Current approaches for diagnosing and managing breakthrough pain

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Physiopathology of breakthrough pain

Classification	Tissue damage	Semantic descriptors	Proposed treatment
Somatic nociceptive	Body tissues	Aching Throbbing Stabbing	Opioids
Visceral nociceptive	Organs	Deep Dull Aching	Opioids
Neuropathic	Nervous system	Burning Tingling Lancinating	Adjuvant analgesia

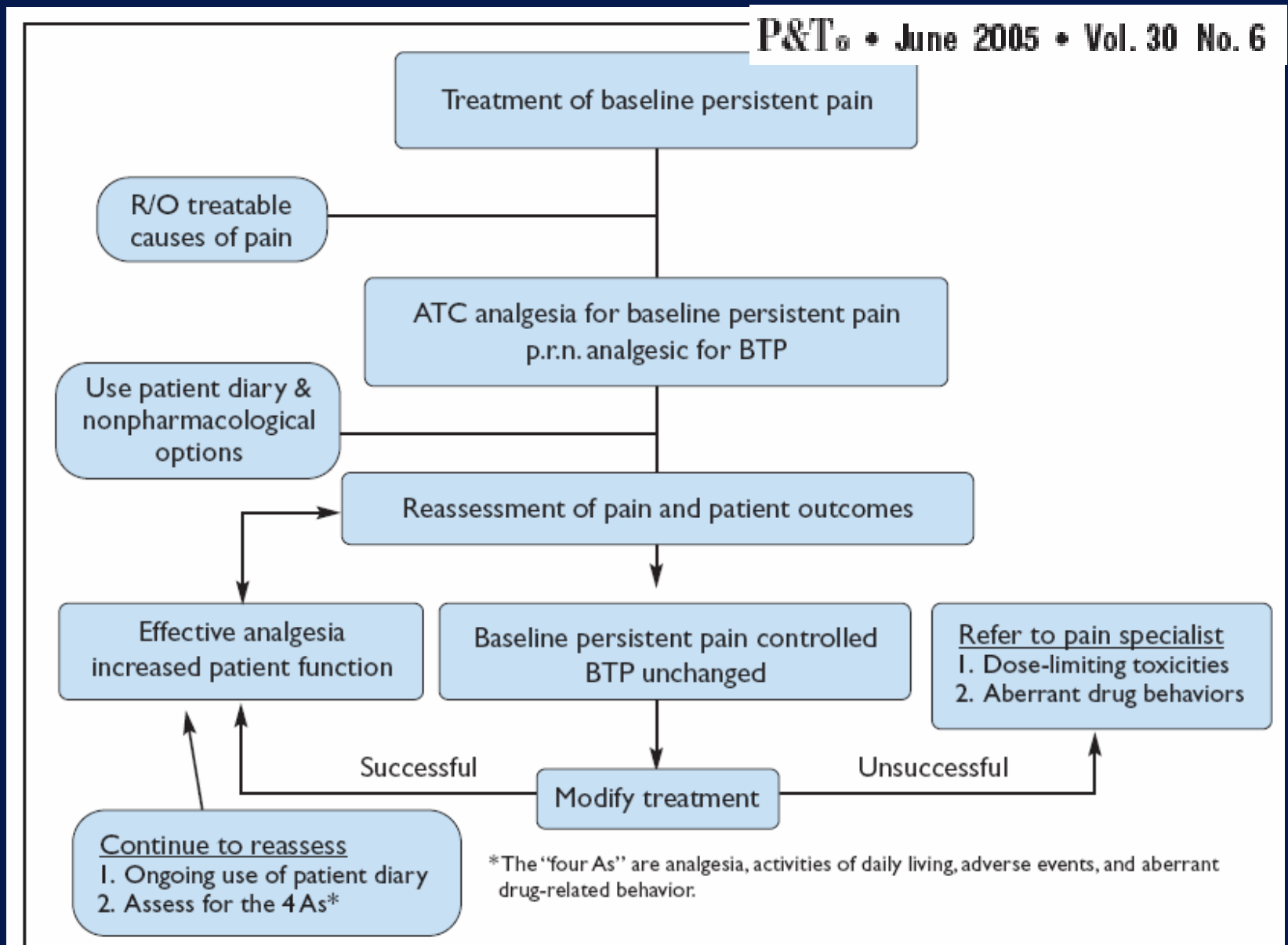
Prevalence of breakthrough pain

- **The major differences reported in literature regarding the evaluation of the incidence of breakthrough pain are most probably due to the various care settings and the different definitions given to BTP. It may partly explain the great variation in treatments…**
  - 51–63% of inpatients referred to cancer pain service[1]
  - 67% of outpatients in multi-national study[2]
  - 81.2% of outpatients[3]

1. Portenoy RK. Pain 1990;41:273-281
2. IASP Task Force on Cancer Pain. Portenoy RK. 15th Annual Scientific Meeting of the American Pain Society, November 14-17, 1996, Washington DC. Abstract
3. Di Palma M, Poulain P. BTP French Study Group, JPSM, 2000;20,6:S59

Management of breakthrough pain

Consensus Panel recommandations for the assessment and management of BTP



Management: For which episodes?

- Mode of expression
- Duration
- Intensity
- Physiopathology

Dose adjustments

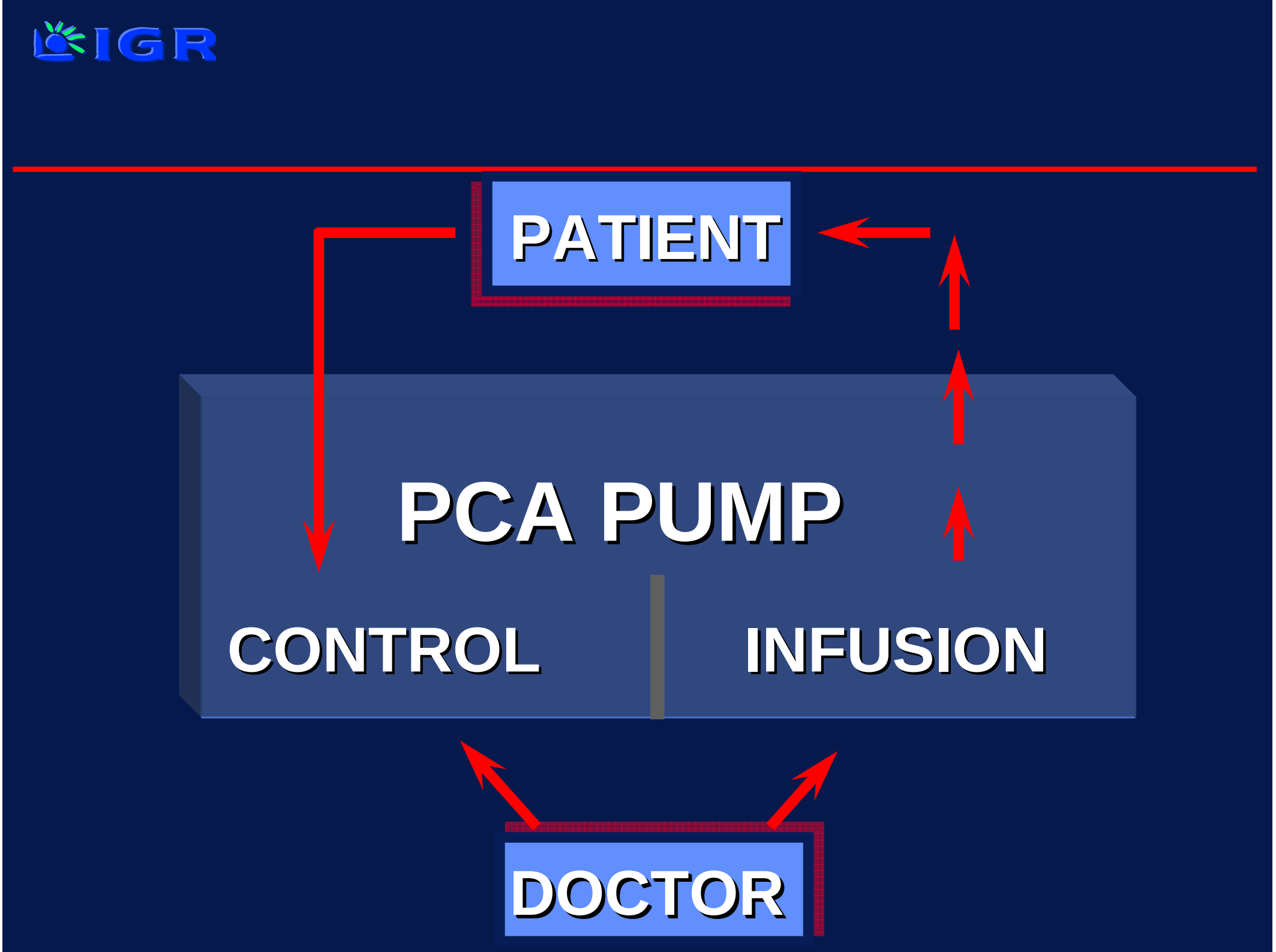
- Little correlation exists between the daily opioid dose and the dose needed for BTP
- Notion of dose and product titration
- Given this disparity, the dose of an IR opioid should be tailored to the individual according to:
  - The onset of the BTP episode
  - The duration of BTP
  - The patient's tolerability to the IR opioid used

Breakthrough pain: Which medication?

	Onset of analgesia	Duration	Formulation
Morphine	20-40 min	4 hours	Capsules Tablets Liquids
Oxycodone	30 min	4–6 hours	Tablets Liquids
Hydromorphone	30 min	4 hours	Capsules Tablets
Fentanyl	5–15 min	1–3 hours	OTFC – FEBT Liquids
Sufentanil	5–10 min	30 min – 2 hours	Injectable

Routes of administration

- **Patient-controlled analgesia:**
  - Oral formulations: tablets, drops, liquids
  - By pumps: IV, subcutaneous, epidural
  - Transmucosal: buccal, sublingual, nasal


IGR
PATIENT
PCA PUMP
CONTROL
INFUSION
DOCTOR

Morphine

- **WHO guidelines**
- **EAPC guidelines**
  (British Journal of Cancer 2001; 84: 587–93)

The simplest method of dose titration is with a dose of normal release morphine given every 4 hours and ***the same dose for breakthrough pain***

This ‘rescue’ dose may be given as often as required (up to hourly) and the total daily dose of morphine should be reviewed daily

The regular dose can then be adjusted to take into account the total amount of rescue morphine

Morphine

- **EAPC guidelines:**
  - If pain returns consistently before the next regular dose is due the regular dose should be increased
  - In general, normal-release morphine does not need to be given more often than every 4 hours and modified-release morphine more often than 12 or 24 hours (according to the intended duration of the formulation)
  - Patients stabilized on regular oral morphine require continued access to a rescue dose to treat ‘breakthrough’ pain

Morphine: Limitations

- The systemic availability of morphine by the oral route is poor (20–30%) and this contributes to a sometimes unpredictable onset of action and great interindividual variability in dose requirements and response (Glare and Walsh, 1991)
- Active metabolites may contribute to toxicity, particularly in patients with renal impairment (McQuay and Moore, 1997)
- And some types of pain do not always respond well or completely to morphine, notably neuropathic pain
- **However, none of the alternatives to morphine has so far demonstrated advantages which would make it preferable as the first line oral opioid for cancer pain**
- Morphine remains our first choice but for reasons of familiarity, availability and cost rather than proven superiority

Morphine and breakthrough pain

- There are no randomised controlled trial data to establish the appropriate dose of morphine for breakthrough pain
- Anecdotal experience supports the use of doses varying from 30 to 100% of the 4-hourly dose
  –Portenoy and Hagan, 1990.
- The optimal dose for breakthrough pain can only be determined by titration, we suggest that a simple approach is to use the equivalent 4-hourly dose of morphine – EAPC Guidelines

Morphine

- **Normal (immediate) release formulations:**
  - Tablets: May be crushed
  - Capsules: May be opened
  - Drops: The exact amount: young children, elderly people, fragile populations...
  - Liquids:
    - Dilution by pharmacists
    - Ampoules
    - Individual unit dose vials

Oramorph

- Immediate release solution
- Rapid onset of action
- Available as single dose
- 3 different doses (10 mg, 30 mg or 100 mg) – colour coded
- Drops

Oramorph

Easy-to-administer formulation; can be given either:

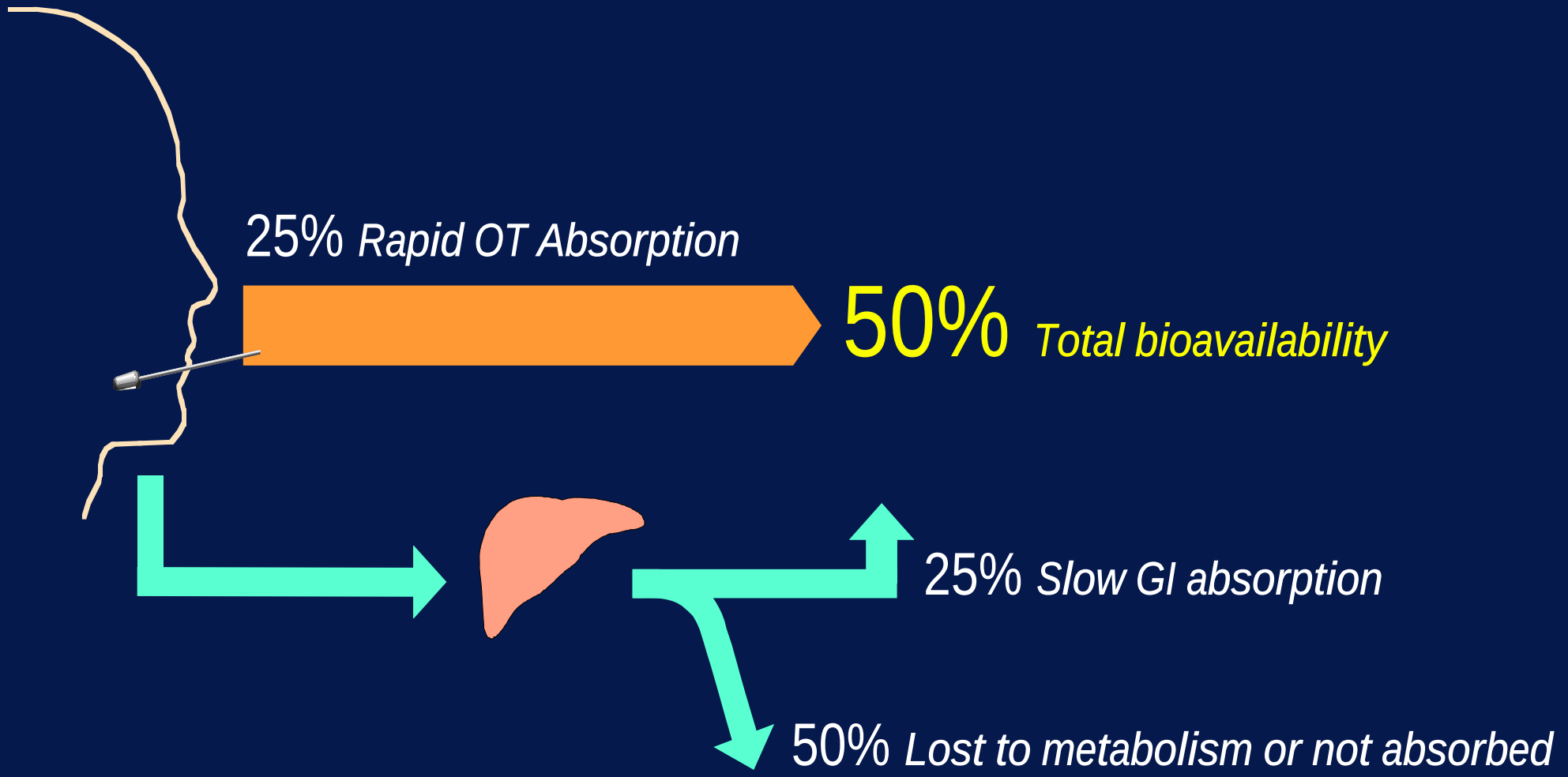
- **In liquid, for easy ingestion, or added to drinks/semi-solids or through a tube**
- **Via enteral feeding**

Fentanyl

- **Transmucosal**
  - OTFC
  - Nasal spray (post-operative data)
  - Effervescent buccal tablets (FEBT)
- **EAPC:**

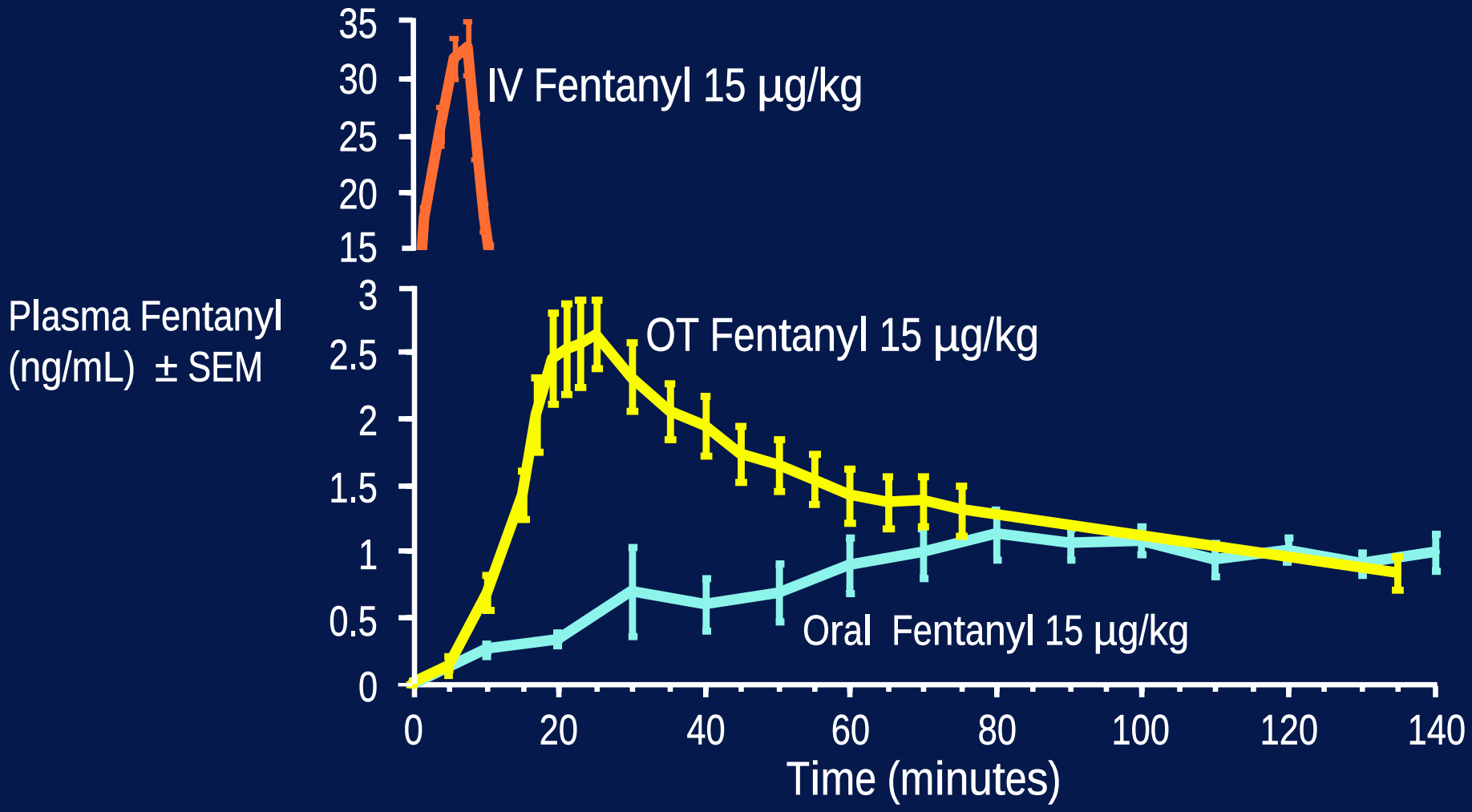
  "Oral transmucosal fentanyl citrate (OTFC) is an effective treatment for 'breakthrough pain' in patients stabilized on regular oral morphine or an alternative step 3 opioid"

Total Fentanyl bioavailability with OTFC is 50%



Streisand JB, et al. Anesthesiology 1991;75:223-9

Pharmacokinetics of oral transmucosal, IV, and oral Fentanyl delivery

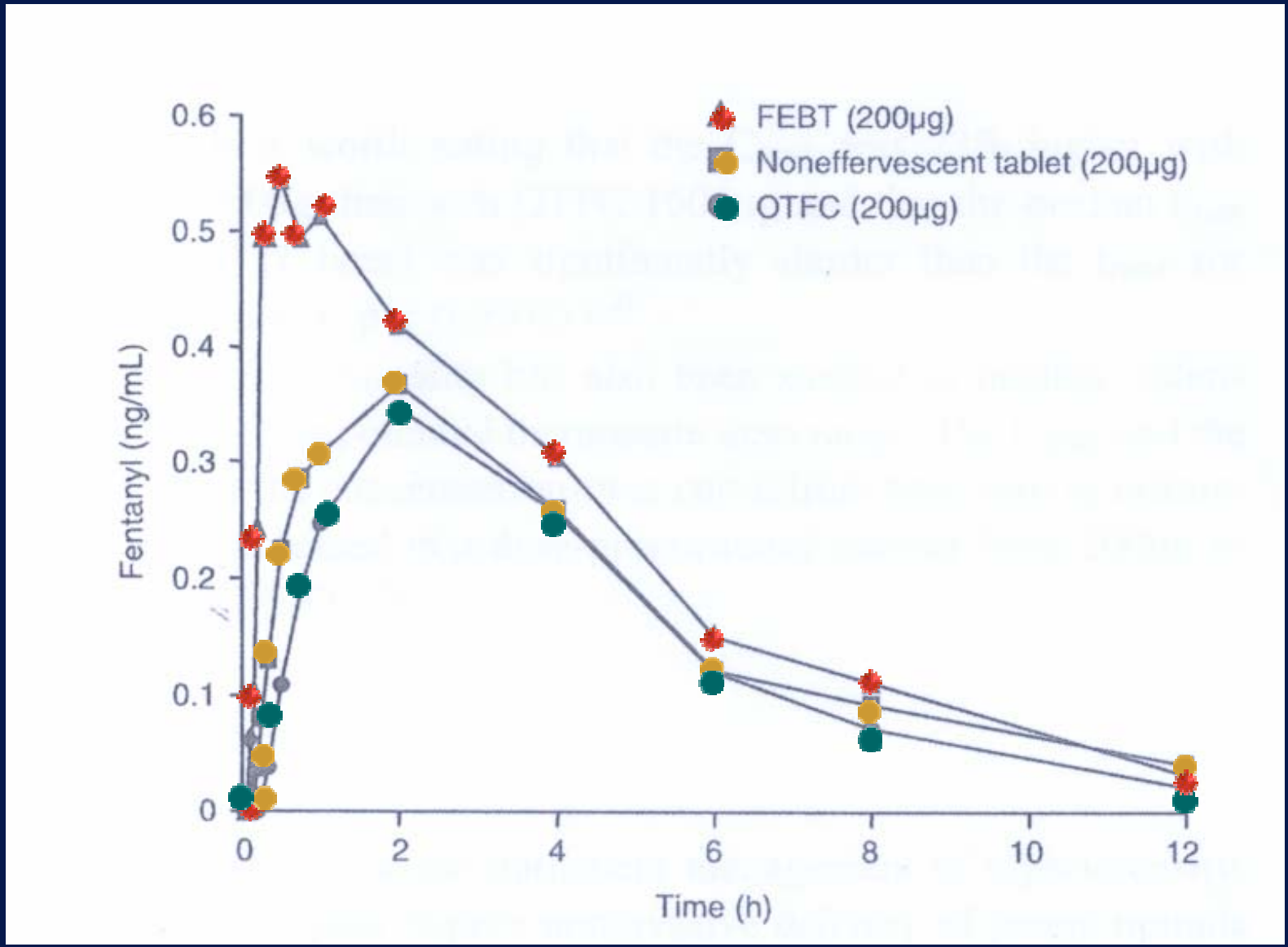


Streisand JB, et al. Anesthesiology 1991;75:223-9

F E B T

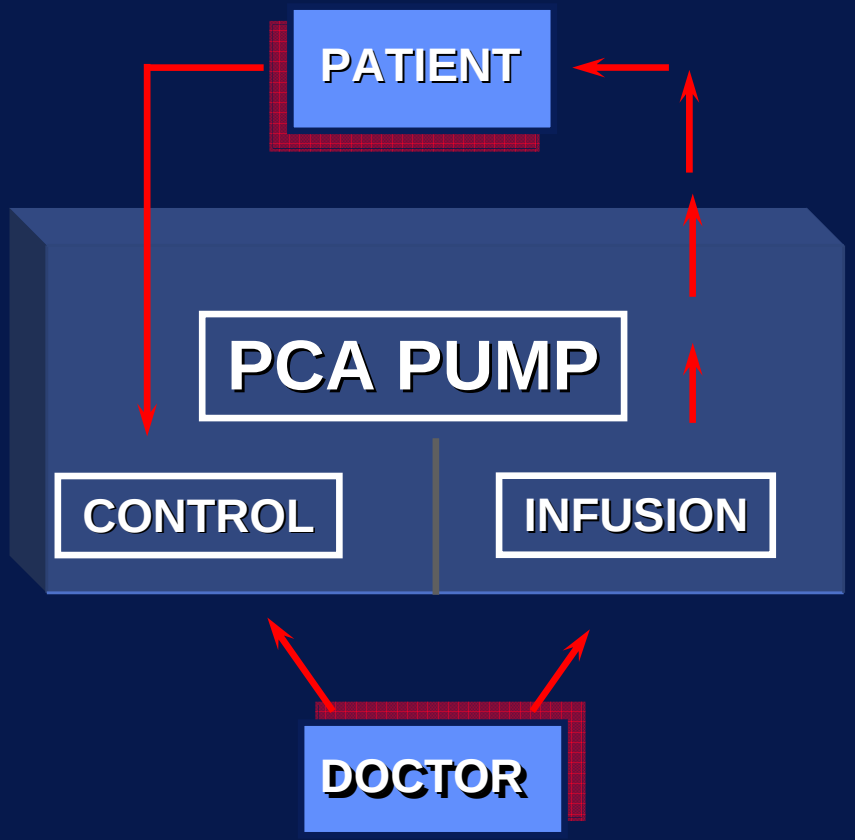
- Preliminary results
  - Successful Dose Finding with Fentanyl Effervescent Buccal Tablets: Combined Results of Open-Label Titration Dose Finding. Portenoy et al. - Poster #731, APS San Antonio 2006
  - Comparative Bioavailability of the Novel Fentanyl Effervescent Buccal Tablet Formulation: An Open-Label Crossover Study. Darwish et al. - Poster #730, APS San Antonio 2006
  - Patients' Experience with Fentanyl Effervescent Buccal Tablets: Interim Analysis of a Long-Term, Multicenter, Open-Label Study in Cancer-Related Breakthrough Pain. Segal et al. - Poster #732, APS San Antonio 2006
  - Open-Label Study of Fentanyl Effervescent Buccal Tablets in Patients with Noncancer Pain and Breakthrough Pain: Patient Preference Assessment. Webster et al. - Poster #804,

Fentanyl Effervescent Buccal Tablet



Sufentanil

- By parenteral route only: pumps are required
- Rapid onset of action
- High cost



Conclusion

- Breakthrough pain is still not a well-agreed entity and this broad concept needs to be clarified
- It is a major problem for the quality of life of patients because of its frequency and intensity and the lack of standard treatment
- It's physiological mechanism needs to be well-identified before prescribing an adapted treatment
- Morphine remains the most prescribed analgesic
- Patients' and physicians' education is required to improve this situation