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Research Paper

Antipsychotics-Associated Serious Adverse Events in Children: An Analysis of the FAERS Database

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Abstract

Objective: The reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) from 1997 to 2011 were reviewed to assess serious adverse events induced by the administration of antipsychotics to children.

Methods: Following pre-processing of FAERS data by elimination of duplicated records as well as adjustments to standardize drug names, reports involving haloperidol, olanzapine, quetiapine, clozapine, ziprasidone, risperidone, and aripiprazole were analyzed in children (age 0-12). Signals in the data that signified a drug-associated adverse event were detected via quantitative data mining algorithms. The algorithms applied to this study include the empirical Bayes geometric mean, the reporting odds ratio, the proportional reporting ratio, and the information component of a Bayesian confidence propagation neural network. Neuroleptic malignant syndrome (NMS), QT prolongation, leukopenia, and suicide attempt were focused on as serious adverse events.

Results: In regard to NMS, the signal scores for haloperidol and aripiprazole were greater than for other antipsychotics. Significant signals of the QT prolongation adverse event were detected only for ziprasidone and risperidone. With respect to leukopenia, the association with clozapine was noteworthy. In the case of suicide attempt, signals for haloperidol, olanzapine, quetiapine, risperidone, and aripiprazole were detected.

Conclusions: It was suggested that there is a level of diversity in the strength of the association between various first- and second-generation antipsychotics with associated serious adverse events, which possibly lead to fatal outcomes. We recommend that research be continued in order to gather a large variety and quantity of related information, and that both available and newly reported data be placed in the context of multiple medical viewpoints in order to lead to improved levels of care.

Key words: antipsychotics, children, serious adverse events, FAERS, data mining, pharmacovigilance

Introduction

Second-generation antipsychotic drugs (SGAs) are thought to provide different therapeutic outcomes from first-generation antipsychotic drugs (FGAs), due to their relatively low affinity for dopamine D_2 receptors and affinities for other receptors. SGAs are believed to improve negative symptoms, depression

and quality of life more than FGAs [1]. Medical doctors understand that improved efficacy for these problems is a great advantage of SGAs; however, little information is available concerning their superiority [1]. Weight gain, hyperprolactinemia, and extrapyramidal symptoms (EPS) are commonly found in patients treated with FGAs or SGAs [2-5]. Additionally, neuroleptic malignant syndrome (NMS), QT prolongation, leukopenia, and suicidal behavior are reported for both [2-5]; however again, we do not have a consensus on which is better. Additionally, in 2009, a meta-analysis was published to compare the safety and efficacy of FGAs and SGAs, in which 150 double-blind studies were included with 21,533 participants [1]. The analysis concluded that SGAs differed in many properties and were not a homogenous class, strongly suggesting the importance of detailed investigation of each drug [1].

Recently, the use of antipsychotics, especially SGAs, has been increasing in children. This is, in part, explained by their off-label uses, including those for Attention Deficit / Hyperactivity Disorder (ADHD) [6-8]. In the USA, the use of SGAs for children has been approved since 2006, and this has also contributed to the increase. The surveillance of adverse event reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) suggested that antipsychotics are included in the top 5 reported suspect therapeutic drug classes in children [9]. In this study, the FAERS database was used to assess the associations between 5 representative SGAs and adverse events in children. A FGA, haloperidol, and the recently developed aripiprazole were also subjected to the investigation, and we focused on 4 rare adverse events, including NMS, QT prolongation, leukopenia, and suicidal behavior. Data mining algorithms were used for the quantitative detection of signals [10-18], where a signal means a statistical association between a drug and an adverse event or a drug-associated adverse event.

Methods

Data sources

Input data for this study were taken from the public release of the FAERS database, covering the period from the fourth quarter of 1997 through the third quarter of 2011. The total number of reports used was 4,671,217. Besides those from manufactures, reports can be submitted from health care professionals and the public. The database's data structure adheres to the international safety reporting guidance issued by the International Conference on Harmonisation ICH E2B. A data set consists of 7 data tables: report sources (RPSR), patient demographic and administrative information (DEMO), drug therapy start and end dates (THER), indications for use/diagnosis (INDI), drug/biologic information (DRUG), adverse events (REAC), and patient outcomes (OUTC). Preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) serve as the terminology for registration of adverse events in REAC table. Here, version 16.1 of MedDRA was used.

Before data mining was executed, several pre-processing steps of FAERS were undertaken. First, duplicated reports, which appear with multiple CASE field values in the database, were filtered by applying the FDA's recommendation of adopting the most recent CASE number. This processing step reduced the number of reports from 4,671,217 to 3,472,494, a 25.7% reduction. Next, in order to account for registration of arbitrary drug names including trade names and abbreviations, which is permissible within the FAERS system, drug names were mapped into unified generic names via text mining. As a part of the standardization process, GNU Aspell was applied to detect spelling errors. Additionally, records of side effects that are not registered as associated with the use of a pharmaceutical, such as foods, beverages, or other medical treatments including radiation therapy were eliminated. Similarly, adverse event records with ambiguous drug names such as generic "beta blockers" were filtered out. As a final filter, only records were retained in which demographic information indicated that children less than 12 years old were the recipients of treatment. After applying this pre-mining filter pipeline, the total number of reports used was 94,635. Consequently, a total of 1,098,811 co-occurrences were found in 94,635 reports, where a co-occurrence was a pair constituting a drug and a drug-associated adverse event.

Definition of adverse events

According to MedDRA version 16.1, NMS, QT prolongation, leukopenia, and suicide attempt are coded with preferred terms PT10029282, PT10014387, PT10024384, and PT10042464 with 7, 10, 5, and 5 lower level of terms (LLTs) assigned, respectively.

Signal Detection Data Mining

Once a collection of filtered adverse event records are assembled, a key question is how to weight and extract meaningful events as adverse event signals. To this end, a number of algorithms have been developed, where the common element of the algorithms is that signals are defined as those events reported with a greater frequency than can be expected, given an estimated expectation for reporting frequency derived from the drugs and ADRs (adverse drug reaction events) in the record collection to be

analyzed [14-18]. The algorithms used in this study include: (1) the proportional reporting ratio (PRR) [10] which is used by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK; (2) the reporting odds ratio (ROR) [11] in use at the Netherlands Pharmacovigilance Centre; (3) the information component (IC) criteria [12] employed by the World Health Organization (WHO); (4) and the empirical Bayes geometric mean (EBGM) [13] which is a part of FDA analytical methods.

The PRR, ROR, IC, and EBGM methods all employ the use of 2x2 confusion matrices of drug-event counts; that is, a drug and an event are placed on the rows and columns of a matrix, and the frequency of the four possible outcomes is tabulated. Where the algorithms then differ is that IC and EBGM use Bayesian reasoning, while the PRR and ROR methods take the frequentist approach to statistical inference. Readers are encouraged to consult the references of each method to obtain extended details.

Here, we summarize the ways in which each test uses its reasoning and formulation to "detect" a signal. First we consider the classical, frequentist statistical approaches. In the PRR method, a signal is detected if the number of co-occurrences is 3 or more, and additionally, if the PRR is 2 or more with an associated χ^2 value of 4 or more [10]. Using ROR, when the lower bound of the 95% two-sided confidence interval exceeds 1, it is an indication of an ADR signal [11].

Next, we consider the Bayesian methods for signal detection. The IC algorithm performs signal detection via the IC025 metric, which is a lower bound of the 95% two-sided confidence interval of IC, with an ADR signal indicated by the IC025 value exceeding 0 [12]. For the EGBM method, a lower one-sided 95% confidence bound of the EBGM, termed the EB05 metric, is used; EB05 is greater than or equal to 2.0 results in an ADR signal [13].

Finally, we need a criterion to unite our use of the various signal detection methods. In this study, we elect for the most direct, simple strategy: an adverse event is drug-associated when at least 1 of the 4 algorithms meets its above criteria for signal detection.

Results

The total number of drug and reported adverse event co-occurrences with haloperidol was 1,600, with 2,802 for olanzapine, 2,440 for quetiapine, 519 for clozapine, 623 for ziprasidone, 5,219 for risperidone, and 2,553 for aripiprazole, representing 0.146%, 0.255%, 0.222%, 0.047%, 0.056%, 0.475%, and 0.232% of all co-occurrences in children in the filtered database, respectively. In total, 181, 345, 313, 119, 139, 380, and 269 adverse events were extracted as antipsychotics-associated adverse events with 999, 1,644, 1,386, 310, 361, 3,104, and 1,530 co-occurrences with a signal detected, respectively.

The signals for NMS were detected with the 5 antipsychotics other than clozapine and ziprasidone, and signal scores for haloperidol and aripiprazole were greater than for other antipsychotics in Table 1. As for QT prolongation, signals were detected for only ziprasidone and risperidone, and signal scores suggested a stronger association for ziprasidone (Table 2). The signal scores for leukopenia are listed in Table 3. Although signals were detected for quetiapine, clozapine, and risperidone, the association with clozapine was noteworthy. Table 4 shows the signal scores for suicide attempt, and signals for 5 antipsychotics; haloperidol, olanzapine, quetiapine, risperidone, and aripiprazole, were detected.

Table 1. Signal scores for antipsychotics-associated neuroleptic malignant syndrome.

Antipsychotics	N	PRR (χ2)	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Haloperidol	8	26.92 (174.0)*	27.98 (13.77, 42.18)*	2.71 (1.72, 3.71)*	22.97 (12.11)*
Olanzapine	3	5.74 (7.5)*	5.81 (1.86, 9.77)*	1.21 (-0.31, 2.73)	2.27 (0.83)
Quetiapine	8	17.62 (109.2)*	18.30 (9.02, 27.59)*	2.55 (1.56, 3.54)*	15.03 (6.97)*
Clozapine	N.A.				
Ziprasidone	N.A.				
Risperidone	10	10.28 (75.0)*	10.76 (5.70, 15.83)*	2.41 (1.52, 3.31)*	8.15 (3.79)*
Aripiprazole	14	29.54 (357.0)*	31.64 (18.36, 44.92)*	3.30 (2.53, 4.07)*	26.82 (16.85)*

N: the number of co-occurrences. N.A.: Not Available

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean. CI: the confidence interval (two-sided for ROR and IC, and one-sided for EBGM).

An asterisk (*) indicates a statistically significant association, i.e., the adverse events are detected as signals.

Table 2. Signal scores for antipsychotics-associated QT prolongation.

Antipsychotics	N	PRR (χ2)	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Haloperidol	2	1.41 (0.0)	1.41 (0.35, 2.47)	0.06 (-1.72, 1.84)	0.97 (0.31)
Olanzapine	1	0.40 (0.4)	0.40 (0.06, 0.75)	-1.19 (-3.46, 1.08)	0.40 (0.09)
Quetiapine	3	1.39 (0.1)	1.39 (0.45, 2.33)	0.15 (-1.36, 1.66)	1.05 (0.41)
Clozapine	N.A.				
Ziprasidone	15	27.83 (353.1)*	28.25 (16.86, 39.64)*	3.32 (2.59, 4.05)*	25.07 (16.02)*
Risperidone	9	1.95 (3.3)	1.96 (1.02, 2.90)*	0.76 (-0.16, 1.68)	1.65 (0.94)
Aripiprazole	3	1.33 (0.1)	1.33 (0.43, 2.20)	0.11 (-1.40, 1.62)	1.02 (0.39)

N: the number of co-occurrences. N.A.: Not Available

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean. CI: the confidence interval (two-sided for ROR and IC, and one-sided for EBGM).

An asterisk (*) indicates a statistically significant association, i.e., the adverse events are detected as signals.

Table 3. Signal scores for antipsychotics-associated leukopenia

Antipsychotics	N	PRR (χ2)	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Haloperidol	N.A.				
Olanzapine	2	0.82 (0.0)	0.83 (0.21, 1.45)	-0.44 (-2.22, 1.34)	0.69 (0.22)
Quetiapine	11	5.25 (33.6)*	5.30 (2.92, 7.68)*	1.89 (1.05, 2.73)*	3.77 (2.19)*
Clozapine	8	18.15 (111.3)*	18.30 (9.07, 27.52)*	2.56 (1.57, 3.54)*	15.33 (27.65)*
Ziprasidone	N.A.				
Risperidone	9	2.00 (3.6)	2.01 (1.04, 2.98)*	0.79 (-0.13, 1.71)	1.68 (0.96)
Aripiprazole	2	0.91 (0.0)	0.91 (0.23, 1.59)	-0.35 (-2.13, 1.43)	0.74 (0.24)

N: the number of co-occurrences. N.A.: Not Available

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean. CI: the confidence interval (two-sided for ROR and IC, and one-sided for EBGM).

An asterisk (*) indicates a statistically significant association, i.e., the adverse events are detected as signals.

Table 4. Signal scores for antipsychotic-associated suicide attempt.

Antipsychotics	N	PRR (χ2)	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Haloperidol	5	9.36 (29.4)*	9.47 (3.91, 15.03)*	1.84 (0.63, 3.06)*	4.65 (1.75)
Olanzapine	10	10.69 (78.3)*	10.96 (5.84, 16.08)*	2.44 (1.55, 3.32)*	8.56 (3.97)*
Quetiapine	6	7.36 (26.9)*	7.46 (3.33, 11.60)*	1.84 (0.72, 2.96)*	4.03 (1.79)
Clozapine	N.A.				
Ziprasidone	1	4.80 (0.4)	4.81 (0.67, 8.94)	0.34 (-1.94, 2.62)	1.15 (0.25)
Risperidone	13	7.45 (66.5)*	7.69 (4.41, 10.96)*	2.30 (1.51, 3.08)*	5.75 (3.24)*
Aripiprazole	4	4.68 (8.2)*	4.72 (1.76, 7.69)*	1.28 (-0.06, 2.62)	2.36 (1.00)

N: the number of co-occurrences. N.A.: Not Available

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean. CI: the confidence interval (two-sided for ROR and IC, and one-sided for EBGM).

An asterisk (*) indicates a statistically significant association, i.e., the adverse events are detected as signals.

Discussion

According to some recent reports, number of prescriptions for antipsychotics among younger patients has been increasing [6-8]. Furthermore, the Guideline "Clinical Investigation of Medicinal Products in the Pediatric Population" [19], which was developed by the ICH expert working group, categorized "children" as 2 to 11 years. Therefore, in this study, we focused on children less than 12 years old.

NMS is a rare, but potentially fatal complication of treatment with antipsychotic medication and is characterized by the development of severe muscle rigidity and hyperthermia, first described by Delay et al. in 1968 [20]. In spite of the long period of time since the first description, to the best of our knowledge, there have been few reports concerning the association between SGAs and NMS in children. In our study, signals were detected for 5 antipsychotics, i.e., haloperidol, quetiapine, ziprasidone, risperidone, and aripiprazole (Table 1). Signal scores were higher for haloperidol and aripiprazole than for the other antipsychotics, suggesting that SGAs show lower susceptibility to NMS. The precise pathophysiology of NMS remains unknown. It has been suggested that NMS is the result of dopamine D_2 receptor blockade [20-22], whereas, dopamine D_2 receptor antagonism does not fully explain all of the signs and symptoms of NMS [22]. According to antipsychotic receptor-binding profiles, relative affinities for the dopamine D_2 re-

ceptor of haloperidol and aripiprazole are higher, and those of quetiapine and risperidone are lower [4, 21]. Moreover, aripiprazole controls the dopaminergic function by acting as a partial agonist of dopamine D_2 receptor subtypes, while high concentrations of aripiprazole induce dopaminergic blockade [4]. Therefore, our observation may be partially attributed to these drug action mechanisms.

QT prolongation is also a serious adverse event accompanying the administration of SGAs, and results from blockade of the delayed rectifier potassium current (IKr). It is associated with presyncope, syncope, polymorphic ventricular tachycardia, the subtype torsade de pointes, and sudden cardiac death [23]. Poluzzi et al. reported the torsadogenic risk of antipsychotics including QT prolongation using FAERS [24], and Wenzel-Seifert et al. suggested that QT prolongation occurs most significantly with ziprasidone in SGAs [25]. However, neither of them provided data after stratifying by age. Here, the signals for QT prolongation were detected for ziprasidone and risperidone, with the signal score being higher for the former than the latter (Table 2). In this study, it was confirmed that ziprasidone is most strongly associated with QT prolongation in children.

Hematologic abnormalities induced by antipsychotics may be life-threatening in some patients. Several studies revealed the association between clozapine and leukopenia in children, and clozapine is generally recommended for drug-resistant cases [26-28]. In addition, Etain et al. reported that leukopenia was induced by risperidone [29]. Our results reproduced these observations, but the signal was also detected for quetiapine (Table 3).

The incidence of suicide attempt is more frequent in individuals with schizophrenia than in general [30, 31]. Previous studies suggested that the suicide risk differs among antipsychotics [30-33]; however, the impact of antipsychotics on suicide attempt has been a matter of controversy. Moreover, adherence to antipsychotics is likely to reduce the suicide risk [30], so suicide attempt in individuals who take antipsychotics may be due to weakness of efficacy. On the other hand, an adverse event is generally defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment [34]. Therefore, in this study, we regarded suicide attempt accompanied with the administration of antipsychotics as adverse events even if it derives from weakness of efficacy, and FAERS database was reviewed in order to confirm if the suicide risk differs among antipsychotics and is associated with them. As a result, signals were detected for antipsychotics other than clozapine and ziprasidone, and the scores were higher for olanzapine and risperidone (Table 4). Tiihonen et al. revealed that use of clozapine might be more effective than that of other antipsychotics for reducing suicidal attempt [30]. This might have contributed to the lack of a signal detection for clozapine.

In conclusion, reports in the FAERS database were reviewed to assess the antipsychotics-associated serious adverse events in children. Based on 94,635 reports from 1997 to 2011, it was suggested that there is a level of diversity in the strength of the association between various first- and second-generation antipsychotics with associated serious adverse events, which possibly lead to fatal outcomes. We recommend that research be continued in order to gather a large variety and quantity of related information, and that both available and newly reported data be placed in the context of multiple medical viewpoints in order to lead to improved levels of care.

Abbreviations

EBGM: empirical Bayes geometric mean; FDA: Food and Drug Administration; FAERS: FDA Adverse Event Reporting System; FGAs: first-generation antipsychotic drugs; IC: information component; MedDRA: Medical Dictionary for Regulatory Activities; NMS: neuroleptic malignant syndrome; PRR: proportional reporting ratio; PT: preferred term; ROR: reporting odds ratio; SGAs: second-generation antipsychotic drugs

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Competing Interests

The authors have declared that no competing interest exists.

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