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# SAFETY AND FEASIBILITY OF S-CAINE PATCH USE IN CHILDREN UNDER THE AGE OF THREE

## a pilot study

**BRITT ANCIAUX**
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## List of abbreviations

| | |
|---|---|
| A.E. | adverse event |
| $AUC_{0-t}$ | area under the curve |
| AVPU | alert, verbal, pain, unresponsive |
| BELAC | Belgian Laboratory Accreditation Corporation |
| CHADD | controlled heat-assisted drug delivery |
| Cmax | the maximum concentration (mg/L) |
| GCS | Glasgow Coma Scale |
| GX | glycinexylidide |
| HPLC-UV | high-performance liquid chromatography with ultraviolet detection |
| IQR | interquartile ranges |
| IV | intravenous |
| $k_e$ | the elimination rate constant |
| LLOQ | lower limit of quantification |
| MEGX | monoethylglycinexylidide |
| MENA | Middle East and North Africa |
| PDA | Phosphodiode Array |
| PICU | paediatric intensive care unit |
| r | Pearson's correlation |
| RCT | randomised controlled trial |
| SD | standard deviation |
| Tmax | the associated time to reach the Cmax (minutes) |
| $t_{1/2}$ | plasma half-life |
| WFH | weight for height ratio |

## Abstract

**Background:** Local anaesthesia of intact skin before performing painful punctures in children is considered essential. The topical S-Caine patch have proven to be safe and efficient (containing a 1:1 eutectic mixture of 70mg lidocaine and 70mg tetracaine, and an air-activated heating element), yet until today only approved for use in children over the age of three years. This study aims to evaluate the safety and feasibility of the use of S-Caine patches in children under three.

**Methods:** In this open-label, single-dose pharmacokinetic pilot study, all children younger than three years admitted to a tertiary teaching hospital, with central venous or arterial catheters, were eligible for inclusion. During four hours following a 30 minutes skin application of one S-Caine Patch, plasma levels of lidocaine were determined with a validated liquid chromatography Phosphodiode Array method. The safe plasma concentration threshold was defined as 0.100 mg/L, or one-tenth of the lowest concentration reported to be clinically relevant. The maximum concentration (Cmax; mg/L) and the associated time (Tmax; minutes) were measured, and compared between groups. Local and systemic adverse events (A.E.'s) were monitored, and compared among three age groups. Ease of application and overall satisfaction were scored by the nurse, using a Likert scale.

**Results:** Thirty patients were included and stratified into three age groups: 0-6 months (n=10), 6-12 months (n=10), and 12-36 months (n=10) old. Median concentrations [IQR] were 0.005 [0]; 0.005 [0]; 0.020 [0.036]; 0.020 [0.025]; 0.015 [0.022]; 0.013 [0.018] mg/L at 0; 15; 30; 60; 120; and 240 minutes after application, respectively. Regardless of age, lidocaine plasma concentrations did not exceed the safe threshold, except in one patient (Cmax 0.110 mg/L at 30 minutes) without any clinical repercussions, however. Nineteen subjects (63.3%) demonstrated very mild to moderate local effects (erythema, blanching or oedema), and one (3.3%) had more than moderate erythema. All local effects spontaneously disappeared within 30 minutes after patch removal, except for three patients in whom erythema lasted longer. No serious patch-related AE's were noted. In 28 patients (93.3%), the patch was easy to apply, in two patients (6.7%) patches did release too early. Overall satisfaction was excellent or good.

**Conclusion:** This pilot study suggests that the use of S-Caine Patch in children younger than three years old could be safe and feasible. This study continues on a larger scale to confirm these results.

**Keywords:** paediatrics; pain; anaesthetics local; lidocaine; safety; feasibility

# 1. Introduction

## 1.1. The importance of local anaesthesia

Children at the emergency department or the paediatric intensive care unit (PICU) often require cannulation for the administration of intravenous (IV) medications or fluids, venous or arterial punctures to obtain blood samples, lumbar punctures to obtain cerebrospinal fluid, bladder punctures to obtain sterile urine samples, and vaccination procedures. While commonly tolerated in adults, in children these procedures can be very painful, making children suffer more anxiety and stress (causing "needle phobia"), and can violate trust (between child, parents, and the caregiver).[1,2] More specifically, it appears that children who are mechanically ventilated suffer two times more procedures than children who are not ventilated, with skin-breaking procedures considered the most painful.[3]

Unfortunately, doctors and nurses often fail to recognise the pain, anxiety, and discomfort associated with these punctures.[1, 4] Therefore, effective and appropriate therapy for the management of pain and stress in children undergoing painful invasive interventions, is considered essential and should be carried out in a systematic and multifunctional way.[5] In the past 20 years, improvements in pain recognition have led to changes in pain management approaches.[6] Nonpharmacologic or stress management and emotional support are essential for the child to provide a comfortable environment. Pharmacologically, pain relief can be obtained with the administration of analgesia.

Various methods are already available and have been used to reduce the pain of invasive procedures. Traditional methods of local anaesthesia or infiltration are effective (e.g. Lidocaine 1% or Bupivacaine 0.25%), yet require subcutaneous injection again causing pain and anxiety, which limits their use. Another way is to anesthetise the skin before performing the punctures with the use of non-invasive topical anaesthetic creams, e.g. liposomal lidocaine, liposomal tetracaine, or a eutectic mixture (i.e. a mixture with a melting point lower than that of the individual components, defined by Sethna et al.[7]) of prilocaine and lidocaine (EMLA®). Local anaesthetics have proven to be effective in controlling pain in minor dermatological procedures and puncture incidents, by blocking voltage-gated sodium

channels and thereby preventing the initiation and conduction of nerve action. However, there are some drawbacks: (1) limited delivery of topical anaesthesia by the presence of the stratum corneum of the dermis, a considerable barrier to the passive absorption of drugs[8, 9], (2) methods that may be slightly uncomfortable, resulting in adverse events, e.g. local erythema, (3) a time-consuming process that is not immediately effective; EMLA® under an occlusive layer, for example, requires at least 60 minutes to provide adequate analgesia, (4) in some cases too complex to be widely used (by means of specialised requirements).[10] Ideally, a local anaesthetic should be safe, with minimal local side effects and no systemic toxicity, and should provide rapid and long duration of action.[1]

### 1.2. The test product

A relatively new and faster tool for local analgesia is the application to the intact skin of an S-Caine Patch [Synera® (USA), Rapydan® (Europe)]. This patch contains 70 mg lidocaine and 70 mg tetracaine in a 1:1 eutectic mixture for topical use.[7] By means of an air-activated heating element, *CHADD (Controlled Heat-Assisted Drug Delivery)*, a controlled level of heating (39-41°C) is generated for about two hours.[8, 11] This local warmth induces changes in skin permeability, enhancing faster transdermal drug delivery into the dermis[12] and increasing the distribution of local blood circulation.[13] Moreover, it provides vasodilation[14], making veins more visible and easier to puncture and dwell in IV lines, although some local erythema may occur in addition.[7, 15] Subsequently, the active S-Caine patch provides a faster onset of effective anaesthesia (within 30 minutes after application as compared to 60 minutes using EMLA®), a longer-lasting anaesthetic effect (about 120 minutes), up to a favourable depth (6.8 mm) into the skin and underlying tissues.[7, 9, 16, 17] In addition, the application and removal of the patch can be more convenient, as creams and gels usually need an occlusive layer and applying and removing them can lead to a messy environment.[18]

Subsequent punctures through anaesthetised skin are considerably less painful, sometimes even painless, after applying and removing this patch for sufficient pain relief. In a study of 64 children, aged three to seventeen years old, who required IV access or blood sampling, the pain of the procedure was

compared after a 20-minute application of a patch with lidocaine/tetracaine or a patch with placebo. Significantly greater pain relief was obtained by the patch compared to placebo, and more children reported no pain using the active patch (59% versus 20%).[7] Within the same age group, another randomised controlled trial (RCT) involving 45 children of the same age group, reported even more favourable results (75% versus 35%).[2] Regarding the success rate of needle procedures at the first attempt of IV cannulation, a multicentre randomized controlled trial by Cozzi et al. [19] reported a higher procedure success rate in children aged three to ten years receiving the heated lidocaine/tetracaine patch (92.4%) as compared to EMLA® cream application (85.0%). This indicates that the application of an S-Caine patch in children over three years old provides sufficient local anaesthesia within 30 minutes.

The recommended dose per 24 hours is a maximum of four patches in adults, and two patches in children older than three, with an application time of 30 minutes per patch.[20] Several studies evaluated the effects of application time and the heating effect of the lidocaine/tetracaine patch. In a small RCT by Marriott et al.[12] 12 adult subjects completed four treatment periods (2-, 4- or 12-hour application of four heated patches; or 4-hour application of four unheated patches). During the first two hours of application in each heated-patch group, the plasma concentrations of lidocaine increased rapidly with mean Cmax values of 0.182 (± 0.051) mg/L in the 2-hour group. In the 4- and 12-hours groups the concentration rose to 0.257 (± 0.059) and 0.303 (± 0.081) mg/L, respectively. The area under the curve ($AUC_{0-t}$, i.e. the variation of a drug plasma concentration over time) showed no significant difference between the 2- and 4-hour groups. However, between the 4- and 12-hour groups the $AUC_{0-t}$ increased twofold with a threefold increase in application time. This study suggested that the rate of lidocaine administration was prolonged in time, but without any further rise in concentration between 4 and 12 hours, and without significant effect of application time on elimination kinetics ($k_e$, elimination rate constant, and $t_{1/2}$, plasma half-life). In subjects who received unheated patches, plasma lidocaine concentrations were five and three times lower than those with the heated patch after 30 and 60 minutes, respectively.

### 1.3. Lidocaine and tetracaine

In order to verify the safety of the S-Caine patch in children younger than three years old, it is important to assess all clinical, pharmacological, and side effects of both relevant products (lidocaine and tetracaine) described in the literature. Systemic exposure may occur, depending on the dose, duration of application, thickness and condition of the skin.

Lidocaine is an amide-type anaesthetic, which is mainly metabolised in the liver by cytochrome P450 to various metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX). MEGX has similar pharmacological activity to lidocaine and may therefore contribute to toxicity. Following IV administration, a steady-state distribution volume is estimated at 0.8-1.3 L/kg[20], with the peak plasma concentration after 1.7 hours ($T_{max}$ = 1.7 hours)[21, 22] and a plasma half-life ($t_{1/2}$) of approximately 1.8 hours (ranging from 90 to 120 minutes) in children. In elderly patients, the $t_{1/2}$ of lidocaine is 2.5 hours, which may be prolonged in patients with cardiac and hepatic failure due to impaired clearance.[9] The plasma half-life of a 30-minute skin applied S-Caine patch in the elimination phase, i.e. the terminal half-life ($t_{½}$el), was determined at 12 hours in previous studies. However, the $t_{½}$el is independent of the administration form, but appears to be prolonged by the delayed release of the patch.[23] Over 98% of the lidocaine degradation products are excreted by the kidney, with a systemic clearance rate of 0.48-0.60 L/h/kg, of which less than 10% unchanged in adults and about 20% in infants.

Considering possible systemic toxicity; central nervous system toxicity (restlessness, dizziness, light-headedness, visual and auditory disturbances)[21, 24-26], cardiac depression[27], or arrhythmia may occur in adults at lidocaine plasma concentrations exceeding 5 mg/L.[8] Due to differences in paediatric pharmacokinetic features, signs of toxicity may occur at even lower drug levels in young children[1, 24], i.e. 1.000 mg/L, also the lowest concentration reported to be clinically relevant (anti-arrhythmic effect) in adults.[26] These differences in pharmacokinetic features include: an increased body surface area-to-body mass ratio; immature liver and kidney function with impaired drug metabolism and excretion; and impaired plasma protein binding with toxicity at lower doses of the drug.[1, 28, 29]

Tetracaine, also known as amethocaine, is an amino ester molecule used in many formulations: intrathecal local anaesthetic, eye drops, topical gels for mucosal use in rigid and flexible endoscopy, and topical analgesics gels and patches (LATgel, Ametop®, Rapydan®, and Synera®). This amide-type anaesthetic is unstable and has a very short half-life as well in vivo as in vitro, as it is rapidly hydrolysed by pseudo-cholinesterase to p-butylaminobenzoic acid and dimethylaminoethanol in plasma.[1, 9, 30] According to a review by Tadicherla et al.[8], no tetracaine plasma levels above 0.0009 mg/L were detected in adults after 30 to 60 minutes of S-Caine patch application in several clinical pharmacological studies.[9, 13] Because of the very short half-life in vitro, useful studies in the literature to estimate tetracaine's systemic safety in young children are very scarce.[20] One study found tetracaine levels of maximum 0.065 mg/L in children aged seven to twelve years, after application of one S-Caine patch. The same study observed mean tetracaine Cmax of <0.0009 mg/L and 0.0007 (0-0.0397) mg/L in two children of four months to two years, and seven children aged three to six years, respectively.[20] From a critical point of view, this study did not take into account the in vitro stability issues, which may have resulted in falsely low concentrations. From topical skin applications in older children, no systemic tetracaine toxicity has been reported. One incident was reported in 2012 following the application of 4% tetracaine gel to the skin of a 24 weeks gestational age extremely low birth weight (900 gram) premature with Beckwith-Wiedemann syndrome, who developed arrhythmia only resolving after two atropine injections. [31]

Tetracaine 4% gel has proven to be effective for reducing pain during venepuncture and IV cannulation, but failed to prove effectiveness during neonatal heel pricks.[1,32] Regarding safety, except for the arrhythmia in one very low birthweight premature with Beckwith-Wiedemann syndrome, there are no reports of systemic toxicity. Yet tetracaine entails vasodilatory effects, thus more erythema.[33-35] Lidocaine-prilocaine cream, however, may cause skin blanching as a side effect, as EMLA® predominantly acts as a vasoconstrictor.[35] Moreover, severe methaemoglobinemia cases have been reported after the use of EMLA® cream, leading to toxic symptoms ranging from cyanosis and dizziness to seizures, arrhythmia, and even death.[25]

### 1.4. Current use of local anaesthesia in children younger than three years old

The use and administration of analgesics in young children compared to adults is disproportionate, lags behind and varies between the different age groups. Far too often, invasive procedures are not adequately covered by adequate procedural or maintenance analgesia. In addition, knowledge of pharmacokinetic data in children is limited, especially in those under the age of three. As most physicians lack awareness of possibilities and dosage in children, fearing to overdose or yield side effects like respiratory distress and physical dependence, analgesics are often underdosed in young children. [6, 36]

For infants up to the age of three months, oral glucose as a 24 or 30% solution may provide analgesia (objectified through decreased painful facial expressions), e.g. for capillary or venous blood sampling to determine glycemia or bilirubinaemia, to fill up the Guthrie chart; for the removal of urine sample bags; or for the intramuscular injection of immunisations.[37] However, given its short duration of action (estimated five minutes), it is not sufficiently effective for longer or more painful procedures.

Currently, the two most commonly used local anaesthetics in paediatric clinical practice are lidocaine-prilocaine cream (EMLA® 5%, a eutectic mixture of lidocaine and prilocaine) and tetracaine gel (amethocaine 4%, Ametop®). EMLA® requires an application time of at least 60 minutes to provide effective analgesia, lasting for about one to two hours. Tetracaine 4% gel only needs to be applied 30 minutes before the painful procedure and has a longer duration of action (four to six hours).[38] Given this faster time of onset, tetracaine gel is considered to be the first choice in acute settings.[34] A Cochrane systematic review by Lander et al.[39] concluded that "amethocaine significantly reduced the risk of pain associated with a venepuncture or cannulation, as compared to EMLA®; when pain data were combined into a pain metric (RR: 0.78, 95% CI 0.62 to 0.98), when the pain was self-reported by children (RR: 0.63, 95% CI 0.45 to 0.87) or observed by the investigators (RR: 0.71, 95% CI 0.52 to 0.96)" *(p.1)*. This pain reduction was found to be even more effective when tetracaine 4% gel was applied for 30 to 60 min before IV cannulation.

A meta-analysis by Pywell et al.[4] included three randomised controlled trials to determine whether amethocaine made first-time cannulation in children more easier and successful, and therefore a better experience for the children, their family and the healthcare providers. In the open randomised trial by Van Kan et al.[40] including ten patients one to five years of age, lidocaine-prilocaine cream seemed more effective than tetracaine 4% cream (97% versus 76%), but according to the authors the practical benefits of the latter (shorter time of application, vasodilation, and overall lower cost) outweighed this difference.[40] Both RCT's by Arendts et al.[38] and Newbury and Herd[41] including children (one to twelve years old, and three months to fifteen years old, respectively) at a paediatric emergency department needing IV catheter insertion, could not demonstrate a difference in the first attempt success rates between tetracaine gel and EMLA® (75% versus 74%).[38, 41]

The application of the S-Caine Patch has proven to be safe and efficient, but has only been approved for use in children over the age of three years. Little to nothing is known about the safety of S-Caine patch use in children younger than three years old. Only one study attempted to assess the systemic exposure and safety of S-Caine patches in children under three years of age. Unfortunately this study provided uncertain conclusions, as only four patients had complete pharmacokinetic sampling.[20] Due to the lack of relevant clinical studies the use of S-Caine patches in this age group - yet exposed to many painful skin procedures and multiple attempts to puncture and cannulate veins - is currently not recommended.

### 1.5. Objectives and hypothesis

The present study aims to evaluate following research question: "Is the use of S-Caine Patch safe and feasible in children younger than three years old?"

If the hypothesis would prove to be right, i.e. the use of S-Caine Patch in children younger than three years old is safe and feasible, a very vulnerable group of paediatric patients could benefit from a device/drug that has proven its efficacy, safety, and feasibility in older children. As it is a patient's right to be entitled to as much prevention or reduction of pain as possible, this would allow obeying the law,

and treating small children painlessly. There would no longer be an age barrier to use the analgesic patch. If the hypothesis would prove to be wrong, alternatives will have to be considered in order to provide adequate and sufficient pain relief for the very youngest patients.

## 2. Methods

### 2.1. Study Design

This prospective, randomised, non-blinded study was conducted for 21 months between August 01, 2019, and May 01, 2021, in the Department of Paediatrics and the Paediatric Intensive Care Unit of the Universitair Ziekenhuis Brussel, Belgium. The study protocol was reviewed and approved by the Ethical Committee of the University Hospital Brussels, Belgium; and by the Belgian Federal Agency for Medicines and Health Products. All data were collected using a prospectively designed paper registration form. Written informed consent was obtained from the patient's legal guardian.

### 2.2. Study Population and Setting

In this single-centre, open-label, single-dose pharmacokinetic study, combined with a questionnaire completed by the nurses applying the product, all children eligible for inclusion (i.e. those children not meeting the exclusion criteria, see Table 1) were stratified into three groups: 0-6 months old; 6-12 months old, and 12-36 months old. This final sample size was based on practical considerations and standard protocols for pharmacokinetic studies. After a statistical power analysis, the desired number of subjects to be included was estimated at a 100 patients.

All subjects eligible for inclusion, completed the flowchart questions (Figure 1). They all had to be already in possession of a catheter, in place for reasons external to this study. Included patients were flagged in the electronic medical patient record, to avoid repeat inclusions or duplicated application of patches. In addition to the subdivided age categories and the access port used to take blood samples, gender, weight (kg), height (cm), ethnicity (Caucasian, MENA, Black), and site of patch application were also registered.

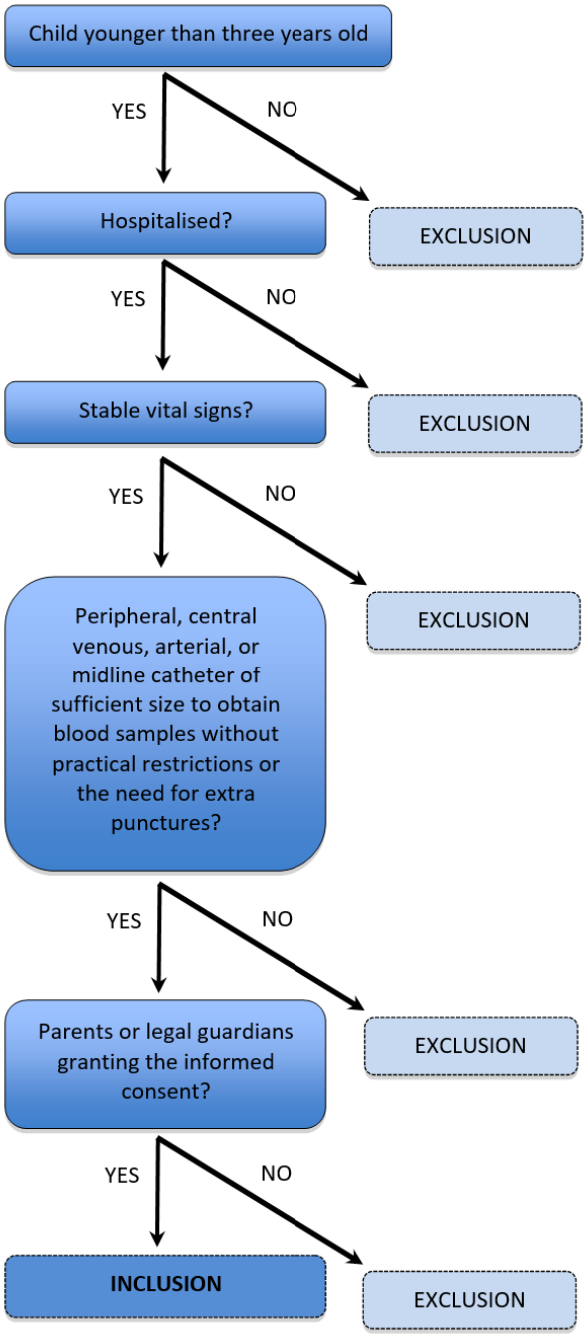
Subjects were excluded from study participation based on any of the following criteria (Table 1): patients who were older than three years old, not admitted to the hospital, in absence of a catheter allowing unrestricted blood sampling, or had a premature birth (gestational age < 37 weeks) or < 3 kg.

Those who needed a warming blanket in the 24 hours before inclusion, who had metabolic, liver, or kidney diseases, who showed life-threatening pathology (respiratory, circulatory, or neurological impairment or instability), or who suffered from bronchopulmonary dysplasia, methemoglobinemia[25], or anaemia (plasma haemoglobin levels < 11 g/dL or haematocrit levels < 30%) were not included. Skin diseases (hypersensitive skin, atopic dermatitis, damaged, denuded, or broken skin at the designated patch site), known allergy or sensitivity to lidocaine and/or tetracaine or other local anaesthetics of the amide or ester type, or to one of the components of the S-Caine Patch (e.g. sulphites, adhesives)[42], prevented the use of patches. Patients who received products containing lidocaine, and/or tetracaine within 24 hours before inclusion were excluded, similar to those with a history of cocaine use or other drugs that might cause an additive pharmacological effect with either lidocaine and/or tetracaine (e.g. receiving breastfeeding was excluded if the mother had a history of cocaine use). Finally, patients were excluded if parents did not sign informed consent or were withdrawn.

*Table 1: Exclusion criteria.*

| **Exclusion criteria** |
|---|
| Older than three years old, not admitted to the hospital, or in absence of a catheter allowing unrestricted blood sampling |
| Premature birth (gestational age < 37 weeks) or < 3 kg |
| Metabolic, liver, or kidney diseases |
| Respiratory, circulatory, or neurological impairment or instability |
| Bronchopulmonary dysplasia, methaemoglobinemia**[25]**, or anaemia (plasma haemoglobin levels < 11 g/dL or haematocrit levels < 30%) |
| Skin diseases (hypersensitive skin, atopic dermatitis, damaged, denuded, or broken skin at the designated patch site), known allergy or sensitivity to lidocaine and/or tetracaine, to one of the components of the S-Caine Patch (e.g. sulphites, adhesives)**[42]** or other local anaesthetics of the amide or ester type |
| Received products containing lidocaine, and/or tetracaine within 24 hours before inclusion |
| History of cocaine use or other drugs (e.g. receiving breastfeeding if the mother had a drug abuse history) |
| Informed consent not approved by legal guardian or parents |

*Figure 1: Inclusion/exclusion flowchart.*



### 2.3. Workflow

To evaluate the safety and feasibility of the use of S-Caine Patch in children younger than three years old, plasma levels of lidocaine following skin application of one S-Caine Patch were determined, local and systemic possible adverse events after application of one S-Caine Patch were monitored, and finally, the ease of applying and removing the patch was evaluated (Table 2).

Six whole blood samples were taken (1.2 ml per sample, a total amount of 7.2 ml per patient), all from the already present catheter, away from the skin zone where the patch was applied to. Before sampling, any products and drugs being administered through the catheter were removed by first drawing 3 ml of whole blood in a syringe, not being used for the study. This blood was given back to the patient right after sampling, according to hospital guidelines for blood sampling in infants and young children.

After completing the checklist of inclusion/exclusion criteria and obtaining written informed consent, the first blood sample needed to be obtained immediately (maximum 15 minutes) before application of the patch. Subsequently, one S-Caine Patch (containing 70 mg lidocaine and 70 mg tetracaine for topical use) was applied for 30 minutes to intact skin. As localisations on the skin corresponded to the places where punctures would normally be performed, the following were allowed: elbow fold, back of the hand, shoulder (deltoid immunisation location), upper leg (quadriceps immunisation location), inguinal region (location of femoral artery and vein punctuation), L1-L2 location on the dorsum (lumbar puncture location), suprapubic (bladder puncture location) or other (to be specified). Given the presence of parabens in the S-Caine patch as excipients, and concerns regarding metabolic immaturity and the possibility of damaged skin in this area, the patch couldn't be applied in the nappy area.[43] Since the systemic exposure of the two active substances also depends on the thickness of the stratum corneum[29] of the skin (varying between different body parts and ethnicity)[44] as well as the skin condition, the examiner specified the localisation where the patch was applied.

The other five plasma samples were obtained to determine plasma levels of lidocaine: 15 minutes after application of an S-Caine Patch, at the time of patch removal (when applied for 30 minutes), and at subsequent scheduled times up to four hours after patch application (Table 2). The blood samples were labelled with the patient's identification and were internally transported to and processed by the accredited lab of the Universitair Ziekenhuis Brussel, Brussels, Belgium. Whole blood samples for the determination of lidocaine were considered relatively stable, as in vitro stability of lidocaine is guaranteed for 48 hours at room temperature (20°C).[45] Therefore, time of transport and storage temperature in the meantime did not affect lidocaine levels. To separate plasma, blood samples were centrifuged at 3000 rpm for ten minutes, then being stored at -20°C until analysed. All analyses were performed by the BELAC (Belgian Laboratory Accreditation Corporation) accredited lab of the leading study centre, by a validated liquid chromatography Phosphodiode Array (PDA) method with a limit of quantification of 1 microgram per liter (0.001 mg/L) for lidocaine concentrations. The chromatography lidocaine peak was verified and confirmed by using the UV-spectrum of lidocaine. The precision – i.e. how close measurements of the same concentration are to one another – of the liquid chromatography PDA method with ultraviolet detection was estimated at 6.3% at a concentration of 0.286 mg/L, and at 4.1% at a concentration of 0.072 mg/L. When the total lidocaine concentrations were determined, these results (blinded to the researchers) were kept in a database available at the lab of the Universitair Ziekenhuis Brussel.

To assess the feasibility of using the patch, the treating nurse scored the ease of use of the patch in this age category, using a Likert scale. This is a five-point scale expressing the level of agreement to a statement, with 5=excellent, 4=good, 3=average, 2=poor, 1=very poor.[46] These scores were assigned using a predefined questionnaire, based on the following questions: How easy was the application of the patch? Was the size of the patch adapted to the size of the patient? Did the patch stick close to the skin? Was it possible to leave the patch uncovered? Was the patch easy to release after 30 minutes? Was the removal of the patch painless?

*Table 2: Scheduled samples and evaluations/monitoring.*

| Time (minutes) | -15 | 0 | 15 | 30 | 60 | 120 | 240 |
|---|---|---|---|---|---|---|---|
| **Informed Consent by a legal guardian** | x | | | | | | |
| **Patch application** | | x | | | | | |
| **Patch removal** | | | | x | | | |
| **Blood sample** | x | | x | x | x | x | x |
| **Evaluation of local skin** | x | x | x | x | x | x | x |
| **Evaluation of systemic effects** | x | x | x | x | x | x | x |
| **Evaluation of ease of use** | | x | x | x | | | |

## 2.4. Variables

### 2.4.1. Pharmacokinetic Variables

The safe plasma concentration threshold was defined as 0.100 mg/L, or one-tenth of the lowest concentration reported to be clinically relevant (anti-arrhythmic effect) in adults, or possible toxic in young children. In case levels exceeded 0.100 mg/L, the treated physician was warned for safety reasons and a further analysis was performed to detect separate levels of free and bound lidocaine. The lab results were kept in a hidden segment of the patient file, with restricted access, given to the researchers at the end of the study.

All concentrations at time -15 min (before the application of the patch), reported as below the lower limit of quantification (LLOQ < 0.010 mg/L and not negative), were assumed to be equal to 0.005 mg/L for the calculations. The maximum concentration (Cmax; mg/L) and the associated time (Tmax; minutes) were measured.

*Table 3: Measurements, calculations, units and thresholds.*

| Product | Parameter | Unit | Threshold alert | Stop threshold |
|---|---|---|---|---|
| **Lidocaine** | Cmax | mg/L | 0.100 | 1.000 |
| | Tmax | minutes | | |

### 2.4.2. Adverse events

Local adverse events at the skin site were registered separately on the registration form, pre-listing the most common side effects reported in the literature.[2, 15, 47] Monitoring of possible local adverse events after application of one S-Caine Patch was performed by post-treatment assessment and evaluation of the skin at the patch application site at the time of patch removal, and at the scheduled intervals as described in Table 2. Following local adverse events could be registered and given a severity score ranging from zero to four, according to a primary skin irritation scoring system[48] (Table 4): redness of skin under the active product site or under the adhesive patch borders, blanching of skin, oedema, blistering of the skin, itching, hives or rash with spots, discoloration, and/or pain.

*Table 4: Assessment of topical adverse reactions according to a primary skin irritation scoring system.*

| score | erythema and eschar formation scale | oedema formation scale | blanching scale |
|---|---|---|---|
| **0** | No | no | no |
| **1** | very slight (barely perceptible) | very slight (barely perceptible) | very slight (diffuse with indistinct outline) |
| **2** | well defined | slight (<1 mm raised) | more intense (with half of the treated site perimeter outlined) |
| **3** | moderate-to-severe | moderate (>1 mm raised) | marked (with distinct outline) |
| **4** | severe (beet redness and/or injuries in the depth of skin) | severe (>1 mm raised beyond area of application of patch) | severe (with a clear outline) |

Monitoring of possible systemic adverse events was performed at the same time intervals, by evaluation of the vital signs: oxygen saturation, respiratory rate, heart rate and -rhythm, blood pressure, body temperature, diuresis, and level of consciousness. All study subjects remained under monitoring and medical supervision at least eight hours after application of the patch. However, considering the clinical experience reported in research studies and the pharmacokinetics of these agents, patients who remained asymptomatic for four hours after the exposure were eligible to be discharged.[21]

### 2.4.3. Stopping criteria

The immediate interruption of the individual inclusion were plasma lidocaine concentrations 0.500 mg/L (as the lowest plasma level to be clinically relevant is ≥ 1.000 mg/L), local pain, itching, hives or rash with spots, blistering at the application site, desaturation below 90% in room air, any signs of respiratory distress, arrhythmia, bradycardia or hypotension (defined as below-normal range according to the Broselow tape)[49], decrease in consciousness (AVPU score not Alert, or GCS < 13/15) or convulsions. If plasma lidocaine concentrations ≥ 1.000 mg/L reached in one or more of the samples of one or more of the subjects, further enrolment of new subjects was to be immediately abandoned.

## 2.5. Data Analysis

Statistical analysis was performed using SPSS version 27.0 (IBM Corporation, Armonk, NY). The normal distribution of continuous quantitative variables (age, weight, height, Cmax) was assessed by Kolmogorov-Smirnov tests. Normally distributed continuous data were expressed as mean ± standard deviation (SD), or median [interquartile ranges (IQR)] for skewed variables. Categorical variables were presented as frequencies with percentages. To assess the homogeneity of variances, Levene's test was used. P-values < 0.05 were considered statistically significant. The measured lidocaine plasma concentrations were compared to the clinically relevant threshold concentration (1.000 mg/L), using a One-Sample T-test. Baseline characteristics were compared between groups using Student t-tests for two, and one-way ANOVA tests for groups with more than two categories. A multivariate model for the effect of gender, access, and application site, with a correction for weight for height ratio (z-scores based on standardised growth curves from birth to maturity in Flanders, Belgium[50]) as covariate, was used. Pearson's correlation (r) coefficients were used to assess the relationship between the maximum concentrations and the weight for height ratio. A Pearson's correlation coefficient was considered as 'poor' when $0 < r < 0.3$. To test the comparison of two categorical variables – i.e. erythema at time 30 minutes and the different age groups – a Chi-Square test or a Fisher Exact test was used when conditions were not met. Kruskal-Wallis H test was used to assess feasibility scores obtained by the Likert Scale, with three categorical, independent age groups.

# 3. Results

## 3.1. Enrolment

A staggered enrolment was performed with initially 33 patients who met the inclusion criteria, of which 30 patients were stratified into three age groups: 0-5 months (n=10), 6-11 months (n=10), and 12-36 months (n=10) old. One patient (a two-year-old girl) was withdrawn from the study because her midline catheter occluded as a result of dislodgement, and the patch spontaneously detached after 15 minutes. As the entire procedure could not be performed, she was not included in the analyses. Two parents did not grant informed consent because of personal reasons. Baseline demographic characteristics of the overall study population are summarised in Table 5.

*Table 5: Baseline demographic and clinical characteristics of the overall study population (n=30).*

| **Patient Characteristics** | **Total (n=30)** |
|---|---|
| **Demographics** | |
| Age, years | 0.86 ± 0.66 |
| Female gender (n, %) | 13 (43.3%) |
| Weight, kg | 7.95 ± 2.87 |
| Height, cm | 69.96 ± 12.82 |
| Weight for Height | -0.45 ± 1.87 |
| Ethnicity (n, %) | Caucasian = 18 (60.0%)<br>MENA = 9 (30.0%)<br>Black = 3 (10.0%) |
| **Clinical variables** | |
| Age groups (n, %) | 0-6 months = 10 (33.3%)<br>6-12 months = 10 (33.3%)<br>12-36 months = 10 (33.3%) |
| Access (n, %) | Central venous catheter = 19 (63.3%)<br>Arterial catheter = 11 (36.7%) |
| Application of the patch (n, %) | Elbow fold = 12 (40.0%)<br>Upper leg (Quadriceps) = 8 (26.7%)<br>Dorsum (L1-L2) = 6 (20.0%)<br>Foot = 2 (6.7%)<br>Back of the hand = 1 (3.3%)<br>Suprapubic = 1 (3.3%) |

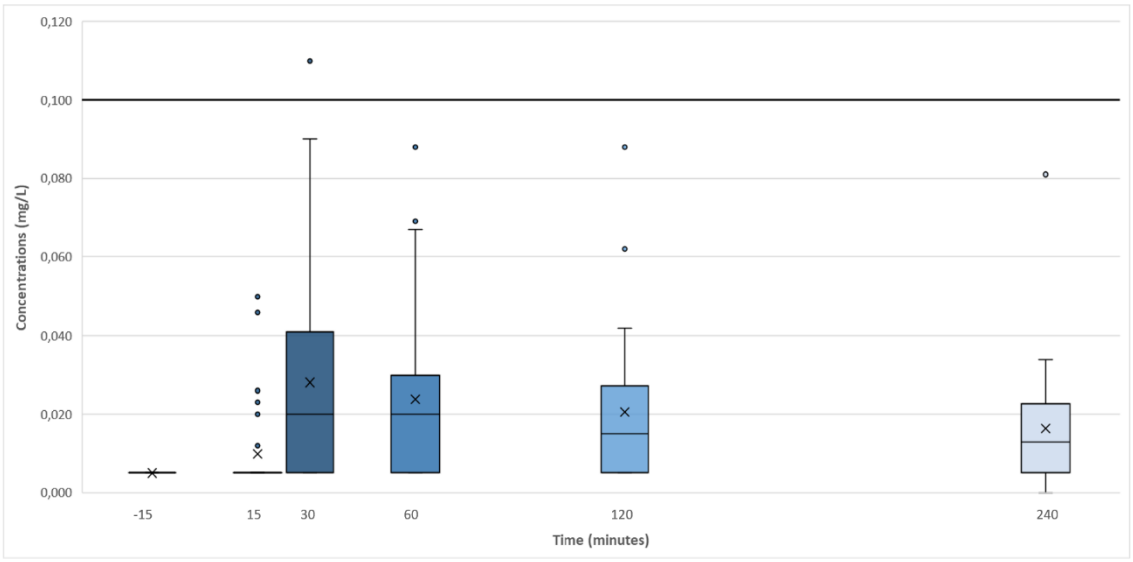
## 3.2. Safety

### 3.2.1. Pharmacokinetic Properties

The lidocaine plasma concentrations aligned over time are presented in a Box Plot Graph (Figure 2). Median concentrations [IQR] were 0.005 [0]; 0.005 [0]; 0.020 [0.036]; 0.020 [0.025]; 0.015 [0.022]; 0.013 [0.018] mg/L at 0; 15; 30; 60; 120; 240 minutes after application, respectively. In the majority of cases (52%) the maximum lidocaine plasma concentration was reached 30 minutes after application of the patch, corresponding with the time the patch was removed. The concentrations decreased over time but still did not reach ≤ 0.005 mg/L after four hours. For one male patient of ten months, no concentration measurement was performed at 240 minutes.

Compared to the clinically relevant threshold concentration (1.000 mg/L), the measured lidocaine plasma concentrations remained far below this threshold ($p<0.001$). Regardless of age, lidocaine plasma concentrations did not exceed the predefined safe plasma concentration threshold of 0.100 mg/L, except in one male patient of two months and nine days (Cmax 0.110 mg/L at 30 minutes). Immediately after patch removal, this concentration decreased to below the threshold (0.030 mg/L at 60 minutes).

*Figure 2: Lidocaine plasma concentration during and after application of the S-Caine patch in children under the age of three. The black line denotes the predetermined safety threshold at 10% of the clinical relevant concentration.*



The relationship between maximum concentration and independent variables is shown in Table 6. There were no statistically significant differences among gender, access, age groups, ethnicity, or application site of the patch on Cmax, using univariate as well as multivariate testing. Only the main effects were noted, as the two- and three-way interactions were also not significant: age group*gender (p=0.327); age group*ethnicity (p=0.956); age group*access (p=0.517); age group*application site (p=0.075); gender*ethnicity (p=0.166); age group*gender*ethnicity (p=0.508).

A Pearson-correlation was conducted to examine the relationship between Cmax and the weight for height ratio (WFH). Cmax was poorly related to WFH, r(28) = 0.006 (p=0.974). The effect size for WFH ($r^2$=0.000036) indicated that WFH did not account for the variability in Cmax.

*Table 6: Outcome of the safety results by comparing independent variables with the dependent variable Cmax, using One-Sample T-test, Independent Two-Sample T-tests, and One-way ANOVA tests for univariate analysis. Multivariate analysis with covariance on WFH, adjusting for age. *Statistically significant.*

| **Cmax** | **n** | **Mean ± SD** | **p-value univariate** | **p-value multivariate** |
|---|---|---|---|---|
| Safe threshold concentration (0.100 mg/L) | 30 | 0.034 ± 0.027 | <0.001* | |
| **Gender** | 30 | | 0.690 | 0.486 |
| Male | 17 | 0.035 ± 0.031 | | |
| Female | 13 | 0.031 ± 0.022 | | |
| **Access** | 30 | | 0.420 | 0.783 |
| Arterial catheter | 11 | 0.029 ± 0.018 | | |
| Central venous catheter | 19 | 0.037 ± 0.031 | | |
| **Age groups** | 30 | 0.034 ± 0.027 | 0.552 | 0.624 |
| 0-6 months | 10 | 0.038 ± 0.035 | | |
| 6-12 months | 10 | 0.026 ± 0.017 | | |
| 12-36 months | 10 | 0.037 ± 0.028 | | |
| **Ethnicity** | 30 | 0.034 ± 0.027 | 0.671 | 0.760 |
| Caucasian | 18 | 0.037 ± 0.031 | | |
| MENA | 9 | 0.029 ± 0.022 | | |
| Black | 3 | 0.025 ± 0.020 | | |

*Table 6: continued.*

| | | | | |
|---|---|---|---|---|
| **Application site** | **30** | **0.034 ± 0.027** | **0.622** | **0.683** |
| Elbow fold | 12 | 0.035 ± 0.018 | | |
| Upper leg (Quadriceps) | 8 | 0.044 ± 0.037 | | |
| Dorsum (L1-L2) | 6 | 0.030 ± 0.031 | | |
| Other | 4 | | | |
| **Weight for Height ratio** | 30 | -0.45 ± 1.87 | 0.974 | 0.676 |

### 3.2.2. Adverse events

Results of secondary outcomes are summarised in Figure 3. Nineteen subjects (63.3%) demonstrated very slight to moderate local effects (erythema, blanching or oedema), and one (3.3%) had more than moderate erythema. Erythema was reported in all 20 patients at the time of patch removal (at 30 minutes); two patients had additional blanching of the skin or oedema, respectively. All local adverse events (A.E.'s) spontaneously disappeared within 30 minutes after patch removal, except for three patients demonstrating longer erythema at the application site. The number of patients who presented with erythema at a time 30 minutes per different age group is shown in Figure 4. Six out of ten patients in the first age group showed erythema at 30 minutes, in the second and the third age groups eight out of ten patients. The Fischer Exact test showed no statistically significant difference between erythema and age group (p=0.122).

No serious patch-related A.E.'s were observed. Two patients did show systemic effects (notably desaturation and vomiting), but both in the context of their illness leading to their hospitalisation at the time of inclusion, as confirmed by the supervising physician.

*Figure 3: Local adverse events of the S-Caine Patch at 30 minutes (number of patients), specified by a skin irritation scoring.*

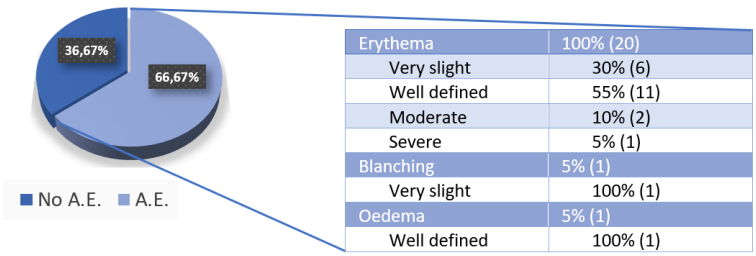
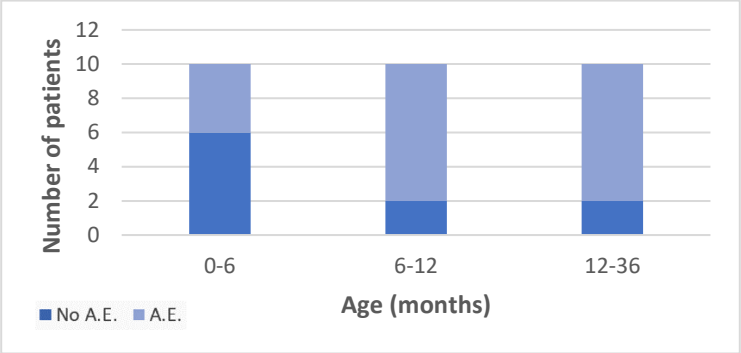


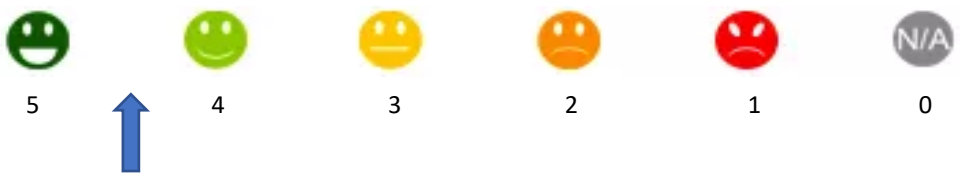
*Figure 4: Number of patients per age group (months) with erythema at 30 minutes.*




### 3.3. Feasibility

In 25 patients (83.3%) a Likert score of 4 or 5 out of 5 was assigned at both 0 (patch application) and 30 minutes (patch removal). The median Likert score was 5 (mean score was 4.4 ± 0.86) at the time of application and median 5 (mean 4.4 ± 0.93) at the time of removal (Figure 5). There was no significant difference between the Likert scores compared among age groups, using a Kruskal-Wallis H test: p=0.095 and p=0.517 at 0 minutes and 30 minutes, respectively. The mean Likert scores at 0 and 30 minutes for the first age group (0-6 months) were 3.9 ± 1.10 and 4.2 ± 1.03. The second (6-12 months) and third (12-36 months) age group scored 4.8 ± 0.42 and 4.2 ± 1.14; and 4.5 ± 0.71 and 4.7 ± 0.48, respectively. In 28 patients (93.3%), the patch was easy to apply according to the nurse, in two patients (6.7%) patches did release too early.

*Figure 5: Satisfaction using Likert Scale with mean score 4.4 (arrow) at both 0 and 30 minutes.*



## 4. Discussion

### 4.1. Safety

The results of this study, combined with previous reports, provisionally support the safety of the S-Caine patch in children under three years of age and the unlikelihood that this patch would lead to systemic toxicity.

In all 30 subjects, lidocaine plasma concentrations during and after application of the S-Caine patch were observed over time, with the highest median [IQR] lidocaine plasma concentrations reached at 30 minutes, 0.020 mg/L [0.036]. Concentrations were decreasing over time, although not reaching ≤ 0.005 mg/L after four hours. However, this was expected, as a study by Marriott et al.[12] demonstrated earlier that baseline concentration was still not re-achieved 24 hours after applying the same patch. Moreover, it was not considered ethically acceptable to determine later concentrations drawing more than six blood samples per patient, in children of such a young age. Since the present study is a safety study with emphasis on maximum concentrations not exceeding safe thresholds, the observation that concentrations following Cmax decreased over time and never fluctuated with an upward trend, was considered reassuring.

Although slightly higher mean blood lidocaine levels were noticed in the youngest subjects (0-6 months old), with mean Cmax of 0.038 ± 0.035 mg/L, as compared to the middle (6-12 months old) and oldest group (12-36 months old), with Cmax 0.026 ± 0.017 mg/L and 0.037 ± 0.028 mg/L, respectively, the mean Cmax seemingly is not significantly influenced by age. These findings are not entirely consistent with the results of a single paediatric study in four children under three (Eurocept International B.V. SmPC Rapydan)[20], suggesting lidocaine exposure after 30 minutes of S-Caine patch application is inversely correlated with age. Drawing conclusions about the correlation between age and lidocaine AUC and Cmax needs further study with more subjects.

The maximum lidocaine plasma concentrations measured during this study remained far below the toxic concentrations reported in the literature.[20, 24, 25] Regardless of age, lidocaine plasma concentrations in this study did not exceed the safe plasma concentration threshold of 0.100 mg/L, except in one patient of the prime age group, with Cmax 0.110 mg/L at 30 minutes. A previous report by Qin et al.[51] indicated that the precision of high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method ranged from 1.4% to 7.9% (with lower precision for lower concentrations and conversely) with an accuracy between 91.7% and 106.5%. With a precision of about 5% for the measurement result of 0.110 mg/L, the safe threshold would have been exceeded, however, only to a limited extent (0.105 - 0.116 mg/L). In the present study no concerns were raised as subsequent concentrations in this patient immediately declined to below safe thresholds, and no clinical repercussions were observed.

Two thirds of the subjects demonstrated local effects (erythema, blanching, and oedema). All of them had mild to moderate local erythema, explainable by cutaneous vasodilatory action and local heating by the patch.[13, 14] All local adverse events spontaneously disappeared within 30 minutes after patch removal; except for three patients demonstrating longer erythema at the application site. This occurrence of erythema following 30 minutes application of a lidocaine/tetracaine patch is consistent with results of previous studies[7], but with a considerable higher prevalence than in older children (aged three to 17 years, approximately 30%)[2] and in adults (reported prevalence ranging from 3 to 10%).[42, 47] This marked occurrence of erythema may be explained by the fact that younger children have a skin more sensitive to absorption, as it differs in pharmacokinetics partly due to the increased skin surface area-to-body weight ratio.[1, 29] Among the three age groups of this study population, no significant difference in the occurrence of erythema was observed. Other application site reactions have been described: contact dermatitis, rash, and skin discoloration (in less than 4%); and pruritus, pain, allergic reactions, blisters, paraesthesia, or vesiculobullous rash (in less than 1%)[42]. None of these were observed in this study.

There were no serious patch-related adverse events observed in this study population, again consistent with results of previous studies.[9, 13, 16, 17] Although it is unlikely that the use of a single S-Caine patch would induce systemic toxicity, it is not excluded that the simultaneously or directly consecutively application of multiple S-Caine patches in the same patient may result in higher plasma levels of local anaesthetics, entailing an increased risk of systemic toxicity.[22]

### 4.2. Feasibility

Given the results of this study, the use of S-Caine in children under the age of three years is considered feasible.

Overall satisfaction of the nurses at the application of the patch was excellent or good, with a mean Likert score of 4.4 out of 5, at both 0 (patch application) and 30 minutes (patch removal). The first age group (0-6 months) were given a slightly lower Likert score at the time of patch application (mean Likert score at 0 minutes = 3.9), indicating some nurse dissatisfaction compared to the other two age groups. Written comments revealed that nurses estimated the size of the patch is not adapted to the smaller body surface of this age group. Once the patch was applied to the skin, satisfaction slightly improved (mean Likert score at 30 minutes = 4.2).

The one drop-out patient (because of occlusion of the midline catheter and prematurely detached patch), had a single effect on nurse satisfaction (Likert score 4 and 1). However, this result would not have influenced the overall positive satisfaction rate.

### 4.3. Limitations

The inclusion of the number of patients proceeded at a slower rate than initially hoped. The sample size included the most vulnerable group, especially hospitalised children under three years of age, during an inclusion period that coincided with the crisis accompanying the coronavirus pandemic. With

a limited number of subjects, the sample size may have been too small to detect small differences in secondary outcomes, as other local or systemic adverse events.

No significant associations between the mean Cmax and other independent variables (gender, ethnicity, access, and application site), with a correction for weight for height ratio, were encountered. It has been repeatedly described in previous studies that the thickness of the stratum corneum of the epidermis is inversely proportional to absorption when a drug is administered percutaneously[8, 9, 29], and which can be positively correlated with pigmentation.[44] However, the sample size of patients with dark-pigmented skin (n=3) in the present study was too limited to indicate significant measurable differences in lidocaine absorption. The same lack of impact seemed to occur regarding the application site, consequently also the local skin thickness, with no difference in absorption of lidocaine at the elbow fold (n=12), upper leg (n=8) and lower back (n=6) site. Hereby, no firm conclusions could be drawn between Cmax and the independent variables as the feet (n=2), suprapubic region (n=1) or back of hand (n=1), due to the limited number of exposed patients. In addition, it would be hazardous to conclude there were (no) differences in skin absorption based on these small variances in concentrations (0.034 ± 0.027 mg/L) in comparison with the clinically relevant concentration values (≥ 1.000 mg/L).

The exact time of Cmax could not be determined as blood sampling was done at specified times. A potential increase in Cmax between blood samples taken at 15 and 30 minutes, or between blood samples taken at 30 and 60 minutes, could not be excluded. Consequently, the time of Cmax may not have corresponded fully with the time of observation of erythema, and hence a statistical correlation could not be analysed. For example, redness could occur at 31 minutes and Cmax at 42 minutes, but both would be reported at 45 minutes.

Concentrations of MEGX, the primary metabolite of lidocaine, produced in the liver, were not determined in the present study. Previous studies[12,52] have already indicated that transdermal absorption of lidocaine from a heated patch is not able to induce toxicity, partially as it is unknown

whether lidocaine is metabolised in the dermis.[21] A lidocaine/MEGX concentration ratio of 4/1 has been reported in healthy adults after the simultaneous application of three topical lidocaine patches. If a similar ratio would have occurred in the present study, the total exposure to the active compound would still have been well below the mentioned toxic lidocaine thresholds. [52]

Tetracaine concentrations were not analysed as tetracaine is an amino ester that rapidly degrades in human plasma due to the presence of esterases.[1, 30] This breakdown might therefore be prevented by collecting the blood samples on ice, sending them immediately to the laboratory for analysis, centrifuging at 4°C, freezing the dialysates at -20°C and storing them at -80°C[13], or adding buffering solutions and additives (e.g. neostigmine methylsulphate, an esterase inhibitor) to the plasma.[51, 53] However, these precautions could not have guaranteed detection of tetracaine concentrations and were not practically feasible in this study. In addition, tetracaine has a short half-life, which, however, determines the time of sampling and does not affect the analytical method. Whether tetracaine concentrations in plasma would have been below the detection limit of < 0.010 mg/L of the PDA method, could not be stated as this has not been tested nor validated.

## 5. Conclusion

Children younger than three years old undergoing painful punctures or procedures would benefit from adequate pain relief, such as provided by the S-Caine patch containing lidocaine and tetracaine. This pilot study suggests that the use of S-Caine Patches in children under the age of three may well be safe, as plasma lidocaine concentrations remained far below any safety threshold, and only transient minor local adverse events were seen. Feasibility was scored positive, although improvements to the patch are necessary, regarding adhesion and size. This study will continue on a larger scale to confirm these results.

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VRIJE UNIVERSITEIT BRUSSEL

# Toestemmingsformulier openbaarmaking masterproef

Student
Naam : Anciaux Britt
Rolnummer : 0517345
Opleiding : Master in de Geneeskunde
Academiejaar : 2020-2021

Masterproef
Titel : Safety and feasibility of S-Caine patch use in children under the age of three: a pilot study
Promotor : Prof. Dr. Gerlant van Berlaer

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