Paracetamol (acetaminophen) route in palliative care (PC) patients: Intravenous versus subcutaneous route pharmacokinetics study protocol for a randomized trial = ParaSCIVPallia

CURRENT STATUS: ACCEPTED

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Abstract
Background: Among palliative care (PC) patients who are administered paracetamol, the subcutaneous (SC) route is often an alternative to the intravenous (IV) route. Yet pharmacological and clinical data are lacking. Many French palliative teams are now empirically using paracetamol by the SC route, but there are no data to support this practice.
Aim: Compare pharmacokinetic (PK) parameters between the IV and SC routes for PC patients.
Design: A randomized, open, crossover study in two PC centers. The primary endpoints are AUC0-t, AUC0-, Cmax, and Vd et t1/2. All adverse events will be reported for a safety analysis.
Setting/participants: 20 adult PC patients with an IV device, having spontaneous pain, not related to care, with a numeric pain rate scale > 3/10, or having a systematic prescription of paracetamol in the usual treatment. They also have to meet all eligibility criteria.
Conclusion: First study comparing PK parameters for IV paracetamol versus SC paracetamol.
Trial registration: Clinical trial register number NCT03944044, 2019-06-04 https://clinicaltrials.gov/ct2/show/NCT03944044
Committee for the protection of persons (CPP) 18.09.05.58206 approval 2018/10/4
National Drug Safety Agency (ANSM: Agence Nationale de Sécurité Médicament) MEDAECNAT-2018-09-00009 approval 2018/11/29

Background
In France, paracetamol (acetaminophen) is the first treatment, non-opioid, which is used in the current pain management. This treatment is prescribed in different routes of administration according to possibilities by the patient to take it.
In palliative care (PC), many injectable drugs are used by subcutaneous (SC) route\(^1\)\(^2\) to prevent the patient from having a venous track and iterative puncture or for patients with damaged venous access. Many French palliative teams are now empirically using paracetamol by SC route\(^3\). A recent French study carried out by Leheup et al.,\(^3\) conducted in 160 patients hospitalized in the PC units of three hospitals in France from 2014 to 2017, evaluated the tolerability of SC paracetamol administration by a prospective multicenter observational study. Of the 160 patients, 44 (28%) presented at least one non-serious local adverse event (oedema in 29, erythema in 5, pain in 15, haematoma in 2, pruritus in 1, and localized inflammation in 2). No serious adverse events were
observed. Factors associated with the occurrence of local adverse events were younger age, administration in the arm and thorax, and a high number of daily administrations. At minimum, this study shows a good safety of paracetamol using the SC route.

Sometimes, there is no any other alternative drug or route of administration: excessively poor venous access, no possibility of oral intake, or no possibility of mobilizing the patient for using the intrarectal route. Furthermore, the rectal route has an inconstant biodisponibility.

In the face of this, we built a study to compare the pharmacokinetics (PK) of SC and intravenous (IV) routes in the same patient in a PC situation, to determine if there is a PK equivalence between these two modes of administration.

If IV and SC routes are similar, a larger study should be done on a population of PC patients to evaluate safety and efficacy of the SC route for paracetamol administration.

Methods And Designs

The design of this study is based on other PK studies.4-8

Study Setting

This is a comparative, randomized, open, crossover, bicenter clinical trial (Pain and PC Department of University Hospital, Caen, France and Regional PC Unit, Fondation de la Miséricorde, Caen, France) with SC and IV paracetamol injections successively given to each patient.

This study received the ethical approval of Committee for the protection of persons (CPP) and National Drug Safety Agency (reported “Ethics approval and consent to participate” paragraph)

All investigators have received a “Good Clinical Practice” training and sponsor monitored the study according to this recommendations.

All the quantitative analyses will be conducted according to the principles of Good Laboratory Practice.

Objectives

The main objective is to demonstrate a PK equivalence between the two routes of administration (IV and SC). The secondary objectives are to compare the efficacy of these two modes of administration on pain and to explore global and cutaneous tolerance of paracetamol used by SC route.
Outcomes

The main judgement test will be paracetamol blood concentration.

Curves will be established for each patient, and we will determine and compare for each route of administration and for each patient AUC0-t, AUC0-¥, Cmax, and Vd et t1/2. Data will also permit us to compare PK characteristics between all of the patients.

Secondary evaluation criteria will be the pain evaluation by NPRS throughout the duration of the protocol, and the clinical evaluation of safety by the nurse.

Eligibility Criteria

Inclusion Criteria

1- Patients ≥ 18 years old, hospitalized
2- Patients in a PC situation
3- Patients having an IV device with the presence of a venous reflux (implantable venous site, PICC line, central track)
4- Patients having spontaneous pain, not related to care, with a numeric pain rate scale (NPRS) > 3/10, or having a systematic prescription of paracetamol in the usual treatment
5- Patients able to do an auto-evaluation of their pain by NPRS
6- No contraindications of paracetamol
7- No contraindications of alternative antalgic (low and strong opioids, non-steroidal anti-inflammatory)
8- Possibility to not take paracetamol in the previous 24 hours before inclusion
9- Patients with a blood test dating back less than 7 days, without severe renal (DFG > 30 or hepatic failure (SGPT/SGOT > 350 UI/L, Bilirubin > 40 µmol/L, TP <50%) and
10- Patients related with a French social security regime
11- Patients accept to participate in the study, with written consent

Exclusion criteria

1- Patients under legal protection
2- Patients who participate in another study less than 30 days before
3- Patients weighing less than 50 kg
4- Patients having a contraindication to the SC route
5- Pregnant or breastfeeding woman
6- Patients having a paracetamol administration less than 24 hours before the beginning of the inclusion
7- Patients having a low opioid less than 2 hours before or a strong opioid less than one hour before the beginning of administration of paracetamol
8- Patients having a fever
9- No possibility of communication

**Experimental Plan / Intervention**

**Sample Size**

As we could not find any information in the literature on the variability of the PK parameters in a palliative care population, we relied on the number of subjects included in clinical studies with a similar methodology\(^4,10-13\) and decided to include 20 patients. This number is also in line with the recommendations of the European Medicines Agency\(^9\) which sets at 12 the minimum number of patients to be included in a bioequivalence trial.

Patients who do not complete the study will be replaced by new patients in order to reach a total of 20 subjects in the statistical analysis.

All steps are resumed in table 1, with the SPIRIT advice.

**Pre-inclusion:**

Patients will be screened by investigators according to eligibility criteria. Patients will sign a consent form after receiving oral and written information from a physician investigator involved in this project. After inclusion, they will be randomly assigned, using block randomization, by using Ennov clinical® software, based on a list prepared by the study statistician (using block randomization), to SC before IV paracetamol injection or IV before SC with a washout period of 24 hours between the 2 injections. This washout period was determined since half-life of paracetamol was commonly described
(Summary of product characteristics) as ranging from 1 to 4 hours depending on the administration routes. An almost complete elimination may be considered after 5 to 6 half-lives. Then, after 24 hours, paracetamol can be considered completely eliminated.

**Inclusion:**

**Day (D) -1**
- Verification of eligibility criteria
- Explanation of the study to patients: information about predictable modalities, constraints and risks of the study
- Collect the signed consent
- Informatic Block Randomization (Group SC-IV or Iv-SC)
- Stop paracetamol
- Alternative antalgics prescription

**Day (D) 0:**
- Collect the patient characteristics: Temperature; Size; Gender, Liver and kidney history, Main disease. The specific body weight that will be used for drug dosing and pharmacokinetic calculations was also collected.
- Collect all current treatments
- Adapt pain management treatment and if the patient has paracetamol in his treatment, the practitioner must prescribe alternative antalgics.
- Plan for collection of alternative antalgics from D1 to D2: hours of administration dosage.
- First blood test: Albumin, Liver function tests (glutamic-oxaloacetic transaminase serum (SGOT), glutamic pyruvic transaminase (SGPT), gamma-glutamyltransferase (GGT); alkaline phosphatase); kidney function tests (creatinine, glomerular filtration rate (GFR)), human chorionic-gonadotropin, beta subunit (βhCG) (only childbearing woman).

**D1:**
- Dosage of paracetamol in blood before any administration (=TO). The blood sample must be done at the precise timetable specified in the protocol.
- Administration of 1000 mg of paracetamol, by the first route of administration designated by randomization and with infusion pump Volumat® or Volumed® at the rate of 100 ml in 30 min (200 mL/hour).
- Carry out blood quantitative analysis of paracetamol, according to the following parameters and depending on the route done first:
  - IV way: (after paracetamol administration and every blood puncture, rinsing the central track by 10 mL of physiological serum) 0.75, 1, 1.5, 2, 4 and 8 hours
  - SC way: (after every blood puncture, rinsing the central track by 10 mL of physiological serum): 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 and 8 hours.
- At each blood test, the patient will undergo a NPRS and an assessment of the tolerance.

**D2:**

Twenty-four hours after first administration of paracetamol (washout)

The patient will receive paracetamol by the second route of administration according to the randomization in the same timeline as D1.

In any moment, if pain is not well controlled, the investigator practitioner must prescribe alternative drugs, and all treatment that he will consider necessary to obtain relief. Any adverse events, other unidentified effects of trial intervention and any alternative drugs used have to be listed in the electronic Case Report Form (eCRF) of the patient and declared to the promoter, following the procedure described in the protocol.

**Ending-Protocol Visit:**

Every Patient will have an exam on the fourth and the thirtieth day of the protocol for safety monitoring of the subcutaneous route of administration. In case of adverse events, long term monitoring will be proposed and a specialist opinion will be requested if the investigating physician or the promoter deems it necessary.
| Visits                        | VS (D-1) | VI (D0) | V1 (D1) | V2 (D2) | V4 (D4) | V6 (D30) |
|------------------------------|----------|---------|---------|---------|---------|---------|
| Collect the eligibility criteria | X        | X       |         |         |         |         |
| Informed consent             |          | X       |         |         |         |         |
| Collect patients’ characteristics |         | X       |         |         |         |         |
| Allocation (IV-SC or SC-IV)  |          |         |         |         |         |         |
| First blood test             |          |         |         |         |         |         |
| Paracetamol IV administration |          |         |         |         | X or    | X       |
| Paracetamol SC Administration |          |         |         |         |         | X or    |
| Plasmatic paracetamol        |          |         | X       | X       |         |         |
| concentrations              |          |         |         |         |         |         |
| Prescription of alternative  |          |         | X       | X       | X       | X       |
| pain drugs                   |          |         |         |         |         |         |
| Temperature                  | X        | X       |         |         | X       |         |
| Central track monitoring     |          |         |         |         | X       | X       |
| Pain monitoring              | X        | X       |         |         | X       | X       |
| Tolerance monitoring         | X        | X       |         |         | X       | X       |
| Adverse events monitoring    | X        | X       |         |         | X       | X       |

Table 1: Protocol Steps and Intervention-SPIRIT Figure

**Data Collection Methods**

Due to the study methodology, patients and investigators cannot be blinded. The outcomes assessors will not be blinded either.

Every participant will be assigned a unique electronic- Case Report Form (eCRF).
Pharmacokinetic Data

Pharmacokinetic sampling procedure.

Blood samples (2 ml) will be collected in dry tubes free of gel at 0.75, 1, 1.5, 2, 4 and 8 hours after paracetamol intravenous administration or 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 and 8 hours after SC administration. They will be rapidly transported to the laboratory.

Assay method.

After centrifugation, serum samples will be immediately used for quantification of acetaminophen with the EMIT tox TM Acetaminophen Assay, which is a homogeneous enzyme immunoassay performed in AU 5800 clinical chemistry systems (Beckman Coulter, France). The limit of quantification is 0.12 mg/L. Precision is better than 6% for three quality control levels. The quantitative analyses will be conducted according to the principles of Good Laboratory Practice (GLP).

Pharmacokinetic calculations.

Paracetamol concentrations obtained after IV and SC administrations will be analyzed using a 1-compartment open model (because the paracetamol pharmacokinetic is known to be linear). The apparent first order elimination rate constant (ke) and the corresponding apparent elimination half-life (t1/2 = Ln2/ke) will be determined by least squares regression analysis of the terminal phase of the serum concentration-time curve. The apparent first order absorption rate (ka) and the corresponding apparent resorption half-life (t1/2 = Ln2/ka) will be determined by least squares regression analysis of the resorption phase from the serum concentration-time curve obtained after subcutaneous administration. The maximum observed serum concentration (Cmax) and the time required to reach Cmax (Tmax) will be calculated using the following formula: Tmax = Ln(Ka/Ke) / (Ka-Ke) and Cmax=C0.(e-Ke.Tmax- e-Ka.Tmax). The AUC 0-infinity will be calculated using the linear trapezoidal rule over the interval of 0 to 8 h (AUC -8 h) and extrapolated to infinity with the following equation: AUC 0-infinity = AUC 0-8 h + C8 h/ke. The bioavailability (f) corresponds to the ratio AUC 0-infinity (after SC administration) / AUC 0-infinity (after IV administration). The volume of distribution will be evaluated with the equations Vd = D/C0 (IV) and Vd = f.D/C0 (SC). The total clearance (CL) will be calculated from the equation CL = Ke.Vd.
Data Analysis

The following PK parameters: AUC0-t, AUC0-¥, Cmax, Vd, and T1/2, whose distributions are known to be approximately log-normal, will be described for the 2 modes of administration in the form of geometric means with geometric coefficients of variation. Tmax will be summarized by a median and quartiles.

The parameters AUC0-t, AUC0-¥, Cmax, Vd and T1/2 will then be log-transformed and compared between the 2 modes of administration using a linear regression model taking into account the following effects: treatment sequence (IV – SC or SC – IV), subjects (nested in the treatment sequence), treatment period (period 1 or period 2) and treatment (mode of administration: IV or SC).

For each parameter, the difference between the two modes of administration will be tested, based on the P-value associated with the treatment effect. A non-parametric test (Wilcoxon signed-rank test) will be used for Tmax.

The bioequivalence between the 2 modes of administration will be tested for AUC0-t, AUC0-¥ and Cmax, based on the 90% confidence interval of the ratio of the geometric means (SC vs IV). According to the recommendations of the European Medicines Agency,9 we can conclude bioequivalence if the confidence interval is fully within the range [80%-125%].

Pain scores will be compared between the 2 modes of administration by paired T-tests or Wilcoxon signed-rank tests, depending on the form of the distribution.

Data will be analyzed based on a per protocol analysis. Statistical significance will be set at P < 0.05. Data will be analysed at the Biostatistics and Clinical Research Unit of Caen University Hospital, with SPSS and R software.

Adverse Events Data

All adverse events will be collected, from consent to the end of patient participation, and reported to the sponsor. Serious adverse reactions (SAR) will be qualified as expected or unexpected by the sponsor. Expected SAR related to paracetamol are thrombocytopenia, leucopenia, neutropenia, hypersensitivity, hypotension, increased transaminases, malaise, tachycardia, flushing, pruritus and erythema. Other SAR will be considered as unexpected.
A Data Safety Monitoring Board (DSMB) will review the safety independently. The DSMB will include three experts: one pharmacologist, one physician pain specialist, and one dermatologist. The sponsor will request DSMB advice in case of Suspected Unexpected Serious Adverse Reaction or any new safety information. The DSMB is charged with providing advices to the sponsor recommendations that include (a) continuation of the study, (b) continuation with modification, and (c) termination of the study.

**Potentially interacting drugs:**

View to the particularity of PC and diversity of treatments received by the patient, we chose to collect through the eCRF every treatment taken by the patient during the study.

Some of them could alter the SC pharmacokinetic parameters, and will be studied closer and discussed in case of strong difference between patients. This was not one of our objectives and will need a further study. We know that administrations of probenecide or salycilamide for example could alter the IV pharmacokinetics of paracetamol, but it does not presume the impact on SC pharmacokinetic. Furthermore, because each patient would have the both route, we will be able to discuss this potential interaction.

**Discussion**

**Limitations**

There are several limitations to our study.

First, our study was not designed to investigate clinical outcomes of efficacy or safety of SC paracetamol. This is a pharmacokinetic analysis, comparing SC to IV pharmacokinetic. The practical implications of our results need to be confirmed by a dedicated larger trial. The efficacy should be studied on a larger sample, in order to compare the pain before and after the injection. The safety also need a larger sample to conclude good tolerance of the SC administration.

Secondly, intra and inter- individual variation in pharmacokinetics would not be statistically analyzed in our study. We know that these variations could have an impact on our results but the study was not designed to answer this question. We wanted first to search a bioequivalence between IV versus SC paracetamol blood concentration, and PK parameters.
Thirdly, the study location on 2 centers helps finding patients that correspond to inclusion criteria. But it could change the way to collect data and bring limits. However the quantitative analysis will be conducted by the same laboratory.

Finally, to perform a pharmacokinetic analysis on PC population creates additional challenges. It could be difficult to obtain consent from these frail patients. Nevertheless, the implementation of this study is a first step for all PC researchers and practitioners to develop even more PC studies.

**Discussion**

Many drugs could be administered by SC route in PC. For antalgic drugs, strong and low opioids are currently used by the SC route, with an equivalence dose from the IV route calculated according to well-known conversion factors. However, there is no study highlighting the equivalence, efficacy and safety of paracetamol administered subcutaneously. Currently, increasingly more PC teams empirically choose to use this method of administration for patients with an impossible venous or oral route. PC practitioners need more evidence-based data, particularly for their frail patients. In these situations, it is difficult to extrapolate from studies in other populations.

Our palliative care study evaluated the pharmacokinetic equivalence between SC and IV route. It could help to determine whether the SC route is a good alternative method of administration for paracetamol.

Our study is the first pharmacokinetic analysis of subcutaneous administration of paracetamol. Our study is one of the first pharmacokinetic study on PC patients. It is a real opportunity to show that studies are technically possible in PC.

**Conclusion**

The ethics committee/institutional approval show that pharmacokinetic clinical trials can be carried out for PC patients.

If an equivalence between the SC and IV routes for palliative care patients is demonstrated, paracetamol may be used by PC teams in a more consensual, secure and scientifically proven way. However, more studies will be necessary to confirm the clinical efficiency.
Trial Status
Protocol version number 3: 04/12/2018. Recruitment begin in april 2019 and will probably be completed in april 2021.

Abbreviations
GFR: glomerular filtration rate;
GGT: gamma-Glutamytransferase;
IV: intravenous;
NPRS: Numeric Pain Rate Scale;
PC: palliative care
PK: Pharmacokinetic;
RPCU: Regional Palliative Care Unit;
SC: subcutaneous;
SGOT: glutamic-oxaloacetic transaminase serum;
SGPT: glutamic pyruvic transaminase;
βhCG: human chorionic-gonadotropin, beta subunit

Declarations

Ethics approval and consent to participate
Committee for the protection of persons (CPP) 18.09.05.58206 approval 2018/10/4
National Drug Safety Agency (ANSM: Agence Nationale de Sécurité Médicament) MEDAECNAT-2018-09-00009 approval 2018/11/29
A consent letter will be signed by each patient included.

Consent for publication
Not applicable

Availability of data and materials
Anonymized data can be made available to investigators upon request to the corresponding author.

Competing interests:
The authors declare that they have no competing interests

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**Author’s Contributions:**

MV, ML and CG had the idea for this study. ML will be a coordinator of the study. MV, ML, LPSP, SG plan to supervise data acquisition and will be responsible for creation and quality of the database. CC and VLB will be responsible for statistical analysis. AA is responsible of IMP circuit. MV, ML and CG drafted the manuscript. MV and ML prepared the final version of the manuscript. All authors read and approved the final manuscript.

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Figures

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