# IS THE ROUTE OF DRUG ADMINISTRATION IMPORTANT?

Dr Andrew Davies FRCP Consultant in Palliative Medicine Royal Surrey County Hospital, Guildford





### Disclosures

I have received honoraria for speaking from Archimedes, Cephalon, Nycomed, Prostrakan, Takeda, and TEVA.

I have received honoraria for attending advisory boards from Archimedes, Cephalon, Grunenthal, MEDA, Nycomed, and Prostrakan.

I have received unrestricted research grants from Cephalon, Nycomed, Prostrakan, and Takeda.

### Disclosures



# Introduction

# Breakthrough pain

European Journal of Pain 13 (2009) 331-338



Review

The management of cancer-related breakthrough pain: Recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland

Andrew N. Davies<sup>a,\*</sup>, Andrew Dickman<sup>b</sup>, Colette Reid<sup>c</sup>, Anna-Marie Stevens<sup>d</sup>, Giovambattista Zeppetella<sup>e</sup>

### Breakthrough pain

Breakthrough pain is "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain".

# **Clinical features**

## Breakthrough pain

- Spontaneous pain
- Incident pain
  - volitional
  - non-volitional
  - procedural

## Breakthrough pain





Vol. 46 No. 5 November 2013

Journal of Pain and Symptom Management 619

#### **Original** Article

### Breakthrough Cancer Pain: An Observational Study of 1000 European Oncology Patients

Andrew Davies, FRCP, Alison Buchanan, BSc, Giovambattista Zeppetella, FRCP, Josep Porta-Sales, MD, Rudolf Likar, MD, Wolfgang Weismayr, MD, Ondrej Slama, MD, Tarja Korhonen, MD, Marilene Filbet, MD, Philippe Poulain, MD, Kyriaki Mystakidou, MD, Alexandros Ardavanis, MD, Tony O'Brien, FRCPI, Pauline Wilkinson, FRCP, Augusto Caraceni, MD, Furio Zucco, MD, Wouter Zuurmond, MD, Steen Andersen, MD, Anette Damkier, MD, Tove Veilgaard, MSc, Friedemann Nauck, MD, Lukas Radbruch, MD, Karl-Fredrik Sjolund, MD, and Mariann Stenberg, MD Royal Surrey County Hospital (A.Dav.), Guildford, Surrey, United Kingdom; University of Surrey (A.B.), Guildford, Surrey, United Kingdom; St. Clare Hospice (G.Z.), Hastingwood, United Kingdom; Catalan Institute of Oncology (I.P.-S.), Bellvitge Biomedical Research Institute, Barcelona, Spain; Centre for Interdisciplinary Pain Management, Oncology and Palliative Care (R.L.), Klagenfurt, Austria; Mobile Palliative Care Unit (W.W.), Hospice Upper Austria, Salzkammergut, Austria; Masaryk Memorial Cancer Center (O.S.), Brno, Czech Republic; Tampere University Hospital (T.K.), Tampere, Finland; University Hospital Lyon-Sud (M.F.), Lyon, France; Polyclinique de l'Ormeau (P.P.), Tarbes, France; University of Athens (K.M.), Athens, Greece; St. Savvas Anticancer Hospital (A.A.), Athens, Greece; Marymount Hospice (T.O.), Cork, Republic of Ireland; Marie Curie Hospice (P.W.), Belfast, United Kingdom; Virgilio Floriani Hospice and Palliative Care Unit (A.C.), National Cancer Institute, Milan, Italy; Department of Anaesthesia, Intensive Care, Palliative Care, Pain Therapy, Hospice and Hospital at Home (F.Z.), Azienda Ospedaliera G. Salvini, Milan, Italy; VU University Medical Center (W.Z.), Amsterdam, The Netherlands; Roskilde Hospital (S.A.), Roskilde, Denmark; Odense University Hospital (A.Dam.), Odense, Denmark; Vejle Hospital (T.V.), Vejle, Denmark; Department of Palliative Medicine (F.N.), University Hospital Göttingen, Göttingen, Germany; University Hospital Bonn (L.R.), Bonn, Germany; Karolinska University Hospital (K.-F.S.), Stockholm, Sweden; and University Hospital Lund (M.S.), Lund, Sweden

 Median number of episodes: 3/day (range: 1/month to 24/day)

 Median time to peak intensity: 10 min (range: < 1 to 240 min)</li>

Incident pain – 5 min Spontaneous pain – 10 min

### Time to peak intensity



 Median duration of untreated episodes: 60 min (range: < 1 to 360 min)</li>

Incident pain – 45 min Spontaneous pain – 60 min

**Duration untreated BTcP episode** 



Severity of pain	Number of patients (n = 1000)
Mild	36
Moderate	337
Severe	618
Not stated	9

Relieving factor	Number of patients (n = 1000)
Yes	656
No	233
Sometimes	107
Not stated	4

Relieving factor	Number of patients (n = 1000)
Pharmacological Rx	294
Non-pharmacological Rx	232
Mixed (pharmacological Rx & non-pharmacological Rx)	120
Not stated	10

- Wrong strategy
- Wrong drug
- Wrong formulation (route)
- Wrong dose
- Multiple pains
- Non-adherence

### **APM Recommendations**





Review

The management of cancer-related breakthrough pain: Recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland

Andrew N. Davies<sup>a,\*</sup>, Andrew Dickman<sup>b</sup>, Colette Reid<sup>c</sup>, Anna-Marie Stevens<sup>d</sup>, Giovambattista Zeppetella<sup>e</sup>

### **APM Recommendations**



- "Ideal" rescue medication:
- Good efficacy
- Rapid onset of action
- Short duration of effect
- Good tolerability
- Easy to use
- Acceptable to the patient
- Available / affordable
- [Can be given by carer]
- [Low risk addiction / diversion]





772 Journal of Pain and Symptom Management

Vol. 47 No. 4 April 2014

### **Review** Article

### A Network Meta-Analysis of the Efficacy of Opioid Analgesics for the Management of Breakthrough Cancer Pain Episodes

Giovambattista Zeppetella, FRCP, Andrew Davies, FRCP, Indra Eijgelshoven, BSc, and Jeroen P. Jansen, PhD

St. Clare Hospice (G.Z.), Hastingwood, Essex; St. Luke's Cancer Centre (A.D.), The Royal Surrey County Hospital, Guildford, Surrey, United Kingdom; Mapi (I.E.), Houten, The Netherlands; and Mapi (J.P.J.) and Tufts University School of Medicine (J.P.J.), Boston, Massachusetts, USA







### Effect of SGD



## **Effect of SGD**

Parameter	Phase 1 (no Rx)	Phase 2 (water)	Phase 3 (pilocarpine)
Tmax median (h)	0.83	0.50	0.67
Cmax mean +/- SD (pg / ml)	626.33 +/- 520.55	694.78 +/- 482.23	703.11 +/- 424.61
AUClast mean (pg.h / ml)	1102.40 +/- 477.98	1165.33 +/- 534.91	1171.60 +/- 475.64

## Tolerability

- Opioid analgesics cause opioid adverse effects
- Opioid analgesics can cause non-opioid adverse effects (e.g. local irritation)
- Opioid side effects may be due to background medication, breakthrough medication, or a combination

Opioid side effects are generally manageable

### Acceptability of different routes of administration



European Journal of Pain 15 (2011) 756-763



Multi-centre European study of breakthrough cancer pain: Pain characteristics and patient perceptions of current and potential management strategies

Andrew Davies<sup>a,\*</sup>, Giovambattista Zeppetella<sup>b</sup>, Steen Andersen<sup>c</sup>, Anette Damkier<sup>d</sup>, Tove Vejlgaard<sup>e</sup>, Friedemann Nauck<sup>f</sup>, Lukas Radbruch<sup>g</sup>, Karl-Frederik Sjolund<sup>h</sup>, Mariann Stenberg<sup>i</sup>, Alison Buchanan<sup>j</sup>

Main reason for not wanting to use oral transmucosal route of administration (n = 29):

- Current / previous problems with mouth 9
- "I don't like the idea of such a product" 8
- Previous bad experience 0
- Concerns about effectiveness 3
- Concerns about side effects 1
- Concerns about addiction 1
- Other reasons 4
- Not stated 3

Acceptability of oral transmucosal route:

- Previous use of route for BTP
- [Danish patients]

73% patients reported existence of at least one regular oral problem

Main reason for not wanting to use intranasal route of administration (n = 82):

- Current / previous problems with nose 13
- "I don't like the idea of such a product" 38
- Previous bad experience 4
- Concerns about effectiveness 5
- Concerns about side effects 2
- Concerns about addiction 4
- Other reasons 5
- Not stated 11

Acceptability of intranasal route:

- Males
- Previous use of route for any condition
- [Danish / Swedish patients]

44% patients reported existence of at least one regular nasal problem

### Health economics



### Health economics

- Adequate pain management is a basic human right
- Uncontrolled cancer pain has a negative impact on health economics
- Controlling cancer pain has a positive impact on health economics
- Prescribing a "cheap" drug that doesn't work is a waste of money



Butler et al. Harm Reduction Journal 2011, 8:29 http://www.harmreductionjournal.com/content/8/1/29

### RESEARCH



**Open Access** 

Abuse risks and routes of administration of different prescription opioid compounds and formulations

Stephen F Butler<sup>\*</sup>, Ryan A Black, Theresa A Cassidy, Taryn M Dailey and Simon H Budman





Drug (trade name)	Cases of "drug dependence"	Cases of "drug abuse"
Effentora®	25	2
Instanyl®	21	17
PecFent®	0	0

Data from European database of suspected adverse drug reaction reports (EudraVigilance) - June 2014

# Conclusion

### Conclusion



"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided".

*Paracelsus* (1493-1541)

### Conclusion



Reassessment



27

Treatment