

# Susceptibility of the Spanish Population to Adverse Effects by Sulfasalazine: Systematic Review

Cayetano Alegre de Miquel, Carlos Santos Ramírez, and Mireia Barceló Bru

Unidad de Reumatología, Hospital Universitario Vall d'Hebron, Barcelona, Spain

**Background:** Clinical experience raises suspicion that the Spanish population could suffer higher rates of side effects of sulfasalazine (SSZ) therapy. We conducted a systematic review of existing literature to analyze the susceptibility to developing adverse events produced by SSZ in the Spanish population.

**Material and method:** A literature search was conducted in EMBASE, IBECs, and MEDLINE from 1973 to March 2007. The items sought were those describing adverse effects, both in text and tables, and reasons for withdrawal, the population under study and discussion of differences in side effects of the different treatment groups.

**Results:** Of the 106 retrieved articles, 36 were selected for review and detailed analysis. 34 articles were selected from MEDLINE and EMBASE and 2 from IBECs. We did not find any study that showed that the Spanish population was more susceptible to SSZ.

**Conclusions:** The adverse effects of SSZ vary with the pattern of acetylation. Thus, in slow-acetylators, depending on the dosage of SSZ, the side effects increase significantly. In the Spanish population slow-acetylators prevalence is higher than in other ethnic groups. Therefore, one could infer that the incidence of adverse side effects by SSZ could be higher in the Spanish population than in others different ethnic groups. We found no evidence that the Spanish population was more likely to suffer adverse effects by SSZ than other ethnic groups.

**Key words:** Sulfasalazine. Adverse effects. Slow acetylation.

## Susceptibilidad de la población española a los efectos adversos por sulfasalazina: revisión sistemática

**Introducción:** La experiencia clínica hace sospechar que la población española pudiera sufrir más efectos adversos por la sulfasalazina (SSZ). Se realizó una revisión sistemática de la literatura existente con el objetivo de analizar la susceptibilidad a desarrollar eventos adversos producidos por la SSZ en la población española.

**Material y método:** Se definió una estrategia de búsqueda bibliográfica sensible en EMBASE, IBECs y MEDLINE desde 1973 hasta marzo de 2007. En los artículos seleccionados se buscó la descripción de los efectos adversos, tanto en el texto como en las tablas, así como los motivos de retirada, la población estudiada y la discusión sobre la opinión de las diferencias en los efectos adversos de los diferentes grupos de tratamiento.

**Resultados:** De un total de 106 artículos rescatados se seleccionaron 36 para realizar un análisis detallado de los 34 artículos seleccionados en MEDLINE y EMBASE y de los 2 de IBECs. No se encontró ningún estudio que evidencie que la población española sea más susceptible a los efectos adversos por SSZ.

**Conclusiones:** Los efectos adversos por SSZ varían según el patrón de acetilación. En la población española la prevalencia de acetiladores lentos es mayor que en otros grupos étnicos; por tanto, cabría inferir que la incidencia de efectos adversos secundarios a la SSZ podría ser mayor en la población española que en otros grupos. No encontramos evidencia en la literatura de que la población española sea más susceptible a los efectos adversos por la SSZ.

**Palabras clave:** Sulfasalazina. Efectos adversos. Acetilación lenta.

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Correspondence: Dr. C. Alegre de Miquel.  
Unidad de Reumatología. Hospital Universitario Vall d'Hebron.  
Pg. de la Vall d'Hebron, 119-129. 08035 Barcelona. España.  
E-mail: calegre@vhebron.net

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## Introduction

Sulphasalazine (SSZ) was synthesized in 1930 through the combination of a compound of the family of aspirin (5 aminosalicylic) and an antibiotic (sulphapyridine). In the fifties it was used as a treatment of rheumatoid

arthritis because it was thought that this disease had an infectious cause, but later fell in disuse and since then has been employed for the treatment of inflammatory intestinal diseases. In the eighties new studies were published in which the use of sulphasalazine for the treatment of rheumatic disease was mentioned, and is currently one of the drugs employed in the treatment of rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies.

In the common practice and publications of Spanish rheumatologists there is a lesser use than in English-speaking countries; among other reasons because it is assumed that SSA is less tolerated by our population. The clinical experience has led to the suspicion that there could be a certain predisposition in the Spanish population for a larger rate of adverse events due to SSZ, perhaps due to the presence of a larger number of slow acetylators, even if the products' information does not refer to this.

Our objective was to compare if the Spanish population is more susceptible to adverse events due to SSZ through a systematic review of the literature regarding this topic.

## Material and Method

### Search Strategy

A systematic review was performed<sup>1-36</sup> on the following databases: EMBASE (in OVID), the Spanish bibliographic index IBECs and in MEDLINE (in PubMed), since 1973 to March 2007. The strategy employed in the different data groups was especially sensitive: "*Sulphasalazine/adverse effects*" (MESH, *medical subheadings*), given that the previous strategies were more restrictive and did not provide enough articles nor were there more informative than those captured through this strategy. Additional filters were applied in the English or Spanish languages and the existence of clinical trials was confirmed through key words (both for clinical trials as for randomized clinical trials). We also cross-referenced with the term (MeSH) "*ethnic groups*."

### Study Selection Criteria

The result of the search was primarily purged by title and abstract or by the complete article in the case the latter was not available. After this process, the rest of the articles were analyzed in detail. Initially, all of the trials and clinical cases which had been carried out in Spanish population or using ethnic groups were selected, without any other limitations, and the studies in children were rejected. Because the results of these searches were null, we extended it to any randomized and placebo-controlled clinical trial that included the description of the adverse

events, without a limitation of the population under study either due to disease or origin. Studies in children were excluded because this population has a different metabolism from adults and this could lead to confusion upon review.

### Outcome Measures

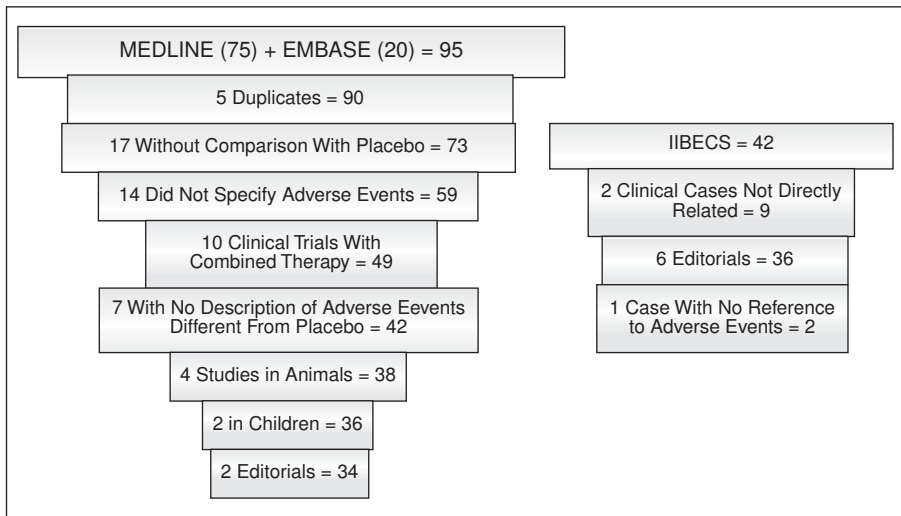
The description of the adverse events, both in the text as in the Tables, as well as the motives for withdrawal, the population studies and the discussion on the authors opinion on the differences regarding adverse events in the different treatment groups were searched for in the selected articles selected.

## Results

The results of the MEDLINE (PubMed) search, depending on the terms and filters applied were: "Sulphasalazine AND adverse effects," 880 hits; "Sulphasalazine AND adverse effects in Spanish language," 12; "Sulphasalazine AND adverse effects in Spanish OR English language," 691. Of these 691, 122 were clinical trials and 75 apart from the controlled trials. We found 66 219 hits regarding ethnic groups, but none cross-referenced with "Sulphasalazine/adverse effects [MESH]." In EMBASE (OVID) the results were "*Sulphasalazine/adverse effects*" was 891, none in Spanish, 678 in English. Of 678, 119 were randomized clinical trials and only 20 were also placebo-controlled. The results of "*Sulphasalazine/adverse effects*" were cross-referenced with 11 787 hits on ethnic groups, and no publications were found.

On IBECs, a Spanish bibliographic index, we used the terms "sulfasalazina" and then "salazopyrina" and "5-ASA." With the term "salazopyrina" we did not obtain any results, nor did we find any with "5-ASA" and with "sulfasalazina" we found 11 hits.

The comparison of the results of the MEDLINE (n=75) and EMBASE (n=20) databases led to 90 articles (5 duplicated articles were discarded) to analyze, discarding 17 for comparing SSZ with other drugs, not with placebo, 14 for not specifying the adverse events or motives for withdrawal, 10 because they were clinical trials with combined therapy, 7 for not describing adverse events different from those of placebo, 4 because they were performed in animals, 2 were editorials, and 2 in children. In total, a detailed review of 34 articles was performed. Of the 11 hits found on IBECs the following were rejected using the title and abstract: 6 editorials or reviews, 2 clinical cases not directly related, and 1 clinical case regarding efficacy without reference to adverse events. Figure shows the flow of the selection process for studies from the 3 databases.



**Figure.** Results of the bibliographic search and selection by title and abstract.

## Detailed Review

We performed a detailed analysis of the 34 selected articles from MEDLINE and EMBASE and the 2 from IIBECs. The frequency of adverse events during treatment (86%), mainly gastrointestinal (61%): anorexia, gastrointestinal, specific skin eruption, alkaline phosphatase glutamic pyruvic transaminase (GPT) elevation, leucopenia, and a reduction in immunoglobulins.<sup>33-35</sup> Most of the adverse events occurred in the 4 days after increasing the dosage and all of them within the first week.

The adverse events we found can be distributed into 2 groups: those which are not dose-dependent (exanthema, bone marrow depression, autoimmune hemolysis, and lung alterations, which generally do not appear at the beginning of treatment) and those which were dose-dependent, which appear after increasing 2 to 4 g/day (nausea, headache, and malaise, closely related with the plasma concentration of total SSZ). These are predominant in slow acetylators, although the acetylation pattern is not the only factor, because SSA is also metabolized through hydroxylation and glucuronization.<sup>35</sup>

Azad et al<sup>36</sup> compared 3 different doses of SSZ (1 g, 2 g, or 4 g) a day in the maintenance of ulcerative colitis. They described that the percentage of the adverse events depended on the plasma concentration, and this on the relationship between the metabolites of total SSZ and free SSZ in plasma. From this study the relationship between the patterns of acetylation with the frequency of the adverse events could be deduced. However, we found no studies that compared whether there are different rates of adverse events due to SSZ between the Spanish population and other ethnic groups.

## Discussion

SSZ is metabolized by intestinal bacteria to its metabolites: sulphapyridine and 5-aminosalicylic acid; the absorbed dose, which then is metabolized in the liver is approximately 15%. The plasma half-life of SSZ is 3.4 to 7.6 h. Then, sulphapyridine is metabolized through acetylation to acetylsulphapyridine; the speed with which it is metabolized to acetylsulphapyridine is dependent of the acetylator phenotype. In fast acetylators it is 10.4 h, while in slow acetylators it is 14.8 h. Approximately 60% of the Caucasian population corresponds to a slow acetylator phenotype, manifested by a lengthening of the plasmatic half-life of sulphapyridine (14.8 h vs the usual 10.4 h), leading to elevated plasma concentrations of sulphapyridine and accumulation of the first metabolite of SSZ with respect to the fast acetylators.<sup>33</sup>

After our bibliographic search,<sup>1-36</sup> we found no evidence in the reviewed literature that the Spanish population is more susceptible to adverse events of SSZ than other ethnic groups.

It is evident that the adverse events of SSZ vary according to the pattern of acetylation. Therefore, slow acetylators, according to the dose of SSZ, will have a significant increase of adverse events.<sup>36</sup>

The prevalence of slow acetylators in the Spanish population is higher than in other ethnic groups.<sup>37,38</sup> Therefore, it could be deduced that the incidence of secondary adverse events due to SSZ is higher in the Spanish population than in other ethnic groups.

However, new comparative studies of adverse events of SSZ would be needed between different population groups in order to confirm this suspicion.

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