysis by Valenzuela et al. [27] describes that INCs are not associated with a significant risk of intraocular pressure elevation or cataract development in patients with AR; however, the risk of glaucoma cannot be eliminated [27]. Intranasal corticosteroids are rarely associated with the occurrence of chorioretinopathy [25].

The most frequently reported ADR was headache (143 reports; 6%). This side effect is qualified as common in Dutch SmPCs. Two meta-analyses by Donaldsen et al. [28, 29] describe the occurrence of this side effect in both children and adults. However, no significant difference was found between the occurrence of headache after the administration of INCs and after the administration of placebo [28, 29], suggesting that headache is caused by other factors. In daily clinical practice, elimination and provocation tests could be performed to identify whether headache is an ADR at an individual level.

Certain ADRs, including anxiety, migraine, palpitations and tinnitus, are not described in Dutch SmPCs, but are reported frequently in the database. Some of these reports were categorised as serious by Lareb.

Anxiety is one of the most frequently reported side effects, but a relatively low ROR (2.3; 95% CI 1.51–3.6) was observed. The occurrence of anxiety when using INCs can be explained as follows. Glucocorticosteroid receptors are located in the brain areas associated with emotions and cognitive functions. The use of GCs may activate these receptors, resulting in neuropsychiatric symptoms [30, 31]. Another database study, performed using VigiBase data, which focused only on neuropsychiatric outcomes after INC administration, also describes that anxiety is commonly reported [31]. Moreover, behavioural changes are commonly reported in paediatric populations after GC inhalation [32, 33]. However, there seems to be no relationship between inhaled GCs and behavioural changes in children [34, 35]. Considering the low bioavailability of INCs, the occurrence of these side effects is also likely to be rare, but on an individual level, neuropsychiatric side effects may occur because of individual vulnerability.

To the best of our knowledge, migraine has not previously been described as an ADR after INC administration. According to another database study, performed using VigiBase data, migraine is also commonly reported [31]. However, the mechanism remains unclear. These authors conducted a follow-up study and found a strong relationship between AR and the occurrence of migraine. Because INCs are the cornerstone treatment in AR, all migraine reports are potentially confounded by indication [36, 37]. Glucocorticosteroids may have a prothrombotic action, which results in complaints, but this is unlikely in the context of INCs considering their low bioavailability [36].

We did not find other reports of palpitations after INC administration in the literature. However, Lareb previously informed the Dutch Medicines Evaluation Board about a possible association on fluticasone (both inhaled and nasal) and palpitations [38]. There are other cardiovascular ADRs reported in our database, including arrhythmia, extrasystoles and tachycardia. A review by Fernandes et al. [39] on the safety of inhaled or systemic GCs in children reported that palpitations were observed in one study. In the literature, cardiovascular side effects are reported after the use of high-dose GCs, particularly when administered intravenously or as oral pulse therapy [40–42].

The exact pathophysiology of tinnitus is not fully understood, and studies describe many factors that may be involved, including the use of medication [43, 44]. However, no reports have been found that describe the occurrence of tinnitus after the use of GCs. Notably, GCs are also used in the treatment of tinnitus that has started suddenly [43].

Because anxiety, migraine, palpitations and tinnitus are ADRs not labelled in Dutch SmPCs, and little is known about the associations from previous studies, attention to this type of ADR in daily clinical practice and research to identify a possible relationship is needed. Elimination and

provocation tests may provide insights into the origin of these ADRs at an individual level.

In a comparable database study by Ahsanuddin et al. [45], data from the Food and Drug Administration Adverse Event Reporting System (FAERS) database was analysed. Five specific adverse events within three medication classes, including INCs, were analysed. Dyspnea, anosmia, ageusia, dysgeusia, epistaxis and headache were side effects with significant proportional reporting ratio and ROR values. These ADRs are also the most common ADRs in the Lareb database. Reporting odds ratio values cannot be directly compared because in the FAERS database study a distinction was made between different INC products [45].

4.2 Serious ADRs

Several systemic ADRs, including adrenal cortical hypofunction, Cushing's syndrome and growth retardation, were reported. These ADRs are known as serious adverse events of INCs and our results indicate an association between INCs and Cushing's syndrome and growth retardation in children.

Four cases of adrenal cortical hypofunction were reported, with relatively low ROR values. Secretion of the natural GC hormone cortisol is regulated by the hypothalamic–pituitary–adrenal axis (HPA axis). The HPA axis activity fluctuates with the circadian rhythm and is subject to a feedback mechanism [46]. Intranasal corticosteroids may suppress the HPA axis, which may lead to clinical adrenal insufficiency. Research shows that INCs do not cause clinically significant suppression of the HPA axis in children and adults, excluding rare reports [28, 29, 46].

Cushing's syndrome is a hormonal disorder caused by prolonged exposure of body tissue to cortisol. In particular, oral administration of GCs has been implicated in the development of Cushing's syndrome, particularly when used over a long period [47]. Occurrence of this ADR is rare, but several case reports of Cushing's syndrome in children have been published, indicating a risk [29, 48–50]. Six cases of Cushing's syndrome were reported in our database and the high ROR values, particularly in children, suggest an association.

Because short-term use of oral and inhaled GCs leads to growth velocity reduction in children, there has been a concern about the potential effects of INCs on growth [51]. Our results describe five cases wherein growth retardation was observed, and the high ROR value might indicate a possible association. Randomised controlled trials on the effect of INCs on growth in children (3 years of age or older) demonstrate contrasting results [52–54]. Randomised controlled trials did not find significant changes in growth velocity associated with INC use, but a few studies noted at least a temporary reduction in short-term growth velocity [29].

Given the low bioavailability of INCs, the occurrence of these systemic ADRs is likely to be rare. However, these findings emphasise the fact that these ADRs should be taken into account at all times. A relevant contributing factor to the development of these ADRs is the use of other GCs. Patients with AR who have co-morbidities such as allergic asthma and topical dermatitis are also often treated with inhaled and topical corticosteroids. These patients are at increased risk of systemic exposure to GCs, which makes patients, particularly children, vulnerable for the development of ADRs as described [52]. Therefore, in daily clinical practice, it is important to monitor growth in children during the use of INCs.

4.3 Differences Between INC Products

The methodology we used cannot provide any indication of differences between safety profiles between the different INCs; however, there are differences in pharmacokinetic characteristics, mainly with regard to absorption properties including lipid solubility [8, 9]. Increased lipophilicity of GCs increases uptake by the nasal mucosa, which results in greater retention within the nasal tissue, prolonged binding to the GC receptor and consequently less unbound GC that may lead to systemic side effects [11, 12]. Our results are not suitable to support the suggestion that the differences in absorption properties may lead to different safety profiles, but in daily clinical practice, differences at an individual level may be observed. In the study of Ahsanuddin et al., [45] higher ROR values were observed for specific INC products, this indicates a stronger potential association between specific INCs and ADRs.

4.4 Administration Technique

It is important to examine how side effects may be prevented. One of the influencing factors may be the technique of INC administration, particularly of a metered-dose spray pump. Theoretically, by teaching an adequate administration technique, adequate treatment of the complaints will be achieved, local side effects will be prevented and patient adherence will improve [11, 19, 55, 56]. We found that few patients administer their intranasal corticosteroid spray correctly [57]. However, research into the correct administration technique is scarce. Which administration technique leads to the highest efficacy and symptom control and the least side effects needs to be investigated extensively.

4.5 Strengths and Limitations

The strength of this study is that the results describe a variety of ADRs that were reported in the nationwide reporting database of the Netherlands Pharmacovigilance Center

Lareb. These ADRs were reported voluntarily by patients and healthcare workers. They make an effort to report clinical information about drug ADRs to share experiences and to warn others. Moreover, the present study provides insights into ADRs in multiple system organ classes, and to the best of our knowledge, this is the first study in Europe to analyse database reports of INCs with this broad approach.

Nevertheless, the study has some limitations. First, causality is hard to establish with these data. In many reports, concomitant medication was mentioned, which may be another influencing factor for the development of the reported ADR, especially medications containing GCs. Second, information about follow-up is limited, including information about rechallenge, previous exposure and the effect of a dose reduction. Third, it cannot be excluded that some reported ADRs are symptoms of the underlying pathology. Fourth, because of underreporting, the results cannot be translated into a large-scale estimation of the occurrence of side effects of INCs worldwide, and true incidences of ADRs cannot be determined.

5 Conclusions

Our study provides insights into real-world safety data by analysing ADRs that might be associated with INCs, reported in the Dutch spontaneous reporting database of the Netherlands Pharmacovigilance Center Lareb. This study underlines the importance of active reporting of ADRs after INC administration to the spontaneous reporting database of the Netherlands Pharmacovigilance Center Lareb; it is of great value to share experiences and to warn others. The study provides an overview of local and systemic ADRs and non-serious and serious ADRs that occur in daily clinical practice after INC use. Many side effects are consistent with what is already known about the safety of INCs. Several serious (systemic) side effects are reported and it is important to realise that INCs may contribute to the development of serious (systemic) side effects such as adrenal cortical hypofunction, Cushing's syndrome and growth retardation, which are ADRs that by many people are often related to (intranasal) corticosteroid use. Moreover, INCs may lead to rarer, more severe side effects including visual disturbances, migraine, palpitations and tinnitus, which are ADRs that many people not often relate to (intranasal) corticosteroid use. When prescribing INCs and discussing treatment, healthcare providers and patients should be aware of the possible ADRs and individual susceptibility. When side effects occur, elimination and provocation tests may be used to identify the origin of these effects at an individual level.

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Declarations

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Conflict of interest Corine Rollema, Eric N. van Roon, Corine Ekhart, Florence P.A.M. van Hunsel and Tjalling W. de Vries have no relevant conflicts of interest.

Ethics approval No ethical approval was necessary for this study because of the retrospective and anonymous study design.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The datasets for this article are not publicly available because of the Lareb data protection policy. Requests to access the datasets should be directed to the first author and will be granted on reasonable request.

Code availability The Structured Query Language statements for the data used in this article are not publicly available because of the Lareb data protection policy. Requests to access the datasets should be directed to the first author and will be granted on reasonable request.

Author contributions The original study protocol was designed by all authors. The query and dataset were established by CE. Data analysis was performed by CR; here, ENR, CE, FPAMH and TWV fulfilled an advisory and supervisory role. The design of the manuscript was determined by all authors, and CR developed the design into this article. All authors contributed to the final data analysis and to manuscript drafting and revision. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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