Randomized Trial

A New Transmucous-Buccal Formulation of Acetaminophen for Acute Traumatic Pain: A Non-inferiority, Randomized, Double-Blind, Clinical Trial

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Background: Acetaminophen (APAP) consumption is large and sometimes excessive, and guidelines suggest to diminish the dosage prescription. In emergency situations of mild/moderate pain intravenous (iv) APAP is recommended, but the route of administration is invasive.

Objective: To determine the efficacy of a new transmucous-buccal (B) pharmaceutical form of 125mg-APAP in patients. To confirm the findings obtained in 2 previous clinical trials in healthy volunteers.

Study Design: A randomized, double-blind, non-inferiority, clinical trial (NCT01586143) was carried out from 03/05/2012 to 13/05/2013.

Setting: The study took place in the Emergency Department of the University Hospital, Clermont-Fd, France.

Methods: Forty-three patients were included and 40 analyzed. Patients were eligible if they had leg or arm traumatic pain of moderate intensity. Pain intensity was measured using a numerical scale (0 – 10) at regular times for 120 minutes and the main endpoint was at 30 minutes. The hypothesis of non-inferiority was formulated from previous works with healthy volunteers. After pain assessment, patients received at baseline 1 g-iv-APAP or saline and concomitantly, 125 mg APAP in 1 mL hydroalcoholic solution (HAS) or placebo (HAS only) was applied in the left mucogingival sulcus. Non-inferiority of the primary outcome was assessed by one-sided 2 group t-test of equivalence in means with equal variances with a non-inferiority limit difference of 1. Other tests were two-sided, with a type I error set at $\alpha = 0.05$.

Results: Intention-to-treat analysis shows that pain intensity of B-APAP and iv-APAP groups were not significantly different at t30 minutes (3 ± 1.3 vs 2.7 ± 1.2, $P = 0.23$, one-sided Student t-test), and at any other times for 120 minutes. The difference of pain intensity between groups was 0.30 with 2-sided IC90% = [-0.38 – 0.98], not including the non-inferiority margin ($\Delta = 1$). Time to exhibit a statistical significance in pain relief from baseline was reached at t10 for B-APAP ($P = 0.03$) and iv-APAP ($P < 0.001$). Patients preferred the buccal rather than the iv route of administration.

Limitations: Small population study with limited doses.

Conclusions: For acute traumatic pain of moderate intensity, B-APAP has a non-inferior analgesic effect compared to iv-APAP for 2 hours. Such a pharmaceutical form would be useful in emergency situations and breakthrough moderate pain episodes. It would diminish APAP consumption per dosage unit, limit the risk of adverse events and toxicity, and adhere to actual guidelines of APAP prescription. It must be now studied in a larger population and with repeated doses.

Key words: Transmucosal delivery, pain, trauma

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Pain is a dominant symptom associated with acute and chronic conditions and acetaminophen (acetyl-p-aminophenol; APAP; paracetamol) is the most commonly used analgesic for mild to moderate acute pain. It is recommended as the first-line drug for acute pain (1,2), as well as for chronic pain of osteoarthritis (3,4), and is a routine analgesic in operating rooms and inpatient wards,. However, its large and excessive consumption in the community (5), sometimes in excess of 4 g/day, the recommended dose in some countries, has led to the emission of warnings for a reduced daily use and dosing of APAP. Recently the Food and Drug Administration reminded health care professionals to stop prescribing and pharmacists to stop dispensing prescription combination drug products that contain more than 325 mg of APAP per tablet, capsule, or other dosage unit (6). In the Accident and Emergency Department (AE), APAP is administered for acute pain mainly intravenously (iv) to avoid the problem of bioavailability linked to the oral route. However, iv administration presents a number of known drawbacks including nursing time to install and control the 15 minute long infusion of APAP with the risk of tissue damage and infection, difficulty to mobilize the patient with the drip, and also a non-negligible cost. It is also associated with difficulties to carry out blood punctures in elderly and frail patients who often have fragile veins and with potential dose-dependent drug interactions as shown in patients who had elevated international normalized ratio (INR) while taking concurrent warfarin and APAP (7). A topical, non-invasive, low-dose APAP formulation with an analgesic efficacy comparable to iv or oral routes could dispense from the risks, constraints, or delays of bioavailability attached to these pharmaceutical forms. Such an APAP form using the transmucous-buccal route of administration has been recently studied in 2 randomized clinical trials (8) where 125 mg B-APAP was shown to be as analgesic as 1 g iv in healthy volunteers. With one-eighth (125 mg) of the usual dosage of 1 g iv-APAP and with lower plasma concentrations, the analgesic effect of B-APAP was shown to last for at least 90 minutes. However, these trials in healthy volunteers were performed in over-sanitized populations: induced pain is different from a real-life acute pain situation and fails to capture the consequences of pain on motivational/affective domains and psychosocial comorbidities (9). In the context of guidelines recommending lower use of APAP doses and in a translational approach, the analgesic property of 125 mg B-APAP has been assessed in real-life patients. The objective of this present trial is to test the hypothesis of a non-inferior analgesia using 125 mg B-APAP or 1 g iv-APAP, with a double-blind randomized controlled design, in patients admitted to the hospital for acute traumatic pain of mild to moderate intensity. This hypothesis stems from findings of previous clinical trials in healthy volunteers (8).

Methods

Study Design

This randomized non-inferiority double-blind controlled clinical trial included patients admitted to the AE of Clermont-Fd University Hospital, France from 03/05/2012 to 13/05/2013. The study was reviewed and approved by the French Institutional Review Board and by the French Drug Agency. It followed standardized ethical and safety Good Clinical Practice Guidelines and procedures were in accordance with the Helsinki Declaration of 1975 (as revised in 1983). It was declared on clinicaltrials.gov (NCT01586143).

A non-inferiority design was chosen to determine whether analgesia provided by B-APAP is not worse than iv-APAP.

All patients were followed by the same medical team and clinical research assistants. A room in the AE was specifically devoted to the trial. Data were collected on Case Report Forms (CRF). Patients were eligible if they had satisfactory inclusion criteria. They were included after signature of the informed consent if they had trauma of the upper or lower limb with pain intensity between 4 and 6 on a (0 – 10) numeric pain rating scale (NS) (ranging from 0 no pain to 10 worst experienced pain). Exclusion criteria included an age < 18years old, a known hypersensitivity to APAP or alcohol, having taken no analgesic in the 6 hours prior to admission, pain > 6, any previous analgesic consumption, and a suspicion of fracture. A diagnosis of fracture in the course of the trial would lead the patient to stop the trial. Pain at inclusion and all along the trial was evaluated by a clinical research nurse who was only in charge of pain evaluations during the trial.

Interventions and Randomization

Patients were randomized in the B-APAP group (125 mg of APAP dissolved in 1 mL of a hydroalcoholic solution [HAS] and iv saline [0.9%]) or B-Pl group (1 mL HAS transmucous-buccal placebo and 1 g iv-APAP). Randomization was done according to the random sequence generated beforehand with a computer soft-

ware program by a clinical research assistant who was not on site and not involved in the trial. Double-blinding was fully respected. Treatments were prepared in the Central Pharmacy of the University Hospital with double-blinding according to Good Pharmaceutical Practice and numbered containers. A research nurse who did not take part in the care and in any of the pain evaluations of the patients prepared the material and the drugs in a room dedicated to clinical research. Considering that 1 g iv-APAP and 0.9% saline pouches did not look alike, each pouch was completely hidden in a fabric sleeve before coming to the patient's room and the nurse who had prepared the drip stayed near the patient until the end of the injection. All the persons involved in the trial were informed to respect double-blinding. Infusion of iv-APAP or saline lasted 15 minutes and concomitantly, B-APAP or B-Pl was applied in the left mucogingival sulcus. The timer was started at t0 when iv injection by the nurse was concomitant with buccal administration (B-APAP or B-Pl) by the medical doctor in charge of the trial. Double-blinding was also fully respected for B-APAP or B-Pl, both colourless liquids and contained in a small similar vial. Patients were asked not to close the mouth or swallow for 01:30 minutes. The remaining material was then discarded by the nurse in a special envelop and sealed in order to avoid any violation of double-blinding.

The nurse who had assessed pain at inclusion assessed pain regularly 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 60 minutes, 90 minutes, and 120 minutes after drug administration (t5, t10, t15, t20, t30, t40, t60, t90, t120) and reported the results on the CRF. She also asked a questionnaire to evaluate the satisfaction of the patients. After 2 hours of evaluation, patients were then allowed to leave the hospital after a physical examination and prescription unless they needed further management.

The allocation sequence was generated by a clinical research assistant of the Clinical Pharmacology Center, a medical AE registrar enrolled the participants, and a clinical research nurse assigned participants to their group. Participants and persons administering drugs or assessing pain were all blinded to group assignments; the success of blinding was evaluated by asking them if the treatment could be guessed and the results showed that blinding was successful.

APAP Pharmaceutical Form

The patented form of transmucous/buccal APAP (Patent Europe N 07871968.9) consists of APAP in a stable and complete dissolution state in a hydro-alcoholic solution containing 50 wt % of alcohol for a rapid absorption through the mucosa of the oral cavity and/or the oropharynx. Full absorption could give 0.015 g alcohol per liter of blood. Glass vials contained 125 mg/mL. This form has been tested with no adverse events in 2 previous clinical trials (NCT00982215 and NCT01206985) (8).

Outcomes

The primary endpoint was the pain intensity at t30 minutes. Secondary endpoints were pain intensity at other times. Patients had to fill out a questionnaire at t20 minutes when the drip was withdrawn, enquiring about satisfaction with the transmucosal drug (very bad, bad, satisfactory, good, very good) and their preference of iv or buccal administration.

Statistical analysis

According to the literature (10,11), previous works (Clinical trials: NCT00982215, NCT00750048 [8]) and considering this study as a non-inferiority trial, a sample size of n = 18 patients by randomized group was estimated necessary to provide 80% statistical power to objectify that B-APAP has an analgesic effect comparable to iv-APAP (one-sided 2 group Student t-test of equivalence in means). Based on investigator judgment of a likely clinically significant difference in pain intensity, the non-inferiority margin Δ was fixed at 1 (12). Therefore, the standard-deviation of pain intensity was fixed at 1.2 and one-sided type I error alpha level at 0.05. Finally, 40 patients in total were considered.

Statistical analysis was performed using Stata software, version 13 (StataCorp, College Station, TX, US). The tests were 2-sided, with a type I error set at α = 0.05 (except concerning primary outcome). Baseline characteristics are presented for each randomized group (B-APAP group or B-Pl group) as the mean ± standard deviation or the median [interquartile range] according to statistical distribution for continuous data, and as the number of patients and associated percentages for categorical parameters. To assess non-inferiority, one-sided 2 group t-test of equivalence in means with equal variances with a non-inferiority limit difference of 1 was proposed. Results were also expressed using 2-sided 90% confidence interval (IC1-2α). These analyses were conducted using CONSORT guidelines, including recommendations on reporting of non-inferiority randomized trials (13). Comparisons between independent groups were analysed using the

Chi-squared or Fisher's exact test for categorical variables, and by Student's t-test or Mann-Whitney test for other quantitative parameters, with normality verified by the Shapiro-Wilk test and homoscedasticity by the Fisher-Snedecor test. Concerning the analysis of repeated measures (pain intensity), a random-effects model was considered, as it was usually proposed, to study the fixed effects group, time-points, and interaction group x time taking into account between and within subject variability. Finally, a descriptive tolerance analysis was performed considering all recorded side-effects.

Results

Among 43 eligible patients, 40 were randomized and analyzed, as shown in the flow chart (Fig. 1). The age range was 34 ± 13 years, with 29 male (32 ± 13 years) and 11 female patients (37 ± 13 years). Although a specific pharmacogenetics profile linked to APAP (14) was not among the inclusion criteria, a retrospective analysis showed that all patients were Caucasian. All patients were admitted for trauma of the upper or lower limb (Fig. 2), mainly lower limb (78%) with sprains and strains of the ankle (50%). Pain evaluation at

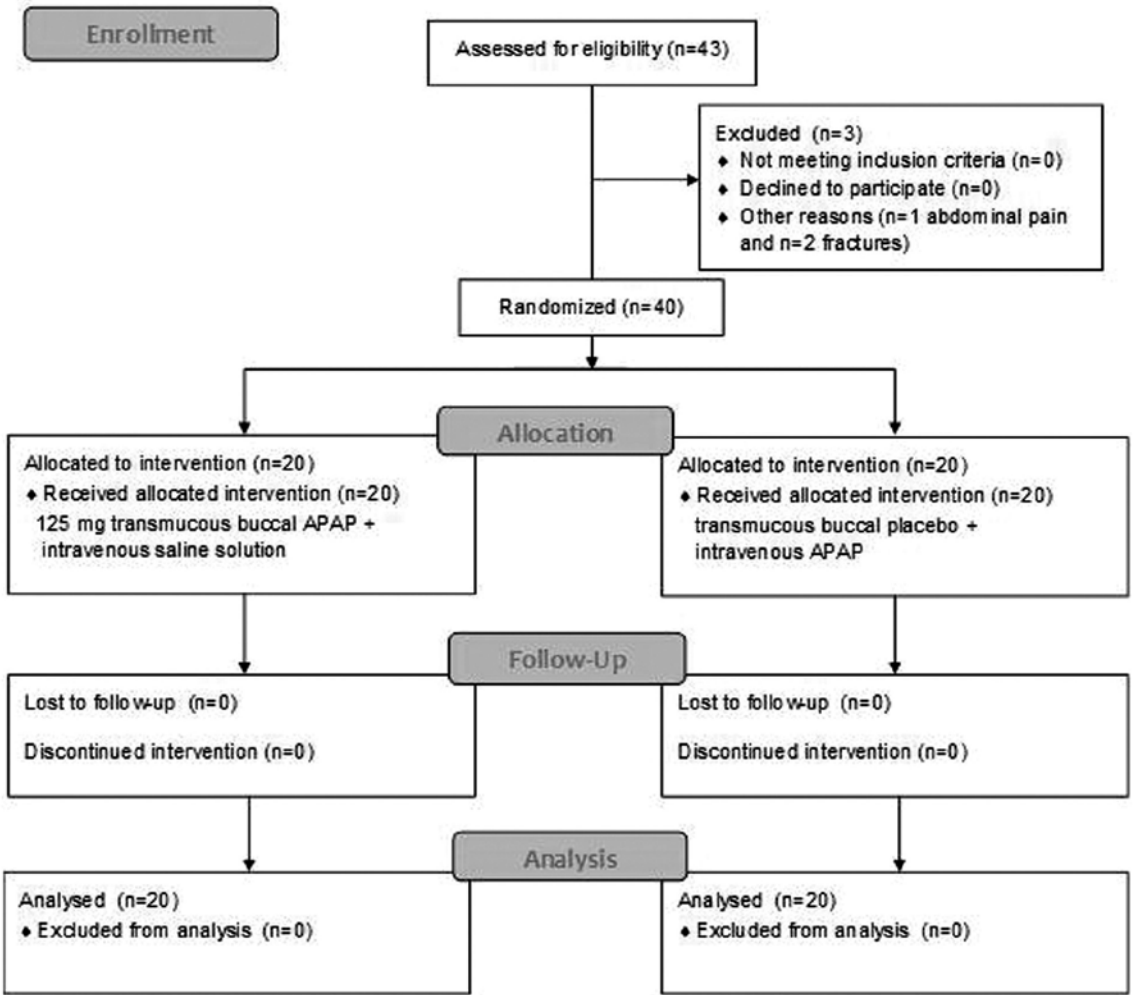

Fig. 1. *Flow chart of the study.*

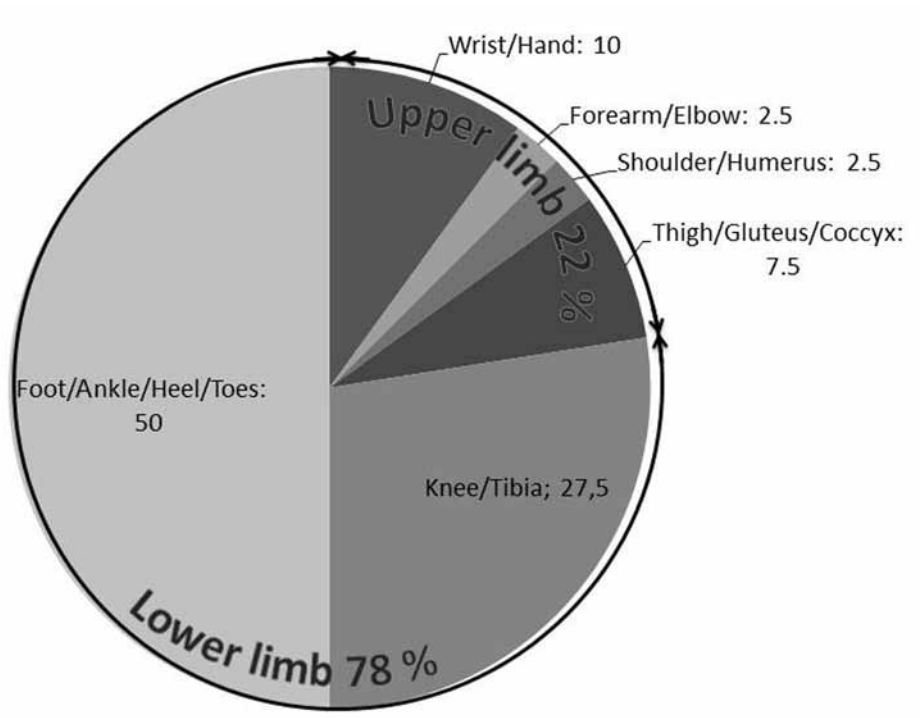

Fig. 2. *Body sites of traumatic acute pain of included patients (% patients).*

admission and inclusion was not significantly different between B-APAP (5.0 ± 0.7) and B-Pl groups (5.05 ± 0.8), and according to guidelines, such pain intensity did not require opiate administration. Pain evaluations along 120 minutes are indicated in Table 1. Pain intensity at t30 minutes of B-APAP and iv-APAP groups were not significantly different (3 ± 1.3 vs 2.7 ± 1.2, $P = 0.23$, one-sided Student t-test). The difference of pain intensity between groups was 0.30 with 2-sided IC90% = [-0.38 – 0.98], not including non-inferiority margin ($\Delta = 1$). Time to exhibit a statistical significance in pain relief from baseline was reached at t10 for B-APAP ($P = 0.03$) and iv-APAP ($P < 0.001$). From t15 and all consecutive times, B-APAP and i-APAP were significantly different from baseline ($P < 0.001$) (Fig. 3). A non-significantly different number of patients reported a diminution at t30 of > 50% of initial pain intensity in B-APAP and iv-APAP (45% vs 55% patients) (Fig. 4) and similar results apply to pain intensity ≥ 3 (35% vs 35%) (Fig. 4). Furthermore, a larger number of patients reported more than 50% pain relief with B-APAP than with iv-APAP at t15 (30% vs 20%) and t20 (40% vs 25%) compared to baseline, while relief with iv-APAP occurred in more patients in the second half of the trial.

Table 1. *Numerical pain ratings along 120 minutes on a 0-10 scale showing a non-significant difference between the pharmaceutical forms.*

	B-APAP	B-pl	*P* Value
Inclusion	5.00 (0.72)	5.05 (0.76)	0.83
T0	5.00 (0.72)	5.15 (0.87)	0.82
T5	4.63 (0.98)	4.58 (1.02)	0.82
T10	4.25 (1.16)	3.90 (1.53)	0.38
T15	3.93 (1.22)	3.48 (1.42)	0.27
T20	3.50 (1.42)	3.13 (1.21)	0.35
T30	3.03 (1.29)	2.73 (1.23)	0.44
T40	2.65 (1.38)	2.35 (1.30)	0.44
T60	2.60 (1.44)	2.48 (1.33)	0.70
T90	2.33 (1.36)	2.30 (1.55)	0.87
T120	2.55 (1.60)	2.013 (1.45)	0.20

The satisfaction questionnaire showed that most patients disliked the taste of both formulations (bad or very bad 90% B-APAP vs 85% B-Pl), but preferred the transmucous-buccal form rather than the iv form (75% vs 25%). No adverse events were observed and tolerance was similarly good in both groups.

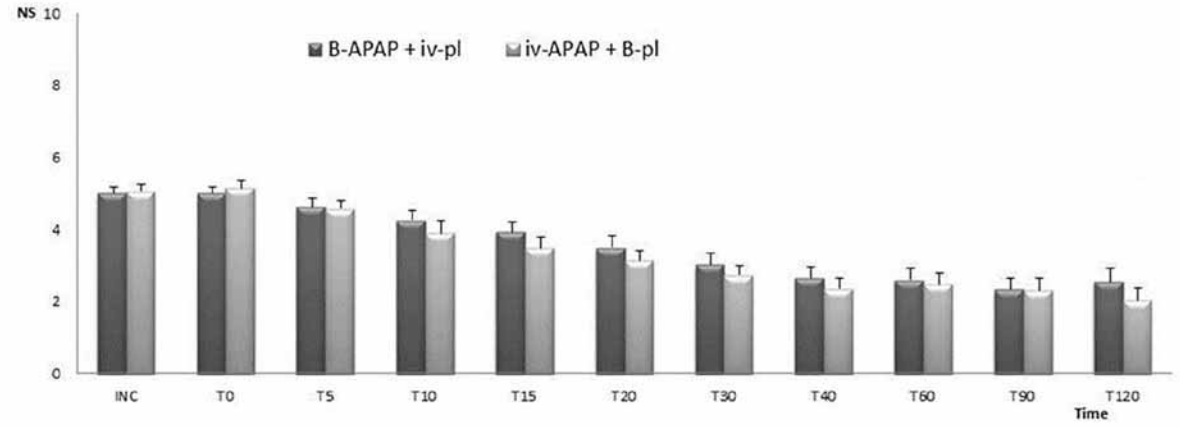

Fig. 3. *Pain intensity evaluated by numeric pain rating scale (NS) showing a non-inferiority analgesia for transmucous buccal APAP (B-APAP) compared to iv-APAP along 120 minutes.*

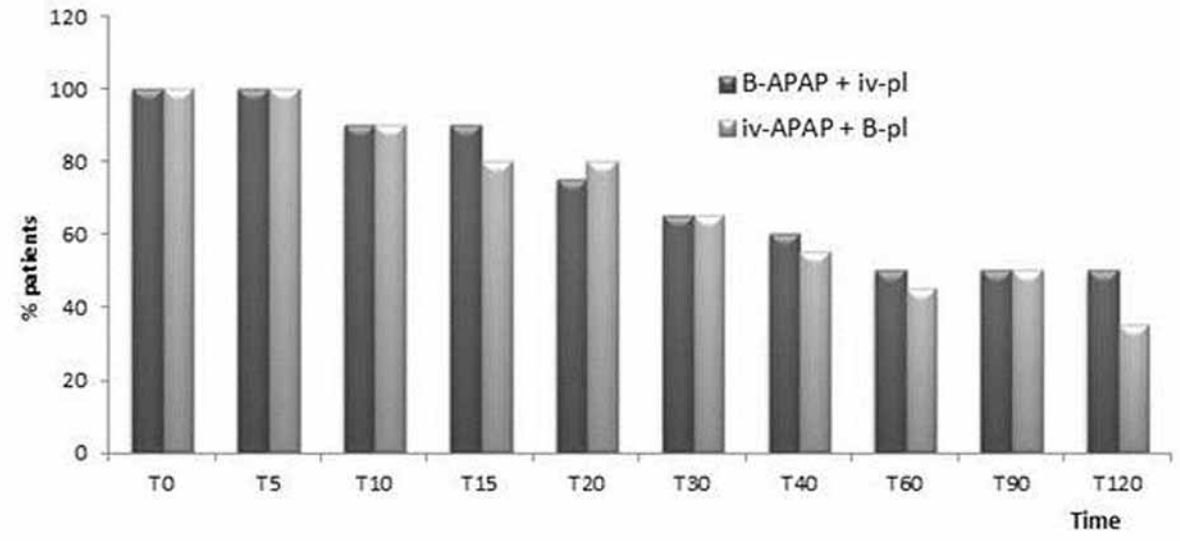

Fig. 4. *Percentage of patients reporting pain intensity ≥3 on a (0-10) numeric pain rating scale for both pharmaceutical forms.*

Discussion

The aim of this study was to confirm in patients previous findings obtained in healthy volunteers where 125 mg B-APAP displayed antinociceptive properties similar to 1 g iv-APAP (8). In 40 patients admitted to the AE with lower or upper limb pain of traumatic origin, the non-inferiority study shows a non-significantly different progressive pain relief along 2 hours for both treatments. Time to significant analgesia occurs 10 minutes after B-APAP or iv-APAP administration and lasts for at least 2 hours. More patients in the B-APAP group report a diminution by half of their initial pain intensity at t15 (30% vs 20%) and t20 (40% vs 25% patients). These results show that B-APAP is analgesic, is not worse than iv-APAP, and confirm that B-APAP may be a valuable alternative to iv-APAP in clinical settings. B-APAP offers a number of advantages compared to iv-APAP that is routinely given in the hospital to patients with moderate pain. With B-APAP, pain improvement

may start slightly earlier than with iv-APAP for a number of patients, and most patients (75%) prefer this non-invasive route of administration, suppressing with this option all the risks and constraints linked to the iv-route. Considering pharmacokinetic aspects, analgesia occurs with lower blood concentrations (8) as the dose is reduced by a factor of 8, a very innovative point in the context of actual guidelines advising to limit APAP consumption.

Although the frequency of administration of B-APAP, the effect of repeated doses, and the relay with other dosages and routes of administration remain to be evaluated, the use of B-APAP may be envisaged to be extended to other populations and situations than AE acute pain patients. Clinicians are indeed missing a fast-acting non-opioid drug for acute pain with a secure tolerance profile, especially in palliative care, geriatrics, and pediatrics. Rapid-onset fentanyl formulations for the management of severe cancer breakthrough pain (15-17) or severe pediatric pain (18) have been developed, but there is today no drug available for mild to moderate pain. One limitation with B-APAP formulation is that it relies on the presence of 1 mL of alcohol, but a number of formulations and over-the-counter medications, especially for acute cough in ambulatory settings, do contain also a small amount of alcohol.

Pharmacologically, these findings challenge a described dose-effect relationship in the analgesia provided by APAP (19) although its effective dose is not well-defined in the literature. A concentration of 10 mcg/mL has been described to be effective but higher or lower concentrations have also been reported (20-24). APAP has also been suggested to be a pro-drug, whose analgesic action would rely, at least in animals, on a metabolite, AM404 (N-(4-hydroxyphenyl)-5Z,8Z,11Z,14Z-eicosatetraenamide), synthetised in the brain from p-aminophenol (produced from APAP by deacetylation in the liver), via the brain enzyme FAAH (fatty acid amide hydrolase) (25). AM404 is a compound able to inhibit the reuptake of anandamide, an endogenous ligand of cannabinoid receptors (CB1 and CB2) located in the central nervous system, suggesting that the mechanism of action of APAP may also involve the endocannabinoid system. NAPQI, the toxic metabolite produced via cytochromes and described in APAP overdose as responsible for hepatic necrosis and hepatic failure, may also have an active role in APAP analgesia (26,27). NAPQI does activate human TRPA1 (transient receptor potential ankyrin 1), a unique sensor of noxious stimuli and as a consequence, reduces voltage-gated calcium and sodium currents in primary sensory neurons (27). The central mechanism of action of APAP has been well demonstrated in humans (28-30) and in animals (31-34). It involves the descending pain modulation pathways, and a number of direct or indirect targets, cyclooxygenases, TRPV1 (transient receptor potential vanilloid 1), serotonin receptors, and calcium channels (35).

In the light of our knowledge on APAP metabolism and analgesic mechanism of action, a number of hypotheses that will need to be tested may be suggested to explain the results obtained with B-APAP (8). These relate on the one hand to the physiology of the buccal mucosa and on the other hand to physicochemical properties of the B-APAP solution. APAP metabolism depends on liver enzymes with deacetylation for the synthesis of p-aminophenol, and cytochromes (those involved in APAP metabolism, CYP1A2, CYP2A6, CYP2D6, CYP2E1, and CYP3A4) but all of these have also been described to be present in the oral mucosa (36,37). An in situ production of APAP metabolites could rapidly reach central targets while bypassing hepatic metabolism in the early minutes of APAP administration.

Physicochemical properties of B-APAP may also play a role in the buccal mucosa and at central level. In the buccal mucosa, the presence of alcohol does enhance the diffusion of lipophilic and small molecular weight APAP by its detersive and vasodilator properties (38,39). The chemical characteristics of the tertiary mixture formed by APAP, water, and alcohol need also to be studied. The solubility of APAP in water is known to be much lower than in alcohol, and alcohol–water binary mixtures are very complex chemical entities. They have been at the heart of constant debate and discussion about hydrophobic interactions (alkyl groups of the alcohol molecules) and the H-bonding interactions (hydroxyl groups of water and alcohol), structural transition in these mixtures, and changes in viscosity (40). The interaction of APAP with water-cage encapsulation and formation of clusters of alcohol molecules, the potential changes of tridimensional APAP size within the mixture need now to be analyzed by spectroscopy (41) and magnetic resonance imaging (42) to evaluate if a change of size could enhance diffusion.

At central level, brain permeation of APAP and its metabolites is limited by the blood-brain barrier (BBB), a physical and biochemical barrier composed of microvascular endothelial cells joined by tight junctions that restrict drug permeability (43). Efflux transporters such as P-glycoprotein (P-gp) further impair brain perme-

ation and a recent animal study showed that a single intra-peritoneal (similar to iv) -APAP dose can lead to transcription of genes and enhance P-gp–mediated transport processes at the BBB one hour and significantly 3 hours after administration in animals (44). Such a transcriptional mechanism may be beneficial to the B-APAP formulation in the context of hydrogen bonding of the APAP, solvent water, and altered carrier- or receptor-mediated transport: these aspects need to be studied specifically using in vitro blood-brain membrane models (45).

Conclusion

Generalization needs to be assessed especially in larger scale studies in vulnerable populations, such as geriatrics, pediatrics, and when swallowing is difficult, and in repeated doses; however, random selection in this trial is an important tenet of external validity.

Taken together, these data indicate that a non-invasive new transmucous-buccal formulation of APAP has analgesic properties comparable to iv-APAP. Such a pharmaceutical form would be useful in emergency situations and breakthrough pain episodes of moderate intensity. It would also diminish APAP consumption per dosage unit, limit the risk of adverse events and toxicity, provide a better comfort for the patient, and would adhere to actual guidelines of APAP prescription.

Author Contributions:

Dr. Pickering had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pickering, Dubray.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Pickering.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Pereira.

Administrative, technical, or material support: Pickering.

Study supervision: Pickering.

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Role of the Sponsors

Unither Laboratories took part in the design of the study but were not involved in the conduct of the study; collection, management, analysis, and interpretation of the data.

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