Relevance of Partial AUC for Locally Applied Oral Products (LAP-Oral)

BIOBRIDGES 2023

DR VIT PERLIK

DR ANURADHA KULASEKARAN

BioBridges 2023, September 21-22, 2023, Prague, CZ

Scope of Presentation

OVERVIEW

- Partial AUC (pAUC) established applicability
- Status core for LAP-Oral
- Relevance of pAUC for LAP-Oral products

EVIDENCE BASE

- Our Approach to Analysis
- Statistical Consideration
- Results
- Evidence based opinion
- Conclusion

Funding: This research was funded by Reckitt Health Ltd, UK.

It was published in Pharmaceutics 2023, 15, 1863.
https://doi.org/10.3390/pharmaceutics15071863

OVERVIEW

Partial AUC (pAUC) Established Applicability

pAUC: time of drug administration until a predetermined time point that is related to a clinically relevant pharmacodynamic (PD) measure

Significant local absorption prior to gastrointestinal absorption of inhaled products[1]

- $pAUC_{0\text{-}30}$ min is a surrogate for efficacy
- $AUC_{0\text{-}t}$ for safety

Early pAUC for single dose prolonged release product[2] & ANDA[3] & Draft ICH M13

- Clinically relevant for exposure-response relationships

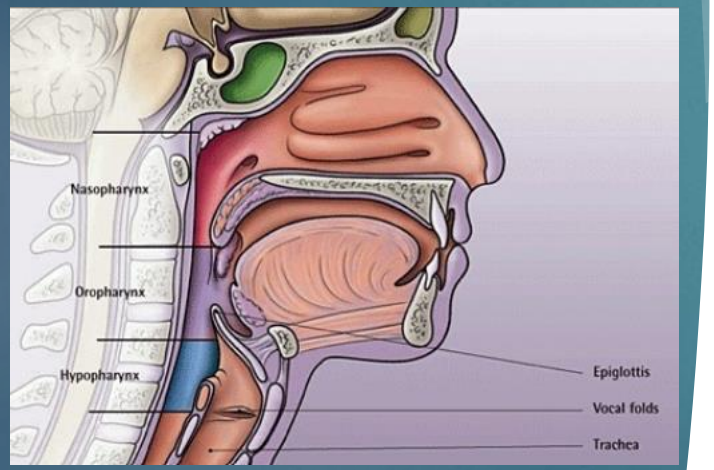
Status core of pAUC for LAP-oral

- No consensus yet

1. Clinical pharmacology and pharmacokinetics: questions and answers | European Medicines Agency (europa.eu):: Evaluation of Orally inhaled Products. 2015
2. Soares, K.C.C.; Chiann, C.; Storpirtis, S. Assessment of the impact of partial area under the curve in a bioavailability/bioequivalence study on generic prolonged-release formulations. Eur. J. Pharm. Sci. 2022, 171, 10
3. Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application | FDA

EVIDENCE BASE

pAUC for LAP-Oral products



Oral drug delivery pharmaceutical forms

- Examples: Lozenges, Sprays, Gels, Granules

NSAIDs (diclofenac and flurbiprofen) at low doses are clinically efficacious in pain relief

Local versus systemic concentration vs effects is incompletely understood

- Substantiated by drug absorption (penetration) of ex-vivo tissue [4,5]
- Evidence of lower plasma to tissue drug concentration ratio [6]
- Clinically higher [7, 5] as well as longer [7] target tissue concentrations [7, 5]

pAUC, a valuable parameter for initial efficacy of low dose flurbiprofen (a LAP-Oral product)

4.Haroutiunian, S.; Drennan, D.A.; Lipman, A.G. Topical NSAID therapy for musculoskeletal pain. Pain Med. 2010, 11, 535–549
5. Kai, S.; Kondo, E.; Kawaguchi, Y.; Kitamura, N.; Yasuda, K. Flurbiprofen concentration in soft tissues is higher after topical application than after oral administration. Br. J. Clin. Pharmacol. 2013, 75, 799–804
6. Hagen, M.; Baker, M. Skin penetration and tissue permeation after topical administration of diclofenac. Curr. Med. Res. Opin. 2017, 33, 1623–1634
7.Efe, T.; Sagnak, E.; Roessler, P.P.; Getgood, A.; Patzer, T.; Fuchs-Winkelmann, S.; Peterlein, C.D.; Schofer, M.D. Penetration of topical diclofenac sodium 4% spray gel into the synovial tissue and synovial fluid of the knee: A randomised clinical trial. Knee Surg. Sports Traumatol. Arthrosc. 2014, 22, 345–350

PAPER DESCRIPTION

pharmaceutics

MDPI

Article

Relationship between Pharmacokinetic Profile and Clinical Efficacy Data of Three Different Forms of Locally Applied Flurbiprofen in the Mouth/Throat

Vit Perlik [1], Anuradha Kulasekaran [2,*], Graça Coutinho [2], Martin Votava [3] and Jean-Michel Cardot [4]

[1] Institute of Pharmacology, First Faculty of Medicine, Charles University, Albertov 4, 12800 Prague, Czech Republic; vitperlik@gmail.com
[2] Reckitt Healthcare Limited, 103-105 Bath Road, Slough, Berkshire SL1 3UH, UK; graca.coutinho@reckitt.com
[3] Cadore INV Scientific Consultant, Akademicka 1, 10800 Prague, Czech Republic; martin.votava@cadoreinv.com
[4] SAS BORVO Consultant, 18 Av de Charade, 63122 Ceyrat, France; j-m.cardot@orange.fr
* Correspondence: anuradha.kulasekaran@reckitt.com

Abstract: This study aimed to link pharmacokinetic (PK) data from different flurbiprofen preparations for the treatment of sore throat with published data to elucidate whether early efficacy is due to the local action of flurbiprofen or a systemic effect after absorption of the swallowed drug. Three comparative bioavailability studies conducted in healthy subjects provided data from flurbiprofen 8.75 mg formulations, including spray solution, spray gel, lozenges, and granules. A parallel interstudy comparison was made of PK parameters, including partial AUCs (pAUCs), using an ANOVA model with the calculation of 90% confidence intervals (CI) for the differences between least squares (LS) means for each of the test groups versus the respective reference groups. All three studies showed bioequivalence for the respective product comparisons. The interstudy comparison showed a slower rate of absorption for granules compared to spray solution (reference) based on T_{max}, C_{max}, and pAUCs for 1 h and 2 h. When $AUC_{0.25h}$ and $AUC_{0.5h}$ were considered, slower rates of absorption were also seen for lozenges and spray gel. The differences correlated with the reported time of onset of action, which is faster for the spray solution (20 min) compared to lozenges (26 min) and granules (30 min). These pAUCs provide useful data that allow for the discrimination between formulations. Moreover, the pAUC values represent <5% of the total AUC, suggesting that the early onset of pain relief is a response to immediate local absorption at the site of action rather than a systemic effect.

Keywords: locally applied locally acting; LALA; GIT; lozenge; throat; flurbiprofen; pharmacokinetics; pharmacodynamic

check for updates

Citation: Perlik, V.; Kulasekaran, A.; Coutinho, G.; Votava, M.; Cardot, J.-M. Relationship between Pharmacokinetic Profile and Clinical Efficacy Data of Three Different Forms of Locally Applied Flurbiprofen in the Mouth/Throat. *Pharmaceutics* **2023**, *15*, 1863. https://doi.org/10.3390/pharmaceutics15071863

Academic Editor: Paulo Paixão

Received: 8 May 2023
Revised: 16 June 2023
Accepted: 16 June 2023
Published: 1 July 2023

1. Introduction

The main objective of developing locally applied products, including non-steroidal anti-inflammatory drugs (NSAIDs), is to ensure that they are delivered locally and exert their effect only at the locally affected site, with any systemic effects being considered undesirable [1,2]. The site-specific absorption of locally applied NSAIDs has been achieved through targeted delivery using various pharmaceutical forms with evidence of local tissue concentration [3,4]. This maximises the local effect of NSAIDs at the site of inflammation while reducing the dose administered to the patient in order to limit systemic exposure and thus potential adverse effects [5,6]. The concept of local delivery of a low dose of the drug for localised effect has been applied successfully to several NSAIDs [7], with efficacy having been demonstrated despite much lower systemic exposure compared with oral administration.

Our Approach – Choice of Studies

Study EudraCT 2018-003175-36 : Two flurbiprofen viscous spray gel formulations compared to a reference spray solution (non-viscous)

Study EudraCT 2011-003332-31: Two flurbiprofen spray solutions compared to a reference lozenge

Study EudraCT 2008-005177-34: Flurbiprofen granules or a lozenge formulation

Journal of Pain Research
Dovepress
open access to scientific and medical research
Open Access Full Text Article
REVIEW

Locally Delivered Flurbiprofen 8.75 mg for Treatment and Prevention of Sore Throat: A Narrative Review of Clinical Studies

This article was published in the following Dove Press journal:
Journal of Pain Research

Ferdinandus de Looze[1]
Adrian Shephard[2]
Adam B Smith[3]

[1]Data Health Australia Pty Ltd (AusTrials), Sherwood, QLD 4075, Australia; [2]Category Development Organisation, Reckitt Benckiser Healthcare Ltd, Slough, Berkshire SL1 3UH, UK; [3]Evidence Generation and Clinical Research, Reckitt Benckiser Healthcare Ltd, Hull, HU8 7DS, UK

Background: Antibiotics are inappropriately prescribed to many people with sore throat. As most cases of sore throat are viral and/or self-limiting, guidelines recommend symptomatic management as first-line treatment. This paper reviews the available clinical evidence for the efficacy and safety of low-dose (8.75 mg) flurbiprofen, locally delivered to the throat for the symptomatic management of pharyngitis/sore throat.

Method: A literature search was performed on 27 February 2019 using PubMed. Studies that met the following criteria were included in a narrative review: (1) studies evaluating the effectiveness of flurbiprofen for pharyngitis/sore throat; (2) randomized controlled studies; (3) locally administered formulation of study drug/comparator; and (4) flurbiprofen administered at 8.75 mg dose (single- or multiple-dose administration).

Results: A total of 17 papers were included in the review: 15 publications reporting data from nine unique clinical studies of flurbiprofen for acute pharyngitis, and two reporting studies of flurbiprofen for the prevention of postoperative sore throat (POST). Studies in acute pharyngitis demonstrated that single- and multiple-dose flurbiprofen 8.75 mg, locally administered in lozenge, spray or microgranule form, was well tolerated and provided early onset and long-lasting symptomatic relief from throat pain and soreness, sensation of swollen throat, difficulty swallowing, and other associated symptoms. This included patients with more severe symptoms, patients with confirmed *Streptococcus* A/C sore throat, and patients taking concomitant antibiotics. In addition, a single preoperative dose of flurbiprofen lozenge was shown to be effective for relieving early POST in patients undergoing general anesthesia.

Conclusion: Locally administered, low-dose flurbiprofen offers a useful first-line treatment option for symptomatic relief in patients with "uncomplicated" acute pharyngitis/sore throat associated with upper respiratory tract infection, thus potentially helping to reduce unnecessary antibiotic prescribing. It also offers an effective preoperative treatment option for the reduction of early POST severity and incidence.

Keywords: flurbiprofen, pharyngitis, sore throat, lozenge, spray, pain relief

Introduction

Pharyngitis is one of the most common reasons patients seek advice from a healthcare provider (HCP) in primary care.[1] Although not life-threatening, pharyngitis, particularly symptoms such as sore throat, can have a substantial negative impact on an individual's daily life.[2] Relief from the severe symptoms of pharyngitis are a key driver of patients' consultations with HCPs, and of antibiotic-seeking behavior,[3,4] with complaints of sore throat constituting between 1% and 4% of all primary care

Correspondence: Adrian Shephard
Reckitt Benckiser Healthcare Ltd, Turner House, 103–105 Bath Road, Slough, Berkshire SL1 3UH, UK
Tel +44 1753 217 800
Email adrian.shephard@rb.com

submit your manuscript | www.dovepress.com
DovePress
https://doi.org/10.2147/JPR.S221706

Our Approach to Analysis

PK studies

- Partial AUC (pAUC) established applicability
- Sampling at least every 5 min for the first 15 min, further sampling at 30 min
- Adequate sampling prior to and around the C_{max} then up to 720 min for full plasma concentrations profile
- Plasma concentrations from all studies combined into one database, pAUCs were calculated using the linear trapezoidal rule to reflect rate of absorption
- pAUCs up to 30 min - tool to separate local absorption from systemic absorption of swallowed drugs

Clinical efficacy studies

- Time to clinically meaningful pain relief (onset of action)[8]

8. de Looze, F.; Shephard, A.; Smith, A.B. Locally Delivered Flurbiprofen 8.75 mg for Treatment and Prevention of Sore Throat: A Narrative Review of Clinical Studies. J. Pain Res. 2019, 12, 3477–3509

Statistical Considerations

- ANOVA model (separate for each product) fitted to ln transformed $AUC_{0\text{-}t}$, C_{max}, and $AUC_{0\text{-}inf}$
  - Fixed terms: treatment, period, sequence, and subject nested within sequence
- Parallel interstudy comparison based on the same ANOVA model
  - Fixed terms for treatment
- 90% CI for the differences between least square means for each of the test groups vs reference group calculated
- Reference scaling used to take potential study design differences into account
- Linear regressions used to compare behavior of respective formulations
  - Reference scaled early pAUCs (0-15 and 0-30 min) and
  - Time to clinically meaningful pain relief (onset of action)

Results – Parallel Comparison

Variable	Test Product (8.75 mg)	Ratio vs. Reference Value %	90% CI	*p* Value
$Ln(C_{max})$	Lozenges	98.91	86.78–112.75	0.89
	Granules	86.31	75.72–98.39	0.06
	Spray gel A	91.69	80.44–104.51	0.87
	Spray gel B	89.41	78.44–101.92	0.93
$Ln(AUC_{0-t})$	Lozenges	101.61	89.71–115.10	0.83
	Granules	96.48	85.18–109.28	0.63
	Spray gel A	97.33	85.93–110.25	0.81
	Spray gel B	93.06	82.16–105.40	0.89

- Bioequivalence of tested formulations and reference with respect to extent of absorption (AUC_{0-t})
- Possible differences for rate of absorption (C_{max})
- Slower rise in plasma for granules when compared to spray solution
- Consistent with cross-over data from individual studies

9. Perlik, V.; Kulasekaran, A.; Coutinho, G.; Votava, M.; Cardot, J.-M. Relationship between Pharmacokinetic Profile and Clinical Efficacy Data of Three Different Forms of Locally Applied Flurbiprofen in the Mouth/Throat. Pharmaceutics 2023, 15, 1863. https://doi.org/10.3390/ pharmaceutics15071863

Results - pAUCs

Variable	Test Product 8.75 mg	Ratio vs. Reference Value %	90% CI	*p* Value
$Ln(AUC_{2h})$	Lozenges	98.95	87.66–111.69	0.89
	Granules	83.25	73.76–93.97	0.01
	Spray gel A	92.12	81.61–103.98	0.87
	Spray gel B	88.55	78.46–99.95	0.87
$Ln(AUC_{1h})$	Lozenges	93.83	80.58–109.26	0.49
	Granules	65.49	56.24–76.26	>0.001
	Spray gel A	84.12	72.24–97.96	0.42
	Spray gel B	85,54	73.45–99.61	0.85

Variable	Test Product 8.75 mg	Ratio vs. Reference Value %	90% CI	*p* Value
$Ln(AUC_{0.25h})$	Lozenges	59.86	43.99–81.47	0.01
	Granules	25.65	18.85–34.91	>0.001
	Spray gel A	65.18	47.89–88.70	0.002
	Spray gel B	73.60	54.08–100.17	0.86
$Ln(AUC_{0.5h})$	Lozenges	82.40	66.81–101,63	0.13
	Granules	46.52	37.72–57.38	>0.001
	Spray gel A	73.27	59.40–90.36	0.08
	Spray gel B	79.88	64.77–98.52	0.85

- Statistically significant difference between granules formulation and spray solution for all pAUCs
- $pAUC_{1h}$ and $pAUC_{2h}$ do not differentiate lozenges from spray solution formulation
- Difference between lozenges and spray solution at $AUC_{0.25h}$ with similar trend for $AUC_{0.5h}$
- pAUCs indicate more clearly PK differences between formulations

9. Perlik, V.; Kulasekaran, A.; Coutinho, G.; Votava, M.; Cardot, J.-M. Relationship between Pharmacokinetic Profile and Clinical Efficacy Data of Three Different Forms of Locally Applied Flurbiprofen in the Mouth/Throat. Pharmaceutics 2023, 15, 1863. https://doi.org/10.3390/ pharmaceutics15071863

Results – Clinical Relevance

Variable	Test Product 8.75 mg	pAUC Mean (ng*h/mL)	Onset of Action (min)	Correlation Coefficient
$Ln(AUC_{0.25h})$	Flurbiprofen spray solution	84.6799375	20	0.99993962
	Flurbiprofen lozenges	48.1690717	26	
	Flurbiprofen granules	24.5129494	30	
$Ln(AUC_{0.5h})$	Flurbiprofen spray solution	301.695563	20	0.94568955
	Flurbiprofen lozenges	242.743302	26	
	Flurbiprofen granules	152.584266	30	

- Linear correlation between pAUC and onset of action demonstrated
- Link between the extent of absorption of flurbiprofen in the first 15–30 min and the time of onset of action (pain relief) established

9. Perlik, V.; Kulasekaran, A.; Coutinho, G.; Votava, M.; Cardot, J.-M. Relationship between Pharmacokinetic Profile and Clinical Efficacy Data of Three Different Forms of Locally Applied Flurbiprofen in the Mouth/Throat. Pharmaceutics 2023, 15, 1863. https://doi.org/10.3390/ pharmaceutics15071863

Conclusion

- PK data for LAP-oral flurbiprofen demonstrated similarity for AUCt based on "conventional" BE criteria (80–125 %) and marginal differences for Cmax (spray solution, spray, lozenges and granules)
- Different time to onset of action for respective formulations (spray – lozenges – granules)
- Significant PK differences demonstrated based on $pAUC_{0.25h}$ and $pAUC_{0.5h}$ surrogate of local absorption among formulations
  - Whereas $pAUC_{1h}$ and $pAUC_{2h}$ not sensitive enough for onset
- Strong correlation between the onset of action and $pAUC_{0.25h}$ and $pAUC_{0.5h}$

Evidence-Based Opinion

- pAUCs provide useful data that allow discrimination between flurbiprofen formulations
- Moreover, these data are clinically relevant based on parallel interstudy comparison
- Early pAUCs as a surrogate for comparison of early pain relief in LAP
- Use of pAUCs in line with:
  - EMA OIP, MR and LALA, M13 (early onset of action if clinically relevant)
  - FDA recommendations for pAUCs based on clinical relevance

Thank You for Your Attention

Acknowledgments Paper

- Anuradha Kulasekaran
- Graça Coutinho
- Martin Votava
- Jean-Michel Cardot

- Reckitt for funding this research

Acknowledgments Colleagues

- My colleagues from Synavia
- Prof. Ondrej Slanar
- Institute of Pharmacology, First Faculty of Medicine, Charles University

vitperlik@gmail.com