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Alternative Routes of Opioid Administration

Mark Watling
Archimedes Pharma Ltd

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SOCIETÀ ITALIANA DI CURE PALLIATIVE SICP ONLUS

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Alternative Routes of Opioid Administration

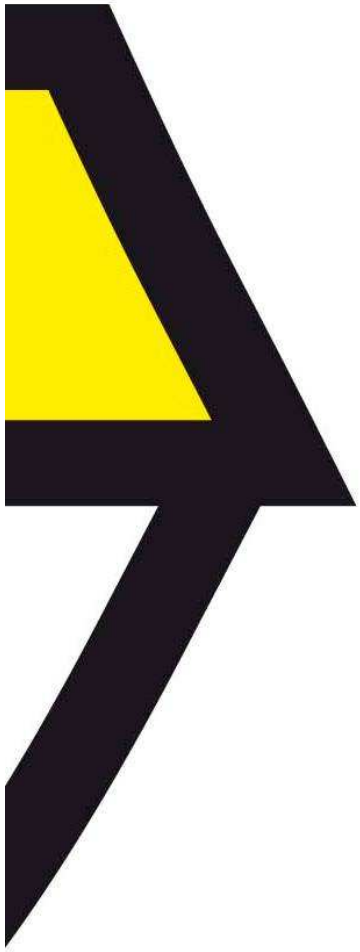
- Which opioids…?
- Which routes of administration…?
- Factors influencing choice of opioid and route
- What can novel routes offer...?
- Intranasal administration as an example

Which Opioids...?

- Although various types of opioid are in clinical use
  - Mixed μ-agonist/antagonists (*e.g.*, butorphanol)
  - Partial μ-agonists (*e.g.*, buprenorphine)
  - Weak μ-agonists (*e.g.*, codeine, hydrocodone, propoxyphene)
  - Potent μ-agonists (*e.g.*, morphine, methadone, oxycodone, hydromorphone, fentanyl, sufentanil)

  …only the latter are widely used in palliative care in situations where unmet clinical need calls for the investigation of new routes of delivery

Alternative Routes of Opioid Administration

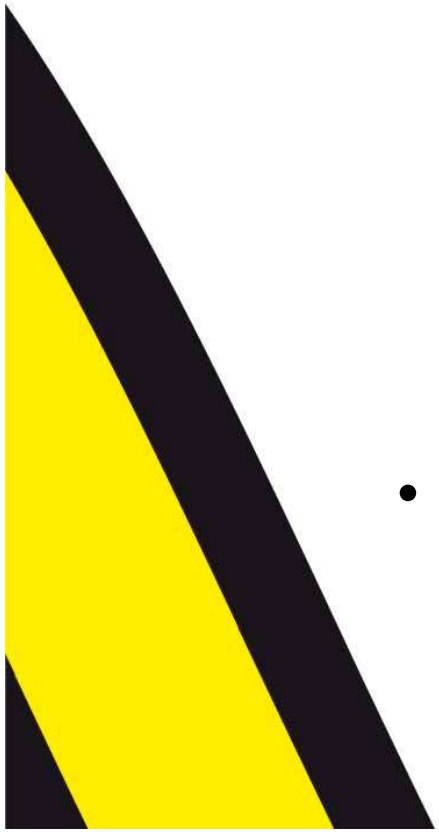


- Many routes of administration for potent opioids have been in use for a long time, and are widely accepted as ‘established’[1]
  - Oral
  - Intravenous
  - Subcutaneous
  - Intramuscular
  - Rectal
  - Intraspinal / epidural
  - Transdermal patch
- This presentation will explore more recent, novel routes – with particular focus on the intranasal route

1. Alexander-Williams JM & Rowbotham DJ. *Br J Anaesth* 1998; **81:** 3 – 7

Novel Routes of Opioid Administration

- Novel routes of administration that have been explored include
  - Oral Transmucosal
  - Sublingual
  - Intranasal
  - Inhaled
  - Iontophoretic Transdermal
  - Metered Dose Transdermal Spray
- But what are they trying to achieve…?



Factors Influencing Choice of Opioid and Route

- The patient's pain:
  - Severity
  - Duration
  - Speed of onset
  - Opioid responsiveness

- The patient's circumstances:
  - Side effect experience / prior opioid exposure
  - Ease of administration / Level of clinical support
  - Patient preference

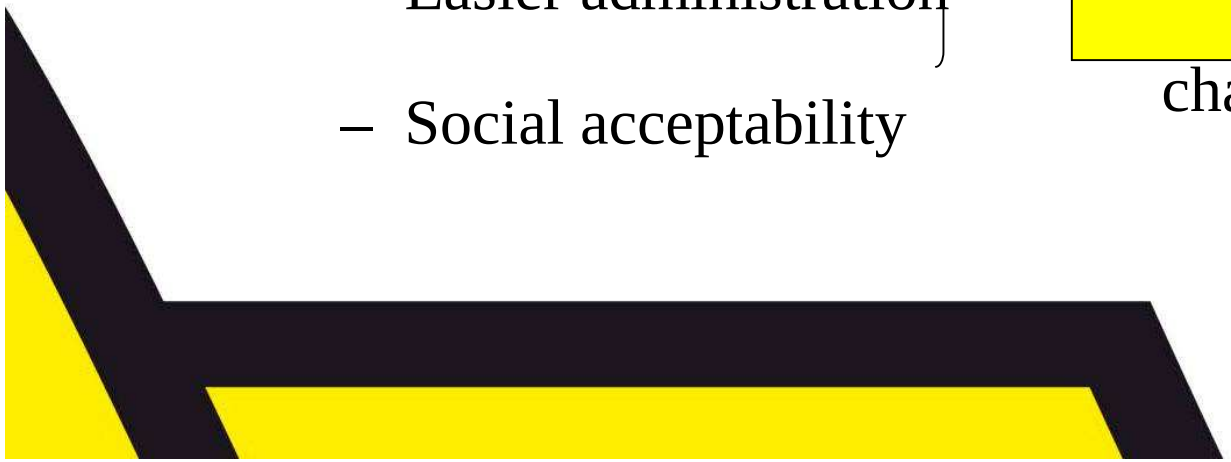
What Can Novel Routes Offer...?

- The principal ambitions for novel routes are to provide:
  - Appropriate onset and duration
  - Better side effect experience

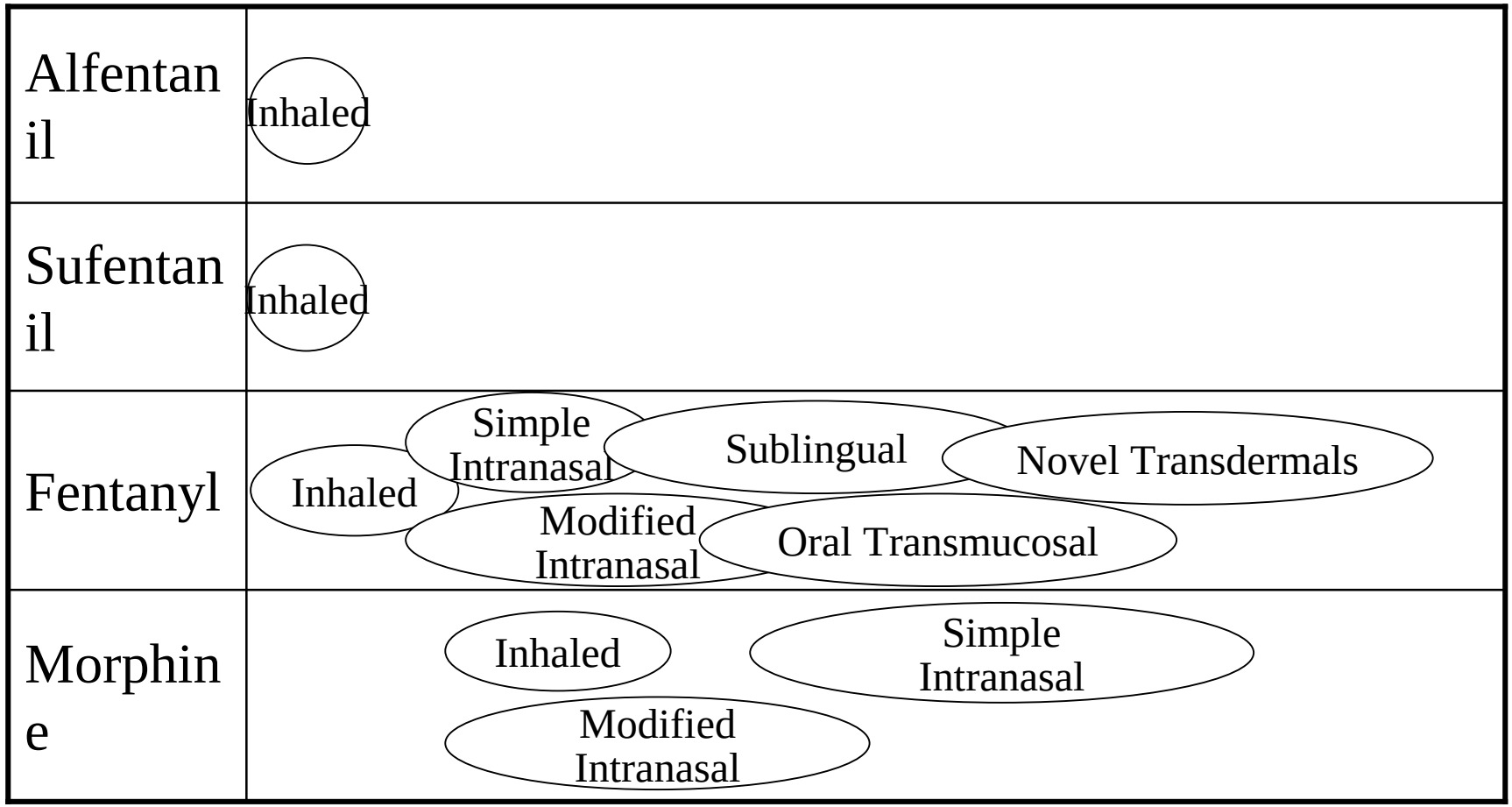
  } + = A better match to pain characteristics

  - Easier administration
  - Social acceptability

  } + = A better match to patient characteristics

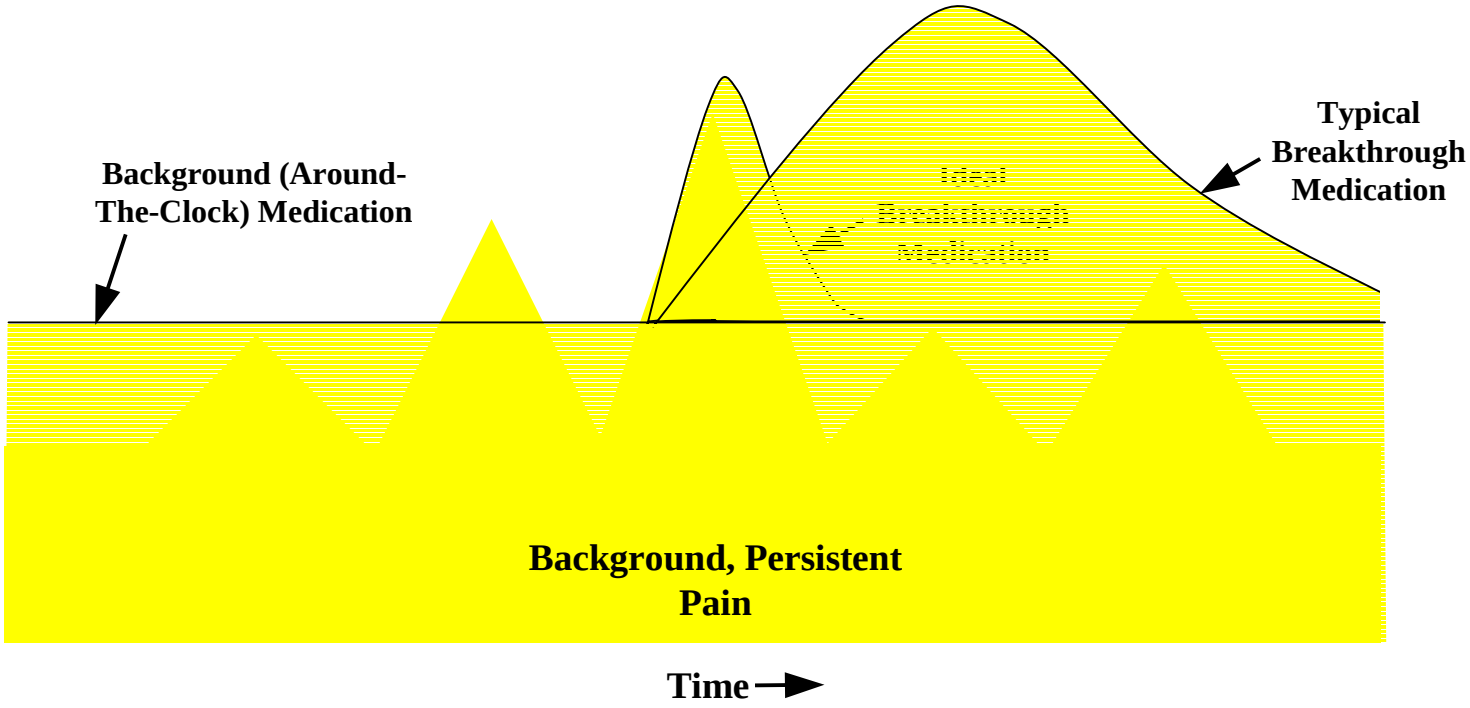


Which Novel Route and Which Opioid...?



Breakthrough Cancer Pain

Transient exacerbation or recurrence of pain in someone who has mainly stable or adequately relieved background pain [1]

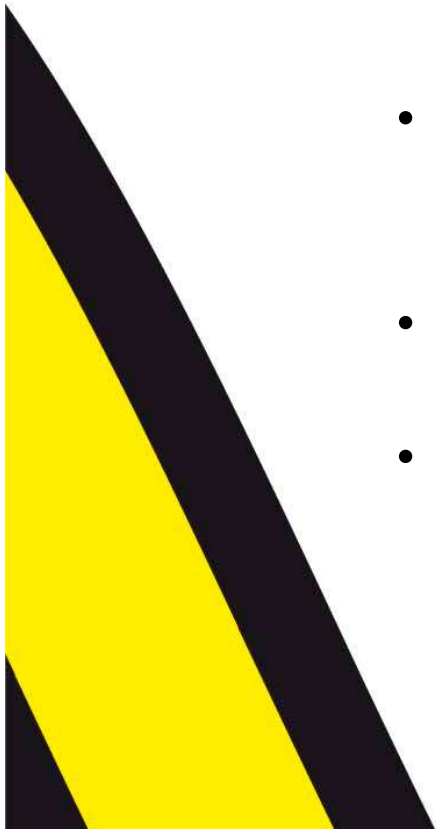


1. Portenoy RK & Hagen NA, 1990; *Pain* **41**: 273 – 281

So Why Use Nasal Delivery…?

Positives

- Nasal mucosa has large surface area for absorption that is highly permeable, highly vascularised
- Drugs absorbed avoid first pass metabolism to increase bioavailability
- High patient acceptability / familiarity
- For some drugs, bioavailability and onset of effect can approach those of intravenous injection



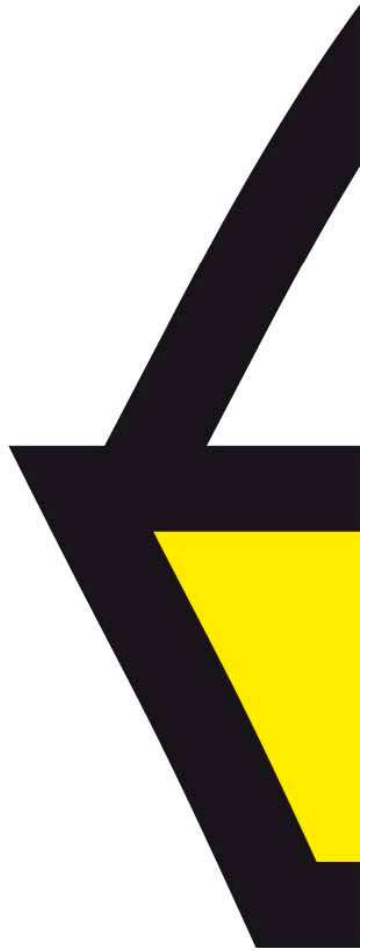
…and Why Not Use Nasal Delivery?

Negatives

- Many drugs are
  - Hydrophilic (*e.g.*, morphine)
  - Have poor solubility (*e.g.*, chlorpromazine)
  - Very large (*e.g.*, proteins / vaccines)
- Limited volume capacity of the nasal cavity restricts dose volume – ruling out low potency drugs
- Powder formulations may present dose flexibility problems
- Liquid formulations may present ‘run-off’ problems

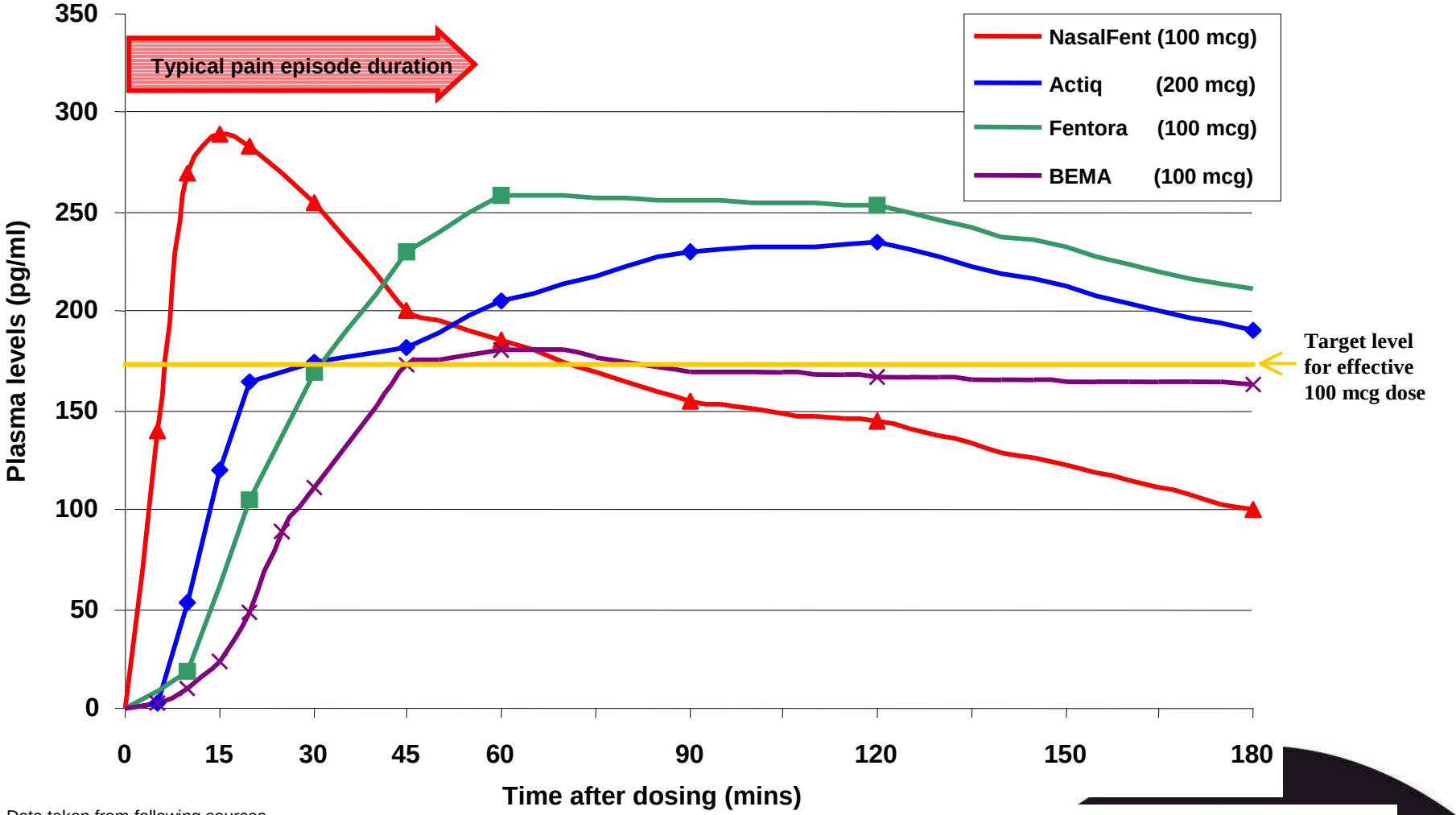
Opioids by the Intranasal Route

- Numerous opioids have been tried intranasally
  - Morphine [1]
  - Diamorphine [2]
  - Oxycodone [3]
  - Hydromorphone [4]
  - Fentanyl [1]
  - Sufentanil [5]
  - Alfentanil [6]
- Various small pilot studies have been published suggesting that the lipophilic drugs such as fentanyl and sufentanil can deliver a rapid onset of action



1. Archimedes Pharma Ltd – Data on File
2. Wilson JA, *et al*. *J Acc Emerg Med* 1997; **14:** 70 – 72
3. Takala A, *et al*. *Acta Anaesth Scand* 1997; **41:** 309 – 312
4. Lacouture P. Poster #240, *American Pain Society*; May 2008
5. Haynes G, *et al*. *Can J Anaesth* 1993; **40:** 286
6. Schwagmeier R, *et al*. *J Clin Anaesth* 1995; **7:** 109 – 113

Nasal Fentanyl: Delivering a Promising Pharmacokinetic Profile

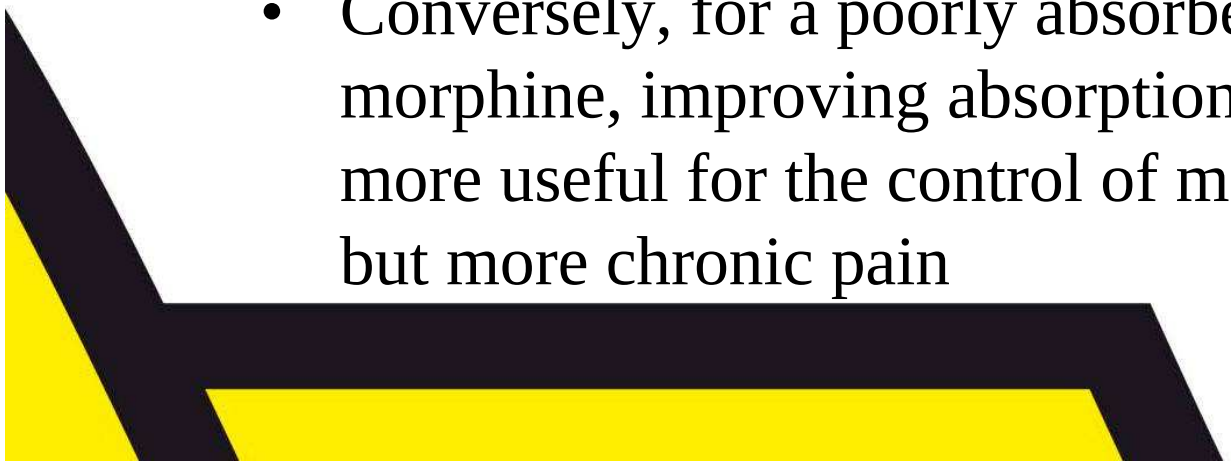


Data taken from following sources
Actiq and NasalFent from ArchimedesPharma Ltd Study CP037/02
Fentora calculated from Darwish, 2006
BEMA calculated from Vasisht, 2008

Note: Data not taken from a direct head-to-head comparison

Modifying Formulations Offer Great Potential

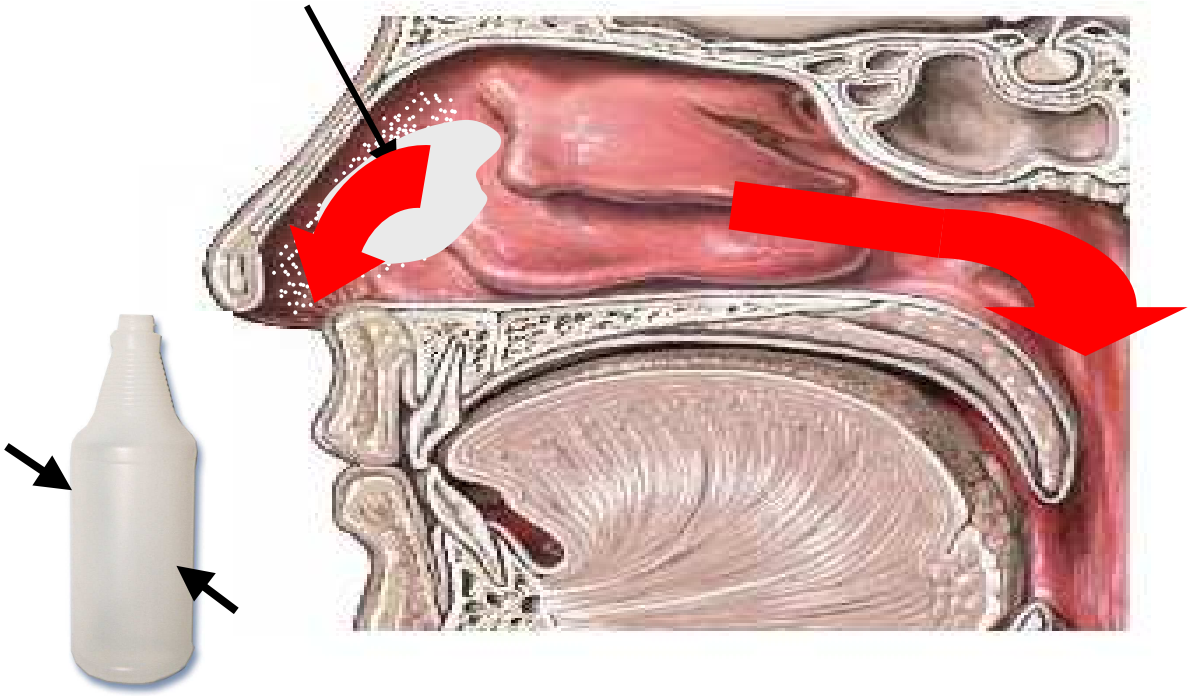
- The idea of using delivery-modifying formulations to optimise intranasal opioids is not new
- For a rapidly absorbed drug such as fentanyl, modulating absorption may better match the time course of the ‘typical’ breakthrough pain episode
- Conversely, for a poorly absorbed drug like morphine, improving absorption may make it more useful for the control of more predictable, but more chronic pain



Archimedes' PecSys® formulation

2. The spray forms a thin layer of gel on contacting the nasal lining

3. This both controls and prolongs the release of fentanyl into the circulation



1. When administered, the fine spray settles on the nasal lining

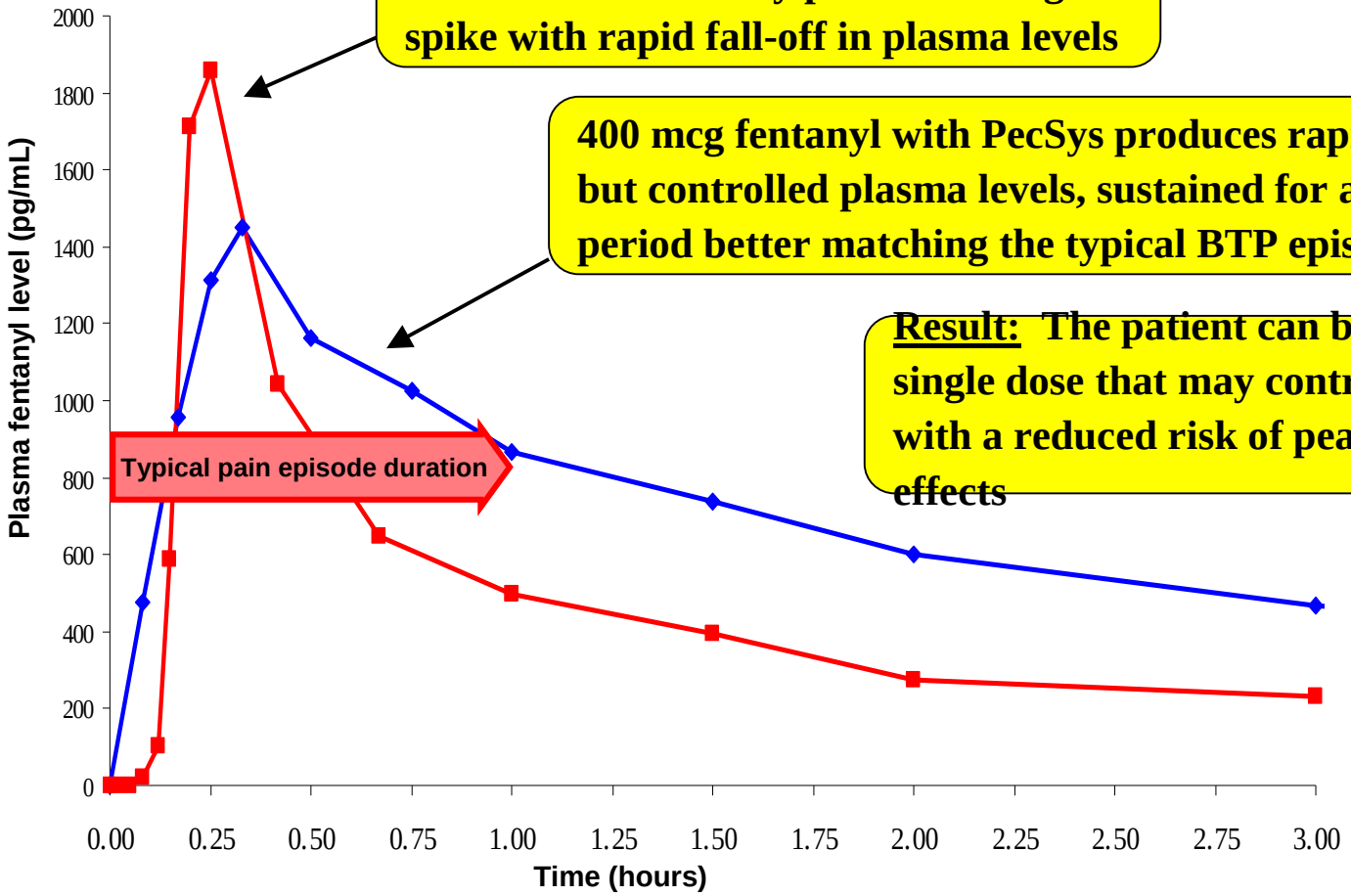
4. The gel also prevents 'run-off' and dripping of the formulation

Archimedes' PecSys® Formulation: Optimising the delivery of fentanyl

200 mcg of a simple fentanyl solution delivered intranasally produces a high spike with rapid fall-off in plasma levels

400 mcg fentanyl with PecSys produces rapid but controlled plasma levels, sustained for a period better matching the typical BTP episode

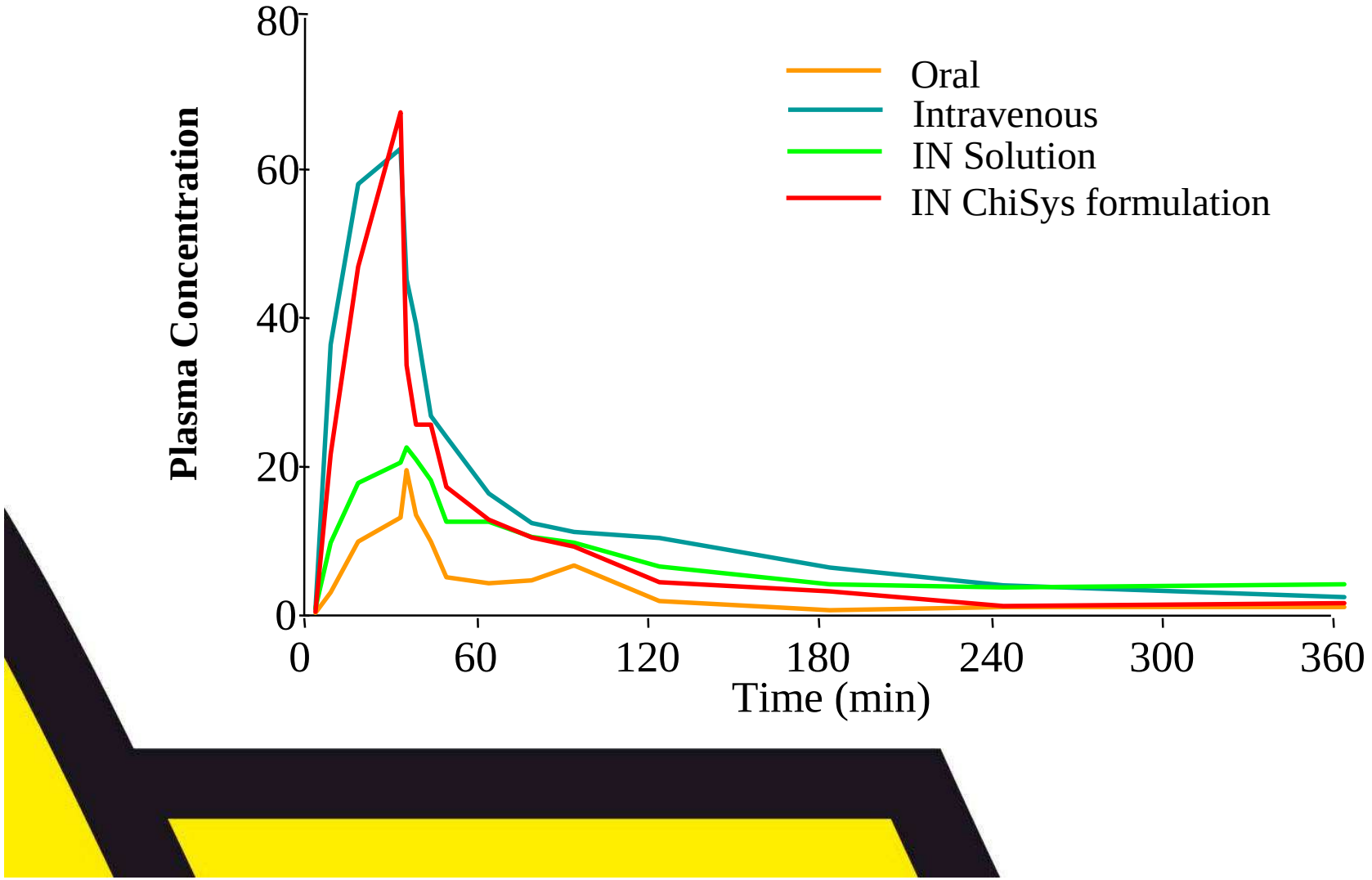
<u>Result:</u> The patient can be titrated to a single dose that may control their pain with a reduced risk of peak-related side effects



1. Archimedes Pharma Ltd, NasalFent Study CP042/04
2. Nycomed Patent WO/02/09707, 2002

Archimedes' ChiSys®: Improving bioavailability

Oral *vs* Nasal vs Intravenous Morphine Formulations



What about Other Nasal Pathology…?

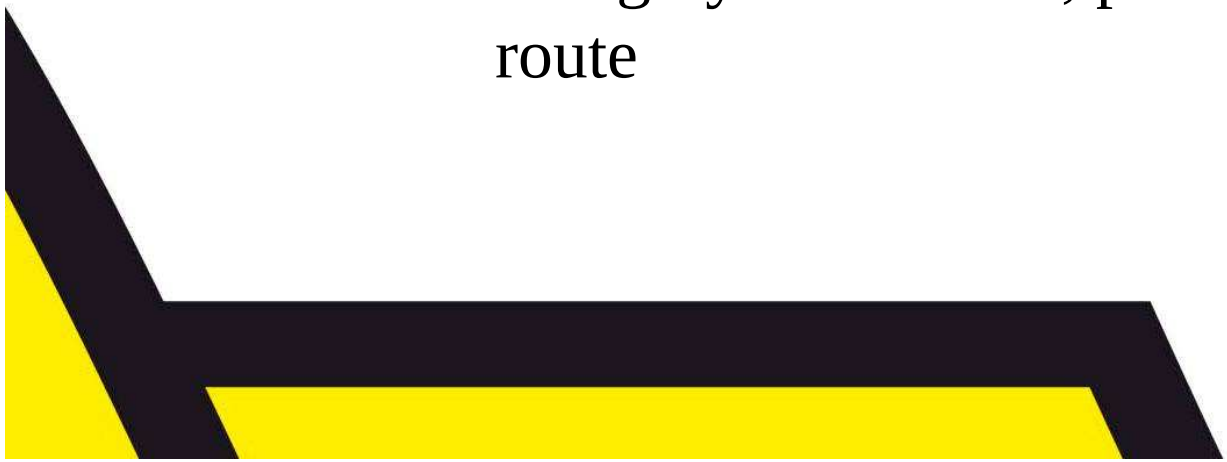
- Can the presence of nasal pathology such as rhinitis (coryzal or allergic) affect absorption or tolerability?
- Studies with other classes of drugs have revealed no consistent adverse effects of concomitant rhinitis [1,2]
- A study of nasal fentanyl with Pecsys in patients with acute allergic rhinitis revealed no clinically significant effect on pharmacokinetic profile or tolerability [3]

1. Argenti D, *et al. J Clin Pharmacol* 1994; **34:** 854 – 858
2. Larsen C, *et al. Eur J Clin Pharmacol* 1987; **33:** 155 – 159
3. Archimedes Pharma Ltd, NasalFent Study GP048/07

Conclusion: This does not appear to be a problem

The Intranasal Route: Promising Better Delivery of Opioids

- The intranasal route promises to provide a better route of administration for opioids
- This promise addresses both principal areas of clinical need:
  - Targeted, consistent delivery of pain relief
  - A highly convenient, patient-acceptable route



Thank you!

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