First-Generation H1-Antihistamine Prescribing in Hospitalized Patients: A Quality Improvement Measure

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Abstract
First-generation H1-antihistamines are commonly utilized in hospital, however, these agents are associated with a number of undesirable adverse effects such as central nervous system (CNS) depression, cardiotoxicity and death in overdose.

We performed a retrospective analysis of all first-generation antihistamine prescriptions at the Regina General Hospital over the past year from January 1, 2019 – January 1, 2020. A total of 6,972 prescriptions were written during the study period, 6,692 (96%) of which were for first-generation antihistamines. The largest number of prescriptions for first generation antihistamines was in surgery, followed by internal medicine, and obstetrics and gynecology.

Physicians, pharmacists, and nurses in these areas may benefit from education around the potential for serious harm of first-generation antihistamines and the availability of safer alternatives. Additionally, limiting access to first-generation antihistamines in hospital would encourage safer prescribing habits and familiarity with second-generation agents.

Résumé
Les antihistaminiques H1 de première génération sont couramment utilisés en milieu hospitalier. Toutefois, ces agents sont associés à un certain nombre d'effets indésirables comme la dépression du système nerveux central (SNC), la cardiotoxicité et le décès causé par une surdose.

Nous avons effectué une analyse rétrospective de toutes les ordonnances d'antihistaminiques de première génération délivrées à l'hôpital régional de Regina au cours d'une année, soit du 1er janvier 2019 au 1er janvier 2020. Au total, 6972 ordonnances ont été rédigées au cours de la période à l'étude, dont 6692 (96 %) pour des antihistaminiques de première génération. Le plus grand nombre d'ordonnances d'antihistaminiques de première génération ont été rédigées en chirurgie, suivie de la médecine interne et de l'obstétrique et de la gynécologie.

Les médecins, les pharmaciens et les infirmières de ces secteurs pourraient tirer profit d'une formation sur le potentiel de dangerosité des antihistaminiques de première génération et sur l'existence de solutions de
Background

H₁-antihistamines (AHs) downregulate allergic inflammation directly through the H₁-receptor by interfering with histamine action. H₁-AHs are functionally classified into two groups: first-generation AHs readily cross the blood–brain barrier (BBB) and occupy H₁-receptors located on postsynaptic membranes of histaminergic neurons throughout the central nervous system (CNS), whereas second-generation AHs do not readily cross the BBB.¹⁻⁴

First-generation H₁-AHs are commonly utilized in hospital for the treatment of allergic conditions, such as urticaria, angioedema, and allergic rhinitis. These older, first-generation agents were first licensed in the 1940s, and as a result have not been studied adequately in healthy adults, let alone in special populations or with respect to drug–drug interactions.³ First-generation AHs, such as diphenhydramine and hydroxyzine, have poor receptor selectivity and nonspecifically bind muscarinic, serotonin, α-adrenergic receptors, as well as cardiac potassium ion channels. This leads to a number of undesirable and potentially life-threatening adverse effects, including the CNS depression, cardiotoxicity, and toxicity in overdose.³⁻⁵

Newer second-generation AHs, such as cetirizine and loratadine, are highly specific for the H₁-receptor and do not carry the same risk of adverse effects as first-generation agents.³ They have been rigorously studied in healthy young adults, children, elderly, and persons with hepatic and renal impairment.⁵⁻⁷ High-quality trials have proven second-generation AHs to be superior in safety, faster or equivalent in onset of action, with improved efficacy, length of action, and potency compared to older first-generation AHs.⁴⁻⁸ As a result, second-generation AHs are now considered first line for the treatment of urticaria and allergic rhinitis.⁸⁻¹⁰

In this retrospective analysis, we seek to establish the proportion of all antihistamines that are first-generation AHs prescribed over a 1-year period in hospitalized patients at a single center in Saskatchewan. We will highlight high-risk patient populations (i.e., the elderly, children, and pregnant women) and identify departments that may benefit from education, in an effort to limit the prescribing of first-generation AHs in the future.

Methods

Aim

We aim to establish the proportion of first-generation antihistamines prescribed of the total number of antihistamines at the Regina General Hospital (RGH) in Saskatchewan over a 1-year period, both in the emergency department and other hospital wards. We hypothesize that the number of first-generation antihistamines prescribed at the RGH over the study period to be higher than that of second-generation agents.

Design

We performed a retrospective analysis of all first-generation antihistamine prescriptions at the RGH over the past year, from January 1, 2019 to January 1, 2020. The primary end point is the proportion of first-generation antihistamines prescribed compared to all H₁-AH prescriptions over the past year at the RGH. Secondary end points include: (i) rate of second-generation antihistamine prescribing during the study period, (ii) number of patients under the age of 18 years prescribed a first-generation antihistamine, (iii) number of patients over the age of 65 years prescribed a first-generation antihistamine, and (iv) the service wards prescribing the first-generation antihistamine.

Statistical analysis

Based on national hospitalization data, the prevalence of antihistamine or allergy events at the emergency departments is low at 1%.⁹ Therefore, the sample size for a two-sample t-test with a 0.05 two-sided type I error rate and 80% power to detect a standardized effect size of 0.20 is estimated to be 191. Therefore, we aimed to review approximately a minimum of 200 patient charts, depending on the number of patients hospitalized with anaphylactic reaction events during the specified time period. Demographic characteristics and clinical variables were analyzed using the Chi-square test for categorical variables and t-test or nonparametric tests for continuous variables. All analyses were performed using SPSS, given the overall small sample size; clinical outcomes
were presented as means, medians, and/or proportions when appropriate.

Results

Between January 1, 2019 and January 1, 2020, there were a total of 6972 prescriptions for first- and second-generation antihistamines. Of the prescriptions written, 96% (6692) of these were for first-generation antihistamines (Table 1). Overall, there were a total of 278 prescriptions for second-generation antihistamines, which makes up 4% of the total antihistamine prescriptions during the study period. Of the first-generation antihistamines prescribed, diphenhydramine was overwhelmingly the most common at 97% (6476), followed by cyproheptadine 0.17% (12), promethazine 0.090% (6), and chlorpheniramine 0.075% (5). Of the total number of prescriptions for diphenhydramine, intravenous (IV) administration made up 69% (4459) of prescriptions and 31% (2017) were oral prescriptions. The largest number of prescriptions for first-generation antihistamines was in surgery with a total of 1902 prescriptions, followed by internal medicine (1660), obstetrics and gynecology (875), and intensive care (713) (Table 2).

In our cohort, there were 2460 patients aged 65 years and older (Table 3). Of these 2460 patients, 95% (2330) were prescribed first-generation antihistamines. The total number of H1-AH prescriptions to patients under the age of 18 years during the study period was 229 (Table 3). Two hundred and seven first-generation antihistamines were prescribed, accounting for 90% of all antihistamines prescribed to pediatric patients. Only 22 (10%) of patients under the age of 18 years were prescribed a second-generation agent.

Four hundred and fifty three pregnant women were prescribed first-generation antihistamines during the study period. Of these prescriptions, 442 (98%) were for first-generation antihistamines. Only 11 (7%) of the antihistamines prescribed in this population were second-generation antihistamines (Table 4).

<table>
<thead>
<tr>
<th>Service wards</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Emergency medicine</td>
<td>217 (3.1%)</td>
</tr>
<tr>
<td>Family medicine &amp; adult psychiatry</td>
<td>476 (6.8%)</td>
</tr>
<tr>
<td>Intensive care</td>
<td>713 (10.2%)</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>1660 (23.8%)</td>
</tr>
<tr>
<td>Obstetrics &amp; gynecology</td>
<td>875 (12.6%)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>158 (2.3%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>2873 (41.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>6972</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age groups</th>
<th>First- generation antihistamine</th>
<th>Second- generation antihistamine</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 18 years old</td>
<td>207</td>
<td>22</td>
<td>229 (3.3%)</td>
</tr>
<tr>
<td>18–65 years old</td>
<td>4155</td>
<td>128</td>
<td>4283 (61.4%)</td>
</tr>
<tr>
<td>Over 65 years old</td>
<td>2330</td>
<td>130</td>
<td>2460 (35.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>6692</td>
<td>280</td>
<td>6972</td>
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<tr>
<th>Pregnant (%)</th>
<th>Total</th>
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<tbody>
<tr>
<td>First-generation antihistamine</td>
<td>442</td>
</tr>
<tr>
<td>Second-generation antihistamine</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>453</td>
</tr>
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</table>
Discussion

It is well established that first-generation AHs have the potential to inflict serious harm. First-generation AHs derive from the same chemical stem from which cholinergic muscarinic antagonists, sedatives, antipsychotics, and antihypertensive agents were also developed. As a consequence, they have poor receptor selectivity and nonspecifically bind muscarinic, serotonin, α-adrenergic receptors, as well as cardiac potassium ion channels. This poor receptor selectivity leads to a number of undesirable and life-threatening side effects including CNS depression, toxicity in overdose, QT prolongation, and torsade de pointes. Hospitalized patients, particularly the elderly, children, and pregnant women have an amplified risk of adverse effects due to acute illness, polypharmacy, and multiple medical comorbidities.

At our center, we hypothesized that first-generation AHs are being prescribed preferentially in those over the age of 65 years, and indeed, we found that 95% of all prescriptions in this age group received first-generation agents. This raises safety concerns, as it is well described in the literature that first-generation AHs penetrate the blood–brain barrier readily and interrupt normal histamine neurotransmission.1–3 This disruption leads to a number of consequences including daytime somnolence, sedation, drowsiness, fatigue, and impaired concentration and memory.2,10 These effects may be more pronounced in elderly persons, as it is estimated that 25% of individuals older than 65 years have some cognitive impairment, often with no overt sign of dysfunction.11 Indeed, in older adults (age 70 and older), administration of first-generation AHs has been found to be associated with an increased risk of delirium, urinary catheterization, and prolonged hospital stay.12

Cardiotoxicity is another significant concern in older adults, and in those with underlying cardiovascular diseases. First-generation H1-AHs have antimuscarinic and α-adrenergic blockade activity and may cause dose-related prolongation of the QT interval.2 This is thought to occur by blockade of the rapid component of delayed rectifier potassium current in cardiac myocytes, which can lead to torsade de pointe and sudden cardiac death.3 Risk of cardiotoxic effects is enhanced when first-generation AHs are combined with other QTc-prolonging agents (e.g., antiarrhythmic drugs, macrolides, and fluoroquinolones).1 Therefore, combinations of such drugs should be avoided when possible, particularly in patients at elevated risk, for example, those with congenital long QT syndrome, electrolyte abnormalities, recent myocardial infarction, or congestive heart failure. There is no significant concern of cardiotoxicity with second-generation H1-AHs such as cetirizine, desloratadine, fexofenadine, and loratadine, and therefore they should be used preferentially in this subset of patients.2

A total of 229 antihistamines were prescribed to pediatric patients (less than 18 years of age) in 1 year at our institution, and of these 90% were first-generation antihistamines. This is undesirable, as the safety of first-generation AHs has not been established in the pediatric population and cases of toxicity and death have been documented in overdose. Even at recommended doses, first-generation AHs may cause paradoxical agitation and sedation, which may adversely affect a child’s learning ability. In 2003, 28,092 exposures to diphenhyramine were reported to poison control centers in the United States—11,355 (40.4%) of these cases were in children under the age of six years, resulting in at least six fatalities.15 Long-term safety of the second-generation H1-AHs, namely, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, has been documented in randomized controlled trials in children as young as 1 to 2 years and should be selected preferentially in pediatric patients.2,16

In pregnancy, the first-generation H1-AHs chlorpheniramine and diphenhyramine have a favorable FDA category B rating and are often chosen by obstetricians and primary care providers. Thus, it was not surprising to find that 98% of all antihistamines prescribed to pregnant women at our center were first-generation agents. Aside from the sedating and cholinergic adverse effects first-generation antihistamines pose, there is concern that large doses before delivery can induce contractions due to oxytocin-like effects.17 Furthermore, if a large dose is taken immediately before delivery, the neonate may exhibit withdrawal symptoms including tremulousness and irritability.18 First-generation H1-AHs, particularly those in the phenothiazine class, have also been associated with the sudden infant death syndrome.2 There are reassuring human data for both loratadine and cetirizine in pregnancy; each of these drugs has been studied in a large number of pregnant patients, and they are considered category B.19 For these reasons, second-generation agents are the treatment of choice for urticaria and allergic rhinitis in pregnant and breastfeeding women.

In contrast to the adverse effects described above caused by first-generation antihistamines, second-generation agents are relatively free of adverse effects and appear to have few toxic effects in overdose setting.6,7 Newer generation AHs have been extensively studied over the past 30 years, and are safer, feature faster or equivalent onset of action, and are superior in efficacy compared to first-generation AHs.
Now that generic formulations of these agents are available, the cost is presently comparable. Despite the evidence, it is a common misconception that first-generation AHs have a quicker onset of action, which has been proven inaccurate in clinical studies.\textsuperscript{20,21} In a double-blind placebo controlled trial, both cetirizine and loratadine were found to have significantly faster onset of action, potency, and duration of action when compared to first-generation agents.\textsuperscript{22}

There are several limitations to our retrospective analysis. Firstly, we were not able to compile data regarding the indication for prescribing a first- or second-generation antihistamine in many cases, as this was not routinely documented. There are few clinical scenarios where a first-generation antihistamine may be prescribed preferentially, such as in the case of acute dystonic reactions. In addition, our analysis included only patients who were admitted to the hospital, in the emergency department or in the hemodialysis unit. Prescribing habits in an outpatient setting may not necessarily reflect outpatient prescribing habits and these data cannot be directly extrapolated. Moreover, there are currently no second-generation antihistamines available for administration via the parenteral route (IV or IM), and we do not have the clinical data to assess whether an oral antihistamine would have been appropriate to give these patients who received an antihistamine via the parenteral route.

We have identified wards at our institution with the highest rates of first-generation antihistamine prescribing, with the surgical, obstetrical, and medicine wards being the top three. Physicians, pharmacists, and nurses—especially in these identified areas of the hospital—may benefit from education around the potential for serious harm of first-generation antihistamines and the availability of safer alternatives. It would be in the best interest of our patients to follow the lead of many centers in North America and Europe that have limited access to first-generation AHs in hospitals would encourage safer prescribing habits and familiarity with second-generation agents.

We have highlighted in this review, the many detrimental effects first-generation antihistamines can have on patients—particularly the elderly, pediatric patients, and pregnant women. We have identified departments at the RGH that prescribe a large volume of first-generation antihistamines. However, throughout our institution, first-generation antihistamines are overwhelmingly and preferentially prescribed, despite a well-established body of evidence implicating them in CNS depression, delirium, cardiotoxicity, and death from overdose. This indicates a need for more education regarding the harmful effects of first-generation antihistamines and the availability of safer alternatives. In addition, limiting access to first-generation antihistamines in hospitals would encourage safer prescribing habits and familiarity with second-generation agents.

Conclusions

We have highlighted in this review, the many detrimental effects first-generation antihistamines can have on patients—particularly the elderly, pediatric patients, and pregnant women. We have identified departments at the RGH that prescribe a large volume of first-generation antihistamines. However, throughout our institution, first-generation antihistamines are overwhelmingly and preferentially prescribed, despite a well-established body of evidence implicating them in CNS depression, delirium, cardiotoxicity, and death from overdose. This indicates a need for more education regarding the harmful effects of first-generation antihistamines and the availability of safer alternatives. In addition, limiting access to first-generation antihistamines in hospitals would encourage safer prescribing habits and familiarity with second-generation agents.

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