Study Protocol

"Metamizole and risk of agranulocytosis"

Version 1

25 November 2020

TABLE OF CONTENTS

1 Title

Metamizole and risk of agranulocytosis. Version 0.5 – 23 November 2020.

2 Marketing authorization holder

Not applicable

3 Investigators

Name	Role
Miguel Ángel Macia-Martínez[1]	
Patricia García-Poza[1]	
Elisa Martín-Merino[1]	

[1] Agencia Española de Medicamentos y Productos Sanitarios, Calle Campezo, 1, 28022 Madrid, Spain (AEMPS)

4 Abstract

Title: Metamizole and risk of agranulocytosis. Version 0.3 September 2020

Rationale and background: 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[1]. Agranulocytosis is one of its possible adverse reactions and, although it is rare and has a very low frequency[2], 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[3].

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[3].

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 (see below), 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.

Variables:

Outcome: agranulocytosis.

Exposure: New metamizole or analgesic/ anti-inflammatories users

Data sources: BIFAP.

Study size: *This is a population-based database study*.

Data analysis:

Survival analyses with Cox proportional hazard regression models.

Milestones: *Final study report and manuscripts will be available 12 months after the signature date*

5 Amendments and updates

Date	Amendment	Justification	Protocol section

6 Milestones

Milestone	Planned date
1. Preliminary study plan	September 2020
2. Study protocol	November 2020
3. Ethical and scientific approval	January 2021
4. Data extraction and validation	Date "3"+9 Months
5. Study report	Date "3"+15 Months
6. Manuscripts	Date "3"+18 Months
7. Final report	Date "3"+18 Months

7 Rationale and background

Metamizole is an analgesic and antipyretic agent marketed for more than 50 years in Spain. It is a widely used drug in Spain with the indication of treatment of moderate or severe acute pain in different situations, and as antipyretic when other alternatives are not effective[1]. Agranulocytosis is one of its possible adverse reactions and, although very rare[2], is a serious disorder and can lead to the death of the patient. Agranulocytosis is characterized by a decrease in peripheral neutrophil count to less than <500 cells/mcl due to immunologic or cytotoxic mechanisms[3]. The mechanism of metamizole-induced agranulocytosis has not been completely clarified, but it is generally accepted that this disorder is of immunological origin[4].

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[5].

Despite agranulocytosis is a well-known adverse reaction for metamizole, there has been a recent increase in the reporting of cases to the Spanish pharmacovigilance system. The information of the cases notified in Spain indicates that its number has increased in recent years along with the increase in the consumption of this analgesic (from 3.28 DDD per 1000 inhabitants in 2010 to 5.48 in 2019, with an increase of 40.15%)[6]. However, these data based on spontaneous reporting of cases do not allow for a proper estimation of the incidence

Despite it is a very serious reaction associated to a commonly used drug that continues to be reported, no formal study has been performed in many years and in our country no population-based study using electronic medical records has been performed so far. It is noted that in the last years safety issues of other drugs used in the same indications, like non-steiroidal antiimflamatory drugs[7] or opiates[8], have led to an increasing use of alternatives like metamizole.

Up to date evidence from a pharmacoepidemiological study quantifying the risk of agranulocytosis linked to the use of metamizole would contribute to interpret the increasing reporting rates and to inform on the benefit-risk balance of this drug.

8 Research question and objectives

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 (see below), in the BIFAP population.

9 Research methods

A retrospective cohort study among new users of metamizole, NSAID or Opioids-Paracetamol to assess the comparative risk of agranulocytosis associated with the use of metamizole will be performed.

9.1 Study design

A retrospective cohort study will be conducted among new users of metamizole (oral tablets and vials (because they can be administered orally); exposed cohort) and new users of NSAID (reference cohort) to assess the comparative risk of agranulocytosis. Additionally, a third cohort of new users of Opioids/Paracetamol will be utilized as a secondary reference cohort (negative control) to quantify the increased risk of agranulocytosis with metamizol.

The main comparison, i.e. metamizzol versus NSAID, will provide safety information between treatment alternatives to similar indications and comparable patients. This will minimize the effect of protopatic bias on the estimants.

The secondary comparison, i.e. metamizol versus Opioids/Paracetamol, will provide safety information on the availability to the strategy to find elevated risk versus a negative control Opioids/Paracetamol that have never been associated with agranulocitosis).

9.5 Setting

The **source population** will be patients included in BIFAP from 1st January 2005 to 31st December 2019 (study period).

The **study population** consists of patients from the source population and **new users** of any of the **study drugs** (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), during the study period.

Inclusion criteria:

People will enter into the study at the time they meet all the following conditions (**start date**):

- One year of registration in BIFAP.

- At least one visit to the primary care physician. The purpose of this criterion is to ensure that the baseline clinical information necessary to establish comparability between the cohorts of interest is available.

- Six months prior to the first prescription without any prior prescription/dispensation of any of the medications under study (in all exposed cohorts). Thus, only new users of the study drugs will be included.

- A recorded prescription/dispensation of any of the **study drugs**. Drugs dispensed in the hospital or over-the-counter medications are not included. The date of the first prescription of any of the medications under study will be the "start date" and will define the start of follow-up.

Exclusion criteria (at start date):

- Patients 70 or more years old who do not visit the general practitioner for at least 1 year (due to high suspicion of being in a nursing home: "silent" patients).

- Patients under two years of age (due to neutropenia is common in this age following viral infections).

- Patients with acute/chronic medical conditions where severe neutropenia is a typical, common manifestation (on start date and 1-month before for acute conditions or on start date and any moment before start date for chronic conditions):
    - ✓ Malignancies affecting the hematopoietic system (lymphoma, leukemia, myelodysplastic syndromes, bone marrow metastasis);
    - ✓ Other chronic diseases of the hematopoietic system typically causing neutropenia: Cyclic neutropenia, familiar neutropenia, myelofibrosis.
    - ✓ AIDS (not just HIV infection)
    - ✓ Recent use of cytotoxic drugs (ATC L01), immunosuppressants (ATC L04); until six months before start date.
    - ✓ Recent use of radiotherapy; until six months before start date.
    - ✓ Diseases commonly producing severe neutropenia but (almost) always affecting the other hematopoietic series, due to lack of production (aplastic anemia, megaloblastic anemia (due to vitamin B12 or folate deficit); or increased destruction (hypersplenism). In general Haemoglobin < 10 and Platelets < 100,000. Until six months before start date.

Other conditions (diseases, drugs) that may be risk factors for idiosyncratic agranulocytosis or may occasionally lead or have been associated with (according to literature) severe neutropenia/agranulocytosis will be ascertained and analyzed as co-variates (see section 9.6 Variables: potential confounders)

Each patient will then be followed until the **end of follow up**. End of follow-up will be the first of the following:
- End of the treatment episode (See section 9.6 Variables: Exposure: treatment episodes)
- An idiosyncratic agranulocytosis diagnosis (outcome)
- The end of valid data collection.
- Occurrence of any of the exclusion criteria
- Death
- The patient / practice leaves the BIFAP population
- End of the study period.

9.6 Variables

Outcome

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[9]. This means exclusion of cases related with a toxic effect of drugs (i.e. cytotoxic chemotherapy) and other diseases.

Cases of agranulocytosis will be searched in BIFAP as any of the following:

1. Agranulocytosis as the principal diagnosis in CMBDH registry.

2. Agranulocytosis as a secondary diagnosis in CMBDH registry.

3. Agranulocytosis as a diagnosis code in primary care.

4. Agranulocytosis as a text string in primary care.

Based on this strategy, cases will be classified, in a preliminary phase, looking into the EHR around the diagnosis date (+/- 3 month) as:

- Confirmed case: if there is enough information to confirm a case of agranulocytosis:

  ✓ agranulocytosis as the principal diagnosis in a CMBDH registry

  or

  ✓ agranulocytosis as a secondary diagnosis in a CMBDH registry **plus** a diagnostic code of agranulocytosis in the primary care record.

  or

  ✓ Diagnosis code of agranulocytosis in primary care record plus evidence of hospitalization and lab-values of less than 500 neutrophils recorded around the episode date.

- Possible case: Incomplete information to ensure there is a diagnosis of an incident case of agranulocytosis (to confirm or rule out).

  ✓ Agranulocytosis as a secondary diagnosis in a CMBDH registry without any other confirmatory/discarding information.

  or

  ✓ Diagnosis code of agranulocytosis in primary care record without any other confirmatory/discarding information about the diagnosis and/or the date.

- Excluded case: There is enough information to rule out an incident case of agranulocytosis:

  ✓ Agranulocytosis due to any of the exclusion criteria.

  ✓ Prevalent case of agranulocytosis. Based on any data in the EHR indicating that the case was diagnosed before the start date.

  ✓ Cases related to family history of the patient or to another disease

For the main analysis, we will use only confirmed cases of agranulocytosis if sufficient power. Possible cases will contribute till the stop date (recording of agranulocytosis) as non-cases. As a sensitivity analysis, we will use confirmed and possible cases.

A validation process for both, diagnosis and diagnosis date, including manual review of the potential cases recorded in primary care will be performed blinded to the exposure status of each patient.

Diagnosis date will be defined as one week before the confirmation date (usually the date of the hospitalization). This account for the usual latency time from the first manifestations until diagnosis[10].

Exposure: treatment episodes

Three mutually exclusive comparative new users cohorts (i.e. 6 months free of any of them) will be identified according to the prescription that defines the start date, including 1) metamizol, 2) NSAID and 3) Opioids-Paracetamol)

In order to attribute the effect to a clear exposure, if a patient receives prescriptions for more than one cohort on the start date, that patient will be excluded from the study.

Only the first *treatment episode* will be assessed in this study as risk window, i.e. period in which the event is assumed triggered by the drugs. *Treatment episodes* will be constructed allowing for a 30-day gap between the theoretical end date of a prescription and the subsequent prescription. *Treatment episodes* will be defined as a series of subsequent prescriptions, independent of dose changes and constructed according to the method 2 of Gardarsdottir et al.[11].

Constructing treatment episodes will be based on **estimated duration** of a dispensed prescription and overlapping and gaps of a defined length. The estimated duration will be defined according to standard duration algorithms (in BIFAP) based on directions of the physician (daily posology or mode for the same presentation when not available) and number of pills prescribed.

In case a subsequent prescription for the same drug (or a drug of the same cohort) is collected before the theoretical end date of a previous prescription, the number of overlapping days is added to the theoretical end date of the subsequent prescription. Furthermore, a carry- over time of 30 days is allowed to consider the maximum induction period since the last exposure to the drug (Figure 2).

A new treatment episode will be considered when an interval of more than 30 days occurs between the theoretical end date of a prescription and the prescription date of the subsequent prescription for the same patient.

Figure 1. Constructing drug treatment episodes based on estimated duration of a dispensed prescription and overlapping and gaps of a defined length
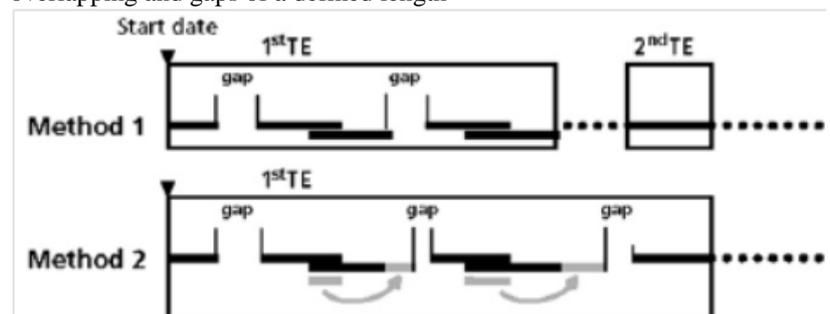
TE: treatment episode

Figure2. Construction of treatments episodes based on date and duration of prescriptions, overlapping and gaps among them
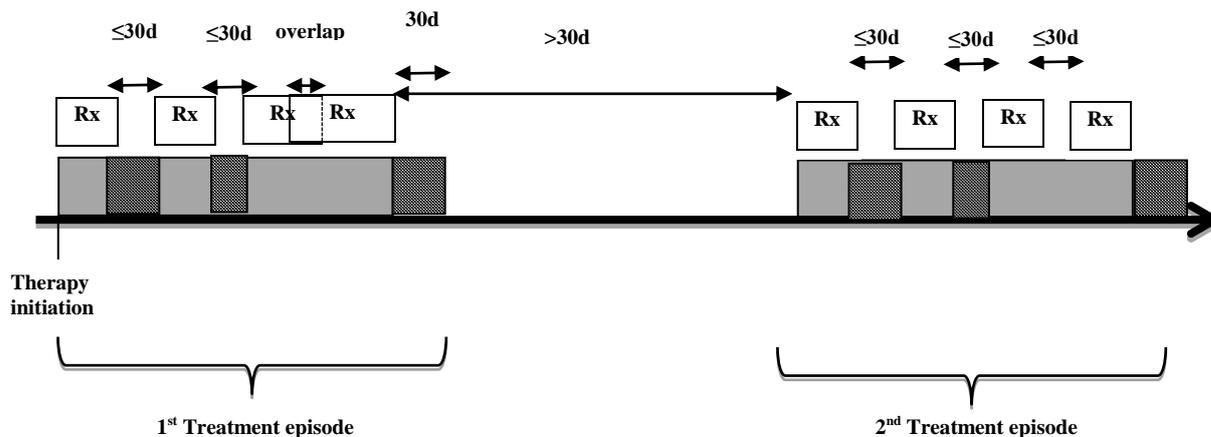
*Note: since we do not know the minimum and maximum time to induce agranulocytosis after a dose for each drug, the treatment episode was similar in all cohorts and based on short-inducing times and on-demand treatments.

Switching or start of a concomitant treatment among cohorts will be stop reason at last prescription date, i.e. in the metamizole cohort if the subsequent prescription within the same treatment episode includes NSAID or Opioids-Paracetamol, the patient is considered to have switched therapy or have concomitant therapy. Thus, the remaining tablet days from the prior prescription are disregarded and the patient is censured, and viceversa, i.e. if a patient in NSAID cohort receive a prescription of MTZ or Opioids-Paracetamol.

Potential confounders

Potential confounders considered in this study are based on literature review as well as on determinants of the treatment prescription. The presence of a confounding variable will be extracted from the computerised medical records prior to or at start date. The CIAP, CIE –based codes systems and ATC will be used to define these risk factors.

Factors that will be included as potential confounders in the multivariate models are:

Calendar year of start date.

Age at start date.

Sex, body mass index (BMI), smoking status and alcohol status will be considered as the last recorded value before start date. Missing values will be included in an additional category.

Drugs that will be included in the model were chosen because they are well-established potential causes of agranulocytosis:

- Anti-inflammatory drugs diclofenac[3], diflunisal, ibuprofen, Indomethacin, Penicillamine, Phenylbutazone, ketorolac.

- Antibiotics: Ampicillin, cefotaxime, Cefuroxime,fusidic acid, imipenem–cilastatin, penicillin G , ticarcillin, Erythromycin, Trimethoprim–sulfamethoxazole, Chloramphenicol, Vancomycin, Dapsone, Piperacillin-tazobactam, meropenem

- Antithyroid drugs, Carbimazole, Methimazole

- Cardiovascular drugs: Clopidogrel, methyldopa, ramipril, Digoxin, Dipyridamole, Propranolol, Ticlopidine, procainamide, flecainide[13], enalapril, captopril, bisoprolol[14], Disopyramide, quinidine, nifedipin, Calcium dobesilate, amiodarone, methyldopa , ramipril

- Gastrointestinal drugs Cimetidine, metoclopramide, Sulfasalazine, ranitidine

- Psychotropic drugs Chlorpromazine, clozapine, fluoxetine, Clomipramine amitryptiline, risperidone, olanzapine,

- Prednisone

- Dermatologic drugs: Dapsone, Isotretinoin

- Antimalarial drugs: Chloroquine, Quinine

- Antifungal agents: Amphotericin B, , terbinafine

- Antiviral agents: Oseltamivir, Ganciclovir, Acyclovir, abacavir[15]

- Anticonvulsants: Carbamazepine, Phenytoin, Ethosuximide, Valproate

- Diuretics: Thiazides, Acetazolamide, Furosemide, Spironolactone

- Sulfonylureas: Chlorpropamide,

- Iron chelating agents: Deferiprone

- Antigout: Allopurinol[16]

Medication will be collected during the 3 months before start date.

Co-morbidities

Concomitant conditions that may be risk factors for idiosyncratic agranulocytosis or may occasionally lead or have been associated to severe neutropenia/agranulocytosis will be ascertained in any suspected case of agranulocytosis and analyzed as co-variate and possible confounder. They include the following comorbidities:
- Chronic conditions/antecedents:
  - ✓ HIV infection

- ✓ Systemic lupus erythematosus, rheumatoid arthritis, Intestinal inflammatory disease, Sjogren's syndrome (autoimmune diseases)
- ✓ Any cancer diagnosis, except basocellular carcinoma[17].
- ✓ Chronic renal impairment
- ✓ Drug allergy
- ✓ Patients with history of idiosyncratic agranulocytosis[16]
- Acute conditions:
  - ✓ Viral: Infectious mononucleosis, acute viral hepatitis, other viral infections
  - ✓ Other acute infections: tuberculosis, typhoid fever, brucellosis, tularemia, malaria, leishmaniasis[18]
  - ✓ Sepsis

Timing of ascertainment will be as follows:

Chronic morbidity will be collected at anytime before start date

Acute morbidity will be collected during 1 month before start date.

10 Data source

10.1 Database characteristics

Table 1. Database Characteristics

	BIFAP
Source population	13.706.810
Year(s) covered for this study	2005-2019
Type of database	Electronic medical records from primary care and linked hospitalisations, including prescribing data with dispensing information. Hospital data includes the CMBDH system. This is an administrative record of all hospital discharges. It includes variables related to the patient and the illness for which he is treated in the hospital and also gathers information about the hospital, the episode and the care process.
Data available since	2001

Demographic variables available	
Date of registration	Yes
Date of transferring out	Yes
Date of birth	YY
Gender	Yes
Drug information available	
Active international coding	ATC
Product coding	CNF
Date of prescribing/dispensing	Yes
Quantity prescribed/dispensed	Yes
Dosing regimen	Yes
Outcome information	
Outpatient primary care diagnosis	ICPC-2, ICD-9
Hospital discharge diagnosis	ICD-10
Laboratory tests	Yes (as requested by GP)
Mortality	Yes (no cause of death)

BIFAP[12] (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care is a non-profit research project funded by

the Spanish Agency for Medicines and Medical Devices (AEMPS). The project started in 2001 and currently includes clinical information of 10.153 physicians (General Practitioners (GPs) and paediatricians). Ten participating Autonomous Region send their data to BIFAP every year. BIFAP database includes anonymized clinical and prescription/dispensing data from around 13.706.810 patients covering around 16.4% of the Spanish population. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2 and ICD-9 code system.

10.2 Period of valid data collection

We will consider the study period from 2005 to 2019 for a valid data period.

The left censoring date is the latest of the following: the date that a practice was enrolled into the database and became up to research standard or the date that a patient enrolled into a practice.

The right censoring date is the earliest of the following: the date a patient was transferred out of the practice, the end of the database data collection, the date that the practice left the database or the patient's latest recorded event date.

11 Study size

Not applicable. This is a population based study.

12 Data management

12.1 Data storage

All data generated in the study will be recorded in a way that allows verification of the published results whilst respecting data protection legislation.

12.2 Data access

Investigators will have access to the data source for data extraction.

13 Data analysis

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.

14 Quality control

Annually, the database is updated following a data gathering process that starts with extraction of data and pseudonimizsation of the EMRs in participating regions. Once transferred to BIFAP, this is followed by a data cleaning in which excluding any patient registry EMR not fulfilling minimum quality requirements is excluded. Consistency and quality control checks are then performed.

15 Limitations of the research methods

15.1 Limitations related to the data source

A major limitation is related to data availability and completeness. Information on important factors such as socioeconomic status is not recorded. Moreover, there will be missing data on weight, height, alcohol and smoking. Hospital information from CMBDH registry is limited to diagnosis code and it is not present in all the Autonomous Regions or in the entire study period; no more information can be obtained with this registry nor drug information on drugs administered in hospitals.

15.2 Limitations related to methodology

Potential limitations of this observational pharmacoepidemiological study arise due to (i) possible misclassification of the exposure status or the outcome; (ii) unmeasured confounding; or (iii) missing data among other.

Mainly, protopathic bias might occur when the drug (whether metamizol or NSAID or Opioids-Paracetamol) is used to treat symptoms of agranulocytosis , promoting reverse causality We will compare the use of three group of drugs with similar indications in order to minimize that bias..

Misclassification of the exposure is a potential concern in pharmacoepidemiological studies using BIFAP since we mainly use prescription data and do not have complete information on the actual drug intake, moreover with this class of drugs that can commonly be taken on demand basis (categorizing as exposed those patients and/or person-time that are non-exposed). In addition, drugs prescribed by physicians other than GPs (frequent MTZ use during hospitalization) or over-the-counter unknown exposure status, could be missed (categorizing as non-exposed patients and/or person-time that are exposed). Also, incorrect calculation of the treatment duration. We do not know to what extent that happen in BIFAP, however, the exposure misclassification (in both directions) is expected to be non-differential among our three cohorts and therefore we may expect a distortion of the risk towards the null value.

Regarding the outcome, most cases of agranulocytosis will only be identified by detection of specific description of recorded codes or texts for agranulocytosis and without link to discharge from hospital. Although a manual review of clinical profiles and estimation of PPV (through the observed false positives) will be performed regardless the cohort (and blinded to the cohort), agranulocytosis diagnosis and date will not be confirmed directly by the PCP or specialist.

Also, although agranulocitosis is a well stablished diagnosis, physicians could record it through a broader diagnosis such as neutropenia or leucopenia. To reject a possible loss of cases of agranulocytosis (false negatives) recorded through those diagnoses, a random subset of them will be manually revised to assess false-negatives and estimate the Negative Predictive Value of the case-finding algorithm.

Also, despite being an important diagnosis, it will be diagnosed mainly in hospital care. It is expected that since it is so serious, the GPs will also register it in Primary Care.

16 Protection of human subjects

Not applicable. Only secondary data sources will be used.

17 Management and reporting of adverse events/adverse reactions

Not applicable, only secondary data will be used.

18 Plans for disseminating and communicating study results

The study results will be disseminated and communicated in scientific journals.

13 References

1. AEMPS. ficha técnica de los medicamentos con metamizol: https://cima.aemps.es/cima/publico/lista.html?multiple=metamizol
2. Ibañez L et al. Agranulocytosis associated with dipyrone (metamizol). Eur J Clin Pharmacol 2005; 60: 821–829
3. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med. 2007 May 1; 146(9):657-65.
4. Jasiecka A, Maślanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. Pol J Vet Sci. 2014;17(1):207-14.
5. Andrès E, Zimmer J, Affenberger S, Federici L, Alt M, Maloisel F. Idiosyncratic drug-induced agranulocytosis: Update of an old disorder. Eur J Intern Med. 2006 Dec; 17(8):529-35.
6. Non-opioid analgesics report of the Spanish Agency of Medicines and Medical devices. https://www.aemps.gob.es/medicamentos-de-uso-humano/observatorio-de-uso-de-medicamentos/utilizacion-de-medicamentos-analgesicos-no-opioides-en-espana-durante-el-periodo-2010-2018/. Accessed 19.11.19
7. AEMPS. MUH (FV), 15/2012 . Seguridad cardiovascular de los AINE tradicionales: conclusiones de la revisión de los últimos estudios publicados. Fecha de publicación: 22 de octubre de 2012. https://www.aemps.gob.es/informa/ni-muh_fv_15-2012/
8. AEMPS. MUH (FV), 5 /2018. Fentanilo de liberación inmediata: importancia de respetar las condiciones de uso autorizadas. Fecha de publicación: 21 de febrero de 2018. https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2018/docs/NI_MUH_FV-5_2018-Fentanilo.pdf
9. James E. Tisdale, Douglas A. Miller. Drug-Induced Diseases. American society of health- system pharmacist. 2nd edition.
10. Ibáñez L, Vidal X, Ballarín E, Laporte JR. Population-based drug-induced agranulocytosis. Arch Intern Med. 2005 Apr 25; 165(8):869-74.
11. Gardarsdottir H, Souverein PC, Egberts ACG, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap. J ClinEpidemiol 2010;63(4):422-7.
12. Maciá-Martínez M-A, Gil M, Huerta C, et al. Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP): A data resource for pharmacoepidemiology in Spain. Pharmacoepidemiol Drug Saf. 2020;1–10. https://doi.org/10.1002/pds.5006
13. UPTODATE
14. Navarro-Martínez R, E Chover-Sierra E, Cauli O. Non-chemotherapy drug-induced agranulocytosis in a tertiary hospital. Hum Exp Toxicol 2016 Mar;35(3):244-50. doi: 10.1177/0960327115580603.Epub 2015 Apr 5.
15. Pick A, Nystrom K. Nonchemotherapy drug-induced neutropenia and agranulocytosis: could medications be the culprit? J Pharm Pract 2014 Oct;27(5):447-52. doi: 10.1177/0897190014546115.Epub 2014 Aug 14.
16. Kaufman DW, Kelly JP, Levy M, et al. The Drug Etiology of Agranulocytosis and Aplastic Anemia: An update of the International Agranulocytosis and Aplastic Anemia Study. Pharmacoepidem Drug Safety. 1993;2:S25. AD
17. Van Staa TP, Boulton F, Cooper C, et al.   Neutropenia and Agranulocytosis in England and Wales: Incidence and Risk Factors. Am J Hematol 2003; 72:248-54.
18. Harrison's Principles of Internal Medicine, 18th Edition Dan Longo, Anthony Fauci, Dennis Kasper, Stephen Hauser, J. Jameson, Joseph Loscalzo Editor McGraw Hill Professional, 2011 ISBN 0071748903, 9780071748902