Child's Nerv Syst (2000) 16:93–100

ORIGINAL PAPER

Antonio Chiaretti
Luigi Viola
Domenico Pietrini
Marco Piastra
Alessandra Savioli
Luca Tortorolo
Massimo Caldarelli
Francesca Stoppa
Concezio Di Rocco

Preemptive analgesia with tramadol and fentanyl in pediatric neurosurgery

Received: 1 July 1999

A. Chiaretti · L. Viola · M. Piastra
L. Tortorolo
Pediatric Intensive Care Unit,
Gemelli Hospital, Rome, Italy

D. Pietrini · A. Savioli · F. Stoppa
Department of Anesthesiology,
Gemelli Hospital, Rome, Italy

M. Caldarelli · C. Di Rocco
Pediatric Neurosurgery, Gemelli Hospital,
Rome, Italy

A. Chiaretti (✉)
Via Fratelli Gualandi, 23,
I-00135 Rome, Italy
Tel.: +39-06-3383703
Fax: +39-06-3383211

Abstract Preemptive analgesia is based on administration of an analgesic before a painful stimulus generates, so as to prevent the subsequent rebound mechanism. Tissue injury results in disruption of the processing mechanisms of noxious stimuli afferent to the CNS (central nervous system) by way of an increase of inputs in the spinal cord. These reactions may be reduced by the administration of opioids. Few studies on preemptive analgesia with opioids in children are available, and none of them is concerned with pediatric neurosurgery. Tramadol and fentanyl are synthetic opioids which are relatively new and act through the activation of pain-inhibitory mechanisms. We conducted a randomized, prospective trial on the preemptive effects in children of these two analgesic drugs, administered according to three different protocols: tramadol as a bolus (1 mg/kg); tramadol by continuous infusion (150 µg/kg per h); fentanyl by continuous infusion (2 µg/kg per h). In all, 42 children undergoing major neurosurgical operations were enrolled in the study, 14 in each treatment group. Each treatment was started at the induction of general anesthesia and continued throughout the entire duration of the operation. The postoperative pain evaluation was conducted in the Pediatric Intensive Care Unit at the end of the surgical operations and involved comparison of any changes in behavioral (AFS scale and CHEOPS score) and hemodynamic (heart rate, respiratory rate, systolic and diastolic arterial pressure, oxygen saturation, O_2 and CO_2 partial pressure) parameters. Only 2 children, both in group A, needed further drug administration postoperatively. No significant side effects were noticed in any of the three groups, except that in group A there was a higher incidence of nausea and vomiting. Tramadol efficacy seems to be better when it is administered in continuous infusion; this treatment modality also leads to fewer adverse effects. Fentanyl, in contrast, proved to be superior to tramadol in the treatment of postoperative pain. In conclusion, preemptive analgesia is a valid technique for the treatment of acute pain in children undergoing major neurosurgical operations.

Key words Pain · Analgesia · Pediatric neurosurgery

Introduction

Pain control is one of the major goals in intensive care units, where it is likely to be applied in the management of critical situations which require safe and efficacious analgesic strategies [28].

In recent years, new drugs and therapeutic regimens have been accepted for postoperative pain relief; one of these is preemptive analgesia [22], based on the administration of an analgesic agent before the onset of a painful stimulus, thus preventing pain rebound during the subsequent postoperative course [2, 19].

A peripheral tissue injury may, in fact, impair the build-up of nociceptive inputs to the central nervous system (CNS), increasing them in the spinal cord [14].

The neurophysiological mechanisms are mediated by different factors, whose effects could be inhibited blocking CNS receptors with opioids [7, 9]. These drugs may attenuate the build-up of primary afferent-evoked depolarization in dorsal horn neurons, thereby inhibiting central sensitization [27]. Therefore, it is fundamentally important that analgesia should be timed in such a way as to obtain effective control of the acute postoperative pain.

Few clinical studies on opioids have been realized to confirm these experimental data, and none has been carried out on neurosurgical patients.

Tramadol and fentanyl are both synthetic opioids, and their clinical applications are relatively recent. The first activates both pain-inhibitory systems, namely opioid and monoaminergic, with a low incidence of respiratory failure [17]. Little data is known about its applications in children [10].

Otherwise, fentanyl is one of the best-known analgesics, even though its use is more restricted owing to the risk of respiratory depression [13].

We have conducted a randomized and prospective study to assess the effectiveness and adverse effects of intraoperative fentanyl or tramadol on postoperative pain in children admitted to the pediatric neurosurgical and intensive care units (PNU and PICU) of Gemelli Hospital in Rome for major neurosurgical operations.

Materials and methods

Forty-two children (20 girls, 47.6%, and 22 boys, 52.4%) with a mean age of 68 (±53.9) months (range 4–196 months) were recruited for the study.

They were to undergo neurosurgical interventions for various disorders: arachnoid cysts in 4 cases (10.1%), lateral ventricle gliomas in 2 (4.4%), cerebral or cerebellar astrocytomas in 7 (15.5%), craniopharyngiomas in 4 (10%), III ventricle gliomas in 4 (10%), brain stem gliomas in 3 (6.6%), medulloblastomas in 6 (13.3%), craniosynostosis in 2 (4.4%), decompression craniotomies in 3 (6.6%), Chiari malformation in 1 (2.2%), cerebral arteriovenous malformation in 1 (2.2%), cerebral rhabdomyosarcoma in 2 (4.4%) and neuroblastoma in 1 (2.2%).

Patients were allocated randomly to three intraoperative treatment groups:

A. Tramadol 1 mg/kg i.v.
B. Tramadol 0.5 mg/kg i.v. followed by continuous infusion at the rate of 150 µg/kg per h
C. Fentanyl by continuous infusion at the rate of 2 µg/kg per h

Each treatment was started during premedication and induction of general anesthesia and has been performed all through the operation.

Premedication included flunitrazepam 0.5 mg/kg p.o. After pre-oxygenation, anesthesia was induced with halothane (inspired fraction: 2–3%) and oxygen, administered with a face mask, or with sodium thiopental 3–5 mg/kg, according to the child's ability to cooperate. Muscle relaxation was obtained with vecuronium bromide 0.08 mg/kg. All patients were intubated and ventilated with Servo-Ventilator 900 C. Isoflurane (1–2 MAC) was used for maintenance of general anesthesia.

Patients were excluded from the study if they had received other analgesic, sedative or relaxant drugs before the operation or if they were affected by concomitant disorders. No analgesic or sedative drugs were given to children admitted to the PICU.

Postoperative pain assessment was started on admission to the PICU 2 h after extubation (defined as 0 h), when the children were breathing spontaneously without oxygen support.

All children had either a peripheral or a central venous line in place and had had a radial artery previously cannulated to make it easier to monitor blood pressure and to obtain blood samples. Patients' parameters, i.e. heart rate (HR), respiratory rate (RR), blood pressure (BP) and oxygen saturation (O_2Sat) were recorded by means of a Hewlett-Packard monitor, model 56S. PICU doctors and nurses were enjoined to look for possible symptoms of pain every so often. Parameters were recorded on a specific card every 4 h (at 4 h, 8 h, 12 h, 16 h and so on), starting from 0 h, whereas HR and RR were recorded every hour. Observation went on for at least 12 h, but not more than 36 h, after the end of the operation. Furthermore, any adverse effects of analgesics were recorded, particularly the number and rate of episodes of vomiting, nausea, apnea and bradycardia.

Pain assessment

The efficacy of the preemptive analgesia was evaluated subsequently in the PICU with reference to behavioral and hemodynamic parameters. For the first, we selected the McGrath Scale or Affective Facial Scale (AFS), and the CHEOPS score. The AFS consists of nine facial expressions, corresponding to adequate scores: the higher the score, the more suffering is the facial expression (Fig. 1) [20]. The CHEOPS score, on the other hand, ranges from 0 to 3 in accordance with the kind of crying, the facial expression, the position and movement of body and legs, and the frequency with which patients touch their own wound. The higher the score, the stronger the pain (Fig. 2) [21].

The other kind of pain assessment used physiological and hemodynamic parameters, such as systolic arterial pressure (SAP), diastolic arterial pressure (DAP), HR and O_2Sat (obtained with instrumental monitoring); and oxygen arterial pressure (P_aO_2) and carbon dioxide arterial pressure (P_aCO_2) obtained in blood samples. Several authors usually refer to these parameters, which correspond to pain perception adequately and objectively, especially in childhood, when self-assessment methods are often difficult to apply [16, 30].

Statistical analysis

Data are presented as median and range (AFS, CHEOPS), incidence rates (nominal quantities, e.g., sex and adverse effects) or

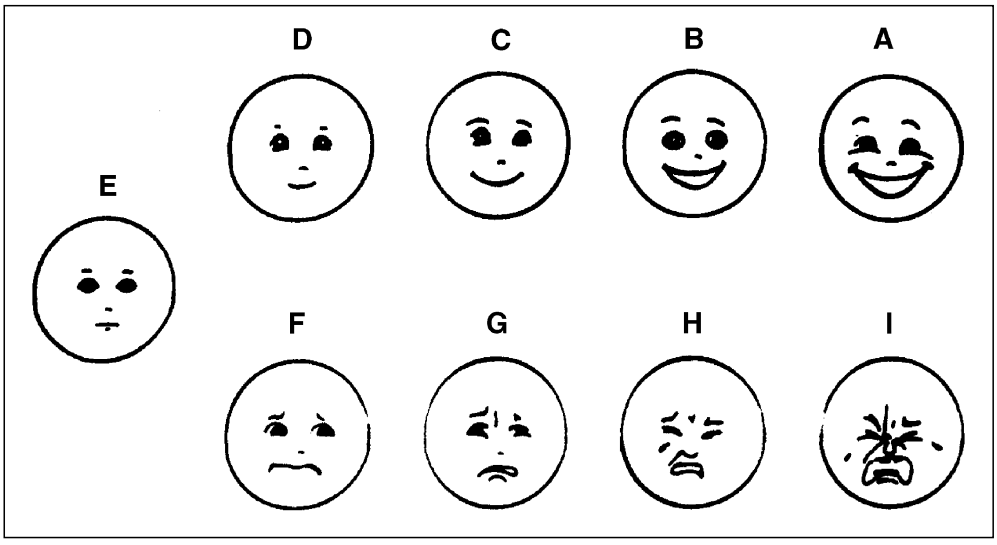

Fig. 1 McGrath Scale or Affective Facial Scale (AFS). It consists of nine facial appearances that represent different and progressively increasing pain intensities. (Scores: *A* 0; *B* 1; *C* 2; *D* 3; *E* 4; *F* 5; *G* 6; *H* 7; *I* 8)

ITEM	BEHAVIOR	SCORE	DEFINITION
Cry	*No cry*	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalizing;silent cry
	Crying	2	Child is crying, but the cry is gentle or whimpering
	Scream	3	Child is in a full-lunged cry;sobbing:may be scored with/whitout complaint
Facial	*Composed*	1	Neutral facial expression
	Grimace	2	Score only if negative facial expression
	Smiling	0	Score only if definite positive facial expression
Child verbal	*None*	1	Child not talking
	Other complaints	1	Child complaints, but not about pain
	Pain complaints	2	Child complaints about pain
	Both complaints	2	Child complaints about pain and about other things
	Positive	0	Child makes any positive statement or talks about other things without complaint
Body	*Neutral*	1	Body (not limbs) is at rest; torso is inactive
	Shifting	2	Body is is in motion in a shifting or serpentine fashion
	Tense	2	Body is arched or rigid
	Shivering	2	Body is shuddering or shaking involuntarily
	Upright	2	Child is in a vertical or upright position
	Restrained	2	Body is restrained
Touch	*Not touching*	1	Child is not touching or grabbing at wound
	Reach	2	Child is reaching for but not touching wound
	Touch	2	Child is gently touching wound or wound area
	Grab	2	Child is grabbing vigorously at wound
	Restrained	2	Child's arms are restrained
Legs	*Neutral*	1	Legs may be in any position but are relaxed
	Squirming/ kicking	2	Definitive uneasy or restless movements in the legs or striking out with feets
	Drawn up/tensed	2	Legs tensed and/or pulled up tightly to body and kept there
	Standing	2	Standing, crouching, or kneeling
	Restrained	2	Child's legs are being held down

Fig. 2 CHEOPS score for assessment of pain-induced behavioral alterations. The score has been created specifically for postoperative pain and consists of six parameters, each one ranging from 0 to 3 according to the clinical evaluation

mean±SD (interval quantities, e.g., age, weight, cardiovascular and respiratory parameters), as appropriate.

We assessed the independence of determination of each datum (Runs test) and the normality of its distribution (Wilk-Shapiro test).

The interval quantities were analyzed at each time point using one-way analysis of variance, and the Kruskall-Wallis test if heterogeneous variances were evidenced, including the three groups of children. Parametric differences among groups were analyzed with the Student-Newmann-Keuls test, using its nonparametric variants for multiple comparisons. Nominal quantities were compared using a Chi-square test or the Fisher test. $P \leq 0.05$ was deemed significant.

Results

There were 14 children in each treatment group. Demographic and clinical data (sex, age, weight, neurosurgical operations, anesthesia and postoperative observation) were comparable in the three groups (Table 1).

Mean durations of anesthesia were 253±60 min in group A; 237.72±88.75 min in group B; and 246.15±54.3 min in group C. Mean durations of observation were 18.9±7.71 h in group A; 19.45±6.45 h in group B; and 18.76±6.19 h in group C.

Table 1 Peculiarities of children allocated to the three treatment groups

Group	No. of patients (%)	Age (months), average ± SD	Sex		Weight (kg) average ± SD	Duration (min) average of anesthesia, ± SD	Observation time (h), average ± SD
			M	F			
A	14 (33.33)	67.8 ± 66.5	10	8	23.01±19.65	253±60	18.90±6.71
B	14 (33.33)	62 ± 50	6	5	21.59±10.38	237.72±88.75	19.45±6.45
C	14 (33.33)	74 ± 47.5	7	7	24.11±18.34	246.15±54.2	18.76±6.19
P-value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	

Table 2 Mean values and standard deviations of physiological parameters recorded for each group[a] during the observation period (*DBP* diastolic arterial blood pressure, *HR* heart rate, *RR* respiratory rate, *SBP* systolic arterial blood pressure)

Group	SBP (mmHg)	DBP (mmHg)	HR (b/min)	RR (b/min)	O_2 Sat (%)	P_aO_2 (mmHg)	P_aCO_2 (mmHg)
A	103.0±6.82	64.6±3.43	124.3±4.62	27.3±2.80	97.6±0.54	80.4±6.14*°	22.2±1.09*°
B	113.0±2.34	65.8±1.09	120.9±6.80	25.2±2.30	97.2±0.83	94.8±9.17°	37.8±6.34°
C	109.8±1.48	65.6±2.60	118.8±4.70	24.8±3.38	97.4±0.54	92.8±3.11*	36.8±1.30*
P-value	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05°*	<0.05°*

[a]Symbols (°*) refer to the groups compared (only A versus B and C)

Table 3 Median scores and their ranges for all behavioral parameters in each group during the observation time

Group	CHEOPS score					
	Cry	Facial	Child verbal	Body	Touch	Legs
A	1.5 (1–3)	1.5 (1–2)	1 (0–2)	1 (1–2)	2 (1–2)	1 (1–2)
B/C	1 (1–3) / 1 (1–2)	1 (1–2)	1 (0–2)	1 (1–2)	1 (1–2)	1 (1–2)
P-value	0.02 at T0 and T4	<0.05 at T0	>0.05	>0.05	0.004 at T4; 0.02 at T8	>0.05

Table 4 Rates of side effects for each treatment group and for all the observation time

Group	Nausea	Vomiting	Diarrhea	Apnea	Bradycardia
A	6	7	0	0	0
B	1	4	1	0	3
C	0	2	0	0	0
P-value	0.03 at T0	>0.05	>0.05	>0.05	>0.05

None of the patients, except for 2 children in group A, required additional analgesia in the postoperative observation period. No significant differences were found among the three groups with regard to SAP, DAP, HR and O_2Sat (Table 2).

A significant difference in postoperative P_aO_2 was found, however: patients who received a single dose of tramadol (group A) showed lower mean values for P_aO_2 (80.4±6.14 mmHg; $P<0.01$) than children in groups B and C (Table 2).

Postoperative P_aCO_2 was also significant: it was found to be lower in group A (22.2±1.09 mmHg; $P<0.008$) than in groups B and C (Table 2).

Respiratory rate values showed a progressive reduction in each treatment group, particularly in patients to whom fentanyl was administered by continuous infusion (group C) and at the 9th and 10th hours of observation ($P<0.04$ and $P<0.02$).

The HR values also declined in the last 8 h of observation, especially in the groups receiving continuous infusions (B and C).

The other physiological parameters (SAP, DAP and O_2Sat) were found to be nearly stable and were comparable in all three groups during the whole postoperative observation.

The CHEOPS score did not reveal any significant differences in children's verbalization, body and legs, while we found higher scores for crying at T0 and T4 ($P<0.02$ for both), that is more pain, in group A (single dose of tramadol) (Table 3). Finally, analysis of the touch scores revealed that more pain was experienced at the 4th and 8th hours of observation by the children in group A than

by those in the other two groups (respectively $P<0.004$ and $P<0.02$) (Table 3).

According to the McGrath Scale or AFS, higher scores (more pain) were present in both groups of children receiving tramadol at the 4th hour of observation than in group C ($P<0.04$). Whereas children in group C had a mean score of 4, patients treated with tramadol presented higher scores (respectively 5.10 in group A and 4.9 in group B). A similar difference was recorded during the following hours of observation, even if, however, it was not statistically significant.

Group A showed a higher risk of nausea (on average, three events at T0, two at T8 and one at T12; $p<0.03$) while group C a lower one (a single event at T8). No episode of nausea was recorded in group B.

No significant difference was documented among the three groups for vomiting: in group A there were two episodes at T0, one at T8 and one at T12; in group B, two at T0, T4 and T8 and one at T12; in group C, only two episodes at T0 (Table 4). We did not record any apnea events, and there was only one episode of diarrhea, in a child treated with tramadol by continuous infusion.

Finally, three episodes of bradycardia (<60 beats/min) were noticed during the first 8 h of observation in a patient in group B, who was affected by a posterior fossa tumor.

Discussion and conclusions

Evidence for the existence of a clinically preemptive effect remains controversial [4]. This technique is based on blockade of the central sensitization before the CNS receives a nociceptive input. Mechanisms of central sensitization are manifold [5]: (1) long-lasting depolarization of dorsal horn neurons by neuropeptides released from afferent neurons and prolonged depolarization induced by *N*-methyl-D-aspartic acid (NMDA) receptors, which activate Ca^{++} channels; (2) metabolic changes induced by afferent inputs, with phosphorylation of proteins and activation of the phospholipase C system, resulting in increased depolarizing responses and increased NMDA-activated currents; (3) brief afferent inputs stimulation of the induction of early intermediate genes (c-fos and c-jun), which regulate preproenkephalin and preprodinorphin mRNA production [12].

Some authors have documented that systemic morphine can suppress noxious stimulus-evoked c-fos immunoreactivity in the rat spinal cord [25], while others have shown an increased dynorphin production after opioids administration [15].

Opioids induce a reduction in central sensitization only at the spinal cord level, whereas it seems that they do not suppress central mechanisms of hyperalgesia completely [1]. The literature includes various studies investigating the preemptive analgesic effects of either systemic or local opioids in adults; their results are conflicting [6, 29].

On the other hand, this technique is rarely considered for children, and at the moment there are no reports on its application in pediatric neurosurgery. However, even data on tramadol and postoperative pain control in children are few and not specific [24, 26].

Tramadol is a central analgesic, which acts through opioid receptors and inhibits the spinal monoaminergic pain pathway [18]. It has proven efficacy in the treatment of chronic and acute postoperative pain, whether moderate or severe [8, 18]. It is noteworthy for its safety: adverse effects are mild and easily preventable [3]. However, there are few studies on its application in childhood and no reports on postneurosurgical pain treatment.

Our results stimulate interesting considerations, even if they are not completely unequivocal. First of all, both drugs showed good analgesic effects, as reported from other studies on preemptive analgesia: only 2 children out of 42 (both in group A) required further analgesic medication in the later postoperative course. No particular side effects were seen with either of these two opioids. We recorded a higher rate of nausea and vomiting in group A (tramadol as a single dose) than in the other two groups. It is therefore useful to bear in mind that our doses did not give rise to any apnea or respiratory events. The literature, as mentioned above, includes no studies on the preemptive effects of tramadol or fentanyl in pediatric neurosurgery. Despite the small number of patients, our study can give interesting information.

Tramadol was shown to be an efficacious analgesic drug, either as a bolus or by continuous administration. We used the same doses as are currently used by international reference sources (1 mg/kg and continuous infusion at 150 μg/kg per h) [10, 11].

Detailed analysis of both groups of children treated with tramadol shows that its analgesic effect seems to be greater when it is administered as a continuous infusion (group B); in group A 2 children needed further amounts of drug in the following postoperative course. P_aO_2 and P_aCO_2 values, therefore, showed a significant difference between groups A and B (mean P_aO_2: 94.8±9.17 versus 80.4±6.14 and mean P_aCO_2: 37.8±6.34 versus 22.2±1.09, respectively), with the evidence of better pain control and normal breathing with continuous infusion of the drug.

In addition, continuous infusion is safer because of the nearly complete lack of adverse effects, that may follow to the bolus administration.

Continuous infusion is more efficacious because of its greater clearance and blood distribution volume in children than in adults [23]. Its half-life, moreover, is relatively brief (4–5 h), and children show a subjective variability for tramadol pharmacokinetics and pharmacodynamics, depending on different sensibility of specific enzymes [17].

Another purpose of our study was to compare the analgesic effect of tramadol with that of fentanyl. Although

our results are not uniform, fentanyl does seem to have greater analgesic effects than tramadol. Either hemodynamic or behavioral parameters, in fact, validate this hypothesis with significant data.

Children in group C (fentanyl by continuous infusion) presented a progressive reduction of HR and BR, which was significantly different from the course in the other groups, particularly at T9 and T10. In contrast, other hemodynamic parameters did not show any significant differences, though it seemed that fentanyl offered better pain control.

In addition, when behavioral responses to pain were assessed, either the CHEOPS score or the AFS scale gave lower scores for children treated with fentanyl by continuous infusion than for those treated with tramadol. The AFS score was clearly lower in group C than in the others (4 versus 4.9 and 5.1, respectively), while the CHEOPS score gave comparable results only for crying, facial expression, and touch.

In conclusion, our findings suggest the following considerations:

1. Both drugs showed notable analgesic efficacy, going on for more than 16 h from the end of the surgical operations. Only 2 children required further analgesic medication in the postoperative course.

2. We did not observe any apnea or respiratory depression events in any of the three groups, confirming that our opioid doses were relatively safe.

3. Tramadol seemed to have a greater effect when administered by continuous infusion than when it was given in a single dose. Moreover, this kind of administration causes fewer side effects.

4. Fentanyl, as described in literature, presented a greater efficacy than tramadol in postoperative pain control: group C showed a progressive reduction of HR and BR and lower CHEOPS and AFS scores than groups A and B, and the differences were significant.

5. Pain control must be one of the goals of postoperative pediatric care. Easy scores such as the CHEOPS and AFS scores could be useful in helping us to administer appropriate analgesic drugs efficaciously.

References

1. Abram SE, Olson EE (1994) Systemic opioids do not suppress sensitization after subcutaneous formalin in rats. Anesthesiology 80:1114–1119
2. Berry FA (1998) Preemptive analgesia for postoperative pain. Paediatr Anaesth 8:187–188
3. Bosemberg AT, Ratcliffe S (1998) The respiratory effects of tramadol in children under halothane anaesthesia. Anaesthesia 53:960–964
4. Breivik H (1994) Preemptive analgesia. Curr Opin Anesthesiol 7:458–461
5. Coderre TJ, Katz J, Vaccarino AL, Melzack R (1993) Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 52:259–285
6. Collis R, Brandner B, Bromley LM, Woolf CJ (1995) Is there any clinical advantage of increasing the preemptive dose of morphine or combining pre-incisional with postoperative morphine administration? Br J Anaesth 74:396–399
7. Dahl JB, Kehlet H (1993) The value of preemptive analgesia in the treatment of postoperative pain. Br J Anaesth 70:434–439
8. Delikan AE, Vijayan R (1993) Epidural tramadol for postoperative pain relief. Anaesthesia 48:328–331
9. Dickenson AH (1991) Mechanism of the analgesic actions of opioids and opioids. Br Med Bull 47:690–702
10. Editorial (1994) Tramadolo analgesia: synergy in research and therapy. Proceedings of a satellite symposium associated with the 7th World Congress on Pain. Drugs 47 [Suppl 1]:20–21
11. Editorial (1995) Tramadol. A new analgesic. Med Lett Drugs Ther 37:59–62
12. Gogas KR, Presley RW, Levine JD, Basbaum AI (1991) The antinociceptive action of supraspinal opioids results from an increase in descending inhibitory control: correlation of behavior and c-fos expression. Neuroscience 42:617–628
13. Gourlay GK, Kowalsky SR, Plummer JL, Cousins MJ, Armstrong PJ (1988) Fentanyl blood concentration: analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67:329–337
14. Griffin MC, Hughes D, Knaggs A, Donnelly MB, Boylan JF (1997) Late-onset preemptive analgesia associated with preincisional large-dose alfentanil. Anesth Analg 85:1317–1321
15. Hylden JK, Nahin RL, Traub RJ, Dubner R (1989) Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation: the contribution of dorsal horn mechanism. Pain 37:229–243
16. Johnston CC, Strada ME (1986) Acute pain response in infants: a multidimensional description. Pain 24:373–382
17. Lee CR, Wessel DL, Woolf CJ, Katz J (1993) Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in acute and chronic pain states. Drugs 46:313–340
18. Lehmann KA, Gogas KR, Collis R, Davis A, et al (1994) Tramadol for the management of acute pain. Drugs 47:19–32
19. Mansfield M, Meikle R, Miller C (1994) A trial of preemptive analgesia. Anaesthesia 49:1091–1093
20. McGrath PJ, Cunningham SJ, Goodman JT, Unruh AM (1986) The clinical measurement of pain in children. Clin J Pain 1:221–227
21. McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J, Chapman J (1985) The Cheops: a behavioral scale to measure postoperative pain in children. In: Fields HL (eds) Advances in pain research and therapy. Raven Press, New York, pp 395–402
22. McQuay HJ (1992) Preemptive analgesia. Br J Anaesth 69:1–3
23. Nossol S (1998) Treatment of pain with sustained-release tramadol 100, 150, 200 mg: results of a post-marketing surveillance study. Int J Clin Pract 52:115–121
24. Ostreikov IF (1993) Use of tramadol during minor surgical interventions in children. Anesteziol Reanimatol 3:28–31

25. Presley R, Menettey D, Levine J, Basbaum AI (1990) Systemic morphine suppresses noxious stimulus-evoked fos protein-like immunoreactivity in the rat spinal cord. J Neurosci 10:323–335
26. Prosser DP, Davis A, Booker PD, Murray A (1997) Caudal tramadol for postoperative analgesia in pediatric hypospadias surgery. Br J Anaesth 79:293–296
27. Richmond CE, Bromley LM, Woolf CJ (1993) Preoperative morphine preempts postoperative pain. Lancet 342:73–75
28. Tobias JD, Rasmussen GE (1994) Pain management and sedation in the pediatric intensive care unit. [Pediatr Crit Care] Pediatr Clin North Am 41:1269–1292
29. Tverskoy M, Oz Y, Isakson A, Woolf CA, et al (1994) Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg 78:205–209
30. Wessel DL, Strada ME, Vaccarino AL, Oz Y, et al (1993) Hemodynamic responses to perioperative pain and stress in infants. Crit Care Med 21 [9 Suppl]:S361–362