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Second-generation antihistamines: a study of poisoning in children

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ABSTRACT

Background and objectives: The toxicity of second-generation antihistamines after an overdose by a child is still unknown. The objective of this study is to use data from Poisons Centres in France to describe the toxicity profile of second-generation antihistamines for children and to compare the severity of poisoning observed from these with a first-generation antihistamine.

Method: This was a retrospective, multi-centre and observational study focusing on human cases of single-substance exposure to a second-generation antihistamine and to mequitazine, reported between 1 January 2001 and 31 December 2016 in Poisons Centres in France.

Results: From a total of 9403 children included, 5980 were exposed to a second-generation antihistamine and 3423 were exposed to mequitazine. The severity of exposure to second-generation antihistamines in children is low: among the children followed until a known outcome, 9% of children were symptomatic and in 97% of cases, the symptoms shown were of a minor-level severity (primarily drowsiness or restlessness). Depending on the substance, children who ingested doses 16 to 69 times the maximum recommended therapeutic dose remained asymptomatic. No deaths or severe symptoms were observed. No cases of lengthening of the QT interval or arrhythmias were identified. Mequitazine led to more symptoms than other substances (14.8% symptomatic children vs. 7.5%, Odds ratio (OR): 2.3 (2.0–2.6), $p < 0.0001$), more symptoms of moderate intensity (1.4 vs. 0.2%, OR: 8.3 (4.1–18.5), $p < 0.0001$) and more hospitalisation (19.1 vs. 8.7%, OR: 2.5, 95% CI: (2.2–2.8), $p < 0.0001$).

Conclusion: The severity of poisoning from second-generation antihistamines appears to be low among children and considerably lower than poisoning caused by mequitazine.

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Introduction

The prevalence of allergic diseases has increased significantly over the course of the last 30 years. According to the World Health Organisation, allergies are the fourth-ranking chronic disease worldwide and allergic rhinitis affects almost 600 million people [1]. The frequency of acute urticaria over the course of the general population's life is around 20% [2]. Among children, the prevalence of allergic rhinitis is 2–25% and asthma is 5–21%, with significant disparities between countries: rates are much higher in Western or industrialised countries [3,4]. According to a British study, 32% of patients with allergies receive treatment with antihistamines [5]. Therefore, antihistamines are very commonly prescribed to the general population. They are also available over the counter and, as such, are often present in household medicine cabinets.

These substances are competitive, reversible H1-receptor antagonists. They relieve the effects of histamine, which is produced by mast cells following an allergic reaction or a non-allergic release of histamines. The first H1 antihistamines, known as first-generation, came onto the market in the 1940s [6]. These first-generation substances, still on the market today, have weak selectivity for H1 receptors and are

able to pass the blood-brain barrier (BBB), which mainly leads to sedative and anticholinergic effects, but also to α -adrenergic receptor and serotonin effects. Mequitazine is a first-generation antihistamine in the phenothiazine family marketed in several countries in Europe, Africa and South America. In France, mequitazine is frequently prescribed (>1 million medical prescriptions in 2005 and 837,000 in 2015 including 30% for the treatment of chickenpox) [7]. In 1981, the second generation of anti-H1 antihistamines, with better selectivity for H1 receptors and less ability to pass the BBB, was commercialised. However, in 1986, reports on the cardiotoxicity of these new substances, terfenadine and astemizole, began to appear, resulting in their removal from the market in 1999. This encouraged the development of research into the mechanisms of cardiotoxicity in medications and subsequently, other antihistamines that were believed to be less cardiotoxic were marketed [6,8]. However, the effects of an overdose, including cardiotoxicity, are not well known and literature on the subject is sparse, notably with regard to children.

The objective of this study is to describe the toxicity profile of second-generation antihistamine exposures for children, a dosage-effect relation and to compare the severity of

poisonings with a first-generation antihistamine such as mequitazine.

Method

This was a retrospective, multi-centre, observational study of anonymous human cases of single-substance exposure to a second-generation antihistamine, reported between 1 January 2001 and 31 December 2016 to Poisons Centres in France and recorded in the national database of poisoning cases (Base Nationale des Cas d'Intoxication – BNCI). This database contains cases of poisoning recorded during telephone consultations and follow up carried out by healthcare professionals of the eight French Poisons Control Centres. Occasionally, data were complemented using hospital discharge reports. This database is authorized by the French Data Protection Authority (CNIL: Commission Nationale Informatique et Liberté, accreditation no. 747735). A total of 350,000 calls are received each year by French Poisons Control Centres and the proportion of calls from physicians is 30% vs. 65% from the general public and 5% from nurses and paramedics. Inclusion criteria were: children aged from birth to 15 years, single-substance exposure through oral administration to second-generation antihistamines (cetirizine, levocetirizine, desloratadine, loratadine, ebastine, mizolastine, fexofenadine, rupatadine and bilastine) or mequitazine, a first-generation antihistamine in the phenothiazine family. The cases for those for whom the ingested dose was unknown were excluded.

After a complete rereading of all the files by two different authors, the following information was analysed to describe the sample group: age, sex, medical history and weight. If it was not given, weight was assessed using a calculation to estimate weight, with the formula “Weight = (3 x age) + 7” if age is more than one year old and with the formula “Weight = 3.5 kg + 20 g/day of life” if the age is less than a year old [9]. To describe the poisoning, the following data was analysed: the year of exposure, circumstances of exposure, the medication in question, the ingested dose in milligram/kg, the treatment given and the place of treatment. The circumstances of exposure were categorised as follows:

- unintentional exposures, which include errors in the perceived risk to the child, corresponding to unintentional exposure, which is linked to the incapacity of the patient to analyse the potential danger of the situation, as well as adverse effects of medication ingested at the therapeutic dose.
- therapeutic mistakes corresponding to an error, regardless of type (prescription, discharge, patient, medication, pharmaceutical form, dosage, method of taking ...), occurring during intention to treat.
- intentional poisoning, including suicide attempts and other instances of intentional poisoning.
- misuse corresponding to an informed intentional overdose on medication in order to increase an effect judged to be insufficient.

Clinical characteristics of exposure were evaluated by gathering the symptoms observed, supplementary examinations, notably electrocardiography (ECG), clinical course and the severity of poisoning. The latter was re-evaluated for each file in accordance with the Poisoning Severity Score (PSS) [10]. The PSS classifies symptoms in five categories: a score of PSS 0 is given when the patient does not present any symptoms; mild, transient and spontaneously resolving symptoms are given a score of PSS 1; pronounced or prolonged symptoms are given a score of PSS 2; severe or life-threatening symptoms are given a score of PSS 3 and death is given a score of PSS 4. The overall PSS evaluates the severity of poisoning retrospectively, once the final outcome is known. The PSS is based on the most severe symptom of poisoning. This score was developed and tested with respect to both functional and lesion-causing toxicants, including medicinal products, and was validated by a prospective, multicentre study [10]. Given that this was a retrospective non-interventional study, and according to French law, the local Ethics Committee waived the need to approve this study.

All cases meeting the inclusion criteria were used for symptom description. The study of the dose-effect relation included only the cases for which patients were monitored by Poisons Centres until the final stage (death, after-effects or healing).

There is no harmonised procedure for patient follow-up in French Poisons Centres. The decision to follow patients depends on each practitioner. Patients for whom minimal clinical effects or no effects are expected are sometimes not followed. The maximum recommended treatment doses, which were compared to the ingested dose, are taken from the ThériaqueTM and PoisindexTM databases. All statistical analyses were performed using the BiostaTGV website (<http://marne.u707.jussieu.fr/biostatgv/>). The comparison of quantitative and qualitative values was carried out by the Mann-Whitney U test and Fisher's exact test, respectively.

Results

General characteristics of the sample group

The initial sample included 11,401 cases of exposure, of which 1998 were excluded because the ingested dose was impossible to determine. In the end, 9403 cases of exposure met the inclusion criteria (Figure 1). Figure 2 presents number of cases by year during the period of inclusion. Of the 9403 included patients, 4352 were female (46.2%), 5023 patients were male (53.5%) and gender was unknown in 29 cases (0.3%). The median age of patients was three years old (range three days to 15 years old). The general characteristics of the sample group are described in Table 1. Figure 3 presents the ingested dose for each molecule. For fexofenadine, the median ingested dose was 12.9 mg/kg (15.6–212.2 mg/kg). A follow up of patients was effectuated by Poisons Centres to a known outcome in 3599 cases. In 478 cases, patients had initial symptoms but were not

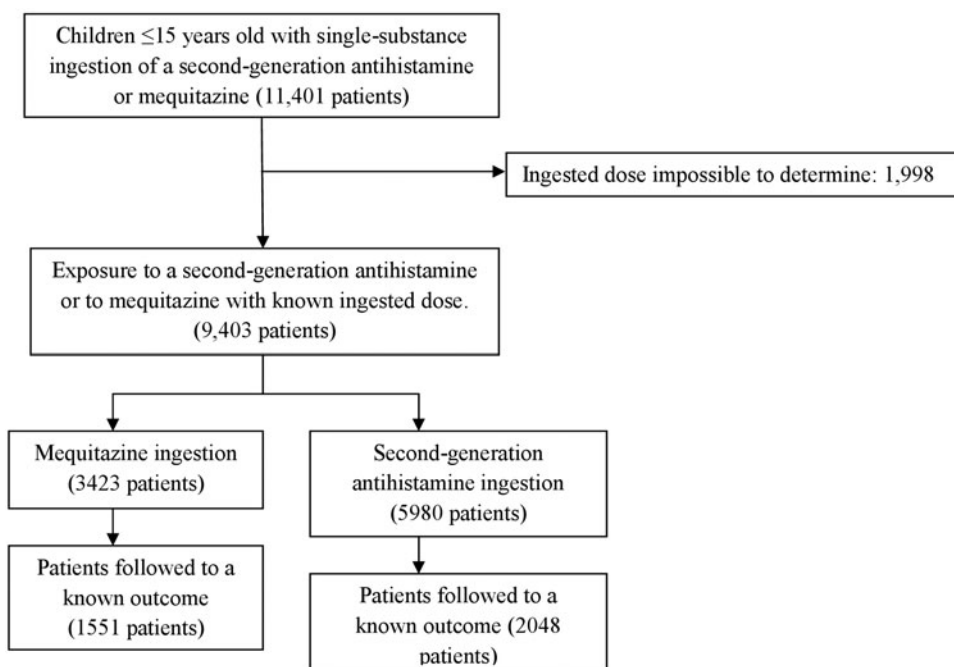


Figure 1. Consort diagram of the patient flow.



Figure 2. Number of cases per year.

monitored past the first call. In 157 cases, data were complemented using hospital discharge reports.

Toxicity profile

Among the children exposed and monitored by Poisons Centres to a known outcome, the majority showed no symptoms (91% for second-generation antihistamines and 81.4% for mequitazine). In all exposed children, symptoms were

recorded in 951 (10.1%) children (7.5% for second-generation antihistamines and 14.8% for mequitazine). The symptoms reported were highly varied. The principal symptoms are presented in Table 2. Other symptoms reported:

- with second-generation antihistamines: tremors ($n=5$), feeling of discomfort ($n=4$), bradycardia [3], mild hypertension ($n=3$), confusion ($n=2$), dyskinesia ($n=2$), mild hypotension ($n=2$), nystagmus ($n=2$), anorexia ($n=2$),

Table 1. General characteristics of patients included.

	Second-generation antihistamines (n = 5980)	Mequitazine (n = 3423)	Total (n = 9403)
Desloratadine	2625	–	–
Cetirizine	1356		
Loratadine	779		
Levocetirizine	412		
Ebastine	540		
Bilastine	107		
Mizolastine	60		
Fexofenadine	57		
Rupatadine	44		
<i>Circumstances of exposure</i>			
Accidental	3468 (58.0%)	2404 (70.0%)	5872 (62.5%)
Therapeutic error	1934 (32.3%)	874 (27.0%)	2808 (29.9%)
Misuse	76 (1.3%)	20 (0.6%)	96 (1.0%)
Intentional or suicidal	213 (3.6%)	6 (0.2%)	219 (2.3%)
Undetermined	289 (4.8%)	119 (2.2%)	408 (4.3%)
<i>Patients followed by Poisons centres to a known outcome</i>	2048 (34%)	1551 (45.3%)	3599 (38.3%)
<i>Median age in year (range)</i>	3 (3 days–15 years old)	3 (7 days–15 years old)	
<i>Age groups (year)</i>			
0–3	2353 (39.3%)	1683 (49.2%)	4036 (42.9%)
3–10	2901 (48.5%)	1684 (49.2%)	4585 (48.8%)
10–15	726 (12.2%)	56 (1.6%)	731 (7.8%)
<i>Gender ratio (M/F)</i>	1.13	1.19	–
<i>Severity in all patients</i>	5,534 (92.5%)	2,918 (85.2%)	8452 (89.9%)
PSS 0	436 (7.3%)	458 (13.4%)	894 (9.5%)
PSS 1	10 (0.2%)	47 (1.4%)	57 (0.6%)
PSS 2	0	0	0
PSS 3	0	0	0
PSS 4			
<i>Severity in patients followed by poisons centres</i>			
PSS 0	1864 (91%)	1262 (81.4%)	3126 (87%)
PSS 1	179 (8.8%)	256 (16.5%)	435 (12%)
PSS 2	5 (0.2%)	33 (2.1%)	38 (1%)
<i>Treatment location</i>			
Home	5185 (86.7%)	2459 (71.8%)	7644 (81.3%)
ED consultation	274 (4.6%)	311 (9.1%)	585 (6.2%)
Hospitalisation	521 (8.7%)	653 (19.1%)	1174 (12.5%)
<i>ECGs performed</i>	129 (2%)	149 (4%)	278 (3%)

PSS: Poisoning Severity Score.

constipation ($n=2$), respiratory depression ($n=2$), dysarthria ($n=1$), loss of consciousness ($n=1$), cyanosis ($n=1$), galactorrhoea ($n=1$), excessive sweating ($n=1$), urinary incontinence ($n=1$), muscle pain ($n=1$) and irregular movements [1].

- with mequitazine: irregular movements [6], trembling ($n=4$), bradycardia [3], cardiac arrhythmias ($n=2$, one premature ventricular contractions and one undetermined), confusion ($n=2$), urinary retention ($n=2$), seizures ($n=1$), loss of consciousness ($n=1$), dyskinesia ($n=1$), constipation ($n=3$), breathing difficulty ($n=1$) and feeling of discomfort ($n=1$).

Some symptoms like galactorrhoea, excessive sweating, urinary incontinence and muscle pain are unlikely related to the exposure. All substances caused symptoms and five led to moderately severe symptoms: mequitazine (47 cases), cetirizine (five cases), desloratadine (two cases), ebastine (two cases) and levocetirizine (one case). The PSS two cases for the second generation antihistamines are presented in Table 3. In the majority of cases of children followed by Poisons Centres, the severity of the symptoms was minor as 92% of symptomatic children developed symptoms classified as PSS 1 (97% for second-generation antihistamines and 89% for mequitazine). Only 1% (0.2% for second-generation

antihistamines and 2.1% for mequitazine) developed moderately severe symptoms (PSS 2).

Among the 3424 children exposed to mequitazine, 47 developed at least one symptom of moderate severity (PSS 2). In the majority of cases (64%), the children developed hallucinations associated with psychomotor agitation and/or drowsiness, tachycardia $>160/\text{min}$, lengthening of QTc $>450\text{ ms}$, seizures or limb spasms. No cases classed as PSS 3 or 4 in severity were observed

Cardiotoxicity

For second-generation antihistamines, among the 795 children who were examined in accident and emergency, an ECG was carried out for 129 of them and there was no evidence of lengthening of the QT interval or cardiac arrhythmias.

For mequitazine, three cases of lengthening in the QT interval during the ECG were observed in this study but none of which were above 500ms or considered clinically significant. In the first case, which involved a child of two years old who ingested 15 mg or 1.15 mg/kg, of mequitazine and did not present any clinical symptoms, the value of the QT interval was not specified but it normalised before they left accident and emergency. In the second case, which

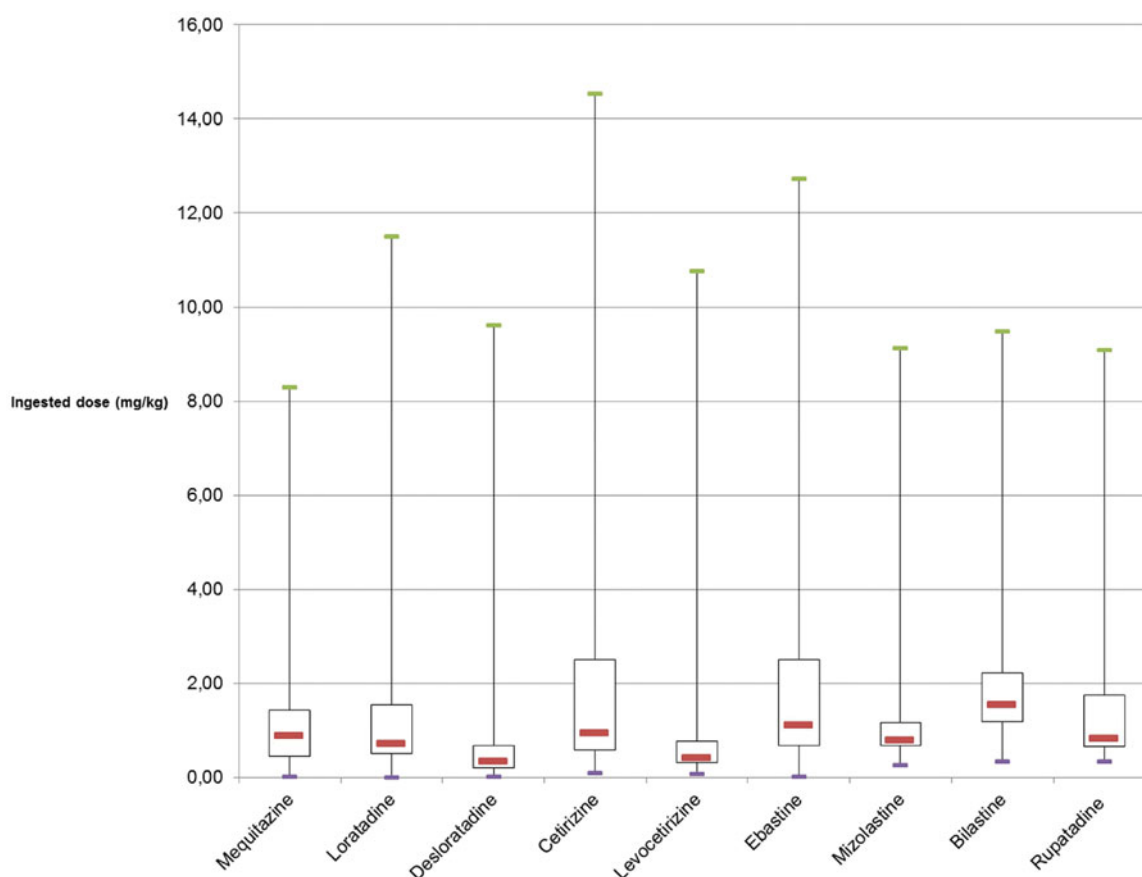


Figure 3. Boxplots of ingested dose for each molecule. For fexofenadine, the median ingested dose was 12.9 mg/kg (15.6–212.2 mg/kg). Results are expressed as median, interquartile ranges and extreme values.

Table 2. Description of primary symptoms observed.

Symptoms	Second-generation antihistamines, <i>n</i> = 5980 (2048 of whom were monitored by Poisons Centers)	Mequitazine, <i>n</i> = 3423 (1551 of whom were monitored by Poisons Centers)	Total
Drowsiness/asthenia	218	253	471
Restlessness	52	116	168
Nausea/vomiting	56	33	89
Tachycardia	35	25	60
Digestive pains	34	16	50
Hallucinations/delirium	8	30	38
Headaches	31	4	35
Mydriasis	16	17	33
Cutaneous rash/cutaneous outbreak	17	12	29
Dry mouth	11	9	20
Ataxia	9	11	20
Diarrhoea	16	3	19
Dizziness	15	–	15

concerned a child of two years old who had ingested 15 mg or 1.1 mg/kg, of mequitazine, the QTc had lengthened to 463 ms combined with bradycardia of 72/min before normalising to 392 ms and a heart rate of 140/min the day after exposure. The last case concerned a two-year-old child weighing 15 kg, who accidentally ingested 20 mg of mequitazine or 1.4 mg/kg. The child also showed visual hallucinations, mydriasis and restlessness, followed by psychomotor retardation. The measure of the QT interval was not specified in the file but normalised after 24 h of observation. A case of cardiac arrhythmia (not specified in the medical record) was highlighted in a child of four years old who incorrectly received 0.38 mg/kg of mequitazine. The child remained

asymptomatic and the ECG normalised over the course of observation in accident and emergency. Finally, salvos of ventricular extrasystoles were observed on the ECG of a four-year-old child who accidentally ingested 40 mg of mequitazine or 2.86 mg/kg.

Study of the dose-effect relation

The study of the dose-effect relation focuses on the files for which patients were monitored by Poisons Centres until the final stage. Table 4 presents the averages of doses ingested according to the appearance or absence of symptoms. There is a significant difference between the doses with and

Table 3. Description of cases with moderate severity after ingesting a second-generation antihistamine.

Case	Sex/age	Molecule and dosage	Therapeutic dosage for child	Symptoms
1	F/4 years old	Cetirizine, 0.30 mg/kg per day for seven days	Yes	Child treated with 10 drops of cetirizine per day for seven days. Delirium and hallucinations appeared on day 5.
2	M/9.5 years old	Cetirizine, 0.42 mg/kg	Yes	Symptoms appeared at the third hour after therapeutic dose of cetirizine, including loss of touch with reality, nystagmus, headaches, hypotonia and fall without tonic/clonic seizure, wetting self or biting tongue.
3	M/3 years old	Cetirizine, 3.60 mg/kg	No	Hallucinations and restlessness appeared a few hours after accidentally ingesting four 10 mg tablets of cetirizine.
4	F/10 years old	Cetirizine, 0.49 mg/kg	No	Confusion with temporal/spatial disorientation, incoherent speech and headaches four hours after accidentally taking two 10 mg tablets of cetirizine.
5	F/8 years old	Cetirizine, 0.65 mg/kg	No	Symptoms of intense restlessness, aggressiveness, hallucinations, dry mouth 2–4 h after intentionally ingesting two 10 mg tablets of cetirizine during a family dispute.
6	M/3.5 years old	Desloratadine, 4.70 mg/kg	No	Symptoms of sinus bradycardia (75/min), digestive pains and drowsiness after accidentally ingesting an alleged fifteen 5 mg tablets of desloratadine.
7	F/4 years old	Desloratadine, 0.06 mg/kg	Yes	Child treated with 1.25 mg of desloratadine (single dose). Persistent restlessness and hallucinations (seeing spiders) occurred for 24 hours a few hours after ingestion.
8	M/15 years old	Ebastine, 0.50 mg/kg	No	Overdose in attempted suicide by an adolescent who ingested six tablets and had hallucinations, high blood pressure (160/90 mmHg), digestive pains and mydriasis, which developed positively in a few hours.
9	F/3 years old	Ebastine, 8.30 mg/kg	No	Restlessness, abnormal head and hand movements after accidental ingestion of an alleged 10 tablets of ebastine in orodispersible form.
10	F/15 years old	Levocetirizine, 0.67 mg/kg	No	Alleged ingestion of seven 5 mg tablets of levocetirizine in a suicidal context. Appearance of hallucinations and delirium, progression unknown (loss of vision)

Table 4. Comparison of doses with and without effects for all molecules in patients followed by poisons centres to a known outcome.

	Symptoms	Average ingested dose (mg/kg) $\pm$ SD	P Value
Mequitazine ($n = 1551$)	PSS 0 ($n = 1262$)	1.15 ± 0.88	<0.0001
	PSS 1 and 2 ($n = 289$)	1.43 ± 0.98	
Desloratadine ($n = 915$)	PSS 0 ($n = 843$)	0.83 ± 1.10	0.004
	PSS 1 and 2 ($n = 72$)	1.41 ± 1.48	
Cetirizine ($n = 447$)	PSS 0 ($n = 408$)	2.20 ± 2.35	0.1
	PSS 1 and 2 ($n = 39$)	2.88 ± 3.04	
Loratadine ($n = 209$)	PSS 0 ($n = 184$)	1.53 ± 1.65	0.07
	PSS 1 ($n = 25$)	1.76 ± 1.43	
Ebastine ($n = 228$)	PSS 0 ($n = 201$)	2.10 ± 1.96	0.01
	PSS 1 and 2 ($n = 27$)	4.31 ± 3.65	
Levocetirizine ($n = 151$)	PSS 0 ($n = 135$)	0.76 ± 0.79	0.3
	PSS 1 and 2 ($n = 16$)	1.02 ± 0.93	
Bilastine ($n = 38$)	PSS 0 ($n = 37$)	2.50 ± 2.06	–
	PSS 1 ($n = 1$)	N/A	
Fexofenadine ($n = 23$)	PSS 0 ($n = 21$)	18.40 ± 15.4	0.44
	PSS 1 ($n = 2$)	21.57 ± 10.92	
Rupatadine ($n = 22$)	PSS 0 ($n = 21$)	32.51 ± 2.46	–
	PSS 1 ($n = 1$)	N/A	
Mizolastine ($n = 16$)	PSS 0 ($n = 15$)	1.55 ± 2.18	–
	PSS 1 ($n = 1$)	N/A	

PSS: Poisoning Severity Score.

without symptoms for mequitazine, desloratadine and ebastine. Clinical effects were reported at therapeutic doses for the following substances: desloratadine ($n = 22$, one of which is PSS 2), cetirizine ($n = 17$, one of which is PSS 2), loratadine ($n = 4$) levocetirizine ($n = 2$), ebastine ($n = 1$) and mequitazine ($n = 43$, eight of which are PSS 2). For mizolastine, rupatadine, fexofenadine and bilastine, the clinical effects were observed only when beyond the maximum recommended therapeutic dosage.

For each substance, Table 5 presents the minimum dose ingested by symptomatic children, the maximum dose ingested by asymptomatic children and the ratio between the maximum dose without symptoms and the maximum recommended therapeutic dose. It can be seen that the maximum doses without symptoms observed are between 16 and 69 times higher than the maximum recommended dose, depending on the substance.

Table 5. Comparison of minimum doses with effect (PSS1 and PSS2), maximum doses without effect and recommended therapeutic doses in children with known outcome.

Molecule	Minimum dose with observed symptoms (mg/kg)	Maximum dose without observed symptoms (mg/kg)	Maximum recommended therapeutic dose (mg/kg)	Ratio of maximum dose without symptoms/maximum therapeutic dose
Mequitazine	0.02	7.4	0.25	30
Desloratadine	0.02	9.6	0.14	69
Cetirizine	0.19	14.5	0.47	31
Loratadine	0.30	11.5	0.40	29
Ebastine	0.43	10.0	0.46	22
Levocetirizine	0.12	4.8	0.17	28
Bilastine	0.87	9.5	0.46	21
Fexofenadine	13.9	73.2	4.60	16
Rupatadine	0.48	9.1	0.23	40
Mizolastine	0.39	9.1	0.23	40

Table 6. Comparison of the severity of intoxication according to the type of molecule ingested.

<i>n</i> =	Second-generation antihistamines <i>n</i> = 5980	Mequitazine <i>n</i> = 3424	<i>p</i> Value	Odds ratio (95% CI)
Children with effect (PSS 1 and 2)	446 (7.5%)	505 (14.8%)	<0.001	2.3 (2.0–2.6)
Children with moderate poisoning (PSS 2)	10 (0.2%)	47 (1.4%)	<0.001	8.3 (4.1–18.5)
Asthenia or drowsiness	218 (3.6%)	253 (7.4%)	<0.001	2.1 (1.7–2.6)
Restlessness or hallucinations	60 (1.0%)	146 (4.3%)	<0.001	4.4 (3.2–6.1)
Hospitalisation	521 (8.7%)	653 (19.1%)	<0.001	2.5 (2.2–2.8)

PSS: Poisoning Severity Score.

Comparison between mequitazine and other substances

Mequitazine was responsible for 82% of cases of moderate severity in this study. When comparing the severity of intoxication observed between mequitazine and all other substances, it can be seen that mequitazine led to significantly more symptoms than other substances (14.8% symptomatic children vs. 7.5%, odd ratio (OR): 2.3, 95% confidence interval (CI): 2–2.6, $p < 0.0001$), more symptoms of moderate intensity (1.4% PSS2 vs. 0.2%, OR: 8.3, 95% CI: 4.1–18.5 $p < 0.0001$). Children were more often hospitalised after ingestion of mequitazine (19.1 vs. 8.7%, OR: 2.5, 95% CI: 2.2–2.8, $p < 0.0001$; Table 6).

Discussion

In this study, the severity of pediatric poisoning from second-generation antihistamines appears to be low. In fact, only 9% of children followed by Poisons Centres were symptomatic. Ninety seven percent of symptomatic children presented with symptoms of low-level severity (PSS 1). No deaths or severe symptoms (PSS 3) were observed. Effects were reported for low doses, which were sometimes below the maximum recommended therapeutic dose. The ratio of the maximum ingested dose without symptoms to the maximum recommended therapeutic dose was very high for the majority of substances: depending on the substance, children who ingested doses 16 to 69 times the maximum recommended therapeutic dose remained asymptomatic. The safety profile for second-generation antihistamines regarding overdoses among children therefore appears to be very satisfactory. These results are consistent with studies on the effectiveness and tolerance acquired by children for desloratadine, rupatadine, ebastine, loratadine, fexofenadine and levocetirizine [11–19].

In this study, the primary symptoms observed in overdoses were drowsiness and anticholinergic symptoms. These effects, largely described with first-generation antihistamines at therapeutic doses, were observed here, but to a lesser degree and in cases of overdose. In the literature, some rare and isolated cases of overdoses have been described. In an infant of 18 months, 180 mg of cetirizine or 13.8 mg/kg, led to agitation, irritability and then drowsiness [20]. Another infant of 18 months also ingested 180 mg of cetirizine and presented with signs of agitation for 12 h. The child's ECG was normal in the 15th hour [21]. A child of four years old ingested 60 mg of cetirizine or 3.17 mg/kg and showed signs of drowsiness for six hours. The child's ECG remained normal [22]. An overdose of 300 mg of loratadine for a child of six years old caused tachycardia of 150/min. No lengthening of the QT interval was observed [23]. No case of overdose in children was described for the other substances.

With regards to the cardiotoxicity of second-generation antihistamines, there was no evidence of lengthening of the QT interval in this study. No cases of arrhythmia, repolarisation troubles or cardiac conduction disorders were reported. The first second-generation antihistamines, astemizole and terfenadine, lengthened the QT interval, leading to torsades de pointes and arrhythmia due to a lengthening of the action potential by inhibiting the hERG potassium channels [24–26]. For substances in this study, pre-clinical studies showed that at an elevated concentration, the hERG potassium channels are blocked by ebastine and mizolastine and that the duration of the action potential is noticeably increased by ebastine [27–30]. In contrast, fexofenadine, desloratadine and cetirizine are very weak inhibitors of these channels [31–33]. Other *in vivo* studies showed that intravenous ebastine lengthened the QT interval in the ECG [34]. During clinical trials, it was shown that ebastine, at five times the therapeutic dose, significantly lengthened the QT interval [29]. Clinical trials did not find any cardiotoxicity for children

with cetirizine, loratadine, levocetirizine, desloratadine, ebastine, fexofenadine and mizolastine [8,12,19,27,32,35]. Pharmacovigilance and case reports demonstrate rare cases of arrhythmias and long QT interval with fexofenadine and cetirizine, primarily with predisposing conditions [8].

Mequitazine, a first-generation antihistamine in the phenothiazine family, is the most highly represented antihistamine in this study: it is the substance for which Poisons Centres were most frequently contacted, compared to other substances. However, mequitazine presents a less favourable safety profile. In this study, it led to significantly more symptoms than second generation antihistamines: 15% of children were symptomatic, compared to an average of 7.5% with other substances. Mequitazine was responsible for 82% of moderately severe cases in this study (PSS 2). When comparing the frequency and severity of symptoms observed between mequitazine and all other substances, it can be seen that mequitazine led to twice as many symptoms as other substances, eight times more symptoms of moderate intensity, two times more sedation and 4.4 times more paradoxical signs of restlessness and hallucinations. Children were significantly more often hospitalized after ingestion of mequitazine. No deaths or severe poisoning were reported with mequitazine in our study but first-generation antihistamines like diphenhydramine or doxylamine were the cause of several child deaths by criminal, suicidal or unintentional means reported in the literature [36–40]. The most common symptoms observed in severe cases are delirium, cardiac dysrhythmias, seizures and coma [41]. Although still frequently prescribed and available over the counter in France, first-generation antihistamines are no longer recommended. International guidelines and consensus conferences recommend the use of second-generation antihistamines when treating allergic rhinitis, allergic conjunctivitis and urticaria and the Global Allergy and Asthma European Network (GA²LEN) warned about the risks linked to the use of first-generation antihistamines [2,3,42,43]. It was also revealed that first-generation antihistamines reduced the academic performance of children with chronic allergies, unlike second-generation antihistamines [44–46]. It can be seen that there has been a clear reduction in the number of cases of exposure to mequitazine reported to Poisons Centres since 2014.

The limitations of this study are linked to its retrospective nature. Doses ingested are estimated doses. In some cases, weights were estimated. Most cases were not followed leading to unknown patient outcomes. None of the cases had confirmatory plasma concentrations. Not all cases are called in to Poisons Centres either from home or hospital. A limited number of patients received electrocardiogram monitoring. Finally, other first-generation antihistamines were not investigated.

Conclusion

This study aims to provide reassurance with regards to the toxic risks, notably cardiac, in the event of an overdose on second-generation antihistamines by children under 15 years

old. Outside intentional ingestion by a child or predisposed cardiovascular factors such as congenital long QT syndrome, hospital monitoring may not be necessary in case of unintentional ingestion. Mequitazine presents a less favourable safety profile in overdose.

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