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Original Article

Ibuprofen and risk of hypoglycemia in diabetic and non-diabetic consumers: analysis of international pharmacovigilance data

Mulugeta Russom[1,2]*, Filipos Yohannes[3], Abel Tekle[3], Ruth Ghirmay[3]

[1]Eritrean Pharmacovigilance Centre, National Medicines and Food Administration, Asmara, Eritrea.

[2]Department of Medical Informatics, Erasmus Medical Centre, Rotterdam, the Netherlands.

[3]Orotta College of Medicine and Health Sciences, Asmara, Eritrea

*Corresponding author

Mulugeta Russom, Eritrean Pharmacovigilance Centre, National Medicines and Food Administration, Asmara, Eritrea, Tel: +291-7197450; e-mail: satiswt@gmail.com

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Keywords

- Ibuprofen
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- Diabetic and non-diabetic
- Causation
- VigiBase

Abstract

Introduction: Ibuprofen was associated with hypoglycemia in a single published case report in a diabetic patient. It, however, has never been associated so far with hypoglycemia in previously healthy non-diabetic individuals and thus, it is not listed as adverse effect in its summary of product characteristics approved by major regulatory authorities.

Objective: This study was conducted to assess the causal relationship between ibuprofen and hypoglycemia in diabetic and non-diabetic individuals.

Materials and Methods: Analysis of the literature and the WHO global database of individual case safety reports, VigiBase, was made to explore evidence on the association of ibuprofen and hypoglycemia. The unpublished data and the currently available published toxicological, biological, clinical and epidemiological evidence, if any, was systematically organized using Austin Bradford Hill criteria, a causality assessment framework, to assess the causal link between ibuprofen and hypoglycemia.

Results: In VigiBase, there were 125 cases of hypoglycemia associated with ibuprofen, reported from 19 countries. About 50% had history of diabetes. Ibuprofen was reported as sole suspect in 36.8% of the cases and the only drug administered in18.4%. Hypoglycemia resolved following discontinuation of ibuprofen in 21.6% and recurred in three patients with rechallenge. Outcome was fatal in 10.5%. Where ibuprofen was solely administered, median time-to-onset of hypoglycemia was one-day following administration of the drug. In an experimental study, a significant decrease in blood glucose level was observed at a higher dose of ibuprofen compared to a low-dose.

Conclusion: Currently available totality of evidence reflects a possible causal association between ibuprofen and hypoglycemia that need to be substantiated with further studies.

ABBREVIATIONS

ATP: Adenosine Triphosphate; **EMA**: European Medicines Agency; **IC**: Information Component; **ICSR**: Global Individual Case Safety Reports; **MedDRA**: Medical Dictionary for Regulatory Activities; **MHRA**: Medicines and Healthcare Products Regulatory Authority; **NEC**: Not Elsewhere Classified; **NSAIDs**: Nonsteroidal Anti-Inflammatory Drugs; **ROR**: Reporting Odds Ratio; **SmPC**: Summary of Product Characteristics; **UMC**: Uppsala Monitoring Centre; **US-FDA**: United States Food and Drug Administrations.

INTRODUCTION

Ibuprofen is one of the most commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) of the class propionic acid derivatives; which is approved for use in the symptomatic treatment of rheumatoid arthritis, juvenile arthritis, and osteoarthritis [1]. It is also approved for pain, ankylosing spondylitis, acute gouty arthritis, tendinitis, bursitis, headache, postoperative dental pain and swelling, and primary dysmenorrhea [1]. US-FDA prescribing information for Ibuprofen has mentioned hypoglycemia as an adverse effect on its last update (Jun 6, 2020) in which the frequency was not reported [2]. A single case report of hypoglycemia and serious hospitalization in a patient with diabetes mellitus on oral hypoglycemic agent was also reported following the use of ibuprofen [3]. There have been also long-established studies that implicated high

doses of salicylates to cause decreased blood sugar level [4,5]. The provision of ibuprofen lysine injection for patent ducts arteriosus closure in pediatric patients has been also associated with hypoglycemia [2]. But, one systemic review conducted to assess the safety of concomitant use of hypoglycemia inducing drugs and NSAIDs reported that there are not enough arguments to contraindicate the use of NSAIDs with hypoglycemia-inducing drugs [6]. To the best of the authors' knowledge, there have been no case series assessments or published case reports that associated ibuprofen with hypoglycemia on healthy non-diabetic patients. The summary of product characteristics (SmPC) of the European Medicines Agency (EMA) and UK's Medicines and Healthcare Products Regulatory Agency, Healthcare Products Regulatory Agency (MHRA) does not also include any mention of hypoglycemia on its March 2020 revision [7]. Recently, the Eritrean National Pharmacovigilance Centre received two cases with recurrent episodes of hypoglycemia on previously healthy patients without diabetes following use of oral ibuprofen. The aim of the present study therefore was to assess the causal relationship between ibuprofen and hypoglycemia in diabetic and non-diabetic patients using the WHO global database of individual case safety reports, VigiBase.

MATERIALS AND METHODS

Study designs and data sources

This study was descriptive analysis that used the Austin Bradford Hill's criteria or guidelines [8] as a causality assessment framework to assess the causal relationship between ibuprofen and risk of hypoglycemia. Hill`s criteria are a set of guidelines which are widely accepted in assessing causation. It involves use of guidelines and judgments and has been used in toxicology and pharmacoepidemiology for causal inference. The Austin Bradford Hill criteria used for judging the evidence of causality include: strength of association, temporal relationship, consistency of the association, plausibility (be biological, pathological or pharmacological), dose–response relationship, experimental evidence, specificity of the cases, coherence and analogy. Their application in pharmacoepidemiology and toxicology are explained in detail elsewhere [8]. In this study, a rigorous literature review was carried out to identify reports or published information that associate hypoglycemia with ibuprofen and the available evidence is organized into Hill's criteria (Table 1).

The WHO global database of individual case safety reports, VigiBase, was used as the main data source for this study. VigiBase is the world's largest pharmacovigilance database consisting over 23.5 million reports (as of October 2020). The database currently pools safety data related to medical products from around 140 countries since 1968.

Data retrieval approach

Data mining in the WHO global database was carried out using VigiLyze, a data mining and analysis tool of that database, on October 18, 2020. 'Ibuprofen' as active substance and 'hypoglycemic conditions NEC' (high level reaction term) were used as search criteria. Both qualitative and quantitative analysis was carried out and the retrieved data was exported to excel spreadsheet for further descriptive analysis. The database automatically analyses the number of hypoglycemic cases with a sole suspect of ibuprofen, the number of contributing countries, cases with positive dechallenge and rechallenge, seriousness of the cases, outcome of the hypoglycemic conditions and the measure of the strength of association, information component (IC) value or Reporting Odds Ratio (ROR). The IC value for the ibuprofen-hypoglycemia combination was also noted. The IC value is a measure of the disproportionality of a drug - adverse drug reaction pair in the database [9]. A positive $IC_{0.25}$ value (the lower border of the credible interval for the IC value >0) is "a traditional threshold which indicates that a drug-ADR pair is reported more often than expected based on all reports in the database", thus showing a statistical signal. From the retrieved qualitative data, time to onset of hypoglycemia (calculated as date hypoglycemia started subtracted from the start date of

Table 1: Summary results of the causality assessment in case series on ibuprofen and hypoglycemia using Austin Bradford Hill criteria.

Criteria	Outcome
Strength of association	The association of hypoglycemia and ibuprofen, based on WHO global database, was weak with negative IC value.
Consistency of cases	Different cases of hypoglycemia, both in diabetic and non-diabetic patients, have been reported from different parts of parts of the world over the years. In several cases, hypoglycemia manifested shortly following use of ibuprofen and recovered on withdrawal of the product.
Specificity of the association	In 23 cases, ibuprofen was solely administered, without other concomitants.
Temporal relationship	In several cases, hypoglycemia manifested shortly, in few days, following administration of ibuprofen. On the cases where ibuprofen was the only drug administered, patients experience hypoglycemia with a median onset of one-day.
Dose-response relationship	An experimental study that assessed the effects of ibuprofen in conventional dosage on glucose homeostasis, in diabetic patients, reported a small but statistically significant reduction of glucose level at higher dose, while no change was observed in lower dose [19].
Biological mechanism or plausibility	The mechanism is generally unknown but possibly, ibuprofen might cause hypoglycemia by inhibiting ATP sensitive potassium channels and cause depolarization with in the beta cells of the pancreas which in turn leads to increased insulin release [18].
Experimental evidence	Experimental study in isolated islet cells from mouse exposed to NSAIDs showed increase in insulin secretion through inhibition of ATP-sensitive potassium channels[18]. There were also several cases of hypoglycemia with positive dechallenge and three cases with positive rechallenge.
Analogy	Hypoglycemia is reported as an adverse effect in propionic acid derivatives like naproxen [14,15]. which are similar in many properties with ibuprofen.
Coherence	Not applicable.

ibuprofen intake), the number of cases in which ibuprofen is solely administered, median age, outcome of hypoglycemia and causality were assessed.

Case assessment

All cases of hypoglycemia encountered following the sole administration of ibuprofen, cases with positive dechallenge and rechallenge and the published case reports of hypoglycemia related to ibuprofen were subjected to causality assessment using the Naranjo adverse drug reaction probability scale [10]. The reason for selecting these cases for individual causality assessment was to identify reports with 'probable' or 'certain' causal relationship. To avoid individual inter-rater variability, the research team, together, made the assessment at the same time and decided based on consensus. Finally, causal inference at aggregate level was assessed using the Austin Bradford Hill causality assessment criteria or framework [8].

Literature search and labeling

To check whether there is an established relationship or association between ibuprofen and hypoglycemia, first SmPCs of ibuprofen approved by different regulatory authorities such as EMA/MHRA [7] and US-FDA [2] were reviewed. Furthermore, searches were made on Google Scholar and PubMed using 'ibuprofen' AND 'hypoglycemia' OR 'hypoglycemia' OR 'hypoglycaemia' OR 'reduced blood sugar' as titles. Clinical and pre-clinical data was also explored. The online drug information databases such as Martindale: The Complete Drug Reference [11], Drugdex [12] and SIDER side effects resources [13] were also searched.

To avoid confounding effect of hypoglycemic agents and being diabetic itself, a sub-group analysis to explore the causal relationship between ibuprofen and hypoglycemia in non-diabetic cases was also carried out.

RESULTS

Literature Search and Labeling

Up on a review of a literature, we found one published case report of serious hypoglycemia (40mg/dL) associated with ibuprofen in a diabetic patient taking sulfonylurea, glibenclamide 2.5mg daily[3]. The case report shows that the patient was first recovered after discontinuation of ibuprofen and then reaction recurred following re-introduction of the drug. The authors suspected that the event might be caused due to interaction of ibuprofen and glibenclamide. In non-diabetic patients, there is no such association neither in the literature nor in SmPCs of ibuprofen.

The SmPC of ibuprofen approved by the EMA/MHRA had no mention of hypoglycemia as adverse effect [7], but the US-FDA prescribing information has stated hypoglycemia as an adverse effect in diabetic patients, with unknown frequency [2]. The other drug classes of ibuprofen, propionic acid derivatives, have conflicting information whether they cause hypoglycemia or not. Naproxen was mentioned to be associated with hypoglycemia in the US-FDA prescribing information [14], but not in the SmPC approved by the EMA/MHRA [15]. Similarly, hypoglycemia has not been associated with ketoprofen [16] and flurbiprofen [17] in the SmPC approved by EMA/MHRA.

The effect of NSAIDs on hypoglycemic conditions was also explored. There is a study that demonstrated NSAIDs could potentially cause hypoglycemia by inhibiting the Adenosine Triphosphate (ATP)-sensitive potassium channels in the beta cells [18]. Another study that assessed the effects of NSAIDs in conventional dosage on glucose homeostasis in diabetic patients reported a statistically significant but small change in glucose level (from 196±60 to 179±47mg/dL) with the administration of relatively higher dose of ibuprofen, 600mg three times a day compared to a 300mg three times daily dose [19]. Salicylates have also been reported to be associated with lowering blood sugar and enhancing glucose-stimulated insulin secretion in diabetic and non-diabetic patients [5] .

Reports in the WHO Global Database of Individual Case Safety: Reports

Since 1975, a total of 146 cases of hypoglycemia associated with ibuprofen were retrieved from the WHO global database reported from 19 countries. By setting the database at de-duplicate level, 21 cases were found to be suspected duplicates, thus, removed from the dataset. Manual search was also made to identify further potential duplicates which could not find any and therefore, 125 cases were qualified for analysis (Figure 1). The cases were mainly reported from the US (55), UK (14), Germany (10), Netherlands (8), Spain (7), France (6) and Australia (5). Thesources of primary reporters were physicians (44.4%), pharmacists (8.1%), other healthcare professionals (8.1%), non-healthcare professionals/consumers (11.3%) and it was unknown in 28.2%.

The median age of the cases was 55 years (range: 1-95) and more than a quarter (31.5%) were aged 44 years and below. Sex was reported in 118 cases, of which 54.2% were females and 45.8% males. Metformin (18.5%), insulin (17.7%) and paracetamol (12.9%) were the top three co-reported drugs with ibuprofen (Table 2). About half, 49.6%, had history of diabetes and the rest, 50.4%, were non-diabetic patients (Figure 1).

The strength of association of ibuprofen and hypoglycemia in the WHO global database was weak (IC_{025}: -2.3 and ROR_{025}: 0.2). In 36.8% of the cases, ibuprofen was reported as a sole suspect drug and in 18.4 % ibuprofen was the only drug administered

Table 2: Top 10 medicines co-reported with ibuprofen associated with hypoglycemia in the WHO global database of individual case safety reports.

Co-reported medicines	Total	Percent
Metformin	23	18.5
Insulin	22	17.7
Paracetamol	16	12.9
Acetylsalicylic acid	11	8.9
Glibenclamide	8	6.5
Glimepiride	6	4.8
Glipizide	6	4.8
Lisinopril	6	4.8
Celecoxib	5	4.0

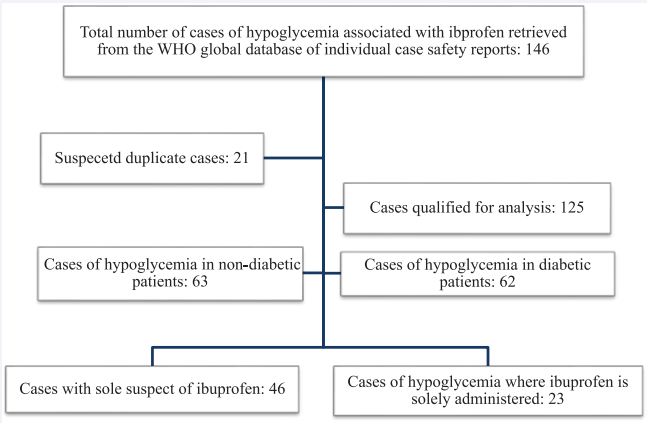

Figure 1 Summary of hypoglycemic cases related to ibuprofen reported to the WHO global database of individual case safety reports between 1975 and October 18, 2020.

(Figure 1). Hypoglycemia resolved following discontinuation of ibuprofen in 21.6% and the reaction recurred in three patients when ibuprofen was re-introduced. It is, however, unknown which of the cases had rechallenged with ibuprofen. Outcome was reported to be fatal in 10.5% of all cases and recovering/recovered in 52.8% of the cases. In the rest of the cases, outcome was not documented.

To minimize potential confounders, the authors made sub-group analysis on the cases of hypoglycemia reported following the sole intake of ibuprofen (had no other concomitants). In total, there were 23 cases of hypoglycemia with similar male to female ratio. Age was reported in 15 cases with a median of 41.5 years (range: 2 – 74 years). Route of administration was reported in 18 cases and in all of them it was administered orally. None of these patients were diabetic and in 7 cases hypoglycemia resolved after discontinuation of ibuprofen. Time to onset of hypoglycemia from start of ibuprofen was reported in nine cases with median of one day (range: 1 – 2 days). Outcome was either unknown or not documented in majority of these cases. In some cases, action taken and outcome of hypoglycemia were either unknown or not reported.

Causality assessment

Of the cases reported to the WHO global database, we found 21 probably related cases with ibuprofen as the cases had positive dechallnge and no alternative explanation was reported. In all these cases, hypoglycemia was reported following the sole administration of ibuprofen, with no other concomitants, and in many of these cases, reaction recovered after withdrawal of ibuprofen. The only published case report was also assessed for causality and it was found to be 'possible'. Though the case had a positive dechallenge and rechallenge infromation, a possible alternative explanation (being diabetic) was identified and thus, classified as 'possible'.

After identifying and organizing the available evidence on the association of interest, Hill's criteria were used to assess causality in a case series (Table 1).

DISCUSSIONS

Evaluation of the currently available evidence shows that there is a 'possible' causal association between ibuprofen and hypoglycemia in diabetic and non-diabetic consumers. The facts that hypoglycemia has been observed shortly following administration of ibuprofen, several cases were improved with discontinuation of the product and the event recurred in few cases after its re-introduction, supports the causal inference. In some non-diabetic cases, the association was very specific as hypoglycemia was reported with the sole intake of ibuprofen and similar cases were consistently reported from different geographical regions. This is also another evidence that supports the causation.

A single clinical experimental study, conducted on diabetic patients, also found that ibuprofen at relatively higher daily dose caused a significant reduction of glucose level compared to a smaller dose, which suggests a dose-response relationship [19]. As that experiment is the only available evidence on dose-response relationship, it cannot give conclusive evidence and thus, its reproducibility need to be further investigated.

The mechanism by which how ibuprofen could cause hypoglycemia is not clearly known. There is, however, a proposed general mechanism on how NSAIDs cause reduction in blood glucose levels [18]. Normally, an ATP-sensitive potassium channels, molecular sensor of cellular metabolism, regulates insulin secretion from the beta cells [20]. An experimental study shows that NSAIDs such meclofenamic acid inhibits ATP-sensitive potassium channels that cause depolarization of the beta cells of the pancreas which in turn leads to increased insulin release [18]. The increase in insulin release is likely to cause hypoglycemia. This might be worse in diabetic patients as NSAIDs and sulphonylureas could have a synergistic effect on inhibition of ATP-sensitive potassium channels. Being a class of NSAIDs, ibuprofen might also follow a similar mechanism in causing hypoglycemia but it requires further experimental studies.

The fact that hypoglycemia is mentioned as adverse effect of naproxen, propionic acid derivative [15], which is a drug class of ibuprofen, might also strengthen the causation. It is however important to note that hypoglycemia has never been associated with other propionic acid derivatives such as ketoprofen [16] and fluribiprofen [17]. Strength of association was the only Hill's criterion that failed to support this causation. This shows either the rarity of the ibuprofen-induced hypoglycemia or the statistical signal is masked by other adverse effects of ibuprofen and frequency of other drugs-induced hypoglycemia in the WHO global database of individual case safety reports. Taking the high global consumption data of ibuprofen [21] into account, the risk of hypoglycemia might be very rare but still important as the product is available over-the-counter and consumers are likely to overdose themselves with the intention to get better benefits.

Use of the Austin Bradford Hill causality assessment framework which is a rigorous method for assessing causation was the main strength of the study. The study had the following several limitations that need to be considered. Due to the nature of the study design, the authors could not validate the diagnosis of the cases and readers should note that the cases had varying levels of information. Although a substantial number of the events were marked as "serious," including deaths, the degree, duration, and/or reversibility of hypoglycemia in some of the cases

were unknown or not reported. As the cases were voluntarily reported, incidence of ibuprofen-induced hypoglycemia could not be computed which is an inherent limitation of a spontaneous reporting system. This causal link is a hypothesis made based on the currently available totality of evidence that need to be further substantiated and should not be considered as conclusive.

CONCLUSIONS

The plausible temporality, dose-response relationship, having cases with positive dechallenge and rechallenge, the consistency of the cases and specificity of the association, the available experimental evidence and analogy supports a causal association between hypoglycemia and ibuprofen, in both diabetic and non-diabetic consumers, that need to be further substantiated. The authors remind healthcare professionals to monitor patients taking ibuprofen and aware consumers on the potential risk of hypoglycemia. Manufactures and regulators are also recommended to ensure inclusion of hypoglycemia as a possible adverse effect of ibuprofen and aware healthcare professionals and consumers on the potential risk.

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ETHICAL CONSIDERATIONS

Ethics approval and consent to participate

As the study used retrospective data from the WHO global database, ethical approval and consent for participation is not required for authorized professionals of countries participating in the WHO program for international drug monitoring.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to agreements between contributors of data to the database used (VigiBase) and the custodian of the database. National Centres (mainly drug regulatory authorities) constituting the WHO Programme for International Drug Monitoring contribute data to VigiBase and the Uppsala Monitoring Centre is the custodian in its capacity as WHO collaborating centre for international drug monitoring. Some subsets of the data may be available from the corresponding author on reasonable request.

Authors' contributions

Conceptualization: Mulugeta Russom; Design and Methodology: All authors; Data mining, analysis and interpretation: All authors; Writing original draft: Mulugeta Russom, Filipos Yohannes and Abel Tekle; Review and editing: Ruth Ghirmay; Supervision: Mulugeta Russom. Finally, all authors agreed the article to be published and be accountable for all aspects of the work.

Disclaimer

The association presented in this manuscript is those of the authors and does not represent the opinion of the WHO or the Uppsala Monitoring Centre, Sweden

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