Metamizole and Acute Kidney Injury (M-AKI)

First published: 29/09/2025

Last updated: 07/10/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000740

Study ID

1000000740

DARWIN EU® study

No

Study countries

☐ Netherlands

Study description

Herein, a retrospective cohort study using electronic health records (EHR) from a major Dutch academic hospital (Amsterdam UMC) is conducted to assess the kidney safety profile of metamizole (dipyrone) use.

For this, adult inpatients (target population) who have undergone a recent

surgery (postoperative setting) are selected.
The assigned treatment strategies (metamizole; active comparators: opioids, NSAIDs) are investigated to test a potential causal link between metamizole and acute kidney injury characterised by a set of predefined estimands.

Study status

Ongoing

Research institutions and networks

Institutions

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 23/05/2024

Institution | Educational Institution | ENCePP partner

Amsterdam UMC

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

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Study timelines

Date when funding contract was signed

Planned: 01/11/2022

Actual: 01/11/2022

Study start date

Planned: 01/03/2023

Actual: 01/03/2023

Data analysis start date

Planned: 11/09/2025

Actual: 11/09/2025

Date of final study report

Planned: 30/01/2026

Sources of funding

- Other public funding (e.g. hospital or university)

More details on funding

This work was supported by Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO; Dutch Research Council) [KICH1.ST01.20.011] and co-funded in-cash by Dutch Kidney Foundation and National Intensive Care Evaluation (NICE) foundation, and in-kind by PHARMO Institute for Drug Outcomes Research, Castor, InsightRX, Z-Index, Digital Health Link.

Study protocol

HARPER Protocol - Metamizole and Acute Kidney Injury (M-AKI).pdf (1.13 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

https://www.pharmacoinformaticslab.nl/en/leapfrog/

Methodological aspects

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

New user active comparator cohort study. A temporal relationship between exposure (initiation of metamizole) and outcome (incident AKI), and accurate risk estimation. This study design reduces confounding by indication, prevalent user bias, and fits neatly into the target trial emulation framework.

Main study objective:

The primary objective of this study is to assess if metamizole, used in inpatient postoperative settings, increases the risk of acute kidney injury (AKI) compared to opioids or non-steroidal anti-inflammatory drugs (NSAIDs). The primary endpoint is AKI, defined using serum creatinine measurements as per the Kidney Disease: Improving Global Outcomes (KDIGO) for AKI.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Dolamizol, Novalgin, Nolotil

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

METAMIZOLE

Anatomical Therapeutic Chemical (ATC) code

(N02BB02) metamizole sodium

metamizole sodium

Medical condition to be studied

Acute kidney injury

Population studied

Short description of the study population

First ever inpatient administration of metamizole users in a postoperative setting (i.e., up to 7 days after surgery). Patients who were prescribed metamizole up to 14 days prior to surgery were excluded, as they were likely to be prevalent users.

Patients on multimodal analgesia (i.e., receiving more than one pain relief medication) within 1 hour of surgery were excluded, because it was considered that these medications were intended to be given together.

Patients with acute kidney injury or acute kidney disease episodes up to one week prior to surgery were excluded. Patients who had acute dialysis 14 days prior to exposure or on chronic dialysis were excluded, too.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Special population of interest

Renal impaired

Estimated number of subjects

11000

Study design details

Setting

This is a retrospective cohort study conducted at Amsterdam University Medical Centre (Amsterdam UMC) in the Netherlands. Time period of study was between January 2018, 1 and December 2024, 31 were included.
Patients with multiple hospitalisation episodes were assigned the same patient ID. Inclusion criteria:
1) Adults admitted to Amsterdam UMC for more than 24 hours;
2) Post-operative pain management setting.
Exclusion criteria:
1) Kidney transplant in the past year from index date;
2) On chronic dialysis;
3) Acute dialysis episode within the past 14 days;

4) Pre-exposure acute kidney injury or acute kidney disease seven days prior to or on index date;
5) No metamizole or comparator use 14 days prior to treatment initiation;
6) Pregnant women;
7) Patients with a treatment switch or add-on within 1-hour of the initial administration of a pain management drug (i.e., metamizole, NSAIDs, or opioids).

Comparators

Opioids (i.e., morphine, buprenorphine, oxycodone, and piritramide), NSAIDs (i.e., aceclofenac, dexketoprofen, diclofenac, phenylbutazone, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, etoricoxib, parecoxib, celecoxib, piroxicam, propyphenazone, tiaprofenic acid, high-dose acetylsalycilic acid, and diflusinal).

Outcomes

The primary outcome of interest is AKI occurring during hospitalisation, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria from 2012, based on changes in serum creatinine and/or urine output.
This outcome is clinically meaningful, well-standardised, and captured in hospital electronic health records from Amsterdam UMC, where outpatient and inpatient data is routinely collected.
Acute kidney injury is a frequent and serious complication in postoperative patients, which is associated with increased morbidity, long-term damage of kidney function, and prolonged hospitalisations. Non-steroidal anti-inflammatory agents are known to contribute to AKI through kidney damage and dysfunction. On the other hand, opioids are not known to cause AKI, but they have been associated with respiratory depression and addiction as adverse drug events. Metamizole (dipyrone) is an alternative non-opioid analgesic often thought to

have a different kidney safety profile.
Thus, outcome was selected to address a clinically and pharmacologically relevant safety question. This is important given the debate regarding the balance between analgesic efficacy and kidney safety in the postoperative setting.

Data analysis plan

Propensity score model: multinomial logistic regression. treatment (i.e., metamizole, NSAIDs, opioids) = confounders. The selected confounders are those which affect the exposure-outcome relationship as well as the ‘ mediator’ (i.e., intercurrent event) and outcome relationship. Stabilised inverse probability of treatment weights will be calculated from this model.

Censoring and intercurrent event models: pooled logistic regression models to estimate the probabilities of remaining uncensored and free of intercurrent events over time, conditional on treatment and relevant time-varying covariates. Stabilised inverse probability weights for censoring and intercurrent events will be derived.

Weighting: Inverse probability weights for censoring, intercurrent events will be combined with treatment weights to create composite stabilised weights.

Outcome model: cumulative incidence curves will be generated for each treatment group using inverse probability weighting with the composite weights to adjust for confounding, censoring, and intercurrent events. For the controlled direct effect, the estimator corresponds to the complement of a weighted Kaplan-Meier estimator. The risk difference and risk ratio comparing cumulative incidences at 14 days will be calculated.

Documents

Study, other information

HARPER Supplement - Metamizole and Acute Kidney Injury (M-AKI).pdf (1.34 MB)

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), other

Amsterdam UMC electronic health records

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

CDM Mappings

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown

Procedures

Procedure of data extraction

SOP 002 Reuse of care data for the purpose of research - RDM - Amsterdam UMC v3.pdf

English (267.53 KB - PDF)

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