« Multimodal Analgesia and nefopam:
from guideline to clinical practice in France »



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BIOCODEX

POSTOPERATIVE PAIN MANAGEMENT

1. Objectives of postoperative pain management
2. Postoperative hyperalgesia and the risk of chronic postsurgical pain
3. Key principles of postoperative pain treatment
4. Nefopam at the crossroad of multimodal analgesia:
   - nefopam specificities
   - nefopam in practice

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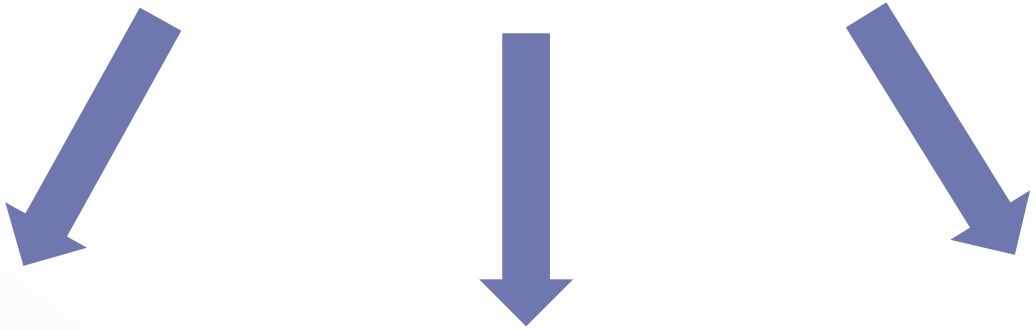
Effective postoperative analgesia

why?



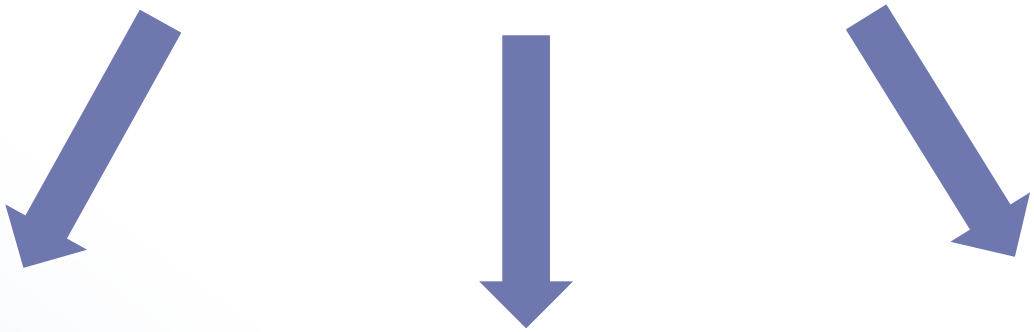
Humanitarian objective

To facilitate “ERAS”

To prevent CPSP

Effective postoperative analgesia

why?



Humanitarian objective

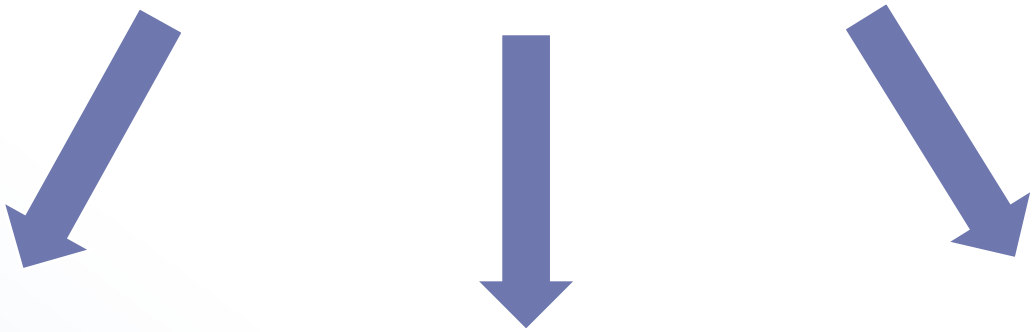
To facilitate "ERAS"

To prevent CPSP

Patient request…
Patient rights

Effective postoperative analgesia

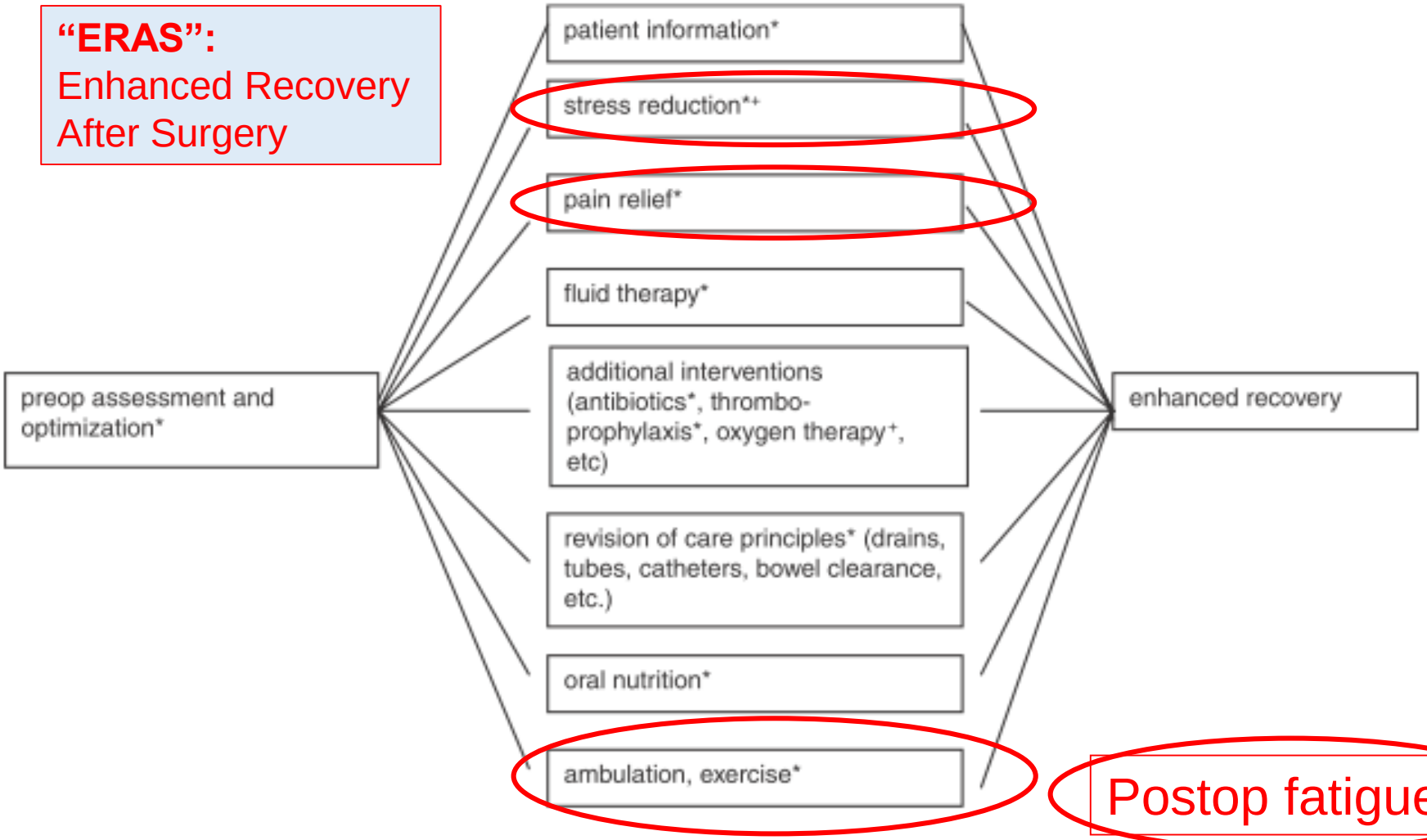
why?



Humanitarian objective	**To facilitate “ERAS”**	To prevent CPSP

ERAS: multimodal strategy in perioperative care

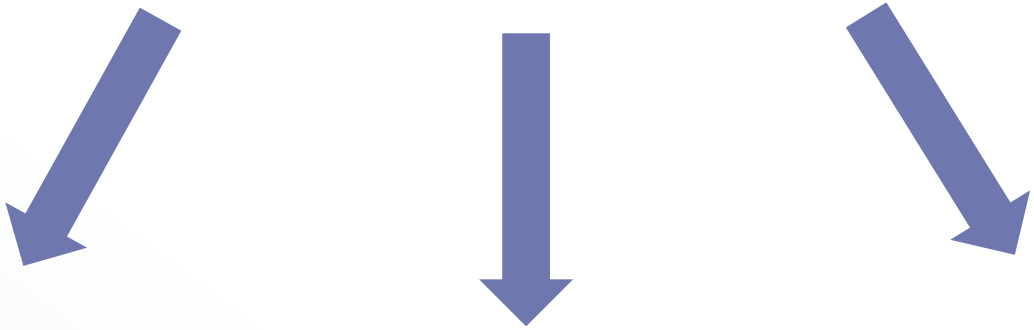
“ERAS”:
Enhanced Recovery After Surgery



Kehlet and Wilmore, Ann Surg 2008

Effective postoperative analgesia

why?

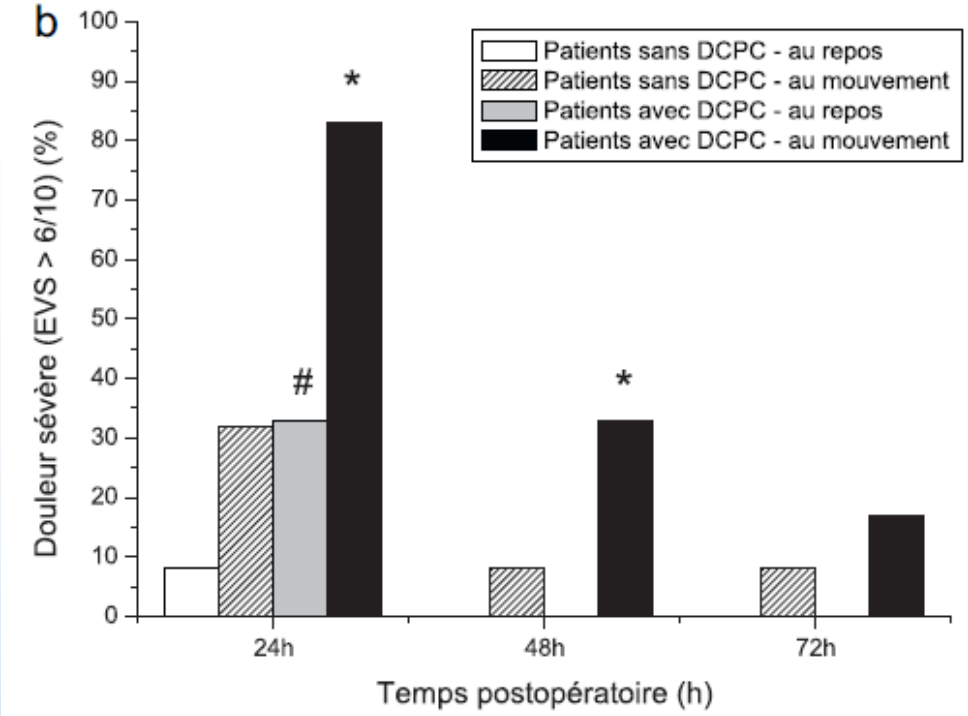


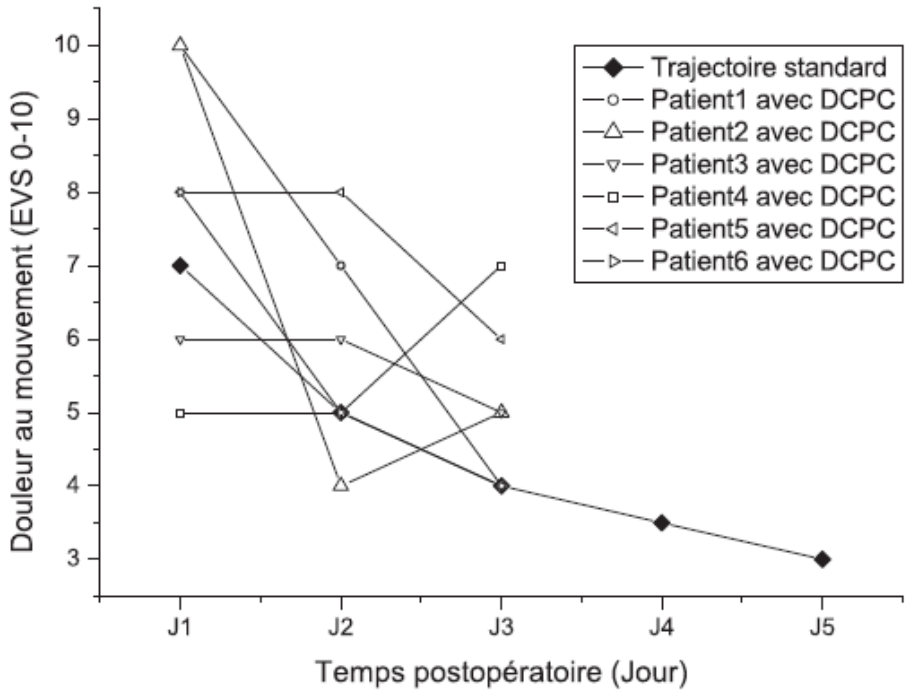
Humanitarian objective	To facilitate “ERAS”	**To prevent CPSP**

High postoperative pain level = risk factor of chronic postsurgical pain

Postoperative pain trajectories to identify risk of chronic postsurgical pain in living donors for liver transplantation

Laparotomy





A Bonnet, P Lavand'homme et al. Ann Fr Anesth Reanim 2012;31:945-9.

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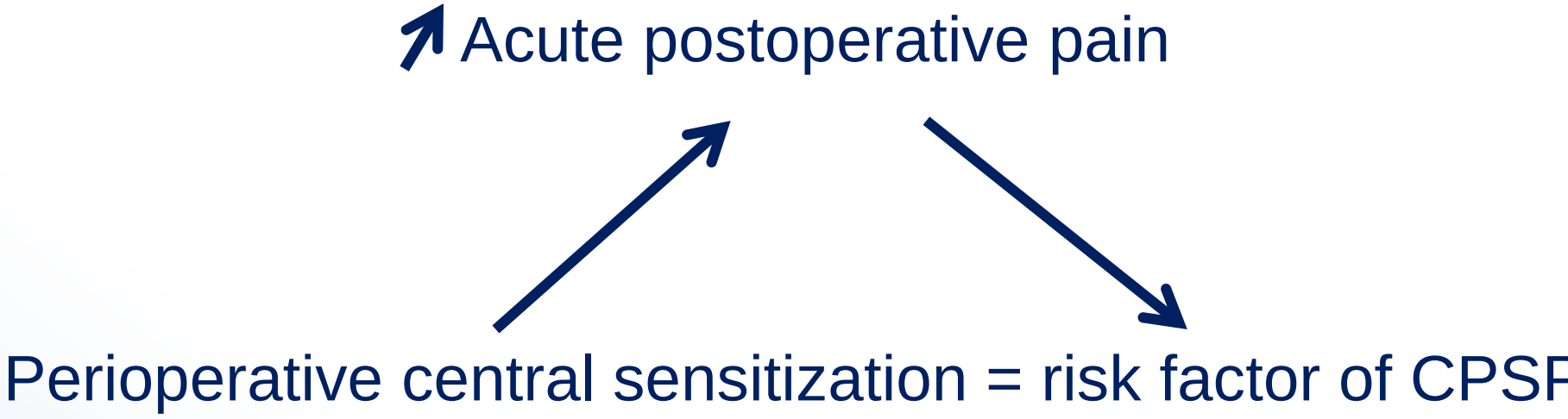
Acute postoperative pain
Perioperative central sensitization = risk factor of CPSP

POSTOPERATIVE PAIN MANAGEMENT

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Ideal analgesia for ERAS program

- Analgesic efficacy at **mobilization**
- Modulation of **inflammatory** response
- Maximal **opioid sparing effect**: at least 40%
- Utilization of **pharmacological** analgesic **complementarity**
  - Multimodal analgesia
- Analgesia **adapted to surgery**.

POSTOPERATIVE PAIN MANAGEMENT

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SPECIFITIES OF NEFOPAM AND ITS POSITION IN MULTIMODAL ANALGESIA

Clinical and Experimental Pharmacology and Physiology (2016) **43**, 3–12 doi: 10.1111/1440-1681.12506

INVITED REVIEW

Nefopam analgesia and its role in multimodal analgesia: A review of preclinical and clinical studies

Philippe Girard,* Marcel Chauvin† and Marc Verleye*

**Pharmacology Department, Biocodex, Compiègne, and †Department of Anaesthesia, Hôpital Ambroise Paré, Boulogne, France*

Nefopam

- Analgesia
- Another characteristic : shivering inhibition

Agenda

- Nefopam mode of action
  - Analgesia: antinociception and antihyperalgesia
  - Shivering inhibition
- Nefopam: component in multimodal analgesia
- Nefopam use in practice

Agenda

- **Nefopam mode of action**
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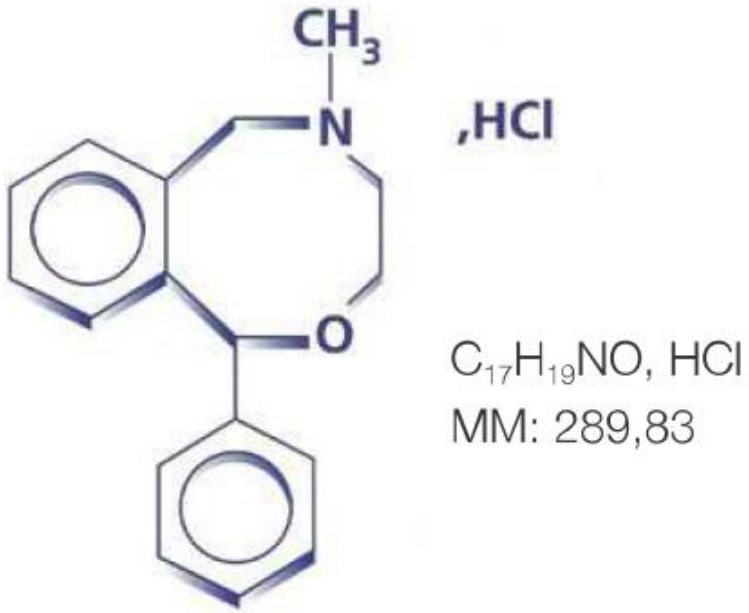
Nefopam (Acupan®)

- **Benzoxacine: Cyclic analogue of orphenadrine**



At the crossroad of multimodal analgesia.

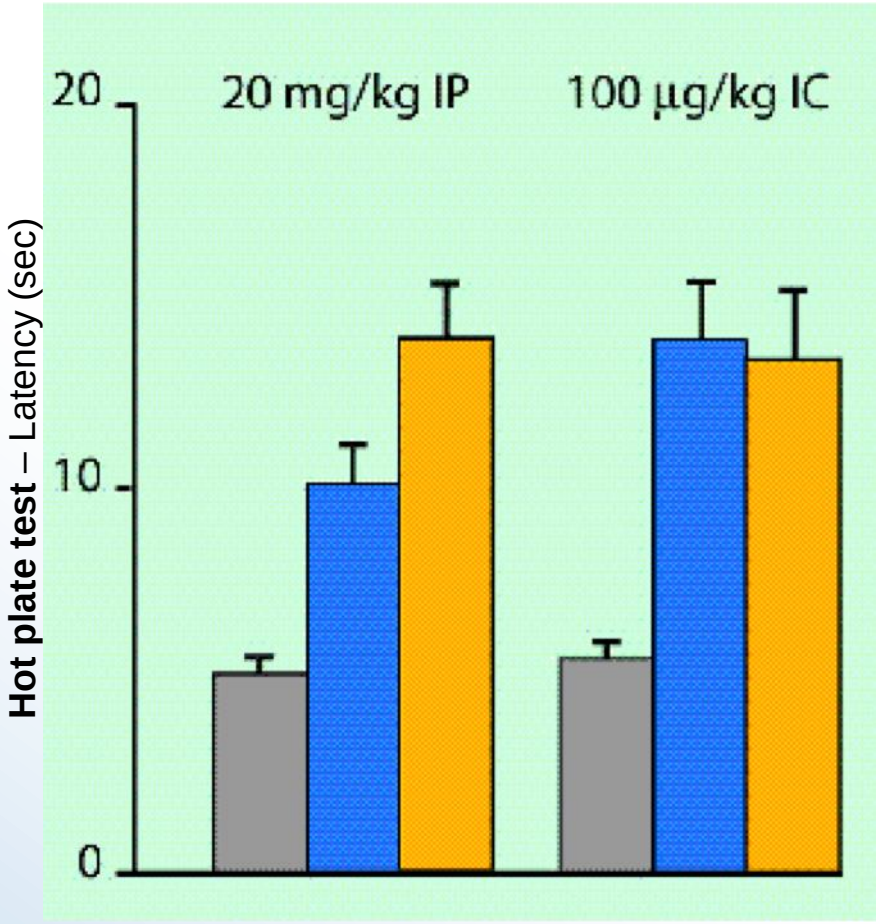
Nefopam: Mechanisms of action

- **Central Action (CNS) :**
  - Spinal et supra-spinal levels of action.

- **No action upon opioid receptors.**

Nefopam – mode of action

- **No binding to opioid receptors**



Nefopam analgesia was not antagonized by naloxone.

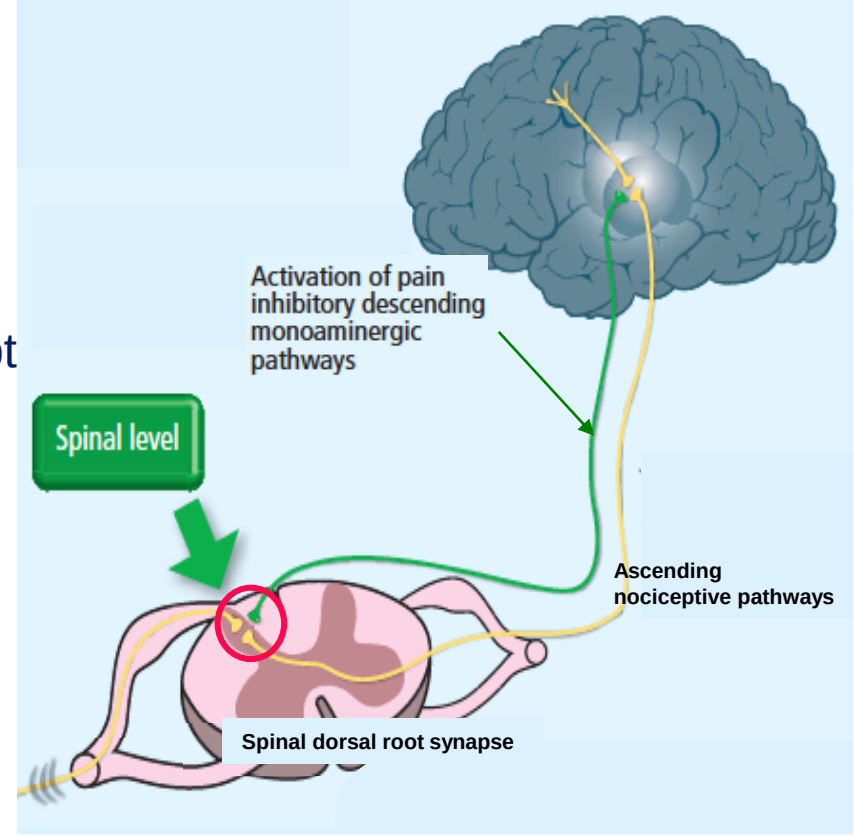
Piercey and Schroeder. Eur J Pharmacol 1981;74:135-40.

Nefopam: analgesic properties

- Intensifies descending monoaminergic inhibitory pathways

- By inhibition of monoamine recapture: [2]
  - Serotonin, dopamine, noradrenaline [3]

- Activity modulated by monoaminergic recept
  - Adrenaline: α_1 and α_2 [2]
  - Dopamine: D_2 [2]
  - Serotonin: **5-HT$_{1B}$**, **5-HT$_{1C}$** [2] and **5-HT$_7$** [4]



1. Guirimand F. Le néfopam diminue fortement le réflexe nociceptif de flexion RIII chez l'homme, Pain, 1999.
2. Girard p. *et al.*, Nefopam analgesia and its role un multimodal analgesia: a review of preclinical and clinical studies, Clin Exp Pharmacol Physiol, 2016.
3. Girard p. *et al.*, Role of catecholamines and serotonin receptor subtypes in nefopam-induced antinociception, Pharmacological Research, 2006.
4. Lee *et al*., Intrathecal nefopam-induced antinociception through activation of descending serotonergic projections involving spinal 5-HT7 but not 5-HT3 receptors,Neuroscience Letters, 2015.

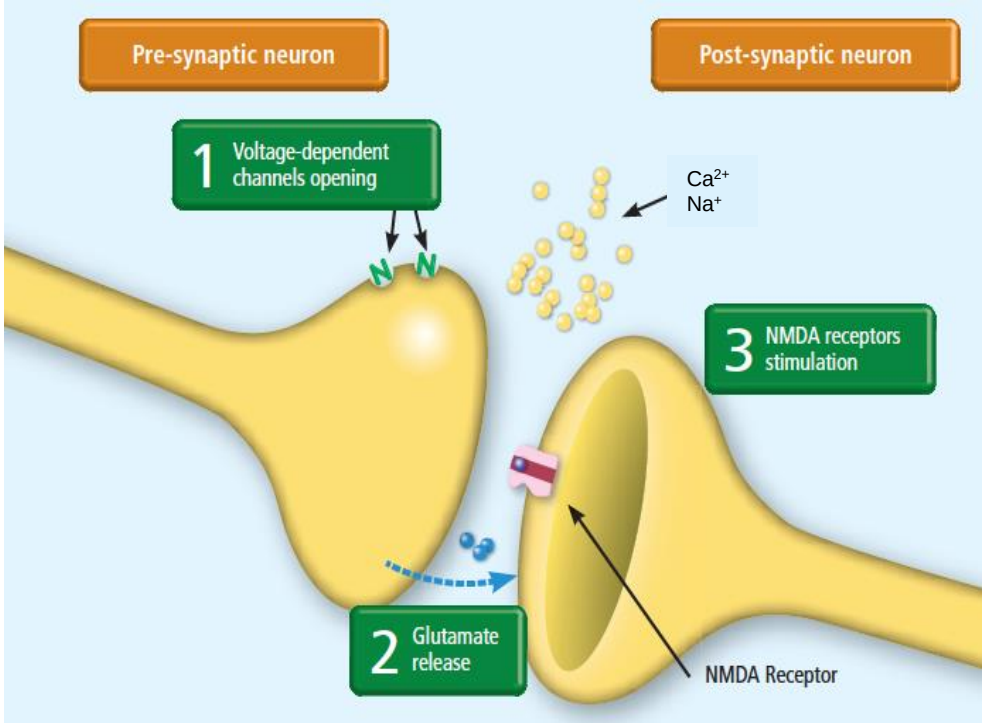
Nefopam: antihyperalgesic properties

Nefopam decreases neuron excitability: [1]

- By blocking voltage-sensitive sodium **(VSSCs)**[1] and calcium channels (**TRPV1**) [2, 3]

- Decrease in glutamate release [1]

- **Decrease in the stimulation of postsynaptic NMDA receptors, which are involved in hyperalgesic mechanisms.** [2]



1. Verleye, nefopam blocks voltage-sensitive sodium channels and modulates glutamatergic transmission in rodents, brain research, 2004.
2. Girard p. *et al.*, Nefopam analgesia and its role un multimodal analgesia: a review of preclinicall and clinical studies, clin exp pharmacol physiol, 2016.
3. Verleye m, contribution of transient receptor potential vanilloid subtype 1 to the analgesic and hyperalgesic activity of nefopam in rodents, pharmcaology, 2009.

Nefopam – Analgesic properties

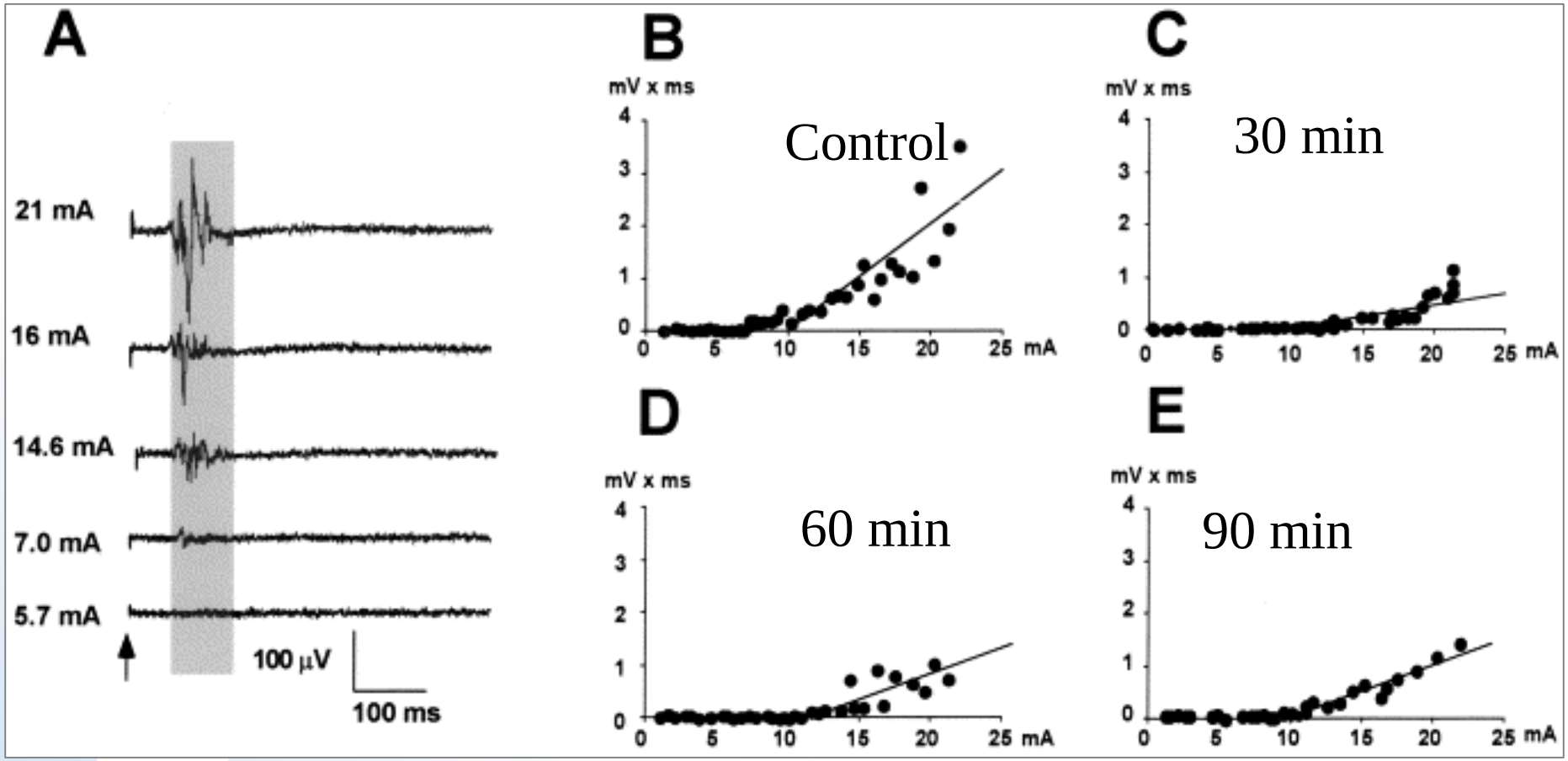
- **Nefopam Analgesia:**
  - **Antinociception**
  - **Antihyperalgesia**

Nefopam: an antinociceptive substance

- **Antinociceptive substance:**

  - Substance that increases the nociceptive threshold in all areas of the body

Nefopam and RIII reflex



IV 20 mg/5 min nefopam = IV 0.2 mg/kg morphine

Guirimand et al. Pain 1999;80:399-404.

Nefopam: antihyperalgesic action

- **Explained by its actions on pain sensitization targets**
  - Monoaminergic pathways
  - Voltage dependent channels

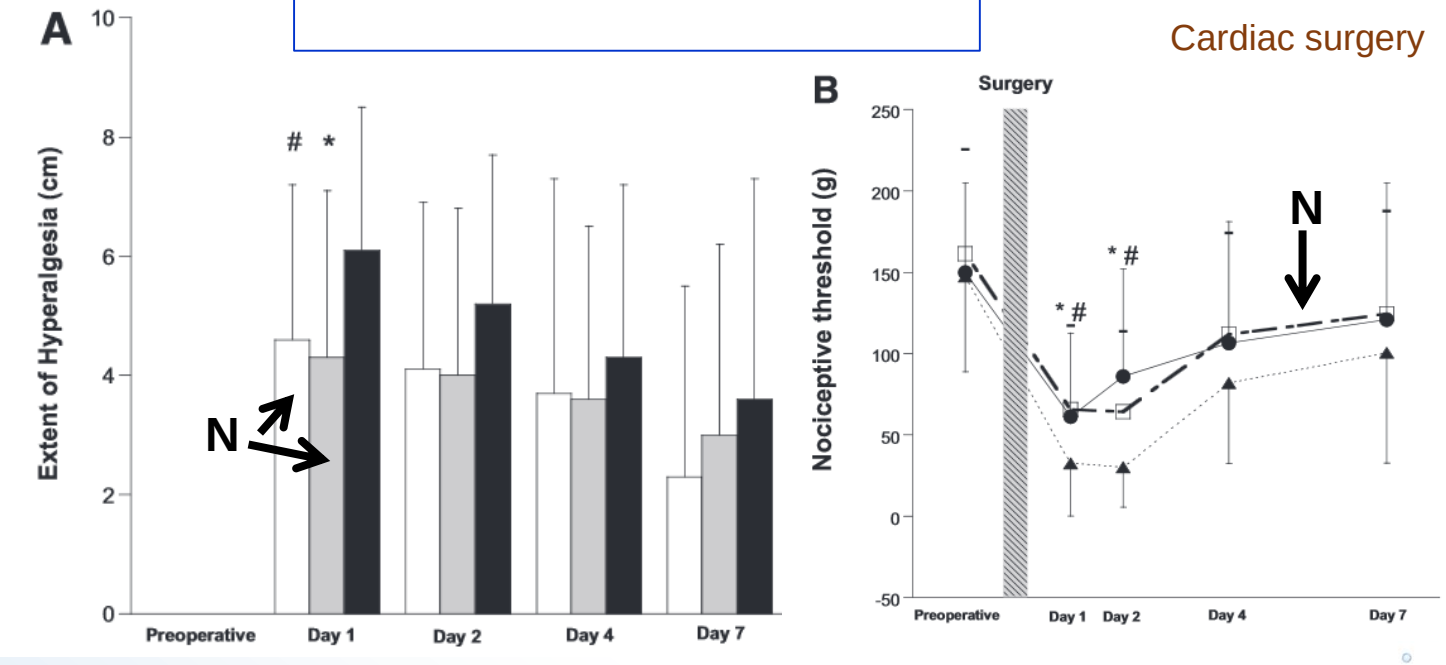
- **And confirmed by experimental and clinical studies**

[1]Verleye et al. Brain Res 2004;1013:249-55.
[2]Tirault et al. Anesth Analg 2006;102:110-7.

Nefopam: antihyperalgesic action

Secondary hyperalgesia = central sensitization

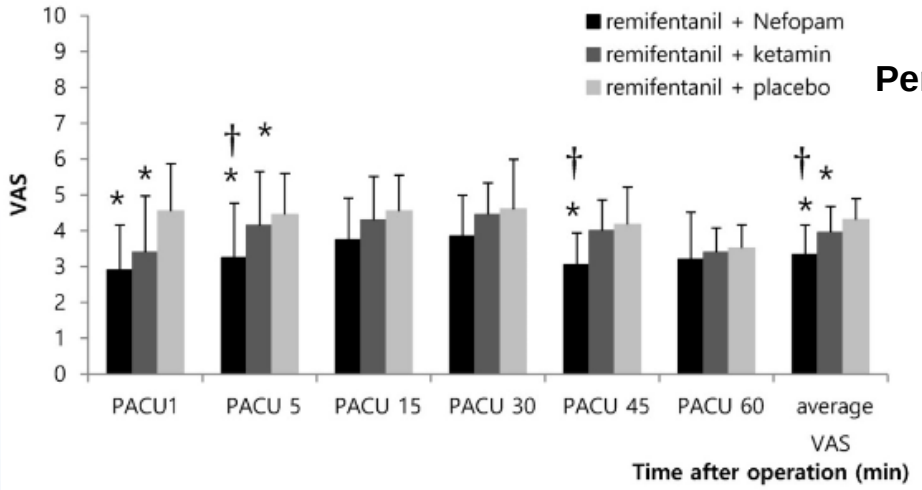
Cardiac surgery



Richebé et al. J Cardiothoracic Vasc Anesth 2013;27:427-35.

Per operative administration: nefopam is as effective as ketamine on post operative pain

Cholecystectomy - Laparoscopy



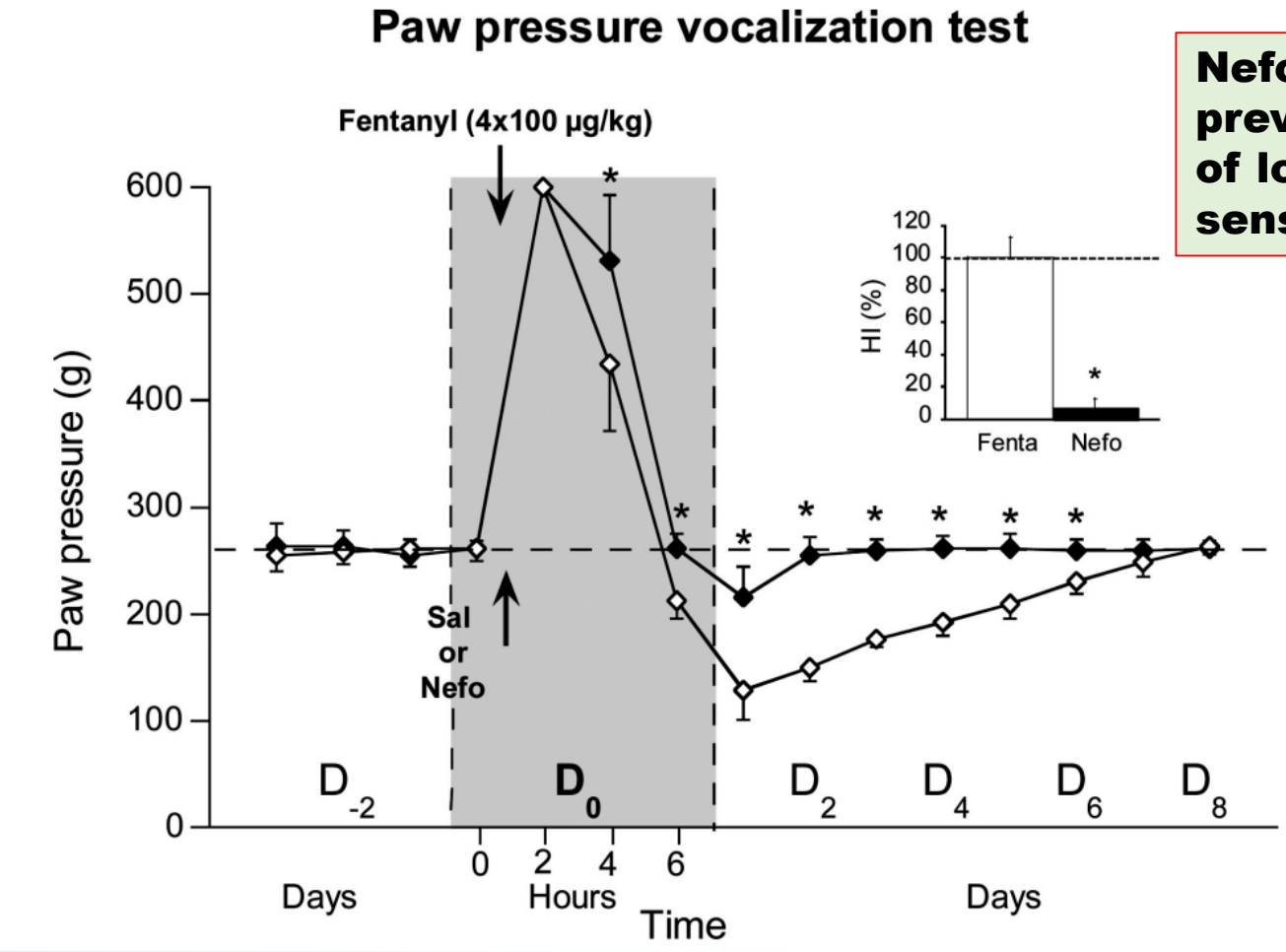
Perop administration.

Nefopam:
0,3 mg/kg
65 µg/kg/h

Ketamine:
0,3 mg/kg
180 µg/kg/h

Kim EM et al. Int J Med Sci 2017;14:570-7.

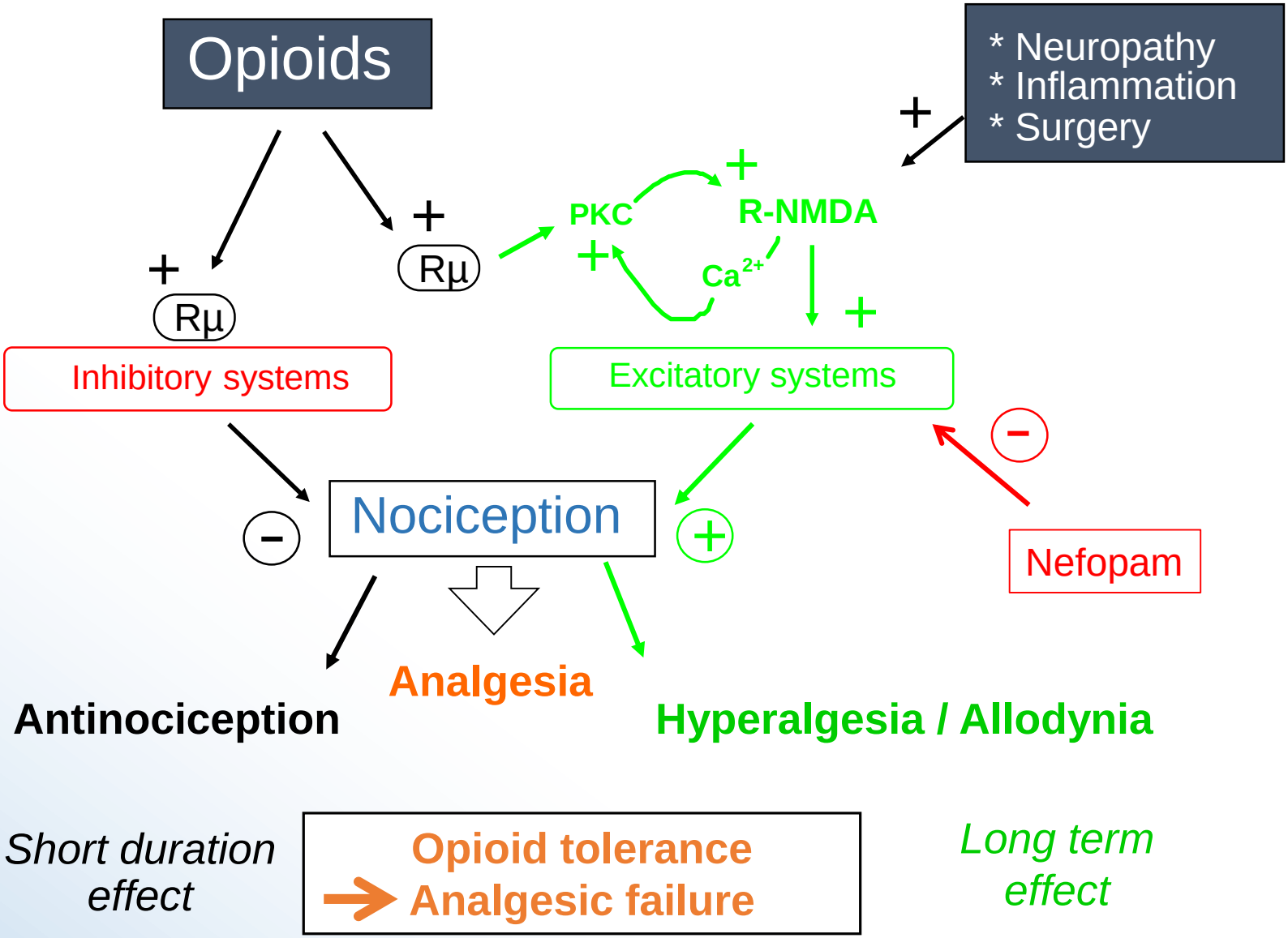
Nefopam: prevention of opioid induced hyperalgesia



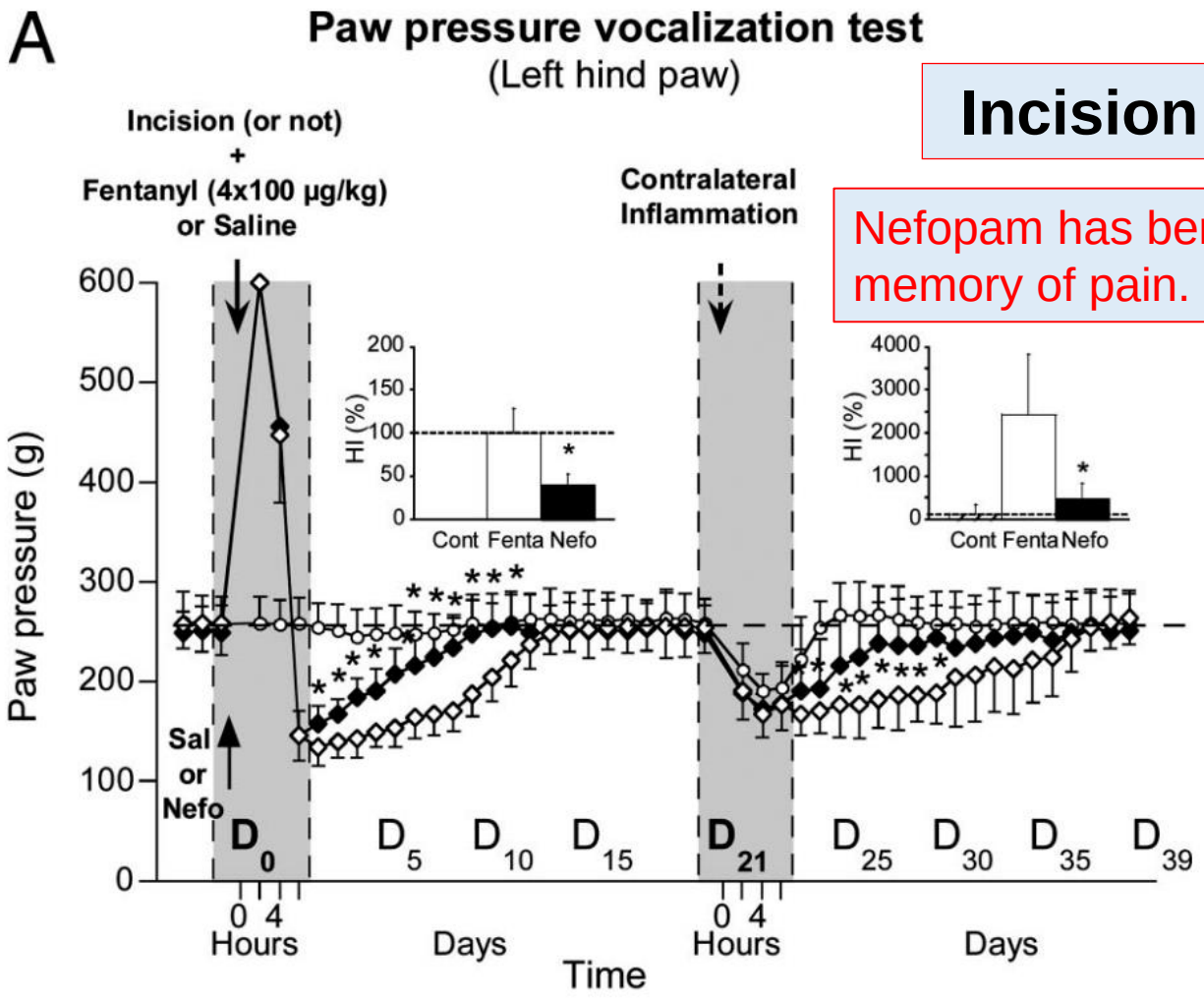
Nefopam: prevention of long-term sensitization

Laboureyras et al. Anesth Analg 2009;109:623-31.

Dual effect of opioids: neurobiological process



Antihyperalgesic effect



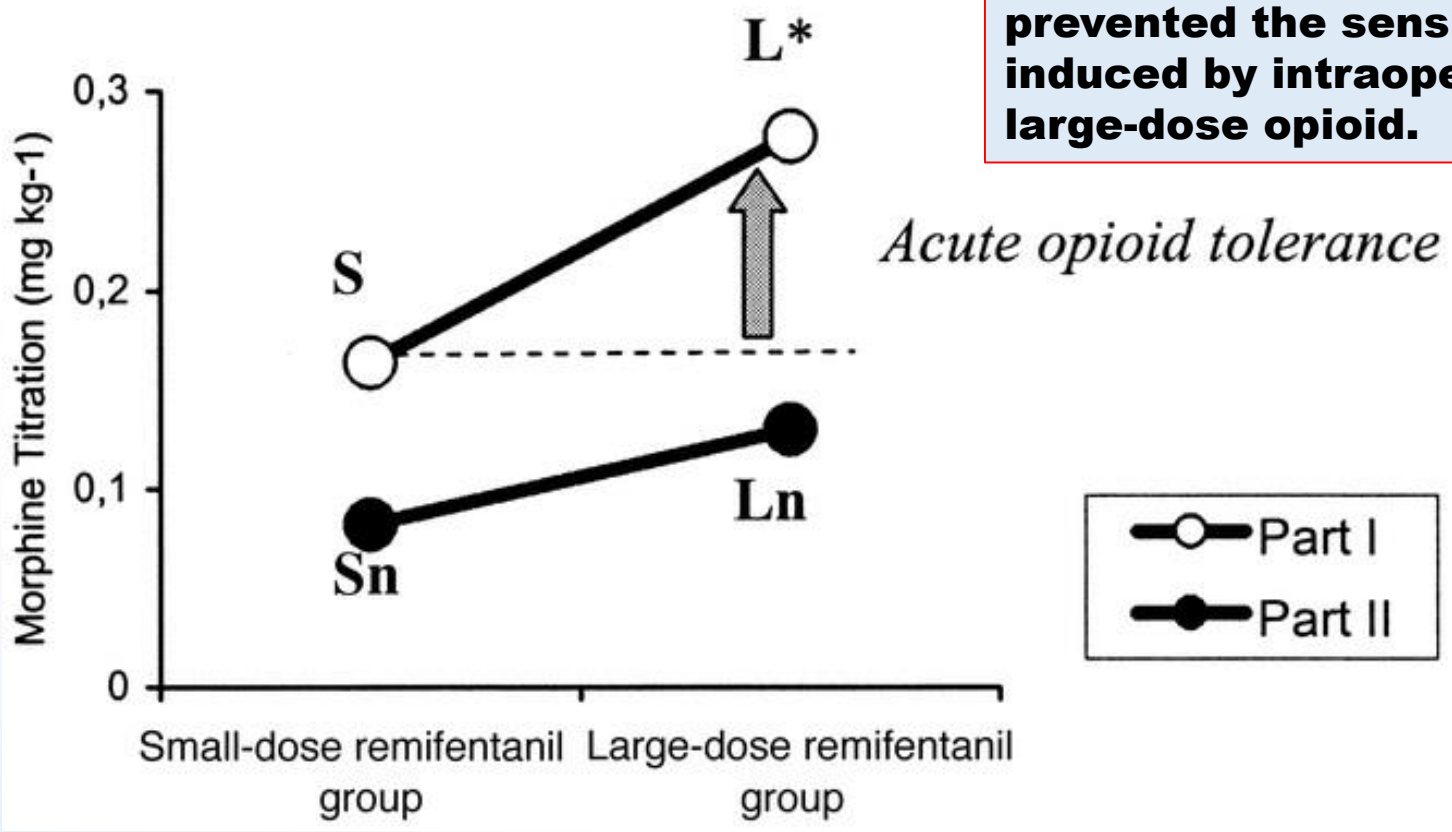
Incision + opioids

Nefopam has beneficial action on memory of pain.

Laboureyras et al. Anesth Analg 2009;109:623-31.

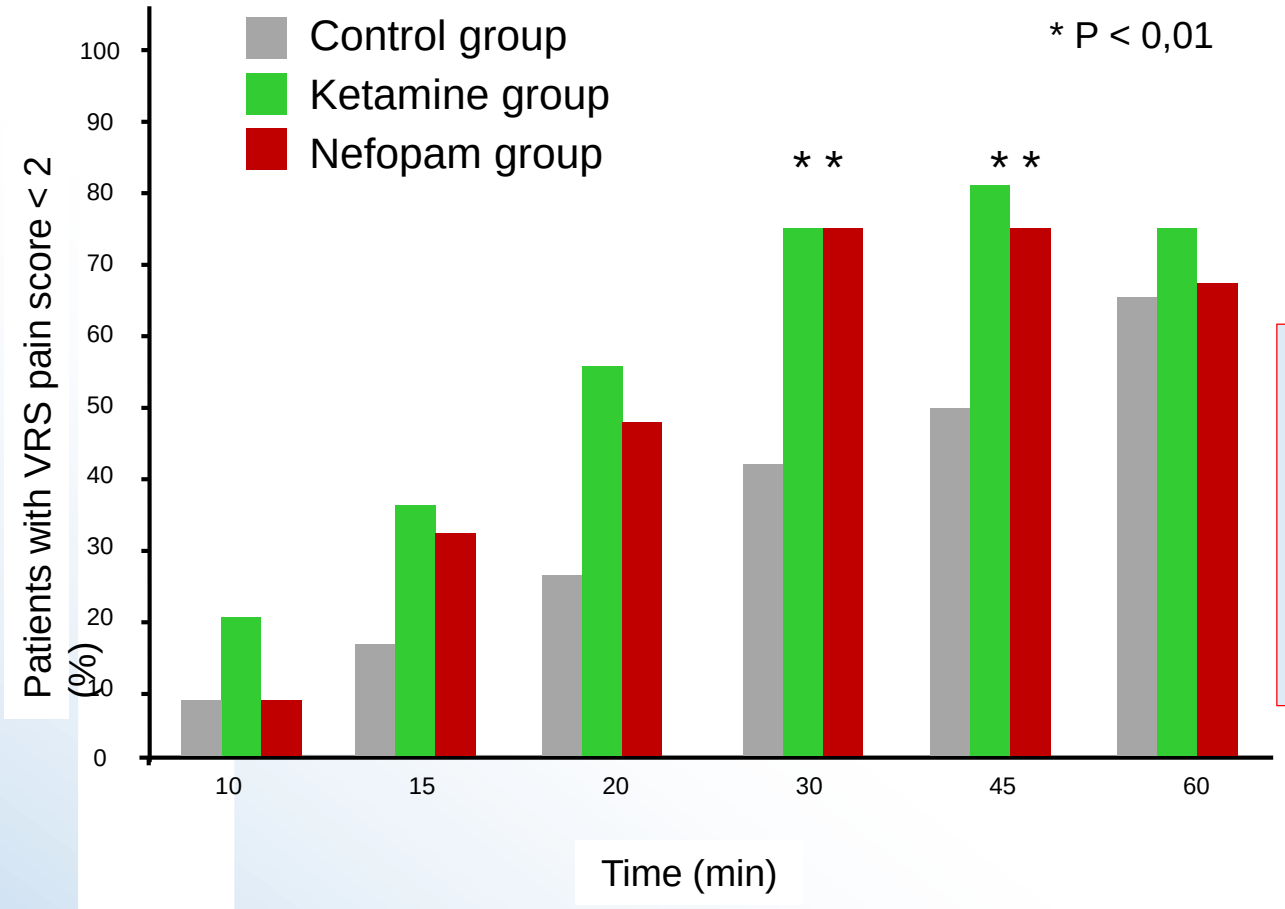
Nefopam – Prevention of acute opioid tolerance

Nefopam pre-treatment has prevented the sensitization induced by intraoperative large-dose opioid.



Tirault et al. Anesth Analg 2006;102:110-7

Nefopam – Acute opioid tolerance treatment

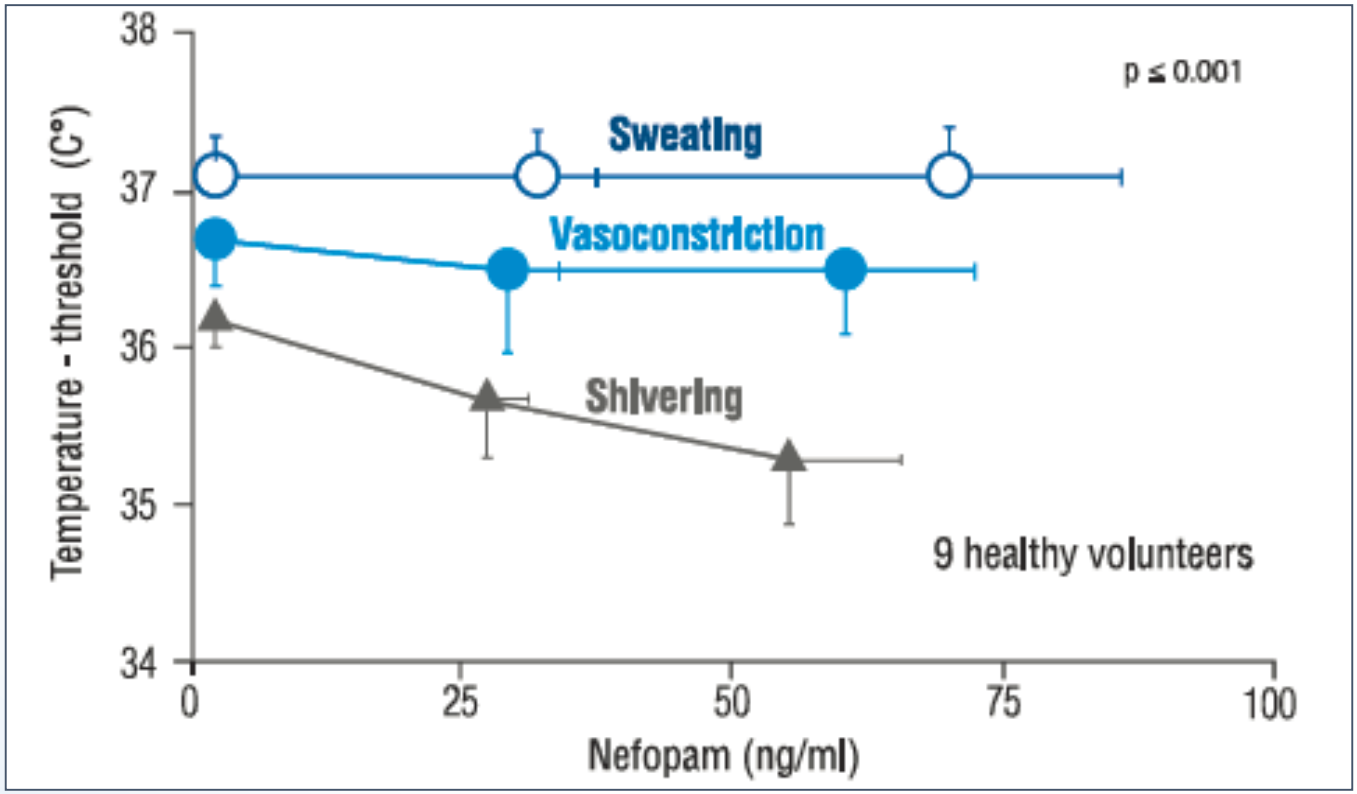


➔ **50%** morphine-sparing effect in the 2 treated groups

➔ **In the placebo group, 4 failures** of morphine titration (2 unrelieved pain and 2 inadequate ventilation) vs. **no failure in the two treated groups**
N = 25 patients/group

Kapfer et al. Anesth Analg 2005;100:169-74.

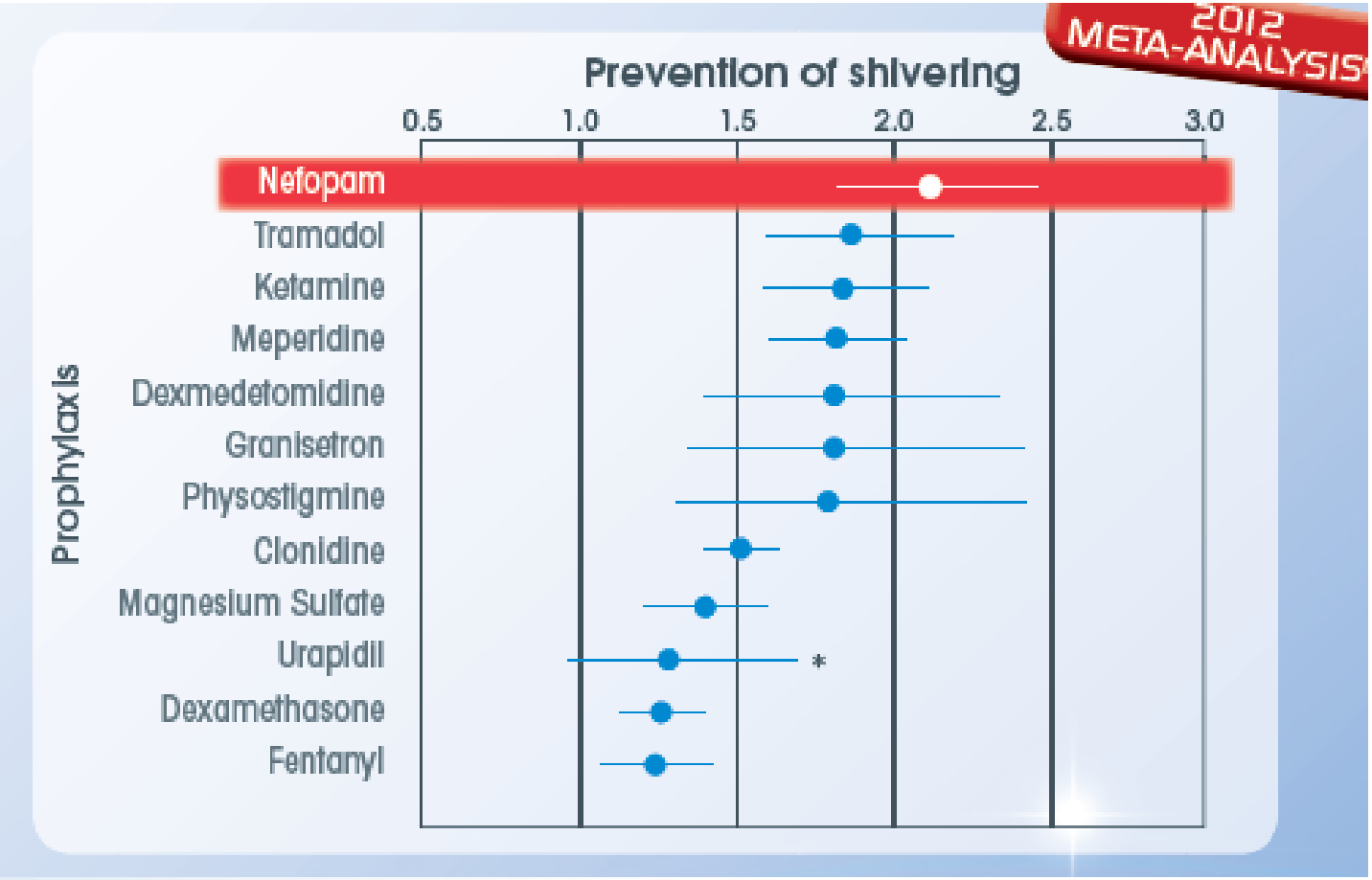
Nefopam - Prevention of shivering



Dose dependent reduction of shivering threshold

Alfonsi et al. Anesthesiology 2004;100:37-43.

Nefopam - Prevention of shivering



Parks S et al. Crit Care Med 2012;40:3070-82.

Agenda

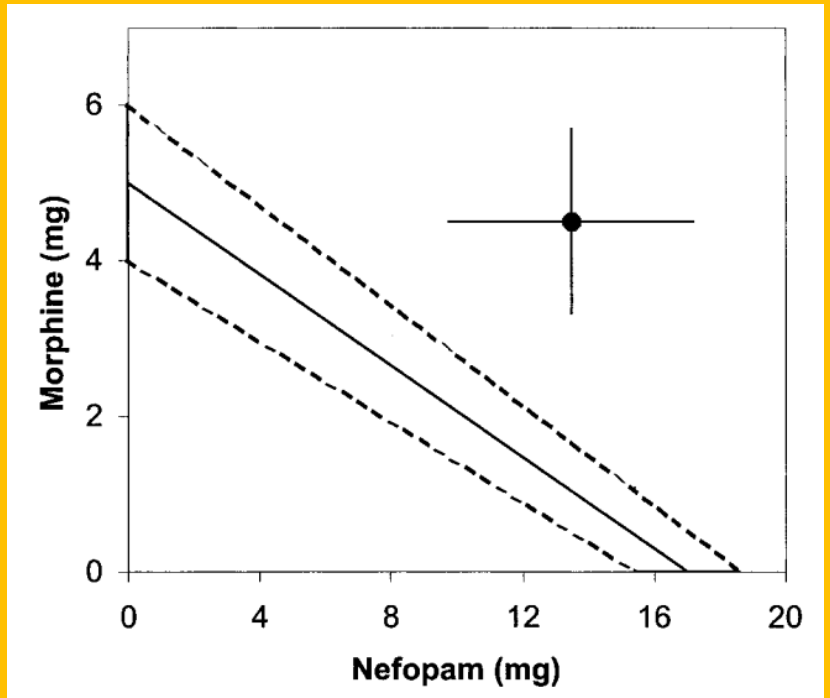
- Nefopam mode of action
  - Analgesia: antinociception and antihyperalgesia
  - Shivering inhibition
- **Nefopam: component in multimodal analgesia**
- Nefopam use in practice

Nefopam: component of multimodal analgesia

Morphine – Nefopam combination

Nefopam - Morphine Interaction

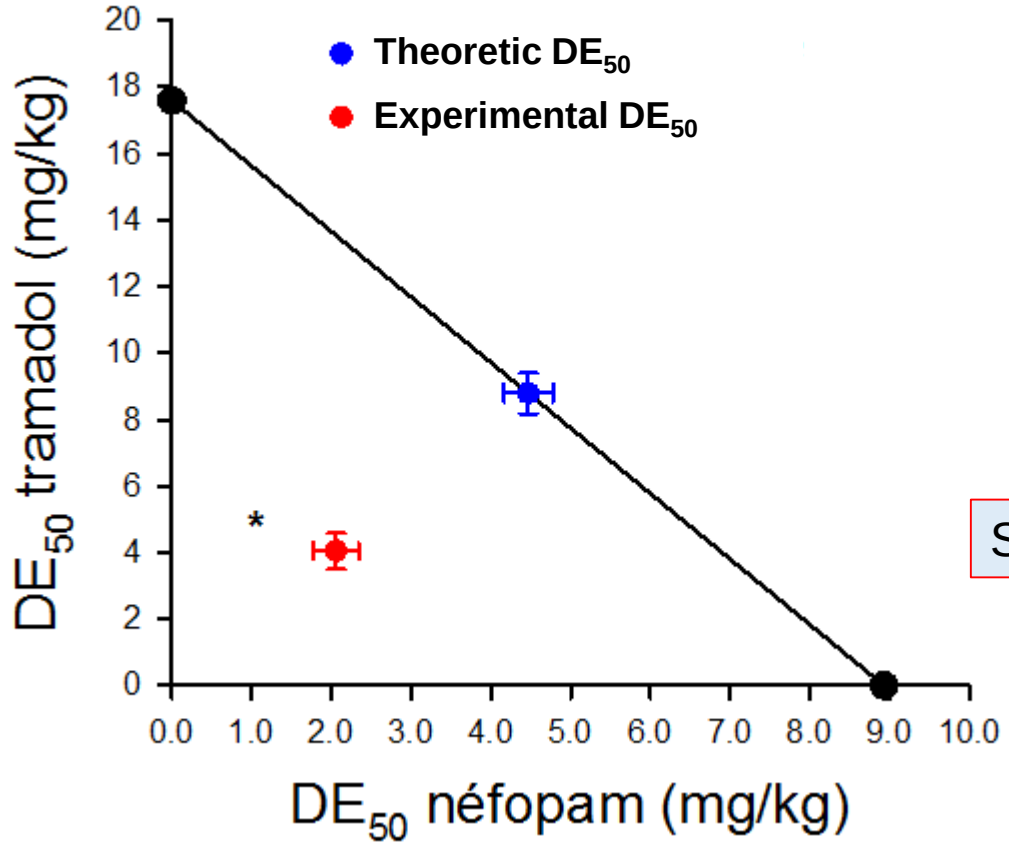
Synergy in an experimental study.
Girard et al. Pharmacol Biochem Behav 2004;77:695-703.



- **Moderately painful surgeries (PACU)**
- **Determination of ED50 of each drug using an up-down sequential technique (Dixon)**
- **Infra-additive interaction between nefopam and morphine**

Beloeil et al. Anesth Analg 2004;98:395-400.

Tramadol/nefopam interaction



Study in rats
(hot plate test)

Supra-additive interaction

Girard et al. 2012.

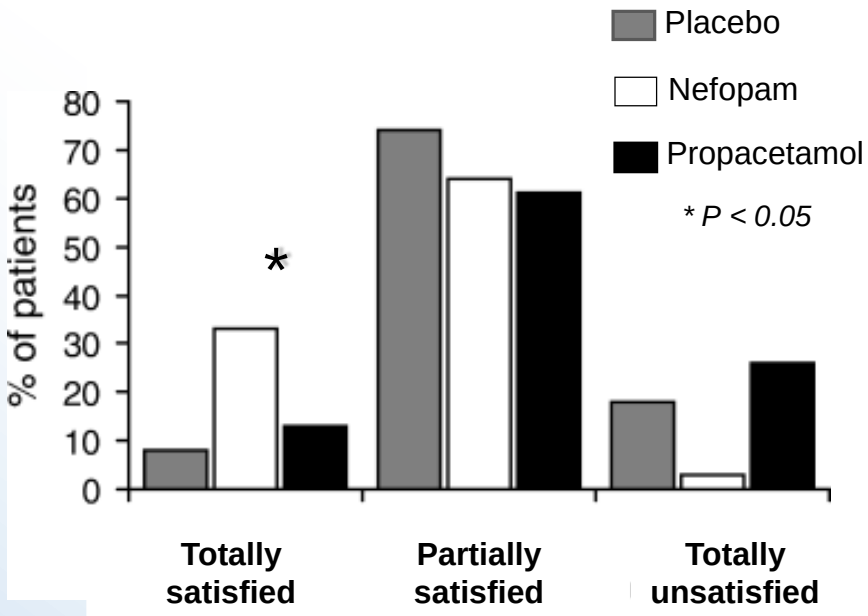
Nefopam and opioid sparing effect

	Surgery	Administration Dose/day	Duration of the study	**Opioid sparing effect**
Mc Lintock 1988	Abdominal (n=53)	IM 80 mg	24 h	**30%** *(44 vs. 62 mg)*
Du Manoir 2003	Ortho LL (n=200)	IV discontinuous 120 mg	24 h	**22%** *(21 vs. 27 mg)*
Tramoni 2003	Abdominal (n=62)	IV continuous 80 mg	48 h	**33%** *(39 vs. 58 mg)*
Mimoz 2001	Liver (n=110)	IV discontinuous 120	24 h	**50%** *(21 vs. 43 mg)*

Nefopam: analgesic efficacy

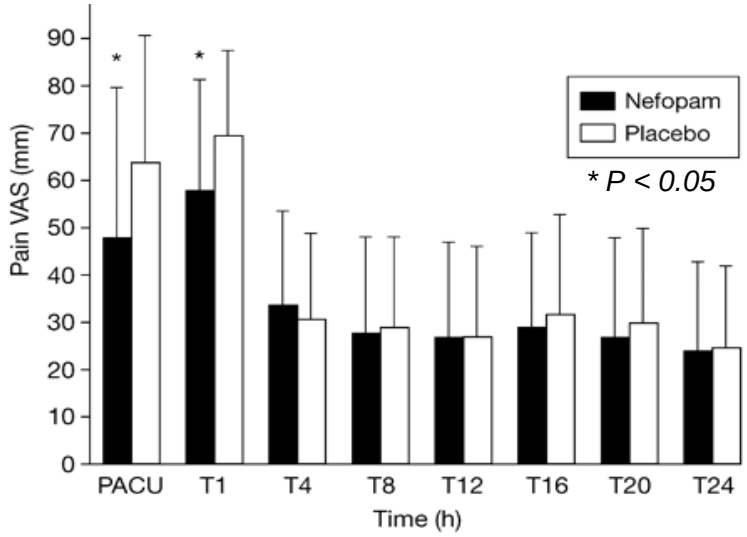
Hepatic resection

Mimoz et al. Anaesthesia 2001.



Hip arthroplasty

Du Manoir et al. Br J Anaesth 2003.



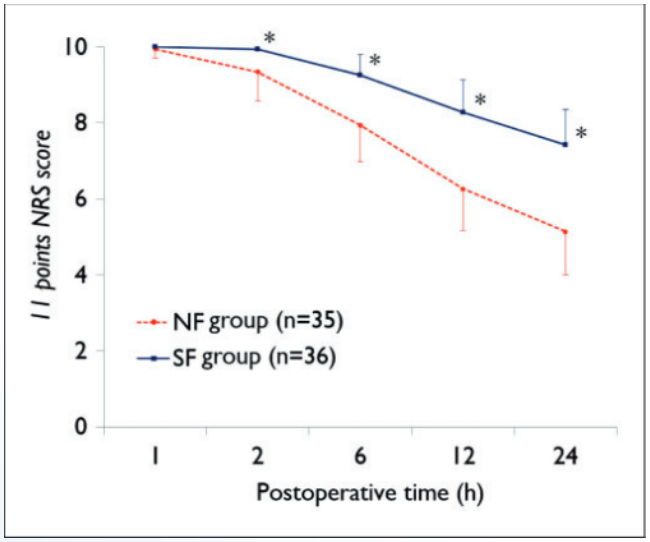
Opioid side effects

Kapfer et al.
Anesth Analg 2005

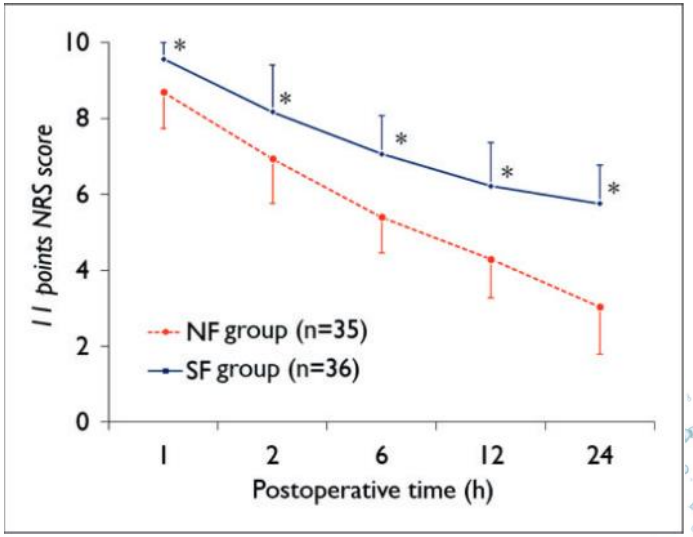
Nefopam + fentanyl

Laparotomy

At mobilization



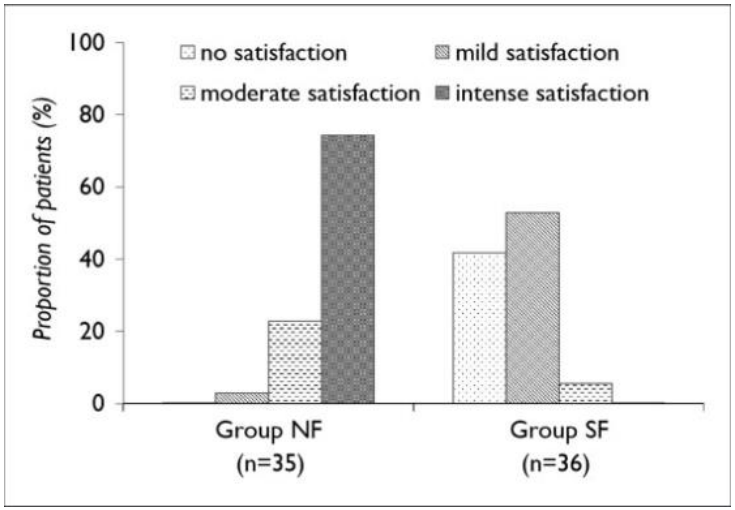
At rest



34% of fentanyl spare at 24 h

Jin HS et al. J Int Med Res 2016;44:844-54.

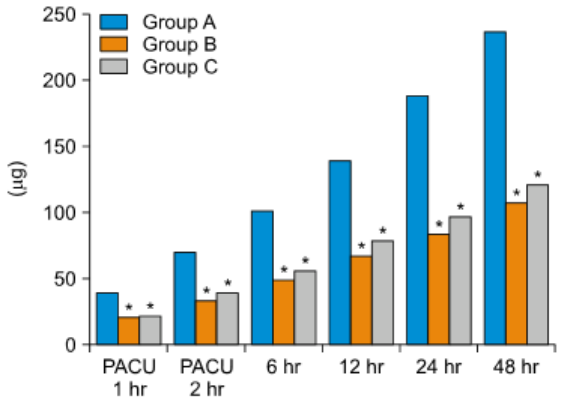
Nefopam + fentanyl



Jin HS et al. J Int Med Res 2016;44:844-54.

Nefopam + fentanyl

Hysterectomy - Laparoscopy



2 groups of nefopam (B et C)

Fentanyl spare:
- 54,5% in group B
- 48,9 % in group C

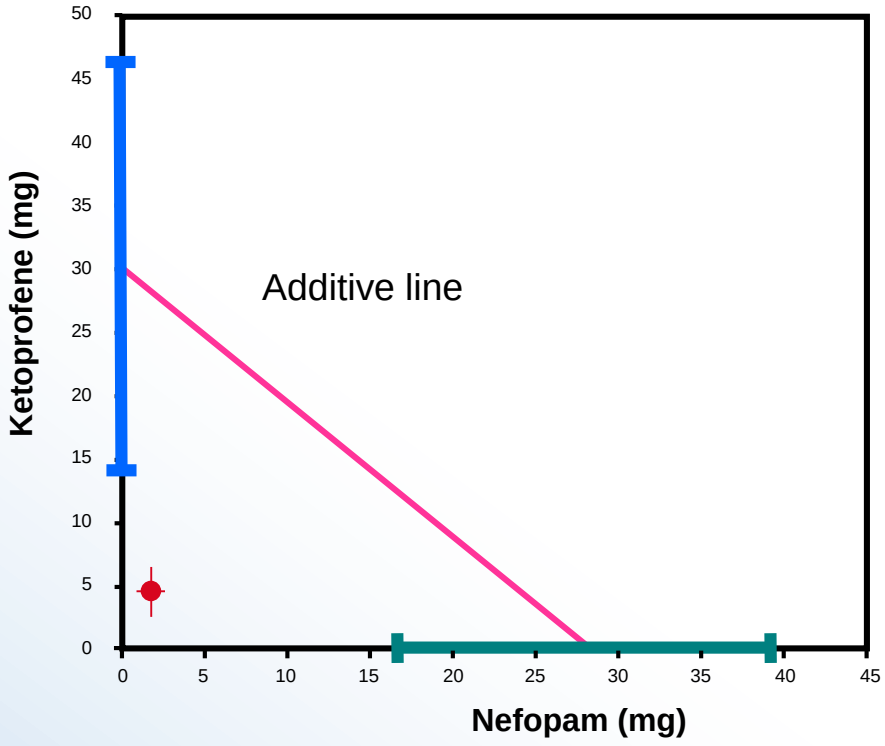
EVA = NS

Moon JY et al. Korean J Pain 2016;29:110-8.

Nefopam: component of multimodal analgesia

Nefopam – Non-opioid analgesic combination

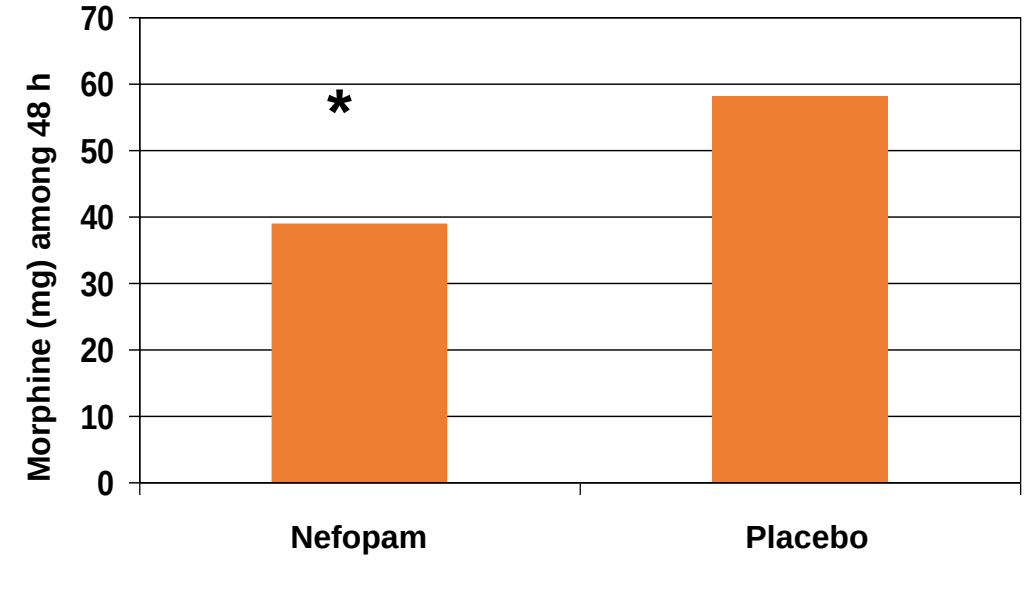
Nefopam + NSAIDs



- **Moderately painful surgeries (PACU)**
- **Determination of DE50 of each drug using an up-down sequential technique (Dixon)**
- **Supra-additive interaction between nefopam and ketoprofen**

Delage et al. Anesthesiology 2005;102:1211-6.

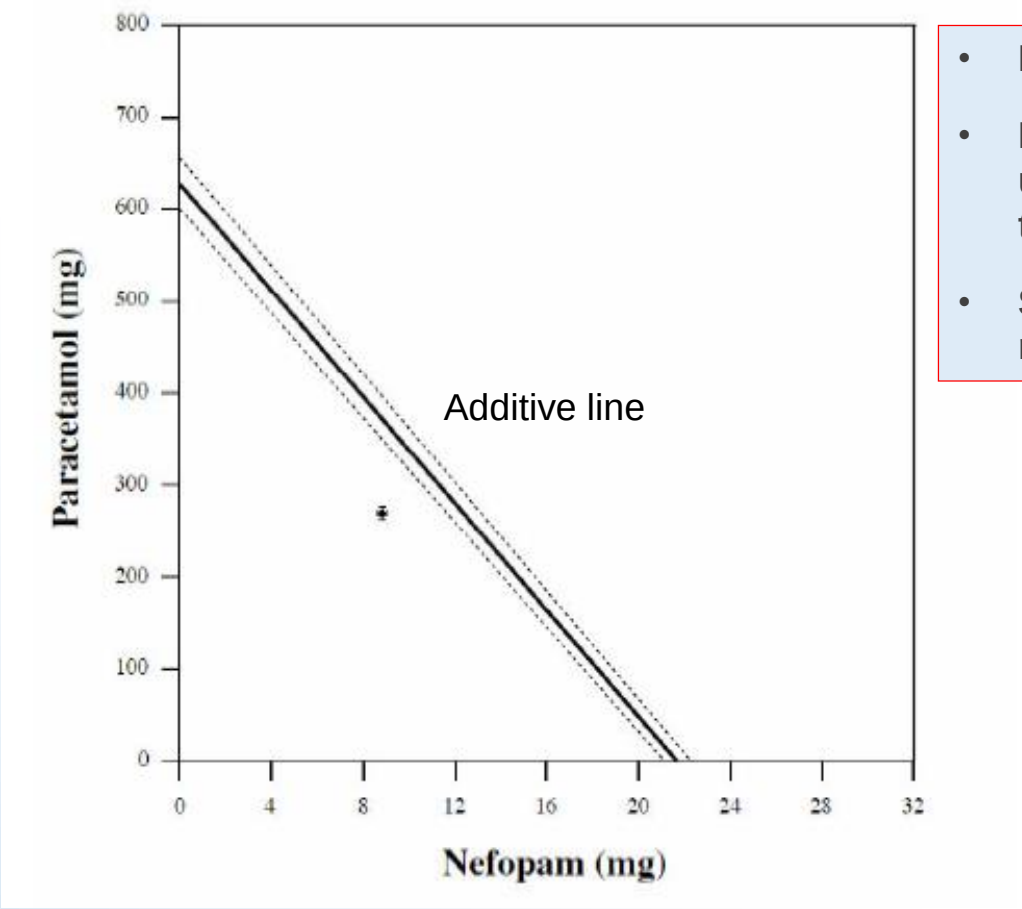
Nefopam + paracetamol



- Abdominal surgery by laparotomy
- Propacetamol (8 g/d) to all patients
- Nefopam (80 mg/d at D1 and D2) vs. placebo
- PCA morphine.

Tramoni et al. Eur J Anaesthesiol 2003;20:984-92.

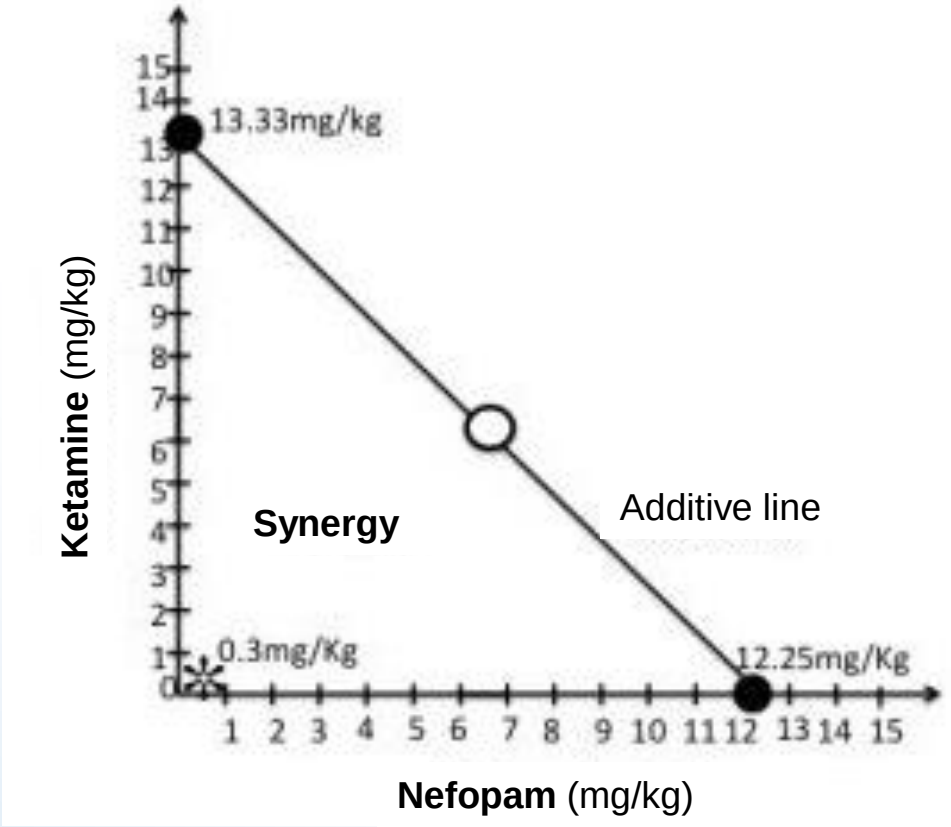
Nefopam + paracetamol



- **Moderately painful surgeries (PACU)**
- **Determination of ED50 of each drug using an up-down sequential technique (Dixon)**
- **Supra-additive interaction between nefopam and paracetamol.**

Van Elstraete and Sitbon. Minerva Anesthesiol, 2013;79:232-9.

Nefopam + ketamine

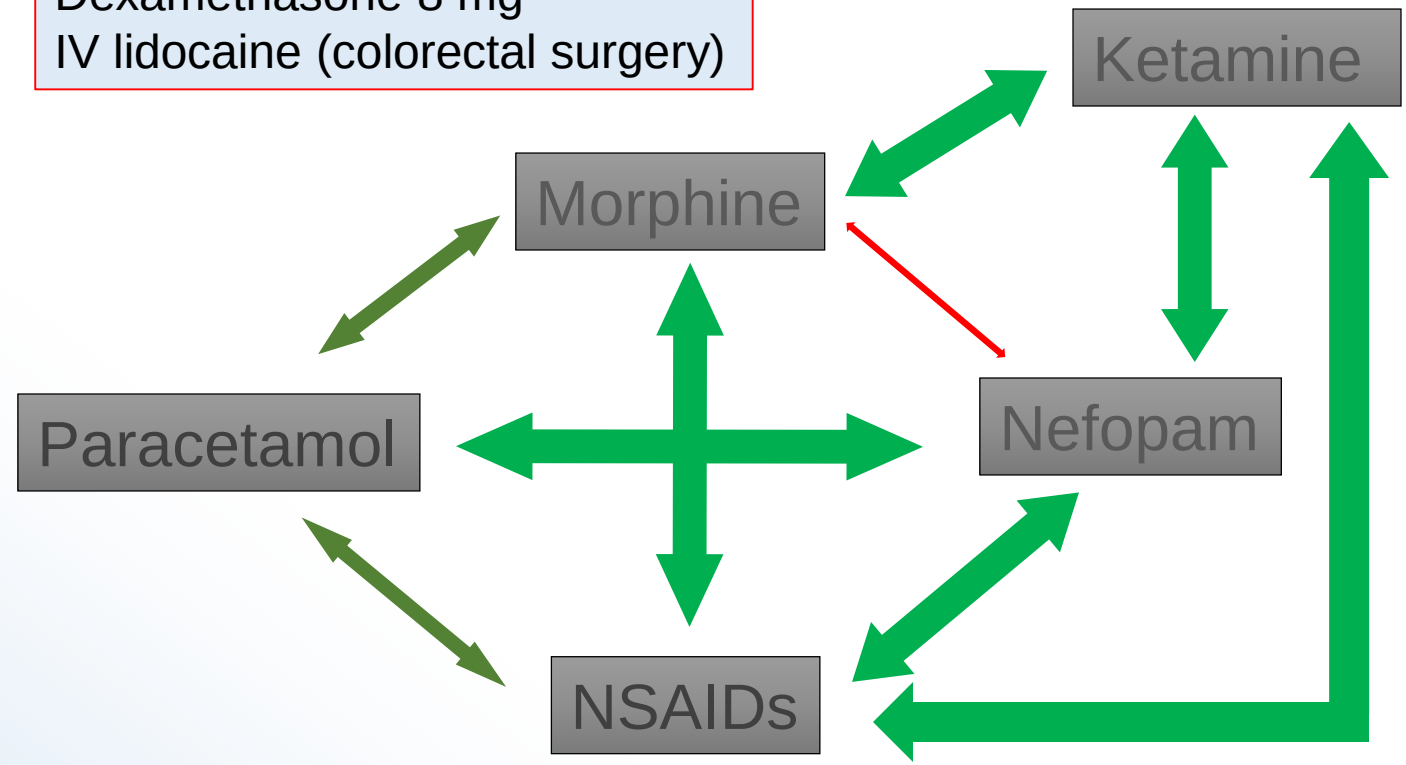


- **Experimental model (rat) of opioid induced hyperalgesia**
- **Strong supra-additive interaction**

Sitbon et al. ASA 2012.

Multimodal analgesia

Dexamethasone 8 mg
IV lidocaine (colorectal surgery)



Supra-additive Additive Infra-additive

Nefopam and multimodal analgesia

- **Nefopam – Morphine combination:**
  - produces a significant opioid sparing effect
  - with a reduction in opioid side effects
  - and an improvement in analgesic quality

- **Nefopam – AINS interaction is very strongly synergistic**

- **Nefopam – paracetamol combination is also interesting…**

…as nefopam – ketamine association.

Agenda

- Nefopam mode of action
  - Analgesia: antinociception and antihyperalgesia
  - Shivering inhibition
- Nefopam: component in multimodal analgesia
- **Nefopam use in practice**

Nefopam – Safety

- No depressive action on respiratory function
- No action on blood coagulation
- No antipyretic effect
- Great security of utilization : very high therapeutic index (= 40)

Potential side effects

- **Nefopam side effects:**
  - Nausea / vomiting
  - Sweating (5 to 25%)
  - Local pain at the site of injection
  - Dizziness
  - Tachycardia, urine retention, dry mouth
  - Increase of intraocular pressure in acute angle glaucoma

But, some of these side effects are prevented by a slow rate of IV infusion (20 mg over 30 min) +++ because…

- **Risk factors of nausea, vomiting, sweating and tachycardia:**
  - Speed of injection
  - Injected dose
  - Continuous vs. discontinuous

Systemic pharmacokinetics (Cmax and Tmax)

Nefopam-Morphine association and nausea-Vomiting

	Mode of administration And total dose	1st Injection	Nausea		vomiting		
Mc Lintock et al., 1988	IM 80 mg	Preop	30%	vs 35%	9%	vs 15%	
Du Manoir et al., 2003	IV., Discontinuous 120 mg	Perop	44%	vs 44%	21%	vs 20%	**IV 30 min**
Tramoni et al., 2003	IV., continuous 80mg/j	Postop	19 %	vs 38%	-		**IV cont.**
Mimoz et al., 2001	IV., Discontinuous 120 mg	Perop			17%	vs 39%	**IV 60 min**

Nefopam

Placebo

Nefopam – Contra-indications

- Children below 15 y.o., in absence of clinical data
- Convulsions or past history of convulsive disorders (serotonin re-uptake)
- Uretroprostatic disorders (risk of urinary retention)
- Acute angle glaucoma (risk of intraocular hyper pressure)
- Pregnancy and lactation.

Nefopam – Precautions for use

- **Precautions for use:**

  - Patients with hepatic insufficiency

  - Patients with renal insufficiency, particularly in elderly patients because of urinary elimination of the active metabolite (DMN)

➔ ***necessity to adapt the posology***

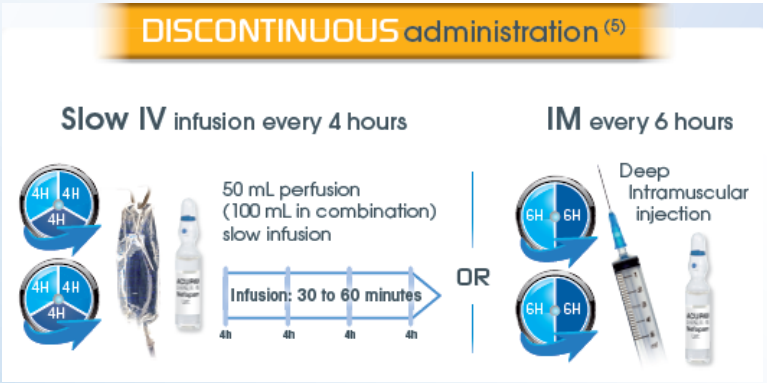
  - Has to be prescribed with precaution to patients with tachycardia.

Nefopam – Posology

- **To obtain the peak effect of nefopam in the immediate postoperative period, it is recommended:**

  - To start its administration (20 mg) intraoperatively, at least 1 h before the presumed end of surgery

  - To continue postoperatively with 80 to 120 mg (4 to 6 ampoules) over 24 hours
    - Discontinuously with a slow IV infusion (20 mg over 30 to 60 min) or continuously with an IV infusion
    - Or subcutaneously

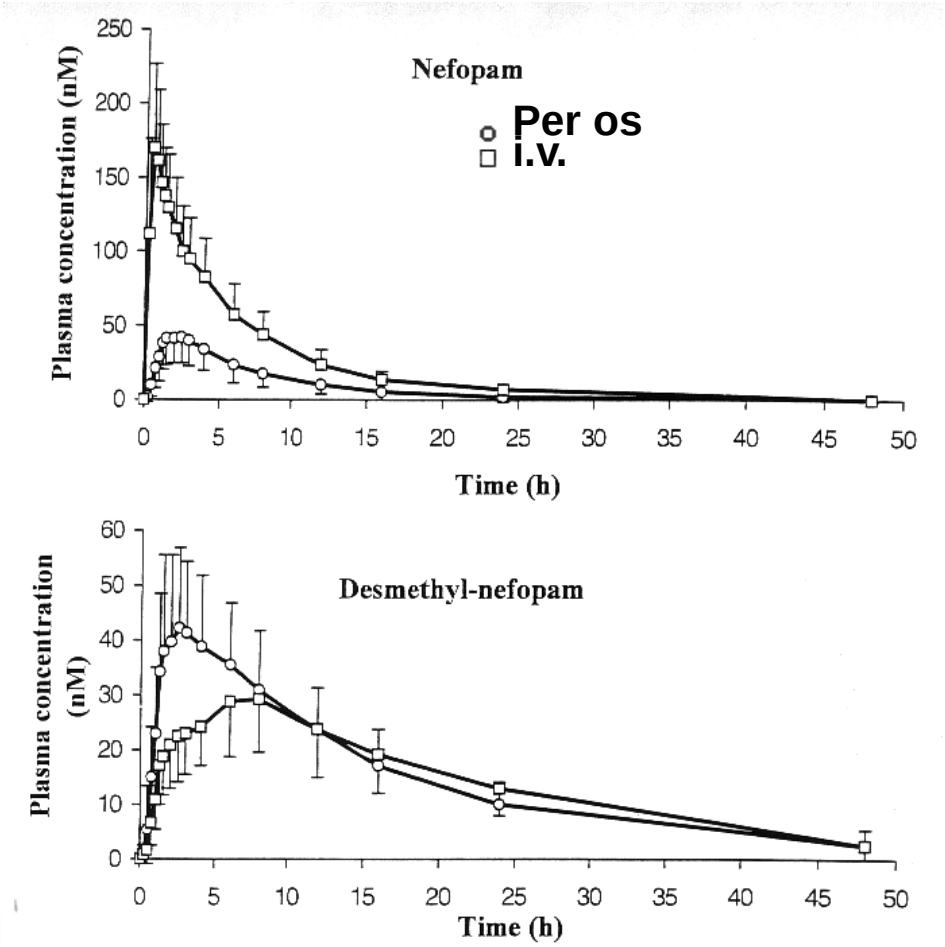




Plasma pharmacokinetics of oral nefopam

- Low oral bioavailability (36 %)
- **DMN:** active metabolite
- **PO 20mg = IV 20 mg**

(nefopam orally active)



Aymard et al. Pharmacol Toxicol 2003;92:279-86.

Conclusion – nefopam

- **Powerful analgesic**
- **Antihyperalgesic properties**
- Important component of **multimodal analgesia**
- **No major CI** in postoperative period
- Important: **administration in IV slow infusion** (no direct IV bolus) in order to decrease side effects
- Advantages to start the **administration intraoperatively** (anticipated and preventive analgesia)
- Also effective **orally**
- Another property : **treats and prevents the postoperative shivering**

→ **Many advantages in comparison to other analgesic drugs.**