

Final Study Report

Study Title:

Treatment of acute locomotoric pain in the geriatric patient: comparison of efficacy and safety between step 2 (weak opioids) and step 3 (strong opioids) of the WHO pain ladder.

Behandeling van acute locomotorische pijn bij de geriatrische patiënt: vergelijking naar effectiviteit en veiligheid tussen trap 2 (zwakke opioïden) en trap 3 (sterke opioïden) pijnstilling van de WHO-pijnladder.

EudraCT number: 2016-002379- 89

Eudamed number: -

Study protocol code: AGO/2016/007; Belgisch Registratienummer B670201629071

ClinicalTrial.gov identifier: -

Sponsor: UZ Ghent

National Coordinator/ Coordinating Investigator: dr. Wim Janssens

Funder: none

Date of report: 31 Augustus 2021.

Name and signature Sponsor:

JANSEN'S WY

Date signature Sponsor:

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5.1 Inclusion criteria	Fout! Bladwijzer niet gedefinieerd.
5.2 Exclusion criteria	Fout! Bladwijzer niet gedefinieerd.
5.3 Primary endpoint	Fout! Bladwijzer niet gedefinieerd.
5.4 Secondary endpoints	Fout! Bladwijzer niet gedefinieerd.
5.5 Procedures	Fout! Bladwijzer niet gedefinieerd.
5.6 Randomisation and blinding	Fout! Bladwijzer niet gedefinieerd.
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1. Introduction

Geriatric patients often experience pain, leading to great agony. Review of literature teaches us that acute pain is present in more than two out of three hospitalized patients in an acute geriatric ward and only half of them are treated adequately with pain medication. Undertreatment of pain leads to delirium, psychological suffering, inability to participate with medical and/or physiotherapeutic treatment, among other things. Furthermore, pain causes a more rapid functional decline leading to more frailty.

To this day, there is not enough scientific evidence concerning the approach of acute pain in a geriatric patient, due to heterogeneous patient population in studies (incl. polypharmacy, comorbidities,...), extensive exclusion criteria of the published studies, challenging characterization of the different types of pain and frequent overlap and heterogeneity of etiology amongst others.

The current guidelines advise that clinicians choose a certain pharmacological preparation adapted to the 'individual needs of the patients'.

This study focusses on how to treat a geriatric patient with acute locomotoric pain in a non-surgical setting by comparing opioids of WHO pain ladder step II (tramadol) with step III (oxycodone) by investigating efficacy and safety.

2. Objectives of the study

2.1 Primary objectives

The primary end point of this study is the difference in drop in average numeric rating scale after 7 days between the group treated with tramadol and the one treated with oxycodone.

2.2 Secondary objectives

Secondary end points included:

- After how many days (comparing both groups on the speed of drug effect) was there an acceptable level of pain control?
- Can a difference in the intake of emergency medication be perceived?
- Do both groups differ on the nature and frequency of side-effects?
- Does one group differ from the other with respect to the occurrence of severe side-effects?
- Can one see a difference between the two groups regarding the functionality of the patient (measured through Katz scale)?

3. Investigational Medicinal Product

Composition and dosing

Patients will be divided into 2 groups:

- Group 1: TramadolR retard 2x50mg(8u + 20u) + TradonalR odis 50mg if necessary (max 4x/day), orally administered
- Group 2: OxycodoneR 2x5mg (8u + 20u) + OxynormR instant 5mg if necessary (max 6x/day), orally administered

- Tradonal retard® 50mg: tramadol hydrochloride; excipient: saccharose 9.375mg per capsule
- Tradonal odis® 50mg: tramadol hydrochloride; excipients: ethylcellulose, copovidon, siliciumdioxide, mannitol (E421), crospovidon, aspartaam (E951), peppermint 'rootbeer' aroma, magnesiumstearate.
- Oxycontin® 5mg: oxycodonhydrochloride; excipient: 73.4mg lactose
- Oxynorm instant® 5mg: oxycodonhydrochloride; excipients: 2,7mg aspartaam (E951), 0,34mg cineol and 14,2mg sucrose.

All the medication used, is commonly used medication in good clinical practice.

Producer

- Tradonal retard®: Meda Pharma nv Terhulpesteenweg 166, 1170 Brussel, Belgium
- Tradonal odis®: Meda Pharma nv Terhulpesteenweg 166, 1170 Brussel, Belgium
- Oxycontin®: Mundipharma Comm. VA - Blarenberglaan 3 C - 2800 Mechelen - Belgium
- Oxynorm instant®: Mundipharma Comm. VA - Blarenberglaan 3 C - 2800 Mechelen - Belgium.

Distributor

- Hospital pharmacy, University Hospital, De Pintelaan 185, 9000 Gent, Belgium
- Hospital Pharmacy, AZ Sint-Vincentius, Schutterijlaan 34, 9800 Deinze, Belgium

Packaging

Commercial package

Administration

Orally

Labelling

Following information will be added with an extra label:

"Productnaam"
Sponsor: UZ Gent
Contactpersoon: dr. Wim Janssens, De Pintelaan 185, 9000 Gent, + 32 9 332 2348
Studie code: 2016-002379-89 ; AGO/2016/007
Proefpersoon identificatienummer:

Storage conditions

Corresponding normal good practice.

Known side effects of the medication

- Nausea/vomiting
- Constipation
- Impairment of liver function
- Falls
- Delirium
- Urinary retention
- QT interval prolongation
- Serotonin syndrome

Drug accountability

Drug accountability has been documented.

4. Investigational Medical Device

Not applicable.

5. Study Protocol Summary

This study contains a multi-centric non-blinded prospective and randomized analysis of 49 patients above the age of seventy. Each patient included, has been hospitalized on an acute geriatric unit with acute mild up to severe locomotoric pain (inclusion: occurrence within the last 72 hours with numeric rating scale > 5). Patients needed to be capable to give informed consent, to take medication by mouth and render pain ratings three times a day (numeric rating scale). Not receiving pain medication prior to hospitalization - except for paracetamol and/or NSAIDs (WHO step I) – and not needing surgical treatment formed a further requirement for inclusion.

The patients who were included were divided, according to a predefined randomization technique, into two groups. One group received tradonal retard ® 50mg (twice daily) and tradonal odis ® 50mg (four times daily as a maximum) as emergency medication. The other group received oxycontin ® 5mg (twice daily) and additional- oxynorm instant ® 5mg (maximum six a day) if necessary.

Data concerning pain relief effect (numeric rating scale) and possible side-effects (especially delirium, obstipation, nausea/vomitus, problem of falls, serotonin syndrome, liver function disorders and conduction disorders) were gathered. Furthermore data regarding functionality (using Katz-scale) was logged and patients were screened for depression (through Geriatric Depression Scale or GDS). To that end patients received daily follow-ups.

If one of the exclusion criteria appeared after the initial inclusion, the follow-up period was stopped prematurely. Likewise, if a severe adverse event occurred or if due to insufficient efficacy the pain medication was adapted, the follow up period stopped.

All data was collected on paper. For statistical analyses, the software of IBM SPSS Statistic version 25 was used.

The postulated numbers, a minimum of 52 patients for each group, for 90% power (mean difference 0, standard deviation 1,4, $\alpha = 0.025$) could, unfortunately, not be attained during the inclusion period (1 October 2016 till 31 December 2020). This can be attributed to multiple explanatory factors.

6. Study analysis

6.1 Sample size calculation:

Studie 2 superiority (trap2 vs Trap2+ trap 1):

Ha: real difference in average NRS score after 2 days: ≥ 1

Mean difference in NRS after 2 days of medication: < 1

H0: (wish to reject): no difference

Two-Sample t Test for Mean Difference

Fixed Scenario Elements

Distribution	Normal
Method	Exact
Number of Sides	2
Alpha	0.05
Standard Deviation	1.4
Null Difference	0

Computed N per Group

	Mean	Nominal	Actual	N per
Index	Diff	Power	Power	Group
1	0.4	0.8	0.801	194
2	0.4	0.9	0.901	259
3	1.0	0.8	0.803	32
4	1.0	0.9	0.906	43

Rekening houden met drop-out van 8 per groep = 102 patiënten includeren

7. Independent Ethics Committee and Competent Authority

Initial approval Ethics Commission: 18 September 2016 (including: protocol, ICF, Investigator brochure) (Belgisch Registratienummer B670201629071).

Title of the study: "behandeling van acute locomotorische pijn bij de geriatrische patiënt: vergelijking naar effectiviteit en veiligheid tussen trap 2 (zwakke opioïden) en trap 3 (sterke opioïden) pijnstilling van de WHO-pijnladder."

B.U.N.: B6702020000339

OVERVIEW APPROVED DOCUMENTS		
Initial submission: <ul style="list-style-type: none"> - Protocol, dd 12SEP2016 - ICF, dd 12SEP2016 	Approval Central EC: 18SEP2016	Approval FAGG: 27JUL2016
Amendment 1: extra site (Jan Palfijn) <ul style="list-style-type: none"> - Protocol, dd 03FEB2017 - ICF, dd 03FEB2017 	Approval Central EC: 15MAR2017	Approval FAGG : NA
Amendment 2: extension of study duration	Approval Central EC: 21SEP2018	Approval FAGG: NA
Amendment 3: <ul style="list-style-type: none"> - ICF v.2 dd. 15MAY2020 	Approval Central EC: 26JUN2020	Approval FAGG: NA

8. Results

8.1 Subject enrollment and demographics

All patients who were hospitalized at an acute geriatric ward at AZ St-Vincentius Deinze during the inclusion period (October 2016- September 2020) were screened. All patients hospitalized at the acute geriatric ward of UZ Gent from November 2019 till April 2020 and those hospitalized at AZ Jan Palfijn from May till September 2020 were screened.

Due to the extensive exclusion criteria, only 42 patients hospitalized at AZ St-Vincentius Deinze, 6 patients hospitalized at UZ Gent and one patient hospitalized at AZ Jan Palfijn were included.

All patients were born between 1922 and 1946, aged 74 till 97 years old. Forty three included patients were female (87.8%), six were male.

In total, 25 patients were randomized into WHO I treatment group, 24 patients were randomized into WHO II treatment group. The average geriatric risk profile (GRP score) was 2.7. Forty one patients (83.6%) lived at home, 19 of them without any professional support. Six of the included patients were living in a service flat. Only one of the included patients originated from a residential care home. Consequently, 95.9% of the included patients had a good functional profile (Katz 0 or A). Only two of the 49 patients had a Katz B score. None of the included patients were fully dependent on others (Katz C).

The majority of patients had a fracture explaining the acute pain (38 patients). Two of the included patients had an acute deterioration of known degenerative neuromuscular disease, nine patients were diagnosed with a bruise. Almost half of the included patients (49%) had pain localized at the trunk, 36.7% had pain at the legs, five patients had pain at the arms. Two of the 49 patients mentioned pain at multiple sites.

The cumulative rating scale-geriatric score (CIRS-G score) was 6.6 average, fluctuating from 1 till 15. The average number of taken medications at home was 7.4 daily. Three quarters of the

included patients were not taking paracetamol or non-steroid anti-inflammatory drugs (WHO I) when they were hospitalized.

8.2 Study specific results

1. Primary End point

- There was no statistic significant difference between the two groups in the timing when a mean numeric rating scale ≤ 1 was reached, this was seen als 'full pain control'. (p-value 0.484, Mann-Whitney U-Test)
- The two groups were compared to see when there was a significant pain controlling effect of the drug. This was evaluated by looking when the mean daily numeric rating scale had dropped 2 points relative to the value to begin with. (p-waarde 0.408, Mann-Whitney U-Test)
- The two study groups were also compared when the last pain flare (NRS ≥ 5) was seen. There was no statistic significant difference, p-value 0.309.

2. Secondary end point

- Adverse events:

	Number tramadol group (naranjo score)	Number oxycontin group (naranjo score)	Total	p-value
Nausea	12 (0-7)	3 (3-8)	15	0.011
Nausea in need of treatment with anti-emetics	5 (3)	2	7	0.220
Urinary retention (exclusion criteria: solely because of comfort)	3 (2-3)	1 (6)	4	0.296
Obstipation (3days without faeces)	17 (3-6)	17 (3-6)	34	1
Confusion	9 (0-7)	6 (3-6)	15	0.404

Confusion in need of treatment	4 (3-7)	2 (3-4)	6	0.413
Fall	3 (3)	1	4	0.296
Newly development of liver function abnormalities	2	0	2	0.157
QTc-prolongation (newly developed)	1	1 (3)	2	0.976
Convulsions	1	0	1	0.322

In conclusion, the only statistic significant difference between the two study groups concerning adverse events was seen in the occurrence of nausea (p-value 0.011). Most of the cases were mild, without need for treatment.

Other trends were more confusion and need for treatment with psychofarmaca in the tramadol study arm, more falls and more liver function abnormalities when using tramadol, although these trends were not statistical significant. Serious adverse events were reported in three patients, all treated with tramadol cfr. Infra.

The most frequent occurring adverse event was obstipation, reported by nearly two thirds of the patients.

- Functional decline (Katz): results yet to follow.

9. Safety

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, ...)
109	Tramadol	N	Acute pulmonary edema	Transfer intensive care unit, no further data
111	Tramadol	N	Convulsions upper limb	De-challenge: full resolution. No re-challenge.
120	Tramadol	N	Acute delirium	Stop tramadol, full resolution. No re-challenge.

10. Device deficiencies

Not applicable.

11. Protocol deviations

UZ Gent – monitoring visit dd. 27 FEB 2018
DESCRIPTION
For the first 13 included patients, protocol deviations concerning ICF procedure, eligibility, and study drug administration occurred. For the violation concerning ICF procedure, reference on the PD log was made to this monitoring visit report. Monitor advised site to document all protocol deviations on the protocol deviation log
AZ Sint-Vincentius Deinze – monitoring visit dd. 20APR2018
DESCRIPTION
No extra label is added on the commercial package of the study medication, to be reported in NTF.
Drug accountability is not documented, to be reported in NTF.
Late SAE reporting for subject 111: 30 days after awareness of study staff.

All protocol deviations were discussed during the Close Out Visit dd. 25 MAR 2021 and resolved, if still possible.

12. Discussion and overall conclusions

Discussion is yet to follow.

Overall conclusion: we were not able to detect a significant difference in the efficacy of tramadol versus oxycodon. Adverse events had the tendency to be more frequent in the tramadol study group, although the only statistic significant difference was seen in the report of nausea (without the need for treatment). A follow-up study with more specific/detailed inclusion and exclusion criteria and a larger number of patients is necessary to draw evidence-based conclusions.

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