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The European Journal of Pain is the journal of the European Federation of Chapters of the International Association for the Study of Pain (EFIC). It is a multi-disciplinary journal that aims to be a global forum on all aspects of pain and its management. The journal differs from existing pain journals in its clinical and educational emphasis. The journal publishes clinical and basic science research papers relevant to all aspects of pain and its management, including specialties such as anaesthesia, dentistry, neurology and neurosurgery, orthopaedics, palliative care, pharmacology, physiology, psychiatry, psychology and rehabilitation; socio-economic aspects of pain are also covered.

The journal publishes original clinical and basic science articles; reviews on pertinent topics not recently covered by other international journals; clinical and experimental notes, such as case reports of educational or scientific value, qualified and long-term clinical observations, technical advances in clinical practice and experimental research, therapeutic studies or experiments with negative results and pain-provoking procedures; short communications on clinical or basic science articles; and letters to the Editor. The journal will also include the following commissioned articles: invited commentaries; tutorials with questions and answers; and mini-reviews updated by a board of specific editors. A bulletin board will notify about new scientific and therapeutic developments, relevant issues of other publications, and major meetings, European training programmes, etc.

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Subscription details

European Journal of Pain
ISSN 1090-3801, Volume 7, 2003
Published bimonthly by Saunders, Elsevier Science Ltd.

Publication information: European Journal of Pain (ISSN 1090-3801)
For 2003, volume 7 is scheduled for publication. Subscription rates are available upon request from the Publisher or from the Regional Sales Office nearest you or from this journal's website (http://www.elsevier.com/journal/ejpain). Further information is available on this journal and other Elsevier Science products through Elsevier's website (http://www.elsevier.com). Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by standard mail (surface within Europe, air delivery outside Europe). Priority rates are available upon request. Claims for missing issues should be made within six months of the date of dispatch.

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USA mailing notice: European Journal of Pain (ISSN 1090-3801) is published bimonthly by Elsevier Science Ltd (PO Box 211, 1000 AE Amsterdam, The Netherlands). Annual subscription price in the USA US$ 303 (valid in North, Central and South America), including air speed delivery. Periodical postage rate paid at Jamaica, NY 11431.

USA POSTMASTER: Send address changes to European Journal of Pain, Publications Expediting Inc., 200 Meacham Ave, Elmont, NY 11003.

AIRFREIGHT AND Mailing in the USA by Publications Expediting Inc., 200 Meacham Avenue, Elmont, NY 11003.

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Typeset by Scientific Publishing Services, Chennai, India.
Printed in the UK by Latimer Trend & Company Ltd, on acid-free paper.
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Parents’ perceptions of their 1–6-year-old children’s pain

Päivi M. Kankkunen\textsuperscript{a,*}, Katri M. Vehviläinen-Julkunen\textsuperscript{a},
Anna-Maija K. Pietilä\textsuperscript{a}, Pirjo M. Halonen\textsuperscript{b}

\textsuperscript{a} Department of Nursing Science, University of Kuopio, P.O. Box 1627, Kuopio 70211, Finland
\textsuperscript{b} Computing Centre, University of Kuopio, P.O. Box 1627, Kuopio 70211, Finland

Abstract

Background of the study. Parents’ perceptions of children’s pain may have influence on how children’s postoperative pain is alleviated at home after discharge from hospital.

Purpose of the study. To describe parents’ perceptions of 1–6-year-old children’s pain.

Methods. Mothers (\textit{N} = 201) and fathers (\textit{N} = 114) whose child had undergone a day surgery in 10 Finnish central hospitals between October 2000 and September 2001 filled in a questionnaire including statements of pain perceptions, a Visual Analogue Scale to assess children’s pain intensity and Parents’ Postoperative Pain Measure (PPPM) to measure children’s pain behaviours.

Results. Most of the parents suggested that adults have the responsibility to alleviate child’s pain and that alleviation of child’s postoperative pain prevents the child’s fears during future visits in child welfare clinic. However, majority of parents described that postoperative pain decreases every day or that pain is always a part of surgery. Differences in parents’ perceptions were found by both parents’ and children’s background variables. Parents’ perceptions of children’s pain were related to children’s pain intensity and pain behaviours after surgery.

Conclusions. Parents’ perceptions of children’s pain were related to children’s pain after surgery at home. Adequate information of children’s pain should be provided to the parents before discharge to promote children’s pain alleviation at home. Special attention should be paid on parents’ expectations of boy’s higher pain tolerance.

Keywords: Parents; Pain perceptions; Children; Postoperative pain

1. Background of the study

Adequate pain assessment and management is essential after paediatric surgery. Despite the increased knowledge of children’s pain management, recent studies have shown that children’s pain remains poorly managed by both the parents (Finley et al., 1996; Hamers et al., 1998) and nursing personnel (Salojärvi, 1999). Evidence also exists to show that children have severe pain postoperatively even after minor surgery (Kokki and Ahonen, 1997; Gauthier et al., 1998; Munro et al., 1999).

Fairly little is known about the reasons why children’s postoperative pain may remain poorly managed at home. Research around this topic has been very limited and focussed mostly on parents’ perceptions of the use of analgesics to alleviate children’s pain (e.g., Gedaly-Duff and Ziebarth, 1994; Finley et al., 1996; Forward et al., 1996). These studies are also mostly conducted in USA and Canada, which limit their utilisation in Scandinavia because of possible cultural differences related to perceptions of pain.

It is suggested that perceptions, or even myths, about pain may influence parents’ responses to children’s pain. The general myth that children do not experience pain as intensely as adults may lead to undertreatment of children’s pain (Hodges, 1998; Kankkunen et al., 2002). It is also widely believed that children tolerate discomfort well because they may increase their physical activity or sleep for long periods after painful procedures (Lutz, 1986). However, this kind of behaviour may also indicate that children use increased activity or sleeping...
as methods of distraction to cope with the pain (Vehviläinen-Julkunen et al., 1999) and, therefore, should be understood as pain indicators.

In conclusion, it can be stated that parents' perceptions of children's pain may prevent effective pain relief in children. However, fairly little is known what kind these perceptions are, and how they are related to children's pain intensity and pain behaviours after surgery.

The purpose of this study was to describe parents' perceptions of 1–6-year-old children's pain. Research questions were the following:

(1) What kind of perceptions do parents have of 1–6-year-old children's pain?

(2) How do parents' perceptions of children's pain differ by parents' (gender, age, own experiences of surgical pain) and children's (age, gender) background variables?

(3) How are parents' perceptions of 1–6-year-old children's pain related to parent-rated children's postoperative pain intensity and pain behaviours after a minor day surgery?

The study complements a larger research project focusing on pain assessment and alleviation undertaken by Pölkki et al., 2001 and Kankkunen et al., 2002.

2. Study ethics

The ethical boards of each 10 central hospital accepted the study. Participation was voluntary for the parents. In addition, verbal information of the study was provided to the parents by the contact persons in each ward and in a covering letter. The parents were told about the purpose of the study, the sample and publication of the findings. They were advised how to fill in the questionnaire and they were provided with the possibility to contact the first author if they had any further questions. No reminders were sent to the parents because they were allowed to respond anonymously (Burns and Grove, 1997, p. 204). The hospitals and wards are not named because of fairly small samples of some of them.

3. Data, methods and instruments

During the year 2000, altogether 22,904 surgical procedures were conducted with 1–6-year-old children by day care basis. From this population, a convenience sample of 1000 children (4.4% of the population) were selected to represent the population. The parents of these children (500 mothers and 500 fathers) were invited to participate the study, from 19 wards, in 10 central hospitals, where most of children's day surgery was conducted during the year 2000 (STAKES Tieto, 2000).

The data were collected between October 2000 and September 2001. The parents were invited to participate in the study during the day of child's surgery by nurses working in children's day surgery units. First, the nurse asked parents' verbal consent to participate the study. In addition, the nurse provided the parents with instructions on how to fill in the questionnaire. Both parents or only the mother or father were invited to participate depending on who wanted to participate. Exclusion criteria were: the parent did not stay at home with the child during the day of surgery, the parent did not speak Finnish, or the child had some physical or mental chronic condition.

During the data collection period, the strike of Finnish physicians started in March 2001 and continued till August 2001. Four of the hospitals selected to this study participated in the strike. Therefore, from the 1000 questionnaires, only 840 questionnaires were divided to the parents by the end of August 2001 and 397 of them were responded and returned. Data collection was finished because of the consequences of the strike, such as overloading of work of hospital staff and possible decrease in their motivation to invite the parents to participate in the study because of lack of time. Out of the 397 questionnaires 32 were excluded because of child's age (more than six or less than one years), missing data (N = 26) or because the questionnaires were returned after the analysis of data was conducted (N = 24). Thus, altogether 315 questionnaires were included in the analysis (Fig. 1).

The intensity of children's postoperative pain was assessed by the parents using a Visual Analogue Scale (VAS). The parents were asked to make a mark on the 100 mm line indicating the child's worst pain at home. The one end of the line had the anchor "no pain" and the other "pain as bad as it could possibly be" (e.g., Flaherty, 1996). For further analysis the VAS scores were divided to less than 30 mm (no/mild pain) and more than 30 mm (moderate/severe pain) (see e.g., Finley et al., 1996).

Children's pain behaviours were measured by using the Finnish version of Parents' Postoperative Pain Measure (PPPM). The original Canadian instrument consisted of 29 children's pain behaviours which were measured in a dichotomous level with alternatives "yes" or "no" depending on if any of the behavioural changes were identified in the child. It has been validated in Canada (Chambers et al., 1996; Finley et al., 1999; McGrath et al., 1999) and in Finland (Kokki, 2000).

To reduce the items of the PPPM in this study, correlation co-efficiencies between each of the 29 PPPM variables were computed. Based on correlations within these 29 PPPM variables more than 0.40, the version with 15 items (see Table 1) seemed to be most appropriate because all of its variables were highly correlated to each other and the item-scale correlation was high.
POPULATION

22,904 day surgeries in 1-6-year-old children / year in Finland

Central hospitals Regional hospitals Health care University hospitals Private hospitals centres
n=11,797 (52%) n=3,864 (17%) 

SAMPLE

500 mothers and 500 fathers of children undergoing day surgery (4.4% of the population)

SELECTION OF HOSPITALS

Central hospitals from southern (n=3), northern (2), eastern (n=3) and western (2) Finland conducting more than 100 day surgeries in 1-6-year-old children during a three-month period

RESEARCH PROPOSALS

Proposals (n=9) accepted in ethical boards between August 2000 and January 2001

DATA COLLECTION

October 2000 - August 2001
Strike of Finnish physicians between 12.03 - 17.08.2001

FINAL DATA

840 questionnaires divided to parents
397 questionnaires returned and 82 excluded
315 questionnaires included in the analysis
Mothers (n=201)
Fathers (n=114)

Fig. 1. Process of data collection.

<table>
<thead>
<tr>
<th>Items and frequencies of PPPM15 (n = 315)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have more trouble getting to sleep than usual</td>
<td>14</td>
</tr>
<tr>
<td>Act more cranky than usual</td>
<td>33</td>
</tr>
<tr>
<td>Whine or complain more than usual</td>
<td>38</td>
</tr>
<tr>
<td>Cry more easily than usual</td>
<td>39</td>
</tr>
<tr>
<td>Play less than usual</td>
<td>41</td>
</tr>
<tr>
<td>Not do the things s/he normally does</td>
<td>28</td>
</tr>
<tr>
<td>Act more quiet than usual</td>
<td>34</td>
</tr>
<tr>
<td>Have less energy than usual</td>
<td>37</td>
</tr>
<tr>
<td>Refuse to eat</td>
<td>22</td>
</tr>
<tr>
<td>Eat less than usual</td>
<td>52</td>
</tr>
<tr>
<td>Cry more than usual</td>
<td>32</td>
</tr>
<tr>
<td>Grow or mean more than usual</td>
<td>33</td>
</tr>
<tr>
<td>Not let you out of his/her sight</td>
<td>31</td>
</tr>
<tr>
<td>Want to be close to you more than usual</td>
<td>60</td>
</tr>
<tr>
<td>Act more difficult to comfort than usual</td>
<td>18</td>
</tr>
</tbody>
</table>

between the whole scale and each of the items of PPPM15. Later, a summarised variable was developed of the 15 items correlating with each other with \( r > 0.40 \). For further analysis, the scores of the summarised PPPM15 were divided to ratings below seven and above seven based on cross-tabulation with VAS scores (less and more than 30 mm).

The scale measuring parents' perceptions of children's pain consisted of a five-point Likert-scale instrument with 19 statements of pain perceptions (see Table 4). The alternatives for responding ranged from "totally agree" (1), "mostly agree" (2), via "cannot say" (3), to "mostly disagree" (4), and to "totally disagree" (5). The instrument was developed based on existing literature of common perceptions or myths of pain (e.g., Forward et al., 1996; Tyrrell, 1997; Hodges, 1998; Douglas, 1999; Ramer et al., 1999) and findings of a Finnish family
interview study (Kankkunen et al., 2002) where the parents were asked about their perceptions of children's pain.

Frequencies were used to describe the background variables of parents and children and parents' perceptions of children's pain. Cross-tabulation with χ² test were used to examine the differences in parents' perceptions of children's pain by children's and parents' background variables. In addition, cross-tabulation was used to explore the relationship between parents' perceptions of children's pain and parents-rated children's pain intensity (VAS scores) and pain behaviours (PPPM scores). Findings with a p-value less than 0.05 were considered statistically significant. Cronbach's α was used to examine the internal consistency of the scale measuring parents' perceptions of children's pain.

4. Results

4.1. Description of the study participants

The age of the parents ranged from 20 to 56 with the mean age of 33 years. More than half of them (n = 167) had comprehensive school as their basic education. One-fourth (n = 80) of the parents were working in health care or social welfare. Two-thirds of the parents had undergone a surgical procedure (Table 2).

Half of the children were 1–2 years old, and their mean age was 3 years. Two-thirds (n = 195) of them were boys. More than half of the children had undergone a throat surgery (Table 3). VAS scores varied between 0 and 10 with the mean score of 2.5. One-third (36%) of the children were assessed to have moderate or severe pain (VAS scores more than 30 mm). In addition, one-third of the children were described to have more than seven out of 15 pain behaviours at home.

4.2. Parents' perceptions of children's pain

Most of the parents suggested that adults have the responsibility to alleviate the child's pain and that alleviation of the children's postoperative pain prevents their fears during future visits in child welfare clinic. Less than half of the parents stated that postoperative pain decreases every day, pain is always a part of surgery, and that their child cannot pretend to have pain. A minority of the parents described that the child's organs are not developed enough to feel pain, and the child tolerates pain more than adults. Some parents also stated that pain threshold of their child is higher than of adults, and that they respect their child if the child does not complain pain (Table 4).

4.3. Differences in parents' perceptions of children's pain by parents' age, own experiences of surgical pain and gender

Less than half (43%) of parents aged 20–29 years stated that their child would not remember the pain after a few days while the rate among more than 40-year-old parents was 67% (p = 0.02). Parents' own experiences of surgical procedures had no statistically significant relationship to their perceptions of children's pain.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Background information of the parents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Background information</td>
</tr>
<tr>
<td>Parents' age (years) (N = 315)</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>25</td>
</tr>
<tr>
<td>30–39</td>
<td>65</td>
</tr>
<tr>
<td>40–56</td>
<td>10</td>
</tr>
<tr>
<td>Basic education (N = 315)</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>7</td>
</tr>
<tr>
<td>Comprehensive school</td>
<td>53</td>
</tr>
<tr>
<td>Senior high school</td>
<td>40</td>
</tr>
<tr>
<td>Vocational education (N = 315)</td>
<td></td>
</tr>
<tr>
<td>Vocational school</td>
<td>3</td>
</tr>
<tr>
<td>Vocational college</td>
<td>43</td>
</tr>
<tr>
<td>Polytechnic</td>
<td>6</td>
</tr>
<tr>
<td>University</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
</tbody>
</table>

| Line of activities (N = 311) | |
| Health care/social welfare | 25 |
| Industry | 12 |
| Business | 9 |
| Building | 8 |
| Farming/forestry/fishing | 6 |
| Transport/storage/data communication | 6 |
| Accommodation, restaurant | 6 |
| Public administration/national defense | 5 |
| Education | 5 |
| Electrical/gas/water installation | 3 |
| Financing | 2 |
| Other | 13 |
Table 4
Parents’ perceptions of children’s pain (%)

<table>
<thead>
<tr>
<th>Perceptions of children’s pain</th>
<th>Totally agree</th>
<th>Mostly agree</th>
<th>Cannot say</th>
<th>Mostly disagree</th>
<th>Totally disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults have the responsibility to alleviate my child’s pain (N = 314)</td>
<td>85</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Alleviation of my child’s postoperative pain prevents the child’s fears during future visits in child welfare clinic (N = 314)</td>
<td>62</td>
<td>29</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative pain decreases every day (N = 313)</td>
<td>41</td>
<td>48</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pain is always a part of surgery (N = 314)</td>
<td>44</td>
<td>42</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>My child cannot pretend to have pain (N = 312)</td>
<td>43</td>
<td>23</td>
<td>12</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Postoperative pain is acceptable because of benefits in my child’s health in future (N = 314)</td>
<td>26</td>
<td>36</td>
<td>15</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>I always try to protect my child from pain (N = 314)</td>
<td>20</td>
<td>35</td>
<td>8</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>I consider my child’s pain frightening (N = 314)</td>
<td>15</td>
<td>27</td>
<td>12</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>My child does not remember pain after a few days (N = 313)</td>
<td>13</td>
<td>32</td>
<td>16</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Pain is a normal part of my child’s life (N = 313)</td>
<td>13</td>
<td>24</td>
<td>14</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>My child has no pain if she can sleep (N = 314)</td>
<td>10</td>
<td>27</td>
<td>15</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>My child should learn to tolerate pain (N = 314)</td>
<td>6</td>
<td>31</td>
<td>17</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>My child’s organs are not developed enough to feel pain (N = 314)</td>
<td>5</td>
<td>5</td>
<td>19</td>
<td>13</td>
<td>58</td>
</tr>
<tr>
<td>I permit my child to hurt herself during everyday activities, such as playing, because pain belongs to these activities in childhood (N = 314)</td>
<td>3</td>
<td>20</td>
<td>9</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>I respect my child if he/she does not complain pain (N = 314)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>My child tolerates pain more than adults (N = 313)</td>
<td>1</td>
<td>13</td>
<td>23</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>Pain threshold of my child is higher than of adults (N = 314)</td>
<td>1</td>
<td>13</td>
<td>24</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>My child does not feel pain as much as adults (N = 314)</td>
<td>1</td>
<td>5</td>
<td>12</td>
<td>11</td>
<td>71</td>
</tr>
<tr>
<td>My child must cope with the pain by her/himself (N = 314)</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>20</td>
<td>73</td>
</tr>
</tbody>
</table>

Fathers, more often than mothers, stated that their child should learn to tolerate pain and the child should cope with the pain by her/himself. In addition, more than two-thirds of the fathers considered the child’s postoperative pain acceptable because of the benefits in the child’s health in future. Similarly, fathers, more than mothers, considered that their child was capable to pretend to have pain (Table 5).

Table 5
Differences in parents’ perceptions of children’s pain by parents’ gender (%)

<table>
<thead>
<tr>
<th>Perceptions of children’s pain</th>
<th>Totally agree</th>
<th>Mostly agree</th>
<th>Cannot say</th>
<th>Mostly disagree</th>
<th>Totally disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My child should learn to tolerate pain (N = 314)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fathers</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>Mothers</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>14</td>
<td>82</td>
</tr>
<tr>
<td>My child must cope with the pain by her/himself (N = 314)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fathers</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>Mothers</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>14</td>
<td>82</td>
</tr>
<tr>
<td>Postoperative pain is acceptable because of benefits in my child’s health in future (N = 314)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fathers</td>
<td>29</td>
<td>40</td>
<td>17</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Mothers</td>
<td>24</td>
<td>33</td>
<td>14</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>My child cannot pretend to have pain (N = 312)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fathers</td>
<td>27</td>
<td>30</td>
<td>15</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Mothers</td>
<td>51</td>
<td>20</td>
<td>10</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

\* \(p < 0.05\).

\** \(p < 0.001\).
Table 6
Differences in parents’ perceptions of children’s pain by children’s age (%)

<table>
<thead>
<tr>
<th>Perceptions of children’s pain</th>
<th>Child’s age (years)</th>
<th>Totally agree</th>
<th>Mostly agree</th>
<th>Cannot say</th>
<th>Mostly disagree</th>
<th>Totally disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My child cannot pretend to have pain</td>
<td>1–2</td>
<td>53</td>
<td>21</td>
<td>11</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>(N = 306)</td>
<td>3–4</td>
<td>33</td>
<td>25</td>
<td>11</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>33</td>
<td>23</td>
<td>14</td>
<td>25</td>
<td>5*</td>
</tr>
<tr>
<td>My child does not remember pain after a few days (N = 307)</td>
<td>1–2</td>
<td>16</td>
<td>32</td>
<td>23</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>12</td>
<td>27</td>
<td>9</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>10</td>
<td>35</td>
<td>8</td>
<td>31</td>
<td>17***</td>
</tr>
<tr>
<td>Alleviation of my child’s postoperative pain prevents the child’s fears during future visits in child welfare clinic (N = 308)</td>
<td>1–2</td>
<td>56</td>
<td>33</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>62</td>
<td>26</td>
<td>10</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>72</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>0*</td>
</tr>
</tbody>
</table>

*p < 0.05.
**p < 0.01.

Table 7
Ratings of VAS scores by parents’ perceptions of children’s need to cope with their pain by themselves (%) (N = 310)

<table>
<thead>
<tr>
<th>Children need to cope with their pain by themselves VAS</th>
<th>&lt;30 mm</th>
<th>&gt;30 mm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totally agree</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mostly agree</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cannot say</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mostly disagree</td>
<td>20</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Totally disagree</td>
<td>69</td>
<td>80</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 8
Differences in parents’ perceptions of children’s pain by PPPM scores

<table>
<thead>
<tr>
<th>Perceptions of children’s pain</th>
<th>Totally agree</th>
<th>Mostly agree</th>
<th>Cannot say</th>
<th>Mostly disagree</th>
<th>Totally disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My child does not feel pain as much as adults (N = 309)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPPM &lt; 7</td>
<td>1</td>
<td>7</td>
<td>13</td>
<td>13</td>
<td>66</td>
</tr>
<tr>
<td>PPPM &gt; 7</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>6</td>
<td>83*</td>
</tr>
<tr>
<td>My child does not remember pain after a few days (N = 309)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPPM &lt; 7</td>
<td>16</td>
<td>28</td>
<td>16</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>PPPM &gt; 7</td>
<td>6</td>
<td>43</td>
<td>14</td>
<td>25</td>
<td>12*</td>
</tr>
</tbody>
</table>

*p < 0.05.

4.4. Differences in parents’ perceptions of children’s pain by children’s age and gender

Boys (43%), more than girls (28%), were expected to learn to tolerate pain (p = 0.007). The youngest children, more often than older children, were not considered capable to pretend pain, and they were considered to forget their pain in a few days. Alleviation of child’s postoperative pain was considered to prevent the child’s fears during future visits in child welfare clinic mostly with oldest children (Table 6).

4.5. Relationship between parents’ perceptions of children’s pain and parent-rated children’s postoperative pain intensity and pain behaviours

The intensity of pain was assessed to be lowest among children whose parents did not expect their child to cope with their pain by themselves (Table 7).

Less pain behaviours were identified in children whose parents stated that their children do not feel pain as much as adults. Additionally, parents who thought that their child would not remember the pain after a few days, identified less pain behaviours in their children (Table 8).

5. Discussion

5.1. Discussion of the findings

The purpose of this study was to describe parents’ perceptions of 1–6-year-old children’s pain. Most of the parents suggested that adults have the responsibility to alleviate the child’s pain and that alleviation of the children’s postoperative pain prevents their fears during future visits in child welfare clinic. However, contrary to research-based understanding of children’s pain, the parents also stated that postoperative pain decreases
every day and pain is always a part of surgery which
This kind of perceptions may lead to the situation where
parents do not consider children's pain alleviation as a
goal, but, merely, will let the child suffer for a few days
postoperatively. In addition, pain experiences that are
very individual, cannot be predicted to decrease day by
day after surgery in all children for example after ade
noiectomy.

A minority of the parents suggested that child's or
gans are not developed enough to feel pain. However,
scientific evidence exists showing that even infants sen
sate pain despite the fact that their physiological pain
mechanisms are not fully developed (Maunukela, 1993,
177-178). It is obvious that scientific findings of the
area of children's pain have not reached the parents.
However, it could be assumed that hospital staff con
ducting day surgery could teach the parents about these
subjects.

According to results of this study, some parents be
lieve that children do not feel pain as much as adults.
These perceptions combined with lack of training are
suggested to be one of the most common reasons why
children are left to suffer unnecessarily from pain also by
the nurses (Hodges, 1988). Therefore, it is not surprising
that also parents have this kind of misleading percep
tions of children's pain.

A minority of the parents described that the children
are supposed to cope with the pain by themselves, and
the parent respected children if they did not complain
pain. These perceptions may reflect Finnish culture
where pain tolerance may be highly valued both in
adults and children. Cultural research in pain field has
been very limited in Finland. However, in a compari
son study among European countries it was found that
Finnish parents were likely to refuse from pain medi
cation (Ahonen et al., 1997, 285). Parents shared the
opinion that analgesics should not be taken immediately
and especially they should not be given to the children at
the first opportunity. It seems that a part of Finnish
parents value pain tolerance that may be deeply em
bedded in our cultural heritage.

Parents' gender was found to be related to their
perceptions of children's pain. Fathers, more often than
mothers, stated that their child should learn to tolerate
pain and the child should cope with the pain by her/him
self. Similarly, fathers, more than mothers, consid
ered that their child was capable to pretend to have pain.
These perceptions may reflect the need for high pain
tolerance in men's culture. On the other hand, it is
possible that fathers do not know their children as well
as mothers, and, therefore, are not aware of how well
their children can feel pain.

Boys, more than girls, were expected to learn to tol
erate pain. It is suggested that boys may be taught not to
cry or act like a baby (Bonham, 1996). However, it is
obvious that the boys show more controlled pain re
sponses because of social and cultural expectations while
girls are expected to express their pain more openly
(Lutz, 1986). In this case, boys' pain may remain un
identified and poorly managed.

The youngest children, more often than older chil
dren, were not considered capable to pretend pain, and
they were considered to forget their pain in a few days.
However, findings of a Finnish study (Kotiniemi, 1997)
showed that experiences of pain predicted behavioral
changes in children even several weeks postoperatively.

The intensity of pain was assessed to be lowest among
children whose parents did not expect their child to cope
with their pain by themselves. It is possible that these
parents actively tried to alleviate their child's postope
rative pain based on their understanding of child's pain.
Additionally, less pain behaviours were identified in
children whose parents stated that their children do not
feel pain as much as adults. Also parents who thought
that their child would not remember the pain after a few
days, identified less pain behaviours in their children.
Possibly these parents tended to underestimate their
child's postoperative pain because their misleading per
ceptions of children's pain.

5.2. Study limitations

Content validity of the instrument (Burns and Grove,
1997, 330) measuring parents' perceptions of children's
pain was increased by using existing international litera
ture of these perceptions and findings from a national
family interview study focussing on children's pain as
essment and alleviation at home (Kankkunen et al.,
2002). Cronbach's $\alpha$-co-efficient (0.58) showed moderate
internal consistency of the instrument. The $\alpha$-co-efficient
would have been higher if statements "I consider my
child's pain frightening", "adults have the responsibility
to alleviate my child's pain", "my child cannot pretend
t to have pain", "alleviation of my child's postope
rative pain prevents the child's fears during future visits
in child welfare clinic" and "I always try to protect my
child from pain" had been removed.

External validity of the study was increased by writ
en and verbal instructions for the parents. The PPPM is
fairly easy to use because of the dichotomous response
alternatives. However, rating the intensity of children's
postoperative pain in VAS scores may have been dif
cult for some parents. The questionnaire including the
statements measuring parents' perceptions of children's
pain was pre-tested with 27 parents whose child had
undergone a day surgery in Central Finland's Central
Hospital. Some minor changes were done based on
parents' suggestions.

The situation in Finnish health care during and after
the longlasting and disturbing physicians' strike may
have influenced the findings. Phone calls to contact
persons showed that the hospital staff was very busy
during the period of data collection. In addition, children's day surgeries were cancelled in the hospitals participating in the strike.

The findings of this study cannot be generalised to all Finnish parents because the sample did not present the population in a satisfactory level. First, it is obvious that parents whose child had no postoperative pain did not respond the questionnaire. Only 12% of the children whose parents filled in the questionnaire had no pain which indicate that parents may have believed that this study was focussed only on those children who had more pain. Secondly, only the biological parents responded the questionnaire.

5.3. Conclusions and implications

In this study, new knowledge was found about parents' perceptions of children's pain. Parents seemed to have both adequate and misleading perceptions of children's pain. Fathers were found to accept children's pain more than mothers. The boys were expected to tolerate pain more than girls. Several perceptions were related to children's postoperative pain intensity.

These findings can be utilised in family-centred children's day surgery. In day surgery the parents could be provided with adequate information about children's pain to decrease their misleading perceptions of children's pain tolerance. In addition, especially the parents of boys should be encouraged to alleviate the child's postoperative pain. In addition, especially fathers could be taught to protect their children from pain.

The results of this study showed challenges for further research. (1) Intervention studies are needed to test how teaching of children's pain affects parents' perceptions of children's pain. (2) Culturally oriented research is needed to understand how pain perceptions are developed and transmitted to next generation in different cultures. (3) Children's views of their experiences of postoperative pain alleviation at home should be explored. (4) The competence of hospital staff to educate the parents of children's pain should be investigated.

Acknowledgments

This study was funded by Hoitotieteiden tutkimusseura (Finnish Association of Caring Sciences), Sairaanhoitajien koulutussäätiö (Foundation of Nurse Education), Foundation for Paediatric Research, and the Finnish Post-Graduate School in Nursing Science.

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Ramer L, Richardson JL, Cohen MZ, Redney C, Danley KL, Judge EA. Multimodal pain assessment in an ethnically diverse group


Colored pain drawings: preliminary observations in a neurosurgical practice

Roberto Masferrer\textsuperscript{a}, Virginia Prendergast\textsuperscript{b,*,} Peter Hagell\textsuperscript{c}

\textsuperscript{a} Masferrer Neurosurgical, Colorado Springs, CO, USA
\textsuperscript{b} Barrow Neurological Institute, Phoenix, AZ, USA
\textsuperscript{c} Section of Restorative Neurology, Department of Clinical Neuroscience, University Hospital, Lund, Sweden

Received 1 February 2002; accepted 7 October 2002.

Abstract

Background: Black and white pain drawings were introduced as a proposed means to identify patients, presenting with low back pain, who demonstrated functional overlay upon neurological testing. The use of color may enhance the usefulness of such pain drawings, but has not been described for adult patients.

Aims: To retrospectively explore the use of colored pain drawings in patients with neck, low back, or radicular pain.

Methods: Patients with neck, low back, or radicular pain referred to a community-based neurosurgical practice for evaluation during 1 year (n = 359) depicted their pain on anatomical drawings using colored pencils representing different pain characteristics. Patients with abnormal (n = 55) and normal (n = 54) pain drawings were selected for this study. Use of medications, findings on physical examination, radiographic findings, activity levels, Waddell signs, and pending litigation were recorded and compared between patients with normal and abnormal pain drawings, as assessed according to the Ransford penalty point system.

Results: Patients whose colored pain drawings were abnormal, demonstrated a greater use of medications, more non-focal clinical findings, Waddell signs, impaired activity levels, involvement in pending litigation, and significantly fewer pathological radiographic findings than patients with normal pain drawings.

Conclusions: Our findings agree with previous observations using black and white pain drawings, indicating that colored pain drawings are no less useful than the black and white approach. Further research is necessary to examine the psychometric properties and clinical usefulness of colored pain drawings to predict outcomes and/or determine treatment.

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Keywords: Colors; Low back pain; Pain assessment; Pain drawings; Waddell signs

1. Introduction

The purpose of assessing patients with back pain is to identify the anatomical pathology and etiological basis of their complaints in order to offer optimal intervention. Despite advances in diagnostic studies and operative procedures, patients who seek treatment for back pain still constitute a diagnostic and therapeutic challenge (Graver et al., 1988; Ohnmeiss et al., 1995; Raskin et al., 1998; Spengler et al., 1990).

Early identification of patients with a psychological component that could adversely affect outcome has been recommended (Dzioba and Doxey, 1984; Long, 1981; McNeil et al., 1986; Öh Lund et al., 1996; Ransford et al., 1976; Spengler et al., 1990; Taylor et al., 1984; Waddell et al., 1988). Nevertheless, many neurosurgeons fail to obtain pre-operative psychological assessments (Brown, 1989). Yet patients deemed "operative failures" may have significant psychological factors that either generated or magnified the patient's original complaint. The temptation has been to blame the failure on patient "craziness" rather than deficient pre-operative selection (Brown, 1989, p. 171).

Ransford et al. (1976) first proposed using pain drawings to assess back pain and sciatica after noting an association between abnormal pain drawings and abnormal psychological profiles suggesting that pain
drawings could be used to predict psychological overlay. To assist interpretation and quantification of pain drawings, a scoring system of penalty points awarded for diffuse, non-anatomical features, was proposed.

In our clinical experience with black and white pain drawings, when more than one symbol is used to represent multiple pain characteristics in a monochromatic fashion, pain drawings can become difficult to interpret. Therefore, we substituted symbols with colors. Here we explore the feasibility of such an approach. Specifically, the frequencies of various indices of non-organic overlay among patients presenting with normal and abnormal colored pain drawings are explored.

2. Patients and methods

2.1. Patients and pain drawings

Pain drawings from all patients (n = 359) referred to a community-based neurosurgical practice (in Colorado Springs, CO, USA) for evaluation of spine problems during one calendar year were reviewed (see below). Written permissions were obtained from all subjects.

Patients used colored pencils to indicate current pain location and characteristics on a standard anteroposterior, asexual, faceless, full-body human figure. Colors were arbitrary assigned for the traditional symbols used by Ransford et al. (1976): red = stabbing; orange = burning; blue = numbness; green = pins and needles; and brown = aching. No other instructions were provided, and there was no time limit for completing the task. Using Ransford's criteria for penalty points (Ransford et al., 1976), all pain drawings were classified as "normal" (<3 points) or "abnormal" (≥3 points) by two raters (R.M. and V.P.) blinded to patients' medical data and outcomes.

Raters agreed on classification of pain drawings in 330 of 359 cases. The remaining 29 patients were excluded. Fifty-five patients (17%) produced abnormal pain drawings (abnormal group). From the remaining 275 patients, every fifth patient on the patient list was selected to comprise a control group. One control case was excluded because of incomplete records, resulting in a total of 54 patients.

2.2. Data collection and analyses

At their initial examination, information on medications; pending litigation (i.e., pursuit of a legal settlement for work related accidents, auto accidents, or other issues related to their current medical complaints); current work status; and pain intensity was collected.

Patients underwent a complete neurological examination and diagnostic studies were reviewed. The presence of non-organic physical signs, as described by Waddell et al. (1980), was recorded. Patients demonstrating three or more such signs were considered displaying Waddell signs. All patients had undergone radiographic studies, primarily magnetic resonance imaging (MRI), spinal radiography, and/or electromyography. Other patients were referred with computed tomography (CT) scans or CT myelograms. Pathology was classified according to radiographic findings, as assessed by one of us (R.M.). Patients' activity levels were assessed as none, partial, or full according to their reported ability to sustain their normal activities as an employee, homemaker, or student.

Categorical data from the two groups were compared by means of Fischer's exact test. Continuous data were compared by an unpaired t test. The a-level of significance (2-tailed) was set at <0.05.

3. Results

All patients completed their pain drawings and did not express any difficulties in understanding the task or the use of colors to depict different pain characteristics.

The mean age (±SD) for the abnormal and control groups were 49.7 (±14.5) and 55.0 (±15.2) years, respectively (P = 0.067). There were more females (34) than males (21) in the abnormal group (P = 0.022), but not in the control group (23 women and 31 men; P = 0.178). Further comparisons between patients with normal and abnormal pain drawings are presented in Table 1 and representative examples of the two are provided in Fig. 1.

Patients in both groups were on multiple medications, e.g., non-steroidal anti-inflammatory drugs (NSAIDs) combined with muscle relaxants and/or narcotic analogesics. Use of narcotic analogesics and psychopharmacological drugs (i.e., antidepressants and/or anxiolytics) was significantly more common in patients who produced abnormal pain drawings than among controls. Furthermore, 28% of control patients did not use any drugs; this was the case only in 9% of those with abnormal drawings (P = 0.014).

The most common primary pathology was disk herniation and/or spinal stenosis (Table 1). Other pathological entities included compression fractures, degenerative disc disease, and synovial cysts. Among patients who produced abnormal pain drawings, 11 did not show any radiographic evidence of spinal pathology, whereas all patients in the normal group did. Findings on the physical examination were in accordance with those from radiographic studies. Positive findings on clinical examinations, i.e., motor, sensory, and/or reflex deficits concordant with radiographic findings, were found in all but three patients in the control group compared to 30 of the 55 patients with abnormal pain drawings (P < 0.001). Waddell signs also were signifi-
Table 1
Comparison between patients with abnormal colored pain drawings (n = 55) and a group of normal control pain drawings (n = 54)

<table>
<thead>
<tr>
<th>Medications*</th>
<th>Control group (no. of patients)</th>
<th>Abnormal group (no. of patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>15</td>
<td>5</td>
<td>0.014</td>
</tr>
<tr>
<td>Non-narcotic analgesia*</td>
<td>35</td>
<td>38</td>
<td>0.687</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>18</td>
<td>30</td>
<td>0.034</td>
</tr>
<tr>
<td>Psychopharmacological drugs*</td>
<td>4</td>
<td>20</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pathology*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNP/Stenosis</td>
<td>50</td>
<td>35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>13</td>
<td>1.000</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Clinical exam*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive findings</td>
<td>51</td>
<td>30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Waddell signs*</td>
<td>1</td>
<td>21</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Activity level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>12</td>
<td>0.008</td>
</tr>
<tr>
<td>Partial</td>
<td>6</td>
<td>27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fall</td>
<td>46</td>
<td>16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pending litigation*</td>
<td>13</td>
<td>30</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Patients may be on more than one medication.
† NSAID’s and/or muscle relaxants.
‡ Antidepressants and/or anxiolytics.
§ As defined by means of radiographic studies (see Section 2). Multiple pathological processes were evident in several patients in each group.
∥ HNP = herniated nucleus pulposus.
^ Positive = dermatoma/myotomal and/or reflex changes noted on examination.
© Presence of three or more non-organic physical signs, as described by Waddell et al. (1980).
‡ Pursuit of a legal settlement for work related accidents, auto accidents, or other issues related to their current medical complaints.

Fig. 1. Representative examples of (A) normal and (B) abnormal pain drawings. (A) Organic colored pain drawing of a 28-year-old female with large, L5-S1, HNP lateralized to the left. Drawing depicts classic sciatic pain associated with appropriate dermatomal innervation. (B) Non-organic colored pain drawing of a 66-year-old female referred for evaluation of neck pain. No radiographic pathology depicted on cervical MRI. Diffuse, non-dermatomal, total body pain with multiple pain characteristics. See Section 2 for color scheme explanation.
cantly more common in the abnormal group $(P < 0.001)$.

Fewer patients within the abnormal group maintained full work, school, or homemaking activities compared to those in the control group (Table 1). Pending litigation was also significantly more common in the abnormal group, where 55% of patients reported injuries sustained on the job or as a result of a motor vehicle accident compared to 24% in the control group $(P = 0.002)$.

An additional observation (data not shown) was that eight patients (six women, two men) with abnormal pain drawings, but none in the control group, drew facial characteristics in addition to limb and/or torso pain (Fig. 1B).

4. Discussion

We substituted colors for traditional black and white symbols in the use of pain drawings. Patients who produced abnormal colored pain drawings had fewer pathological findings on radiographic and clinical examinations than patients whose pain drawings corresponded to dermatomal or myotomal patterns of innervation. In addition, they used more medications, were involved in more litigious issues, and maintained a lowered activity level than patients with normal pain drawings.

We did not discriminate between acute and chronic pain. This is a potential weakness because patients with pain lasting more than 6 months may have a clinical profile similar to patients with depression (Almey, 1987). Thus, it is possible that chronic pain is over represented among patients who exhibited abnormal pain drawings. Nevertheless, several of our findings displayed clear and significant discrepancies between the two groups, which strengthens the findings. Furthermore, because the samples in this study were drawn from a total annual patient population in a community-based practice, the external validity of our findings should be relatively high. To our knowledge, this is the first description of the use of colored pain drawings in patients with spinal disorders. This renders the findings particularly interesting and calls for comparison with previous studies using traditional, black and white pain drawings.

Abnormal black and white pain drawings have been associated with multiple, non-organic physical signs, and dysfunction. In their analysis of 650 patients with chronic low back pain, Chan et al. (1993) found that 81.7% of patients with three or more Waddell signs had a non-organic pain drawing. Among those displaying all five Waddell signs, 94.6% had a non-organic pain drawing. Similarly, Öhlund et al. (1996) found that abnormal pain drawings were associated with a tendency to somatize and with a prolonged delay in returning to work. These past clinical observations with traditional black and white pain drawings appear to be in agreement with our findings using colored pain drawings. In our sample, signs of non-organic overlay were all significantly more common among patients with abnormal pain drawings.

Psychological components of the pain experience have been recognized as factors that can affect outcomes. For example, investigators have found elevated Minnesota Multiphasic Personality Inventory (MMPI) scores and abnormal pain drawings to be associated with poor outcome (Dzioba and Doxey, 1984; Spengler et al., 1990; Taylor et al., 1984). Furthermore, Kjellby-Wendt et al. (1999) found that patients discontent with their outcomes following surgical resection of lumbar disc herniation scored higher on measures of depression and anxiety before as well as after surgery, and also had a prolonged delay in returning to work. Although some authors (Long, 1981; Dzioba and Doxey, 1984) have suggested that pain drawings can predict abnormal psychological profiles according to the MMPI, the underpinning evidences are not strong. For example, Von Baeyer et al. (1983) found that the correlation between abnormal pain drawings and the MMPI hysteria scores ranged between 0.02 and 0.28. Hence, no more than about 8% of the variation in MMPI scores could be explained by patients’ pain drawings. This calls for caution in interpretation of pain drawings beyond what they primarily are purported to communicate (i.e., pain distributions and characteristics) and does not support substitution of psychological assessment.

The pain drawing template used for the anterior body in this study was faceless. An interesting observation in this regard was that eight of the patients producing abnormal pain drawings also drew in facial characteristics (Fig. 1B). Faceless templates have been used in approximately half of the previous pain drawing studies (Chan et al., 1993; Öhlund et al., 1996; Ohnmeiss et al., 1995; Parker et al., 1995; Rankine et al., 1998; Ransford et al., 1976; Taylor et al., 1984). Whether patients have drawn-in facial features as part of their pain drawing has, however, not been reported. Although our current sample is too small to allow for any firm interpretations, the fact that all facial characteristics appeared in the group of patients with abnormal pain drawings raises the possibility that this could be an additional red flag. If so, it would also seem feasible to advocate the use of faceless over other templates.

Existing color studies have been limited to psychiatric or pediatric settings, among which only the latter have used colors for pain drawings (Claworthy et al., 1999; Unruh et al., 1983). Different cultures associate different colors to various emotions (Williams et al., 1996). Therefore, it is not unlikely that different color schemes should be used in different cultural and/or ethnic groups.
of patients. Such cultural concerns are, however, probably not restricted solely to the use of colors. For example, in a Swedish study using traditional black and white pain drawings, Udén et al. (1988) found a higher frequency of abnormal pain drawings among non-Scandinavians than Scandinavian subjects.

5. Conclusions

Our findings show that spinal patients with abnormal colored pain drawings used more medications, had more non-focal symptomatology, impaired activity levels, pending litigation, and less pathology than those with normal drawings. Our findings do not indicate that colored pain drawings introduce any disadvantages compared to black and white pain drawings, and support the notion that colored pain drawings are able to communicate patients’ perceived pain. Further research is warranted to better understand the values and limitations of this patient-derived modality of assessment, such as its psychometric properties and clinical usefulness to predict outcomes and/or determine treatment.

References


Patient reporting of adverse drug reactions: useful information for pain management?

Narumol Jarernsiripornkul\textsuperscript{a}, Janet Kraska\textsuperscript{b,\ast}, R. Michael E. Richards\textsuperscript{c}, Phillip A.G. Capps\textsuperscript{d}

\textsuperscript{a} Department of Clinical Pharmacy, Khon Kaen University, Thailand
\textsuperscript{b} College of Pharmacy Practice, Coventry, UK
\textsuperscript{c} Faculty of Pharmacy, Health Sciences Mahasarakham University, Thailand
\textsuperscript{d} School of Pharmacy, The Robert Gordon University, Aberdeen, UK

Received 22 April 2002; accepted 7 October 2002

Abstract

Background. Patients' perceptions of adverse effects caused by the medicines they are prescribed may influence how they use these medicines. Little is known about patients' perceptions of the adverse effects of specific drugs in everyday use and whether these differ from those identified by clinical trials and standard post-marketing surveillance methods.

Aim. To compare reports of perceived adverse drug reactions (ADRs) obtained directly from patients taking tramadol to those found in clinical trials and two methods of post-marketing surveillance.

Method. Postal questionnaire distributed to 1048 patients who had a prescription for tramadol dispensed over a 3-month period.

Results. Most (84\%) of the 344 respondents reported at least one symptom perceived as an ADR to tramadol. Dry mouth, light-headedness and constipation were most commonly reported. Almost half (48\%) rated their most bothersome symptom as at least moderate and 43\% claimed to have reported symptoms to their doctor. Perceived problems had led 38 respondents to stop taking tramadol. The 10 most frequently reported symptoms were all previously reported ADRs to tramadol. Although relatively minor, all 10 also appeared in reports to the UK Committee on the Safety of Medicines (CSM) and in prescription event monitoring. For many symptoms, the estimated range of frequency was in line with published reports, but considerably higher than that of post-marketing surveillance methods.

Conclusions. Symptoms were reported by the majority of respondents and for many symptoms the frequency was high. Many patients did not report symptoms they perceived to be adverse effects to their doctor. The results indicate that patient perceptions of potential ADRs are relevant and should be an integral part of a pain management strategy.

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Keywords: Adverse drug reactions; Patient self-reporting; Tramadol; Pain management

1. Introduction

Managing pain effectively in individual patients requires that clinicians are aware of patient perceptions of the medications they receive. For example the patient's perceptions of adverse effects caused by their medication could have a major influence on the effectiveness of their therapy. Information on adverse effects is available to prescribers through manufacturers and in the literature. For new drugs, this is based on clinical trials, which are acknowledged as only identifying a proportion of potential adverse effects (Moore et al., 1998) and which also do not reflect everyday practice. Post-marketing surveillance schemes, such as the UK's Yellow Card scheme and prescription event monitoring (PEM), seek to identify further reactions occurring in normal use of a drug, but can suffer from under-reporting (Fletcher, 1995; Inman and Pearce, 1993; Martin et al., 1998; Rogers et al., 1988). Both these schemes rely on the
patient reporting their experiences to a prescriber and on
that experience being acknowledged and recorded in
medical notes. They do not accept reports directly from
patients. While prescribers may be aware of published
data on adverse effects, they may be less willing to ac-
knowledge that in everyday use of drugs, patients' ex-
periences may differ from these.

There is evidence that many patients with chronic pain
self-medicate with analgesics and alternative therapies in
addition to taking prescribed drugs (Long and Wynne,
1996), indicating lack of pain control. Patients may also
take medicines differently from how they were prescribed
(Read and Kriska, 1998; Ready et al., 1982). Their per-
ceptions of adverse events which they associate with drug
therapy can contribute to failure to take medicines op-
timally and may therefore be of importance in enabling a
management strategy to be agreed (Donovan et al., 1989)
and concordance to be reached (RPSGB, 1997).

Patients' perceptions may be considered of limited
value, since patients may not be regarded as able to
discriminate effectively between symptoms attributable
to individual drugs or diseases. However, health pro-
fessionals have similar problems (Bateman et al., 1992;
Scott et al., 1987). A patient-completed questionnaire,
screened by a health professional, could enable the
identification of symptoms, which patients perceive as
being related to their drug therapy. This may identify
and quantify commonly occurring symptoms which pa-
tients find bothersome. It has also been suggested that
patient self-monitoring could enable earlier detection of
symptomatic reactions to new drugs and to identify es-
abled ADRs (Egberts et al., 1996; Mitchell et al.,
1994). Thus a further potential benefit could be increased
reporting to authorities of the symptoms reported.

A generic checklist has been developed which patients
can complete enabling them to report to a health pro-
fessional the symptoms they believe to be due to a par-
ticular drug (Jarensirisiripornkul et al., 2002). Such a
questionnaire has been suggested as a tool for use in
clinical trials (Cals, 2001), but could also be used as a
post-marketing surveillance tool. Using this it should be
feasible to determine symptoms identified by respondents
as perceived ADRs to a particular drug and to compare
them to those found by other methods. This checklist was
studied in patients taking tramadol to determine the
symptoms which patients perceived could be due to this
drug. The results were compared to data obtained from
Yellow Card reports and data from an unpublished PFM
study as well as to data from published studies.

2. Method

The development of the checklist has been described
in detail elsewhere (Jarensirisiripornkul et al., 2002). It
consisted of three sections:

- demographic details, concurrent therapy and disease
  states;
- a series of symptoms and opportunity to add other
  symptoms, which was divided into body systems or
  regions, questions relating to most bothersome symp-
  toms, symptom severity and reporting of symptoms
to the GP;
- reasons for stopping drug and symptoms appearing
  after stopping.

After obtaining ethics committee approval, ques-
tionnaires were sent to patients from all general prac-
tices in the Grampian region of Scotland, which agreed
to participate (79/97), who had been prescribed tram-
adol over the period January to March 1997. These were
sent out 6 months after the prescription was dispensed
and all questionnaires returned within 3 months of issue
were included in the analysis. Patients under 16 years
old and those resident in nursing homes were excluded.
As the pilot study had indicated the receipt of the ques-
tionnaire might generate anxiety, no reminders were
issued. The questionnaire asked respondents to report
symptoms they had experienced which they thought
were due to tramadol over the previous year. The
number of Yellow Card reports sent to the Committee
on the Safety of Medicines (CSM) by participating
practices concerning tramadol over the same period was
obtained for comparison. Data on symptoms reported
on all Yellow Cards since product launch and data from a
PEM study were obtained from the CSM and Pro-
fessor R. Mann (personal communication), respectively.

Symptoms were classified, using a system developed
specifically for the study (Jarensirisiripornkul et al.,
1998; Jarensirisiripornkul, 2001), into four categories for
causality. The literature on ADRs was used in this process,
to identify whether each symptom was previously de-
scribed as an ADR to any of the drugs. Standard texts
were used in attributing symptoms to disease states.
Comparisons between sub-groups were made using the
chi-squared test for association. Comparisons of the
most frequently reported symptoms by the different
methods were made using the Z test for two propor-
tions. A P value of 0.05 was chosen as indicating sta-
tistical significance.

3. Results

3.1. Demographic data

A total of 1048 postal questionnaires were sent to
patients prescribed tramadol, from whom 344 valid re-
sponses were obtained (32.8% response rate). Of these
respondents, 115 (33.4%) were male and 227 (66.0%)
were female. 2 (0.6%) did not specify. The mean ± SD age
of the respondents was 57.4 ± 16.9 years with the majority
falling into the ages of 60–79 (38.9%) and 40–59 (33.4%).
The majority of the respondents (81%) were taking between one and six concomitant drugs, although the range was between 0 and 16. The frequency of taking tramadol was reported as two, three and four times daily by 32.6%, 25.9% and 20.6%, respectively. The most frequent indication for use was back pain (25.3%), followed by other bone or muscle pains (17.7%), unspecified pain (17.2%) and osteoarthritis (15.4%).

3.2. Frequency of symptom reports and stopping tramadol

A total of 289 (84.0%) respondents reported at least one symptom; the remaining 55 (16.0%) reported no side effects experienced. There were 92 different symptoms and 2333 total symptoms reported (median = 4.5, range = 0–51). Over one-third of respondents (112) were taking other analgesics. These patients reported similar numbers of symptoms to those who were not taking other analgesics in addition to tramadol ($\chi^2 = 0.77$, df = 3, $P$-value = 0.86). Respondents were asked to rate the severity of the symptoms, which bothered them most using the scale very severe, severe, moderate, mild, minimal. There were 93 (27.0%) who perceived the severity of their most bothersome symptoms as moderate, 48 (13.9%) as severe and 24 (7.0%) as very severe.

A significant association was found between the severity rating of the most bothersome symptoms and the number of symptoms reported ($\chi^2 = 14.59$, df = 6, $P = 0.02$) (Fig. 1). Patients who perceived the most bothersome symptoms as severe were also significantly more likely to have informed their doctors about symptoms reported in the questionnaires, compared with those who perceived the symptoms as mild ($\chi^2 = 11.05$, df = 2, $P = 0.004$).

Almost half of the patients claimed to have told their doctors about some symptoms (70, 20.3%) or all symptoms (77, 22.4%). Only 17 reports were received by the CSM relating to tramadol from the participating medical practices in the period covered by the study.

There were 126 respondents who claimed to have stopped taking tramadol. Of these 27% claimed to have done so because they felt they no longer needed it and a further 20% felt it was not helping them. Thirty-eight respondents (11.0% of the total 344 respondents) claimed to have stopped taking tramadol because either they or their doctor identified a problem with it.

3.3. Symptoms reported

All of the 10 symptoms most commonly reported by respondents were known side effects of tramadol. These are listed in Table 1 as percentages using different denominators, i.e., number of respondents, number of patients prescribed tramadol during the study period and total number of reported symptoms. No data were available on non-responders. However in order to enable a range of potential frequencies of each symptom to be estimated, an assumption was made that these patients experienced no symptoms which they perceived to be due to tramadol. This range was therefore calculated using the total number of patients prescribed tramadol (best case scenario) and the number of respondents (worst case scenario) as denominators.

Unusual tiredness/weakness (24) and increased sweating (23) were the symptoms reported as most bothersome with the highest frequency.

Only 10 patients reported symptoms which started after stopping tramadol, all of which differed and only one of which, reduction in sleeping, is a known withdrawal effect.

All symptoms reported were classified using data provided by patients about concomitant therapy and

![Fig. 1. Severity of most bothersome symptoms in relation to number of symptoms reported by patients prescribed tramadol.](image-url)
Table 1
The 10 most frequently reported symptoms in 344 respondents taking tramadol

<table>
<thead>
<tr>
<th>Reported symptoms in rank order of frequency</th>
<th>Frequency of reported symptoms</th>
<th>N = 344*</th>
<th>N = 1048*</th>
<th>N = 2333*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>112</td>
<td>32.6</td>
<td>10.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>85</td>
<td>24.7</td>
<td>8.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>84</td>
<td>24.4</td>
<td>8.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Increased sleep</td>
<td>70</td>
<td>20.3</td>
<td>6.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>69</td>
<td>20.1</td>
<td>6.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Flushing</td>
<td>67</td>
<td>19.5</td>
<td>6.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>66</td>
<td>19.2</td>
<td>6.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Unusual tiredness/weakness</td>
<td>64</td>
<td>18.9</td>
<td>6.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Itching of skin</td>
<td>65</td>
<td>18.9</td>
<td>6.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>56</td>
<td>16.3</td>
<td>5.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*Number of respondents (worst case scenario).

++Number of questionnaires sent (equivalent to number of patients prescribed tramadol – best case scenario).

**Total number of reported symptoms.

Disease states into one of four categories: probably caused by tramadol, possibly caused by tramadol, unlikely to be an ADR to tramadol and unattributable (Jarensiripornkul et al., 2002). Out of the 2333 perceived symptoms reported, 1246 (33.4%) were classified as possibly caused by tramadol, with a further 321 (13.8%) classed as probably caused by the drug. These were all known side effects of tramadol, but in the case of those classed as possibly caused by tramadol, were also potentially attributable to concomitant drugs and disease states. Thus approximately two-thirds of symptoms reported by patients were known side effects of tramadol. Of the remaining symptoms, 456 (19.5%) were classed as unlikely to be an ADR to tramadol because they were known side effects of other concomitant therapy or symptoms potentially caused by diseases present. There were 310 (13.3%) symptoms which could not be attributed to any of the drugs or disease states reported by the patient.

Five of the 10 most frequently reported symptoms were among the 10 symptoms most commonly reported to the CSM at the time of the study. These were increased sweating, nausea/vomiting, itching of skin, dizziness or vertigo and increased sleep. The remaining top 10 symptoms on Yellow Card reports were headache, rashes, hallucinations, convulsions and confusion. Patients frequently reported dry mouth, light-headedness, constipation, increased sleep, flushing and unusual tiredness/weakness, which were less common among CSM reports (Table 2).

Direct comparison to reported events in prescription event monitoring was not feasible due to the differing methods involved in reporting and terms used. However, six of the symptoms most frequently reported in the present study (light-headedness, constipation, increased sleep, nausea/vomiting, unusual tiredness/weakness and dizziness/vertigo) were similar to frequently reported events in a PEM study.

4. Discussion

The feasibility of using a generic questionnaire to seek patients’ views on symptoms they have experienced
which they perceive to be due to a drug they have taken has been demonstrated (Jareemisiripornkul et al., 2002). Approximately two-thirds of the symptoms reported by patients who had taken tramadol were known side effects of the drug. The symptoms reported with highest frequency were all common in published studies. Almost 15% of the respondents had stopped taking tramadol because their condition had improved, while others had taken it for over one year, suggesting that it was being used for acute as well as chronic pain. Eleven percent of respondents however had stopped taking it because of a perceived problem. Almost half of all respondents described the symptom(s) which bothered them the most as moderate, severe or very severe. This was reflected in the proportion of respondents who claimed to have reported symptoms to their doctor. Patients who gave symptom ratings of severe or very severe were also likely to report a high number of symptoms, hence may have over-reported.

It must be acknowledged that patients who responded may be those most likely to have experienced perceived adverse effects and the response rate was relatively low, although similar to that found in other similar studies (Mitchell et al., 1988; Willison et al., 1995). However there were a substantial proportion (16%) of respondents who reported having experienced no potential side effects. Most patients reported only a few symptoms. The coincidence of these with published reports of common side effects (Cossman and Kohnen, 1995; Dayer et al., 1994; Micromedex, 1998; Moore and McQuay, 1997) suggests that this questionnaire is a useful method of estimating the incidence of adverse effects.

A summary of tramadol safety data which included post-marketing surveillance studies covering more than 21,000 patients (Cossman et al., 1997) reported the most frequently documented ADRs to be nausea/vomiting, dizziness, drowsiness, tiredness, sweating and dry mouth. All of these were among the top 10 reported symptoms in the present study. The range of potential incidences obtained in this study is also similar to those in published studies for most symptoms (Cossman and Kohnen, 1995; Crighton et al., 1997; Dayer et al., 1994; Hopkins et al., 1998; Micromedex, 1998; Moore and McQuay, 1997; Sunshine, 1994; Willison et al., 1995). This study found a high incidence of light-headedness, which is rarely identified as a side effect. Dizziness however is commonly reported with similar incidence to that found here (Cossman and Kohnen, 1995; Lewis and Han, 1997; Sunshine, 1994) and also had a high incidence rate in a PEM study of tramadol. In PEM studies, a number of different terms reported by doctors, such as light-headedness, are combined to form higher-level terms. This illustrates the difficulties in making comparisons of reports from different studies. It may also indicate that patients are unable to distinguish between these symptoms.

Dry mouth was the most common symptom reported in the present study, occurring in much higher incidence than found elsewhere (Cossman and Kohnen, 1995; Lewis and Han, 1997). The types of symptoms reported commonly here compared to those reported to the CSM suggests that while patients tend to report mostly minor symptoms, health care professionals report more serious symptoms. This has also been found elsewhere (Mitchell et al., 1988, 1989; van den Beten et al., 1999). In particular drowsiness, tiredness and dry mouth, the most frequently documented adverse effects of tramadol in clinical and post-marketing surveillance reports (Dayer et al., 1994). As tramadol was a 'black triangle' drug at the time of the study, all potential adverse effects should have been reported to the CSM, even those which are minor or well known. Given the known problems of under-reporting with the Yellow Card system (Fletcher, 1995; Rogers et al., 1988), the higher frequencies of minor symptoms found among patient reports is not surprising.

A pilot study of this method using co-proxamol (paracetamol + dextropropoxyphene) found few reports of nausea/vomiting compared to the frequency in the present study (Jareemisiripornkul et al., 1998). This difference is in line with other studies comparing the two drugs (Cossman et al., 1997; Micromedex, 1998) and adds further credence to the method as a potentially useful means of detecting the incidence of perceived adverse effects.

The data suggest that large proportions of patients may experience adverse effects which, although relatively minor, almost half regard as moderately or severely bothersome. Patients may not always report symptoms they suspect to be adverse effects to their doctor. However the results presented here show that 42% of those who claimed to have such symptoms did say they had done so. What is not known is the extent to which doctors and other health care professionals acknowledge patients' perceptions of ADRs as potentially important in managing pain. The results of this study indicate that patient perceptions of potential ADRs are relevant. Therefore logically they should form an integral part in determining a pain management strategy.

Acknowledgments

The authors are grateful to the GPs who agreed to allow questionnaires to be issued to their patients, to the Pharmacy Practice Division of the Common Services Agency of the Department of Health for help in identifying patients, and to the patients who responded. We also acknowledge the assistance of the CSM and Professor R. Mann in supplying data and are grateful to
Ms. Deborah Layton for valuable advice and comment on PEM data. The authors have no interests to declare.

References


Long term depression of human nociceptive skin senses induced by thin fibre stimulation

Hans-Jörgen Nilsson, Elia Psouni, Jens Schouenborg*

Section for Neurophysiology, Department of Physiological Sciences, University of Lund, BMC-F10, Tornävagen 10, Lund S-221 84, Sweden

Received 22 April 2002; accepted 22 October 2002

Abstract

We have recently shown that stimulation, through a multi-electrode array, of thin nerve fibres close to the dermo-epidermal junction in the skin, produces powerful inhibition of itch and, to a lesser degree, cutaneous pain in humans. Here, we have studied the induction time and frequency dependency (range 1–10 Hz) of the inhibitory effects of such stimulation on itch, mechanical, and thermal pain, in 20 healthy subjects. Sixteen electrodes applied on the skin were consecutively stimulated using a method termed cutaneous field stimulation (CFS). The results show that different treatment periods with CFS were required for the induction of significant inhibitory effects on different nociceptive qualities: 1st heat pain (1 min), itch (3 min), 2nd heat pain (6 min), pinch evoked pain (8 min). Six to ten minutes stimulation sufficed to induce peak inhibitory effects on all the sensory qualities while longer stimulation (up to 40 min) did not cause significantly stronger inhibition. The effects on itch, 1st and 2nd heat pain lasted over 55 min after termination of CFS. There was no effect on prickle. No significant difference in inhibitory effects of different stimulation frequencies (1, 4 and 10 Hz/electrode) was found. The induction time and effective stimulation frequencies may suggest that the underlying mechanisms are similar to those of long term depression (LTD) previously described in the spinal cord in animal experiments. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Pruritus; Pain; Nociception; Analgesia; Somatosensory; TENS

1. Introduction

It is well known that interactions can occur between different senses in the central nervous system. For example, tactile stimulation (cf. Melzack, 1985) and thick fibre stimulation can instantly inhibit pain (Eriksson and Sjölund, 1976; Sjölund and Eriksson, 1979) while painful or intense mechanical stimulation can inhibit itch (McMahon and Koltzenburg, 1992; Nilsson et al., 1997; Ward et al., 1996). Furthermore, prolonged conditioning stimulation of thin myelinated and unmyelinated fibres innervating skin or deep tissues can produce substantial and durable inhibition of segmental spinal nociceptive transmission in animals (Chung et al., 1983, 1984a; Lee et al., 1985; Sandkühler et al., 1997; Sjölund, 1985, 1988; Woolf et al., 1980) and pain in humans (Andersson, 1979; Eriksson et al., 1979; Woolf, 1979).

Using a multi-electrode array (4 x 4 matrix) with the electrode tips introduced close to the dermo-epidermal junction, it was possible to stimulate cutaneous C and Aδ fibres at tolerable levels within defined skin areas in humans (Nilsson et al., 1997). This stimulation, termed cutaneous field stimulation (CFS), resulted in a powerful and long lasting inhibition (4–8 h) of experimental itch in all subjects tested (Nilsson et al., 1997). Recently, inhibitory effects lasting up to 7 h were found in a controlled clinical study on chronic itch (Nilsson et al., 2003). In another study, it was found that other cutaneous nociceptive qualities were differentially affected, suggesting that different nociceptive qualities are subject to differential control (Nilsson and Schouenborg, 1999).

It is not known, however, if the inhibitory mechanisms acting on different nociceptive qualities differ with respect to input parameters such as stimulation frequency and duration.
The aim of this investigation was to clarify the underlying neural inhibitory mechanisms via characterisation of the induction time and frequency dependency of the inhibitory effects of CFS on the major cutaneous nociceptive qualities. Such data may also allow a comparison with "memory-like" phenomena such as LTD previously described in animal experiments (Linden and Connor, 1995; Sandkühler et al., 1997). Finally, in view of the robust inhibitory effects of CFS on itch and pain, information on the induction time and effective stimulation frequencies may be of potential clinical importance.

2. Material and methods

2.1. Participants and ethical considerations

Experiments were performed on 20 healthy Caucasian subjects, age 20–30 years. All participants were students without any prior or ongoing skin or neurological disease or prior connection to the study. No one was taking any anti-allergic or anti-nociceptive medication.

The study was performed in accordance with the World Medical Association Declaration of Helsinki (52nd amendment, 2000). The project was approved in advance by a regional ethical committee and each subject gave written consent. Participants were informed that the effects of a harmless electrical stimulation technique (CFS) were to be tested on several sensory modalities. The information made available to them included technical aspects of the device used for stimulation (CFS) as well as the procedure to be employed during testing. Participants were not given any information regarding the theoretical background of this investigation or possible outcomes. To avoid potential bias, none of the authors were involved in the testing sessions. These were lead by a University employee otherwise unconnected to the study and without any knowledge as to the nature of the project.

2.2. General experimental set-up

Subjects were initially divided into two treatment groups of 10 (Groups 1 and 2). In both groups, histamine-evoked itch, fabric-evoked prickle, noxious pinch, heat pain thresholds and intensity of first and second heat pain during and after CFS were measured. However, the two groups received slightly different instructions regarding how to use the CFS, in terms of when to cease the treatment (see Section 3). Half of the participants from each treatment group (randomly selected) participated in a new round of tests where all the above noxious qualities except prickle were measured again (N = 10, Group 3). All sensory testing was made on the right volar forearm at exactly the same skin area that received the treatment. Within each subject group, the results obtained for each type of treatment on each sensory modality and at each testing instance, were pooled and averaged.

Subjects were tested on several (4–5) occasions. A pause of at least three days between testing sessions was used in order to minimise possible cumulative effects of repetitive CFS treatments. The first occasion involved repeated tests on each sensory modality (except itch, which was tested only once), without any treatment. This served several purposes: (1) to acquaint the subjects with sensory stimuli and other measurements, (2) to evaluate possible effects of repeated sensory stimulation of the baseline itself and (3) to obtain baseline values for histamine produced itch. The different sensation intensities were measured using a Visual Analogue Scale (VAS, length 100 mm presented horizontally, marked with "no pain/prickle/itch" on the left end and "maximal imaginable pain/prickle/itch": see Aitken, 1969; Price, 1999; Price et al., 1994). In no case was there a significant shift in baseline values over time, indicating that the test procedure per se did not have any impact on the perception of the various sensory stimuli.

On the following testing occasions CFS was applied using different treatment parameters in a random order (see Section 3 for specifics). Within each group, every subject tried all types of treatment. Initiating each experiment, a control test session was carried out for about 10–15 min prior to the initiation of treatment, followed by three post-treatment test sessions. In cases of pinch, 1st and 2nd heat pain, the sensory stimulation was repeated twice, with a 1-min interval in between.

Post-treatment stimulation of the same sensory modality was carried out three times, at 5, 25 and 55 min post-treatment, that is with an inter-stimulus interval of first 20 and then 30 min. Prickle stimulation always came first while heat and mechanical pain stimulation was randomised across subjects and across trials. Since the histamine induced itch sensation lasts about 1 h (Handwerker et al., 1991, 1987; Magerl and Handwerker, 1988; Magerl et al., 1990), histamine was not given during the control session and was always administered as the last stimulus in each experiment. The histamine-induced itch during the first experiment served as baseline for this sensation.

Local skin temperature was measured prior to each test session, using an infrared thermometer (TherMonitor, C-1600, Linear Laboratories).

2.3. Treatment with CFS

It is known that the dermo-epidermal junction is an area richly innervated by thin afferent fibres (Fundin et al., 1994; Kruger et al., 1985; Shelley and Arthur, 1957). For localised stimulation of thin myelinated and un-
myelinated fibres in the superficial skin, CFS was applied (Nilsson et al., 1997; Nilsson and Schoenborg, 1999; Schoenborg et al., 1994). CFS uses a flexible rubber plate equipped with 16 needle-like electrodes regularly fixed at 2-cm intervals (4 \times 4 matrix). The plate is gently pressed against the skin, thereby introducing the electrode tips adjacent to the receptors and free nerve endings in the epidermis and superficial part of dermis (see Arthur and Shelley, 1959; Fundin et al., 1994; Kruger et al., 1985; Shelley and Arthur, 1957). Since the electrodes traverse the electrically isolating layer of the epidermis and the current density is high near the sharp electrode tips, the voltage and current necessary to stimulate cutaneous nerve fibres are small, typically less than 10 V and 0.8 mA. As the current density decreases rapidly with distance, localised stimulation is achieved.

The 16 electrodes that serve as cathodes were stimulated consecutively (one at a time) with a constant current stimulator at equal time intervals. The rationale behind consecutive stimulation is to present the spinal cord with a continuous barrage of impulses in thin fiber A6 and C afferents, while yet decreasing fatigue. From receptive field studies in the dorsal horn it is known that maximal activation of dorsal horn neurones can be reached by stimulating small areas within their receptive field. This sequential stimulation was repeated 1, 4 or 10 times/s, i.e., the current stimulator delivered in total between 16 and 160 pulses/s (inter-stimulus intervals of 62.5, 15.6 or 6.25 ms, respectively). A self-adhesive surface electrode (Uni-patch, Re-Ply) served as anode and was placed about 10 cm proximal to the cathode.

A pinching, slightly burning sensation was always induced upon initiation of CFS, but on constant stimulation intensity, this sensation faded within minutes. There were no after sensations upon turning the stimulator off.

3. Treatment protocol

Total treatment periods with CFS in the first round of testing (Groups 1 and 2) ranged between 8 and 40 min (8, 10, 25 and 40 min). The stimulation frequency was kept either at 1, 4 or 10 Hz per CFS needle electrode. In the second round (Group 3; 10 subjects taken from the initial two groups), treatment periods of 1-6 min were applied (CFS frequency at 4 Hz per needle electrode). As a control for effects of ‘electrode plate without current’ versus CFS, sham stimulation was given to all participants in Group 3, using a CFS electrode applied 25 min without current.

Participants in the first round were instructed to increase the intensity of the treatment stimulation to their perception threshold (T, usually corresponding to 0.3–0.4 mA) and thereafter to increase up to 2T over the next 10 min. They subsequently maintained this intensity for the rest of the treatment period. On one occasion they were instead instructed to try to reach 2T within 10 min but to turn off the current as soon as the pinching/burning sensation disappeared. This turned out to occur, on average, 8 min after the onset of CFS.

Same instructions were given to participants who came back for a second round of experiments but the current was turned off by the experimenter, either 1, 3 or 6 min (4 Hz/electrode) after the CFS intensity had reached their perception threshold.

3.1. Induction and quantification of fabric-evoked prickle sensations

Prior to commencing the study, several types of woollen cloths were evaluated for different characteristics of prickliness. Four types of cloth were picked out with increasing coarseness of texture, ranging from the softest woollen fleece to a harsh jute cloth. Hence, non-prickly, slightly, moderately and severely prickly fabrics were used to evoke the sensation of prickle (Cervero et al., 1994; Garsworthy et al., 1988). A piece of each of the four fabrics (45 × 95 mm) was sewn onto slightly larger pieces of cloth with a uniform back. The fabrics were applied, in a random order, face down on the right volar forearm of the subjects. Visual cues as to the nature of the fabric were thus avoided. Participants were consecutively instructed to press repeatedly the finger tips of their left hand on the outside of the cloth and rate the sensation of prickle on a horizontal VAS (length 100 mm) marked with “no prickle” and “maximal prickle” at respective ends (see Aitken, 1969; Price, 1999; Price et al., 1994). They were given careful instructions to rate the degree of prickliness only and to disregard all other qualitative sensory aspects induced by the stimuli.

3.2. Induction of heat pain and quantification of thresholds and intensity

To elicit a sensation of heat pain, the right volar forearm was stimulated with a CO2-laser (Directed Energy, Model 220 Laser System, unfocused beam diameter 4.5 mm, 10 W, up to 20 ms). Two skin sites were stimulated in each test session. Care was taken never to stimulate the same site twice. There was a pause of at least 1 min in between stimulations. To define the thermal pain threshold, the stimulation duration was gradually increased, starting with clearly innocuous intensities, until the subject verbally indicated the sensation of minimal pain (defined as the first feeling of pinprick). During the entire experiment, moderate heat pain was evoked by laser pulse 10 ms longer than that of the initial threshold. This intensity did not produce noticeable trauma to the skin other than a minimal rash. Pain intensity was indicated on a horizontal VAS.
(100 mm) marked with “no pain” and “maximum pain” at respective ends. CO₂-laser stimulation regularly elicited a double pain sensation, termed 1st and 2nd heat pain, the late component appearing with a delay of roughly 1 s from onset of the stimulus. These two components are known to be dependent on impulses in Aδ and C fibres, respectively (Bromm et al., 1984; Bromm and Treede, 1987). First and second pain was indicated on separate VAS, presented directly after one another.

3.3. Induction and quantification of mechanical pain

An arterial clamp (2 N/mm²) applied to the skin of the right volar forearm during 10 s was used for noxious pinch. Two skin sites were stimulated for each test session and care was taken never to stimulate the same site twice. There was a pause of 1 min in between stimulations. The pain intensity at the end of the stimulation was rated on a horizontal VAS (see previous section).

3.4. Induction and quantification of itch

In each experiment, itch was the final sensation to be tested. Itch was induced by transdermal iontophoresis of histamine (Handwerker et al., 1991; Handwerker et al., 1987; Magel and Handwerker, 1988; Magel et al., 1990). Briefly, an agar gel containing a histamine solution (1% histamine dihydrochloride in distilled water) was poured into a small cylinder containing a silver electrode and allowed to congeal. This agar electrode, serving as anode, was then applied to the skin of the right volar forearm at the time point 60 min post-treatment. Electrically conducting flexible plates (Uni-patch, Re-Ply) served as cathode. A current of 1 mA was then passed through the skin over 30 s. All subjects were trained to record perceived itch intensity 70 min post-treatment, using a horizontal VAS (length 100 mm) marked with “no itch” and “maximal itch” at respective ends (Hägermark and Wahlgren, 1992).

3.5. Data analysis

To get the mean magnitude of the effect of CFS on each sensory modality during the observation time, the area under the VAS time-curve (AUC) divided by the observation time was calculated. The mean magnitude of the effect was then expressed in percentage of baseline. For all sensory modalities except itch, sensory intensities as measured just prior to the treatment served as baseline. For itch, it was the itch intensity measured during the first experiment (without treatment) that served as baseline for all subsequent itch measurements.

The non-parametric Wilcoxon's signed ranks test with Bonferroni's correction for multiple comparisons was used both when matched comparisons over time were made within the same group, and to detect any differences in inhibitory effects between respective AUC. Significant differences were assumed at the level of p < 0.05. Mean or normalised AUC values and SEM are indicated.

4. Results

Generally, best effects of CFS were always attained at the same observation time (5 min post-treatment) after which the effects gradually decreased (Fig. 3). In some cases, notably on heat pain and itch, there was still a clear effect at the end of the observation time (55 and 70 min post-treatment, respectively).

There was an increase in skin temperature (ranging from 105.1% of control AUC ± 1.2 to 110.0% of baseline AUC ± 1.0, P < 0.01 for all parameters used) after CFS regardless of parameters used, including sham stimulation. There was no difference in effect on skin temperature between the different treatment parameters.

4.1. Sham stimulation

In Group 3 (N = 10), the effect of sham stimulation (25 min, no current) was tested on itch, mechanical and thermal pain. As can be seen in Fig. 1, there was no noticeable effect on any of the skin senses tested. Thus, the prickling sensation caused by the CFS electrode plate itself is not sufficient to induce any analgesia or relief of itch.

4.2. Effects of CFS on histamine evoked itch

Histamine was applied only once per experimental session, 60 min post-treatment, and the ensuing itch was recorded 10 min later. As can be seen in Fig. 2, 3 min of CFS (4 Hz) treatment was sufficient to produce a significant inhibitory effect of histamine-evoked itch. The maximum inhibitory effect on itch was attained after 8 min of CFS at 4 Hz (13.8% of baseline ± 5.3, p < 0.01). No significant difference between stimulation frequencies of 1, 4 and 10 Hz was found.

4.3. Effects of CFS on Aδ fibre mediated heat pain

As can be seen in Fig. 3, a short lasting inhibitory effect on Aδ fibre mediated heat pain (1st pain) was evident already after 1 min of CFS (4 Hz). Maximum inhibitory effect was attained after 6 min of treatment (4 Hz) (70.6% of baseline AUC ± 13.6, p < 0.001). Longer stimulation did not increase the inhibitory effect. The inhibitory effect after 6 min of CFS was statistically different from those induced by sham stimulation (p < 0.001) and 3 min CFS (p < 0.01) (see also Fig. 4). There was no statistically significant difference in effects between different stimulation frequencies (1, 4 or 10 Hz for 25 min) on 1st heat pain.
Fig. 1. Effects of sham stimulation (CFS for 25 min without current) on different nociceptive qualities. All sensory tests were made on the right volar forearm. Mean sensory intensities for each modality before (unfilled bars) and after sham-CFS (striped or filled bars) at indicated times are shown. Statistical comparisons were made between baseline values and mean values after sham stimulation (i.e., the control condition). In the case of itch, 70 min after conditioning stimulation corresponds to 60 min after CFS and 10 min after application of histamine. ns = non-significant, N = 10. Error bars indicate + SEM.

Fig. 2. A comparison of the effects of different CFS frequency and duration (bottom diagrams) on itch. Mean itch intensities before (unfilled bars) and after CFS (filled bars) at indicated frequencies and durations are shown here. Effects of different frequency applied on each CFS electrode on top, and of different duration of CFS on bottom diagrams. Statistical comparisons were made between baseline values and mean values after CFS. ns = non-significant, *p < 0.05, **p < 0.01, N = 10 in each group. Error bars indicate + SEM.

4.4. Effects of CFS on C-fibre-mediated heat pain

A significant inhibitory effect on heat pain was attained after 6 min of CFS (4 Hz) (Fig. 3). Maximum effect was attained after 10 min of CFS (4 Hz) (52.9% of baseline AUC ± 12.5, p < 0.001) and increasing the time of the treatment further did not induce stronger inhibitory effects (Fig. 4). There was no statistically significant
Fig. 3. Time course of effects on 1st and 2nd heat pain and pinch evoked pain after different durations of CFS. Mean sensory intensities for each modality before (unfilled bars) and after CFS (filled bars) at indicated post-treatment times are shown here. 1st and 2nd heat pain and pinch evoked pain are shown from top to bottom diagrams. Statistical comparisons were made between baseline values and mean values after treatment. ns = non-significant; *p < 0.05, **p < 0.01, ***p < 0.001, N = 10 subjects in each group. Error bars indicate±SEM.

difference in effects between different stimulation frequencies (1, 4 or 10 Hz for 25 min) on 2nd heat pain.

4.5. Effect of CFS on heat pain thresholds

A significant increase in heat threshold was attained already after 1 min of CFS (4 Hz). Maximum increase in pain threshold was evoked after 8 min of CFS (4 Hz) (124.3% of baseline AUC±9.0, p < 0.01). Treatment times exceeding 8 min did not cause a further increase of the heat pain threshold. Again, there was no significant difference between the effects of 1, 4 and 10 Hz on the heat pain threshold.

4.6. Effect of CFS on mechanical nociception

A significant decrease in mechanical pain intensity was attained after 8 min of CFS at 4 Hz (70.5%±10.3, p < 0.001, see Fig. 4). Notably, shorter lasting treatment was ineffective and increasing the time of the treatment further did not induce significantly stronger inhibitory effects. There was no significant difference between the effects of 1, 4 and 10 Hz on pinch-evoked pain.

Prickle was not affected by CFS, irrespective of the treatment parameters of CFS and fabric used, confirming previous findings (Nilsson and Schouenborg, 1999).

5. Discussion

The present study shows that the peak, or near peak, effects of CFS on most nociceptive qualities is reached already after a treatment duration of 6–10 min. No clear frequency dependency within the range 1–10 Hz was found. The induction time and effective stimulation frequencies may suggest that the underlying mechanisms are similar to those of long term depression (LTD) previously described in the spinal cord in animal experiments (Sandkühler et al., 1997). The present study confirms previous findings that different nociceptive skin
senses can be differentially affected by stimulation of thin afferent fibres (Nilsson and Schouenborg, 1999) and, in addition, suggests that different treatment times with CFS are required for inhibition of the respective skin senses. Previous studies have shown that the CFS effect can be very long lasting (up to 7 h, Nilsson et al., 2003). To minimize possible cumulative effects, a pause of at least 3 days was employed between consecutive CFS treatments in the present study. Furthermore, a random order of conditioning and a semi-random order of test stimulations was used. Therefore, it is conceivable but unlikely that the present conclusion regarding different treatment times for different skin senses is confounded by the repetitive CFS treatment.

5.1. On possible placebo effect induced by CFS

It is known that placebo effects can be induced by virtually any kind of treatment (Beecher, 1955; Turner et al., 1994). In previous studies where CFS was used, TENS was included, partially to check for possible placebo effects. Both CFS and TENS induced prominent sensations in those studies, the apparatuses looked similar and the treatment procedures were the same. In those studies, there were no evidence of a substantial placebo effect of CFS (Nilsson et al., 1997; Nilsson and Schouenborg, 1999). In the present study, there was no further inhibitory effect on any tested sensation with increasing the duration of the treatment above 8 and up to 40 min or increasing the stimulation frequency to 10 Hz as compared to 4 Hz. This finding adds support to the notion that there is a significant effect of CFS over and above placebo, since a placebo reaction would be expected to be larger for more intense and prolonged stimulation (Turner et al., 1994). The fact that, in the present study, all collection of data were carried out by an independent member of staff, unaware of the study's theoretical background and ex-
pected results may have contributed to keeping any placebo effects at low levels.

5.2. Effects of varying CFS parameters on skin temperature

In a previous study, homotopic and treatment with CFS (4 Hz/electrode and 25 min duration) induced an increase in skin temperature (Nilsson and Schouenborg, 1999). In the present study, a minor but in most cases statistically significant increase in local skin temperature was found following each type of treatment with CFS. It is known that sensory stimulation, such as TENS and acupuncture, may affect the general skin temperature, presumably through actions of the sympathetic nervous system (Dyrehag et al., 1997). The present finding that also sham stimulation induced an increased skin temperature indicates a non-specific, perhaps placebo-like, effect of the experimental set-up.

5.3. On the lack of "wind-up" following repetitive stimulation of thin cutaneous fibres

Repetitive stimulation of cutaneous nerves at intensities suprathreshold for C fibres and frequencies around 1–2 Hz can result in a prominent enhancement ("wind-up", see Mendell, 1966; Mendell and Wall, 1965; Sandkühler et al., 1997; Schouenborg and Sjölund, 1983; Wagman and Price, 1969; Woolf and King, 1987) of the evoked discharges in nociceptive dorsal horn neurones. Typically, wind-up is observed in neurones receiving a convergent input from nociceptors and tactile receptors (often referred to as wide dynamic range neurones). This phenomenon is known to occur also after natural stimulation of C fibres (Schouenborg, 1984). Furthermore, long-lasting central sensitisation in nociceptive pathways can occur after repetitive stimulations of nociceptive C fibres and after injury (Svensen et al., 2000). The absence of hyperalgesia after stimulation of nociceptive C fibres (Nilsson et al., 1997) at frequencies known to produce wind-up and central sensitisation (Woolf, 1996) therefore needs an explanation. A key to this problem may be that, in the cases where wind-up has been observed, a relatively large group of nerve fibres from the same skin area have been stimulated simultaneously, thus allowing for spatial summation centrally. By contrast, during CFS, patches of nociceptive nerve fibres (around each electrode) are stimulated consecutively. Thus, it may be that wind-up and central sensitisation phenomena are critically dependent on spatial summation.

5.4. On the mechanisms underlying the inhibitory effects caused by CFS

Evidence for a central antipruritic and antinoceptive segmental action of CFS has been presented elsewhere (Nilsson et al., 1997, 2003). Moreover, it is known that stimulation of thin primary afferents, at frequencies similar to those used in the present study, can induce depression of second order neurones in the dorsal horn in vivo (Chung et al., 1983, 1984b; Sandkühler et al., 1997; Sjölund, 1988; Woolf, 1983). In rat spinal cord slices, long term depression (LTD, cf. Linden and Connor, 1995) of sensory transmission in substantia gelatinosa neurones after low frequency stimulation of dorsal roots (1 Hz, 15 min) at intensities activating Aδ and C fibres has been demonstrated (Sandkühler et al., 1997). The duration of the ensuing depression of transmission was reported to last up to 2.5 h. These parameters are close to those used in this study. Hence, it is conceivable that CFS induces an antipruritic and antinoceptive state similar to that of LTD. However, in view of the differential effect of CFS on induction times and magnitude of inhibition of different nociceptive qualities, the precise inhibitory mechanism acting on the different nociceptive qualities may be different.

Acknowledgments

This project was supported by the Swedish Medical Research Council projects no. 10569 and No. 1013, the Medical Faculty of Lund, Alice and Knut Wallenberg’s foundation, ASTRA Inc., Elsa and Thoresten Segerfalk’s foundation, Crafoord’s foundation, Greta and Johan Kock’s foundations. The skilful assistance of Susanne Rosander-Jönsson is gratefully appreciated.

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Pain as presenting symptom in Lyme neuroborreliosis

Leif Dotevall, a,*, Tore Eliasson, b Lars Hagberg, a Clas Mannheimer b

a Department of Infectious Diseases, Sahlgrenska University Hospital Ostra, Göteborg SE-416 85, Sweden
b Department of Internal Medicine, Sahlgrenska University Hospital Ostra, Göteborg SE-416 85, Sweden

Received 22 March 2002; accepted 23 October 2002

Abstract

Neurogenic pain with radiculitis is often the starting symptom in adult patients with tick-borne Lyme neuroborreliosis and in some cases the only clinical manifestation. Cranial paresis and other neurologic signs usually occur after the onset of pain. The present paper describes four patients who had severe pain as the main presenting symptom of Lyme neuroborreliosis. Opioids had good short-term effect in two of the cases. Oral doxycycline treatment was used successfully to eliminate the infection.

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Keywords: Lyme neuroborreliosis; Neurogenic pain; Radiculitis; Opioid treatment

1. Introduction

Neurologic symptoms are the most frequent extra-cutaneous manifestations in European patients with Lyme borreliosis, a tick-transmitted infection caused by various genospecies of Borrelia burgdorferi sensu lato (Burgdorfer et al., 1982). The typical early syndrome in neuroborreliosis has been characterised as a triad of radicular pain, cranial or peripheral paresis, and lymphocytic meningitis (“Bannwarth’s syndrome”) (Bannwarth, 1941). Especially the painful sensory radiculitis is a major symptom at onset in adults patient with Lyme neuroborreliosis (Hansen and Lebec, 1992). The pain has been reported to be the only clinical manifestation in about 20% of the patients with neuroborreliosis (Kristofferitsch et al., 1983). The radicular pain in neuroborreliosis is often alarming and causes anxiety and restlessness. It may radiate from the spine into an extremity, the neck or the trunk and is described as “sharp and jabbing or deep and boring” (Logican, 1997). It is often accompanied by patchy areas of unpleasant hyperaesthesia or dysesthesia (Hansen and Lebec, 1992). The symptoms may sometimes be mistaken as zoster herpetic, disc herniation with nerve root compression, or visceral pain.

An early diagnosis of neuroborreliosis is of utmost importance since the risk of postinfectious neurologic sequelae will increase with longer pretreatment duration (Dotevall et al., 1999). Therefore the clinician has to be aware of Lyme neuroborreliosis as a differential diagnosis in patients with radiculitis pain, both in endemic and non-endemic areas for Lyme borreliosis. This paper describes four patients who presented with severe pain as the main symptom of early Lyme neuroborreliosis. Opioids were found to have short-term effect on pain in two of the patients.

2. Case reports

2.1. Case 1: Early lymphocytic meningoradiculitis

A 63-year-old woman was admitted with 3 weeks of severe and increasing toothache-like asymmetric back pain radiating towards the abdomen. This tearing and migrating pain was completely different from what she had experienced before. The onset of the pain was subacute and it was worse during the night and disturbed her sleep. After 2 weeks, she also experienced dysesthesia and hyperaesthesia in the pain-affected
area. Her walk started to become slightly unsteady. There was no history of cutaneous erythema.

Physical examination revealed only a diffuse tenderness in the abdomen and slight decreased perception of touch along arcus costae on both sides, not restricted to specific dermatomes. There was no other areas of sensory deficits. Her appearance was healthy and there were no signs of paresis or other neurological deficits. The peripheral reflexes were normal and Babinski's sign was absent. Her gait was normal without any signs of ataxia. No neck stiffness was found. The temperature was normal. X-ray over the lumbar columna, ultrasonography over the abdomen, and skeletal scintigram were all normal. Sedimentation rate and white cell count were also normal. Since she recently had visited a highly endemic area for tick infections, a lumbar puncture was performed. A meningeal pleocytosis was found with $165 \times 10^6$/L of monocytes. Cytology of the cerebrospinal fluid (CSF) revealed reactive lymphocytes and plasma cells. The CSF protein concentration was elevated (2.2 g/L) and IgG oligoclonal bands were found. IgG antibody test against borrelia (DAKO, commercial ELISA method against purified flagellum antigen of Borrelia burgdorferi sp.) was strongly positive both in serum and CSF. Later, the patient recalled a tick-bite in the neck area a few weeks before the onset of symptoms.

Before the diagnosis was established, the patient was treated with transcaneous electrical nerve stimulation, but only with minimal effect on the pain. Diazepam had no effect on the pain, but 5 mg of morphine given intravenously resulted in almost complete pain relief for 5 h. After treatment with oral doxycycline 400 mg daily, the pain disappeared within 3 days. Antibiotic treatment was given for 10 days resulting in complete recovery at follow-up. CSF analysis 6–8 weeks later showed a decrease in the monocyte cell count to $22 \times 10^6$/L and almost normalised protein concentration (0.68 g/L).

2.2. Case 2: Lyme meningoradiculitis mistaken as visceral pain

A 66-year-old previously healthy woman was admitted to a district hospital with a history of 3 days increasing severe radicular pain radiating forward to the left inguinal region. The pain was described as deep and excruciating and was worse than the patient ever had experienced before. She also complained of severe fatigue, nausea, and insomnia. There was no history of tick-bite or skin rash.

Physical examination and routine laboratory parameters such as sedimentation rate and white cell count were remarkably normal despite patient's subjective symptoms with severe sensation of pain. Neurological examination performed by the general practitioner found no reflex losses and no signs of muscle weakness. An opioid (pethidin hydrochloride) was injected intramuscularly. Temporarily pain relief was obtained for about 1 h. X-ray over the lumbar region only revealed a low disc between L5 and S1. The patient was referred to the Gynaecology department for consultation. A tenderness was found over the suprapubic area and due to the severe general symptoms of the patients, an explorative laparotomy was performed. However, only an enlarged myomatous uterus was found. Hysterectomy and salpingo-oophorectomy was done, but the pathological examinations from uterus only showed a benign myoma. The patient was sent home, but the pain continued postoperatively and was described as "piercing" and "jabbing." In addition, the patient started to experience touch-induced paresthesias over crista iliaca (dermatomes ThXII-L1). She was readmitted and at this point neurological examination confirmed a slight sensory deficit and hyperesthesia located in the left inguinal region, but no other signs of peripheral neuropathy. The tendon reflexes were normal and there was no sign of paresis of the extremities. There were no signs of enlarged regional lymph nodes or hip joint abnormality.

Hydromorphone and paracetamol in combination with codeine reduced the pain (but not the paresthesia) for a very short period, while transcutaneous nerve stimulation had no effect. Investigation with computerised tomography and intravenous urography revealed no pathology. The character of the pain was interpreted mainly neurogenic. Lumbar puncture was performed 4 weeks after onset of symptoms. CSF pleocytosis was found with $148 \times 10^6$/L mononuclear cells and increased CSF protein (0.94 g/L). Lyme neuroborreliosis was considered and IgG antibody test against Borrelia was positive in both serum and CSF. Oral doxycycline treatment 400 mg daily was given for 21 days. The pain disappeared within 10 days. Lumbar puncture 6 weeks later showed normalised cell count and protein concentration in the CSF. At follow-up 8 weeks after onset of symptoms she still experienced some paraesthesia in the inguinal region.

2.3. Case 3: Lyme meningomyeloradiculitis

A 69-year-old woman with a history of mastectomy due to breast cancer 5 years earlier, was admitted with severe migrating pain in both legs during the last 8 weeks. The pain radiated down on the anterior side of lower legs without distinct dermatome localisation. In parallel, increasing weakness in both legs were experienced during a period of 2 weeks. She did not see her doctor until she was almost unable to walk.

Physical examination revealed signs of a myelopathy and paraparesis of supranuclear origin with sphincter dysfunction. The knee and ankles reflexes were increased and a bilateral Babinski's sign was found. An asymmetrical patch-like sensory deficit was found at the L3-L4 dermatomes for pin and touch, but with no distinct
border. There was a marked muscle weakness of both legs but she was able to stand without support. There was no muscular atrophy or visible fasciculations.

An expanding spinal process was suspected and she was immediately sent for an acute computerised tomography over the spine, which turned out to be normal. However, a lumbar puncture showed pleocytosis with $346 \times 10^6/L$ mononuclear cells and increased CSF protein (3.0 g/L). CSF cytology showed reactive lymphocytes and no tumour cells. Protein electrophoresis of CSF revealed increased IgG index and IgG oligoclonal bands. Bacterial culture was normal. IgG antibody test against Borrelia was positive both in serum and CSF, and Lyme myelomeningoradiculitis was suspected.

Oral doxycycline 400 mg daily was given for 21 days. The pain started to decrease after 2 days and was completely disappeared after 11 days. The paresis of the lower extremities improved and after 2 weeks she was able to walk without support. CSF analyses 6–8 weeks later showed that the mononuclear cell count had decreased to $26 \times 10^6/L$ and protein concentration (0.74 g/L). At follow-up, the urine bladder showed no residual urine, but there were still some signs of bilateral limb paresis, although her muscular function was improved. No electromyography was performed.

2.4. Case 4: Bannwarth's syndrome with meningo-radiculitis and cranial nerve palsy

A 47-year-old woman with a history of chronic back pain since her youth. She was admitted to the hospital because of a 2 weeks history of increasing burning and migrating thoracic pain with exacerbation at night. The pain was different from her earlier experience, and she reported that the tormenting sensation was relieved when she was walking or moving. Physical examination including neurological evaluation at first was completely normal. The peripheral reflexes were normal and no sensory deficits were found. Sedimentation rate and white cell count were normal. As a first-line treatment non-steroid anti-inflammatory drugs (NSAID) were given, but without any effect. When the patient mentioned a “rash” on the right side of the abdomen with a duration of 1 week before the onset of pain, herpes zoster neuralgia was suspected and antiviral therapy (aciclovir) was started. The pain progressed and radiated to both arms and became so severe that an epidural catheter was considered for pain relief. At this point the pain was clearly neuralgic. A left side facial palsy developed within 2 days. Spinal tap revealed CSF pleocytosis with $608 \times 10^6/L$ mononuclear cells and increased CSF protein (3.3 g/L). IgG antibody test against Borrelia was negative in serum but positive in CSF. A computerised tomography of the brain was normal.

Lyme neuroborreliosis with meningo-radiculoneuritis was suspected and oral doxycycline 400 mg daily was started and given for 17 days. On the second day after start of treatment the peripheral facial palsy progressed and became bilateral. A right-sided glossopharyngeal paresis was also found on the second day of treatment. Following antibiotic treatment the thoracic pain decreased during 3 days thereafter, and the right-sided facial palsy and glossopharyngeal paresis disappeared slowly during the treatment period. The left-sided facial palsy and the pain in the left arm were still present several months after treatment. CSF analyses 6–8 weeks after treatment showed that the mononuclear cell count had decreased to $45 \times 10^6/L$ and protein concentration was almost normal (0.66 g/L).

3. Discussion

In patients with early symptoms of Lyme neuroborreliosis severe radicular neuropathic pain often appear before the onset of cranial paresis. In a Danish study 86% of the patients experienced radiculitic pain, beginning 5–90 days (median 19 days) after the erythema migrans (Hansen and Lebech, 1992). The symptoms may be dramatic and often puzzling to the consultant doctor, as noted in the first historical report on neuroborreliosis in 1922 (Garin and Bujadoux, 1922).

An often described clinical finding is that the pain in Lyme neuroborreliosis does not completely follow the dermatome or the territory of the peripheral nerves. It may migrate during the course of the disease and often has nocturnal exacerbation, as Bannwarth noted in his original paper (Bannwarth, 1941). The character of the pain in the adult patients with Lyme neuroborreliosis is most often neuralgic, although a component of nociceptive pain due to inflamed meninges or joints probably contributes to the severe discomfort. Neck stiffness is seldom found in adult patients with Lyme neuroborreliosis despite of the meningeal inflammation and lymphocytic pleocytosis in the cerebrospinal fluid. A discrepancy between the alarming history and the rather healthy appearance of the patient is often noted. Few clinical findings may be found before the onset of cranial paresis. The skin area involved by pain may be dysthetic or hyperpathic, and slight touch may cause discomfort. Sensory loss in the affected area is seldom found. The intensity of the pain has been shown to increase with age (Hansen and Lebech, 1992). The radicular pain characteristic in adults is often missing in children with Lyme neuroborreliosis, and cranial paresis and diffuse neck pain are the most frequent presenting symptoms in the paediatric patients (Christen et al., 1993).

These case reports indicate that Lyme neuroborreliosis is an important differential diagnosis in patients with radicular pain during the summer and fall in Borrelia-endemic areas. Lumbar punctures should be
considered early in the examination of patients with neurogenic, often asymmetric pain in combination with other neurologic symptoms such as dysesthesia, facial palsy, and peripheral or central paresis. A useful clinical definition of Lyme neuroborreliosis is shown in Table 1 (Dotevall, 1999). Only a positive antibody test in serum has low predictive value for Lyme neuroborreliosis, and CSF examinations are strongly recommended for the diagnosis. In almost all patients with Lyme neuroborreliosis the antibody test against flagellum antigen is positive at admission either in serum or CSF. However, in few patients with very short duration of infection, antibody levels against Borrelia may be negative the first weeks due to slow induction of antibody production. In some cases antibody levels are first detected in CSF as in case 4.

Adequate antibiotic treatment is needed for efficacious therapy of the central nervous system infection and to achieve sustained pain relief. The treatment relieves the radicular pain within 1–7 days, but dysesthesia may remain for months although the symptoms will be less pronounced (Hansen and Lebech, 1992). Intravenous penicillin G or ceftriaxone is often recommended for the treatment of Lyme neuroborreliosis. Oral doxycycline is a more convenient alternative for patients above the age of 8. Doxycycline has been compared with intravenous penicillin G and found to be equally effective (Karlsson et al., 1994) and oral treatment with doxycycline will result in CSF antibiotic concentrations above MIC for Borrelia burgdorferi sp. (Dotevall and Hagberg, 1989). Clinical sequelae persisting after adequate antibiotic treatment is more common in patients with delayed diagnosis.

The pain in Lyme neuroborreliosis will most often not respond to analgesics as paracetamol or acetyl salicylic acid. In our cases, opioids had temporarily good effect on the pain in cases 1 and 2, even though neuropathic pain commonly is regarded as opioid resistant (Armér and Meyerson, 1988). Despite this commonly accepted principle, there have been several reports on good opioid effect on neurogenic pain as described in two of the above four cases (Portenoy et al., 1990; Rowbotham et al., 1991). These two cases indicate that the relieving effect of opioids does not exclude that the pain is caused by Lyme neuroborreliosis, although a comprehensive analysis of the medical history and the neurologic signs in combination with early cerebrospinal examinations are the most important means to a correct diagnosis of this tick-borne cause of pain.

References


Antinociceptive effects of RB101(S), a complete inhibitor of enkephalin-catabolizing enzymes, are enhanced by (+)-HA966, a functional NMDA receptor antagonist: a c-Fos study in the rat spinal cord

Jaroslava Buritova, a,*, Stéphanie Le Guen, a Marie-Claude Fournié-Zaluski, b Bernard P. Roques, b Jean-Marie Besson a

a Physiopharmacologie du Système Nerveux, INSERM U161, 2 rue d’Alésia, 75014 Paris, France
b Laboratoire de Pharmacochimie Moléculaire et Structurale, INSERM U266, CNRS URA D1500, Paris, France

Received 22 April 2002; accepted 23 October 2002

Abstract

The effects of the S enantiomer of RB101, a complete inhibitor of enkephalin-catabolizing enzymes, alone or in combination with a functional NMDA receptor antagonist, (+)-HA966 were studied on the spinal c-Fos protein expression in the carrageenan model of inflammatory noiception. One hour 30 min after intraplantar carrageenan in awake rats, c-Fos immunoreactive (c-Fos-IR) nuclei were preferentially located in the laminae I–II and V–VI of the spinal dorsal horn, i.e., spinal areas containing numerous neurons responding exclusively, or not, to peripheral noiceptive stimuli. RB101(S) (5, 10, 20 and 40 mg/kg i.v.) dose-dependently reduced the total number of carrageenan-evoked c-Fos-IR nuclei (r = 0.53, P < 0.01), with 49 ± 3% reduction (P < 0.001) for the highest dose. Two highest doses of RB101(S) (20 and 40 mg/kg) significantly reduced the number of carrageenan-evoked c-Fos-IR nuclei in both superficial I–II (32 ± 7% and 36 ± 5% reduction, respectively, P < 0.05 for both) and deep V–VI (42 ± 6% and 61 ± 2% reduction, respectively, P < 0.001 for both) laminae. The effects of RB101(S) were naltroxone-reversible. Combination of low doses of RB101(S) (2.5 or 10 mg/kg i.v.) and an inactive dose of (+)-HA966 (2.5 mg/kg s.c.) produced supra-additive effects (39 ± 4% and 51 ± 5% reduction of the total number of c-Fos-IR nuclei, respectively, P < 0.001 for both). These effects were partially reversed by naltroxone. These results provide evidence for the potent effects of combination of RB101(S) and (+)-HA966. Considering the absence of major opioid side effects of RB101(S) and the marked increase of its antinociceptive effects by NMDA receptor antagonist, this type of drug combination could have beneficial therapeutical application.

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Keywords: c-Fos; Spinal cord; RB101; Carrageenan inflammation; Endogenous enkephalins; NMDA receptor antagonist

1. Introduction

The clinical use of opioids, such as morphine, is wide in the management of pain, but unfortunately, limited by various side-effects (for example: development of tolerance and dependence, respiratory depression, constipation; see references in Jaffe, 1990). To reduce such side-effects liability there is still considerable interest in the strategy based on the protection of the endogenous opioid peptides (enkephalins), from their degradation and inactivation by the peptidases (for review see Noble et al., 1999; Roques et al., 1993). The mixed inhibitors of zinc-metallopeptidases, elicit various pharmacological properties deriving from this protection, such as antinociceptive effects (for review see Roques et al., 1993). Among these inhibitors, RB101, a complete inhibitor of enkephalin-catabolizing enzymes, has been shown to cross the blood brain barrier (Fournié-Zaluski et al., 1990).
producing antinociceptive effects after systemic administration in animal models of pain (Fournie-Zaluski et al., 1992; Noble et al., 1992; Maldonado et al., 1994; Noble and Roques, 1995). There is considerable evidence that N-methyl-D-aspartate (NMDA) receptors contribute to the induction and maintenance of central hyperalgesia in animal models and clinical trials of pain (for review see Dickinson et al., 1997). In inflammatory pain models, NMDA receptor antagonists have been demonstrated to reduce the hypersensitivity states, in particular to reduce the second phase of the formalin response (Haley et al., 1990; see Millan and Seguin, 1993, 1994 and references therein) and the hyperalgesia associated with Freund’s adjuvant-evoked polyarthritis (Ren et al., 1992a; Ren and Dubner, 1993) or carrageenan-evoked inflammation (Ren et al., 1992b; Yamamoto et al., 1993). However, the clinical use of NMDA receptor antagonists is limited by their side-effects (Kemp and Leeson, 1993). A possible strategy to reduce such side-effect liability consists in the study of low-dose combinations of NMDA receptor antagonists with agents acting at different receptor systems (Buritova et al., 1996a), especially opioid system (Chapman and Dickinson, 1992; Chapman et al., 1995; Honoré et al., 1996; Dickinson et al., 1997; Kauppila et al., 1998; Christensen et al., 1998, 1999; Besson, 1999).

In the present study, we have studied the effect of combinations of low doses of the isomer S of RB101, a complete inhibitor of enkephalin-catabolizing enzymes, and (+)-HA966 in the carrageenan model of inflammatory nociception in the awake rat. (+)-HA966 is a low-efficacy partial agonist at the glycine site of NMDA receptor complex, which acts as a functional NMDA receptor antagonist (Singh et al., 1990; see refs. in Kemp and Leeson, 1993). In our previous studies, we have demonstrated that both (+)-HA966 (Chapman et al., 1995) and RB101 (Honoré et al., 1997; Le Guen et al., 1999) dose-relatedly reduce carrageenan-evoked spinal c-fos protein expression to date there is considerable evidence that at the spinal cord level, especially in the dorsal horn, the c-Fos protein expression provides an indirect marker of neuronal population involved in spinal nociceptive transmission and reflects also the long-term intracellular events associated with sustained spinal nociceptive processes (Hunt et al., 1987; for review see Chapman and Besson, 1997; Harris, 1998). The “c-Fos technique,” based on the immunohistochemical investigation of c-Fos protein expression in the central nervous system, has been shown to be suitable for study of the effects of various endogenous or exogenous substances involved in nociceptive processes, particularly at the spinal cord level (see references in Chapman and Besson, 1997). Moreover, this technique was sensitive enough to detect the additive or supra-additive effects of combinations of various antinociceptive and/or antiinflammatory substances (see references in Chapman and Besson, 1997).

In the first part of this study we have evaluated the effect of systemic pre-administration of various doses of RB101(S) on carrageenan-evoked spinal c-Fos protein expression in the awake rat. In the second part of this study we have investigated the effect of combination of RB101(S) and (+)-HA966. Low doses of RB101(S) was selected from the first part of the study, and the inactive dose of (+)-HA966 was previously ascertained under the same experimental conditions of carrageenan model of inflammatory nociception (Chapman et al., 1995; Buritova et al., 1996a; Honoré et al., 1996).

2. Methods

2.1. Experimental animals

Two experiments were performed on 80 adult male albino Sprague-Dawley rats (75 carrageenan-stimulated and 5 nonstimulated rats; Charles River, France), weighing 225-250 g. Guidelines on ethical standards for investigations of experimental pain in conscious animals were followed (Zimmermann, 1983). Rats were kept in an animal room at a constant temperature of 22 °C, with a 12-h alternating light–dark cycle.

2.2. Drugs

RB101 (N-[(R,S)-2-benzyl-3[(S)(2-amino-4-methylthio)butyl]dithio]-1-oxopropyl]-L-phenylalanine benzyl ester) was synthetized as previously described (Fournie-Zaluski et al., 1992). RB101 was dissolved in vehicle: ethanol (10%), Cremophor EL (10%) and distilled water. (+)-HA966 ((+)-(3R)-3-amino-1-hydroxy-pyrrolidin-2-one, Tocris Cookson, United Kingdom) was dissolved in bi-distilled water. Naloxone hydrochloride (Sigma–Aldrich Chimie, Germany) was dissolved in saline (0.9% NaCl).

2.3. Inflammatory nociceptive stimulation

Peripheral inflammation was induced by intraplantar (i.pl.) injection of carrageenan (1% carrageenan, SIGMA; 6 mg in 150 µl of saline (0.9% NaCl)) in the right hind paw of awake rats. We considered two parameters of peripheral edema: paw diameter, the measure of the edema in the site of inflammatory stimulation due to i.pl. injection of carrageenan, and ankle diameter, the measure of the extension of the edema. For each rat one measure of both paw and ankle diameters was performed immediately before perfusion (for more details see Methods in Buritova et al., 1996b).

Rats were perfused 1 h 30 min after i.pl. carrageenan. This delay was chosen as an optimal postinjection delay

1. c-Fos-IR, c-Fos immunoreactive/immunoreactivity.
according to our previous studies of effects of RB101 on carrageenan-evoked spinal c-Fos protein expression (Honoré et al., 1997; Le Guen et al., 1999) and considering the duration of action of RB101 (around one hour) in numerous analgesic tests, such as the hot-plate test and phenylbenzoquinone-induced writhing in mice and the tail-flick and electric stimulation tests in rats (Noble et al., 1992). In the present study, control rats receiving an intraplantar injection of saline were not included since we have previously shown negligible spinal c-Fos protein expression after intraplantar saline (n < 3 c-Fos-IR nuclei per section L4–L5) which was not significantly different from spinal c-Fos protein expression in nonstimulated rats (Honoré et al., 1995a).

2.4. Experimental design

In the first experimental series, the effects of RB101(S) on spinal c-Fos protein expression and peripheral edema, 1 h 30 min after i.pl. carrageenan, were studied. RB101(S) (5, 10, 20 or 40 mg/kg, n = 5 in each group) was injected intravenously (i.v.) into the rat tail vein 10 min prior to i.pl. injection of carrageenan. In addition, the effect of co-administered RB101(S) and naloxone was investigated. One group of rats (n = 5) received a combination of RB101(S) (40 mg/kg i.v., 10 min before i.pl. carrageenan) and naloxone (1 mg/kg i.v., 10 min before and 30 min after i.pl. carrageenan). A control group of carrageenan-stimulated rats (n = 5) received vehicle (10 min prior to i.pl. carrageenan). In addition, three nonstimulated rats (without carrageenan injection) were included in the experiment, receiving intravenous injection of 40 mg/kg of RB101(S) and rats were perfused 1 h 40 min after this injection.

In the second part of this study, the effects of a low doses of RB101(S) (2.5 and 10 mg/kg i.v., 10 min prior to i.pl. carrageenan, n = 6 for each group) and combinations of these doses of RB101(S) with inactive dose of (+)-HA966 (2.5 mg/kg; n = 6 for each group) on spinal c-Fos protein expression and peripheral edema, 1 h 30 min after i.pl. carrageenan, were studied. (+)-HA966 (2.5 mg/kg) was injected subcutaneously (s.c.) into the scruff of the rat neck 30 min prior to i.pl. carrageenan. Control rats (n = 9) received a combination of s.c. saline (30 min prior to i.pl. carrageenan) and i.v. vehicle (10 min prior to i.pl. carrageenan). In addition, the effect of naloxone on the effects of combination of RB101(S) and (+)-HA966 was investigated. Two groups of rats (n = 6 for each) received a combination of RB101(S) (2.5 or 10 mg/kg i.v., 10 min prior to i.pl. carrageenan) and (+)-HA966 (2.5 mg/kg s.c., 30 min prior to i.pl. carrageenan) plus naloxone (1 mg/kg i.v., 10 min before and 30 min after i.pl. carrageenan).

In the present study, the inactive dose of (+)-HA966 (2.5 mg/kg s.c.) was chosen considering our previous c-Fos protein study of effects of (+)-HA966 (0.5, 2.5 and 10 mg/kg s.c.) in the carrageenan model of inflammatory noceision (Chapman et al., 1995). Note that doses up to 33 mg/kg s.c. of (+)-HA966 produce antinociceptive effects in formalin test in the absence of motor deficit in mice (Millan and Seguin, 1993).

2.5. Immunohistochemistry

One hour 30 min after i.pl. carrageenan, rats were deeply anesthetized (Pentobarbital, 55 mg/kg i.p.; Sanofi) and perfused intracardially with the phosphate buffered saline 0.1 M (PBS) followed by 4% paraformaldehyde in 0.1 M phosphate buffer (PB). The spinal cord was then removed and postfixed for 4 h in the same fixative, and cryoprotected with 30% sucrose in PB for 16 h. Frozen serial frontal sections (40 μm thick) of the lumbar enlargement (from L2 to L6) were cut and collected in PB. As previously described (Honoré et al., 1995a), immunohistochemistry of the free floating sections was performed with polyclonal antiserum, generated in rabbits and directed against the c-Fos protein (Santa Cruz Biotechnology; SC52 solution, 0.1 mg/ml; diluted at 1:30,000), using the conventional avidin–biotin–peroxidase complex method. The tissue sections were incubated for 30 min at room temperature in a blocking solution of 3% normal goat serum in phosphate buffer 0.1 M + saline 0.9% (PBS) with 0.3% Trion X (NGST) and were then incubated for 16 h at room temperature in the primary antiserum directed against the c-Fos protein. The incubated sections were washed three times in PBS and incubated in biotinylated goat antirabbit antiserum (Vector Laboratories, BA-1000) for 1 h at room temperature, then washed twice in PBS and incubated for 1 h in avidin–biotin–peroxidase complex (Vector Laboratories, PK-6100). Finally, the sections were washed three times in PBS and developed in chromogen solution (Vector Laboratories, SK-4600; 5 drops in 10 ml of PB 10 mM) for 5 min. and were then washed three times in PB to stop the staining reaction. The sections were mounted on gelatine-subbed slides and air dried. Mounted sections were dehydrated through a graded alcohol series (70%, 95% and 100%), xylen treated and cover-slipped with Eukitt mounting medium. As immunohistochemistry of different experiments might vary, the spinal cord sections of rats from the same experiment were immunoreacted at the same time, to justify the use of statistical tests.

2.6. Counting of c-Fos-immunoreactive (c-Fos-IR) nuclei

We have previously shown that the most numerous carrageenan-evoked c-Fos-IR nuclei were localized in the lumbar spinal cord at the level of L4–L5 segments (Honoré et al., 1995a), so in this study, the number of c-Fos-IR nuclei was counted in 10 randomly selected sections from the L4–L5 segments in each animal. As previously described (Honoré et al., 1995a), c-Fos-IR nuclei in the rat lumbar spinal cord were plotted and
counted with a camera lucida attachment through four defined regions: superficial laminae of dorsal horn (laminae I–II), nucleus proprius (laminae III–IV), deep laminae of the dorsal horn (laminae V–VI), and the ventral horn (laminae VII–X). For each animal, two counts were made: (1) the total number of c-Fos-IR nuclei in the gray matter for 10 sections through L4–L5 segments, and (2) the number of c-Fos-IR nuclei per specific defined region of the spinal gray matter in these 10 sections. Results are given as mean number of c-Fos-IR nuclei per section per experimental group. The investigator responsible for plotting and counting the c-Fos-IR nuclei was blind to the experimental situation.

2.7. Statistical analyses

Statistical analyses were performed to compare the total number of carrageenan-evoked c-Fos-IR nuclei, using 1-way analysis of variance for the different experimental groups, and 1-way analysis of variance for the different groups and the laminar region. To compare the ankle or the paw diameters we used 1-way analysis of variance for the different groups. For multiple comparisons, Fisher’s protected least significant difference (PLSD) test was used. Linear regression has been used for dose-dependent effects of RB101(S) on a single parameter. Significance was accepted with \( P < 0.05 \).

3. Results

In carrageenan nonstimulated rats receiving intravenous RB101(S) (40 mg/kg) alone, negligible c-Fos protein expression was observed in the dorsal horn of the lumbar spinal cord (< 5 c-Fos-IR nuclei per section in segments L4–L5). In contrast, 1 h after injection of carrageenan, c-Fos-IR nuclei were numerous in the ipsilateral dorsal horn of the spinal cord (93 ± 5 and 91 ± 3 c-Fos-IR nuclei per section in segments L4–L5 for carrageenan controls in the first and second experimental series, respectively). Importantly, the number of carrageenan-evoked c-Fos-IR nuclei and their laminar distribution were similar in the control groups for two experimental series. Carrageenan-evoked c-Fos-IR nuclei were preferentially located in the superficial (I–II; 48% and 51% of the total number of c-Fos-IR nuclei per section in the first and second experimental series, respectively) and deep (V–VI; 35% and 33% in the first and second experimental series, respectively) laminae of the dorsal horn, while few c-Fos-IR nuclei were observed in the nucleus proprius (5% and 4% in the first and second experimental series, respectively) and the ventral horn (12% for the both first and second experimental series) of the spinal cord (Fig. 1A). c-Fos-IR nuclei were virtually absent in the contralateral lumbar spinal cord (< 5 c-Fos-IR nuclei per section).

3.1. Effects of RB101(S) on carrageenan-evoked spinal c-Fos protein expression

In the first experimental series, pretreatment with RB101(S) (5, 10, 20, and 40 mg/kg i.v.) dose-dependently reduced the total number of carrageenan-evoked c-Fos-IR nuclei (regression coefficient \( r = 0.63, P < 0.01 \)), with 49 ± 3% reduction (\( P < 0.001 \)) for the highest dose. h 30 min after i.pl. carrageenan, the effects of RB101(S) (5, 10, 20 and 40 mg/kg i.v.) were significant considering the total number of c-Fos-IR nuclei in segments L4–L5 (\( F(7, 28) = 16.52, P < 0.001 \)) and their laminar distribution (\( F(5, 96) = 243.48, P < 0.001 \)). Laminar analysis revealed that the higher doses of RB101(S) (20 and 40 mg/kg i.v.) significantly reduced the number of carrageenan-evoked c-Fos-IR nuclei in both superficial I–II (32 ± 7% and 36 ± 5% reduction, respectively, \( P < 0.05 \) for both) and deep V–VI (42 ± 6% and 61 ± 2% reduction, respectively, \( P < 0.001 \) for both) laminae of the spinal dorsal horn (Fig. 2). As shown in Fig. 2 the reducing effects of the highest dose of RB101(S) (40 mg/kg i.v.) were reversed by naltroxone (1 + 1 mg/kg i.v.).

3.2. Effects of the combination of RB101(S) and (+)-HA966, a functional NMDA receptor antagonist, on carrageenan-evoked spinal c-Fos protein expression

In the second experimental series, low doses of RB101(S) (2.5 and 10 mg/kg i.v.) were inefficient and weakly efficacious at reducing the carrageenan-evoked spinal c-Fos protein expression, respectively, (4 ± 5% and 19 ± 4% reduction of the total number of carrageenan-evoked c-Fos-IR nuclei, \( P > 0.05 \) and \( P < 0.01 \), respectively; Figs. 3 and 4, Table 1). The weak effects of RB101(S) (2.5 and 10 mg/kg i.v.) were essentially observed at the level of the deep laminae V–VI (16 ± 4% and 24 ± 3% reduction of the number of carrageenan-evoked c-Fos-IR nuclei, \( P < 0.05 \) and \( P < 0.001 \), respectively). In contrast, combination of low doses of RB101(S) (2.5 or 10 mg/kg i.v.) and an inactive dose of (+)-HA966 (2.5 mg/kg s.c.) produced supra-additive effects (39 ± 4% and 51 ± 5% reduction of the total number of carrageenan-evoked c-Fos-IR nuclei, respectively, \( P < 0.001 \) for both; Figs. 3 and 4, Table 1). These supra-additive effects were observed in both superficial (I–II) and deep (V–VI) laminae of the spinal dorsal horn (Figs. 3 and 4, Table 1). As shown in Table 1 and Figs. 3 and 4, these supra-additive effects were partially reversed by naltroxone (1 + 1 mg/kg i.v.).

3.3. Carrageenan-evoked peripheral edema

One hour 30 min after i.pl. injection of carrageenan, ipsilateral peripheral edema was developed. Both the paw and ankle diameters of the carrageenan-injected hind paw were enhanced (see controls in Table 1),
whereas contralateral hind paw was unaffected. Neither RB101(S), naloxone nor the combination of RB101(S) and (+)-HA966 influenced the carrageenan-evoked peripheral edema (Table 1).

4. Discussion

The present results demonstrated that the isomer S of RB101, a complete inhibitor of enkephalin-catabolizing enzymes (Fournie-Zaluski et al., 1992), dose-dependently decreases carrageenan-evoked spinal c-Fos protein expression, in a naloxone reversible manner. In addition, the combination of weakly efficacious doses of RB101(S) and an inactive dose of (+)-HA966, a functional NMDA receptor antagonist (Singh et al., 1990, see refs. in Kemp and Leeson, 1993), produced supra-additive effects which were partially reversed by naloxone. Furthermore, neither RB101(S) alone nor the combination of RB101(S) and (+)-HA966 influenced the peripheral edema, suggesting that this interaction takes place principally at central level (spinal and/or supraspinal).

In good agreement with our previous studies (Honore et al., 1995b, 1997; Le Guen et al., 1999), 1 h 30 min after intraplantar injection of carrageenan, c-Fos-IR nuclei were numerous in the ipsilateral spinal cord and were localized predominantly in the superficial (I-II) and deep (V-VI) laminae of the dorsal horn of the L4–L5 segments. This laminar pattern is in concordance with the spinal areas containing neurons activated by noxious stimuli driven exclusively, or not, by noxious stimuli (see references in Besson and Chaouch, 1987; Willis and Coggeshall, 1991). Furthermore, the number of carrageenan-evoked c-Fos-IR nuclei was highly reproducible and homogenous, with a similar laminar distribution, for control carrageenan groups in two experimental series performed in the present study.

Preadministration of S isomer of RB101 (10, 20, or 40 mg/kg, i.v.), dose-dependently reduced the number of carrageenan-evoked spinal c-Fos-IR nuclei, in a naloxone reversible manner. In contrast, intravenous RB101(S) (40 mg/kg) did not induce spinal c-Fos expression in carrageenan nonstimulated rats. Our results are in good agreement with previous studies which have
shown that systemic administration of racemic RB101 dose-dependently reduce noxiously evoked spinal c-Fos protein expression due to the noxious heat (Abbadie et al., 1994) and the intraplantar carrageenan (Honoré et al., 1997), in a naloxone reversible manner. In the present study, RB101(S) had no effect on peripheral oedema, suggesting that the effects of this compound are principally at the central level, i.e., at a least part, at the spinal cord level. The effects of endogenous enkephalins projected from degradation by RB101(S) on noxiously evoked c-Fos protein expression could result from a direct action (presynaptic and/or postsynaptic) at the spinal cord level (Duggan and North, 1984; Lombard and Besson, 1989), but also from an indirect action by reinforcement of the inhibitory descending system (see references in Basbaum and Fields, 1984). However, a peripheral site of action cannot be totally excluded since it has been shown that the antinociceptive effects of systemic RB101 on responses to noxious pressure of rat inflamed hind paw are partially blocked by methyl-Naloxonium which does not cross the blood brain barrier (Maldonado et al., 1994).

The behavioral hyperalgesia associated with the carrageenan model of inflammatory nociception has been shown to be mediated, at least in part, by spinal NMDA receptor activation (Ren et al., 1992b; Yamamoto et al., 1993; Rygh et al., 2001). We have previously shown that
carrageenan-evoked spinal c-Fos protein expression is NMDA receptor mediated (Chapman et al., 1995). This previous study demonstrated that (+)-HA966 (0.5, 2.5 and 10 mg/kg s.c.) dose-relatedly reduced the carrageenan-evoked spinal c-Fos protein expression (Chapman et al., 1995). As discussed in Section 1, (+)-HA966 is a low-efficacy partial agonist at the glycine site of NMDA receptor complex, which acts as a functional NMDA receptor antagonist (Singh et al., 1990, see refs in Kemp and Leeson, 1993). The major finding of the present study is the evaluation of effects of the combination of RB101(S) and (+)-HA966 in carrageenan model of inflammatory nociception. For this combination, we have used the dose of 2.5 mg/kg of (+)-HA966 which had no effect on the spinal c-Fos expression and the peripheral edema observed at 1 h 30 min after intraplantar carrageenan (Chapman et al., 1995; Honoré et al., 1997). In contrast, combination of this inactive dose of (+)-HA966 and low doses of RB101(S) produced supra-additive effects on carrageenan-induced spinal c-Fos protein expression. These effects were significant in the superficial (Laminae I–II) and deep (Laminae V–VI) dorsal horn of the spinal cord which contains numerous neurons receiving nocuous inputs (see Besson and Chaouch, 1987; Willis and Coggeshall, 1991, and references therein). Here again, the peripheral edema was not influenced by this combination, suggesting that the interaction between RB101(S) and (+)-HA966 and its effect on noxiously evoked c-Fos protein expression was mainly due to a spinal and/or supraspinal site of action.

Our results suggest that the supra-additive effect of the combination of RB101(S) and (+)-HA966 was mediated, at least a part, via opioid receptors since it has been partially reversed by naloxone. The supra-additive effects observed in this study could be due to a functional potentiation between the effects of the two compounds on pre- or postsynaptic level. RB101(S) may act via opioid system to the reduction of presynaptic neurotransmitter release, including excitatory amino acids (EAA) acting on the NMDA receptors, and (+)-HA966 may act postsynaptically further reducing the NMDA receptor mediated events leading to sensitization of the postsynaptic neurons (see references in Dickenson et al., 1997). At the postsynaptic level, other mechanisms may contribute to effects of RB101(S) and (+)-HA966, since it has been shown that opioids, via a direct postsynaptic (protein kinase C mediated) action, modulated NMDA receptor-evoked responses of trigeminal neurons (Chen and Huang, 1991).

The present results showing supra-additive effects of the combination of systemic RB101(S) and (+)-HA966 are reminiscent of our previous results showing a supra-additive effect of combination of systemic morphine and (+)-HA966 in the same experimental paradigm, i.e., on the carrageenan-evoked spinal c-Fos protein expression (Honoré et al., 1996). In addition, electrophysiological studies have shown that intrathecal NMDA receptor antagonists reveal the effects of low-inactive dose of morphine in depressing neuronal activity at the spinal dorsal horn level (Chapman and Dickenson, 1992). Behavioral studies have demonstrated that a combination of intrathecal morphine and NMDA receptor antagonists produced additive effects on thermal hyperalgesia (Yamamoto and Yaksh, 1992) and mechanical allodynia (Nichols et al., 1997) in different models of neuropathic pain. Furthermore, a combination of systemic morphine
Table 1
Effects of combination of RB101(S) (2.5 or 10 mg/kg i.v.) and (±)-HA966 (2.5 mg/kg s.c.) on the carrageenan-evoked spinal c-Fos protein expression and peripheral edema in the awake rat (n = 6 for each group)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg s.c.)</th>
<th>Number of c-Fos-IR nuclei/section</th>
<th>Total number</th>
<th>Laminae I-II</th>
<th>Laminae V-VI</th>
<th>Paw diameter (cm)</th>
<th>Ankle diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>-</td>
<td></td>
<td>91 ± 3</td>
<td>46 ± 3</td>
<td>30 ± 2</td>
<td>0.95 ± 0.02</td>
<td>0.91 ± 0.02</td>
</tr>
<tr>
<td>RB101(S)</td>
<td>2.5</td>
<td></td>
<td>87 ± 5 (4.5 ± 5)</td>
<td>49 ± 4 (0 ± 8)</td>
<td>25 ± 1 (16 ± 4)</td>
<td>0.99 ± 0.01</td>
<td>0.95 ± 0.03</td>
</tr>
<tr>
<td>RB101(S) + HA966</td>
<td>2.5 ± 2.5</td>
<td></td>
<td>55 ± 4 (39 ± 4)</td>
<td>31 ± 2 (32 ± 5)</td>
<td>16 ± 1 (47 ± 4)</td>
<td>0.92 ± 0.02</td>
<td>0.93 ± 0.03</td>
</tr>
<tr>
<td>RB101(S) + HA966 + Naloxone</td>
<td>2.5 ± 2.5 ± 1</td>
<td></td>
<td>73 ± 4 (20 ± 4)</td>
<td>38 ± 3 (17 ± 7)</td>
<td>22 ± 1 (26 ± 3)</td>
<td>0.92 ± 0.03</td>
<td>0.96 ± 0.04</td>
</tr>
</tbody>
</table>

Results are expressed as mean value (±SEM) for the total number of Fos-IR neurons per section in L4–L5 segments (total number) and in superficial (Laminae I–II) and deep (V–VI) laminae of the spinal dorsal horn, and as mean value (± SEM) of the diameter of the paw and ankle angles (Paw Diameter, Ankle Diameter), 1 h after i.p. injection of carrageenan. Note that in carrageenan nonstimulated rats, the values for paw and ankle diameters are 0.47 ± 0.02 cm and 0.74 ± 0.02 cm, respectively. Results expressed as percentage reduction of control value of studied parameters are presented in brackets. Significance compared to control group (n = 6) was performed using ANOVA and Fisher’s PLSD test (P < 0.05, *P < 0.01, **P < 0.001).

and a NMDA receptor antagonist, (±)-HA966, dose-dependently increased the mechanical response thresholds (Christensen et al., 1998, 1999) and struggle latencies in the hot noxious test (Christensen et al., 1998) in rat models of neuropathic pain.

In conclusion, the present results provide evidence for the potent effects of combination of RB101(S) and (+)-HA966, a functional NMDA receptor antagonist, on the carrageenan-evoked spinal c-Fos protein expression. Considering the absence of major opioid side effects of RB101(S) and the marked increase of its antinociceptive effects by NMDA receptor antagonist, this type of drug combination could have beneficial therapeutic application.

Acknowledgments

This research was supported by grants from the Ministère de l’Education Nationale, de la Recherche et de la Technologie (France), the Association pour la Recherche sur le Cancer (ARC no. 9605) and the European Community (BMH4 CT98 2267). Le Guen was supported by a fellowship from the Mission Interministérielle de Lutte contre la Drogue et la Toxicomanie (MILDT 98BD11). We gratefully acknowledge Mr. R. Rambur for the assistance in the preparation of photomicrographs.

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