Metamizole and risk of agranulocytosis

First published: 27/08/2021

Last updated: 30/01/2025

Study Finalised

Administrative details

EU PAS number

EUPAS41314

Study ID

48963

DARWIN EU® study

No

Study countries

Spain

Study description

Metamizole is an analgesic and antipyretic marketed for more than 50 years in our country. It is a widely used drug in Spain with the indications of analgesic in different situations of moderate or severe acute pain, and antipyretic when other alternatives are not effective. Agranulocytosis is one of its possible

adverse reactions and, although it is rare and has a very low frequency, it is serious and can lead to the death of the patient. It is characterized by a decrease in peripheral neutrophil count to less than <500 cells/mcl due to immunologic or cytotoxic mechanisms. Most, but not all, instances of agranulocytosis result from exposure to drugs (idiosyncratic drug-induced agranulocytosis), and either the drug itself or a metabolite may be causative. Despite agranulocytosis is a well-known adverse reaction for metamizole, there has been an increase recently in the reporting of cases of agranulocytosis to the Spanish pharmacovigilance system. Despite it is a very serious reaction that continues appearing, no study has been performed in years in our country and none with BIFAP. There is a need to carry out a new pharmacoepidemiological study that addresses the issues raised, using secondary sources of information that may be available in health information systems.

Research question and objectives:
Objective: Estimation of the risk of agranulocytosis associated with the use of metamizole compared to other analgesics / anti-inflammatories with similar use profile, in the BIFAP population.

Study design: comparative cohort study. Population: New users of metamizole or other analgesics / anti-inflammatories aged above 2 years, without alterations in bone marrow function (e.g. during or after treatment with cytostatic agents) or diseases of the hematopoietic system.

Data analysis: Survival analyses with Cox proportional hazard regression models.

Study status
Finalised

Research institutions and networks

Institutions

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | **EU Institution/Body/Agency** | **Not-for-profit** | **Regulatory Authority** | **ENCePP partner**

Contact details

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Study timelines

Date when funding contract was signed
Planned: 01/06/2020

Actual: 01/06/2020

Study start date
Planned: 19/09/2022

Actual: 19/09/2022

Data analysis start date
Planned: 19/10/2022

Date of interim report, if expected
Planned: 16/11/2022

Date of final study report
Planned: 19/01/2023

Actual: 08/11/2023

Sources of funding

- Other

More details on funding

AEMPS's own resources. No funding has been received.

Study protocol

Metamizole_Protocolo_v1_25112020.pdf (723.49 KB)

Metamizole_Protocolo_v2_09092022 .pdf (1.05 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Other study registration identification numbers and links

Approved by BIFAP Scientific Committee number 18_2020

Approved by Ethical Committee for Medical Research: Comité de Ética de la Investigación con Medicamentos de la Region de Madrid (CEIm-R) on 8 February 2021 (Acta 02/21)

Methodological aspects

Study type

Study type list

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Patients aged ≥2 years in 2005-2022 were followed from the day after their 1st metamizole or NSAID dispensation up to the end of the first continuous treatment period (i.e. having <30 days without supply) to identify hospitalizations due to idiosyncratic agranulocytosis.

Main study objective:

The objective of this proposal is the estimation of the risk of agranulocytosis associated with the use of metamizole compared to other analgesics / anti-inflammatories with similar use profile, in the BIFAP population.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Metamizole; other analgesics / anti-inflammatories (Ibuprofen, diclofenac, naproxen, dexketoprofen and the rest of ATC M01A, single drug; or paracetamol, codeine or tramadol as single drugs and in fixed dose combinations or simultaneous prescription

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Study drug International non-proprietary name (INN) or common name

CODEINE

DICLOFENAC

IBUPROFEN

PARACETAMOL

TRAMADOL

Anatomical Therapeutic Chemical (ATC) code

(M01A) ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS

ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS

(N02AA79) codeine, combinations with psycholeptics

codeine, combinations with psycholeptics

(N02AJ06) codeine and paracetamol

codeine and paracetamol

(N02AJ13) tramadol and paracetamol

tramadol and paracetamol

(N02AX02) tramadol

tramadol

(N02BB02) metamizole sodium

metamizole sodium

(N02BB52) metamizole sodium, combinations excl. psycholeptics

metamizole sodium, combinations excl. psycholeptics

(N02BB72) metamizole sodium, combinations with psycholeptics

metamizole sodium, combinations with psycholeptics

(N02BE01) paracetamol

paracetamol

(N02BE51) paracetamol, combinations excl. psycholeptics

paracetamol, combinations excl. psycholeptics

(N02BE51) paracetamol, combinations excl. psycholeptics

paracetamol, combinations excl. psycholeptics

Medical condition to be studied

Agranulocytosis

Idiopathic neutropenia

Population studied

Short description of the study population

Patients aged ≥2 years in 2005-2022 new users (i.e. 1st dispensation after ≥6 months without prescription) of metamizole, NSAID or opiates-paracetamol. Patients diagnosed with any of the conditions where severe neutropenia is a common manifestation were excluded (i.e. lymphoma, leukaemia, myelodysplastic syndromes, bone marrow metastasis, cyclic neutropenia, familiar neutropenia, myelofibrosis, AIDS, recent –6 months- use of cytotoxic or immunosuppressant drugs or radiotherapy, aplastic or megaloblastic anaemia, hypersplenism or prior non-idiosyncratic neutropenia). Patients with prior idiosyncratic neutropenia or agranulocytosis were also included, which were considered as confounders.

Age groups

- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

7000000

Study design details

Setting

Primary care and linked hospital records in Spain.

Comparators

- Non-steroidal anti-inflammatory drugs-NSAID.
- Opiates-paracetamols as negative control.

Outcomes

The outcome of interest is idiosyncratic agranulocytosis which is clinically defined as a reduction in the peripheral ANC to <500 cells/mm3 plus compatible symptomatology. To identify all incident cases of agranulocytosis during treatment periods, idiosyncratic neutropenias recorded in hospital discharge registries were captured. Then, agranulocytosis cases were identified through manual review of patients' clinical histories blinded to drug used.

Data analysis plan

As internal validation of the outcome, potential cases identified will be manually reviewed (blinded to drug use) in order to confirm the diagnosis record. Baseline characteristics will be summarized as means and standard deviations or proportions where appropriate. Two survival analyses with Cox proportional hazard regression models will be applied to estimate the risk of agranulocytosis (crude and adjusted hazard ratios, HR) during metamizole treatment episode:

1. versus NSAID as reference cohort
2. versus Opioid- paracetamol as a negative control

An STATA v15 procedure using automatic backward stepwise selection of potential confounders will be performed. Analyses will be stratified by sex, age and the possible effect modifiers.

Summary results

Overall, 26 hospitalised agranulocytosis occurred, 5 in the 1st week (and so removed in main analysis) and 21 thereafter.

IR of agranulocytosis was 14.20 (N=5 cases) and 8.52 (N=3), 1.95 (N=6) and 1.62 (N=5) and 4.29 (N=15) and 3.72 (N=13) per 107 person-weeks of continuous treatment using the date of hospitalization or 7 days before, respectively.

Two, 0 and 2 of cases identified in both analyses had neoplasia in every cohort, respectively.

Adjusted HR of agranulocytosis associated with metamizole was 7.20 [1.92-26.99] and 4.40 [95% CI: 0.90-21.57] versus NSAID, and 3.31 (1.17-9.34) and 2.45 [0.68-8.83] versus opioid-paracetamol, respectively. HR of neutropenia with metamizole was 2.98 [1.57-5.65] versus NSAID.

Documents

Study, other information

Abstract to EMA catalog.pdf (245.59 KB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes