Systematic Review on the Safety of Concomitant Use of Hypoglycemia-Inducing Drugs and Non-Steroidal Anti-Inflammatory Drugs in Patients With Musculoskeletal Pathology

Estíbaliz Loza
Servicio de Reumatología, Hospital Clínico San Carlos, Madrid, Spain

Objectives: To analyze the safety of combining non-steroidal anti-inflammatory drugs (NSAID) and hypoglycemia-inducing drugs. Methods: A systematic review following a sensitive search strategy was performed. All articles published in MEDLINE (since 1961), EMBASE (since 1961), and Cochrane Library, up to December 2007, were examined. Selection criteria: the population (subjects taking hypoglycemia-inducing drugs: insulin or oral antidiabetic drugs [OAD]), the intervention (concomitantly use of NSAID), and the outcomes related to safety (gastrointestinal, renal, cardiovascular toxicity) and glycemic control. Titles and abstracts of retrieved articles meeting inclusion criteria from the search were reviewed. Only randomized controlled trials (RCT), or cohort studies were included. Results: A total of 33 studies were reviewed in detail, and 11 were finally included, 10 low quality RCT, and 1 prospective cohort study with moderate quality, which included 199 patients. All patients were diabetics; mostly young or middle aged men, on different NSAID and hypoglycemic drugs. There was no evidence of important changes in patient’s glycemic controls, nor in their renal function, when combining NSAID with hypoglycemia-inducing drugs. Moreover, there is no clear increase in the number of serious side effects. Conclusions: According to the published evidence, there are not enough arguments to contraindicate the use of NSAID with hypoglycemia-inducing drugs (insulin or OAD).

Key words: Non-steroidal anti-inflammatory drugs. Steroids. Hypoglycemia-inducing drugs.
Palabras clave: Antiinflamatorios no esteroideos. Esteroides. Hipoglucemiantes.

Introduction

The use of non-steroidal anti-inflammatory drugs (NSAID) is very frequent in patients with musculoskeletal disease. Different studies have shown the relationship of NSAID with gastrointestinal complications, some potentially severe such as ulcers, hemorrhage, or digestive tract perforation. On the other hand, in the same way it has been demonstrated that NSAID consumers have other possible independent risk factors for these digestive complications and adverse events of some other nature. Among others, advanced age, a history of gastroduodenal ulcers or the use of other drugs such as anticoagulants, have been considered. With relation to the less frequent or less studied adverse events related to NSAID, the medical literature and some pharmacokinetics studies point to the possibility of the appearance of severe hypoglycemia due to NSAID use in patients undergoing treatment with hypoglycemic drugs. Acute renal failure and lactic acidosis cases have also been described. Because in rheumatology it is frequent to follow cases with rheumatic disease who also are undergoing treatment with hypoglycemic drugs, both oral antidiabetics (OAD) and/or insulin, and because it is likely that many of them might merit an NSAID, determining the possible effects of the concomitant use of NSAID and hypoglycemic drugs (especially related with glucose control and renal function) is of great interest in our clinical environment. Therefore, the objective of this systematic review is to search for published evidence on the concomitant use of NSAID and hypoglycemic drugs in order to contribute to a better management of our patients.

Material and Methods

A systematic review was done to analyze the safety of the concomitant use of NSAID and hypoglycemic drugs. The selection criteria for the studies were: a) studies in which patients took hypoglycemic drugs (both OAD and insulin), without restrictions regarding type, dose or administration route of the hypoglycemic drug; b) studies in which the patients, in addition to hypoglycemic drugs, concomitantly took and NSAID, without restrictions regarding the type and dose of NSAID, but excluding studies in which the subjects took NSAID at an antiplatelet dose and not for analgesia and/or anti-inflammatory purposes, as well as topical treatments; c) to evaluate the safety of the simultaneous use of these medications we included studies that analyzed the following variables: gastrointestinal, renal, cardiovascular or glycemic control (fasting and postprandial serum glucose or glycosylated hemoglobin); and d) clinical trials (CT) and cohort studies (prospective or retrospective), excluding those studies that only presented pharmacokinetic and/or pharmacodynamic data, as well as studies in healthy volunteers and in animals. Regarding the language, articles in english and spanish were selected. The following electronic databases were searched, up until December 2007: MEDLINE (from 1960), EMBASE (from 1980), and the Cochrane Library (Central). Both MeSH and free text formats were searched. No limits were set for the publication dates. The specific search strategies are detailed in Tables 1 and 2. No manual searches of national (SER) or international (ACR, EULAR) meetings was detailed in Tables 1 and 2. No manual searches of national (SER) or international (ACR, EULAR) meetings was carried out, due to the great volume of abstracts recovered from the electronic databases. A single reviewer analyzed the resulting papers, as well as carried out the detailed analysis of those articles included. The results of the search was first thinned out by title and abstract, or by reading the whole article in the case it lacked an abstract, in 20 minute sessions maximum. Articles which explicitly examined the use of NSAID and hypoglycemic drugs were selected for a detailed review, as well as those dealing with the concomitant treatment of comorbid states. After this process, the remaining articles were analyzed in detail. Finally, a manual search with the references of the selected articles was carried out for their detailed analysis. All of the references were recovered from the internet and introduced into Procite 5.1 software in order to ease their management. To evaluate the methodological quality of the included studies, a Jadad score (1 to 5, was used, considering articles of good quality those with a Jadad score of 3-5) for the CT and the Oxford quality score for the cohort studies.

Results

The results of the search are detailed in Figure 1. Of the recovered articles, for their detailed analysis, 11 were finally included; 10 are CT and 1, a prospective cohort study. The main results of the included studies will be discussed in the following paragraphs (Table 3). The list of excluded articles and the cause for their exclusion are detailed in Table 4. Of the 36 articles selected for their detailed review, 28 explicitly analyzed the concomitant use of NSAID and hypoglycemic drugs, the rest (8) did not, but 3 of them provided enough information for their inclusion.

**Summary of the Evidence in NSAID With Hypoglycemic Drugs**

As has been commented, 11 articles were included, 10 CT, generally low regarding quality (9 were Jadad 1 or 2 and only 1, Jadad 4), and a prospective cohort study of moderate quality (2c). The duration of follow-up varied between 3 days and 3 years. A total of 199 subjects, all diabetic and mostly young or middle aged men, were analyzed. The studies analyzed the safety of the concomitant use of insulin or OAD with different NSAID and all of them at a different dose. Studies were approved by the ethics committees and patients signed informed consent before entry. Most analyzed in detail the evolution of glycemic control in patients and adverse events, at least generally.

Regarding the safety results, not enough evidence was found to contraindicate the concomitant use of these drugs. This is based on the fact that no clear association between the combined use of these drugs and the appearance of problems in glycemic control, renal function and severe gastrointestinal events was seen.

**Results in Detail of the Combined Use of NSAID and Hypoglycemic Drugs**

The following data stands out among the results of the CT included in the systematic review:
In the study by Baggio et al., the use of ITF-128 with insulin, in comparison with insulin monotherapy, did not produce major changes in blood pressure, heart rate, glycemia, glycosylated hemoglobin, glycosuria, or renal function tests. According to the CT by Christiansen et al., the use of indomethacin 400 mg/day with insulin, in comparison with baseline values, did not significantly modify the glycemia, glycosuria, glycosylated hemoglobin, and renal function.

Cohen et al. proved that the use of ibuprophen 2400 mg/day or sulindac 400 mg/day with OAD or insulin, did not lead to changes in glycemia, glycosylated hemoglobin, cholesterol, or renal or liver function. On the other hand, no differences were seen in the number of severe adverse events with NSAID and insulin.

According to the CT by Cunha-Vaz et al., sulindac 400 mg/day with insulin, compared to insulin monotherapy, was not associated with an increase in the number of adverse events.
### TABLA 3. Included Studies, Characteristics, and Main Results

<table>
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<tr>
<th>Study</th>
<th>Participants and Intervention</th>
<th>Results</th>
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<tr>
<td><strong>Baggio</strong>&lt;sup&gt;a&lt;/sup&gt;; CT placebo control; follow up 165 days; Jadad 2</td>
<td>n=26 IDDM (42.2% women; mean age, 37 years). LC: albuminuria (15-300 mg/day) &gt; 3 years, normal renal function. CE: AHT, other, non-insulin drugs. ITF-182, 2250 mg/day + insulin. Insulin + placebo</td>
<td>In the ITF-182 group there were no statistically significant changes in BP, HR, glycemia, HbA1c, glomerular filtration, blood chemistry.</td>
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<td><strong>Christiansen</strong>&lt;sup&gt;b&lt;/sup&gt;; CT double blind, placebo control; follow up, 3 days; Jadad 2</td>
<td>n=9 IDDM (100% males; age, 19-30 years). EC: diabetic microangiopathy, other NSAID. Indomethacin 140 mg/day 3 days + insulin (n=9). Placebo + insulin (n=9)</td>
<td>No statistically significant changes in the indomethacin group in: glycemia, HbA1c, glycemia. In comparison to placebo, no significant differences were seen if GF, GFF, GPF.</td>
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<td><strong>Cohen</strong>&lt;sup&gt;c&lt;/sup&gt;; CT placebo control; 24 week follow-up; Jadad 2</td>
<td>n=18 patients with DM and peripheral neuropathy (100% male; mean age, 58.4 years), 12 with insulin and 6 with oral antidiabetics. EC: other neuropathies, severe claudication. Ibuprofen 2400 mg/day 8 weeks (n=18). Sulindac 400 mg/day 8 weeks (n=18). Placebo 50 mg/day 8 weeks (n=18). Continued use of antidiabetic drugs</td>
<td>NSAID did not modify: cholesterol, HbA1c, postprandial glucose, creatinine, hepatic function, proteinuria 24 h. Mild adverse gastrointestinal events: ibuprofen (n=5), sulindac (n=0) (P&lt;.006), placebo (n=0); graves: ibuprofen (n=1), sulindac (n=0) (P=.243), placebo (n=0).</td>
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<td><strong>Cunha-Vaz</strong>&lt;sup&gt;d&lt;/sup&gt;; CT double blind placebo control; 6 month follow-up; Jadad 4</td>
<td>n=18 IDDM (28% women; mean age, 34 years; mean duration of DM, 10.3 years). EC: &gt;5 microaneurisms in the posterior pole of the eye, proliferative retinopathy, other serious complications of DM, liver and renal disease, hematologic, cardiovascular, problems, hyperthyroidism, active peptic ulcer or digestive hemorrhage, malignant disease, pregnancy. Sulindac 400 mg/day + insulin 6 months (n=8). Placebo + insulin 6 months (n=10)</td>
<td>Effects on vision: alterations in permeability, sulindac + insulin (6 eyes) versus placebo + insulin (17 eyes) (P=.001); increase in the size of microaneurisms, sulindac + insulin (n=3) versus placebo + insulin (n=2) (P=.184); new microaneurisms, sulindac + insulin (n=1) versus placebo + insulin (n=3) (P=.441). Adverse events: 1 upper digestive tract hemorrhage in the sulindac group.</td>
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<td><strong>Hattori</strong>&lt;sup&gt;e&lt;/sup&gt;; CT; 3 years follow-up; Jadad 2</td>
<td>n=40 DM2 (49% women; mean age, 60 years). EC: poor glycemic control. Sulindac 200 mg/day (n=16). Control (n=24). Continued use of antidiabetic medication</td>
<td>Non-proliferative diabetic retinopathy: sulindac (n=0), control (n=3) (P=.283). Proliferative diabetic retinopathy: sulindac (n=0), control (n=1) (P=.295). No changes in BP, HbA1c nor severe adverse events in the sulindac group.</td>
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<td><strong>Hommel</strong>&lt;sup&gt;f&lt;/sup&gt;; CT double blind placebo control; 2 week follow-up; Jadad 2</td>
<td>n=8 DM1 insulin dependent with diabetic neuropathy (100% women; mean age, 36 years). Indomethacin 150 mg/day + insulin 3 days (n=8). Placebo + insulin 3 days (n=8)</td>
<td>Compared to placebo, indomethacin reduced in a significant manner: urinary excretion of PGE2, GF, albuminuria and fractioned excretion of albumin.</td>
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<td><strong>Nilsen</strong>&lt;sup&gt;g&lt;/sup&gt;; cross CT; 18 days follow-up; Jadad 1</td>
<td>n=8 DM1 insulin dependent with microalbuminuria (87.5% women; age, 22-43). EC: HF, liver failure, serious infections. Naproxen 1000 mg/day + insulin 4 days (n=8).</td>
<td>Placebo + insulin 4 days (n=8). In comparison with placebo, naproxen significantly reduced the excretion of prostaglandin E2, no differences in the reduction of albumin or the glomerular filtration.</td>
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<td><strong>Oili</strong>&lt;sup&gt;h&lt;/sup&gt;; CT; 11 week follow-up; Jadad 2</td>
<td>n=16 NIDDM + RA/OA/shoulder arthritis (69% women; age, 31-62 years). Piroxicam 40 mg/day + antidiabetics 3-9 weeks (n=16). Placebo + antidiabetics at week 1, 2, 10, 11 (n=16)</td>
<td>In comparison with the placebo period, the use of piroxicam was not associated to significant changes in glycemia, glycosuria, weight or adverse events.</td>
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<td><strong>Pedrazzi</strong>&lt;sup&gt;i&lt;/sup&gt;; CT placebo crossed control, 15-day follow-up; Jadad 2</td>
<td>n=24 NIDDM + OA (50% women; mean age, 71). OAD + indoprophen 600 mg/day 4 day (n=12)/ placebo 5 days (n=12). OAD + placebo 4 days (n=12)/ placebo 5 days (n=12)</td>
<td>In comparison with the placebo period, the use of indoprophen was not associated to significant changes in fasting glucose and an oral load of glucose. No adverse events were detected.</td>
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<td><strong>Shah</strong>&lt;sup&gt;j&lt;/sup&gt;; CT; 5 week follow-up; Jadad 2</td>
<td>n=22 controlled NIDDM &gt;6 months + rheumatic symptoms NSAID (age, 42-69 years). Chloropromazine (62.5-375 mg/day) + indoprophen 1200 mg/4 weeks (n=11). Chlorpromazine (125-250 mg/day) + phenylbutazone 300 mg/4 weeks (n=11)</td>
<td>Phenybutazone produced a significant reduction in fasting glucose, with no relation to postprandial readings. Indoprophen was not associated to significant changes in baseline or postprandial glucose.</td>
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<td><strong>Whiting</strong>&lt;sup&gt;k&lt;/sup&gt;; Prospective cohorts; 19 day follow-up; quality 2c</td>
<td>n=10 DM. EC: renal, cardiac, hematologic, ophthalomic or liver disease, DBP &gt; 100 mmHg, allergic to sulphonamides, OAD or NSAID. Naproxen 750 mg/day 4 days. Tolbutamide 1 g/day 7 days</td>
<td>No statistically significant differences seen in postprandial glucose (P=.95) nor in the nadir (P=.25) with naproxen.</td>
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*The noted criteria are defined as follows: AHT indicates arterial hypertension; BP, blood pressure; CT, clinical trial; DBP, diastolic blood pressure; DM, diabetes mellitus; EC, exclusion criteria; GFF, fraction of glomerular filtration; GF, glomerular filtration; HbA1c, glycosylated hemoglobin; HR, heart rate; IDDM, insulin dependent diabetes mellitus; NIDDM, non insulin dependent diabetes mellitus; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; OAD, oral antidiabetics; PGE2, prostaglandin E2; RA, rheumatoid arthritis; RPF, renal plasma flow.*

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Hattori et al.,\textsuperscript{11} saw that the use of sulindac 200 mg/day with OAD or insulin did not produce important changes in blood pressure and glycosylated hemoglobin or severe adverse events.

Hommel et al.,\textsuperscript{12} saw that the use of indomethacin 150 mg/day, in comparison with insulin monotherapy, produced a reduction in the excretion of PGE2, glomerular filtration, albuminuria, and fractioned clearance of albumin.

Nilsen et al.,\textsuperscript{13} saw that the use of naproxen 1000 mg/day with insulin, compared to insulin alone, led to a larger reduction in urinary excretion of PGE2. No differences were seen in relation to albuminuria and glomerular clearance.

Oli et al.,\textsuperscript{14} describes that the use of peroxicam 40 mg/day with OAD, compared to OAD without NSAID, was not associated to significant changes in glycemia, glycosuria, weight or other adverse events.

Pedrazzi et al.,\textsuperscript{15} mentioned that the use of OAD with indoprophen 600 mg/day, in comparison with OAD monotherapy, was not associated to significant changes in fasting glucose nor after an oral load of glucose and no adverse events were detected.

Shah et al.,\textsuperscript{16} showed that the use of chlorpropamide with phenylbutazone 300 mg/day was associated to a significant reduction in fasting glucose, but not in postprandial measurements. On the other hand, the use of OAD with indoprophen was not associated to changes in fasting or postprandial glucose levels.

In this systematic review of the literature, the safety of the concomitant use of hypoglycemia-inducing drugs and non-steroidal anti-inflammatory drugs (both OAD and insulin) were analyzed. In order to reach this objective, an extensive search of the main available bibliographic databases, as has been described in the

\begin{table}[h]
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\caption{Excluded Studies (by Author and Publication Date) and Motives for Exclusion\textsuperscript{*}}
\begin{tabular}{ll}
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Study & Motive for Exclusion \\
\hline
Aguilar\textsuperscript{a} (1986) & Use of low-dose(antiplatelet) ASA as NSAID \\
Anderson\textsuperscript{a} (2002) & Healthy volunteers \\
Bakris\textsuperscript{a} (1995) & Use of high dose NSAID concomitantly with misoprostole \\
Chlud\textsuperscript{a} (1977) & No relationship with research question \\
Day\textsuperscript{a} (1995) & Healthy volunteers \\
de Cosmo\textsuperscript{a} (1993) & Use of low-dose(antiplatelet) ASA as NSAID \\
Farker\textsuperscript{a} (2002) & No indication on whether hypoglycemic medication is employed \\
Hartmann\textsuperscript{a} (1990) & Healthy volunteer \\
Haupt\textsuperscript{a} (1987) & German language \\
Kubacka\textsuperscript{a} (1986) & Healthy volunteers \\
Mathiesen\textsuperscript{a} (1988) & No new data is given for the review in comparison with that published by another article in the same group of patients (Hommel 1987) \\
Micossi\textsuperscript{a} (1978) & Unclear whether patients received hypoglycemic drugs \\
Morrison\textsuperscript{a} (1982) & Healthy volunteers \\
Pereira\textsuperscript{a} (2000) & No hypoglycemic drugs are employed \\
Pereira\textsuperscript{a} (2001) & No hypoglycemic medication is taken \\
Pfeifer\textsuperscript{a} (1993) & Clear clinical data on efficacy, not safety \\
Poggi\textsuperscript{a} (2006) & No analysis of clinical effect, only pharmacokinetics/dynamics \\
Price\textsuperscript{a} (2003) & Clinical case \\
Rudberg\textsuperscript{a} (1993) & All data is related with intense exercise \\
Sharma\textsuperscript{a} (1989) & Topical NSAID \\
Shimura\textsuperscript{a} (2007) & Topical NSAID \\
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\end{tabular}
\textsuperscript{*ASA indicates acetyl salicylic acid; NSAID, non-steroidal anti-inflammatory drugs.}
\end{table}

\textbf{Discussion}

In this systematic review of the literature, the safety of the concomitant use of NSAID and hypoglycemic drugs (both OAD and insulin) were analyzed. In order to reach this objective, an extensive search of the main available bibliographic databases, as has been described in the
“Material and Methods” section. We only included CT and quality cohort studies, considering that this is the best way to answer the research question. In general, we can consider that the use of NSAID with hypoglycemic drugs does not seem to produce important alterations in glycemic control or on the renal function of patients. We did not find a significant increase in the number of adverse events of another nature, such as gastrointestinal.

After the detailed analysis, 11 studies were included (10 CT15-16 and 1 cohort study17). The quality of the CT in general was poor, all were Jadad 1 or 2, excepting one that reached a 4 point score. Regarding the included cohort study, it was moderate in quality, 2c on the Oxford score. It represents one of the main limitations of the study which must be kept present when evaluating the conclusions of this review.

As for the patients studied, 199 were included, all of them diabetic and mostly young or middle-aged males. Only 2 studies15,16 included patients who also had some sort of musculoskeletal disease. Therefore, and given the lack of published evidence with respect to the research question in patients with rheumatic disease, it was finally decided not to restrict the review to this type of patients. This led to, as happened in the case of the quality of the studies, the representativity of the included sample was also limited and does not reflect the spectrum and characteristics of the patients which are normally followed in rheumatology consults. But it is also important to mention that the majority of included patients were young or middle aged, without severe concomitant disease, making the results biased, because these patients can be less predisposed to adverse events.

On the other hand, the NSAID and hypoglycemic drugs studied were diverse, as were the prescribed doses (when recorded) making it difficult to establish comparisons between drug groups.

In relation to the events studied, all of the included articles evaluated glycemic control of patients during follow-up, and most also analyzed clinically relevant and/or severe adverse events such as gastroduodenal ulcer or digestive hemorrhage. In general, these outcome measurements were defined by very similar criteria in all of the studies. As for the results themselves, as has been commented, no evidence of the of problems in glycemic control or renal function by the concomitant use of NSAID and hypoglycemic drugs was seen, as had been indicated by some publications.1-5 Only one study16 described that the association of phenylbutazone with OAD produced a significant reduction in fasting glucose (not clinically important). Nor has it been manifested that it produced a larger number of adverse events such as gastrointestinal. In only one study9 the use of ibuprofen was associated to a larger number of gastrointestinal adverse events, mild in nature, and not associated to an increase in the severe gastrointestinal adverse events.

It is important to note, at this point, that it is occasionally difficult to determine if certain secondary events could be due to the use of NSAID and hypoglycemic drugs, could really be produced by the underlying disease and not its treatments.

Taking into account the limitations found in this systematic review, we consider that other studies are necessary with better methodological quality and more representative, to be able to determine the true effect of the use of NSAID and hypoglycemic drugs, as well as elucidate the possibility that a concrete association of drugs has a better safety profile than others.

Finally, in conclusion, not enough evidence to contraindicate the the concomitant use of NSAID and hypoglycemic drugs was seen, with a 2c degree of evidence and a C/D strength for recommendation.

References
18. Aguilar Munoz A, de la Cruz Cortez JP, Martos Crespo F, Garcia Arres J, de Pablo Molina J, Sanchez de la Cuesta F. [Effect of dipyriramole (225
mg/day) and acetylsalicylic acid (150 mg/day) on various platelet parameters in non-complicated diabetes mellitus. Med Clin (Barc). 1986;86:712-5.