The minimum local analgesic concentration for labor analgesia

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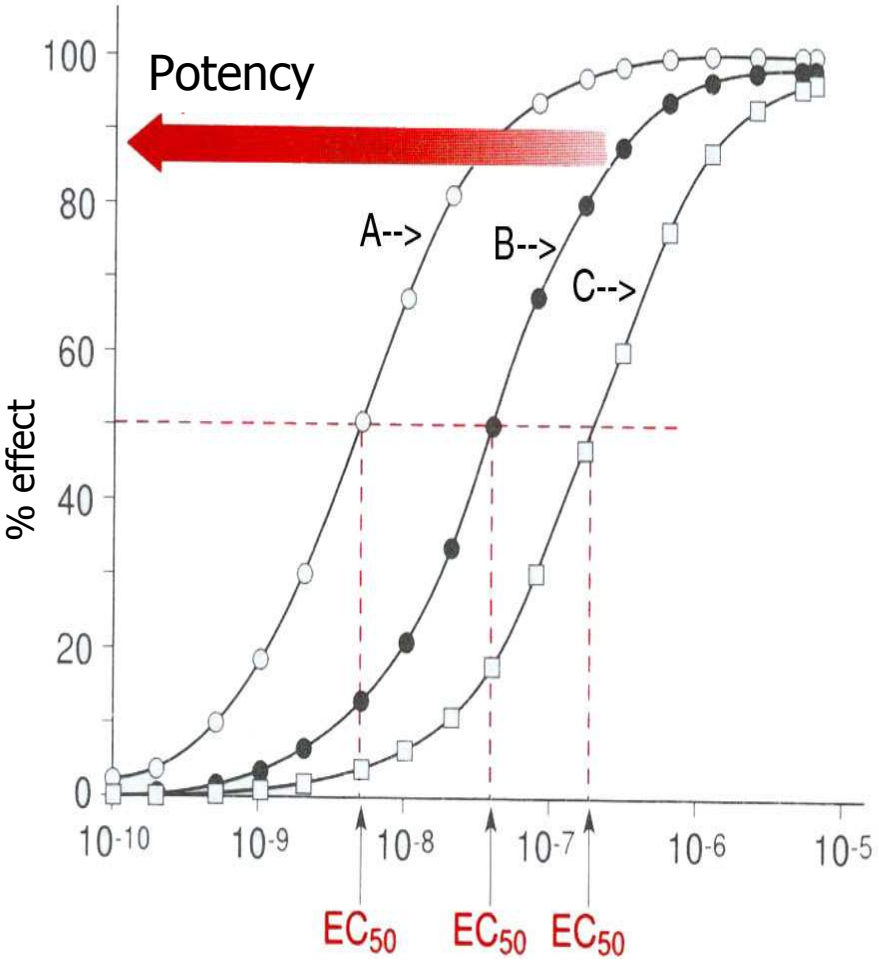
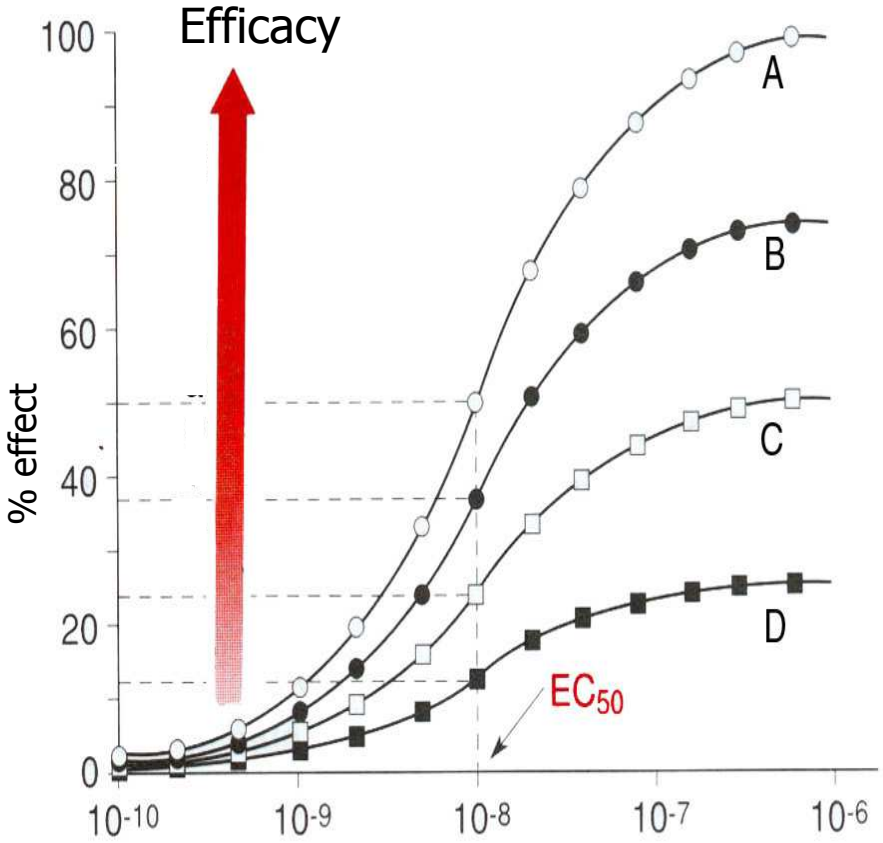
- The up-down sequential allocation model is the first systematic application of dose-response pharmacodynamics to regional anesthesia
- Comparison of drugs *relative potency*

(the ratio of equieffective concentrations) (EC50)

- Potency should not be confused with efficacy
- Efficacy: the maximum effect of a drug (Emax)


Potency
100
80
60
40
20
0
% effect
A-->
B-->
C-->
10-10
10-9
10-8
10-7
10-6
10-5
EC50
EC50
EC50

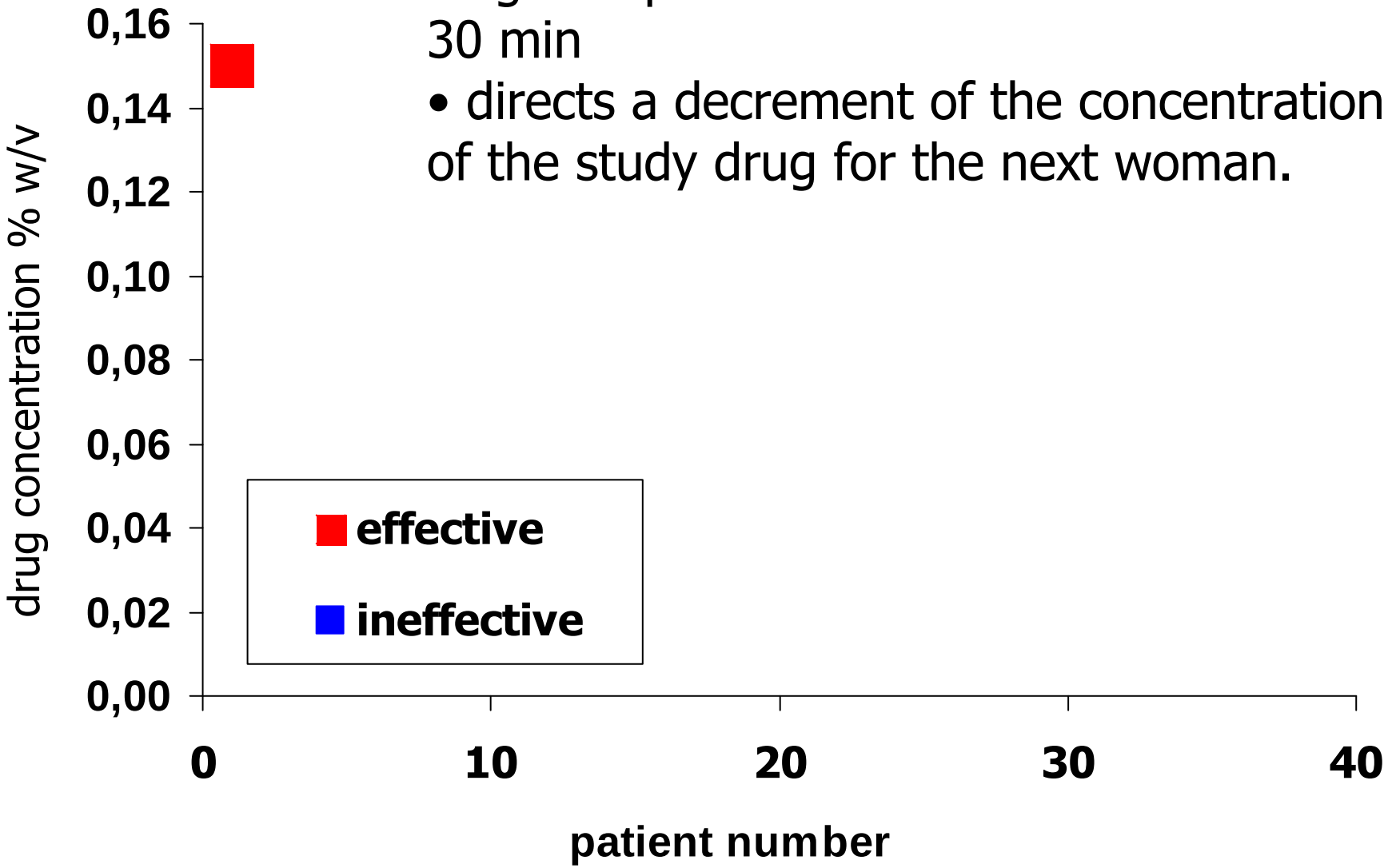

Efficacy
100
80
60
40
20
0
% effect
A
B
C
D
10-10
10-9
10-8
10-7
10-6
EC50

Up-down sequential allocation method

- is ideally suited to sensitivity experiments and has had applications in engineering, psychology, industrial chemistry and anesthesia (MAC)
- the response must be binary (yes/no, dead/alive, effective/ineffective) in an up-down manner with each subsequent patient's dose varying according to the previous patient's response

EFFECTIVE:

- requires a VAPS of 10 mm or less at the height of painful uterine contraction within 30 min
- directs a decrement of the concentration of the study drug for the next woman.



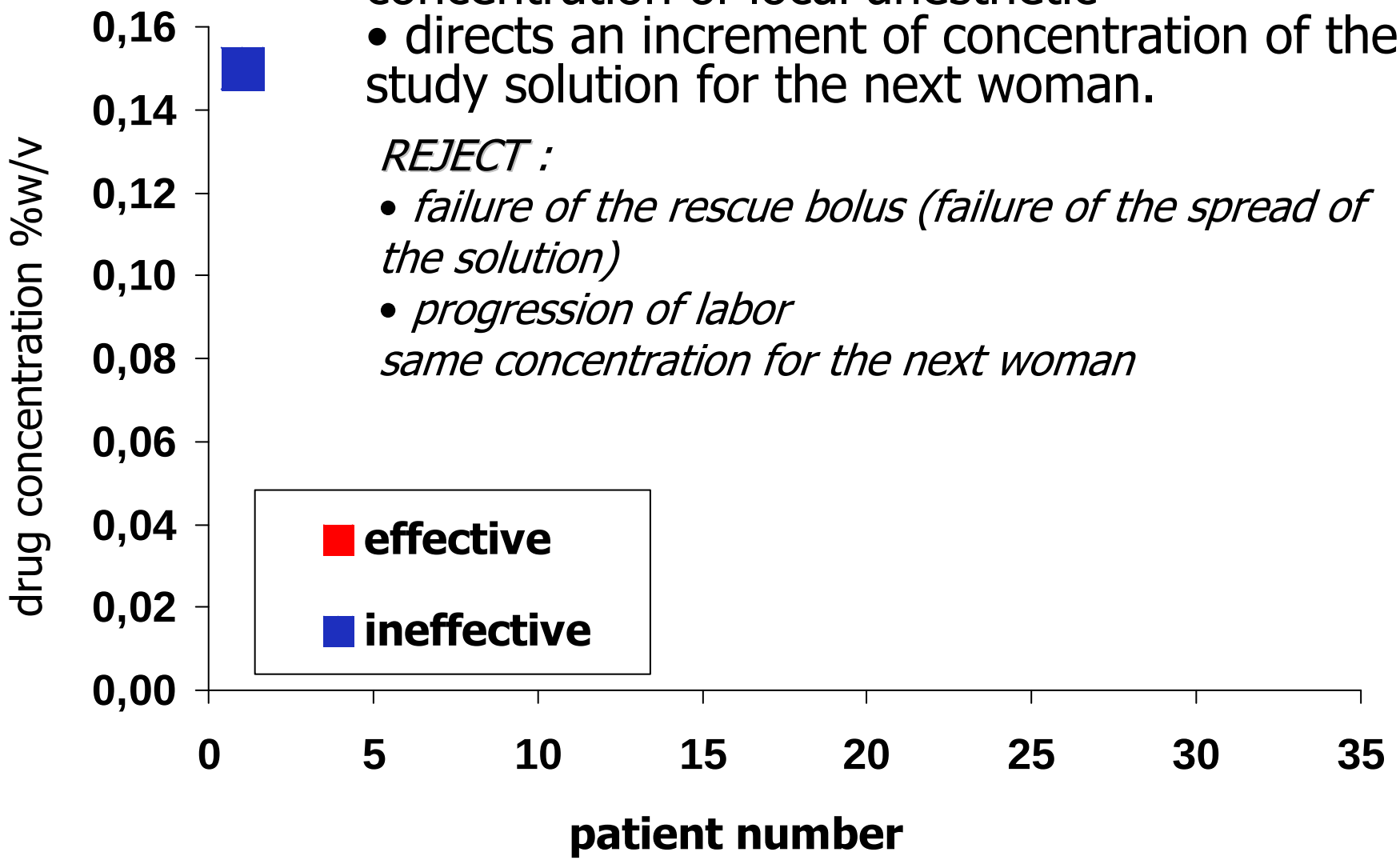
INEFFECTIVE:

- requires a VAPS greater than 10 mm that responds to a rescue bolus with a high concentration of local anesthetic
- directs an increment of concentration of the study solution for the next woman.

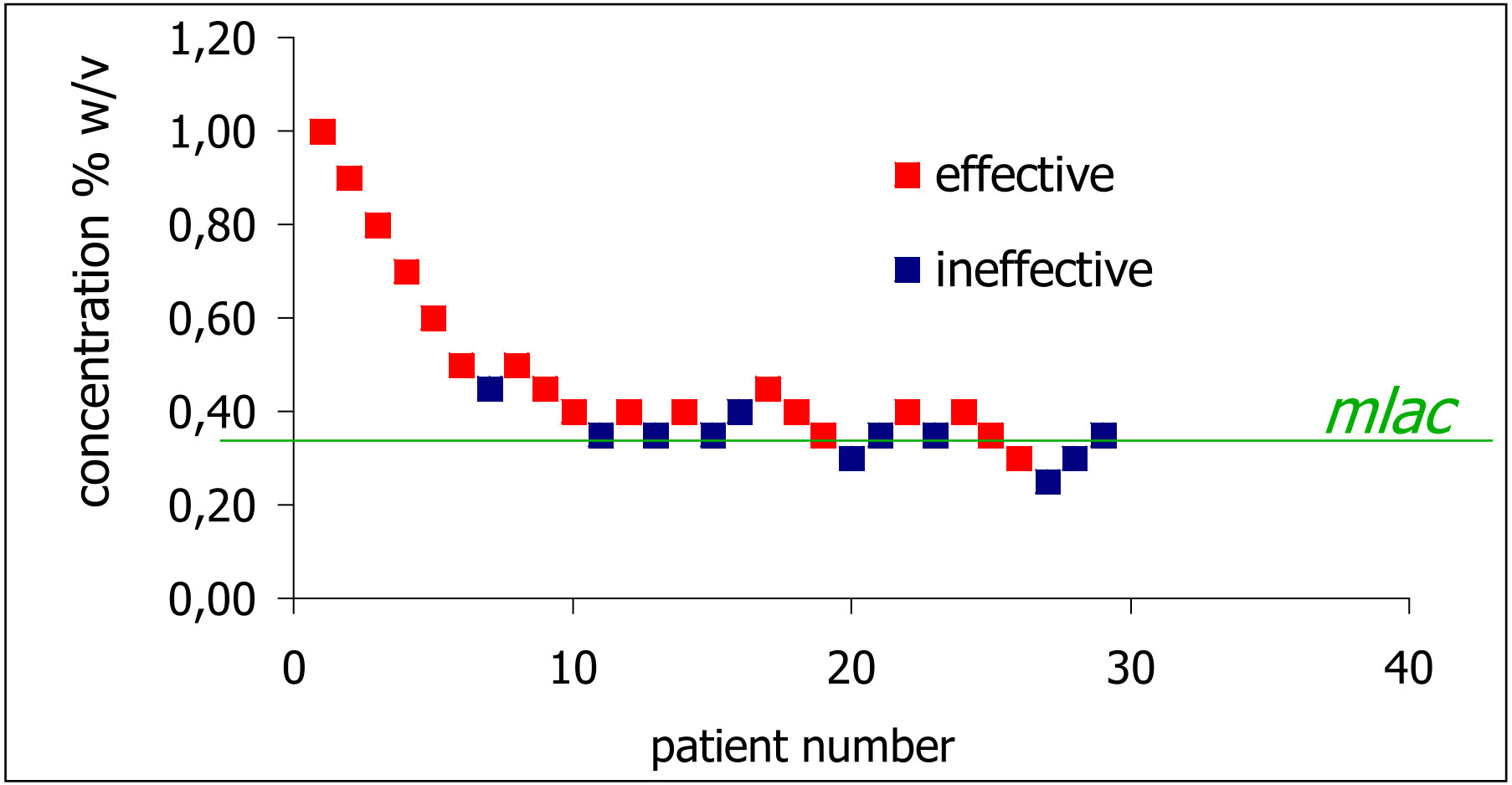
REJECT :

- *failure of the rescue bolus (failure of the spread of the solution)*
- *progression of labor*

same concentration for the next woman



- testing is eventually concentrated around the median
- allows the reduction (30-80%) in the sample size
- increases the accuracy with which the median is estimated



- EC50 - ED50 and relative potencies of local anesthetics
  - Analgesia
  - Motor block
  - Sensory – motor separation
- ED50 and relative potencies of opioids
  - Sparing effect
- Obstetric factors influencing local anesthetic requirements
  - Stage of labor (cervical dilatation)
  - Dystocia
  - Induction of labor

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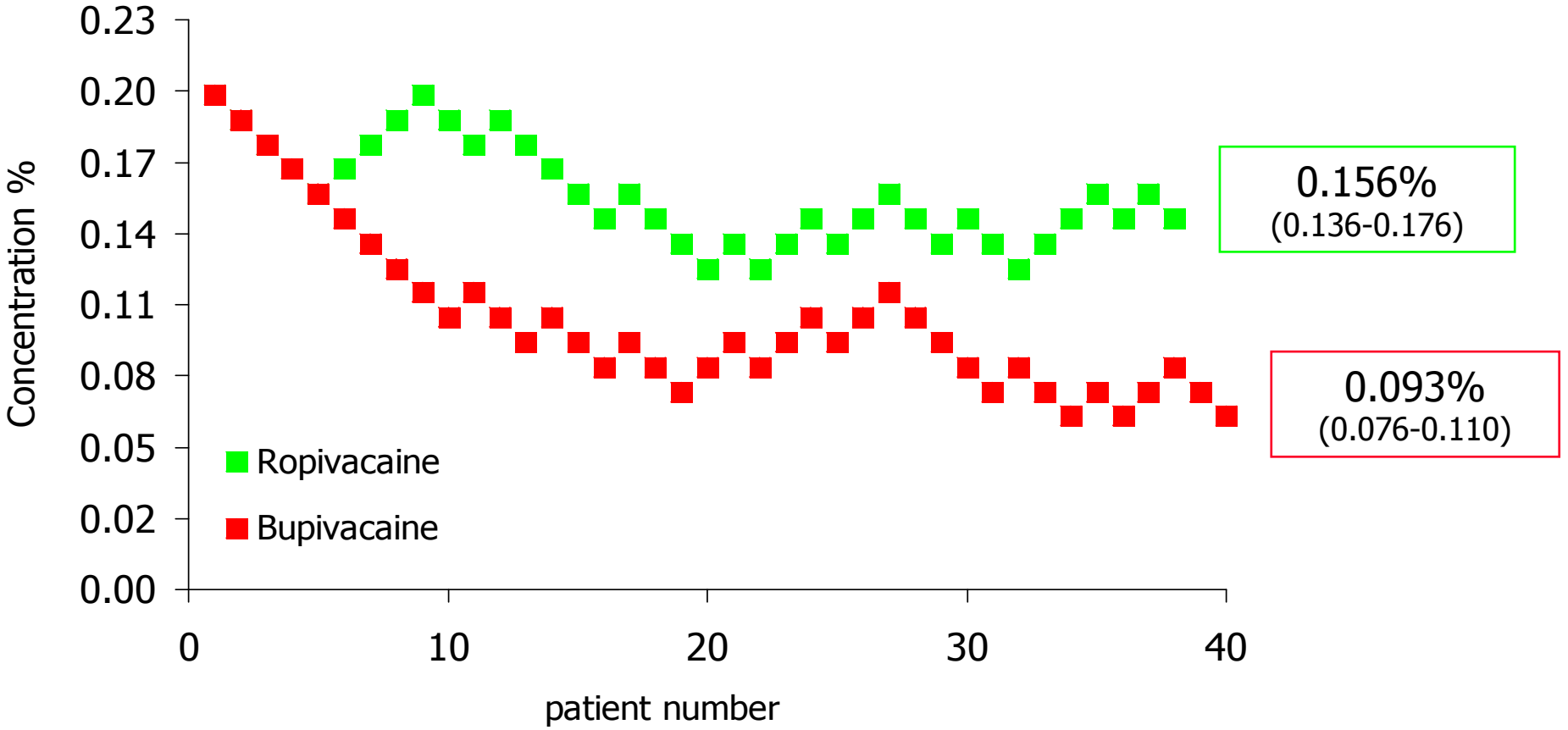
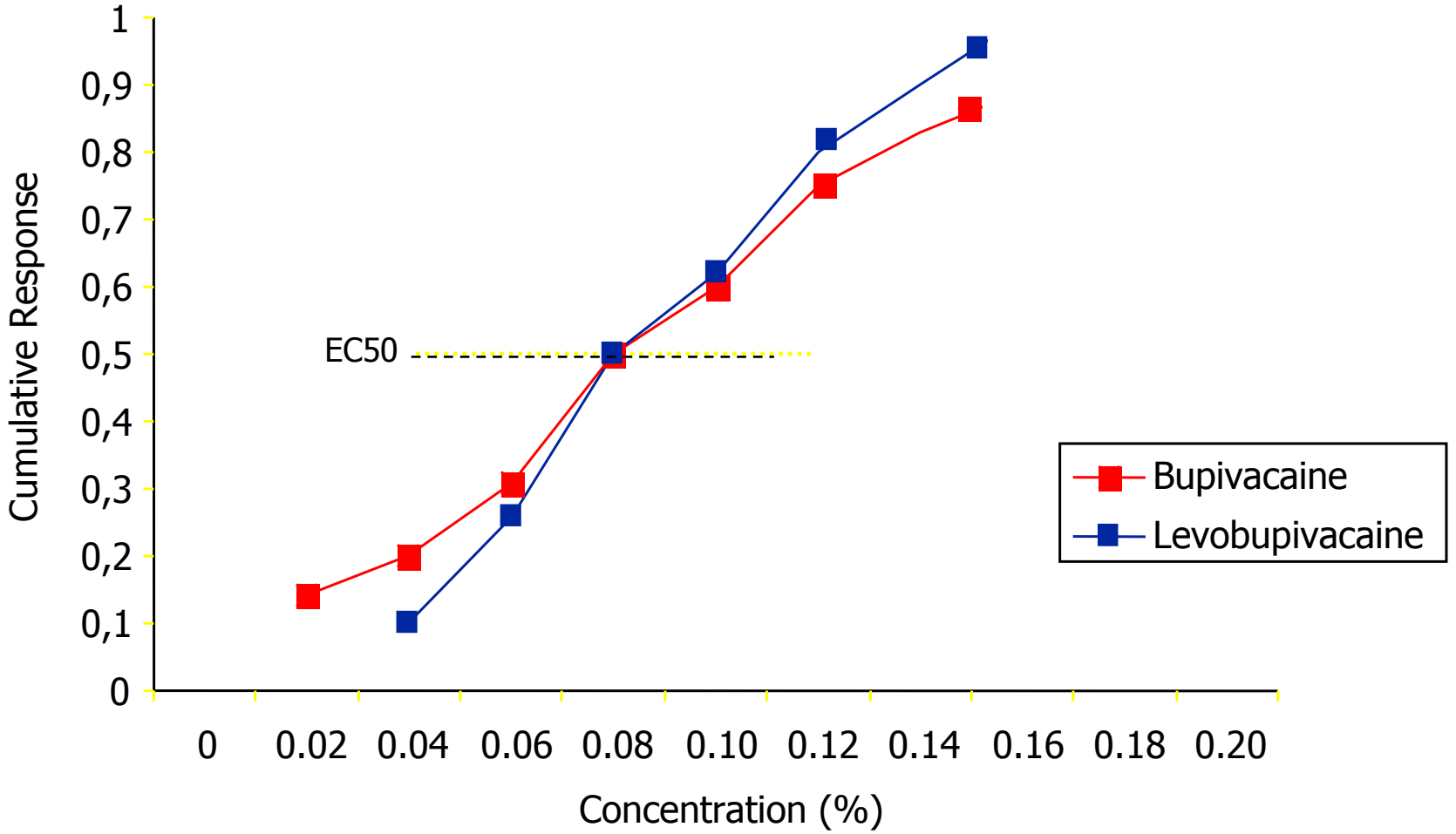
EC50 for Analgesia of Epidural Bupivacaine & Ropivacaine



Potency ratio: 0.60 (0.47-0.75)

Capogna G et Al. BJA 1998

Concentration-response plots for analgesia
Bupivacaine vs Levobupivacaine



Potency ratio: 0.98 (0.67-1.41)

Molar Potency ratio: 0.87 (0.60-1.25)

Lyons G et Al. BJA 1998

Bupivacaine 40% > Ropivacaine

Capogna G et Al. BJA 1998; Polley LS et Al. Anesthesiology 1998

Bupivacaine 2-13% > Levobupivacaine

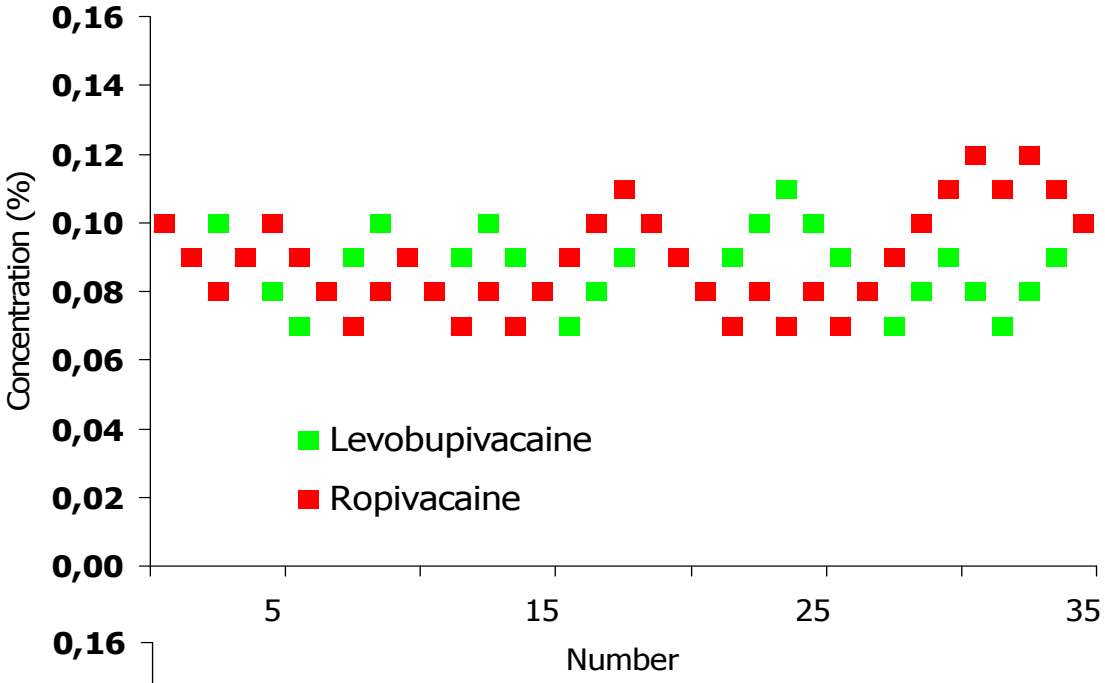
Lyons G et Al. BJA 1998

Levobupivacaine > Ropivacaine?

Levobupivacaine ≥ Ropivacaine

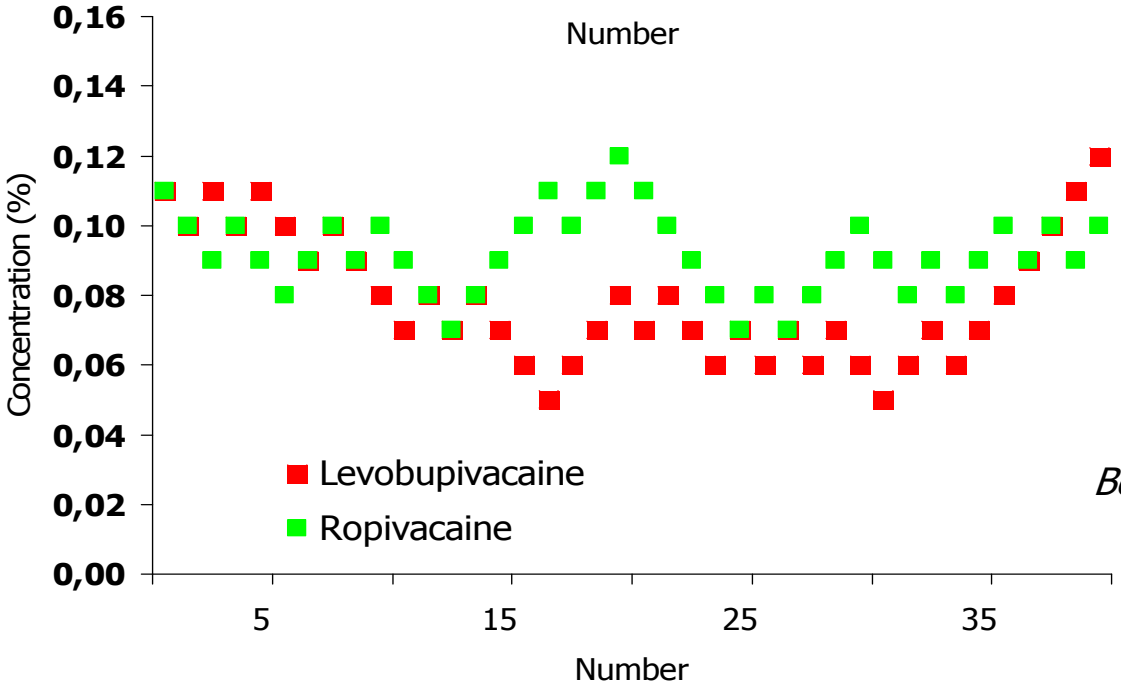
Polley LS et Al. Anesthesiology 2003; Benhamou D et Al. Anesthesiology 2003

MLAC for Analgesia: Ropivacaine vs Levobupivacaine



Potency ratio: 0.98 (0.8-1.2)

Polley LS et Al. Anesthesiology 2003



Potency ratio: 0.84

Benhamou D et Al. Anesthesiology 2003

Controversial results with levobupivacaine

Methodological confounding variables

– Cervical dilatation up to 7 cm *Polley L et Al Anesthesiology 2005*

Threefold increase in EC50 from 2 to 5 cm dilatation *Capogna G et Al. BJA 1998*

– Cervical dilatation assessed 30 min before the study

Possible progression of labor *Polley L et Al. Anesthesiology 2005*

– High % Rejects (second stage of labor before completion of the study) *Polley L et Al. Anesthesiology 2005*

– Low VAPS at inclusion *Benhamou D et Al. Anesthesiology 2005*

– Mixed sample (Parity & Oxitocin?)

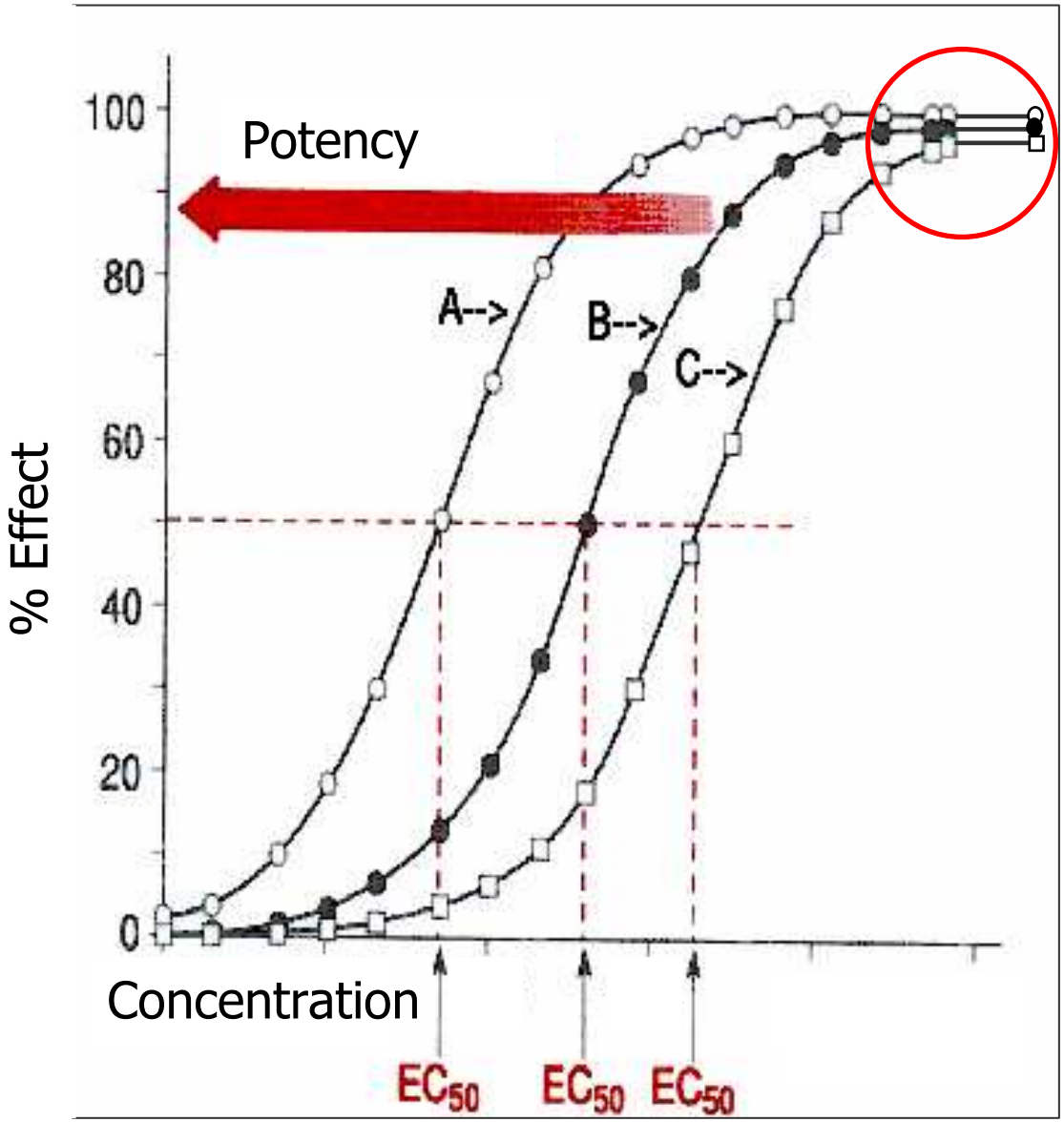
Bupi=Levo=Ropi ?
Bupi>Levo>Ropi ?

- Traditional comparisons: high/equal concentration
  bupi=levo=ropi
  Burke D et Al. Br J Anaesth 1999; Gaiser RR et Al. J Clin Anesth 1997; Writer et Al. Br J Anaesth 1998

- MLAC potency ratio studies: bupi ≥ levo>ropi

- Comparisons at equipotent concentrations
  bupi ≥ levo> ropi
  Fernandez-Guisasola J et Al. Anesth Analg 2001; Camorcia M et Al. Eur J Anaesth 2003;
  Sah N et Al. J Clin Anesth 2007

Analgesic Concentration - Response Curve



Comparisons at high concentrations

MLAC comparison

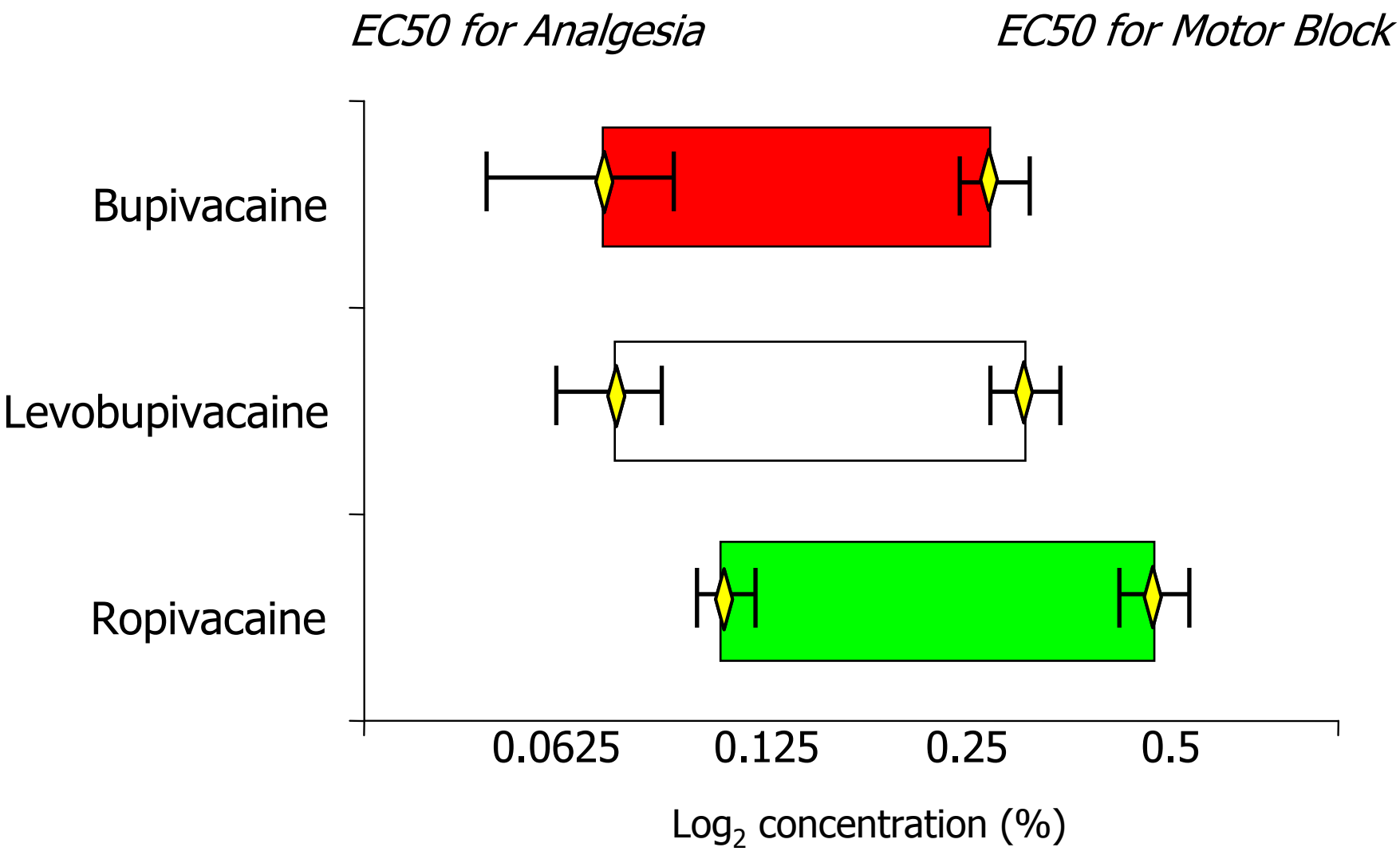
Relative Potencies of Epidural Pipecoloxylidines

Analgesia	*Relative potencies (95%CI)*
Bupivacaine: Ropivacaine	0.60 (0.47- 0.75)
Bupivacaine: Levobupivacaine	0.98 (0.67- 1.41) 0.87 (0.60-1.25)

Motor Block	*Relative potencies (95%CI)*
Bupivacaine: Ropivacaine	0.66 (0.52- 0.82)
Bupivacaine: Levobupivacaine	0.87 (0.77- 0.98)

Polley L et Al. Anesthesiology 1998; Lyons G et Al. Br J Anaesth 1998; Lacassie HJ Anesth Analg 2002; Lacassie HJ Anesth Analg 2003

Epidural Sensory - Motor Separation



Polley LS et Al Anesthesiology 1998 and Lacassie HJ et Al. Anesth Analg 2002 & Anesth Analg 2003

IT Analgesic potency ratio

	Relative potencies (95%CI)
Bupivacaine: Ropivacaine	0.65 (0.56- 0.76)
Bupivacaine: Levobupivacaine	0.81 (0.69-0.94)
Levobupivacaine: Ropivacaine	0.80 (0.70- 0.92)
	Camorcia M et Al. Anesthesiology 2005
Levobupivacaine: Ropivacaine	0.76 (0.50- 0.96)

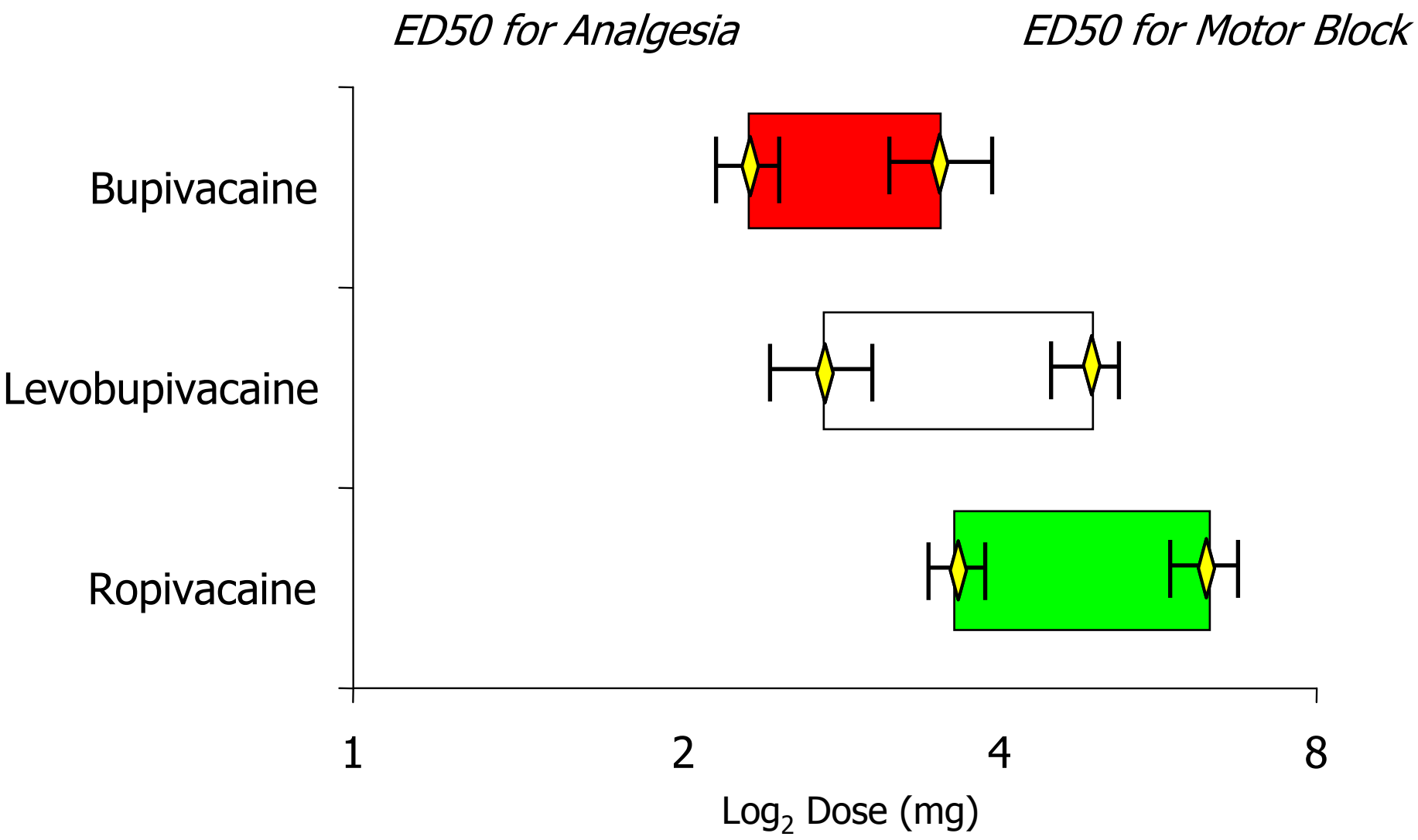
Sia AT et Al. Anesthesiology 2005

IT motor block potency ratio

	Relative potencies (95%CI)
Bupivacaine: Ropivacaine	0.59 (0.42-0.82)
Bupivacaine: Levobupivacaine	0.71 (0.51-0.98)
Levobupivacaine: Ropivacaine	0.83 (0.64- 1.09)

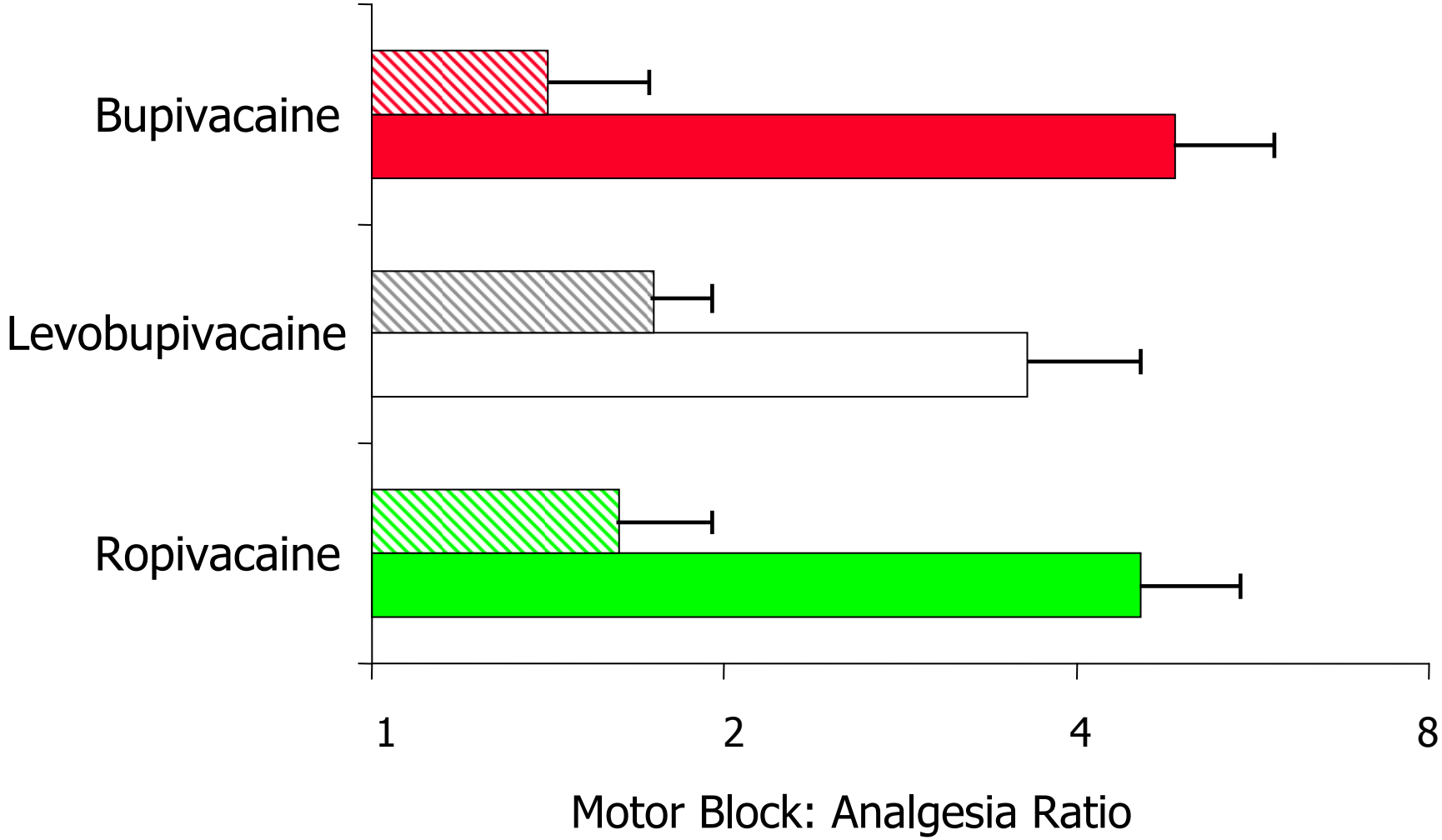
Camorcia M et Al. Anesth Analg 2007

Spinal Sensory - Motor Separation



Camorcia M et Al Anesthesiology 2005 and Camorcia M et Al. Anesth Analg 2007

Epidural / Spinal Separation ratios



Capogna G et Al. Br J Anaesth 1998; Lyons G et Al. Br J Anaesth 1998; Polley L et Al Anesthesiology 1999; Camorcia M et Al Anesthesiology 2005; Camorcia M et Al. Anesth Analg 2007; Lacassie HJ et Al. Anesth Analg 2002 & Anesth Analg 2003

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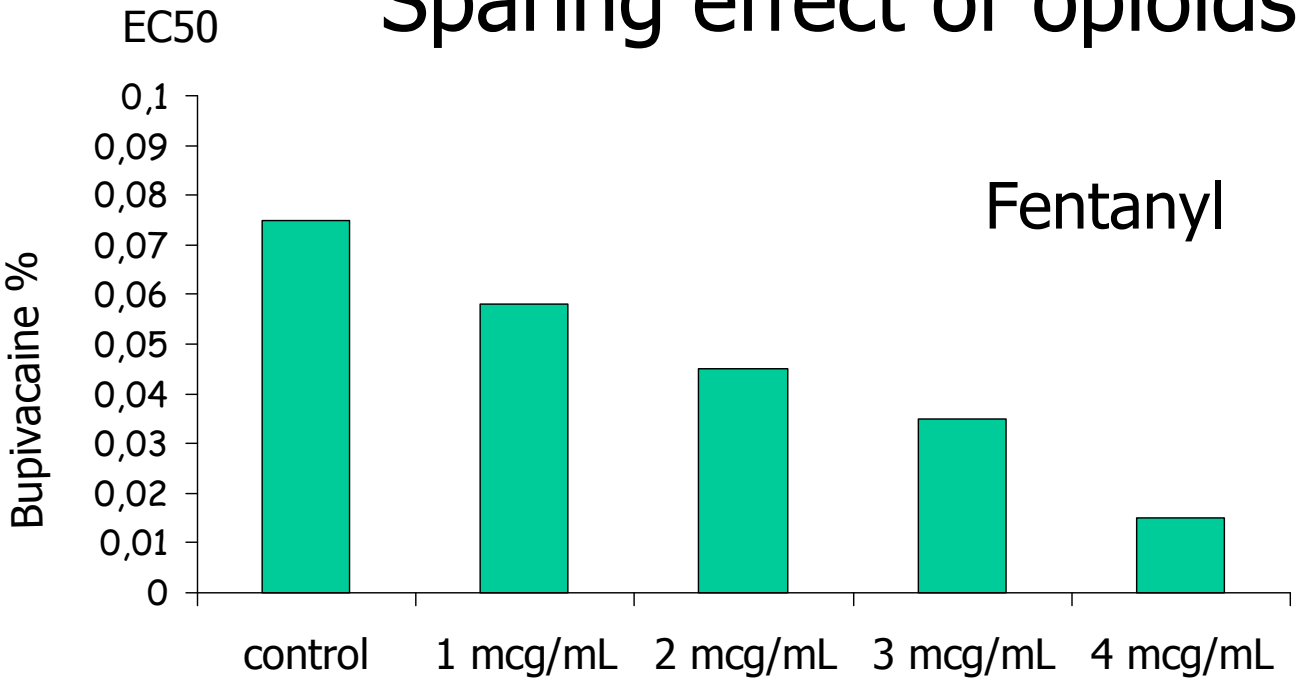
Sparing effect

- Previous studies: No differences in analgesic efficacy with the addition of epidural fentanyl to bupivacaine
Youngstrom P et Al Anesthesiology 1984; Scriutton M et Al. IJOA 1998; Asik I et Al. EJA 2002

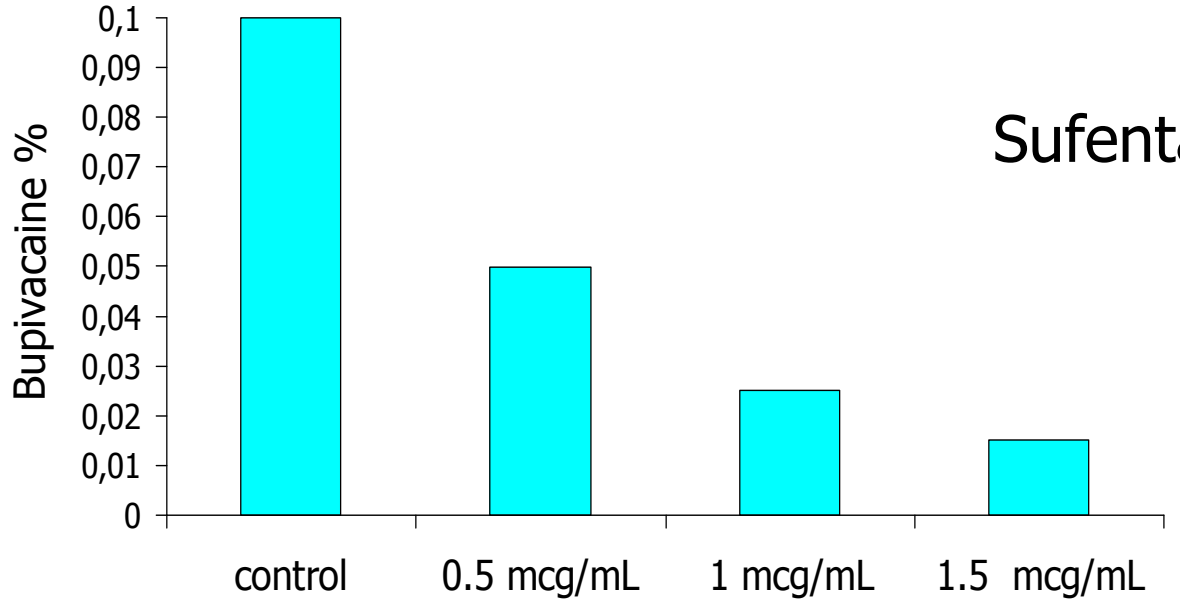
- Fentanyl and Sufentanil: up to 91% reduction in the EC50 for epidural & intrathecal local anesthetics *Polley LS et Al. Anesth Analg 1996; Lyons G et Al. BJA 1997; Polley LS et Al. Anesthesiology 1998; Palm S et Al. Anaesthesia 2001; Stocks G et Al. Anesth Analg 2001; Robinson AP et Al. Anesth Analg 2001, Van De Velde M et Al. IJOA 2007*

- Epinephrine, Clonidine, Neostigmine: statistical but not clinical sparing effect *Kenneth NE et Al. Anesthesiology 1999; Aveline C et Al. Anesth Analg 2002; Polley LS et Al. Anesthesiology 2002*

Sparing effect of opioids



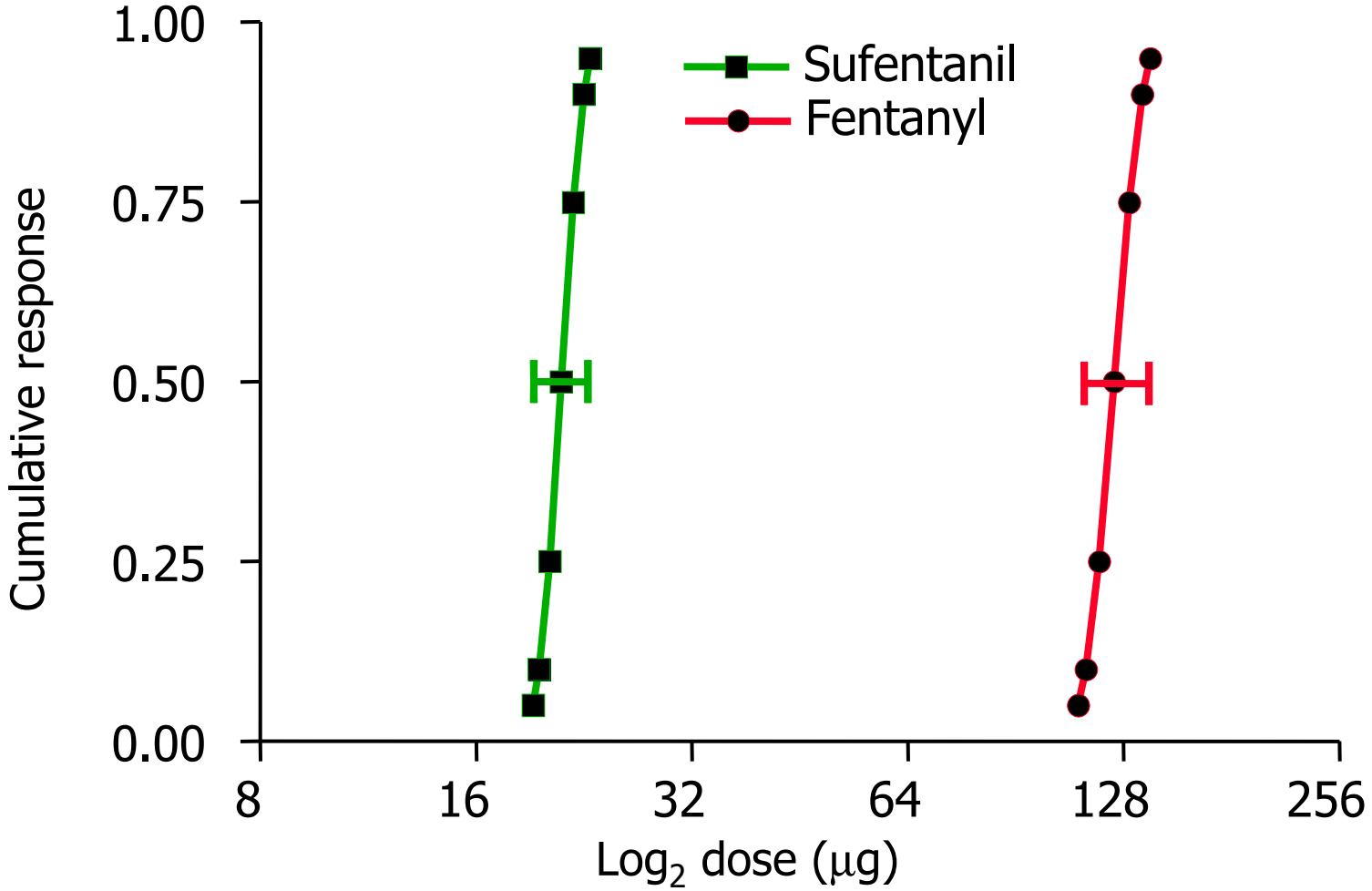
Lyons et Al. BJA, 1997



Polley et Al. Anesthesiology 1998

Relative analgesic potency ratio

Epidural Opioids



Potency ratio: 5.9 (5.6-6.3)

Capogna G et Al. Anesth Analg 2003

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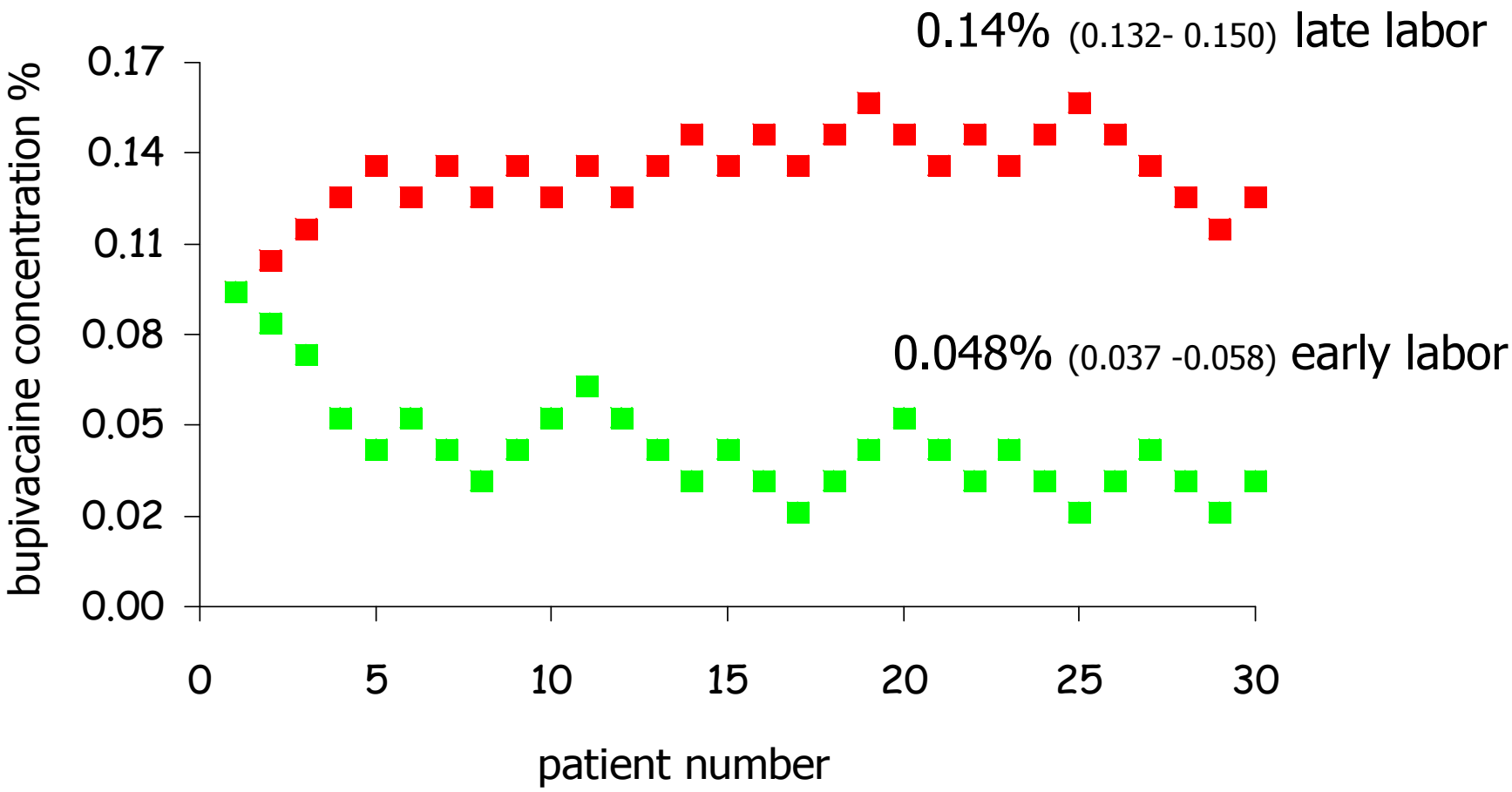
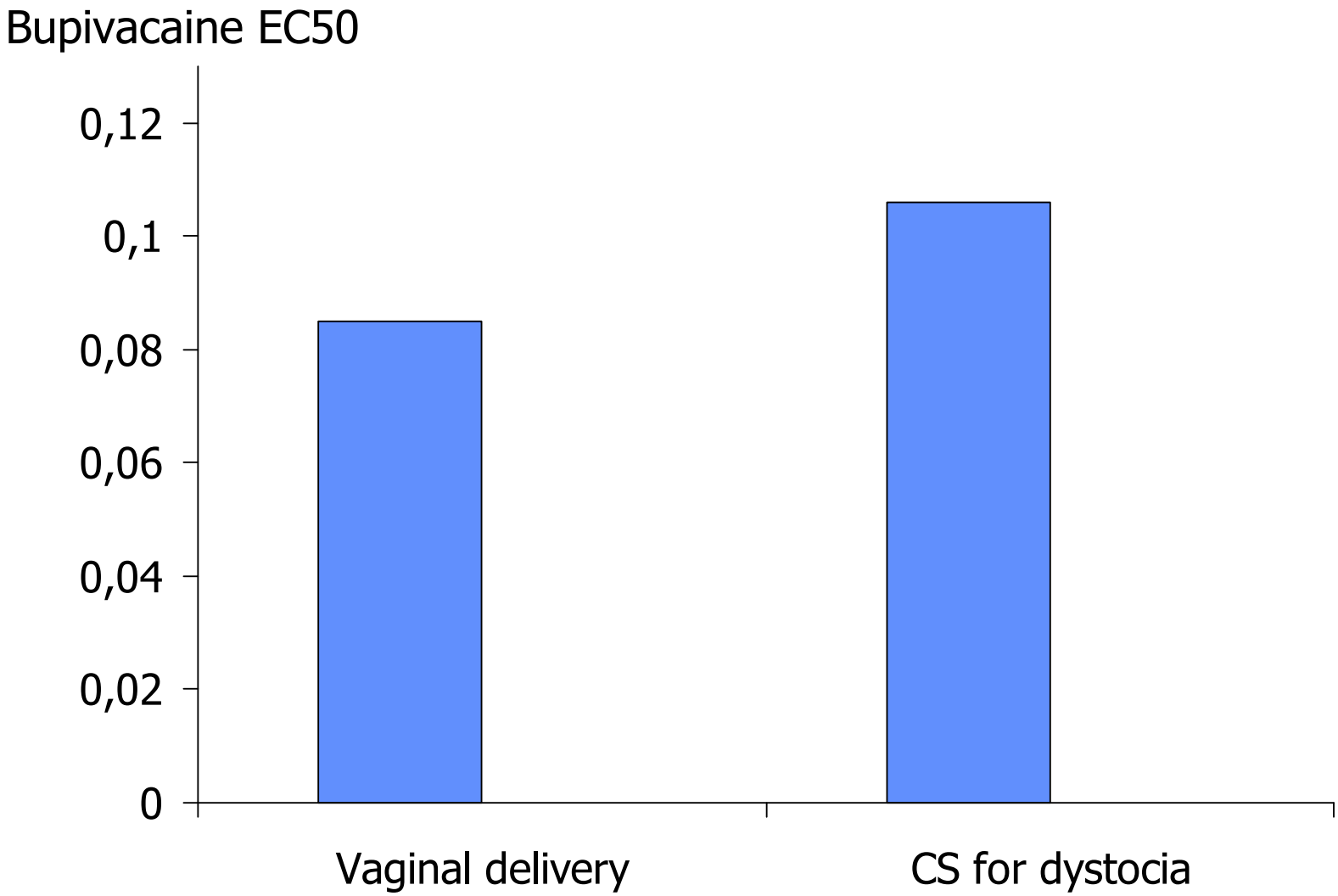
MLAC of Epidural Bupivacaine increases with progression of labor



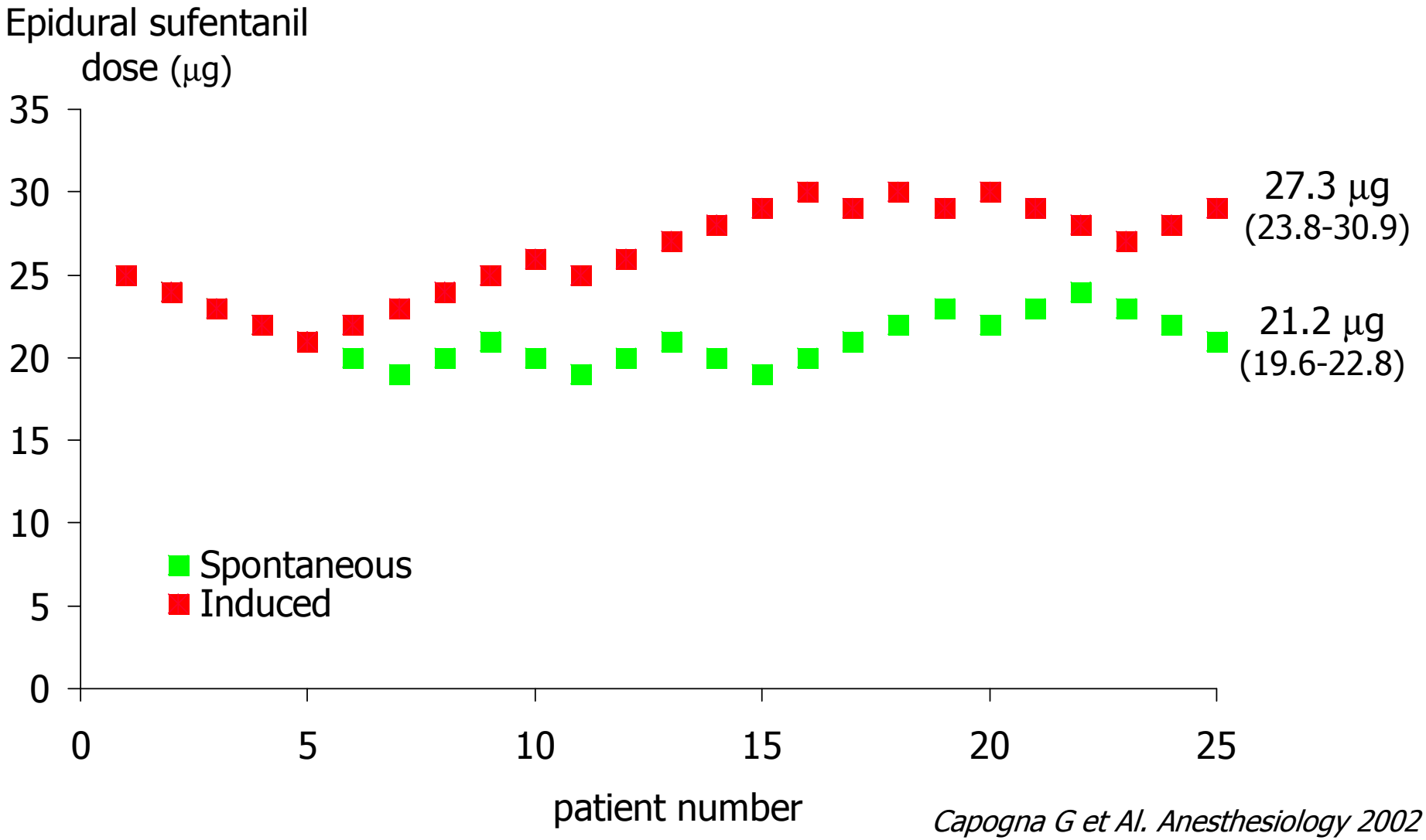
Capogna G et Al. BJA 1998

LA requirements increase in early labor in women with dystocic labors



Panni MK & Segal S. Anesthesiology 2003

Prostaglandin induction of labor increases analgesic requirements



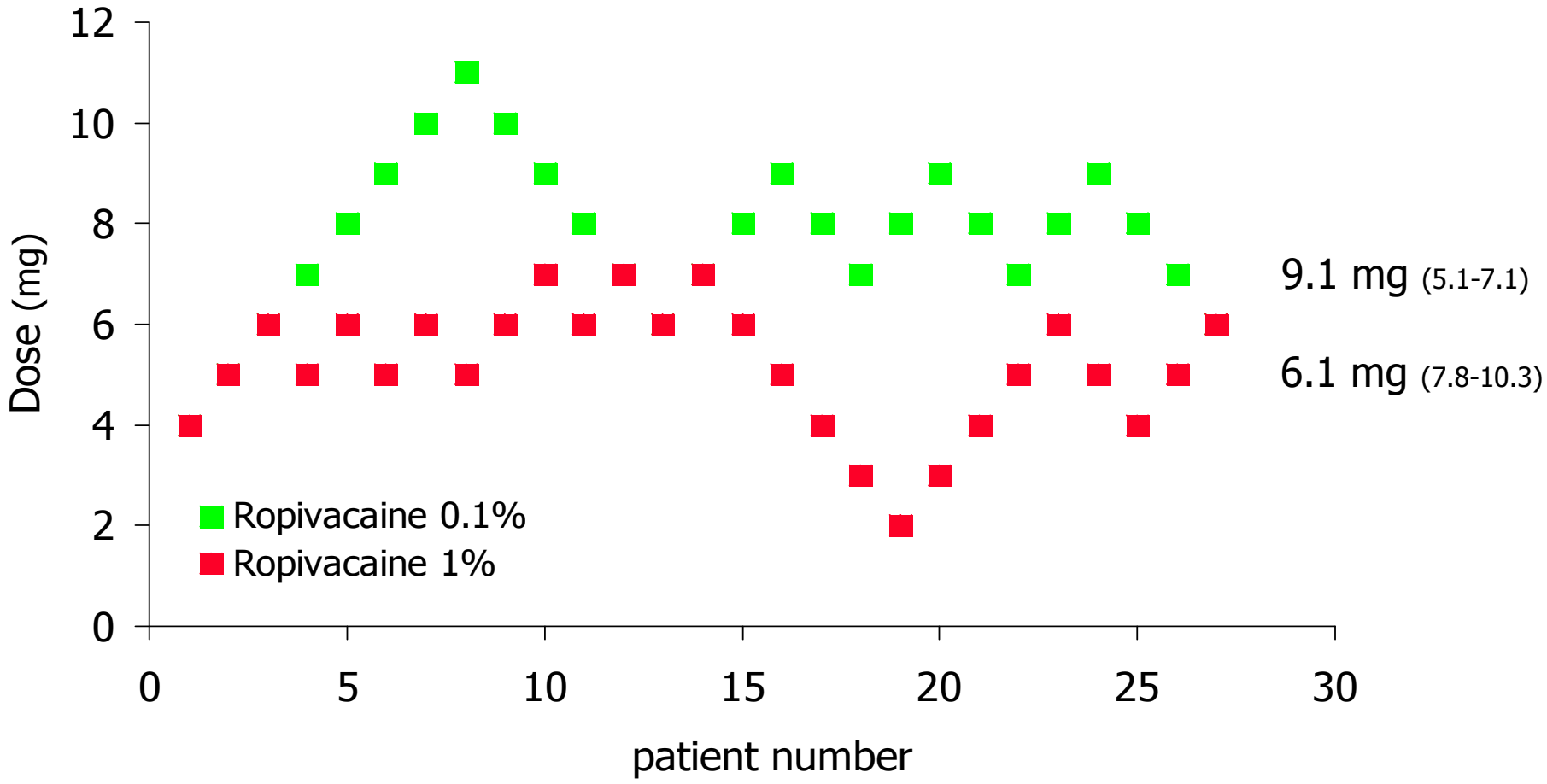
Capogna G et Al. Anesthesiology 2002

Future perspectives

Anesthetic potency and

- Intrathecal Dose & Concentration
- Gender & Pregnancy
- Genetic Factors

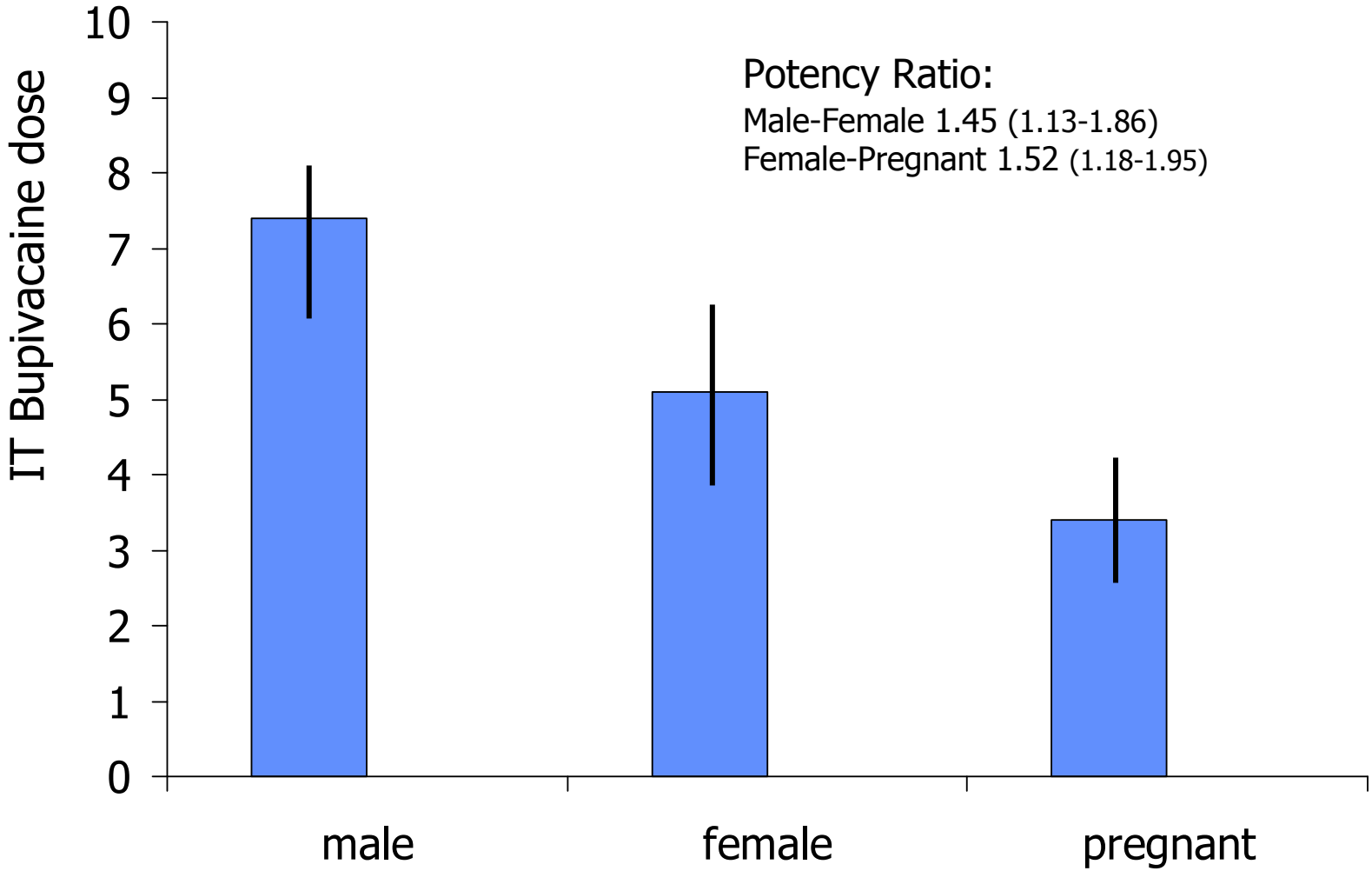
Less concentrated intrathecal solutions cause less motor block



Motor block efficacy ratio: 1.5 (1.2-1.9)

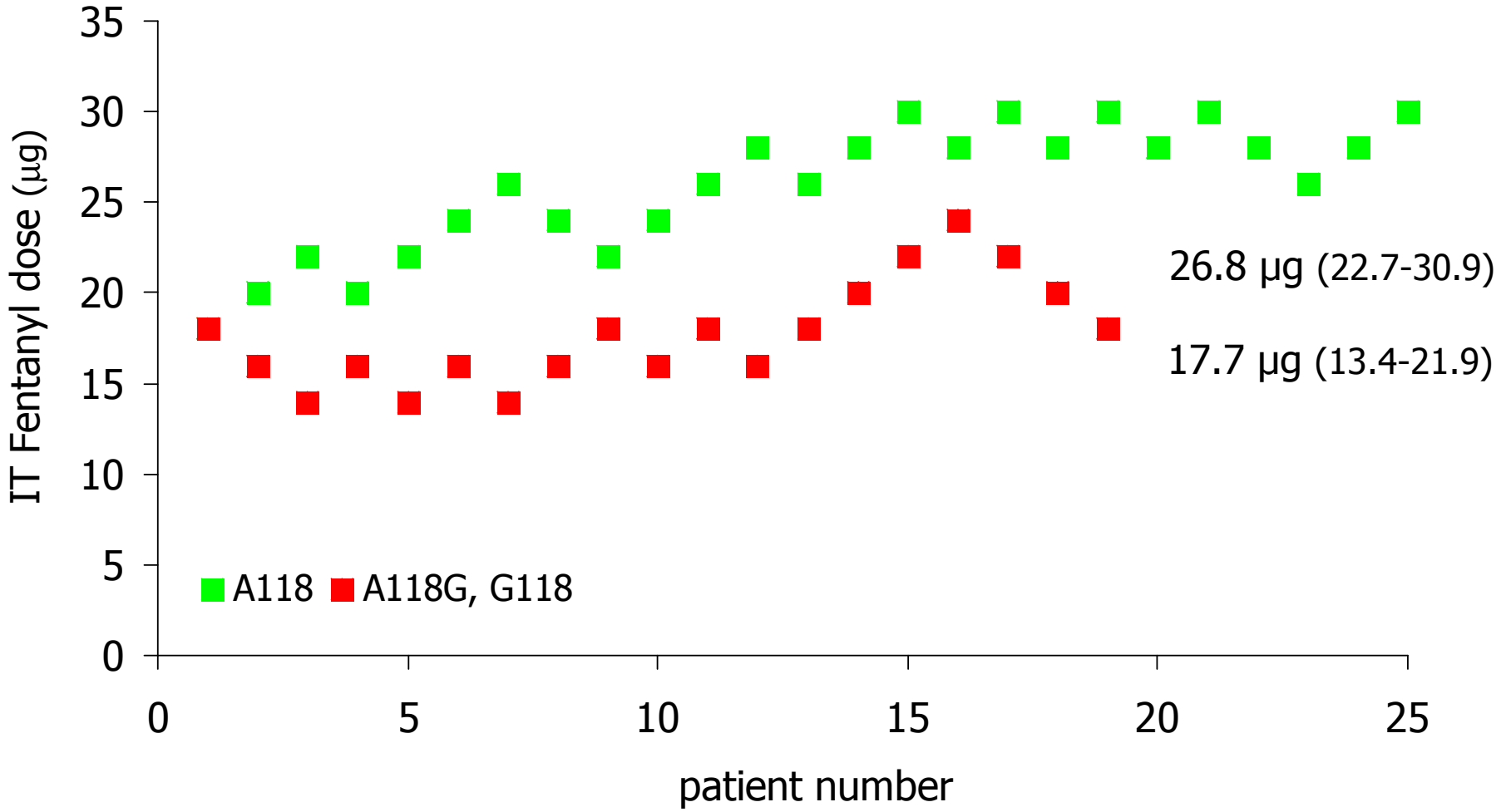
Camorcia M et Al. Anesth Analg 2004

Pregnancy and Gender may affect local anesthetic potency



Camorcia M et Al. IJOA 2007

μ-opioid receptor polymorphism and interindividual opioid requirements



Landau R et Al. Anesthesiology 2005

Conclusions

- Comparison between local anesthetics at equipotent concentrations/doses
- Contribution of opioids to analgesic mixtures
- Pharmacological rationale for labor analgesia
- Tool for assessing the effects of interindividual and labor variables on LA requirements and potency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