

Codeine Use in Postpartum Pain: Keeping *Abreast* of the Issue

Vanessa Paquette BSc(Pharm), ACPR
Doctor of Pharmacy Student
Faculty of Pharmaceutical Sciences
University of British Columbia
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Canadian Birth Statistics

- Over 350,000 live births per year in Canada
- Average length of stay in hospital:
 - Vaginal delivery: < 2 days
 - Caesarean section: < 4 days
- 90% of new mothers initiate breast feeding

Postpartum Pain

- Caesarean Section
 - 26/100 hospital deliveries
 - Pain at the incision site can last for months:
 - 79% up to 2 months
 - 18% up to 6 months
- Episiotomy
 - 20/100 hospital vaginal deliveries
 - 2% of women experience pain up to 6 months after birth
- Perineal Tears
 - 1st and 2nd degree tears in 50/100 vaginal deliveries
 - 3rd and 4th degree tears in 4/100 vaginal deliveries

Postpartum Pain

- Ability to care for newborn
- Daily activities
- Chronic pain
- Postpartum depression

Postpartum Pain



Codeine dangerous for some nursing moms, infants: FDA

| Last Updated: Friday, August 17, 2007 | 4:27 PM ET The Canadian Press

Codeine linked to breastfeeding danger

Warnings and class action suit follow Toronto neonate's poisoning death

National Review of Medicine 2007

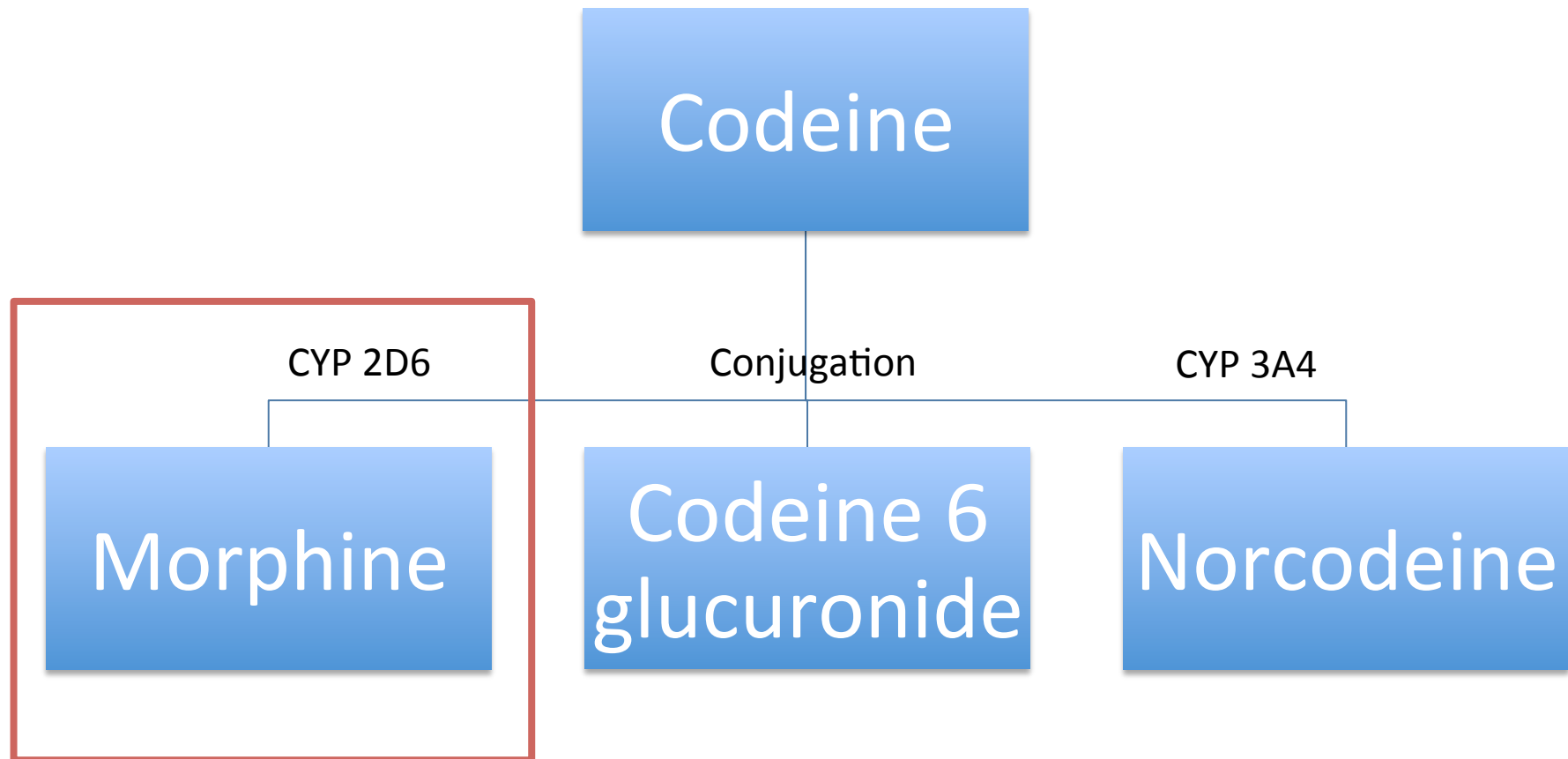
It's time to phase out codeine, doctors urge

CTV News 2010

Codeine use while breastfeeding may be dangerous

CTV News 2008

Codeine Metabolic Pathway



Codeine Metabolic Pathway

- Wide genetic variability in CYP2D6
- Classification of poor metabolizers (PM) or extensive metabolizers (EM)
- PM → therapeutic failure
- EM → overdose and toxicity

Codeine and Breastfeeding

Table I. Summary of available literature reports of maternal codeine use and breastfeeding: infants who experienced CNS depression following exposure to codeine

Reference (year)	Number of infants	Age of infant when ADR began	Adverse Effects
Smith ^[11] (1982)	1	7 days	Bradycardia, CNS depression
Davis and Bhutani ^[12] (1985)	4	4–6 days	Apnea, Bradycardia
Naumburg and Meny ^[13] (1987)	6	0.5–7 days	Apnea, Cyanosis, Bradycardia
Ito et al. ^[14] (1993)	7	<1 month	Drowsiness, Constipation, CNS depression
Koren et al. ^[5] (2006) Madadi et al. ^[6] (2007)	1 ^a	7–11 days	Death
Madadi et al. ^[9] (2008)	17	3 days to 4 months	Sedation, Poor breathing

a This infant is also included as one of the 17 infants in the 2008 study by Madadi et al.^[9]

ADR = adverse drug reaction.



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Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period (Review)

Chou D, Abalos E, Gyte GML, Gülmezoglu AM *Cochrane Review Library 2010*

“More women experienced pain relief with paracetamol compared with placebo (average risk ratio (RR) 2.14, 95% confidence interval (CI) 1.59 to 2.89, 10 studies, 1279 women).”

Ibuprofen versus placebo in the relief of post-episiotomy pain

Curr. Med. Res. Opin., (1981), 7, 423.

Esko Taina, M.D.

*Satakunta Central Hospital,
Pori, Finland*

Received: 12th May 1981

“The results of this study, therefore, confirm the findings of earlier investigations and suggest that ibuprofen is an effective and well tolerated agent for the relief of post-episiotomy pain.”

Safety In Breastfeeding

- Ibuprofen:
 - Compatible with breastfeeding
 - No reports of adverse effects in breastfeeding neonates

- Acetaminophen:
 - Compatible with breastfeeding
 - One report of infant rash

Clinical Question

P	Women requiring analgesia for postpartum pain
I	Non opioid analgesics (NSAIDs, acetaminophen)
C	Codeine + acetaminophen + caffeine (Tylenol 3)
O	Pain relief Patient satisfaction Adverse effects

Search Strategy

Databases	Google, Google Scholar, PubMed, Medline, Cochrane, IPA, ClinicalTrials.gov, Motherisk
Search Terms	Codeine, NSAIDs, acetaminophen (paracetamol), Tylenol 3, postpartum, postpartum pain, perineal pain, episiotomy, Caesarean section, perineal tears
Limits	Human, English, RCTs
Results	4 RCTs
Analyzed	2 RCTs

Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial

**Elizabeth A. Peter,^{*} Patricia A. Janssen,[†] Caroline S. Grange,^{*}
M. Joanne Douglas^{*}**

CMAJ October 30, 2001 vol. 165 no. 9

Peter et al

Design	P, DB, RCT, ITT
Patients	Postpartum women with episiotomy or 3 rd or 4 th degree perineal tears N = 237
Intervention	Ibuprofen 400 mg po q4h prn x 24 h
Comparator	Acetaminophen (600 mg) + codeine (60 mg) + caffeine (15 mg) po q4h prn x 24h
Outcomes	<p>Primary: Severity of pain</p> <p>Secondary: Number of doses of pain medication Overall satisfaction Treatment failures Drug cost Nursing time to dispense medication Side effects</p>

Peter et al

Table 2: Mean ratings of pain intensity and overall satisfaction with pain medication by treatment group

Variable	Treatment group; mean (and SD)		<i>p</i> value
	Ibuprofen	Acetaminophen with codeine	
Pain rating			
Before first request for analgesia	4.2 (2.8)	4.7 (2.5)	0.21
1 h after first dose	3.5 (2.5)	3.3 (2.8)	0.64
2 h after first dose	3.1 (2.4)	3.2 (2.5)	0.75
3 h after first dose	3.5 (2.5)	3.4 (2.5)	0.88
4 h after first dose	3.4 (2.5)	3.7 (2.5)	0.53
12 h after first dose	4.2 (2.6)	3.5 (2.6)	0.70
24 h after first dose	3.2 (2.3)	3.1 (2.6)	0.71
No. of doses in 24 h	3.4 (1.4)	3.3 (1.5)	0.84†
Rating of overall satisfaction with pain medication on visual analogue scale	6.6 (2.7)	6.8 (2.9)	0.87†
Rating of overall satisfaction with pain medication on Feeling Thermometer*	74.7 (21.2)	73.8 (21.7)	0.66†

*See Appendix 1 for details.

†Adjusted for use of forceps.

Peter et al

Secondary Outcome	Ibuprofen	Acetaminophen with Codeine	P value
Treatment Failure (%)	13.8	16	0.46

Cost:

- Ibuprofen \$0.02 per tablet
- Acetaminophen with codeine \$0.05 per tablet

Nursing dispensing time:

- 10 minutes additional time to dispense acetaminophen with codeine

Peter et al

Table 3: Frequency of side effects by treatment group

Side effect	Treatment group; % (and no.) of subjects		<i>p</i> value
	Ibuprofen	Acetaminophen with codeine	
Nausea	4.5 (5/112)	9.2 (9/98)	0.17
Vomiting	2.8 (3/107)	2.1 (2/95)	1.0
Stomach pain	9.2 (10/109)	14.3 (14/98)	0.25
Indigestion	8.1 (9/111)	8.2 (8/98)	0.99
Dizziness	25.2 (28/111)	27.8 (27/97)	0.67
Disorientation	8.1 (9/111)	11.5 (11/96)	0.41
Any side effect	52.4 (54/103)	71.7 (66/92)	0.006

Peter et al

“In conclusion, we found that ibuprofen and acetaminophen with codeine and caffeine were similar in efficacy for the treatment of postpartum pain from episiotomy or third- or fourth-degree tears.”

Peter et al

- Limitations:
 - Small sample
 - Short study duration
 - Forceps-assisted delivery included
 - Many patients stopped rating their pain once they no longer needed analgesia
 - Allocation was broken twice
 - Little information provided on other analgesics given

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Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section

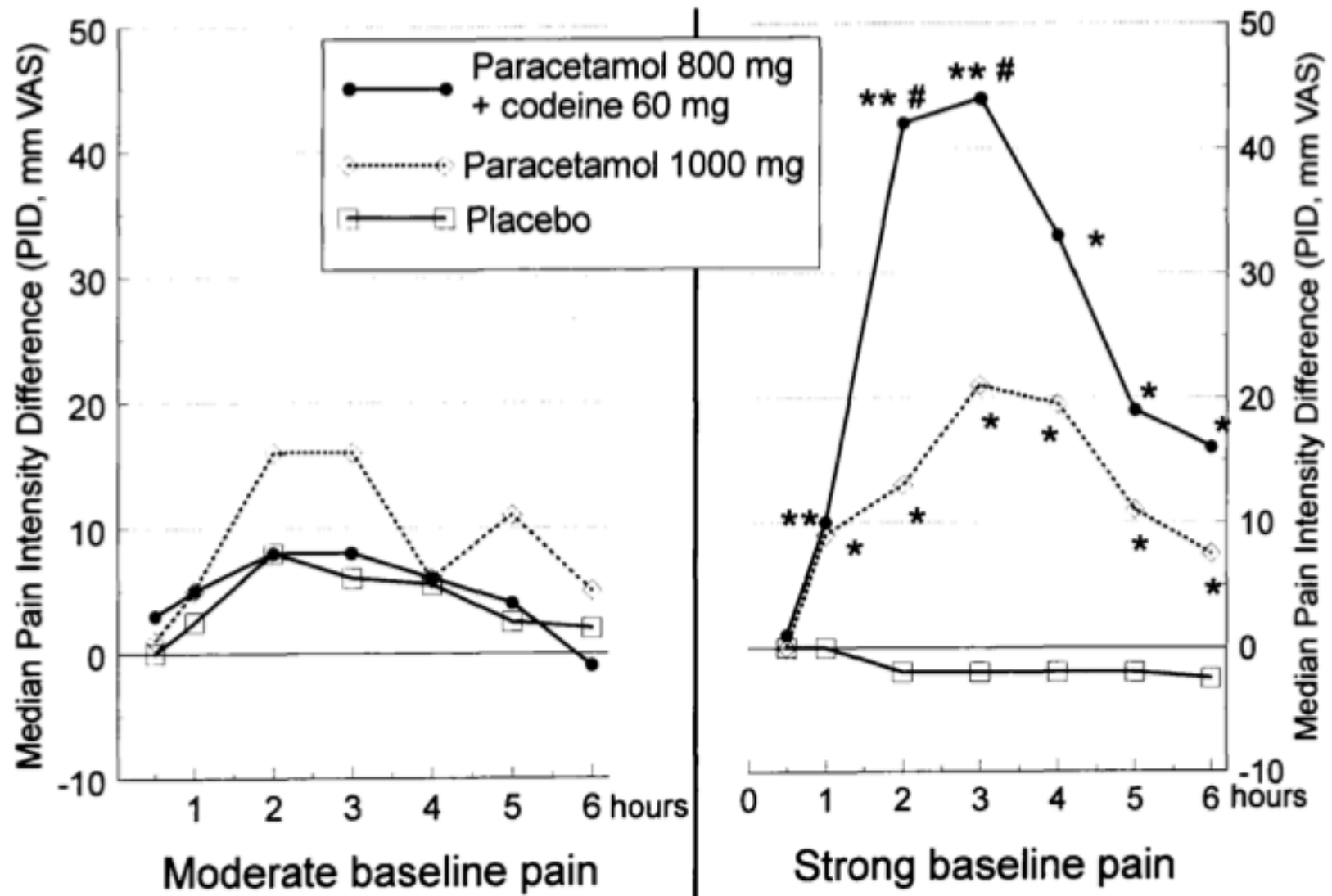
Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial

K. BJUNE, A. STUBHAUG, M. S. DODGSON and H. BREIVIK
Department of Anaesthesiology, Rikshospitalet, University of Oslo, Norway

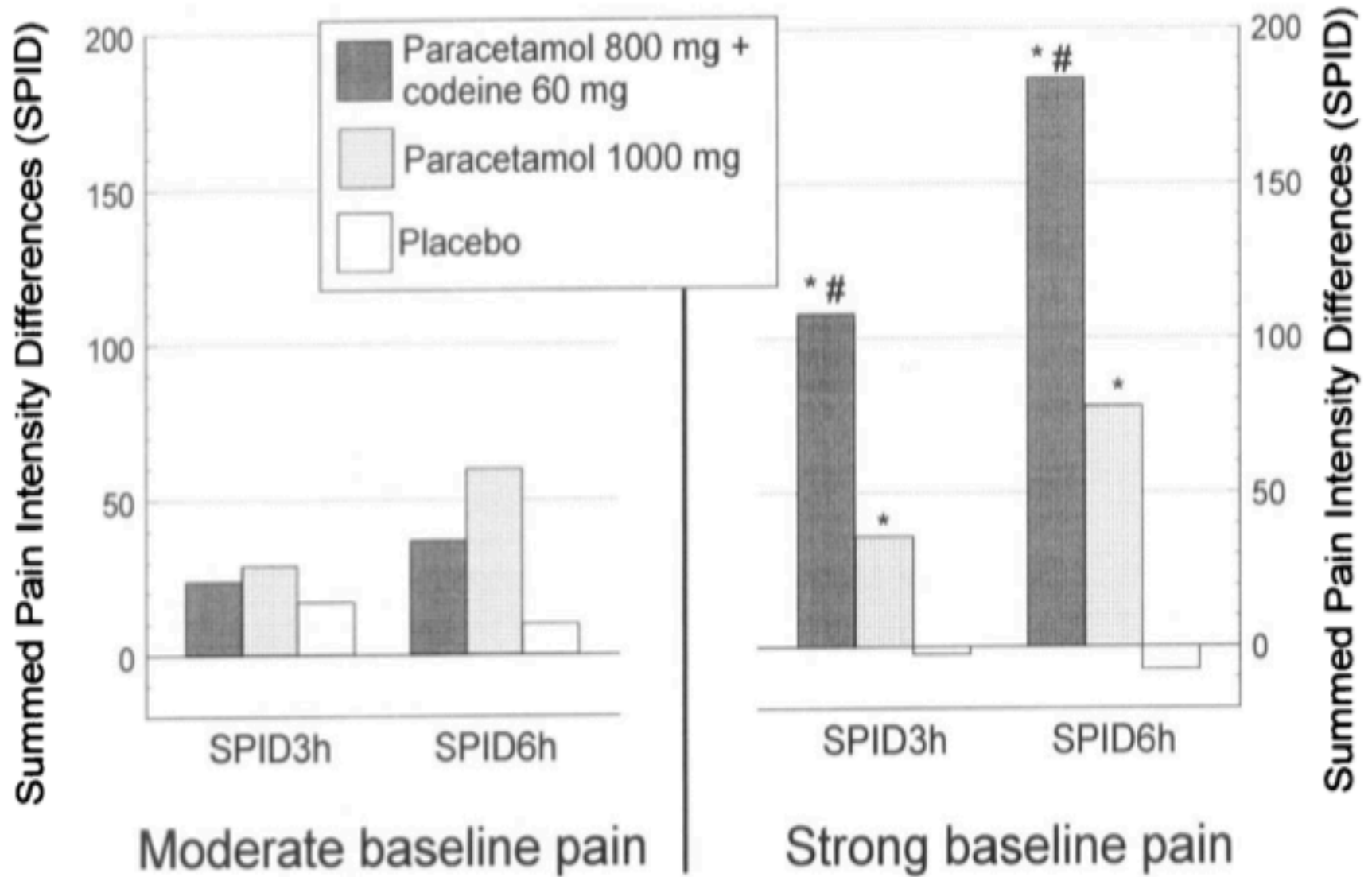
Bjune et al

Design	P, DB, DD, RCT
Patients	Women post Caesarean section Moderate pain: 4 – 6 Severe Pain: > 6 N = 125
Intervention	Acetaminophen 1000 mg po x 1 (n = 50) or placebo (n = 25)
Comparator	Acetaminophen 800 mg + codeine 60 mg po x 1 (n = 50)
Outcomes	Pain intensity Pain relief Patient satisfaction Patients requiring rescue medication Side effects

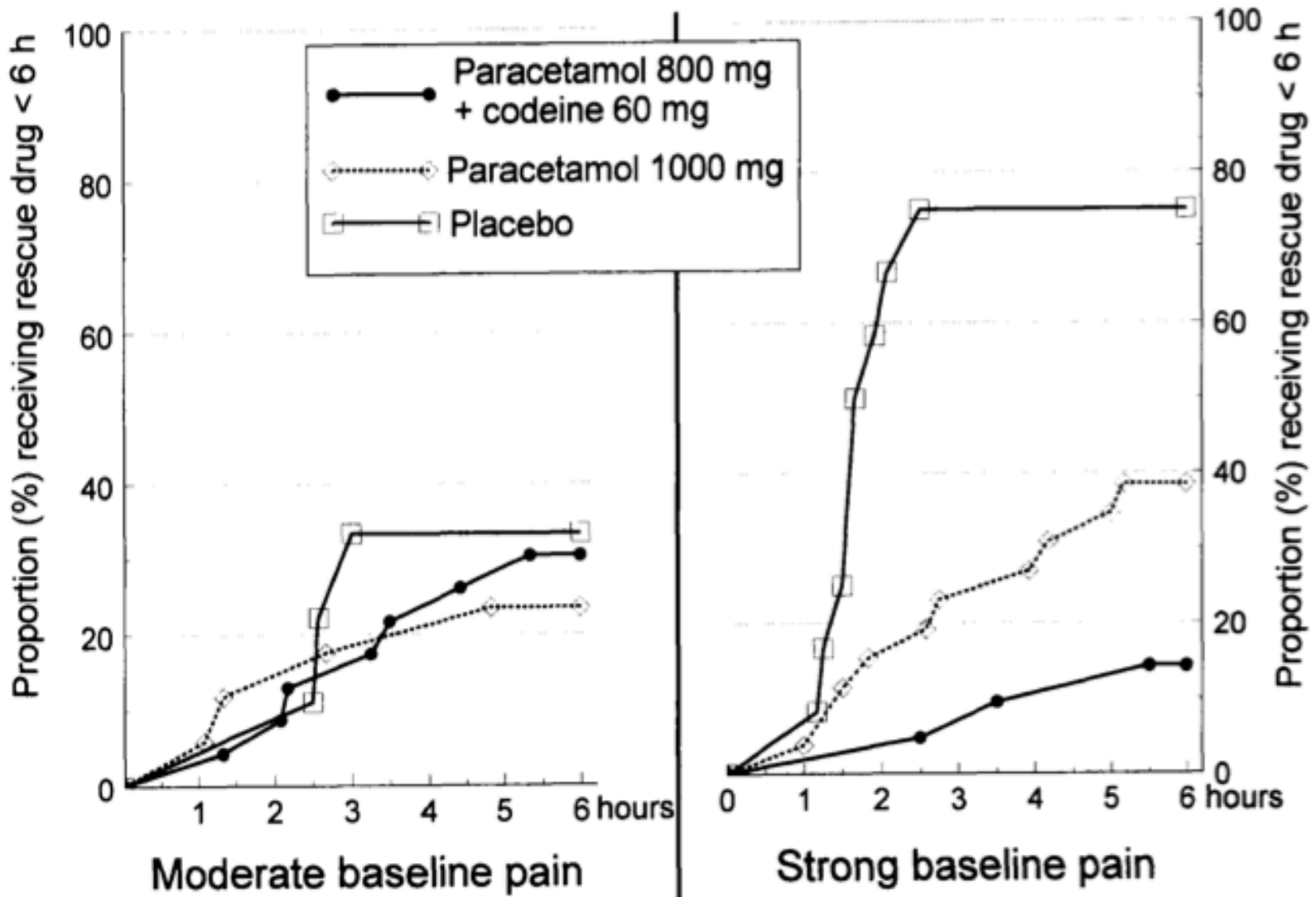
Bjune et al



Bjune et al



Bjune et al



Bjune et al

Table 3

Adverse events.

	n	Side-effect		Type of adverse effect (n)			
		+	-	Sweating	Drowsiness	Nausea	Dizziness
Paracetamol 800 mg + codeine 60 mg	50	10	40	7	2	2	0
Paracetamol 1000 mg	50	10	40	8	3	1	2
Placebo	25	1	24	1	0	0	0
Total	125	21	104	16	5	3	2
Fisher's exact test		NS	NS	NS	NS	NS	NS

Bjune et al

“In conclusion, in patients with strong baseline pain after Caesarean section, the combination of paracetamol 800 mg + codeine 60 mg was significantly superior to paracetamol 1000 mg, both of which were superior to placebo, in all efficacy variables of pain relief after Caesarean section.”

“In patients with moderate baseline pain, there was no difference between the three study drugs in any of the efficacy variables.”

Bjune et al

- Limitations:
 - Small sample size
 - Small placebo groups
 - One dose
 - 17 patients not analyzed due to protocol violation
 - Dose of acetaminophen is lower in combination group

Conclusion

Codeine + Acetaminophen	✘
NSAIDs (Ibuprofen)	✔
Acetaminophen	?

Motherisk Update

Guidelines for maternal codeine use during breastfeeding

Parvaz Madadi PhD Myla Moretti MSc Nada Djokanovic MD MSc Pina Bozzo
Irena Nulman MD FRCPC Shinya Ito MD FRCPC Gideon Koren MD FRCPC FACMT

“...an attempt should be made to decrease the dose or to switch to non-codeine painkillers (eg, non-steroidal anti-inflammatory drugs).”

“The strategy of replacing codeine with another opioid analgesic is troublesome in the absence of safety data and clinical experience.”

Considerations

- BC Women's Hospital recently removed codeine from their PPO for postpartum pain
- Codeine in review for analgesia in the pediatric population across the country – some children's hospitals have removed it from their formulary

Questions

