Oxycodone vs Placebo in Children With Undifferentiated Abdominal Pain

A Randomized, Double-blind Clinical Trial of the Effect of Analgesia on Diagnostic Accuracy

Hannu Kokki, MD; Hannu Lintula, MD; Kari Vanamo, MD; Marjut Heiskanen, RN; Matti Eskelinen, MD

Background: Analgesics for children with acute abdominal pain are often withheld for fear that they might mask physical examination findings and thus might be unsafe. This viewpoint has been challenged recently.

Objective: To evaluate the effects of buccal oxycodone on pain relief, physical examination findings, diagnostic accuracy, and final clinical outcomes in children with acute abdominal pain.

Design: Prospective, randomized, double-blind, and placebo-controlled trial between December 2001 and November 2003.

Setting: University teaching hospital in Finland.

Patients: A total of 104 children aged 4 to 15 years with abdominal pain of less than 7 days' duration were screened, and 63 children with pain scores of 5 or higher on a 10-cm visual analog scale were eligible for the trial.

Intervention: Children were randomized to receive buccally either 0.1 mg/kg of oxycodone hydrochloride (n=32) or the same volume of normal saline (n=31). The same surgeon described the physical findings and indicated a provisional diagnosis and a provisional disposition before the children received the study medication and at 1 hour and 3.5 hours after initial dosing. Pain scores were recorded at baseline and every 30 minutes for 3.5 hours after the first study drug administration.

Main Outcome Measures: Pain intensity difference, presence or absence of abdominal guarding, and diagnostic accuracy.

Results: The demographic characteristics, initial pain scores, and physical signs and symptoms were similar between the 2 groups. Both study drugs were associated with decreasing pain scores. The summed pain intensity difference over 7 observations was significantly greater in the oxycodone group, 22±18 cm, than in the placebo group, 9±12 cm (mean difference 13 cm, with a 95% confidence interval of 2-24 cm; P= .04). The diagnostic accuracy increased from 72% to 88% in the oxycodone group and remained at 84% in the placebo group after study drug administration. Laparotomy was performed in 17 patients in the oxycodone group and in 14 patients in the placebo group. Four patients without appendicitis underwent exploratory laparotomy in each group. One patient in the placebo group was initially diagnosed as having nonspecific abdominal pain, but at 14 hours, she was operated on for appendiceal perforation.

Conclusions: Early administration of buccal oxycodone provides a significant pain relief to children with acute abdominal pain, without adversely altering the clinical signs or obscuring the surgical diagnosis.


Author Affiliations:
Departments of Anesthesiology and Intensive Care (Dr Kokki), Pediatric Surgery (Drs Lintula and Vanamo and Ms Heiskanen), and Surgery (Dr Eskelinen), Kuopio University Hospital, and Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, Finland (Dr Kokki).

Classic teaching in surgery has dictated that the use of analgesics should be withheld from children with acute abdominal pain until a surgeon establishes a definitive treatment plan. It has been claimed that analgesia masks symptoms and physical findings, delays diagnosis, and leads to increased morbidity. Over the past few years, this traditional belief has been challenged. Recent studies in adults have suggested that the early administration of opioid analgesics is safe and does not interfere with the ability to make a correct diagnosis. Until recently, only 1 study has addressed the issue of analgesia for undifferentiated abdominal pain in children. In this study, the authors demonstrated effective pain relief with intravenous morphine in children with acute abdominal pain without causing adverse effects or a delay in diagnosis.

See also page 326

Oxycodone, a semisynthetic μ opioid receptor agonist derived from thebaine, has a similar analgesic efficacy as morphine in patients undergoing surgery. However, because oxycodone does not cause the release of histamine, it might cause less nausea and vomiting, it is less sedating, and it
causes fewer neurological adverse effects than morphine. Because children dislike injections, there has been growing interest in noninvasive methods of opioid administration. Transmucosally (buccal route) administered oxycodone has been recently shown to be effective in the treatment of persistent postoperative pain in children, and because the taste of oxycodone is neutral, children have readily accepted this route. To our knowledge, no study has evaluated the use of buccal oxycodone for the management of acute abdominal pain in children. Therefore, we designed this prospective clinical trial to evaluate the effect of buccal oxycodone on pain reduction, physical examination findings, diagnostic accuracy, and clinical outcome in children with acute undifferentiated abdominal pain.

STUDY METHODS

This prospective, randomized, double-blind, and placebo-controlled clinical trial with 2 parallel groups took place during a 24-month period ending in November 2003 at the Kuopio University Hospital (Kuopio, Finland). The trial was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All parents who agreed to their children’s participation gave written informed consent, and the children provided assent.

Children were eligible to participate in the study if they were aged 4 to 15 years, they came to the emergency department (ED) with undifferentiated acute abdominal pain of less than 7 days’ duration, and they had pain scores 5 cm or higher on a 10-cm-long visual analog scale. Children with abdominal trauma, asthma, hypotension (systolic blood pressure <90 mm Hg), known contraindication to oxycodone, and analgesia use prior to ED arrival were excluded from the study.

INTERVENTION

Participants were randomized into 2 groups by a computer-generated allocation sequence, and a sealed envelope method was used for blinding. A study nurse not involved in the treatment of the child prepared a 2-mL syringe of the study solution with an identical appearance and taste to the saline solution, thus ensuring that children, parents, research nurses, and physicians were blinded to allocation. In 20 cases, the surgeon was asked to judge whether the patient had received oxycodone or placebo. The surgeon was able to correctly identify the type of study medication for 6 children in the oxycodone group and 6 children in the placebo group. The surgeon gave a wrong guess for 6 children in the oxycodone group and 2 children in the placebo group.

The study medication was administered when the children reported a pain score of 5 cm or higher. The patients in the oxycodone group received buccally 0.1 mg/kg⁻¹ of oxycodone hydrochloride (Oxanest 10 mg/mL⁻¹ solution for injection; Leiras Oy, Turku, Finland), and the patients in the placebo group received the same volume of 0.9% sodium chloride. If the pain score was 5 cm or higher in follow-up measurements, the study medication was repeated 1 or 2 times. No other analgesics were allowed during the 3.5-hour study period.

PAIN ASSESSMENT

After screening, the children were instructed to use a visual analog scale to score their pain (left end, no pain; right end, worst imaginable pain). The scale was a rectangle 10 cm long and 2 cm tall containing a red triangle that increased in size from left to right. The children expressed the pain score while the research nurse exerted a light pressure on the abdomen.

Pain scores were recorded at baseline and at 0.5, 1, 1.5, 2, 2.5, 3, and 3.5 hours after the first dose of study medication. At each point, the research nurse recorded vital signs (eg, oxygen saturation with pulse oximetry, blood pressure, and ventilation frequency) and all adverse effects (eg, nausea and vomiting, sedation, and hypotension) with the pain scores.

SURGICAL ASSESSMENT

All 3 surgeons participating in the trial were briefed on the abdominal examination technique. The most important clinical findings suggestive of surgical disease were recorded on a special form (Table 1). The surgeon indicated a provisional diagnosis (acute appendicitis, nonspecific abdominal pain [NSAP], or other), a differential diagnosis, a provisional disposition (observation or operation), and whether abdominal guarding was present or absent. Guarding was defined as voluntary contraction of the abdominal muscles when palpatory pressure was exerted on the abdomen. The guarding sign was interpreted as positive if tenderness was detected either in the right lower quadrant or more diffusely in the right lower quadrant and in other abdominal quadrants.

The same surgeon reexamined the patient at 1 hour after the first dose of the study drug. The surgeon again indicated a provisional diagnosis, a differential diagnosis, a provisional disposition, and the presence or absence of abdominal guarding. If the diagnosis and final disposition were not established at 1 hour, the patient was reevaluated at 3.5 hours and, if necessary, at 6 and 9 hours.

All children were taken to the hospital and followed up for hospital course, discharge diagnosis, and complications. Children for whom a definitive diagnosis was not obtained in the ED were followed up until symptoms resolved spontaneously. These patients were considered to have had self-limited NSAP. Patients with NSAP were followed up by telephone calls at 4 weeks. The final diagnosis was established by reviewing inpatient records. Acute appendicitis was confirmed by histological examination.

OUTCOME MEASURES

The main outcome measurements were the maximal pain intensity difference (PID) and the summed pain intensity differ-

---

Table 1. Baseline Characteristics of the 63 Randomized Participants According to Study Group

<table>
<thead>
<tr>
<th></th>
<th>Oxycodone (n = 32)</th>
<th>Placebo (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11 ± 3</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>19/13</td>
<td>13/18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>41 ± 14</td>
<td>41 ± 14</td>
</tr>
<tr>
<td>Fever ≥37.5°C, yes/no†</td>
<td>8/24</td>
<td>10/21</td>
</tr>
<tr>
<td>Migration of pain, yes/no†</td>
<td>10/22</td>
<td>16/15</td>
</tr>
<tr>
<td>Vomiting, yes/no†</td>
<td>9/23</td>
<td>12/19</td>
</tr>
<tr>
<td>Right lower quadrant pain, yes/no†</td>
<td>28/4</td>
<td>29/2</td>
</tr>
<tr>
<td>Abnormal bowel sounds, yes/no†</td>
<td>2/30</td>
<td>2/29</td>
</tr>
<tr>
<td>Rebound tenderness, yes/no†</td>
<td>27/5</td>
<td>22/9</td>
</tr>
<tr>
<td>Guarding, yes/no†</td>
<td>16/16</td>
<td>13/18</td>
</tr>
<tr>
<td>Pain score, cm</td>
<td>7.1 ± 1.7</td>
<td>6.9 ± 1.4</td>
</tr>
</tbody>
</table>

*Values are numbers of children or mean ± SD.
†The “yes” number indicates the number of children with a clinical symptom or sign that is suggestive of a surgical disease. The “no” number is the number of children who showed no clinical symptom or sign.
ence (SPID), the presence of abdominal guarding before and after medication, and the diagnostic accuracy between the oxycodeine and placebo groups. The maximal PID reflects the peak of the analgesic effect and the area under the time–analgesic effect curve for the intensity; the SPID reflects the cumulative response to the intervention. Pain intensity difference was calculated as \( PID_t = P_0 - P_t \) where \( P_0 \) is the pain intensity at baseline and \( P_t \) the pain at subsequent observations at 0.5, 1, 1.5, 2, 2.5, 3, and 3.5 hours after the first dose of study medication. Summed pain intensity difference was calculated as \( SPID = PID_{0.5} + PID_{1} + \ldots + PID_{3.5} \). We compared also the clinical examination sensitivity (the ability to diagnose a surgical disease), specificity (the ability to diagnose a nonsurgical condition), and diagnostic accuracy (true surgical diseases and true nonsurgical conditions as a proportion of all results) in the 2 groups both before and after study drug administration. Sensitivity was calculated as \( a/(a+c) \), specificity as \( d/(b+d) \), and diagnostic accuracy as \( a+d)/(a+b+c+d) \), where \( a \) represents true surgical diseases, \( d \) represents true nonsurgical conditions, \( b \) represents false-positive decisions, and \( c \) represents false-negative decisions.

**SAMPLE SIZE AND STATISTICAL ANALYSIS**

We designed the study to have an 80% power to detect a 2-fold difference in SPID between the 2 groups at a .05 level of significance. With a 2-sided method, the calculated sample size was 21.

To compare the 2 study groups, we analyzed continuous variables by means of a 2-sided \( t \) test for 2 independent samples. For categorical variables, we used the \( \chi^2 \) test and Fisher exact test. A \( P \) value ≤.05 was considered statistically significant. All analyses were performed using a statistical program (SPSS for Windows 10.0, SPSS Inc, Chicago, Ill).

**RESULTS**

A total of 104 children with acute abdominal pain were assessed for eligibility, but 41 were excluded; 10 refused to participate, and 31 did not meet the inclusion criteria (with pain scores < 5), thus leaving 32 children in the oxycodeine group and 31 children in the placebo group. Most of the children had a primary care referral, so half of the children had indications for surgery when they arrived at the hospital (Figure 1). At baseline, the 2 groups were similar in terms of sex, age, weight, symptoms, clinical findings, and pain scores (Table 1).

Both oxycodeine and normal saline had a significant analgesic efficacy. The mean SPID was more significant in the oxycodeine group, 22±18 cm, than in the placebo group, 9±12 cm (mean difference 13 cm, with a 95% confidence interval of 2-24 cm; \( P = .04 \)) (Figure 2). The mean maximal PID was 3.7±2.8 cm in the oxycodeine group and 2.7±2.6 cm in the placebo group (mean difference 1.0 cm, with a 95% confidence interval of 0.4 to 2.4 cm; \( P = .14 \)). A total of 67 study drug doses (2.1±0.9) was administered in the oxycodeine group and 74 doses (2.4±0.8) in the placebo group.

At baseline, the diagnostic accuracy was nonsignificantly lower in the oxycodeine group (72%) but improved to the level of the placebo group after the administration of study medication (88%, \( P = .12 \), compared with baseline). In the placebo group, diagnostic accuracy remained at 84% predose and postdose (Table 2). Predose abdominal guarding was present in 16 of 32 patients in the oxycodeine group and in 13 of 31 patients in the placebo group. After the administra-
tion of study medication, 7 patients altered their guarding; guarding was normalized in 3 patients and became positive in 3 patients in the oxycodone group compared with 1 normalized guarding in the placebo group (P = .05). Children with postdose guarding underwent appendectomy for acute appendicitis. Predose and postdose guarding was absent in 3 children (in 1 in the oxycodone group and in 2 in the placebo group) with acute appendicitis.

Seventeen of 32 patients in the oxycodone group and 14 of 31 patients in the placebo group underwent exploratory laparotomy. In all children, except 1 in the placebo group, the decision to operate was made at 1 hour after triage. Two patients with localized abscesses, 1 in the placebo group and 1 in the oxycodone group, were operated on at 20 and 24 hours after triage. In clinical examination, both had mild abdominal tenderness, and a correct surgical diagnosis was established already in the ED. However, clinical findings were atypical and confirmatory computed tomography was performed before surgery. Delay in the operations had no clinical consequence for these 2 patients because neither of them had generalized peritonitis at the time of surgery. A 15-year-old girl in the placebo group had no abdominal tenderness at the time of predose or postdose clinical examination, and she was taken to the pediatric ward for follow-up. On the ward, she developed an intensive abdominal pain with persistent abdominal tenderness and was operated on for perforated appendicitis with localized peritonitis at 14 hours after triage.

Twelve patients in the oxycodone group and 9 in the placebo group had histologically confirmed appendicitis. The appendix was abscessed in 1 patient and perforated in 2 patients in the placebo group. Two patients had another surgical disease; 1 patient in the oxycodone group had perforation of the distal ileum and an abscess caused by a plastic splinter, and 1 patient in the placebo group had previously undiagnosed Crohn disease with partial bowel obstruction in the terminal ileum. Four (23%) of 17 patients underwent laparotomy without appendicitis in the oxycodone group compared with 4 (28%) of 14 patients in the placebo group. For 14 children in the oxycodone group and 17 in the saline group, symptoms resolved before a definitive diagnosis occurred. One child in the oxycodone group had a small ovarian cyst confirmed by ultrasonography.

One child experienced headaches and another developed urticaria after receiving oxycodone. No sedation, hypoxia, or hypotension was observed.

Three patients in the placebo group and 1 in the oxycodone group were readmitted. In the placebo group, one 11-year-old girl experienced abdominal pain 3 weeks after discharge, and she underwent exploratory laparotomy with normal findings. Abdominal pain resolved spontaneously in the other 3 patients. All children were asymptomatic at 4 weeks from final discharge.

**COMMENT**

Even though the placebo effect was significant, buccal oxycodone provided significantly better analgesia than buccal saline. Oxycodone did not adversely influence the clinical examination or the appropriateness of the decision to operate; actually, a small, nonsignificant improvement in the diagnostic accuracy was noted in children treated with oxycodone. Moreover, no serious adverse effects or any major untoward outcomes occurred in association with the opioid administration. The only misdiagnosed case was in the placebo group.

One of the main limitations of the present study was that although we enlisted only 3 surgeons to make the abdominal evaluations because we wanted to standardize the clinical examination, the same surgeon performed the pre-study medication and post-study medication examinations for each child. Thus, the previous assessments might have biased the post-study medication diagnoses. Another limitation is that all the patients were admitted to the pediatric ward for observation, so the results should not necessarily be generalized to outpatients. The small sample size might also be considered a limitation of the present trial because evaluating the adverse outcomes of patients, for example, requires more subjects. Lee et al found that 750 patients in both arms of a study should be evaluated to determine whether the use of opioids alters the outcome compared with placebo. However, the present study had a power to evaluate the SPID between the 2 study groups, and for that, the power of study was sufficient. Finally, in the present trial, a surgeon evaluated all children, and therefore, it is open for discussion whether analgesia should be deferred until after physical examination by the surgeon: could children with severe pain be provided with analgesic treatment before a surgeon’s evaluation?

The dangers of early analgesia for patients with acute abdominal pain have long been emphasized. Withholding analgesia has had a theoretical foundation in a desire to avoid masking physical signs. Because the hypothesis was logical, its validity was uncontested for many years. This long-held surgical dogma has recently come under increased scrutiny. Our results are consistent with several recent prospective randomized studies in adults addressing the effects of opioid analgesia on definitive diagnosis and treatment in patients with acute abdominal pain, which have failed to give any evidence that pro-

<table>
<thead>
<tr>
<th>Predose, No. of patients/total patients (%)</th>
<th>Oxycodone (n = 32)</th>
<th>Placebo (n = 31)</th>
<th>Difference in % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>8/13 (62)</td>
<td>9/10 (90)</td>
<td>-28 (-64 to 8)</td>
</tr>
<tr>
<td>Specificity</td>
<td>15/19 (79)</td>
<td>17/21 (81)</td>
<td>-2 (-27 to 23)</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>23/32 (72)</td>
<td>26/31 (84)</td>
<td>-12 (-32 to 8)</td>
</tr>
</tbody>
</table>

**Table 2. Diagnostic Sensitivity, Specificity, and Accuracy in the 2 Study Groups**

Abbreviation: CI, confidence interval.
viding opioid analgesia prior to definitive diagnosis is harmful.\textsuperscript{1-6} Studies among adults have demonstrated that judicious administration of opioids can effectively reduce pain to a greater degree than it does the localization of tenderness and thus might even improve diagnostic accuracy.

To our knowledge, only 1 randomized clinical study about the safety of opioid analgesics in children with acute abdominal pain has been published. Kim et al\textsuperscript{7} assessed the effects of intravenous morphine on physical examinations, diagnostic accuracy, and adverse effects. Pediatric emergency physicians and surgeons independently indicated areas of tenderness to palpation and percussion before and after the administration of either morphine or normal saline. The investigators also recorded provisional diagnoses at 15 and 30 minutes after triage. Morphine administration was associated with a decrease in the number of areas of tenderness as evaluated by pediatricians, but surgeons found no difference in the examination. All children in the morphine group undergoing laparotomy had persistent tenderness to palpation and percussion after analgesia. The authors concluded that intravenous morphine provided significant pain relief to children with acute abdominal pain without adversely affecting the examination. Furthermore, morphine administration did not adversely affect diagnostic accuracy.

In the present trial, buccal oxycodone appeared to be effective in controlling severe abdominal pain because significant pain relief (reduction in pain scores from 7 to 4.5 cm; $P = .05$) was attained even at 30 minutes after the first oxycodone dose. Oxycodone is the most commonly used opioid for surgical patients in Finland.\textsuperscript{8} It is as potent as morphine, but oxycodone does not release histamine and it is less sedating than morphine.\textsuperscript{8,9} In this trial, we evaluated the use of buccal oxycodone because it is an attractive option for opioid administration in children who do not have intravenous lines in place. The bioavailability of buccal oxycodone (55\%) is relatively high, and although the time to peak plasma concentration is relatively long, in most patients significant plasma concentrations are achieved in 15 to 30 minutes postdosing.\textsuperscript{10} It should be noted that buccal drug administration seems to have a significant placebo effect because the children receiving saline also attained moderate pain relief at 30 minutes. However, after 60 minutes, oxycodone performed significantly better than placebo, which is consistent with the pharmacokinetics of buccal oxycodone.\textsuperscript{10}

Abdominal signs are critical for the diagnostic process in children with abdominal pain, but few studies have attempted to evaluate which and how much clinical signs change with the administration of opioids. In 4 previous studies in adults, the investigators concluded that the administration of opioids to patients with abdominal pain resulted in some clinical finding changes,\textsuperscript{1,2,6,16} whereas 1 study reported no changes in peritoneal tenderness.\textsuperscript{7} The literature describes no standards for what constitutes a significant clinical examination change in acute abdomen. Although the decision to operate on the patient is based not on a single sign but on a combination of findings, we used the presence or absence of guarding as the single most important examination finding because 80\% to 91\% of children with acute appendicitis exhibit guarding behavior.\textsuperscript{1,4,16} In our study, preoperative guarding was absent in 3 children with acute appendicitis. After oxycodone administration, 3 children with final diagnoses of appendicitis developed peritoneal tenderness, and guarding disappeared in 3 children with self-limited abdominal pain. Oxycodone administration did not mask or hide clinical examination evidence of peritoneal irritation. Thus, the examination changes represented improvements of the earlier examination findings. The precise reason for the change in abdominal tenderness is unknown. Decrease in abdominal tenderness might be related more to the spontaneous resolution of symptoms in children with self-limited abdominal pain.

Recent literature reports divergent results concerning the effects of opioids on diagnostic accuracy. Some authors suggest that early pain relief would actually facilitate a definitive diagnosis,\textsuperscript{1,2} and others conclude that opioid analgesia is not associated with harmful effects on diagnostic accuracy.\textsuperscript{1,7} Our study showed relationships between the use of oxycodone and an altered diagnosis or treatment. In 5 children, the provisional diagnosis of NSAP changed to the correct diagnosis of appendicitis after the administration of oxycodone; postdose guarding developed in 3 children, but peritoneal tenderness was present already in 2 children with the initial diagnosis of NSAP. Diagnostic sensitivity, the ability to diagnose a surgical disease, increased after the administration of oxycodone, although no changes were noted in diagnostic specificity, the ability to diagnose a nonsurgical disease. In contrast to our results, Kim et al\textsuperscript{7} reported higher specificity in the morphine group, suggesting that morphine might help in finding diagnoses for those children with nonsurgical conditions. Although administering morphine might facilitate the diagnosis of nonsurgical disease, Kim et al noted that their sample size was insufficient to address the question of diagnostic accuracy,\textsuperscript{7} which is consistent with our results with oxycodone.

Appendicitis is the most common indication for emergency laparotomies in children, which meant that in this study, the clinical examination focused especially on children with suspected appendicitis or those with conditions mimicking appendicitis. Most children presenting to the hospital with acute abdominal pain have either acute appendicitis or NSAP,\textsuperscript{17} and surgical conditions other than appendicitis are rare in children aged 4 to 15 years. In the present study, all patients except 3 had either acute appendicitis or NSAP. In some patients, the diagnosis of appendicitis might become clear only after some hours of observation, as occurred in the present study in 1 child with a perforated appendicitis and local peritonitis. She had no abdominal tenderness in preload and postdose clinical examinations, and she was initially misdiagnosed as having NSAP, but at 14 hours after triage, she was operated on for appendiceal perforation. This patient had fewer symptoms and signs of appendicitis than children whose diagnosis was made initially at the ED. Physician errors occur on patients whose symptoms are atypical of the appendix, and errors and delays in surgery will correlate with adverse effects. On the other...
hand, delay often occurs before an accurate diagnosis is established. Eight unnecessary laparotomies were performed on patients without appendicitis who had clinical findings that were similar to those of patients with histologically confirmed appendicitis. However, the “unnecessary” appendectomy rate—4 (23%) of 17 patients in the oxycodone group and 4 (27%) of 14 patients in the control group—is similar to that reported previously. 18

In conclusion, early administration of buccal oxycodone provides significant pain relief to children with acute abdominal pain. Results of this trial support a large-scale trial to further evaluate whether this approach is safe and whether early analgesic treatment affects the ability to diagnose a surgical abdomen.

Accepted for Publication: September 14, 2004.
Correspondence: Hannu Kokki, MD, Department of Anesthesiology and Intensive Care, Kuopio University Hospital, PO Box 1777, FI-70211 Kuopio, Finland (hannu.kokki@kuh.fi).

References