The European Pharmacogenetic Opioid Study

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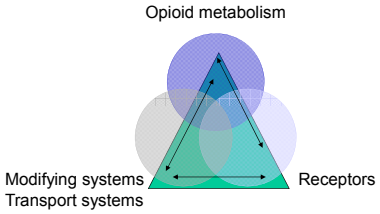
Variation in opioid dose

Genetic variability ?

Different effects from different opioids

Genetic variations and opioids



Most studies performed so far had:

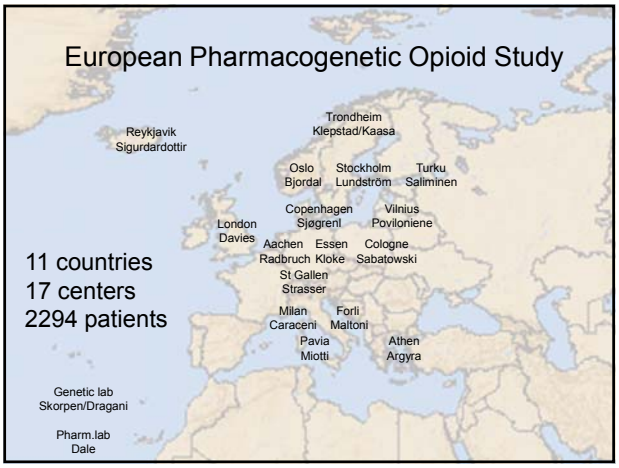
- studied one or two genes
- studied morphine
- small cohorts
- studied volunteers or post-op patients

5

To move forward

- Perform studies in cancer pain patients in palliative care
- Scale the studies to sufficient statistical power.
- Explore the effects of multiple genes
- Study different opioids

European Pharmacogenetic Opioid Study



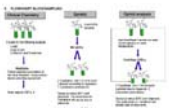
11 countries
17 centers
2294 patients

7

How did we do this?

A dedicated study coordinator (a lots of material should be submitted at the right time, e-mails answered, samples and data collected and quality control of data).

Standardized shipments and tubes for blood sampling, professional edited CRF, scanning of database



Experience in the funding processes, network through EAPC and a track record of deliverables

EAPC

8

Make place for centers special interests

All centers participate as authors

Organize the possibility for doing add-on studies. Examples: Hope and belief, patients barriers, cognitive function.

Win - Win: EPOS get genetic cases, local centers increase number of patients and get data management.

9

Combine knowledge from the experts

Expertise from several facets of palliative medicine
Expertise in genetics, pharmacology and statistics

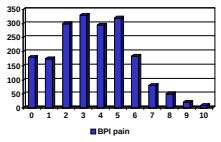
10

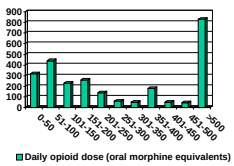
EPOS findings

11

Patients

- Cancer patients using an opioid for moderate or severe pain
  - Morphine 827
  - Oxycodone 445
  - Fentanyl 695
  - Other WHO step III opioids 327
- Age 62 ± 12, Karnofsky 59 ± 17, MMSE 27 ± 3, 82% hospitalized





12

EPOS genetics

13

Opioid dose and genetic variability

IASP

PAIN® 152 (2011) 1139–1145

PAIN®

www.elsevier.com/locate/pain

Influence from genetic variability on opioid use for cancer pain: A European genetic association study of 2294 cancer pain patients

P. Klepstad[a,f,k,*], T. Fladvad[a], F. Skorpen[a], K. Bjordal[b], A. Caraceni[c], O. Dale[a,f], A. Davies[d], M. Kloke[e], S. Lundström[f,g], M. Maltoni[h], L. Radbruch[i], R. Sabatowski[j], V. Sigurdardottir[k], F. Strasser[l], P.M. Fayers[a,m], S. Kaasa[a,n], On behalf of the European Palliative Care Research Collaborative (EPCRC) and the European Association for Palliative Care Research Network

14

Candidate genes

- Opioid receptors
  - OPRM1 (mu opioid receptor)
  - OPRK1 (kappa opioid receptor)
  - OPRD1 (delta opioid receptor)
- Opioid signaling
  - HINT/PKCI (protein kinase inhibitor)
  - GNAZ (G nucleotide-binding protein alpha z)
  - ARRB2 (beta-arrestin)
- Transporters
  - MDR1 (p-glycoprotein transporter)
- Modifying mechanisms
  - COMT (Catachol-O-methyl transferase)
  - GCH1 (GTP cyclohydrolase 1)
  - CNR1 (cannabinoid receptor 1)
  - DRD2 (dopamine receptor D2)
  - DRD3 (dopamine receptor D3)
  - HRH1 (histamine receptor H1)
  - HTR3A (serotonin 5HT-3B receptor), HTR3B, HTR 2A, HTR3C, HTR3D, HTR3E, HTR1, HTR4
  - ADRA2A (alpha 2A adrenergic receptor)
  - MC1R (melanocortin 1 receptor)
  - TACR1 (neurokinin 1 receptor)

15

EPOS candidate gene result

No candidate genes showed a consistent effect on need for opioid dose in both the development and the validation analyses

Sub analyses showed that variations in the beta-arrestin gene had an effect on opioid dose in patients using an opioid for more than 3 months suggesting an effect on opioid tolerance

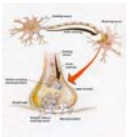
16

EPOS analyses of other genes - GWA

Pooled DNA genome wide analyses of good versus bad opioid responders suggested other genes

- Nerve impulse transmission
  - AGTPBP1 gene, SBF2 gene, DMB gene, ANK3 gene
- Synaptic transmission
  - GABRB2 gene, SLC17A6 gene, SYT5 gene
- Regulation of transcription
  - PHF6 gene, MEIS1 gene, CDCA7L gene, DMRT1 gene
- Cell signal transduction
  - TGFBR3 gene, PLCG2 gene, WWOX gene, DPYD gene

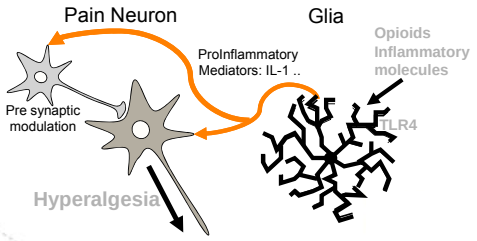
Genetic clustering of European cancer patients indicates that opioid-mediated pain relief is independent of ancestry



17

EPOS analyses of other genes - Inflammation pathways

- Glia cells in the CNS are activated by opioids
- Result in proinflammatory responses
- Increased pain - decreased analgesic effects - tolerance?



18

Interaction pain -opioids - glia Candidate genes

- Pro-Inflammatory
  - IL-1β, IL-1RN, IL-1R1, IL-2, IL-6, IL-6R, IL-12, IL-15, IL-18, IL-18RAP, IFN-Y, TNF-α, CX3CR1, MCP-1, ICE, CCL3
- Anti-Inflammatory
  - IL-10, IL-10Rβ, TGFβ
- Receptor Mediating Glial Activation, Accessory Proteins
  - TLR2, TLR4, MD2, MYD88, CD14, NF-κB
- Generalized Modulators of Response
  - CRP, IDO1, BDNF, GDNF

Pathway analyses

Somogyi, University of Adelaide

19

EPOS genetic - other symptoms - nausea

- Clinical factors
  - Age, Gender, Karnofsky Status, Use of antiemetics, Type of cancer
- Genetic factors
  - Serotonin receptor gene: *HTR3B*
  - Acetylcholine receptor gene: *CHRM3*
  - Catechol-O-Methyl-Transferase gene: *COMT*

20

EPOS genetic - other symptoms - cachexia

- Clinical factors
  - Time since diagnosis, Gender, Type of cancer
- Genetic factors
  - No certain associations
  - Trend for association with Acylpeptide hydrolase APEH (p=0.019)

21

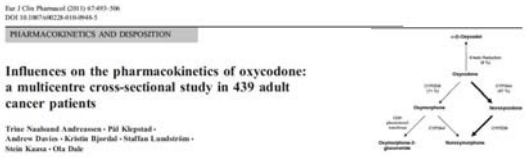
EPOS pharmacology

Oxycodone

22

EPOS oxycodone pharmacokinetics

- Clinical factors
  - Gender, Dose, BMI, Renal function,
- Interactions
  - Number of other medications
  - Use of CYP inhibitors (i.e. haloperidol, paroxitine, flucanozol, chlaritromycin, verapamil)
  - Use of CYP inducers (i.e. carbamazepine, steroids)



PHARMACOKINETICS AND DISPOSITION

Influences on the pharmacokinetics of oxycodone: a multicentre cross-sectional study in 439 adult cancer patients

Trine Naaband Andreassen · Pål Klepstad · Andrew Davies · Kristin Bjordal · Staffan Lundström · Stein Kaasa · Ola Dale

23

EPOS oxycodone pharmacodynamics

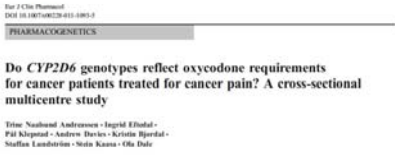
- Analyzed
  - Pain intensity
  - Cognitive function
  - Nausea
  - Tiredness (Sedation)
- Generally neglible association with oxycodone and metabolites serum concentrations.

Andreassen et al. Accepted in J Pain Symptom Manage

24

EPOS oxycodone pharmacogenetics

- CYP2D6
  - 27 Poor Metabolisers, 413 Extensive metabolisers, 10 utrarapid metabolisers
  - Poor metabolisers have lower oxymorphone and noroxymorphone seruym concentrations
  - No differences in clinical outcomes



PHARMACOGENETICS

Do *CYP2D6* genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study

Trine Naaband Andreassen · Ingrid Eftedal · Pål Klepstad · Andrew Davies · Kristin Bjordal · Staffan Lundström · Stein Kaasa · Ola Dale

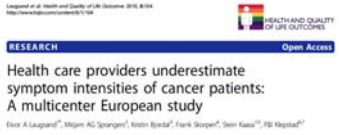
25

EPOS symptoms

26

Symptoms assessment

- Self report versus observer rating- severe or moderate
  - Pain 67 vs 47%
  - Fatigue 71 vs 54%
  - Anorexia 47 vs 25%
  - Depression 31 vs 17 %
  - Constipation 45 vs 30 %
  - Poor sleep 32 vs 21 %
  - Dyspnea 30 vs 16 %
  - Nausea 27 vs 14 %
- Increased risk for underestimation
  - Low Karnofsky
  - High MMS
  - Hospitalized
  - Recent cancer diagnosis
  - Recent start opioid



27

Symptoms in classification

- Part of an EPCRC project for development of a cancer pain classification system
- Identify characteristics that predict pain outcomes

Verified
- Breakthrough pain
- Psychological distress
- Pain intensity

Proposed
- Pain localization, sleep, cancer diagnosis, addiction, pain mechanism

28

Symptom treatment

- Patients inadequately treated (either no treatment or ineffective treatment).
  - Nausea 45%
  - Poor sleep, constipation and depression 60%
- Increased risk associated with provider underestimation, low Karnofsky status, hospitalized and recent start opioids
- Not known if this is true inferior treatment, treatment resistant symptoms or trade off by patients and physicians.

29

Specific symptoms - cognitive function

- One third have cognitive dysfunction measured by the MMSE
- Increased risk associated with opioid dose above 400 mg / day, low Karnofsky score, old age, lung cancer, recent cancer diagnosis, no breakthrough pain
- Fentanyl, morphine and oxycodone - similar cognitive function results when adjusted for other factors.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prevalence and Predictors of Cognitive Dysfunction in Opioid-Treated Patients With Cancer: A Multinational Study

30

The EPOS study

Is an example of that palliative care research expands beyond small sized studies or anecdotal evidence

Is an example of that the European palliative care community can do large scale studies

Is an example of that we in a large sample with clinical data, pharmacological data and genetics can address several research questions

31

Thanks from the EPOS study group

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