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Study of sleep and evaluation of sumatriptan and rizatriptan in the acute treatment of migraine in children and adolescents

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ACADEMIC DISSERTATION

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Helsinki 2008
Yliopistopaino
To Matti, Oskari and Rasmus
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ORIGINAL PUBLICATIONS
ABBREVIATIONS

ANCOVA Analysis of covariance
ANOVA Analysis of variance
ASA Acetylsalicylic acid
AUC Area under plasma drug concentration-time curve
BSA Body surface area
Cmax Peak plasma concentration
CNS Central nervous system
CSD Cortical spreading depression
DHE Dihydroergotamine
EEG Electroencephalogram
EMEA European Medicines Agency
FHM Familial hemiplegic migraine
GABA Gamma-aminobutyric acid
GEE Generalized estimating equation
GSK GlaxoSmithKline
5-HIAA 5-hydroxyindoleacetic acid
5-HT 5-hydroxytryptamine
IHS International Headache Society
MA Migraine with aura
MAO Monoamine oxidase
MAO-A Monoamine oxidase A
MO Migraine without aura
NO Nitric oxide
NSAID Nonsteroidal anti-inflammatory drug
SERT Serotonin transporter
T1/2 Elimination half-life
TGN Trigeminal nucleus
Tmax Time to peak concentration
TTH Tension-type headache
VAS Visual analog scale
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by Roman numerals I-III:


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ABSTRACT

Background and aims. Migraine is a common disease in children and adolescents, affecting roughly 10% of school-aged children. Recent studies have revealed an increasing incidence of childhood migraine, but migraine remains an underrecognized and undertreated condition in the pediatric population. Migraine attacks are painful and disabling and can affect a child’s life in many ways. Effective drug treatment is usually needed. The new migraine drugs, triptans, were introduced at the beginning of the 1990s and have since been shown to be very effective in the treatment of migraine attacks in adults. Although they are widely used in adults, the acute treatment of migraine in children and adolescents is still based on paracetamol and nonsteroidal anti-inflammatory drugs. Some children can control their attacks satisfactorily with these simple analgesics, but at least one-third need more powerful treatments. When this thesis work commenced, hardly any information existed on the efficacy and safety of triptans in children. The study aim was to identify more efficient treatments of migraine for children and adolescents by investigating the efficacy of sumatriptan and rizatriptan in them. Sleep has an impact on migraine in many aspects. Despite the clinical relevance and common manifestation of sleep in the context of migraine in children, very little research data on the true frequency of sleep exist. As sleeping is so often related to childhood migraine, it can be a confounding factor in clinical drug trials of migraine treatments in children and adolescents. How the results of a sleeping child should be analyzed is under continual debate. The aim here was to clarify this issue as well as to evaluate the frequency of sleeping during migraine attacks and factors affecting frequency.

Methods. In Study I, the frequency of children falling asleep during migraine attacks was evaluated from 999 migraine attacks registered in headache diaries. Data were prospectively collected during a previous study of optimal drug treatment of childhood migraine. Study II was a placebo-controlled double-blind two-way cross-over trial investigating the efficacy of nasal sumatriptan in the treatment of migraine attacks in 94 children aged 8-17 years. Each child treated two migraine attacks with study drugs, one being sumatriptan and the other a placebo. Sumatriptan dose was 10 mg for those with a body weight of 20-39 kg and 20 mg for those weighing 40 kg or more. Study III was a placebo-controlled double-blind three-way cross-over trial examining the efficacy of peroral rizatriptan in treating migraine attacks in 116 children aged 6-17 years. Each child treated three migraine attacks with random order study drugs, one being a placebo and two rizatriptan. The
repeated rizatriptan dose tested the stability of the treatment effect in two consecutive attacks. Rizatriptan dose was 5 mg for those weighing 20-39 kg and 10 mg for those 40 kg or more. In both studies, drug efficacy was evaluated with a validated five-face pain intensity scale in a headache diary, the primary endpoint being two grade headache relief or sleeping two hours postdose.

Results. In Study I, 68% of the children at least occasionally slept during a migraine attack. Sleeping was more common in children younger than 8 years than in older age groups; in the younger age group 57% of attacks were relieved by sleep. Pain intensity and duration of migraine attacks increased with age, and this was associated with a lower tendency to fall asleep. In Study II, nasal sumatriptan was superior to placebo (primary endpoint) already one hour postdose and remained superior during the four-hour follow-up. At two hours, 64% of patients after sumatriptan and 39% after placebo experienced headache relief. All other endpoints also favored sumatriptan. In Study III, both doses of rizatriptan were superior to placebo one hour postdose and remained superior during the four-hour follow-up. The response to rizatriptan was very stable over the two consecutive attacks treated. At two hours, 74% of patients after the first and 73% after the second dose of rizatriptan experienced headache relief, in contrast to only 36% after placebo. Rizatriptan offered complete pain-free response more often than placebo, and all other endpoints also favored rizatriptan. No serious adverse effects were observed after sumatriptan or rizatriptan.

Conclusions. Sleeping during migraine attacks is very common, and most children at least occasionally sleep during an attack. Falling asleep is especially common in children under eight years of age and during the first hour after the onset of attack. Children who are able to sleep soon after attack onset are more likely pain-free at two hours. Sleeping probably both improves recovery from a migraine attack and is a sign of headache relief. Falling asleep should be classified as a sign of headache relief in clinical drug trials of migraine treatments in children and adolescents. Both sumatriptan and rizatriptan are effective and well tolerated in treatment of migraine attacks in children and adolescents. The results suggest that nasal sumatriptan 20 mg and rizatriptan 10 mg can be effectively and safely used to treat migraine attacks in adolescents aged over 12 years. Because the treated number of patients under 12 years is small, more studies are needed before sumatriptan or rizatriptan can be recommended for use in this population.
INTRODUCTION

Migraine is the most prevalent neurological disease in children and adolescents affecting 4 to 11% of school-aged children, and up to 25% of adolescents (Mortimer et al. 1992, Abu-Arafeh et al. 1994, Lewis et al. 2002). Recent studies have revealed the increasing incidence of childhood migraine.

Migraine attacks are painful and disabling, and can occur several times each month. They affect a child’s life in many ways, including school performance and relationships with family and peers. However, migraine remains an underrecognized, underdiagnosed, and undertreated condition in the pediatric population. This is, at least partly, because of different clinical characteristics of migraine especially in young children as compared with adults. The underlying migraine pathophysiology is, however, presumably the same in adults and children. Problems in diagnostics include the short duration of childhood migraines, the higher likelihood of a bilateral headache location, and a child’s difficulty in describing headache features and associated symptoms. Early diagnosis and effective treatment are essential in minimizing the impact of migraine on a child’s quality of life and in preventing long-term disability (Winner 2008).

Frequency of migraine attacks in children can often be diminished by lifestyle changes and by avoiding attack triggers. Children use nonpharmacological treatments to treat their migraine attacks more often than adults. However, most children require drug therapy because of the disabling migraine symptoms. Pharmacological treatment of migraine in children has long been based on nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol. Some children can control their attacks satisfactorily with these simple analgesics, but 30-60% need more effective treatments (Hämäläinen et al. 1997). The new migraine drugs, triptans, were introduced at the beginning of the 1990s and have since revolutionized migraine treatment in adults. However, when this thesis work commenced, there was hardly any information on triptan efficacy or safety in children. The purpose of these studies was thus to investigate the efficacy of two of these drugs, intranasal sumatriptan and oral rizatriptan, in children and adolescents.

Sleeping seems to often be related to resolution of migraine attacks in children. Despite the clinical relevance and common manifestation of sleep in the context of migraine in children, very little research data on the true frequency of sleeping exist. As sleeping occurs so frequently, it can be a
confounding factor in clinical drug trials of migraine treatments in children and adolescents. How the results of a sleeping child should be analyzed is under continual debate, should sleeping be taken as a sign of a positive effect of the study drug or should the results of such children be omitted from the analyses. The aim here was to clarify this issue as well as to evaluate the frequency of sleeping during migraine attacks and factors affecting frequency.
REVIEW OF THE LITERATURE

1. Classification and epidemiology of headache in children

Headache, together with abdominal pain and limb pain, is one of the most prevalent types of pain, and the most frequent neurological symptom experienced by children and adolescents. A large epidemiological study reported that 46% of children aged 0-18 years had experienced headache during the preceding three months (Perquin et al. 2000). A German study described a three-month headache frequency rate of 60.5% in children over four years of age (Roth-Isigkeit et al. 2005). A study from Scotland reported the prevalence rate of severe recurrent headache to be 20-25% in children aged 5-15 years, with only slight variation across the age range (Abu-Arafeh et al. 1994). Headaches can be classified according to the International Classification of Headache Disorders (Table 1) (Headache Classification Committee of the International Headache Society 2004). The most prevalent causes of recurrent headache are the primary headaches, in children mainly migraine and tension–type headache.

Table 1. International Classification of Headache Disorders, 2nd edition (Headache Classification Committee of the International Headache Society 2004)

<table>
<thead>
<tr>
<th>Primary headaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Migraine</td>
</tr>
<tr>
<td>2. Tension-type headache (TTH)</td>
</tr>
<tr>
<td>3. Cluster headache and other trigeminal autonomic cephalalgias</td>
</tr>
<tr>
<td>4. Other primary headaches</td>
</tr>
<tr>
<td>Secondary headaches</td>
</tr>
<tr>
<td>5. Headache attributed to head and/or neck trauma</td>
</tr>
<tr>
<td>6. Headache attributed to cranial or cervical vascular disorder</td>
</tr>
<tr>
<td>7. Headache attributed to nonvascular intracranial disorder</td>
</tr>
<tr>
<td>8. Headache attributed to a substance or its withdrawal</td>
</tr>
<tr>
<td>9. Headache attributed to infection</td>
</tr>
<tr>
<td>10. Headache attributed to disorder of homeostasis</td>
</tr>
<tr>
<td>11. Headache of facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures</td>
</tr>
<tr>
<td>12. Headache attributed to psychiatric disorder</td>
</tr>
<tr>
<td>Cranial neuralgias, central and primary facial pain, and other headaches</td>
</tr>
<tr>
<td>13. Cranial neuralgias and central causes of facial pain</td>
</tr>
<tr>
<td>14. Other headache, cranial neuralgia, central or primary facial pain</td>
</tr>
</tbody>
</table>
Migraine is characterized by episodes of head pain that are often throbbing, frequently unilateral, and potentially very severe. In migraine without aura, attacks are usually associated with autonomic symptoms such as nausea, vomiting, or sensitivity to light, sound, or movement. In roughly one-third of migraine patients, attacks are at least sometimes preceded or accompanied by transient focal neurological symptoms, the so-called migraine aura (Goadsby et al. 2002). Migraine patients have a wide spectrum of phenotypes. Some patients have a mild disease with easily controllable attacks, but some have a disabling and chronic condition with frequently recurring attacks and difficult symptoms. The diagnosis of migraine in both adults and children is based on symptoms that fulfill the accepted diagnostic criteria. The diagnostic criteria of migraine, introduced in 1988 by the International Headache Society (IHS), have enabled accurate diagnostics of migraine (Headache Classification Committee of the International Headache Society 1988). The first version of the IHS criteria did not include specific criteria for children. The only modification made was that the duration of attack was allowed to be shorter in children younger than 15 years (2-72 hours) than in adults (4-72 hours). These criteria proved, however, to be suitable in diagnostics of migraine also in children and adolescents (Hämäläinen et al. 1995), and were quite widely adopted for diagnostic purposes. The updated version of IHS criteria introduced in 2004 (Headache Classification Committee of the International Headache Society 2004) includes specific diagnostic criteria also for children (Table 2). The minimum duration of attack was further shortened to one hour, and the attack is considered to end at the time of awakening, if a child falls asleep.

The prevalence of tension-type headache (TTH) varies in different studies according to the criteria applied. The studies that use the International Classification of Headache Disorders criteria (Headache Classification Committee of the International Headache Society 1988) have reported an overall prevalence rate of 10-25% in schoolchildren and adolescents (Anttila 2006). A prevalence rate as high as 73% was reported in Brazil (Barea et al. 1996), but in Scandinavian countries the prevalence of TTH has generally ranged between 10% and 18% (Anttila et al. 2002, Laurell et al. 2004). Consequently, the prevalence of TTH is close to or even higher than the prevalence of childhood migraine, which is considered the most common cause for recurrent headaches in children (Anttila 2006).

Children can have headaches for various secondary reasons, such as intracranial infections or hemorrhages, brain tumors, arteriovenous malformations, disturbances in cerebrospinal fluid flow, systemic diseases,
epilepsy, hypertension, sinusitis, ocular or dental diseases, obstructive sleep apnea, and psychological reasons (Table 1). Serious causes of secondary headache are, however, very rare in children and adolescents. In a Scottish follow-up study, three of 815 patients over a seven-year follow-up had intracranial pathology explaining the headache (prevalence rate 0.37%) (Abu-Arafeh et al. 2005).

Table 2. Updated version of the diagnostic criteria for migraine in children and adolescents (Headache Classification Committee of the International Headache Society 2004).

<table>
<thead>
<tr>
<th>1.1</th>
<th>Migraine without aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>At least five attacks fulfilling criteria B-D</td>
</tr>
<tr>
<td>B.</td>
<td>Headache attacks lasting 1-72 hours (untreated or unsuccessfully treated)(^a)</td>
</tr>
</tbody>
</table>
| C.  | Headache has at least two of the following characteristics:  
  1. unilateral location\(^b\)  
  2. pulsating quality  
  3. moderate or severe pain intensity  
  4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) |
| D.  | During headache at least one of the following:  
  1. nausea and/or vomiting  
  2. photophobia and phonophobia\(^c\) |
| E.  | Not attributed to another disorder |

<table>
<thead>
<tr>
<th>1.2</th>
<th>Migraine with aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>At least two attacks fulfilling criteria B-D</td>
</tr>
</tbody>
</table>
| B.  | Aura consisting of at least one of the following, but no motor weakness:  
  1. fully reversible visual symptoms, including positive features (e.g. flickering lights) and/or negative features (i.e. loss of vision)  
  2. fully reversible sensory symptoms, including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)  
  3. fully reversible dysphasic speech disturbance |
| C.  | At least two of the following:  
  1. homonymous visual symptoms and/or unilateral sensory symptoms  
  2. at least one aura symptom develops gradually over \(\geq 5\) minutes  
  3. each symptom lasts \(\geq 5\) minutes and \(\leq 60\) minutes |
| D.  | Headache fulfilling criteria B-D for 1.1 migraine without aura begins during the aura or follows aura within 60 minutes |
| E.  | Not attributed to another disorder |

\(^a\) When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.  
\(^b\) Migraine headache is commonly bilateral in young children; the adult pattern of unilateral pain usually emerges in late adolescence or early adulthood.  
\(^c\) In young children, photophobia and phonophobia may be inferred from their behavior.
2. Epidemiology of migraine in children

2.1. Prevalence of migraine in children

Before the IHS criteria, many different diagnostic criteria were used, and accordingly, the prevalence of migraine varied greatly in epidemiological studies. Table 3 provides some prevalence rates of migraine in children and adolescents reported in different studies and populations. In general, the prevalence of migraine is around 1-3% before schoolage, 4-11% in children aged 7-11 years, increasing steadily towards adolescence, being 8-23% in those aged 11-15 years (Lewis et al. 2002a). Before puberty, migraine seems to be equally common in both sexes, or even slightly more common in boys, but during and after puberty more common in girls and women (Abu-Arafeh et al. 1994, Lewis et al. 2002a). Boys seem to have onset of migraine at an earlier age than girls. In a Finnish study, of 14-year-old boys with migraine, one-third had their first attack before school age and two-thirds during the first six school years. In girls, only one-fifth had their first attack before school age and four-fifths at the age of 8-14 years (Sillanpää 1983).

The prevalence of migraine in children and adolescents has increased during the last 10-20 years. In a large Finnish population-based follow-up study of children starting school at the age of seven years, conducted in 1974, 1992, and 2002 with identical study methods, the incidence of migraine increased from 19.7 (per 1000 person-years) in 1974 to 58.6 in 1992, and further to 133.2 in 2002. The trend was similar in boys and girls (Anttila et al. 2006). In this study, the older Vahlqvist’s diagnostic criteria, which are less restrictive than IHS criteria (Metsähonkala et al. 1994), were used (Vahlquist 1955). Migraine frequency in 2002, reported also by using the updated version of IHS criteria, was 114.4 per 1000 person-years. The Authors commented that had the IHS criteria been used all three years, the overall incidence rates would likely have been slightly lower, but an increasing trend would still have been apparent. An American study reported a similar increasing trend of migraine prevalence between 1979 and 1981, and between 1989 and 1990 for all age groups (0-99 years) in female subjects, but only a slight increase in incidence rates for male subjects aged 10-19 years (Rozen et al. 1999).
### Table 3. One-year prevalence of migraine (lifetime prevalence in ‘Bille 1962’) in population-based studies.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Country</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bille 1962</td>
<td>Sweden</td>
<td>4440 boys</td>
<td>7-15</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4553 girls</td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>Sillanpää 1983</td>
<td>Finland</td>
<td>1473 boys</td>
<td>7</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1448 girls</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1473 boys</td>
<td>14</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1448 girls</td>
<td></td>
<td>14.8</td>
</tr>
<tr>
<td>Mortimer et al. 1992b</td>
<td>United Kingdom</td>
<td>1083</td>
<td>3-11</td>
<td>3.7</td>
</tr>
<tr>
<td>Abu-Arefeh et al. 1994</td>
<td>United Kingdom</td>
<td>888 boys</td>
<td>5-15</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>866 girls</td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84 boys</td>
<td>7</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85 girls</td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79 boys</td>
<td>13</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69 girls</td>
<td></td>
<td>23.7</td>
</tr>
<tr>
<td>Barea et al. 1996</td>
<td>Brazil</td>
<td>272 boys</td>
<td>10-18</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>266 girls</td>
<td></td>
<td>10.3</td>
</tr>
<tr>
<td>Anttila et al. 2002</td>
<td>Finland</td>
<td>1135</td>
<td>12</td>
<td>13.6</td>
</tr>
<tr>
<td>Özge et al. 2003</td>
<td>Turkey</td>
<td>5562</td>
<td>8-16</td>
<td>10.4</td>
</tr>
<tr>
<td>Laurell et al. 2004</td>
<td>Sweden</td>
<td>685 boys</td>
<td>7-15</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>686 girls</td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td>Zwart et al. 2004</td>
<td>Norway</td>
<td>2811 boys</td>
<td>13-18</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3036 girls</td>
<td></td>
<td>9.1</td>
</tr>
</tbody>
</table>

#### 2.2. Inheritance of migraine

An important aspect of the pathology of migraine is the inherited nature of this disorder. It is clear from clinical practice that many patients have first-degree relatives who also suffer from migraine (Goadsby 2005) and many published studies also have report familial occurrence of migraine (Russell 1997). The familial occurrence of disease is assumed to be either due to shared genes, or shared environmental factors, but the high prevalence of migraine could also cause familial aggregation simply by chance (Russell et al. 1995, Merikangas 1996). The importance of genetic and environmental factors in migraine with aura (MA) has been investigated by using family and twin study designs. A Danish study included 1013 monozygotic and 1667 dizygotic twin pairs of the same gender. The pairwise concordance rate of MA was significantly higher among monozygotic (34%) than dizygotic (12%) twin pairs, emphasizing the importance of genetic factors in MA. However, environmental factors also played a role, as the pairwise concordance rate was less than 100% in monozygotic twin pairs. The risk of
Review of the literature

MA in dizygotic twins (21%) was similar to the recurrence risk in nontwin siblings (27%). The importance of both genetic and environmental factors in MA indicates that a multifactorial inheritance is most likely (Ulrich et al. 1999).

In a Danish family study, the first-degree relatives of subjects with MA had nearly a fourfold risk of MA, but no risk of migraine without aura (MO). The first-degree relatives of subjects with MO had 1.9 times the risk of MO and 1.4 times the risk of MA. The first-degree relatives of subjects who had never had migraine had no increased risk of MA or MO. Spouses of subjects with MO had 1.4 times the risk of MO, whereas spouses of subjects with MA had no increased risk of MA. These different familial patterns indicate that MO and MA have different etiologies. MO seems to be caused by a combination of genetic and environmental factors, whereas MA is probably largely determined by genetic factors (Russell et al. 1995).

3. Pathogenesis of migraine

The pathogenesis of migraine is incompletely understood, although advanced research methods, such as functional neuroimaging, and basic neuroscience studies have yielded a large amount of new information in recent years. Migraine is best understood as a form of neurovascular headache, a disorder in which neural events result in the dilatation of blood vessels, which in turn lead to pain and further nerve activation (Goadsby et al. 2002). All symptoms of a typical migraine headache cannot be explained by a single theory. Migraine is probably most accurately considered a heterogeneous disorder with multiple mechanisms involved in its pathogenesis. The underlying pathophysiology of childhood migraine is presumably the same as in adults, although no research data on this topic exist (Winner 2008).

3.1. Migraine aura

Migraine aura is believed to be caused by a phenomenon known as cortical spreading depression (CSD), first described by Leao in 1944. According to this theory, when the human cortex is activated, a wave of neuronal excitation followed by depression starts to spread along the cortex at a velocity of 2-3 mm/min. CSD is characterized by shifts in cortical steady-state potential, transient increases in potassium, nitric oxide (NO), and glutamate, and transient increases in cortical blood flow, followed by sustained flow decreases. This is manifested clinically as migraine aura (Olesen et al. 1990, Kramer et al. 1998, Silberstein 2004). The initial
Review of the literature

hyperemic phase is followed by reduced cortical blood flow, which moves across the cortex (spreading oligemia) (Olesen et al. 1981). The rate of progression of spreading oligemia is similar to rates of migraine scotoma and CSD, suggesting that they are related (Pietrobon et al. 2003). During visual aura the cortical blood flow decreases by 15-53% and the mean transit time increases 10-54% in the occipital cortex contralateral to the aura. This perfusion defect moves anteriorly (Cutrer et al. 1998). The occipital cortex is especially sensitive to spreading depression, which explains why visual scotoma is the most common form of migraine aura (Wray et al. 1995).

3.2. Migraine headache

The trigeminal nervous system, which innervates the cranial vasculature, and its reflex connections with the cranial parasympathetics form the trigeminoautonomic reflex. This is thought to be essential in the pathogenesis of migraine headache (Goadsby et al. 2002, Silberstein 2004). Activation of the trigeminal nucleus caudalis in the brainstem and trigeminal afferent fibers that innervate large cerebral vessels, pial vessels, large venous sinuses, and duramater is thought to cause perivascular release of vasoactive neuropeptides, such as substance P, calcitonin gene-related peptide, neurokinin A, and nitric oxide (NO). Neuropeptides interact with the blood vessel wall, producing neurogenic inflammation, vasodilatation, plasma protein extravasation, and platelet activation. This leads to central transmission of pain information, and further to migraine headache. Activation of autonomic tracks of the trigeminovascular system produce the associated symptoms of migraine, e.g. nausea and vomiting (Ferrari 1998, Pietrobon et al. 2003, Silberstein 2004). Neurogenic inflammation sensitizes nerve fibres, and they start to respond painfully to previously innocuous stimuli, such as blood vessel pulsations, and other normal activity, such as coughing. This is called peripheral sensitization and partly causes the throbbing headache of migraine (Strassman et al. 1996, Pietrobon et al. 2003). Central sensitization can also occur. Cutaneous allodynia (exaggerated skin sensitivity), which is frequently seen during migraine attacks, is thought to be caused by trigeminal sensitization (Burstein et al. 2000). The absence of cutaneous allodynia may be crucial in reaching positive outcome from triptan treatment (Burstein et al. 2004).
3.3. Why aura leads to headache

Bolay et al. (2002) were the first to show the pathophysiological connection between migraine aura and headache in rodents (Figure 1) (Bolay et al. 2002, Iadecola 2002). How accurately this rodent model mimics the human disease is, however, unclear. Aura does not appear to be an absolute requirement for headache, as in most patients headache is not preceded by aura.

![Diagram of the relationship between cortical spreading depression (CSD) and headache in migraine with aura. CSD was demonstrated to release hydrogen ions (H+), potassium ions (K+), arachidonic acid (AA), and nitric oxide (NO) into the extracellular space of the neocortex. According to this theory, these agents diffuse towards local blood vessels, depolarize perivascular trigeminal terminals, and cause activation of the caudal portion of the trigeminal nucleus (TGN) in the brainstem. At the same time, collateral axons of activated neurons in the trigeminal ganglion (TGG) release pro-inflammatory peptides in the meninges and their vessels, leading to a local inflammatory reaction. The activation of TGN, caused by CSD, produces vasodilatation of meningeal blood vessels through a pathway originating from the superior sagittal sinus (SSN) in the brainstem, and reaches the meningeal blood vessels via the sphenopalatine ganglion (SPG). The perception of pain is mediated by higher-order projections from the TGN. The dashed lines indicate unknown connections. Modified from Iadecola (2002).]
3.4. Serotonin in migraine

The most effective drugs currently used for acute as well as prophylactic treatment of migraine are known to work through serotonin (5-hydroxytryptamine, 5-HT) receptors, implying that serotonin is an important factor in migraine pathogenesis. Serotonin acts mostly as an inhibitory neurotransmitter. There are seven classes of 5-HT receptors (5-HT_1-7) (Hoyer et al. 1994) and five 5-HT_1 receptor subtypes (5-HT_1A, 5-HT_1B, 5-HT_1C, 5-HT_1D, and 5-HT_1F) (Hartig et al. 1996) that mediate pre- and postsynaptic inhibition. The 5-HT_1B, 5-HT_1D, and 5-HT_1F receptors are associated with the treatment of migraine with triptans and ergotamines. The 5-HT_1B receptors are located in cranial vasculature, whereas the 5-HT_1D and 5-HT_1F receptors are located in trigeminal nerve endings (Longmore et al. 1997). Serotonin can have varying effects on vessel tone, causing either vasodilatation or vasoconstriction. Vasoconstriction is mediated by receptors in the 5-HT_1 and 5-HT_2 families. Excitatory effects of serotonin are mediated by the 5-HT_3 receptors, which have a role in nociception and vomiting (Schwedt 2007).

Serotonin is degraded by monoamine oxidase (MAO) into a reactive aldehyde, which is further processed by aldehyde dehydrogenase into the 5-HT primary metabolite, 5-hydroxyindoleacetic acid (5-HIAA). The serotonin transporter (SERT) is responsible for presynaptic reuptake of serotonin. Drugs such as the selective serotonin inhibitors have high specificity for blocking serotonin reuptake by SERT (Schwedt 2007). In the brain, serotonin is stored within synaptic vesicles. When 5-HT neurons are depolarized, serotonin release occurs through Ca^{2+}-dependent exocytosis, which is dependent on the firing rate of serotonergic neurons. Therefore, release of serotonin is decreased by drugs that reduce the firing rate of serotonergic neurons, e.g. agonists of presynaptic 5-HT_1A or 5-HT_1B auto-receptors. After serotonin is released, it is either metabolized into 5-HIAA or decapsulated into serotonergic neurons by SERT. These mechanisms are essential for the maintenance of serotonin homeostasis (Hamel 2007).

Multiple studies of the serotonergic system in the context of migraine have been published. The results are contradictory, but a few trends have been noted. Plasma serotonin levels were altered in subjects with migraine. Between attacks, serotonin levels were lower, whereas 5-HIAA levels were higher, than in nonmigraine controls. During migraine attacks serotonin levels increased, while 5-HIAA levels decreased (Ferrari et al. 1989). The 5-HIAA concentrations in urine increased during migraine attacks (Sicuteri et al. 1961). There is also evidence that brain serotonin synthesis is increased in
patients with migraine (Chugani et al. 1999), and 5-HIAA concentrations are elevated in the cerebrospinal fluid of migraine patients, suggesting increased breakdown of serotonin in the CNS (Kovacs et al. 1989). These observations have led to the hypothesis that a chronically low serotonin disposition could form a biochemical basis of migraine pathogenesis and that a sudden increase in serotonin release could be one of the triggering events leading to migraine attack (Hamel 2007).

3.5. Genetics of migraine

Although family and twin studies show that a genetic component is present in migraine, no genes predisposing to MA or MO have been identified. Family-based linkage studies have elucidated several chromosomal regions linked to these common forms of migraine, but there is little consistency between the studies (Wessman et al. 2004, 2007). The most encouraging approach has been the identification of genes causing a rare migraine subtype, familial hemiplegic migraine (FHM), which is inherited as an autosomal dominant trait with incomplete penetrance. The first locus linked to FHM was mapped to chromosome 19p13 (Joutel et al. 1993), and later, the first mutations in the voltage-gated calcium channel CACNA1A-gene in that area were identified (Ophoff et al. 1996). Mutations in this gene are responsible for about 50% of the identified FHM families, now known as FHM-1 (Ducros et al. 2001). Since then, mutations also on chromosome 1q21-23 in the ATP1A2 gene, encoding the Na⁺, K⁺-ATPase, were identified. This mutation is thought to be responsible for about 20% of the FHM families (FHM-2) (Ducros et al. 1997, De Fusco et al. 2003, Marconi et al. 2003). No definitive phenotypic differences exist between FHM-1 and FHM-2. The penetrance is possibly somewhat lower for FMH-2, and cerebellar signs are mostly associated with FHM-1 (Ducros et al. 2001). Recently, a third locus and gene for FHM, SCN1A on chromosome 2q24, has been identified. This codes for a neuronal voltage-gated sodium channel, and mutations in it have previously been associated with different epilepsy phenotypes (Dichgans et al. 2005).

The main symptoms of FHM are very similar to those of MA. Cortical hyperexcitability followed by increased susceptibility to cortical spreading depression (CSD) are suggested as the underlying shared pathophysiological mechanism of symptoms. Since Ca,2.1 channels play a major role in the release of excitatory neurotransmitter glutamate from cortical neurons, increased Ca²⁺ influx through mutant channels could lead to hyperexcitability (Moskowitz et al. 2004). In accordance with this hypothesis, CACNA1A R192Q knock-in mice show a decreased threshold for CSD (van den
Maagdenberg et al. 2004). Ca\textsubscript{v}2.1 channels were also demonstrated to have a role in modulating trigeminal nociception (Knight et al. 2002). Although no convincing evidence exists of an association between CACNA1A, ATP1A2, or SCN1A and MA or MO, some clinical features (e.g. episodic occurrence of symptoms and existence of triggering factors) support the hypothesis that the common forms of migraine could also be channelopathies (Ptacek 1998). All three FHM genes point to the importance of cell membrane ion-potential balance, which seems to also be the case with other paroxysmal disorders such as epilepsy and cardiac arrhythmias (Hubner et al. 2002). Pathways involving products of these genes remain the top candidates for underlying causes of migraine pathogenesis (Wessman et al. 2004, 2007).

4. Characteristics of migraine in children and adolescents

4.1. Migraine headache

Migraine is a severe, often throbbing headache that is frequently located unilaterally in the temples or frontal head regions in adults. In children, the head pain is more often bilateral, located in the central forehead or the frontal area. During a migraine attack, a child will often look ill and pale. The headache is remarkably severe, and 44% of children under eight years of age and 59% of those over eight years report that they at least occasionally cry because of migraine headache. About 40% of all children have missed school or playschool due to migraine (Mortimer et al. 1992a). Nausea and vomiting are frequent, particularly in younger children. Patients avoid bright lights, loud noise, and strong odors. Headache is typically aggravated by movement and relieved by lying down in a dark room or sleeping.

4.2. Migraine aura

Approximately, one-third of affected children have migraine with aura. Aura is slightly more infrequent in children under eight years of age (Mortimer et al. 1992a). The typical aura is binocular visual impairment with scotoma (77%), distortion or visual hallucination (16%), or monocular visual impairment or scotoma (7%) (Hachinski et al. 1973). Formed illusions (e.g. spots, balloons, colors, rainbows), hemianopia, blurred vision, or micropsia have also been described (Lewis 2007). Other less common auras consist of sensory symptoms or focal motor deficits (hemiplegia). Aura usually precedes the headache by less than 30 minutes, lasts 5-20 minutes, and subsides when the headache appears. Child can also have premonitory symptoms before the attack onset. Mood changes were experienced by 47%
of children 24 hours before attack onset; 64% of these were inhibitory and 36% excitatory. Premonitory symptoms were slightly more often observed in children under eight years of age (Mortimer et al. 1992a).

4.3. Frequency and duration of migraine attacks

Attack frequency and duration often increase with age. In children aged under 14 years, 75% had one or more attacks per month, the median frequency being one per week. The median duration of attack was five hours in children under 14 years of age, and nine hours in those aged 15 or older (Wöber-Bingöl et al. 2004). A British study reported a mean frequency of 6.8 attacks in the previous year in children aged 3-7 years, and the mean attack duration of MA and MO being 7.9 and 18.1 hours, respectively. In older children aged 8-11 years, the mean attack frequency was 11.3 attacks, and the mean attack duration of MA and MO was 13.1 and 17.8 hours, respectively (Mortimer et al. 1992a). In a Finnish study of 3-17-year-old children, 96% reported having at least one attack per month, with a median duration of 12 (range 2-96) hours (Hämäläinen et al. 1996). Short attacks, lasting less than two hours, were experienced by 5.9% of British children under eight years of age and by 11% of those older than eight years (Mortimer et al. 1992a). A combination of short (<1 hour) and longer (>2 hours) attacks can coexist in the same patient (Abu-Arafeh et al. 2004).

4.4. Rare subtypes of migraine

In addition to migraine with or without aura, some rare subtypes of migraine occur also in children.

Basilar migraine represents 3-19% of childhood migraines. The mean attack onset age is seven years. These attacks are characterized by episodes of dizziness, vertigo, visual disturbances, ataxia, or diplopia, followed by a headache that is often occipital. The benign paroxysmal vertigo in young children with abrupt episodes of unsteadiness or ataxia, sometimes nystagmus or pallor, dizziness, and nausea may precede the onset of migraine, as in long-term follow-up many children with these symptoms eventually develop basilar migraine (Lewis 2007).

Confusional migraine is a migraine variant that has perceptual distortions as its main feature. Affected patients, often boys, abruptly become agitated, restless, disorientated, and sometimes aggressive. The confusion phase may last minutes to hours. Once consciousness returns to baseline, the patients
describe an inability to communicate, frustration, confusion, and a loss of orientation to time, and they may not recall any headache phase (Lewis 2007).

Ophthalmoplegic migraine is nowadays categorized under cranial neuralgias, instead of the migraine spectrum. The main feature is painful ophthalmoparesis, but the pain may not be severe. Ptosis, limited adduction, and vertical displacement (as with involvement of the 3rd cranial nerve) are the most common findings. The oculomotor symptoms and signs may appear during the headache phase rather than preceding the headache. The signs may persist for days or even weeks after the headache has resolved (Lewis 2007).

Familial hemiplegic migraine (FHM) is an autosomal dominant form of migraine, as described earlier in Section 3.5. Clinically, FHM is a migraine headache preceded by an aura that has stroke-like qualities, producing some degree of hemiparesis. These transient episodes of focal neurologic deficits precede the headache by 30 to 60 minutes, but occasionally continue hours to days after the headache has resolved. The location of the headache is often contralateral to the focal deficits (Lewis 2007).

Abdominal migraine is characterized by episodic, vague, midline, or periumbilical abdominal pain. Abdominal migraine includes a group of patients who have chronic, recurrent abdominal pain and features that overlap with those of migraine without aura. Abdominal migraine generally occurs in schoolaged children, who report recurrent attacks of dull midline or upper abdominal pain that generally lasts for hours (Lewis 2007).

4.5. Prognosis

Childhood migraine, especially in boys, is thought to have a good prognosis, although longitudinal studies are very few. Migraine that begins before schoolage is reported to disappear more often in boys than in girls, but when migraine begins at the age of 8-14 years, it has better prognosis in girls than in boys. Of those children who at the age of seven years suffered from migraine, attacks disappeared entirely in 22%, were alleviated in 37%, and remained unchanged or became more severe in 41% by the age of 14 years (Sillanpää 1983).

In a Swedish 40-year follow-up study, 23% of childhood migraine patients with a mean attack onset age of six years were permanently migraine-free at puberty or as young adults (between 13 and 25 years). Males were
significantly more often migraine-free (34%) than females (15%). In addition, 22% of patients had been migraine-free for more than two years by that time, but relapsed later and continued to have attacks occasionally, with some migraine-free years in between. In their thirties, 40% of patients were migraine-free, but 38% still had annual attacks. Gender differences were no longer present. In their forties and fifties, 47% and 46% of patients were migraine-free, respectively, but over 50% continued to have at least occasional attacks (Bille 1997).

A similar prognosis was reported in a 20-year follow-up study done in Canada in children and adolescents, whose mean age at the time of diagnosis (study onset) was 11 years. Ten and 20 years later, 60% and 53% of patients, respectively, continued to have migraine attacks (Brna et al. 2005).

5. Diagnosis of migraine in children and adolescents

Headache is a common complaint in children and adolescents, and may be a symptom of a broad range of illnesses from the common cold to intracranial neoplasm. There is no specific diagnostic test for migraine. The diagnosis is based on taking a careful patient history, collecting detailed information about headache characteristics, and performing a clinical examination, to exclude possible other causes of recurrent headache. This usually requires a period of observation (at least 6 months), during which it can be established that the child is otherwise well, and growth and development continue normally. A headache diary is a useful tool during the follow-up period. A combination of features is required for the diagnosis of migraine (diagnostic criteria; Table 2), but not all features are present in every attack or in every patient (Goadsby et al. 2002). Additional diagnostic tests are needed only rarely.

Laboratory tests. The American Academy of Neurology states in the Practice Parameters for Physicians that there is no adequate documentation in the literature supporting the appropriateness of any routine laboratory tests or routine lumbar puncture in the evaluation of recurrent headache in children (Lewis et al. 2002a). They usually do not reveal any clinically relevant diagnostic information, and these tests should therefore be done only when clinically assessed to be necessary.

Electroencephalogram (EEG). Data from four studies in children with all kinds of recurrent headaches and from four studies in children with migraine demonstrated that EEG was either normal or demonstrated nonspecific
abnormalities in most patients. In four studies with migraine patients (n=219 children), 47% had normal EEG, 25% had spike activity, 11% had diffuse slowing, and 27% had other abnormalities. In four studies with all kinds of recurrent headaches (n=929), 75% of patients had normal EEG, 13% had spike activity, 7% had diffuse slowing, and 5% had other abnormalities. There was no significant difference in EEG findings in children with migraine compared with those with all kinds of recurrent headaches. The lack of a difference could be due to 44% of those patients with all kinds of headaches being diagnosed with migraine. No evidence supported that EEG findings would be sufficient in either specificity or sensitivity in individual patients to be clinically useful in the diagnostics of migraine. Furthermore, none of these eight studies reported any patients who subsequently developed new-onset seizures after clinical evaluation for headaches, even when the EEG showed paroxysmal abnormalities. These findings can be summarized as follows: in patients with abnormal EEG, there was no indication that this EEG finding provided any diagnostic information about the etiology of headache. Therefore, routine EEG is not recommended as part of the headache evaluation (Lewis et al. 2002a).

**Neuroimaging studies.** Routine neuroimaging is not indicated for children with recurrent headaches if the findings in neurological examination are normal. Data on 605 of 1275 children from six studies of children with recurrent headaches who were examined by a neurologist and underwent neuroimaging revealed only 14 patients (2.3%) with nervous system lesions requiring surgical treatment. All 14 children had definite abnormalities on examination. No patient with a normal examination had a lesion requiring surgical treatment. If there are clinical abnormalities, such as focal findings, signs of increased intracranial pressure, alteration of consciousness or patient temper, or coexistence of seizures, neuroimaging should be considered. Neuroimaging should also be considered if recent onset of a severe headache, change in the type of headache, or neurologic dysfunction occurs (Lewis et al. 2002a, Lewis 2007).

### 6. Predisposing factors for migraine

Children may be predisposed to migraine by both genetic and environmental factors. Population-based family and twin studies suggest that about half of the variance in migraine prevalence is explained by genetic factors, which leaves a strong role for environmental factors (Bigal et al. 2007).
6.1. Psychosocial factors

In the literature, abundant studies have investigated the effect of psychosocial factors on the prevalence of childhood headache in general, however, these usually have not distinguished migraine from tension-type headache (TTH) or other headache types. Psychosocial factors are generally thought to be more relevant in TTH than in migraine (Karwautz et al. 1999), but many contradictory findings also exist.

In adults, migraine prevalence was higher in the population with lower income and lower education level (Lipton et al. 2007). In American adolescents older than 12 years, low household income was associated with higher prevalence of migraine. However, in adolescents with a strong family history of migraine, household income did not have a significant effect, probably because of the higher biologic predisposition (Bigal et al. 2007). Factors associated with low socioeconomic status, such as stress, poor diet, or limited use of medical care, may increase migraine prevalence in adults (Wadsworth et al. 2005), but in children environmental risk factors associated with low income are unclear.

In a Finnish study, children with migraine lived in more unhappy (and more often poor or very poor) families, with family members having more long-term illnesses and paroxysmal headaches than children with other types of headache. Children with migraine more often had fear of failure at school and a fear of teachers, but no difference existed in bullying, behavior problems, or learning difficulties in migraine patients compared with those with other kinds of headaches (Anttila et al. 2000). An earlier Finnish study reported that stress in school was strongly associated with migraine in 8–9-year-old girls, but problems in peer relationships were most strongly associated with migraine in boys of the same age (Metsähonkala et al. 1998).

An Austrian study reported that migraine patients were more often absent from school due to headache than patients with TTH, but patients with TTH experienced more psychosocial stress factors than migraine patients and headache-free controls. Migraine patients did not differ from headache-free controls in any environmental factors investigated (Karwautz et al. 1999). Children with migraine were reported to have more emotional disorders (anxiety, depression, or other neurotic disorder) than children with nonmigrainous headache (Marates et al. 1982, Guidetti et al. 1998). A Canadian study described no difference between children with migraine and headache-free controls in anxiety or stressful life events scores. However,
41% of children with migraine and 46% of their parents cited stress as a major trigger of migraine attack (Cooper et al. 1987).

6.2. Effect of diet

Evaluation of the role of diet in migraine is complex because multiple triggers and variables may modify an individual’s threshold to pain. Dietary factors may, at least in some patients, have an influence on frequency of migraine attacks. More important, however, is to maintain a well-balanced diet, without fasting or skipped meals, as 20-25% of children report headaches associated with a missed meal (Leviton et al. 1984). In patient-based studies, including both adults and children, the percentage of migraine patients reporting a particular food or drink as a precipitant of an attack has varied from 7% to 44%. In children, cheese, chocolate, and citrus fruit were the principal dietary attack triggers (van den Bergh et al. 1987, Millichap et al. 2003).

A biogenic amine, tyramine, is found in aged cheese and in many other foods and beverages, including wine, beer, beans, and sauerkraut. Normally, ingested tyramine is metabolized by MAO in the gut and liver and conjugated by enzymes so that it fails to enter the systemic circulation. Patients with dietary migraine are thought to have a deficiency in this metabolizing system such that tyramine is absorbed from the gut into the circulation, causing a headache via its vasoconstrictor effects (Smith et al. 1971).

The ingredients in chocolate implicated in the mechanisms of dietary-triggered migraine include phenylethylamine, theobromine, caffeine, and catechin. These chemicals may initiate a headache by altering cerebral blood flow and releasing norepinephrine from sympathetic nerve cells (Millichap et al. 2003).

Abrupt withdrawal from caffeine after regular consumption of large amounts may lead to headaches and exacerbation of migraine. This is thought to occur because of rebound vasodilatation and increased arterial blood flow when caffeine is discontinued after cerebral vasoconstriction during caffeine intake (Couturier et al. 1997). Children and adolescents sometimes consume large volumes of caffeine-containing carbonated drinks daily. Those children who consume 200 mg (e.g. 1.5 liters of cola drinks) or more of caffeine daily may be at risk of caffeine-induced or caffeine withdrawal headache (Hering-Hanit et al. 2003).
Even in moderate amounts of alcohol can trigger a migraine headache in susceptible patients. Tyramine, histamine, phenolic flavonoids, and sulfites are generally involved in the induction of migraine headache by various mechanisms, and are found particularly in red wines (Peatfield 1995).

Patients with migraine often complain of headache related to eating ice cream or other frozen foods. This is probably a cold-induced vasoconstrictor reflex response that is not specific to migraine sufferers (Millichap et al. 2003). Nitrites found e.g. in sausages can function as a chemical migraine trigger. Monosodium glutamate is found in many Asian dishes. It is a potent vasoconstrictor and can cause a group of symptoms known as the monosodium glutamate symptom complex (including headache, flushing, paresthesias, sweating, palpitation, and facial swelling), also known as the ‘Chinese restaurant syndrome’ (Millichap et al. 2003). In addition, many other chemicals have been reported to predispose to migraine attacks.

7. Sleep and migraine

Sleep and migraine are related in many respects. There are several reports of sleep disturbances in children and adolescents with migraine. Besides psychiatric problems, sleep disturbances are the most frequent complaint in children with headaches (Guidetti et al. 1998). Children and adolescents with migraine have described having poorer sleep quality and more difficulties in falling asleep, night awakenings, daytime sleepiness, and nocturnal symptoms, such as sweating, sleep-talking, bruxism, sleepwalking, and nightmares, than headache-free controls (Bruni et al. 1997, Miller et al. 2003, Heng et al. 2006, Isik et al. 2007). In adolescents with migraine, both frequency and intensity of headache, as well as duration of headache history, were related to the occurrence of sleep disturbances (Gilman et al. 2007). All studies agree that it remains unclear whether the occurrence of migraine headache leads to specific sleep disturbance, whether sleep disturbance leads to or contributes to headaches, or whether sleep disturbance and migraine headaches are components of separate clinical syndromes. In any case, bad sleep was reported to be the most frequent triggering factor for migraine attacks in children (Bruni et al. 2007). Further, in children and adolescents who were able to attain better sleeping habits by being instructed on how to improve their sleep hygiene, the mean duration and frequency of migraine attacks were significantly reduced compared with children with migraine who did not receive sleep hygiene guidance (Bruni et al. 1999).
Some clinical, anatomical, biochemical, and physiological evidence supports an inherent association between the normal physiology of sleep and a genesis of migraine in biologically predisposed individuals (Dodick et al. 2003). This theory hypothesizes a close relationship between the hypothalamus and brainstem in controlling physiological sleep and a role of hypothalamus in maintaining a circadian rhythm with melatonin. The hypothalamus has input and output connections to noradrenalin and serotonin repositories in the locus ceruleus and the dorsal raphe in the brain stem, which are thought to be involved in the pathogenesis of migraine. Melatonin might have some analgesic effect on headache. It increases the inhibitory action of gamma-aminobutyric acid (GABA), and thus, raises the threshold of pain circuits. Further, it inhibits the synthesis of prostaglandin E₂, modulates the entry of calcium into cells, diminishes the vasoreactivity of cerebral blood vessels, and can modulate 5-HT₂ receptors on cerebral arteries (Morgan et al. 1994). Both urinary and plasma melatonin were decreased in patients with migraine (Brun et al. 1995).

Sleep has an important role in the natural healing process of migraine attack. This has recently been reflected in the diagnostic criteria of migraine: if a patient falls asleep during an attack, this sleeping time is considered as part of the attack duration (Headache Classification Committee of the International Headache Society 2004). Although the role of sleep in the recovery phase of migraine attack has clinically clearly been observed, scant published data exist on this for both adults and children. The role of sleep in recovery from migraine attack was studied in 310 adults. Half of the patients fell asleep within three hours after taking medication, and the other half was rested without sleep. Of those who fell asleep, 50% had a full recovery, while the same was true for only 31% of the control group (Wilkinson et al. 1978). In a sample of 1283 adult migraine patients, 85% reported that they chose to sleep because of headache, and 75% were forced to sleep or rest because of headache. Of these same patients, 50% reported that their migraine attacks are triggered by sleep disturbance, and they experience headaches that awaken them from sleep (Kelman et al. 2005). In a study of 50 adults with migraine, 14 could shorten their attacks by going to sleep for an average of 2.5 hours (Blau 1982).

Sleep seems to be a very important factor in the healing process of childhood migraine. Resting is probably the most common nonpharmacological way of trying to relieve migraine headache in children, who generally prefer nonpharmacological treatments over pharmacological ones more often than adults. In fact, resting was cited as the primary treatment choice by 28% of
Canadian children with migraine (Dooley et al. 1995). In a study of 34 migraine patients aged 10-17 years, 74% of patients slept during an attack, and 56% were asleep within 30 minutes of attack onset. Their duration of sleep was between 0.5 and 16 hours, and when waking up, nearly 20% had no headache and 69% were markedly improved (Massiou 1997).

Sleeping is also relevant in clinical drug trials. The question is repeatedly raised of how the results of a child who sleeps during a migraine attack should be handled. Should sleeping be taken as a sign of positive effect of the study drug, or should the results of such children be omitted from analyses. The latter option has the risk of skewing the results, as sleeping occurs so frequently. The European Medicines Agency’s (EMEA) Committee for Medicinal Products for Human Use has recommended in its recent ‘Guideline on clinical investigation of medicinal products for the treatment of migraine in children and adolescents’ that falling asleep at two hours after the study agent (with no use of rescue medication and no relapse within 48 hours) could be used as an efficacy endpoint in studies of acute treatment of migraine in children (European Medicines Agency 2006).

8. Assessment of pain in children

Pain assessment, especially in young children, is a challenging task for the clinician. As pain is a subjective experience, self-reported scales are the gold standard in pain assessment and are wildly used and validated in adults (Sriwatanakul et al. 1983, Littman et al. 1985). By contrast, children have limited cognitive and expressive abilities compared with adults, which leads to a special need for self-reporting tools appropriate for children and their stage of cognitive development.

More than forty measurement tools designed for use in children have been published (Hicks et al. 2001). For patients younger than three or four years, pain assessment methods are primarily based on observation. These comprise physiological measures, including the analysis of such vital signs as change in blood pressure and heart rate, and behavioral measures that reflect, for example, the child’s vocalization, movements, irritability and rigidity of the limbs and body (Berde et al. 2002).

From the age of 3-4 years, a child can usually express pain with facial scales, which include sequential drawings or photographs of faces showing different levels of pain intensity. To use this tool, the child needs the cognitive capacity to match pictures of facial expressions to his/her internal state...
(Hicks et al. 2001). The child does not need to be able to count or to use numbers in a categorical fashion, but a basic understanding of the concept of ordering is required. Different versions of these scales have been demonstrated to be valid and reliable in measuring pain in children (Belville et al. 2005). Face scales were preferred to various other scales in all pediatric age groups (Hicks et al. 2001). Color analog scales, i.e. a line with increasing intensity of red color signifying increasing intensity of pain, can also be used for children of 3-8 years (McGrath et al. 1996). Good agreement was reported between face scale and color analog scale in children aged 3-7 years after surgery (Beyer et al. 1990).

From the age of 7-8 years, a child can often adequately use visual analog scales (VASs). The VAS includes a horizontal line of varying length (often 10 cm), with no pain at one end and the worst possible pain at the other end. The patient chooses the point on the line that best expresses the intensity of pain experienced. The VAS is validated and is the most frequently used pain scale in adults and adolescents (Belville et al. 2005).

9. Treatment of migraine in children

As in adults, treatment of migraine in children and adolescents can be divided into nonpharmacological and pharmacological treatments. Pharmacological treatments can further be divided into acute attack treatment and prophylactic treatment, the latter referring to a daily treatment to prevent frequently recurrent migraine attacks.

9.1. Acute treatment

9.1.1. General principles

Although resting without a drug may bring sufficient relief in mild migraine attacks, drug treatment is usually needed. The dose should be sufficient and in a rapidly absorbable form, ideally administered as the first symptoms of an attack appear. Drug treatment should be followed by resting in a dark, quiet room. The Finnish Current Care Guideline of Childhood Headache recommends paracetamol (15 mg/kg; maximum dose 60 mg/kg/day) and ibuprofen (10 mg/kg; maximum dose 40 mg/kg/day) for the acute treatment of migraine in children. Paracetamol is slightly more rapid in action but complete pain-free response after ibuprofen is two times more likely than after paracetamol. Overall, liquid formulations are absorbed faster and suppositories slower than tablets (Suomen Lastenneurologinen Yhdistys ry:n...
If needed, analgesic treatment can be combined with metoclopramide (0.1-0.3 mg/kg/day) to prevent vomiting and improve gastric motility, as gastric stasis and decreased drug absorption often occur with migraine attacks (De Ponti 2000). NSAIDs are not suitable for treating very frequent headaches since frequent administration may lead to exacerbation of headaches (medication-overuse headache).

The Practice Parameters for Physicians produced by The American Academy of Neurology concludes that ibuprofen is effective and paracetamol probably effective, and either can be safely used for the acute treatment of migraine in children. Furthermore, nasal sumatriptan was stated as being effective in the treatment of adolescents aged over 12 years (Lewis et al. 2004a). Similar findings were reported by the American Academy of Pediatrics (Damen et al. 2005), but a recent meta-analysis of all randomized controlled trials on the acute pharmacological treatments of children and adolescents revealed only ibuprofen and nasal sumatriptan to be significantly more effective than placebo (Silver et al. 2008). All of these medications were well tolerated, but significantly more adverse effects were reported for nasal sumatriptan than for placebo (Damen et al. 2005).

9.1.2. Nonsteroidal anti-inflammatory drugs and paracetamol

Ibuprofen and paracetamol are currently the first-line therapies for childhood migraine. These agents are readily available without prescription, are inexpensive, and their efficacy and safety have been best established (Lewis et al. 2004a). However, only two placebo-controlled studies of their efficacy have been published (Hämäläinen et al. 1997c, Lewis et al. 2002b). No published placebo-controlled studies exist of any NSAIDs other than ibuprofen in children.

**Efficacy in children and adolescents.** Both paracetamol (15 mg/kg) and ibuprofen (10 mg/kg) were effective in relieving migraine attacks in a double-blind, three-way, cross-over, placebo-controlled study in 66 children aged 4-16 years. Both ibuprofen and paracetamol were superior to placebo in relieving headache at one and two hours. At two hours, 68% of children after ibuprofen, 54% after paracetamol, and 37% after placebo experienced marked pain relief. Complete pain-free response at two hours was reported by 60% of children after ibuprofen, 39% after paracetamol, and 28% after placebo. No significant differences were present in pain relief responses between ibuprofen and paracetamol at any time-point. Paracetamol seemed to be slightly more rapid in action (at one hour, 39% response vs. 37% response.
after ibuprofen), but complete pain-free response after ibuprofen was two times more likely at two hours than after paracetamol (OR 2.2, 95% CI 1.1-4.0). No significant adverse effects were reported (Hämäläinen et al. 1997c).

The efficacy of ibuprofen suspension (7.5 mg/kg) was studied also in a parallel, double-blind, placebo-controlled trial with 84 children aged 6-12 years (Lewis et al. 2002b). Ibuprofen was more effective than placebo at two hours, as marked headache relief was reported by 76% of the patients after ibuprofen compared with 53% after placebo. At two hours, 44% after ibuprofen and 25% after placebo were completely pain-free. The authors did not report adverse effects. According to these studies, ibuprofen and paracetamol can offer marked headache relief to many children with migraine, but one-third need more effective treatments.

9.1.3. Ergotamine alkaloids

Ergotamine tartrate, originally derived from a rye fungus (Claviceps purpurea), was first isolated from ergot extract in 1918 and was used to treat migraine attacks in 1925. Ergotamine tartrate has serotonergic agonist and α-adrenergic antagonist activity. Dihydroergotamine (DHE) is a derivative of ergotamine with similar receptor actions (Silberstein et al. 1995). The bioavailability of ergotamine tartrate is low and highly dependent on the route of administration. It can be administrated as a sublingual preparation, and in combination with caffeine as an oral tablet and suppository. Caffeine enhances its oral and rectal absorption, but absorption is still erratic and highly inconsistent between individual patients in all administration routes. Ergotamines are prone to produce psychological and physiological dependence as well as vasospasms and ergotamine-overuse and ergotamine-withdrawal headaches. These in addition to administration problems, diminish their usefulness in treatment of migraine (Tfelt-Hansen 2001).

**Efficacy in children and adolescents.** One small placebo-controlled cross-over trial of efficacy of oral DHE (20 μg/kg) in therapy-resistant migraine attacks in children aged 6-11 years has been published (Hämäläinen et al. 1997b). After DHE, seven of 12 children reported at least two-grade pain relief on a five-face pain scale, while two of 13 children improved similarly after placebo. The efficacy of DHE seemed superior to placebo, although statistical significance was not reached, possibly due to the small treatment group.
9.1.4. Triptans

The group of 5-HT agonists, also called triptans, has revolutionized the abortive therapy of migraine attacks in adults over the past 15 years. With their specific mode of action, these drugs can alleviate also systemic symptoms of migraine attack, such as nausea and photophobia, in addition to headache. Currently, seven triptans are available (sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan) with five different drug formulations (nasal spray, rectal, subcutaneous injection, oral tablets, and disintegrating tablets) (Tfelt-Hansen et al. 2000).

Serotonin and its receptors are implicated in the pathophysiology of migraine. Several classes and subclasses of serotonin receptors have been identified. Two of these, 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors, are the ones mainly believed to be involved in migraine. 5-HT\textsubscript{1B} receptors are expressed in the smooth muscle cells of intracranial blood vessels, and 5-HT\textsubscript{1D} receptors on the peripheral and central trigeminal nociceptive nerve terminals. Triptans have high affinities at 5-HT\textsubscript{1} receptor subtypes, mainly the 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors. No profound differences exist between the individual triptans in affinities at the these receptors. Triptans also interact with 5-HT\textsubscript{1A} and 5-HT\textsubscript{1F} receptors, and some have a minor affinity at the 5-HT\textsubscript{7} receptor (Longmore et al. 1997, Schwedt 2007).

Possible mechanisms of triptan action in migraine are as follows: 1) constriction of dilated cranial blood vessels via 5-HT\textsubscript{1B} receptors (Saxena et al. 1989, Humphrey et al. 1991), 2) inhibition of neurogenic inflammation around the blood vessels by reducing neuropeptide release and plasma protein extravasation (Moskowitz 1992), and 3) inhibition of nociceptive transmission centrally within the trigeminovascular system (Goadsby 1997). The importance of each of these mechanisms remains uncertain (Humphrey et al. 1994). Because of the constriction effect of triptans in the cranial vasculature, they should be taken in the headache phase of migraine attack, and not during aura or other premonitory symptoms.

Although the pharmacological mechanism of individual triptans is similar, their pharmacokinetic properties can vary markedly. Especially the newer oral triptans have enhanced pharmacokinetic characteristics compared with the oral formulation of the first released triptan sumatriptan. These include more rapid attainment of therapeutic plasma levels, better oral bioavailability, and greater ability to cross the blood brain barrier. In contrast, these second-generation triptans do not differ much from sumatriptan in their
pharmacodynamic properties, except for being more lipophilic, thus having a
greater potential effect on the central part of the trigeminovascular system
(Tfelt-Hansen et al. 2000). Pharmacokinetic parameters of triptans are listed
in Table 4.

All triptans are effective in migraine therapy. Pain-relief response rates at two
hours post-dose are generally between 50% and 80%, and are superior to
placebo when used in adequate doses, although in comparative trials efficacy
differences are often reported (Tfelt-Hansen et al. 2000, Ferrari et al. 2001b,
Pascual et al. 2007). However, efficacy is not the only factor considered
when choosing an appropriate treatment for a migraine patient. Factors such
as rapidity of onset of action, headache recurrence rate, tolerability, route of
administration, and adverse effects are also important. Furthermore, pain-
relief response to certain triptans can vary greatly between individuals.

Adverse effects. Because of their receptor binding properties, all triptans
have a similar adverse effect profile. They are generally well tolerated when
used appropriately (Nappi et al. 2003). In the human coronary artery, 5-HT$_2$
receptors are the most important receptors mediating vasoconstriction, but
20-30% of the vasoconstriction is mediated by 5-HT$_1$ receptors (Bax et al.
1993). Therefore, 5-HT$_{1B/1D}$ agonists also constrict albeit to lesser extent,
human coronary arteries and can in some cases induce cardiac ischemia.
They are contraindicated in patients with cardiovascular diseases or marked
cardiovascular risk factors, such as angina pectoris, arteriosclerosis, and
uncontrolled hypertension. When used at therapeutic doses in patients
without any coronary artery disorders, triptans are expected to have an
insignificant effect on coronary arteries (Tfelt-Hansen et al. 2000).
Considering the extensive use of especially sumatriptan in the past decade,
the incidence of serious cardiac adverse events has been low (Welch et al.
2000).

Chest symptoms (tightness, pressure, and pain in chest, neck, or throat) are
typical adverse effects of triptans. They are observed in 15-40% of adult
patients after administration of oral or subcutaneous sumatriptan (Dahlof et
al. 1998). The pathophysiology of these chest symptoms remains uncertain,
but they may be also caused by coronary vasoconstriction (Nappi et al. 2003).
Chest symptoms are, however, more often observed in patients who generally
have a lower incidence of cardiovascular risk factors. They are more often
experienced by women than by men, by younger rather than older patients,
and by those with a low rather than a high body mass index (Dahlof et al.
1998).
The mechanisms involved in pathogenesis of CNS adverse effects following the administration of triptans are also obscure. Since several of the central adverse effects (i.e. somnolence, dizziness, thinking difficulty) could overlap with symptoms typically occurring during a migraine attack, it is difficult to evaluate the actual incidence of CNS-associated adverse effects. Up to tenfold differences in the incidence of CNS adverse effects have been detected between individual triptans. The highest incidences have been reported for eletriptan, rizatriptan, and zolmitriptan, and the lowest incidences for almotriptan, sumatriptan, and naratriptan. The probable explanation for these differences is the combination of existing active metabolites and high lipophility of some triptans. Highly lipophilic triptans that penetrate the blood-brain barrier are associated with higher levels of CNS side-effects. Naratriptan (although highly lipophilic), almotriptan, and sumatriptan have no active metabolites and have a relatively low incidence of CNS effects, while frovatriptan, rizatriptan, zolmitriptan, and eletriptan have N-desmethyl active metabolites and a higher incidence of CNS adverse effects (Nappi et al. 2003, Dodick et al. 2004).

9.1.4.1. Triptans in children and adolescents

There is a paucity of controlled data regarding the treatment of migraine with triptans in children and adolescents.

**Sumatriptan.** The efficacy of oral sumatriptan was studied in a small placebo-controlled, cross-over trial of 23 children aged 8-16 years. At two hours, pain relief was reported by 30% of patients after sumatriptan (50 mg, or 100 mg in those over 12 years of age) and by 22% after placebo. The difference was not significant (Hämäläinen et al. 1997a). Trials of nasal sumatripan are reviewed in Section 10.1.

**Eletriptan.** The efficacy and tolerability of eletriptan 40 mg was studied in 274 adolescents aged 12-17 years in a placebo-controlled, double-blind, parallel-group trial. No difference was present in two-hour headache response for eletriptan versus placebo (57% vs. 57%), and no significant improvements were observed for any of the outcomes at one or two hours. Eletriptan 40 mg was well tolerated, and the profile of adverse effects was similar to that observed in adults (Winner et al. 2007).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg) and route of administration</th>
<th>Tmax (h)</th>
<th>Cmax (mg/l)</th>
<th>T_{1/2} (h)</th>
<th>Bioavailability (%)</th>
<th>AUC (ng/mL·h)</th>
<th>Protein binding (%)</th>
<th>Active metabolites</th>
<th>Metabolism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>6 SC</td>
<td>0.17</td>
<td>72</td>
<td>2</td>
<td>96</td>
<td>90</td>
<td>14-21</td>
<td>-</td>
<td>MAO-A</td>
<td>Fowler et al. 1991</td>
</tr>
<tr>
<td></td>
<td>100 PO</td>
<td>1.5</td>
<td>54</td>
<td>2</td>
<td>14</td>
<td>158</td>
<td>-</td>
<td>-</td>
<td>Fowler et al. 1991</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 IN</td>
<td>1.5</td>
<td>13</td>
<td>1.8</td>
<td>15.8</td>
<td>43</td>
<td>-</td>
<td>-</td>
<td>Perry and Markham 1998</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.5 PO</td>
<td>1.5</td>
<td>3.8</td>
<td>2.6</td>
<td>40</td>
<td>21</td>
<td>25</td>
<td>+</td>
<td>CYP1A2 (MAO-A)</td>
<td>Seaber et al. 1998</td>
</tr>
<tr>
<td></td>
<td>5 IN</td>
<td>2</td>
<td>6.6</td>
<td>3</td>
<td>40</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>CYP450 (renal)</td>
<td>Goadsby and Yates 2006</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>2.5 PO</td>
<td>2</td>
<td>12.6</td>
<td>5.5</td>
<td>74</td>
<td>93</td>
<td>20</td>
<td>-</td>
<td>CYP450 (renal)</td>
<td>Tfelt-Hansen et al. 2000</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>10 PO</td>
<td>1.0</td>
<td>19.8</td>
<td>2.0</td>
<td>40</td>
<td>50</td>
<td>14</td>
<td>+</td>
<td>MAO-A</td>
<td>Goldberg et al. 2000</td>
</tr>
<tr>
<td>Eleetriptan</td>
<td>40 PO</td>
<td>1.8</td>
<td>~100</td>
<td>4-5</td>
<td>50</td>
<td>~600</td>
<td>85</td>
<td>+</td>
<td>CYP3A4</td>
<td>Milton et al. 2002, Takiya et al. 2006</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>12.5 PO</td>
<td>2</td>
<td>45</td>
<td>3.5</td>
<td>70</td>
<td>250</td>
<td>40</td>
<td>-</td>
<td>CYP3A4, MAO-A (renal)</td>
<td>Gras et al. 2002</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2.5 PO</td>
<td>3.0</td>
<td>7.0</td>
<td>25.7</td>
<td>29.6</td>
<td>94</td>
<td>15</td>
<td>+</td>
<td>CYP1A2 (renal)</td>
<td>Buchan et al. 2002</td>
</tr>
</tbody>
</table>

AUC, area under the plasma concentration-time curve; Cmax, peak plasma concentration; IN, intranasal; IV, intravenous; PO, oral; SC, subcutaneous; T_{1/2}, plasma half-life; Tmax, time to Cmax; MAO-A, monoamine oxidase-A; CYP450, cytochrome P450; CYP1A2 and CYP3A4, 1A2 and 3A4 isoforms of cytochrome P450. Renal indicates significant renal excretion.
Zolmitriptan. Oral zolmitriptan (10, 5, or 2.5 mg) was compared with placebo in 850 adolescents aged 12-17 years in treatment of a single migraine attack. Headache relief rates at two hours were 54%, 53%, and 57% for zolmitriptan 10, 5, and 2.5 mg, respectively, and 58% for placebo (p=ns) (Rothner et al. 2006). Oral zolmitriptan 2.5 mg was also compared with placebo and ibuprofen (200 or 400 mg) in a three-way cross-over design for treatment of three consecutive migraine attacks in 32 children aged 6-18 years. Pain relief rates at two hours were 28% for placebo, 62% for zolmitriptan, and 69% for ibuprofen (p<0.05) (Evers et al. 2006). Oral zolmitriptan was well tolerated in both of these trials. Zolmitriptan nasal spray 5 mg was studied a randomized, two-attack, cross-over trial with a novel 'placebo challenge' design in 171 adolescents aged over 12 years. Attack was first treated with placebo nasal spray, and no additional medications were taken if a headache response to placebo spray was achieved at 15 minutes. If pain intensity remained moderate or severe, the patients treated the attack with zolmitriptan nasal spray or placebo according to a randomized crossover schedule. The primary efficacy endpoint, headache relief at one hour, was achieved by 58.1% of patients after zolmitriptan and by 43.3% after placebo (p<0.05). Treatment with zolmitriptan nasal spray was well tolerated (Lewis et al. 2007).

Trials of rizatriptan are reviewed in Section 10.2. No placebo-controlled trials of efficacy of naratriptan, almotriptan, or frovatriptan have been published in children and adolescents.

9.2. Prophylactic treatment

Prophylactic treatment should be considered when migraine attacks persist two to three times per month regardless of lifestyle changes and other nonpharmacological interventions, and these attacks result in significant disability to the child life at school or in social relationships. If started, preventive treatment should be used at least 6-12 weeks before it can be considered ineffective. Slowly titrating the dose to an effective level is recommended. When prophylactic treatment is effective, it should be continued at least six months (Winner 2008).

Numerous agents have been used for migraine prophylaxis in children, but only a few controlled clinical trials are available. Clinical trials have not shown that one drug is clearly superior to others when also potential adverse effects are taken into consideration (Pakalnis 2007).
The American Academy of Neurology Practice Parameters for physicians stated that the best research evidence has emerged for the calcium channel blocker flunarizine, which is "probably effective", and can be considered for prophylactic purposes for childhood migraine (Lewis et al. 2004a). However, this evidence is questionable, as none of the studies that showed the efficacy of flunarizine adequately considered its long half-life (almost one month) in their study protocols (Hoppu et al. 1995). Flunarizine can also have marked adverse effects, e.g. sedation, weight gain, and extrapyramidal effects. Insufficient evidence exists for other drugs to make any recommendations for their prophylactic use in childhood migraine (Lewis et al. 2004a). However, increasing data are emerging for efficacy of the antiepileptic drug topiramate in migraine prophylaxis in children. Several small studies over the last years have reported a reduction rate superior to placebo for migraine frequency. Adverse effects are notable and include weight loss, impaired concentration, emotional instability, paresthesias, anorexia, sedation, and abdominal pain. These must be strictly monitored when topiramate is used (Eiland et al. 2007).

Other drugs used for migraine prophylaxis in children, based on varying amounts of research data, include the antihistamines cyproheptadine and pizotifen (also have antidepressive properties), the antidepressants amitriptyline and trazodone, the antihypertensive agents propranolol (and other β-adrenoceptor blockers), nimodipine, and clonidine, the antiepileptic drugs divalproex sodium and gabapentin, the NSAID naproxen, and the natural supplemental agents magnesium oxide, riboflavin, and coenzyme Q10 (Lewis et al. 2004b, Eiland et al. 2007, Pakalnis 2007, Winner 2008).

In Finland, propranolol is probably the most commonly used prophylactic agent in children. It is also the first-line therapy for migraine prophylaxis recommended by the Finnish Current Care Guideline of Childhood Headache (Suomen Lastenneurolooginen Yhdistys ry:n asettama työryhmä 2003), although research for its efficacy is controversial, and superiority to placebo remains unproven (Eiland et al. 2007). It is thought to improve migraines by modulating adenoreceptors or inhibiting serotonin receptors. The recommended dose for children aged seven years and older is 0.5-2 mg/kg/day (max 160 mg/day). Propranolol can decrease blood pressure, reduce heart rate, induce hypoglycemia, and exacerbate asthma symptoms (Suomen Lastenneurolooginen Yhdistys ry:n asettama työryhmä 2003).
9.3. Nonpharmacological treatment of migraine in children

Avoidance of attacks is the simplest approach to nonpharmacological treatment of migraine. As a child with migraine may have a genetic predisposition for this condition, it is usually not possible to prevent attacks completely by avoiding attack triggers. Potential triggers can best be identified by keeping a headache calendar or diary regularly. Lifestyle adjustments are often effective in diminishing attack frequency.

9.3.1. Avoidance of trigger factors

Trigger factors were identified by 18% of children aged 3-7 years with migraine and by 44% of children aged 8-11 years. Dietary factors were reported by 12% of the younger age group and 8% of the older age group. Stress was a precipitant in 6% of the younger group and 14% of the older one. In children over eight years of age, tiredness (8%), exercise (3%), noise (3%), glaring light (3%), missing a meal (3%), and studying (3%) were identified as migraine triggers (Mortimer et al. 1992a). Adolescents are probably more capable of identifying attack triggers than younger children. In those aged 11-15 years, the most frequent triggering factor for migraine headache was bad sleep (32%), followed by emotional distress (28%) (Bruni et al. 2007). Of children aged 6-16 years, 41% cited stress as a trigger for migraine headache. Other triggers were bright lights (28%), overtiredness (26%), exercise (23%), missing meals (10%), and certain foods (8%). No trigger was identified by 26% of children (Cooper et al. 1987).

Children with migraine should maintain a regular daily rhythm, with regular meals (especially breakfast) and sufficient physical exercise and sleep (Hämäläinen 2006). Before considering the elimination of certain foods from the diet, the headache trigger should be identified certainly from carefully filled out headache diaries. The elimination of all possible dietary triggers of migraine is not recommended for safety and nutritional reasons. A well-balanced diet is important, and skipping meals or fasting should be avoided (Millichap et al. 2003). The duration and frequency of migraine attacks can also be reduced by improving sleeping habits with sleep hygiene guidance (Bruni et al. 1999).

9.3.2. Behavioral treatments

Increasing evidence suggests that behavioral interventions, particularly biofeedback and relaxation therapy, might be more effective than commonly
used prophylactic drugs in treating childhood migraine (Hermann et al. 1995, Baumann 2002). The physiological basis for their effectiveness is unclear, but data from one trial suggest that levels of plasma β-endorphin can be altered by relaxation and biofeedback therapies (Helm-Hylkema et al. 1990).

**Acupuncture.** There is some evidence that acupuncture is effective in relieving symptoms in childhood migraine. Frequency and intensity of migraine were reduced in children with migraine who received ten true acupuncture treatments compared with those who received placebo acupuncture (needles in horny layer of epidermis) (Pintov et al. 1997).

**Stress management.** Stress management teaches patients to deal with the affective component of headache, in contrast to relaxation and biofeedback therapies, which focus on self-regulation of physiological responses (Baumann 2002). A widely used technique in stress management is to have a child keep a diary of headaches, stressors, and headache-associated activities to identify behaviors that seem to be related to headaches and then to alter this adverse behavior (McGrath et al. 1995). ‘Confident reassurance’, i.e. reassuring the child and parents that no serious illness is causing the child’s headaches, can lead to headache improvement (McGrath et al. 1995).

**Relaxation therapies.** Relaxation therapies use such techniques as progressive relaxation, self-hypnosis, and guided imagery without employing a feedback apparatus. Several studies have found relaxation therapies to be as effective, or even more effective, in reducing the frequency of migraine headaches than modest doses of a β-blockade medication (Baumann 2002).

**Biofeedback therapies.** Biofeedback therapies use an apparatus to demonstrate a physiological effect. Most commonly in children, thermal biofeedback is used: the child is taught to raise the temperature of a body part, typically a finger, with the temperature expressed by a visual display or an auditory signal (Baumann 2002). Several studies have shown that these techniques can be easily taught to children and that their use is associated with fewer and briefer migraine attacks (Hermann et al. 1995, Powers et al. 2001, Baumann 2002).
10. Characteristics of compounds studied here

Migraine attacks in children and adolescents are of shorter duration than in adults, so the ideal drug for treatment would be a formulation that has a rapid onset of action. It should also be easy and painless to administer, as injection is not favored by most children. When starting this thesis, hardly any information existed on the efficacy and safety of triptans in children. No triptan was licensed for use in children, and oral sumatriptan had failed to prove efficiency in a placebo-controlled trial (Hämäläinen et al. 1997a). As one-third of children with migraine seem to need more efficacious treatments than NSAIDs (Hämäläinen et al. 1997c), there was an absolute need for a better drug for acute treatment of childhood migraine. Intranasal sumatriptan and oral rizatriptan were selected as study drugs. Intranasal sumatriptan is rapid in action, and absorption begins immediately after dosing. It can also be administered if nausea or vomiting impede oral administration. Rizatriptan is the most rapidly absorbed oral triptan. It reaches Cmax quickly; this is favorable when treating childhood migraine, which has a shorter attack duration compared with adult migraine (Tfelt-Hansen et al. 2000).

10.1. Intranasal sumatriptan

Pharmacokinetics. Sumatriptan is a selective agonist of 5-HT\textsubscript{1B/1D} receptor subtypes. After an insufflation, a fraction of the dose is believed to be absorbed initially through the nasal mucosa, while the remainder is swallowed and absorbed through the gastrointestinal tract. This produces multiple peak plasma sumatriptan concentrations (Moore et al. 1997). Interindividual differences exist in absorption of the swallowed portion of the intranasal dose, as the gastric emptying and the small bowel transit rate can vary greatly. Sumatriptan 5, 10, or 20 mg given as a single nasal insufflation in one nostril to adults produced mean Cmax values of 4.7 to 14.4 μg/L in median times of 1-1.5 hours. After a 20-mg intranasal dose, 68-84% of Cmax is achieved already in 15 minutes, whereas comparable serum concentrations after an oral dose require 30-60 minutes (Fowler et al. 1991). Cmax and AUC values increase in a dose-proportional manner after the single dose of 5, 10, and 20 mg (Salonen et al. 1994).

Pharmacokinetic parameters other than those related to absorption are similar after intranasal sumatriptan compared with other administration formulations. Sumatriptan has a large volume of distribution ranging from 170 to 203 L after a single 6-mg subcutaneous dose. Plasma protein binding is low (14-21%) over a wide range of drug concentrations. Distribution of sumatriptan
in the CNS is poor, and penetration across the blood-brain barrier is slow. Sumatriptan is extensively metabolized in the liver, and possibly in the gastrointestinal tract, by monoamine oxidase A (MAO-A) to a pharmacologically inactive indoleacetic acid analog, which is mainly excreted as a free acid and as a glucuronide conjugate in urine. A small proportion of the metabolite is excreted in feces. The T1/2 of the therapeutic dose is about 2 hours, irrespective of the administration route (Fowler et al. 1991, Perry et al. 1998).

Pharmacokinetics in children. The pharmacokinetics of intranasal sumatriptan have been studied in children aged 6-11 years (Christensen et al. 2004) and in adolescents aged 12-17 years (Christensen et al. 2003). The pharmacokinetic parameters after sumatriptan 20 mg in adolescents were similar to those reported for adults, suggesting that adolescents could receive a similar dose to adults. In younger children, sumatriptan dosage was based on age and weight. Children aged 6-8 years and weighing under 25 kg received a dose of 5 mg, those aged 9-11 years and weighing under 40 kg a dose of 10 mg, and those aged 9-11 years and weighing over 40 kg a dose of 20 mg. This dosing scheme resulted in Cmax and AUC comparable with those observed in adolescents and adults after a dose of 20 mg. Other pharmacokinetic parameters were also similar to those in adolescents and adults.

Efficacy. All published controlled trials in adults have confirmed the superiority of intranasal sumatriptan to placebo in relieving migraine headache and other migraine-associated symptoms. Headache relief at two hours was experienced by 55-78% of patients after sumatriptan 20 mg compared with 29-42% of patients after placebo (Perry et al. 1998, Dahlof 1999). A complete pain-free response seems to be dose-dependent, being 26-42% after sumatriptan 20 mg at two hours and 4-20% after placebo (Dahlof 1999). Intranasal sumatriptan has a rapid onset of action, with some patients experiencing headache relief in 15 minutes, which is less than that reported for the oral formulation. Headache relief 30 minutes after intranasal treatment was achieved in 38% of 120 patients, but in only 2% of the 47 patients treated with oral sumatriptan (Rapoport et al. 2004).

Efficacy in children. Efficacy of intranasal sumatriptan in adolescents has been evaluated in a few placebo-controlled studies in recent years. A parallel-group single-attack study in 510 adolescents aged 12-17 years with randomly administered sumatriptan 5, 10, or 20 mg reported that at one hour post-dose 56% of patients after sumatriptan 10 mg and 56% after sumatriptan 20 mg
experienced pain relief, while this was true for only 41% of patients after placebo (p<0.05). At two hours, significantly more patients after sumatriptan 5 mg (66%) reported headache relief compared with placebo (53%; p<0.05). Significance was also approached for sumatriptan 20 mg (63%) compared with placebo (53%; p=0.059). A significantly greater proportion of patients (36%) reported being completely pain-free after sumatriptan 20 mg compared with placebo (25%; p<0.05). Headache recurrence after initial headache relief within 24 hours was reported by 18% and 16% of patients after sumatriptan 5 and 20 mg, respectively. No significant difference existed between these recurrence rates and the rate after placebo (20%) (Winner et al. 2000).

A second trial by the same authors investigated the efficacy of intranasal sumatriptan 5 and 20 mg compared with placebo in a parallel-design single-attack study in 738 adolescents aged 12-17 years. Sumatriptan 20 mg provided significantly greater headache relief than placebo at 30 minutes (42% vs. 33%; p=0.046) and at two hours (68% vs. 58%; p=0.025), but significance was not reached at one hour postdose (61% vs. 52%; p=0.087). Pain-free response was reported more often after sumatriptan 20 mg (44%) than after placebo (30%; p<0.001). Response rates after sumatriptan 5 mg were in general slightly higher than after placebo, but did not reach statistical significance at any time-point. Headache recurrence after initial relief was reported by 24% of patients after sumatriptan 20 mg and by 31% after placebo within 24 hours after treatment (Winner et al. 2006).

Only one placebo-controlled trial of efficacy of intranasal sumatriptan in children under 12 years of age has been published. This small two-way cross-over trial of 14 children aged 6-10 years reported response rates of 86% after sumatriptan 20 mg and 43% after placebo at two hours postdose (p=0.031). Complete pain-free response at two hours was achieved by 64% after sumatriptan and by 14% after placebo (p=0.016). Headache recurrence was not observed (Ueberall et al. 1999).

**Tolerability.** Intranasal sumatriptan is generally well tolerated, and adverse effects are usually mild and transient. However, all adverse effects generally associated with triptan treatment are possible (described in Section 9.1.4.), and intranasal sumatriptan is contraindicated in migraine patients with any cardiovascular risk factors (Perry et al. 1998). There is no evidence of long-term nasal irritation, blockade, or olfactory dysfunction after single or multiple doses of intranasal sumatriptan. The most commonly reported adverse effect, which is not dose-related, is the bitter taste of the drug (Moore et al. 1997).
**Tolerability in children.** The taste disturbance has been the most common drug-related adverse effect also in children and adolescents in all trials. It is the only adverse effect that is significantly more often reported after sumatriptan than after placebo. Other drug-related adverse effects include nausea, vomiting, dizziness, and nasal/throat/tonsil discomfort or burning sensation (Ueberall et al. 1999, Winner et al. 2000, 2006).

The one-year tolerability of intranasal sumatriptan was studied in 437 patients aged 12-17 years at doses of 5, 10, and 20 mg with a total of 3675 drug exposures. Drug-related adverse events were reported in 33% of the attacks after sumatriptan 10 mg, and in 31% of the attacks after sumatriptan 20 mg. Adverse effects did not increase with a second dose or over time. When taste disturbance was excluded from the tabulations, the incidence of drug-related adverse effects declined to 7% with both the 10- and 20-mg doses (Rothner et al. 2000). Another one-year tolerability study with 484 adolescents aged 12-17 years with 4676 drug exposures with one, two, or three doses of sumatriptan 20 mg reported drug-related adverse effects in 19% of attacks. When taste disturbance was excluded from the tabulations, the appearance of adverse effects declined to 4% (Natarajan et al. 2004).

**10.2. Rizatriptan**

**Pharmacokinetics.** Rizatriptan is an orally active serotonin 5-HT$_1$ receptor agonist that binds potentially and selectively to 5-HT$_{1B/1D}$ receptor subtypes. It is available as an oral tablet and as an orally disintegrating tablet (wafer). The minimum effective dose for rizatriptan in adults is 5 mg, with the optimum dose being 10 mg (Dahlof et al. 1999). Oral rizatriptan is readily absorbed from the gastrointestinal tract (~90%), with overall bioavailability being about 45% (Vyas et al. 2000, Goldberg et al. 2001). In adults, C$_{\text{max}}$ and AUC of rizatriptan increases in a dose-proportional manner after single-dose rizatriptan 5 to 60 mg (7.8-90 μg/L and 17.4-394.5 μg•h/L, respectively). The T$_{\text{max}}$ after a single dose of rizatriptan 2.5-60 mg ranges from 0.7 to 2.1 hours. Rizatriptan (5-60 mg) has a faster rate of absorption than oral sumatriptan 100 mg (median 1.3 vs. 2.5 hours) (Sciberras et al. 1997). The absorption seems to be independent of gastric stasis, as both C$_{\text{max}}$ and AUC are similar during and between migraine attacks (Cutler et al. 1999). Rizatriptan is minimally bound to plasma proteins (14%) (Wellington et al. 2002).

Rizatriptan is extensively metabolized by MAO-A, primarily to inactive metabolites, of which most are excreted in urine and small amounts in faeces.
Rizatriptan has one active minor metabolite, N-monodesmethylrizatriptan, which is twice as potent a 5-HT$_{1B/1D}$ agonist as rizatriptan (Goldberg et al. 2000). The mean T$_{1/2}$ of oral rizatriptan 2.5-60 mg is between 1.7 and 2.6 hours (Wellington et al. 2002). The AUC and Cmax are significantly increased with coadministration of rizatriptan with propranolol (but not metoprolol); the dose of rizatriptan should be reduced to 5 mg if administered to a patient also receiving propranolol (Goldberg et al. 2001).

**Pharmacokinetics in children.** The pharmacokinetics of rizatriptan has been studied in 12 adolescents with migraine. Rizatriptan was well tolerated, and the AUC and Cmax after single-dose administration of 10 mg were similar to values observed in adults (Winner et al. 1998).

**Efficacy.** Superiority of rizatriptan over placebo in relieving migraine headache and other migraine-associated symptoms has been found in all published controlled trials in adults (Wellington et al. 2002). A meta-analysis, including seven randomized studies with rizatriptan 10 mg and six studies with rizatriptan 5 mg, reported headache relief response rates of 45% and 38%, respectively (placebo 25%), at one hour, and 71% and 64% (placebo 38%) at two hours (Ferrari et al. 2001a). At two hours, 41% of the patients after rizatriptan 10 mg and 32% after 5 mg were completely pain-free compared with 10% after placebo. Response rates of similar magnitude have been reported in all published clinical trials (Dooley et al. 1999, Tfelt-Hansen et al. 2000, Jhee et al. 2001, Wellington et al. 2002). Headache recurrence rates are relatively high, ranging from 29% to 47% for rizatriptan 10 mg (Jhee et al. 2001).

**Efficacy in children.** Efficacy of rizatriptan 5 mg has been investigated in two placebo-controlled parallel-group single-attack trials in adolescents aged 12-17 years. In the first study, headache relief at two hours was reported by 66% of the 149 patients after rizatriptan 5 mg and by 56% of the 142 patients after placebo (p=ns). Of these patients, 32% after rizatriptan and 28% after placebo were completely pain-free. Headache recurrence was experienced by 14% of those who initially responded to treatment at two hours (Winner et al. 2002). Post hoc analysis showed a significant benefit of rizatriptan over placebo when migraine attacks were treated on weekends (headache relief at two hours 65% vs. 36%, p=0.046). In the second trial, children were instructed to treat an attack on non-school days. Pain relief at two hours was reported by 68.2% after rizatriptan 5 mg and by 68.8% after placebo. Only 30% of subjects treated their attacks on the weekend as instructed; in this
subgroup of patients, rizatriptan was superior to placebo in relieving headache at two hours (75% vs. 58%, p=0.022) (Visser et al. 2004).

**Tolerability.** Rizatriptan is well tolerated and adverse events are usually mild and transient. The incidence of adverse effects was similar after single- and multiple-dose administration (up to 3 doses in 24 hours) and appeared to be dose-related. The most common adverse effect (incidence > 5%) associated with rizatriptan 5 or 10 mg are CNS- or gastrointestinal-related, including fatigue, dizziness, somnolence, and nausea (Kramer et al. 1998). Chest pain is reported by 1-3% of patients after rizatriptan 5 or 10 mg (Goldstein et al. 1998). All adverse effects generally associated with triptan treatment are possible (described in Section 9.1.4.). The overall rate of drug-related adverse effects after a single dose was 22% after rizatriptan 5 mg, 31% after rizatriptan 10 mg, and 16% after placebo. Rizatriptan, like other triptans, is contraindicated in migraine patients with any cardiovascular risk factors (Wellington et al. 2002).

**Tolerability in children.** In two placebo-controlled trials and two open-label multiple attacks studies in adolescents aged 12-17 years, rizatriptan 5 mg was generally well tolerated (Winner et al. 2002, Visser et al. 2004). In the first placebo-controlled trial, 34% of patients after rizatriptan 5 mg and 35% after placebo reported an adverse effect. The most common adverse effects were asthenia, dizziness, dry mouth, nausea, and somnolence. Nausea and somnolence were reported more often after placebo than after rizatriptan. There were no serious drug-related adverse effects (Winner et al. 2002). Results were similar in the second controlled trial. Moreover, in open-label multiple-attack studies (686 patients treating 8734 attacks), drug-related adverse effects were reported by 30% after rizatriptan 5 mg, 30% after rizatriptan 5 mg wafer, and 25% after standard care, the most common adverse events being dizziness, somnolence, and nausea (Visser et al. 2004).

**11. Placebo effect in the treatment of migraine**

Placebo-controlled clinical trials are the gold standard to show the efficacy of drugs. In these, the response to the studied drug should be statistically superior to the response to placebo. This principle is in concordance with IHS guidelines regarding controlled trials of acute migraine medications (International Headache Society Clinical Trials Subcommittee 2000).

Placebos have been reported to improve subjective and objective outcomes in up to 30-40% of adult patients with a wide range of clinical conditions, such
as pain, asthma, high blood pressure, and even myocardial infarction (Beecher 1955, Brown 1998). Patients with migraine can also experience considerable headache relief after placebo. In a meta-analysis of placebo response in 98 trials studying the efficacy of acute migraine treatments in adults using a placebo as a control, headache relief at two hours after placebo was reported by 28.6% of patients, and 8.8% were completely pain-free (Macedo et al. 2006). Another meta-analysis of placebo response in 31 trials comparing the efficacy of different oral triptans and placebo in adults reported a similar response rate of 28.90% (ranging from 17% to 50%) at two hours after placebo, and a pain-free response rate of 6.08% (Loder et al. 2005). In a trial where patients treated moderate or severe migraine attack only with an oral placebo, 37% of patients experienced headache improvement at two hours and 48% within four hours (Jhee et al. 1998).

In clinical trials in children and adolescents with migraine, the placebo responses have generally been much higher than the responses reported in adults. Because of this, a statistical difference between an active treatment and placebo has been challenging to detect, although the responses to active treatments have generally been of a similar magnitude as seen in adults (Lewis et al. 2005). A recent review has evaluated placebo responses in 13 controlled trials of acute migraine treatment in children and adolescents (Fernandes et al. 2008). The placebo responses for pain relief and pain-free rates at two hours were 46% (range 38-53%) and 21% (range 17-26%), respectively. Studies conducted in North American research centers demonstrated higher placebo responses, as did trials that used four-point vs. five-point pain scales. A five-point pain scale might be more sensitive in distinguishing the level of pain in children. Trials with parallel design compared with cross-over design reported higher placebo response rates; the same has also been seen in adult studies (Macedo et al. 2006). One factor probably interacting with the higher placebo response in children is the shorter duration of attacks compared with adults, and thus, a more rapid spontaneous recovery rate.
AIMS OF THE STUDY

Migraine attacks in children and adolescents are painful and disabling, and thus, an effective treatment is needed. A new class of migraine drugs, triptans, were introduced at the beginning of the 1990s and have since been shown to be very effective in the treatment of migraine attacks in adults. Although these drugs are widely used in adults, the treatment of migraine attacks of children and adolescents is still mainly based on paracetamol and ibuprofen or other NSAIDs. These are effective for many patients, but 30% need more powerful treatments. When these studies commenced, hardly any information existed on the efficacy and safety of triptans in children and adolescents. The aim here was to gain information on the efficacy of triptans in children and adolescents as well as to offer a more efficient migraine treatment to this group of patients.

Sleep has a multifold impact on migraine. It is a part of the natural healing process of a migraine attack, and it is the most common and preferred nonpharmacological treatment of a migraine attack in children. It has relevance also in the assessment of drug effects in clinical trials of migraine medicines in children. How a sleeping child should be classified in drug trials is under continual debate. Despite the clinical relevance and common manifestation of sleep in the context of migraine, very little research data on its true frequency exist thus far. An objective here was to gain more information on sleep during migraine attacks.

Specific aims of the studies were as follows:

1. To investigate the frequency of falling asleep and factors influencing this during migraine attacks in children and adolescents aged 4-17 years (Study I).

2. To clarify how the results of a sleeping child should be analyzed in clinical trials with children and adolescents (Studies I-III).

3. To compare the efficacy of intranasally administered sumatriptan and placebo in children and adolescents aged 8-17 years with migraine attacks resistant to NSAID and paracetamol treatments (Study II).

4. To compare the efficacy of oral rizatriptan and placebo in children and adolescents aged 6-17 years with migraine attacks resistant to NSAID and paracetamol treatments (Study III).
5. To evaluate the consistency of response between first and second attacks treated with rizatriptan (Study III).
MATERIALS AND METHODS

1. Ethical issues

The study protocols were approved by the Ethics Committees of the participating hospitals: the Hospital for Children and Adolescents in Helsinki University Central Hospital (Studies II and III), Jorvi Hospital in Espoo (Studies II and III), and Oulu University Central Hospital (Study II). Study I was a prospective study that did not need a new Ethics Committee approval, but the studies during which the material was collected were approved by the Ethics Committees of the Hospital for Children and Adolescents, Jorvi Hospital, and Aurora Hospital in Helsinki. The study protocols of the drug trials (Studies II and III) were approved by The Finnish National Agency for Medicines. The studies were conducted in accordance with the Declaration of Helsinki. Written informed consent from parents of all participating children was obtained before enrolment in Studies II and III. Written assent was obtained from children 12 years of age or older; younger children gave their assent orally.

2. Patient recruitment and follow-up

Study I. The study material, i.e. headache diaries, was collected during the study of optimal drug treatment of childhood migraine performed during 1992-1995 by Dr. Mirja Hämäläinen (Hämäläinen 1997). Headache diaries included here were not included in the analyses of Dr. Hämäläinen’s thesis. All participating children were outpatients of the Hospital for Children and Adolescents, Jorvi Hospital, or Aurora Hospital. Migraine was diagnosed according to IHS criteria for migraine with or without aura (Headache Classification Committee of the International Headache Society 1988).

Study II. Patients were recruited at the headache outpatient clinic set up for the study and run by the author on a weekly basis at the Division of Child Neurology in the Hospital for Children and Adolescents and at the Pediatric Division of Jorvi Hospital. Furthermore, Dr. Mirja Hämäläinen at the Hospital for Children and Adolescents and Dr. Heikki Rantala at Oulu University Central Hospital recruited and followed up some of the patients. Patients were recruited between September 1999 and December 2000, and the trial was completed in March 2001.

Study III. Patients were recruited at the headache outpatient clinic, which was set up for the study and run by the author at the Division of Child
Neurology in the Hospital for Children and Adolescents and at the Pediatric Division of Jorvi Hospital. Furthermore, Dr. Mirja Hämäläinen at the Hospital for Children and Adolescents recruited and followed up some of the patients. Patients were recruited between January 2001 and November 2003, and the trial was completed in February 2004.

**Inclusion criteria in Studies II and III.** Any child aged 8-17 years (Study II) or 6-17 years (Study III) with a body weight of 20 kg or more, referred to a participating hospital or already being treated for migraine at the hospital was eligible to participate in Studies II and III. Migraine was diagnosed according to IHS criteria for migraine with or without aura (Headache Classification Committee of the International Headache Society 1988). Children needed to have at least two migraine attacks per month lasting four hours or more, and to have previously unsatisfactory migraine therapy with paracetamol or NSAIDs. They had to be capable of using a headache diary and a face scale properly.

**Exclusion criteria in Studies II and III.** Exclusion criteria were history of renal, hepatic, or cardiovascular disease or any other disease necessitating continuous daily oral drug therapy. Strong heredity of coronary artery disease in the family, assessed as clinical symptoms in males under 40 years of age or in females under 50 years of age, prevented participation. None of the children received prophylactic drug therapy for migraine at the time of the study.

**Follow-up in Studies II and III.** Before entering the trial, patients were examined in a migraine-free state with complete physical and neurological examinations, a blood sample (complete blood count, sodium, potassium, calcium, inorganic phosphorus, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glucose), and a urine sample (appearance, color, pH, gravity, protein, glucose, ketones) to exclude other etiologies of headache. An EEG or neuroimaging was performed if needed. The pubertal stage of adolescents was assessed by the Tanner scale (Tanner 1962). Patients went through a run-in period (range 0-3.9 months in Study II, and 0-13.7 months in Study III) prior to entering the study. During this period the diagnosis, fulfilment of inclusion criteria, and ability to use the headache diary and pain scale were confirmed. Physical and neurological examinations were performed before and after the run-in period, and after the study drugs were administered. Many of the patients also had additional visits.
3. Patient characteristics

**Study I.** This study included 133 patients with 999 registered migraine attacks. The mean age of the children was 10.8 (range 4.6 to 16.9) years, and 70 (52.6%) were boys.

**Study II.** Altogether 129 patients were recruited to the study, and 94 of these returned their headache diaries. The mean age of these 94 children was 12.4 (SD 2.4, range 8.1-17.5) years, and 51 (54.2%) were boys. Migraine with aura was experienced by 30.9% (n=29/94) of the children. They had a median migraine history of 3.8 (range 0.5-13.5) years, a median attack duration of 8-12 hours, and a median attack frequency of 1 or 2 attacks per week. Patients’ migraine characteristics during the first visit are listed in Table 5.

**Study III.** Altogether 147 patients were recruited to the study, and 116 of these returned their headache diaries. The mean age of these 116 children was 12.0 (SD 2.4, range 6.1-16.1) years, and 63 (54.3%) were girls. Migraine with aura was experienced by 28.5% (n=33/116). They had a median migraine history of 4.0 (range 0.5-12.0) years, a median attack duration of 4-8 hours, and a median attack frequency of 3 or 4 attacks per month. Patients’ migraine characteristics during the first visit are listed in Table 5.

4. Study structure

**Study I.** A prospective study where patients recorded their migraine attacks in a headache diary using either a five-face pain scale, or a 100-mm Visual Analog Scale (VAS) chosen according to the child’s own preference (Figure 2) (Appendix A). A close correlation between the five-face scale and the continuous visual scale has been demonstrated earlier (Maunuksela et al. 1987). To combine information from the two scales, the VAS data were transformed as follows: 0 to ≤12 = grade 1, 13 to ≤37 = grade 2, 38 to ≤62 = grade 3, 63 to ≤87 = grade 4, and 88 to ≤100 = grade 5. Headache intensity was reported at the beginning of the attack, 30 minutes later, and then hourly for a maximum of five hours. Further remarks were made about falling asleep, nausea, vomiting, and other accompanying symptoms. For analyses, attacks were classified according to the mode of ending: 1) attacks that ended in falling asleep (within the first 0.5 hour, between 0.5 and 1 hour, between 1 and 2 hours or 2 hours or more from onset of headache); 2) attacks that ended without sleep (duration less than 2 hours, from 2 to 4 hours, or more than 4 hours); and 3) attacks in which the resolution of symptoms was not registered (duration less than 5 hours or more than 5 hours). For evaluation purposes,
patients were grouped according to their age as follows: patients younger than 8 years, those between 8 and 12 years, and those older than 12 years. The effect of the drugs administered was not analyzed, as the aim of the study was to evaluate what happens in a real clinical situation at home.

**Study II.** The trial was a double-blind, randomized, placebo-controlled, two-way cross-over efficacy study of sumatriptan nasal spray and placebo. Each child treated two migraine attacks at home with study drugs of identical appearance, one being sumatriptan and the other a placebo. Both treatments were given to a child at the visit after the run-in period. They were clearly numbered one (the first treatment) and two (the second treatment) to ensure usage in the proper sequence. The sumatriptan dose was 10 mg for children with a body weight of 20 to 39 kg and 20 mg for those with a body weight of 40 kg or more. Children were instructed to take a single nasal insufflation at the onset of a migraine attack if headache severity was classified as three or more on a five-face pain intensity scale (Figure 2). Rescue medication, NSAIDs or acetaminophen, was allowed at any point if needed, but waiting two hours after taking the study drug was recommended. Headache recurrence after the initial response to the study drug was treated with NSAIDs or acetaminophen, if medication was required.

**Study III.** The trial was a double-blind, randomized, placebo-controlled, three-way cross-over efficacy study of oral rizatriptan and placebo. Each child treated three migraine attacks at home with study drugs packed in capsules of identical appearance, two of them being rizatriptan and one a placebo. Rizatriptan was given twice to test the stability of the treatment effect in two consecutive migraine attacks. All three treatments were given to a child at the visit after the run-in period. They were clearly numbered one (the first treatment), two (the second treatment), and three (the third treatment) to ensure usage in the proper sequence. The rizatriptan dose was 5 mg for children with a body weight of 20-39 kg and 10 mg for those with a body weight of 40 kg or more. Children were instructed to take a single capsule at the onset of a migraine attack if headache severity was classified as three or more on a five-face pain intensity scale (Figure 2). Rescue medication, NSAIDs or acetaminophen, was allowed at any point if needed, but waiting two hours after taking the study drug was recommended. Headache recurrence after the initial response to the study drug was treated with NSAIDs or acetaminophen, if medication was required.
Materials and methods

Table 5. Patients’ migraine characteristics during the first visit in Studies II and III.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study II (n=94)(%)</th>
<th>Study III (n=116)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>70 (74)</td>
<td>87 (75)</td>
</tr>
<tr>
<td>4</td>
<td>23 (25)</td>
<td>27 (23)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Attack frequency per month</td>
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<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>1-2</td>
<td>29 (31)</td>
<td>33 (28)</td>
</tr>
<tr>
<td>3-4</td>
<td>16 (17)</td>
<td>47 (41)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>48 (51)</td>
<td>36 (31)</td>
</tr>
<tr>
<td>Attack duration (hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>4-8</td>
<td>44 (47)</td>
<td>68 (59)</td>
</tr>
<tr>
<td>8-12</td>
<td>26 (28)</td>
<td>32 (28)</td>
</tr>
<tr>
<td>12-24</td>
<td>18 (19)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>over 24</td>
<td>5 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Aura</td>
<td>29 (31)</td>
<td>33 (28)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>90 (96)</td>
<td>112 (97)</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>69 (73)</td>
<td>86 (74)</td>
</tr>
<tr>
<td>Bedridden</td>
<td>93 (99)</td>
<td>116 (100)</td>
</tr>
<tr>
<td>Unilateral headache</td>
<td>54 (57)</td>
<td>82 (71)</td>
</tr>
<tr>
<td>Throbbing headache</td>
<td>61 (65)</td>
<td>109 (94)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>90 (96)</td>
<td>110 (95)</td>
</tr>
</tbody>
</table>

5. Dose selection (Studies II and III)

The selection of dose was based on the mg/body surface area (BSA) observed in adults by using the equation: \( \text{Dose}_{\text{child}} = \text{Dose}_{\text{adult}} \times (\text{BSA}_{\text{child}} / 1.73\text{m}^2) \). The BSA of the child was calculated by the Haycock formula (Haycock et al. 1978): \( \text{BSA (m}^2) = 0.024265 \times \text{Height (cm)}^{0.3964} \times \text{Weight (kg)}^{0.5378} \). Finnish height and weight curves (with plus/minus 2SD) for the appropriate ages were utilized when BSA was changed to kilograms. Sumatriptan 10 mg and rizatriptan 5 mg were selected for children weighing less than 40 kg (but over 20 kg), and sumatriptan 20 mg and rizatriptan 10 mg for those weighing 40 kg or more.
Materials and methods

Figure 2. Pain scales used in Studies I-III.

6. Randomization

Study II. Study drugs and the placebo nasal spray were provided by GlaxoSmithKline (GSK). The 10-mg and 20-mg sumatriptan and placebo nasal sprays were indistinguishable from one another. GSK packed and labeled the study drugs in accordance with a randomization schedule. Randomization was done in the Hospital Pharmacy at Helsinki University Central Hospital by a pharmacist specialized in preparing drugs for clinical trials, but who was not involved in the study. A simple randomization plan generated manually (coin toss method) was used to assign the order (sumatriptan/placebo or placebo/sumatriptan) of each sequentially numbered pair of treatments. The randomization was stratified by dosage (10 and 20 mg).

Study III. Rizatriptan was a commercial product approved for use in adults in Finland (Maxalt®, 5 and 10 mg, Merck&Co). Because a matching placebo was not available, study drugs were packed in capsules for blinding purposes. All capsules were indistinguishable from one another. The Hospital Pharmacy provided, packed, and labeled study drugs in accordance with a randomization schedule. Randomization was done in the Hospital Pharmacy at Helsinki University Central Hospital by a pharmacist specialized in preparing drugs for clinical trials, but who was not involved in the study. A
Materials and methods

simple randomization plan generated manually (coin toss method) was used to assign the order (rizatriptan/rizatriptan/placebo, rizatriptan/placebo/rizatriptan, or placebo/rizatriptan/rizatriptan) of each sequentially numbered set of treatments. The randomization was stratified by dosage (5 and 10 mg).

7. Evaluation of efficacy and adverse effects (Studies II and III)

Headache severity was chosen as the main efficacy variable. The intensity of headache was recorded in a headache diary by using a five-face scale (5 = severe, 3-4 = moderate, 2 = mild, 1 = no pain), which has been validated in children over four years of age (Figure 2) (Maunuksela et al. 1987) (Appendix B and C). Children were asked to record the pain intensity immediately before the treatment, and at 15, 30, and 60 minutes thereafter, continuing hourly for up to seven hours unless the child fell asleep or the symptoms resolved. Furthermore, one and two hours after treatment, the child was asked to assess whether the headache was the same, worse, milder, or absent compared with the initial situation. Headache diaries were filled in by the children themselves. In addition, parents were asked to assess their child’s behavior in a questionnaire covering nausea, mobility, falling asleep, and complaints of pain. Diaries were returned to the investigator at a follow-up visit or by mail.

Primary endpoint. The primary efficacy endpoint was headache relief from severe or moderate pain (≥ grade three) to at least two grades lower two hours after medication. Treatment was classified as successful when pain intensity decreased by at least two grades in the first two hours or the child fell asleep during these two hours and was pain-free upon awakening. Treatment was classified as a failure when pain increased or remained unchanged, decreased by only one grade, or rescue medication was used within two hours.

Secondary endpoints. Secondary endpoints were two-grade headache relief at one, three, and four hours after treatment, complete headache relief at one, two, three, and four hours, the child’s preference of treatments, and the use of rescue medication. If the child fell asleep and was pain-free upon awakening, the treatment was classified as successful at every time-point after falling asleep. If rescue medication was used, the treatment was classified as failure from that time onwards. The same criteria were used when complete pain-free response was assessed. A sleeping child was classified to be pain-free only after waking up without pain. Age and gender may influence the natural
course of migraine, and thus, their effects on treatment response were also analyzed.

**Evaluation of adverse effects.** Children and their parents were asked to observe any adverse events after treatments and report them in the diaries. They were offered the contact information of the investigator to use in any unexpected situation.

8. **Power calculations**

**Study II.** Sample size calculation was based on estimated response rates in previous adult trials. Expected response rates were as follows: response to sumatriptan 60%, response to placebo 40%, response to sumatriptan without response to placebo 36%, and response to placebo without response to sumatriptan 16%. To detect a difference with a power of 80%, a significance level of 5%, and with an estimated drop-out rate of 20-30%, 120-130 patients were required to participate in the trial (Hills et al. 1979).

**Study III.** Sample size calculation was based on estimated response rates in previous adult trials and the response rates in Study II. Expected response rates were as follows: response to rizatriptan 60%, response to placebo 40%, response to rizatriptan without response to placebo 36%, and response to placebo without response to rizatriptan 16%. Furthermore, the three-way cross-over arrangement was estimated to raise the sample size needed by 20%. To detect a difference with a power of 80%, a significance level of 5%, and an estimated drop-out rate of 20-30%, 150 patients were required to participate in the trial (Hills et al. 1979).

9. **Statistical analyses**

The level of statistical significance in all studies and analyses was set at \( p<0.05 \).

**Study I.** Frequency differences in falling asleep in different age and gender groups were analyzed with analysis of variance (ANOVA). The confounding effect of missing data was analyzed with analysis of covariance (ANCOVA). The connection between falling asleep and attack duration was evaluated with \( \chi^2 \)- test. The difference between mean ages was tested with the t-test.

**Study II.** Children who gave complete data about pain intensity after both treatments were included in the primary efficacy analysis. All children who
used at least one treatment were included in the intention-to-treat analysis. Primary efficacy analysis was done with the McNemar nonparametric test for two related samples. Preference and use of rescue medication were analyzed with the sign test. In the intention-to-treat analysis, Generalized Estimating Equation (GEE) analysis (SAS, version 8.1) was applied to calculate differences between the two treatments, and the p-values were then adjusted for period effect. GEE analysis was also used to analyze the effect of age, sex, and treatment period on the response to sumatriptan and placebo. The unpaired data of the first treatment period were analyzed by logistic regression for binary responses. The T-test was used to compare the mean ages of responders and nonresponders to sumatriptan and placebo.

**Study III.** Children who gave complete data about pain intensity after all three treatments were included in the primary efficacy analysis. All children who used at least one treatment were included in the intention-to-treat analysis. The results of the primary efficacy analysis and the intention-to-treat analysis were analyzed separately using logistic models for multiple observations per individual, and were estimated by the GEE method (a logistic model). Stability of the treatment effect in consecutive migraine attacks was analyzed with a model containing the main effects of treatment and period and their interaction term. The effects of treatment, sequence of treatment (rpr, rrp, or prr), period (first, second, or third attack), and carry-over effect in the three-period cross-over design were analyzed to compare the effects of rizatriptan and placebo. The treatment effects between rizatriptan and placebo at different time-points (1, 2, 3, and 4 hours) were compared by McNemar’s nonparametric test for two related samples. In the intention-to-treat analysis, the treatment effects between rizatriptan and placebo at different time-points were tested by logistic regression for binary responses. The effects of age and sex and the usage of rescue medication were analyzed by logistic regression in both primary efficacy and intention-to-treat analyses. The difference between the mean ages of responders and nonresponders to rizatriptan and placebo was tested by the t-test.
RESULTS

1. Frequency of falling asleep during migraine attacks (Study I)

Altogether 999 migraine attacks were registered in the diaries of 133 patients. The mean number of attacks registered by one patient was 7.5 (range 1-49). The visual analog scale (VAS) was used in 409 attacks, and the five-face scale in 590 attacks. The VAS was chosen by older children (mean age 12.1, range 7.6-16.9 years, n=66) than the face scale (mean age 9.5, range 4.6-15.3 years, n=59) (t-test, P<0.0001). Eight patients used both scales. The median maximum pain intensity of all registered attacks was five on the face scale, and 94 on the VAS. The distribution of the maximum pain intensity was similar in both scales.

A total of 329 attacks (32.9%) ended in falling asleep. In 431 attacks (43.1%), the pain resolved without sleep, and in 239 attacks (23.9%) the mode of headache relief was not adequately reported, mostly because the duration of the attack exceeded the five-hour follow-up (n=143, 14.3% of all attacks).

Table 6 presents the sleep frequencies in different age groups. Falling asleep was more common in children under eight years of age than in older patients (ANOVA, p<0.0001), and it was especially common in girls of this age group (girls 70% vs. boys 53%). No significant differences were present in sleep frequencies between older age groups, nor were there age- or gender-related differences in children over eight years of age. Sleeping was more common at the beginning of the attack; in 126 attacks (38%), the child ended up sleeping within the first 30 minutes, in 83 attacks (25%) between 30 minutes and one hour, in 55 attacks (17%) between one and two hours, and in only 65 attacks (20%) after two hours’ observation time. Complete headache relief during the first two hours was more likely in children who slept than in those who did not (80% vs. 38%; χ2, p<0.0001).

Table 6. Falling asleep during migraine attacks in different age groups. Sleep frequency is defined as the proportion (%) of attacks relieved by sleeping in a single patient.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>No. of attacks with sleep/ Total no. of attacks</th>
<th>Sleep frequency, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 years</td>
<td>24</td>
<td>118/209 (57%)</td>
</tr>
<tr>
<td>8-12 years</td>
<td>62</td>
<td>166/503 (33%)</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>47</td>
<td>45/287 (16%)</td>
</tr>
</tbody>
</table>
Of the attacks that resolved without sleep (n=431), 165 (38%) resolved within the first 2 hours, 218 (51%) between 2 and 4 hours, and 48 (11%) in over 4 hours. The study did not analyze the effects of any drug administered, as the main purpose was to see what happens in a real situation at home. Almost all children (n=125/133) used drugs at least in some attacks; the number of drugs varied between one and six.

2. Efficacy of nasal sumatriptan (Study II)

Altogether 129 patients were recruited to the study, and 94 of these returned their headache diaries. Of these patients, 83 used both treatments and 11 used only the first one (sumatriptan n=7; placebo n=4). Patients who used both treatments were included in the primary efficacy analyses (n=83), and all patients who used at least one treatment were included in the intention-to-treat analyses (n=94). Table 7 provides the number of patients, their mean ages, and the mean doses in both treatment groups.

Table 7. Number, mean age, mean weight, and mean dose of patients in each treatment subgroup in Studies II and III.

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>Mean age, years (range)</th>
<th>Mean weight, kg (range)</th>
<th>Mean dose, mg/kg, (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>94 (M 51, F 43)</td>
<td>12.4 (8.1-17.5)</td>
<td>46.7 (22.5-100)</td>
<td>0.36 (0.20-0.50)</td>
</tr>
<tr>
<td>10 mg</td>
<td>31 (M 18, F 13)</td>
<td>10.3 (8.3-13.8)</td>
<td>31.2 (22.5-37.0)</td>
<td>0.33 (0.27-0.44)</td>
</tr>
<tr>
<td>20 mg</td>
<td>63 (M 33, F 30)</td>
<td>13.4 (8.1-17.5)</td>
<td>54.3 (40.0-100.0)</td>
<td>0.38 (0.20-0.50)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>116 (M 52, F 64)</td>
<td>12.0 (6.1-16.1)</td>
<td>45.0 (22.5-84.0)</td>
<td>0.18 (0.12-0.25)</td>
</tr>
<tr>
<td>5 mg</td>
<td>48 (M 20, F 28)</td>
<td>9.9 (6.1-13.9)</td>
<td>31.8 (22.5-39.5)</td>
<td>0.16 (0.13-0.22)</td>
</tr>
<tr>
<td>10 mg</td>
<td>68 (M 32, F 36)</td>
<td>13.5 (10.2-16.1)</td>
<td>54.8 (40.0-84.0)</td>
<td>0.19 (0.12-0.25)</td>
</tr>
</tbody>
</table>

2.1. Primary efficacy analysis. The primary efficacy endpoint (headache relief by two grades on the five-face scale at two hours) was reached clearly more often after sumatriptan than after placebo. Sumatriptan was superior to placebo at already one hour postdose, and it retained its superiority over the four-hour follow-up. Table 8 summarizes the response rates of sumatriptan and placebo in all treated attacks. At two hours, 31% (n=26/83) after sumatriptan and 20% (n=17/83) after placebo were completely pain-free (p=ns). Moreover, 13% (n=11/83) of children after sumatriptan and 12% (n=10/83) after placebo were sleeping at two hours and were pain-free upon waking. Pain-free response rates are summarized in Table 9.
Sumatriptan was preferred by 57% (n=47/83) of children and placebo was by 33% (n=27/83) (p=0.03); and 9 were undecided. Rescue medication was taken by 35% (n=29/83) after sumatriptan, and by 51% (n=42/83) after placebo (p=0.10). The treatment period had no effect on response to either sumatriptan or placebo. There were no differences in pain intensities of the attacks before administration of sumatriptan and placebo, but pain intensity in the attacks treated with sumatriptan 20 mg and placebo appeared to be higher than in the attacks treated with sumatriptan 10 mg (i.e. a higher proportion of patients recorded grade 4 or 5 on the five-face scale; 78 vs. 64%). Age, gender, or puberty stage of the child did not have an impact on the response to sumatriptan. Young age slightly increased the positive response to placebo (mean age 11.74 years for placebo responders vs. 12.71 years for nonresponders at two hours; p=0.07), but gender or puberty stage had no effect on response to placebo. The efficacy rates were similar in children receiving 10-mg and 20-mg treatments. Headache recurrence after initial relief was reported by four children after sumatriptan and by four children after placebo.

Table 8. Headache relief by two grades in 83 children after sumatriptan and placeboS in Study II and in 96 patients after rizatriptan and placeboR in Study III. Primary efficacy analyses. Difference from placebo, * p<0.001; Δ p≤ 0.01.

<table>
<thead>
<tr>
<th></th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>42/83 (51%)Δ</td>
<td>53/83 (64%)Δ</td>
<td>55/83 (66%)Δ</td>
<td>56/83 (67%)Δ</td>
</tr>
<tr>
<td>PlaceboS</td>
<td>24/83 (29%)</td>
<td>32/83 (39%)</td>
<td>37/83 (45%)</td>
<td>39/83 (47%)</td>
</tr>
<tr>
<td>1st Rizatriptan</td>
<td>48/96 (50%)Δ</td>
<td>71/96 (74%)*</td>
<td>79/96 (82%)*</td>
<td>80/96 (83%)*</td>
</tr>
<tr>
<td>2nd Rizatriptan</td>
<td>53/96 (55%)Δ</td>
<td>70/96 (73%)*</td>
<td>73/96 (76%)*</td>
<td>73/96 (76%)*</td>
</tr>
<tr>
<td>PlaceboR</td>
<td>28/96 (29%)</td>
<td>35/96 (36%)</td>
<td>39/96 (41%)</td>
<td>42/96 (44%)</td>
</tr>
</tbody>
</table>

2.2. Intention-to-treat analysis. All 94 children who used at least one treatment were included in the analyses. Altogether 90 children received sumatriptan (10 mg, n=29; 20 mg, n=61) and 87 placebo. Sumatriptan was superior to placebo already 30 minutes after treatment (headache relief, n=28/90 (31%) vs. n=14/87 (16%), p=0.03), and even more clearly thereafter (Table 10). No significant difference was present in complete pain-free response, as 32% (n=29/90) of patients after sumatriptan, and 21% (n=18/87) after placebo were pain-free at two hours. Rescue medication was taken more often after placebo (51%; n=44/87) than after sumatriptan (32%; n=29/90) (p=0.03).
Some children had detected a taste difference between sumatriptan and placebo nasal spray, which could have caused unblinding of the treatments, and thus affecting the results of the second treatment period. Although statistical analyses revealed no sign of a period or carry-over effect, the results of the first period alone were also analyzed. The superiority of sumatriptan was even more obvious in this analysis. The primary efficacy endpoint was reached at one hour in 50% (n=23/46) of attacks after sumatriptan and in 21% (n=10/48) after placebo (p=0.004), and at two hours in 74% (n=34/46) of attacks after sumatriptan, and in 33% (n=16/48) after placebo (p<0.001).

2.3. Adverse effects. Adverse effects were reported by 41 of 94 patients (44%) and in 35 of 90 attacks (39%) after sumatriptan and 7 of 87 attacks (8%) after placebo. No serious adverse effects were observed. Bad taste of the drug was the most commonly reported complaint (n=30/90 (33%) attacks after sumatriptan, n=5/87 (6%) after placebo; p<0.001). Other reported adverse effects were vomiting together with a bad taste (three after sumatriptan, one after placebo), nausea together with a bad taste (one after sumatriptan), nausea (two after sumatriptan, one after placebo), abdominal pain (one after placebo), stiffness in jaws (one after sumatriptan), and feeling of lightheadedness (two after sumatriptan). The incidence of adverse effects was similar in gender and age groups, but more children taking sumatriptan 20 mg experienced adverse effects than those taking sumatriptan 10 mg (44% vs. 28%).

<table>
<thead>
<tr>
<th></th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>15/83  (18%)</td>
<td>26/83 (31%)</td>
<td>38/83 (45%)</td>
<td>42/83 (51%)</td>
</tr>
<tr>
<td>PlaceboS</td>
<td>11/83  (13%)</td>
<td>17/83 (20%)</td>
<td>27/83 (33%)</td>
<td>37/83 (45%)</td>
</tr>
<tr>
<td>1st Rizatriptan</td>
<td>14/96  (15%)</td>
<td>34/96 (35%)*</td>
<td>44/96 (46%)*</td>
<td>48/96 (50%)*</td>
</tr>
<tr>
<td>2nd Rizatriptan</td>
<td>13/96  (14%)</td>
<td>30/96 (31%)*</td>
<td>40/96 (42%)*</td>
<td>42/96 (44%)*</td>
</tr>
<tr>
<td>PlaceboR</td>
<td>10/96  (10%)</td>
<td>17/96 (18%)</td>
<td>17/96 (18%)</td>
<td>21/96 (22%)</td>
</tr>
</tbody>
</table>

Table 9. Complete pain-free response in 83 children after sumatriptan and placeboS in Study II and in 96 patients after rizatriptan and placeboR in Study III. Primary efficacy analyses. Difference from placebo; *p<0.05.
Table 10. Headache relief by two grades in 90 attacks after sumatriptan, and in 87 attacks after placeboS (Study II) and in 212 attacks after rizatriptan and 106 attacks after placeboR (Study III). Intention-to-treat analyses. Difference from placebo, * p<0.001; Δ p≤ 0.01.

<table>
<thead>
<tr>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>48/90 (53%)Δ</td>
<td>60/90 (67%)*</td>
<td>62/90 (69%)Δ</td>
</tr>
<tr>
<td>PlaceboS</td>
<td>25/87 (29%)</td>
<td>33/87 (38%)</td>
<td>40/87 (46%)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>109/212 (51%)*</td>
<td>152/212 (72%)*</td>
<td>164/212 (77%)*</td>
</tr>
<tr>
<td>PlaceboR</td>
<td>30/106 (28%)</td>
<td>41/106 (39%)</td>
<td>45/106 (43%)</td>
</tr>
</tbody>
</table>

3. Efficacy of rizatriptan (Study III)

Altogether 147 patients were recruited to the study. Of these, 96 used all three treatments, 10 used two treatments (rizatriptan, n=13; placebo, n=7), 10 used one treatment (rizatriptan, n=7; placebo, n=3), and 31 used no treatments. Patients who used all three treatments were included in the primary efficacy analyses (n=96), and all patients who used at least one treatment were included in the intention-to-treat analyses (n=116). Table 7 summarizes the number of patients, their mean ages, and the mean doses in the treatments groups (5 and 10 mg).

3.1. Primary efficacy analysis. The primary efficacy endpoint at two hours was reached twice as often after both treatments of rizatriptan as after placebo. Both doses of rizatriptan were superior to placebo at already one hour postdose, and remained superior over the four-hour follow-up. Table 8 summarizes the response rates in all treated attacks. Those children who slept at the current time-point and were pain-free or markedly relieved upon awakening were classified as having a positive treatment response (at two hours: 16 patients after the first rizatriptan, 15 patients after the second rizatriptan, 10 patients after placebo). Even had these sleeping children been classified as having a treatment failure, rizatriptan would have remained superior to placebo in this analysis (p<0.001 at two hours). No difference was found in total pain-free response after rizatriptan and placebo at one hour, but from two hours onwards both doses of rizatriptan were numerically and statistically more effective than placebo in giving complete painlessness. Pain-free response rates are shown in Table 9. The effect of rizatriptan remained very stable over the two treated attacks.

Rescue medication was taken by 18% (n=17/96) and 22% (n=21/96) of patients after the first and the second dose of rizatriptan, and by 40% (n=38/96) of patients after placebo (p=0.004 and p=0.017 between 1st and 2nd
rizatriptan and placebo, respectively). Treatment was classified as excellent or good by 52% (n=50/96) and 53% (n=51/96) of children after the first and the second dose of rizatriptan, but only by 34% (n=33/96) after placebo (p=0.015 and p=0.014 between 1st and 2nd rizatriptan and placebo). No difference existed in pain intensity before administration of rizatriptan and placebo. Nor was there a difference in pain intensity in attacks treated with rizatriptan 10 mg compared with those treated with 5 mg. Before the first and the second treatment with rizatriptan, 63% (n=60/96) and 75% (n=72/96) of patients, respectively, reported headache intensity as being grade 4 or 5 on the five-face scale; 72% (n=69/96) of patients before placebo reported the same.

No carry-over, period, or sequence effect was detected by GEE analysis. Sex had no impact on response to rizatriptan or placebo. When attack was first treated with rizatriptan, children reporting headache relief at two hours were younger than nonresponders (mean age 11.56 years for responders vs. 13.22 for nonresponders; P=0.003). Similarly, younger children who used rizatriptan 5 mg tended to benefit more from treatment in the first rizatriptan period than did those who used the 10-mg dose (log reg, p=0.014). The same effect was not seen in the second period of rizatriptan. Age otherwise did not have an effect on response to rizatriptan or placebo, and the results were similar in children receiving the 5-mg and 10-mg doses.

3.2. Intention-to-treat analysis. All 116 children who used at least one treatment were included in the analysis. Altogether 212 attacks were treated with rizatriptan and 106 attacks with placebo. Rizatriptan dose was 10 mg in 123 attacks and 5 mg in 89 attacks. The two-grade headache relief was reached in 51% (n=109/212) of attacks after rizatriptan, and in 28% (n=30/106) of attacks after placebo one hour postdose (p<0.001). Rizatriptan was superior to placebo also at two, three, and four hours thereafter; response rates are listed in Table 10. Younger children reported headache relief more often after rizatriptan (mean age 11.70 years for responders vs. 12.71 years for nonresponders; p=0.008). There was no similar difference in response to placebo. No difference was found in complete pain-free response after rizatriptan (painless; 14%, n=29/212) and placebo (9%, n=10/106) one hour after treatment (p=0.28). However at two hours, pain-free response was more often reached after rizatriptan (32%, n=67/212) than after placebo (18%, n=19/106)(p=0.011). Rescue medication was taken by 22% (n=47/212) of patients after rizatriptan and by 40% (n=42/106) after placebo (p=0.001). Headache recurrence after initial relief was reported after 5% (n=10/212) of
attacks treated with rizatriptan and after 4% (n=4/106) of attacks treated with placebo (p=0.70).

The results of the first treatment period were also analyzed separately to exclude any period effect, although no period or carry-over effect was detected in GEE analysis. Rizatriptan was more effective than placebo in relieving headache already at one hour (rizatriptan 43%, n=34/79 vs. placebo 24%, n=9/37; p=0.055), even more clearly at two hours (rizatriptan 68%, n=54/79, placebo 41%, 15/37; p=0.005), and remained superior to placebo also at three and four hours.

3.3. Adverse effects. Adverse effects were reported by 14% of all patients (n=16/116), in 9% of attacks (n=20/212) after rizatriptan and 2% of attacks (n=2/106) after placebo (p=0.025). No serious adverse effects were observed. Four patients reported similar adverse effects after both treatments of rizatriptan: one experienced tiredness and dry mouth, one felt a burning sensation in the head, one had flushed cheeks, and one had pain in the ankles. Six children who used both treatments of rizatriptan reported adverse effects after the first rizatriptan, but not after the second (one reported tiredness, one nausea, one faintness and nausea, one had flushed cheeks, one had pain in the cheeks, and one pressure in the throat). Five children who used both treatments of rizatriptan reported adverse effects after the second rizatriptan, but not after the first (three reported tiredness, one vomiting, and one pressure in the throat, cheeks, and head). Furthermore, one child who used only one rizatriptan reported feeling strange after the treatment. Two children experienced adverse effects after placebo (one reported tiredness, and one vomiting). No differences in the incidence of adverse effects were observed for sex and age groups; however, slightly more children taking the 10-mg dose of rizatriptan experienced adverse effects than those taking the 5-mg dose (12% vs. 6%; p=0.12).
DISCUSSION

1. Sleep and migraine

Sleep and migraine certainly seem to be related in many respects. Sleep can either relieve or induce migraine headaches. Insufficient sleep is a well-known headache trigger, and children with migraine have reported more sleep disturbances, such as difficulties in falling asleep, daytime sleepiness, night-awakenings, bruxism, and snoring, than healthy controls. The extent of sleep disturbance correlated well with the severity of the migraine symptoms (e.g. frequency, pain intensity) (Miller et al. 2003, Gilman et al. 2007), but whether headache leads to sleep disturbance or sleep disturbance leads to headache or whether these are separate entities, remains obscure. The role of sleep in the resolution of headache and as part of the natural healing process of migraine attack in both adults and children has long been known. The observation that sleep resolves migraine attacks was first made over 100 years ago by Liveing (Liveing 1873, Blau 1982).

Sleep and resting were cited as the primary treatment option for migraine by 28% of Canadian children; of these only one-third used pain medication during a 10-year follow-up time (Dooley et al. 1995). In our study, nearly all patients used pain medication, mainly NSAIDs or paracetamol (125/133), the effect of which was not analyzed further. Patients had all been referred to specialized healthcare by a general practitioner (GP). They probably suffered from more complicated disease and most likely more often used pain medication than those children who managed with GP treatment, or even without healthcare consultation. Sleep and resting without drug treatment are probably effective and sufficient only in mild migraine attacks. Use of drugs likely did have an effect on headache duration and sleep frequency in Study I. However, the purpose of that study was to evaluate migraine-related sleep in a real clinical situation, where most patients at least occasionally use pain medication.

According to Study I, falling asleep during a migraine attack happens very frequently. Most children (68%) at least occasionally slept during a migraine attack. Sleeping was especially common during the first hour (64% of all attacks relieved by sleep), and those children who were able to sleep were more likely pain-free (80%) at two hours compared with those who did not (38%). A similar finding has been reported in adults; 50% of those who slept were pain-free at three hours compared with 31% of those who did not (Wilkinson et al. 1978).
In children younger than eight years, sleeping was more common than in older age groups. Over half of all attacks (57%) in this age group were relieved during sleeping, the mean sleep frequency (defined as the proportion of attacks relieved by sleep in a single patient) being 62%. This was even more pronounced in girls (70%). No sleep frequency difference was observed between children aged 8-12 years (34%) and those over 12 years (24%). The lower tendency for sleep in older children might be explained by stronger and longer attacks, as headaches in general have been reported to disturb sleep (Bruni et al. 1997). In Study I, although the median maximum pain intensity was high and comparable in both VAS and face scale, the attacks registered with VAS appeared to generally be more painful than attacks registered with face scale. In addition, the duration of attacks registered with VAS more often exceeded the five-hour registration maximum of the headache diary (22% of all attacks registered with VAS) than those registered with the face scale (9% of all attacks registered with face scale). Children who chose to use VAS were older than children who used face-scale (mean ages 12.1 and 9.5 years, respectively), thus, older children appear to have more painful and longer attacks than younger children. A similar trend has been reported in previous trials (Mortimer et al. 1992a, Wöber-Bingöl et al. 2004). Overall, pain intensity and duration of migraine attacks seem to increase with age, and these may be linked to a lower tendency for falling asleep during an attack.

In drug studies of sumatriptan and rizatriptan (Studies II and III), falling asleep was not as common as in the epidemiological study (Study I). In Study II, 13% of patients after sumatriptan and 12% after placebo were sleeping at two hours. In Study III, 17% and 16% after the first and second dose of rizatriptan, respectively, and 10% after placebo were sleeping at two hours. Lower values might be due to patients’ commitment to the study protocol, as they probably tried to stay awake to be able to fill out their headache diaries.

Information about sleep related to migraine attacks in children is important in clinical drug trials and in drafting guidelines on the evaluation of migraine treatments in children, specifically on how to classify a sleeping child. Is it correct to assume that a child who falls asleep after a study drug has experienced headache relief, or should he/she be omitted from the analysis or be classified as a treatment failure because correct registration of pain intensity has not been done. According to Study I, children and adolescents’ falling asleep during migraine attacks is so frequent, that results would be distorted if a sleeping child is automatically excluded from analyses or classified as a treatment failure. In Studies II and III (and in all previous trials of our study group), sleeping was assessed as being a sign of headache relief,
and thus, a sleeping child was classified as having a positive response to the study drug. As placebo responses remained constant and low (close to the values generally observed in migraine treatment trials with adults), falling asleep most likely reflects true headache relief. In considering the results of Studies I, II, and III, this seems to be the correct approach, and thus, can be recommended for future migraine treatment studies in children adolescents. This interpretation has recently also been adopted by The European Medicines Agency’s (EMEA), which recommended in its ‘Guideline on clinical investigation of medicinal products for the treatment of migraine in children and adolescents’ that falling asleep at two hours after the study agent could be used as an efficacy endpoint in studies of acute treatment of migraine in children (European Medicines Agency 2006).

Overall, sleep probably can provide headache relief without other treatments only in mild migraine attacks. It can, however, improve recovery from migraine attack when combined with drug treatment, and is also a sign of headache relief, as a severe headache impedes a patient from falling asleep.

2. Efficacy of intranasal sumatriptan

Sumatriptan was more effective than placebo in relieving migraine pain already 30 minutes after treatment and remained superior throughout the follow-up. Two hours after medication, headache relief by two grades after sumatriptan was experienced nearly twice as often (64%) as after placebo (39%). No difference in response rates existed between sumatriptan 10 and 20 mg. One-third of the patients (31%) were completely pain-free after sumatriptan at two hours; the response compared with after placebo (20%) was not, however, significant. Other endpoints favored sumatriptan, as children subjectively preferred sumatriptan over placebo, and also required less rescue medication after sumatriptan.

Efficacy rates in Study II agree with efficacy rates of sumatriptan 20 mg nasal spray reported previously in adult studies. In these, headache relief response rates have generally ranged between 55% and 78%, and complete pain-relief response rates between 26% and 42% (Perry et al. 1998, Dahlof 1999).

An earlier parallel-group study of 510 adolescents aged 12-17 years, compared sumatriptan nasal spray at doses of 5, 10, and 20 mg with placebo in the treatment of a single migraine attack. The response rates for headache relief at two hours were 66%, 64%, and 63%, respectively, and 53% for
placebo. As the placebo response rate was high, only the response to sumatriptan 5 mg reached statistical significance (Winner et al. 2000). Complete pain relief at two hours was achieved by 36% of patients after sumatriptan 20 mg and by 25% after placebo (p < 0.05). The second trial by the same authors compared the efficacy of sumatriptan nasal spray 5 and 20 mg with placebo in a parallel-group single-attack study in 738 adolescents aged 12-17 years (Winner et al. 2006). Sumatriptan 20 mg provided greater headache relief than placebo at 30 minutes and at two hours (42% and 68% after sumatriptan vs. 33% and 58% after placebo), but did not reach significance at one hour. The response rates after sumatriptan 5 mg were slightly higher than after placebo, but were not significant. Response rates to sumatriptan in both of these trials are of a similar magnitude to Study II. However, in our study, the placebo response rates were markedly lower, and consequently, the differences between placebo and active treatment were more obvious. In Study II, headache recurrence after initial relief was reported by only four children after sumatriptan (5%) and by four children after placebo (5%). That is clearly less than is generally seen in adults (30-46%) (Dahlof 1999), and less than in two other studies in adolescents (16% and 24% after sumatriptan 20 mg) (Winner et al. 2000, 2006). The discrepancy with adult studies might be explained by shorter migraine attacks in children and adolescents than in adults. The reason for lower headache recurrence in Study II compared with other adolescent studies remains, however, unknown.

Only one placebo-controlled trial of efficacy of intranasal sumatriptan in children under 12 years has been published (Ueberall et al. 1999). This small two-way cross-over trial of 14 children aged 6-10 years, reported a headache relief response rate of 86% after sumatriptan 20 mg, and 43% after placebo at two hours postdose. Complete pain-free response at two hours was achieved by 64% after sumatriptan, and by 14% after placebo. Response rates were higher than in Study II and similar to those previously reported in two open-label studies in children after subcutaneous sumatriptan (MacDonald 1994, Linder 1996). There was a clear methodological difference to Study II, as in our study a sumatriptan dose of 10 mg was mainly used in children under 10 years of age (in children weighing less than 40 kg).

A cross-over study design allows a smaller sample size to be used, as patients serve as their own controls. This is especially advantageous when studying treatments in children since smaller number of subjects need to be predisposed to a treatment. Cross-over study designs have, however, the potential for period or carry-over effects, which could skew the results. In
Discussion

Study II, this seemed unlikely according to the statistical analyses. Because one-third of the children could detect a taste difference between sumatriptan and placebo, we analyzed the results of the first treatment period alone to exclude the effect of possible unblinding of the treatments. In this analysis, sumatriptan was even more efficacious than in the primary efficacy analysis (headache relief rate of 74% at two hours), and response to placebo also remained unchanged (33%).

3. Tolerability of intranasal sumatriptan

Although Study II was not specifically designed to study the safety and tolerability of sumatriptan nasal spray, adverse effects were carefully recorded in headache diaries. Sumatriptan was well tolerated, and serious adverse effects were not observed. The most commonly reported adverse effect was a bad taste of the drug, which sometimes was followed by nausea and vomiting. Adverse effects after sumatriptan not connected to the bad taste of the drug were sporadic (n=5/90 attacks) and did not differ from those after placebo (n=2/87 attacks). Similar findings have been reported in all other sumatriptan nasal spray efficacy trials in children and adolescents (Ueberall et al. 1999, Winner et al. 2000, 2006), as well as in two one-year open-label tolerability trials where drug-related adverse effects (taste disturbance excluded) were observed in 4% and 7% of patients (Rothner et al. 2000, Natarajan et al. 2004). In Study II, children taking the 20-mg dose of sumatriptan (mean dose 0.38 mg/kg) reported more adverse effects than those taking the 10-mg dose (0.33 mg/kg) (44% vs. 28%). Also the other two adolescent trials reported similar findings, with overall incidence of adverse effects increasing with larger sumatriptan dosages (Winner et al. 2000, 2006). In one-year tolerability trial, drug-related adverse effects were similar after 10-mg and 20-mg sumatriptan doses (33% and 31%, respectively) (Rothner et al. 2000).

4. Efficacy of rizatriptan

Rizatriptan seemed to be highly effective in treating of migraine attacks in children and adolescents. At two hours after the first and second dose of rizatriptan, 74% and 73% of patients, respectively, experienced headache relief, and 35% and 31% achieved complete pain-free response. Headache relief and complete pain-free response were achieved by 36% and 18% of patients, respectively, after placebo. Both doses of rizatriptan were statistically superior to placebo in relieving headache from one hour onwards and offering a complete pain-free response from two hours onwards. The
results were similar in patients receiving the 5- and 10-mg doses; however, in the intention-to-treat analyses, younger children reported headache relief at two hours more often after rizatriptan than older children (mean age 11.70 years for responders vs. 12.71 years for nonresponders). All other endpoints also favored rizatriptan, as rescue medication was needed more often after placebo, and children’s opinions of the treatment were more positive towards rizatriptan.

Efficacy of rizatriptan in Study III was comparable with the response rates seen in previous trials in adults. In these, headache relief at two hours after rizatriptan 5 or 10 mg has generally been reported by 59-77% of patients (after placebo by 25-40%) (Dooley et al. 1999, Ferrari et al. 2001), and complete pain-free response by 25-44% (after placebo by 7-10%).

Rizatriptan efficacy in Study III was of similar magnitude as in two previous placebo-controlled trials in adolescents. In these single-attack, parallel-group studies with rizatriptan 5 mg in patients aged over 12 years, headache relief was reported by 66% and 68.2% two hours postdose (Winner et al. 2002, Visser et al. 2004). However, no statistical benefit of rizatriptan was shown because of the high placebo response rates of 56% and 68.8%. Interestingly, the placebo response was lower when attacks were treated on weekends (36% and 58%), and statistically superior headache relief to placebo was reached by rizatriptan. The authors suggested that the reason for this difference was probably delayed treatments on schooldays, and thus, spontaneous attack relief by the time the study drug was administered. Overall, headache relief response rates at two hours after rizatriptan were slightly higher in Study III than in these two other studies. This might be explained by the higher rizatriptan dose of 10 mg that was mainly used in children over 12 years of age (for those weighing over 40 kg) in our study. Headache recurrence after initial relief in Study III was rare, reported by 5% of children after rizatriptan, and by 4% after placebo. This is slightly less than the figure reported in the other adolescent trial (14%)(Winner et al. 2002) and markedly lower than that seen in adult rizatriptan trials (29-47%)(Jhee et al. 2001).

Our study was designed to test not only the efficacy of rizatriptan, but also the consistency of response over two treated migraine attacks. As in the adult placebo-controlled study with three or four attacks treated with rizatriptan (Kramer et al. 1998), efficacy in Study III was consistent over the two treated attacks. There was no sign of tolerance to the therapeutic effect of rizatriptan. In two open-label multiple-attack one-year studies in adolescents aged 12-17 years treated with rizatriptan 5 mg (tablet or wafer), the two-hour headache
relief response also remained constant over the treated attacks; the overall response rate was 77% (Visser et al. 2004). Similar findings have been reported in adults with long-term use of rizatriptan (Gobel et al. 2001).

Rizatriptan is absorbed rapidly, which offers a therapeutic benefit when treating children and adolescents, who generally have shorter migraine attacks than adults. In Study III, rizatriptan was encapsulated for blinding purposes, which might have delayed the onset of the therapeutic action of the drug. Encapsulation of sumatriptan tablets has previously been demonstrated to increase the median time to meaningful headache relief by 17 minutes in adults (Fuseau et al. 2001). As the maximum concentration of rizatriptan during and between migraine attacks is achieved in one hour in adults (Cutler et al. 1999, Lee et al. 1999), this potential delay in absorption likely did not affect the results markedly at two hours postdose or later. In addition, any effect of the encapsulation on rizatriptan absorption most likely would lead to underestimation of efficacy. Another methodological concern in the cross-over study design is a possible period effect on results. Although statistical analyses revealed no sign of period or carry-over effect, the results of the first treatment period alone were analyzed as in the previous Study II. Also in this analysis rizatriptan was superior to placebo at one hour and thereafter, headache relief rates at two hours being 68% for rizatriptan and 41% for placebo.

5. Tolerability of rizatriptan

Like the sumatriptan study, Study III was not specifically designed to investigate the safety and tolerability of rizatriptan, but adverse effects were again very carefully recorded in the headache diaries. Adverse effects were reported in 9% of the attacks after rizatriptan and in 2% of the attacks after placebo. Slightly more adverse effects were reported after rizatriptan 10 mg (mean dose 0.19 mg/kg; 12%) than after 5 mg (0.16 mg/kg; 6%). Adverse effects were mild in nature, and rizatriptan seemed to be well tolerated in all age groups. Four patients reported similar adverse effects after both treatments of rizatriptan. If encapsulation affected the rate or extent of rizatriptan absorption, it could have led to an underestimation of the adverse effects.

Rizatriptan 5 mg was well tolerated also in another controlled adolescent trials (Winner et al. 2002, Visser et al. 2004) as well as in two one-year multiple-attack trials (Visser et al. 2004). Adverse effects in controlled trials were reported by 34% and 30% of patients after rizatriptan and by 35% and
25% of patients after placebo, respectively. The most commonly reported adverse effects were asthenia, dizziness, dry mouth, and somnolence. The incidence of drug-related adverse effects was comparable with that reported in adults, and did not differ from that of placebo or standard care (Wellington et al. 2002, Visser et al. 2004).

6. Placebo response and migraine

The placebo response rates in clinical trials in children and adolescents with migraine have generally been much higher than the figures reported in adult studies. One probable reason for this is that migraine attacks in children and adolescents are shorter than in adults, and thus, spontaneous recovery rates are faster. A high placebo response rate renders detection of the true difference between active treatment and placebo more challenging. In US-based trials with sumatriptan nasal spray and rizatriptan, the response rates to active treatments have been similar to those in Studies II and III, and also similar to those seen in adults, but placebo responses have been so high, especially in rizatriptan studies, that a statistical difference has failed to emerge (Winner et al. 2002, Visser et al. 2004). In nasal sumatriptan studies, a significant difference to placebo has sometimes been reached, although placebo relief at two hours has repeatedly been over 50% (Winner et al. 2000, 2006).

In our studies of nasal sumatriptan (Study II) and rizatriptan (Study III), the placebo response remained very stable over the two studies. It was also in the same range as previously described in an ibuprofen-paracetamol trial conducted by our group with similar study methods (Hämäläinen et al. 1997c). The placebo responses in these studies have generally ranged between 36% and 39%; these figures are about 10% higher than those in adult studies (Loder et al. 2005, Macedo et al. 2006).

Many factors may contribute to a placebo response rate: study design, the pain scale used, the study center, cultural aspects such as a child’s eagerness to please the doctor, a child’s previous experiences and expectations of migraine treatment, and other treatment interaction factors, e.g. delays in drug administration (Lewis et al. 2005, Fernandes et al. 2008). A methodological difference in Studies II and III compared with US studies, is that we used a five-face pain scale instead of the four-point validated rating scale preferred in the US ones. The five-point scale may be more sensitive in distinguishing pain level in children, and thus, would be more suitable for use in trials with children. In our studies, falling asleep was classified as a sign of
headache relief. This seems to be the correct approach, as it does not lead to elevated placebo response rates. The US studies had a parallel study design, in contrast to Studies II and III, which had a cross-over design. Trials with parallel design have reported overall higher placebo response rates than those with cross-over design; this has also been seen in adult studies (Macedo et al. 2006). All children who participated in Studies II and III had rather severe migraine symptoms, which were not relieved by NSAIDs or paracetamol. This difference in the inclusion criteria offers one possible explanation for the overall lower placebo responses in Studies II and III than in American studies.

In pain treatment trials, children have generally shown elevated placebo response rates, and the response rate is suggested to be even more pronounced in adolescents (Goodenough et al. 1997). In Study II, placebo response was actually slightly higher in younger subjects. This may be explained by the shorter attacks of young children compared with adolescents, and especially in Study II, by the lower baseline severity of the attacks treated with sumatriptan 10 mg. The same age difference in placebo response was not seen in the rizatriptan study (Study III), nor was there a difference in pain intensity between attacks treated with rizatriptan 5 and 10 mg. A recent review evaluating placebo response in 13 controlled trials of acute migraine treatment in children and adolescents (including Studies II and III of this work) also did not confirm a greater placebo response in younger children (Fernandes et al. 2008). One ibuprofen study has demonstrated a higher placebo response rate in girls (67%) than in boys (43%) (Lewis et al. 2002b), but we found no sex difference in response to either placebo or active treatment.

Recently, both physicians and parents have questioned the appropriateness of using placebo control groups in clinical drug trials with children (Caldwell et al. 2002, Caldwell et al. 2003, Linde et al. 2003, Caldwell et al. 2004). Migraine is a condition in which symptoms appear occasionally, and there is no risk of the disease worsening or any effect on growth and development if symptoms remain untreated. There is probably a greater risk to children with migraine if ineffective or harmful drugs are approved without appropriate assessment in randomized trials than in a short-term use of a placebo in a carefully designed controlled trial (Emanuel et al. 2001, Linde et al. 2003).
7. Clinical implications

Sleeping during migraine attacks is very common. It can both improve recovery from migraine attack when combined with a drug treatment, and serve as a sign of headache relief, as a severe headache impedes a patient from falling asleep. Findings in Studies I, II and III support that falling asleep should be classified as a sign of headache relief in clinical drug trials with children and adolescents. Distortion of results would likely occur if a sleeping child is automatically excluded from analyses or classified as a treatment failure. In Studies II and III, this approach was successfully adopted, as placebo response remained low, suggesting that falling asleep probably reflects true headache relief.

The current standard treatment for migraine attacks in children and adolescents is NSAIDs, especially ibuprofen (10 mg/kg; maximum dose 40 mg/kg/day) and paracetamol (15 mg/kg; maximum dose 60 mg/kg/day). Paracetamol is slightly more rapid in action, but the overall efficacy of ibuprofen seems to be better (Hämäläinen et al. 1997c). At two hours, 60% of patients were completely pain-free after ibuprofen.

Study II and also other published data (Winner et al. 2000, 2006) suggest that sumatriptan nasal spray can be safely and effectively used at the adult dose (20 mg) to treat migraine attacks in adolescents aged over 12 years. Nasal sumatriptan could be beneficial particularly in children who need more effective drugs than NSAIDs. Sumatriptan nasal spray is especially useful when nausea or vomiting occurs and oral administration of drugs is not desirable. Nasal sumatriptan 10 mg is now licensed in the European Union for treatment of migraine attacks in adolescents over 12 years of age; one of the pivotal studies for approval was Study II of this thesis. No difference was observed in efficacy or safety of nasal sumatriptan between children aged 8-12 years and older children in Study II, but because relatively few children in the younger age group have participated in controlled trials to date, the efficacy and safety is not well documented and further studies are required.

In Study III, rizatriptan was found to be an effective and well-tolerated treatment for migraine attacks in children over six years of age and adolescents. Treatment effect remained stable over two consecutive attacks. Two other controlled trials have reported good efficacy rates of rizatriptan 5 mg in adolescents aged over 12 years, although the high placebo response did prevent emergence of statistical significance (Winner et al. 2002, Visser et al. 2004). In two open-label multiple-attack studies, also the tolerance of
rizatriptan 5 mg in adolescents was good (Visser et al. 2004). In Study III, the rizatriptan dose for adolescents weighing over 40 kg was 10 mg, which seemed to offer more efficacy than the 5-mg dose and a similar adverse effect rate. Study III suggests that rizatriptan could be safely and effectively used to treat migraine attacks in adolescents aged over 12 years. Neither the efficacy nor the tolerance of rizatriptan in children from 6 to 12 years of age differed from that of older children. The number of patients and attacks treated in this age group is, however, small, and more studies are needed before the efficacy and safety can be ensured and rizatriptan can be recommended to wider use.

When the efficacy of nasal sumatriptan and rizatriptan are compared, rizatriptan appears to be slightly more effective (about 10% from two hours onwards). The complete pain-free response after rizatriptan also reached statistical significance compared with placebo; however, the pain-free response rates in percentages after rizatriptan and sumatriptan were quite similar. Head-to-head comparisons are impossible to do based on only these two studies, and, as in adults, pain relief response to triptans can vary greatly between children. Moreover, many other individual factors and migraine characteristics need to be considered in choosing an optimal migraine therapy for each child. It would be important, however, to also get oral triptan licensed for children and adolescents as an alternative to sumatriptan nasal spray, as many children dislike using an intranasal spray because of the bad taste.
CONCLUSIONS

Study I: Sleeping during migraine attacks is very common. Most affected children (68%) at least occasionally sleep during an attack. Falling asleep is especially common during the first hour after attack onset. Children who are able to sleep soon after attack onset are more likely pain-free at two hours than those who do not sleep. Sleeping probably both improves recovery from a migraine attack and signals headache relief. In children younger than 8 years, sleeping is more common than in older age groups; over half of all attacks (57%) in this younger age group are relieved by sleeping. Pain intensity and duration of migraine attacks seem to increase with age, and these may be factors explaining a lower tendency for falling asleep during an attack. Children and adolescents fall asleep during a migraine attack so commonly that distortion of results would likely occur in clinical drug trials if a sleeping child is automatically excluded from analyses or classified as a treatment failure. Falling asleep should be classified as a sign of headache relief in clinical drug trials of migraine treatments in children and adolescents.

Study II: Intranasal sumatriptan is more effective than placebo in relieving migraine headache one hour postdose and thereafter in children and adolescents aged 8-17 years. Headache relief by two grades on the five-face pain scale at two hours after sumatriptan (64%) was reported nearly twice as often as after placebo (39%). One-third of patients were pain-free at two hours, but the response was not statistically superior to placebo. Children subjectively preferred sumatriptan over placebo and required less rescue medication after sumatriptan. Intranasal sumatriptan was well tolerated, the most commonly reported adverse effect being its bad taste. No serious adverse effects were observed. Our results suggest that intranasal sumatriptan can be effectively and safely used at an adult dose of 20 mg to treat migraine attacks in adolescents aged over 12 years.

Study III: Rizatriptan is clearly more effective than placebo in relieving migraine headache from one hour onwards in children and adolescents aged 6-17 years. Headache relief by two grades on the five-face pain scale at two hours after both administrations of rizatriptan (74%,73%) was reported twice as often as after placebo (36%). Both doses of rizatriptan were superior to placebo in offering a complete pain-free response two hours postdose and thereafter. Response to rizatriptan remained very constant over two consecutive migraine attacks. Rescue medication was needed more often after placebo, and children subjectively preferred rizatriptan over placebo.
Rizatriptan was well tolerated, and no serious adverse effects were observed. Our results suggest that rizatriptan 10 mg can be effectively and safely used to treat migraine attacks in adolescents aged over 12 years.
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APPENDIX A

Headache diaries in Study I
Headache diary

Choose the face that best tells how you feel.
Cross out the face like this.

 выбранный лицо, я без боли,
я чувствую себя хорошо.

Parents / nurse!
Write date of headache attack and medication.
Follow your child during the attack, and record with a plus sign the space that best describes the child’s behavior after 1/2 hour and every hour until the headache has disappeared.

Your records will give us valuable information for the treatment!
Headache diary  

date_______199__ medication____________

headache intensity at start (child’s own assessment)

30 minutes (child’s own assessment)

one hour (child’s own assessment)

2 hours (child’s own assessment)

3 hours (child’s own assessment)

4 hours (child’s own assessment)

5 hours (child’s own assessment)

Parent’s / nurse’s assessment:

<table>
<thead>
<tr>
<th>start</th>
<th>1/2h</th>
<th>1h</th>
<th>2h</th>
<th>3h</th>
<th>4h</th>
<th>5h</th>
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</thead>
<tbody>
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<td></td>
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<tr>
<td>child cries or complains of pain</td>
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<tr>
<td>child screams/cries loudly</td>
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</tr>
<tr>
<td>child vomited</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>child wants to go to bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>child goes to bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no more headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Headache diary

Write date and any drugs you take.

To describe how you feel and how severe a headache you have, draw a vertical line across the horizontal line.

Examples:
- "unbearable severe headache" like this
- "no headache, feel fine" like this

That you record your headache and how you feel regularly at the times shown in the diary is important. Please underline the words suitable to describe your headache at the start, after 1/2 hour, after one hour, etc. When the headache has disappeared, remember to answer the questions at the bottom of the page.

Your records will give us valuable information for the treatment.
Headache diary  date 199  drugs

at start of headache: right/left/whole head/pulsating/dull

30 minutes headache: right/left/whole head/pulsating/dull

1 hour headache: right/left/whole head/pulsating/dull

2 hours headache: right/left/whole head/pulsating/dull

3 hours headache: right/left/whole head/pulsating/dull

4 hours headache: right/left/whole head/pulsating/dull

5 hours headache: right/left/whole head/pulsating/dull

Before the headache, I could actually feel that it would begin yes/no
Before the headache, I had dizziness/visual disturbances/other symptoms, what

During the headache, I vomited times
During the headache, I had visual disturbances yes/no
During the headache, I felt numbness in the limbs yes/no
APPENDIX B

Headache diary in Study II
Lapsen nimi ja syntymäaika

Valitse kasvokuva joka parhaiten kertoo, miltä sinusta tuntuu, kuinka voit, kuinka kova päënsärkysi on. Vedä rasti kuvan yli näin.

Suosittelemme, että otat lääkkeen vain, jos päënsärky on mielestäsi vähintään yhtä kova kuin nuolen osoittama kuva. Kirjoita päivämäärä ja merkitse voitisi ennen lääkkeen ottoa. Merkitse lääkkeen ottoaika.
On tärkeää, että merkitset päënsäryn ja voitisi jokaisena kysytynä aikana.
Vastaa vielä päënsäryn hävittyä päiväkirjan kysymyksiin.

Vanhemmat / lapsen hoitaja!
Tarkistakaa, että yllämäinstit kohdat on täytetty. Täyttää ne tarvittaessa yhdessä lapsen kanssa.
Seuratkaa lastanne päënsärkykohtauksen aikana ja merkitkää huomioitanne ja vastaava kellonaika, kunnes päënsärky on hävinnyt. Vastatkaa esitettyihin kysymyksiin.

Muistakaa palauttaa päiväkirja lääkärille!
LÄÄKE 1 päivämäärä ______________ klo ________

päänsäryn voimakkuus juuri ennen lääkkeen ottoa (lapsen arvio)

15 minuuttia lääkkeen oton jälkeen (lapsen arvio)

30 minuuttia lääkkeen oton jälkeen (lapsen arvio)

1 tunti lääkkeen oton jälkeen (lapsen arvio)

2 tuntia lääkkeen oton jälkeen (lapsen arvio)

3 tuntia lääkkeen oton jälkeen (lapsen arvio)

Millainen päänsärky oli tunti lääkkeen oton jälkeen?
☐ poissa  ☐ lievempi  ☐ samanlainen  ☐ kovempi

Millainen päänsärky oli 2 tuntia lääkkeen oton jälkeen?
☐ poissa  ☐ lievempi  ☐ samanlainen  ☐ kovempi
4 tuntia lääkkeen oton jälkeen (lapsen arvio)

5 tuntia lääkkeen oton jälkeen (lapsen arvio)

6 tuntia lääkkeen oton jälkeen (lapsen arvio)

7 tuntia lääkkeen oton jälkeen (lapsen arvio)

Kuinka paljon kello oli, kun lääke selvästi helpotti?

Mihin aikaan päänsärky oli kokonaan poissa?

Mihin aikaan muut migreenioireet olivat kokonaan poissa?

Jos päänsärky oli kokonaan poissa 2 tunnissa, palasiko se vuorokauden sisällä (24 tuntia lääkkeen otosta)?

☐ Ei  ☐ Palasi

Vanhempien / hoitajan havaintoja:

lapsi valittaa kipua

lapsi itkee

lapsi oksensi

lapsi menee pitkälleen

päänsärky ohi

lapsi nukahti

Jos lapsi nukahti, oliko päänsärky poissa heräämisen jälkeen?
LÄÄKE 2 päivämäärä _______________ klo _________

Päänsäryn voimakkuus juuri ennen lääkkeen ottoa (lapsen arvio)

15 minuuttia lääkkeen oton jälkeen (lapsen arvio)

30 minuuttia lääkkeen oton jälkeen (lapsen arvio)

1 tunti lääkkeen oton jälkeen (lapsen arvio)

2 tuntia lääkkeen oton jälkeen (lapsen arvio)

3 tuntia lääkkeen oton jälkeen (lapsen arvio)

Millainen päänsärky oli tunti lääkkeen oton jälkeen?
☐ poissa  ☐ lievempi  ☐ samanlainen  ☐ kovempi

Millainen päänsärky oli 2 tuntia lääkkeen oton jälkeen?
☐ poissa  ☐ lievempi  ☐ samanlainen  ☐ kovempi
4 tuntia lääkkeen oton jälkeen (lapsen arvio)

5 tuntia lääkkeen oton jälkeen (lapsen arvio)

6 tuntia lääkkeen oton jälkeen (lapsen arvio)

7 tuntia lääkkeen oton jälkeen (lapsen arvio)

Kuinka paljon kello oli, kun lääke selvästi helpotti?

Mihin aikaan päänsärky oli kokonaan poissa?

Mihin aikaan muut migreenioireet olivat kokonaan poissa?

Jos päänsärky oli kokonaan poissa 2 tunnissa, palasiko se vuorokauden sisällä (24 tuntia lääkkeen otosta)?

☐ Ei  ☐ Palasi

Vanhempien / hoitajan havaintoja:  kellonaika

lapsi valittaa kipua

lapsi itee

lapsi oksensi

lapsi menee pitkälleen

päänsärky ohi

lapsi nukahti

Jos lapsi nukahti, oliko päänsärky poissa heräämisen jälkeen?
Kumpi lääke oli mielestäsi parempi?
Laita rasti sen kohdalle.

Lääke N:O 1  □
Lääke N:O 2  □

Tuliko tutkimuslääkkeistä mitään sivuevaikutuksia?
Lääke 1

Lääke 2

Saiko lapsi jotakin muuta lääketä?
Lääkkeen 1 jälkeen
   □ Ei
   □ Kyllä     Lääkkeen nimi ________________________
                Antoaika ____________________________

Lääkkeen 2 jälkeen
   □ Ei
   □ Kyllä     Lääkkeen nimi ________________________
                Antoaika ____________________________
APPENDIX C

Headache diary in Study III
PÄÄNSÄRKYPÄIVÄKIRJA
LÄÄKETUTKIMUKSEEN

Lapsen nimi ja syntymäaika

Valitse kasvokuva joka parhaiten kertoo, miltä sinusta tuntuu, kuinka voit, kuinka kova päänsärkysi on.
Vedä rasti kuvan yli näin.

![Kuvat ja merkit]

päähän sattuu,
pää on kipeä,
voin huonosti

Suosittelemme, että otat lääkkeen vain, jos päänsärky on mielestäsi vähintään yhtä kova kuin nuolen osoittama kuva.
Kirjoita päivämäärä ja merkitse vointisi ennen lääkkeen ottoa.
Merkitse lääkkeen ottoaika.
On tärkeää, että merkitset päänsäryn ja vointisi jokaisena kysyttynä aikana.
Vastaa vielä päänsäryn hävittyä päiväkirjan kysymyksiin.

Vanhemmat / lapsen hoitaja!
Tarkistakaa, että yllämainitut kohdat on täytetty. Täyttäkää ne tarvittaessa yhdessä lapsenne kanssa.
Seuratkaa lastanne päänsärkykohtauksen aikana ja merkitkää huomioitanne ja vastaava kellonaika, kunnes päänsärky on hävinnyt. Vastatkaa esitettyihin kysymyksiin.

Muistakaa palauttaa päiväkirja lääkärille!
päänsäryn voimakkuus juuri ennen lääkkeen ottoa (lapsen arvio)

15 minuuttia lääkkeen oton jälkeen (lapsen arvio)

30 minuuttia lääkkeen oton jälkeen (lapsen arvio)

1 tunti lääkkeen oton jälkeen (lapsen arvio)

2 tuntia lääkkeen oton jälkeen (lapsen arvio)

3 tuntia lääkkeen oton jälkeen (lapsen arvio)

Millainen päänsärky oli tunti lääkkeen oton jälkeen?
☐ poissa ☐ lievempi ☐ samanlainen ☐ kovempi

Millainen päänsärky oli 2 tuntia lääkkeen oton jälkeen?
☐ poissa ☐ lievempi ☐ samanlainen ☐ kovempi
4 tuntia lääkkeen onton jälkeen (lapsen arvio)

5 tuntia lääkkeen onton jälkeen (lapsen arvio)

6 tuntia lääkkeen onton jälkeen (lapsen arvio)

7 tuntia lääkkeen onton jälkeen (lapsen arvio)

Kuinka paljon kello oli, kun lääke selvästi helpotti?

____________________________
Mihin aikaan päänsärky oli kokonaan poissa?

____________________________
Mihin aikaan muut migreenioireet olivat kokonaan poissa?

____________________________
Jos päänsärky oli kokonaan poissa 2 tunnissa, palasiko se vuorokauden sisällä (24 tuntia lääkkeen otosta)?
☐ Ei ☐ Palasi

Vanhempien / hoitajan havaintoja: kellonaika

lapsi valittaa kipua

lapsi itkee

lapsi voi pahoin

lapsi oksensi

lapsi menee pitkälleen

päänsärky ohi

lapsi nukahti

Jos lapsi nukahti, oliko päänsärky poissa heräämisen jälkeen? __________
päänsäryn voimakkuus juuri ennen lääkkeen ottoa (lapsen arvio)

15 minuuttia lääkkeen oton jälkeen (lapsen arvio)

30 minuuttia lääkkeen oton jälkeen (lapsen arvio)

1 tunti lääkkeen oton jälkeen (lapsen arvio)

2 tuntia lääkkeen oton jälkeen (lapsen arvio)

3 tuntia lääkkeen oton jälkeen (lapsen arvio)

Millainen päänsärky oli tunti lääkkeen oton jälkeen?
☐ poissa    ☐ lievempi    ☐ samanlainen    ☐ kovempi

Millainen päänsärky oli 2 tuntia lääkkeen oton jälkeen?
☐ poissa    ☐ lievempi    ☐ samanlainen    ☐ kovempi
4 tuntia lääkkeen oton jälkeen (lapsen arvio)

5 tuntia lääkkeen oton jälkeen (lapsen arvio)

6 tuntia lääkkeen oton jälkeen (lapsen arvio)

7 tuntia lääkkeen oton jälkeen (lapsen arvio)

Kuinka paljon kello oli, kun lääke selvästi helpotti?

Mihin aikaan päänsärky oli kokonaan poissa?

Mihin aikaan muut migreenioireet olivat kokonaan poissa?

Jos päänsärky oli kokonaan poissa 2 tunnissa, palasiko se vuorokauden sisällä (24 tuntia lääkkeen otosta)?

☐ Ei  ☐ Palasi

Vanhempien / hoitajan havaintoja: kellonaika

lapsi valittaa kipua
lapsi itkee
lapsi voi pahoin
lapsi oksensi
lapsi menee pitkälleen
päänsärky ohi
lapsi nukahti

Jos lapsi nukahti, oliko päänsärky poissa heräämisen jälkeen?
päänsäryn voimakkuus juuri ennen lääkkeen ottoa (lapsen arvio)

15 minuuttia lääkkeen oton jälkeen (lapsen arvio)

30 minuuttia lääkkeen oton jälkeen (lapsen arvio)

1 tunti lääkkeen oton jälkeen (lapsen arvio)

2 tuntia lääkkeen oton jälkeen (lapsen arvio)

3 tuntia lääkkeen oton jälkeen (lapsen arvio)

Millainen päänsärky oli tunti lääkkeen oton jälkeen?
- poissa  - lievempi  - samanlainen  - kovempi

Millainen päänsärky oli 2 tuntia lääkkeen oton jälkeen?
- poissa  - lievempi  - samanlainen  - kovempi
4 tuntia lääkkeen oton jälkeen (lapsen arvio)

5 tuntia lääkkeen oton jälkeen (lapsen arvio)

6 tuntia lääkkeen oton jälkeen (lapsen arvio)

7 tuntia lääkkeen oton jälkeen (lapsen arvio)

Kuinka paljon kello oli, kun lääke selvästi helpotti?

Mihin aikaan päätärky oli kokonaan poissa?

Mihin aikaan muut migreenioireet olivat kokonaan poissa?

Jos päätärky oli kokonaan poissa 2 tunnissa, palasiko se vuorokauden sisällä (24 tuntia lääkkeen otosta)?

☐ Ei ☐ Palasi

Vanhempien / hoitajan havaintoja: kellonaika

lapsi valittaa kipua
lapsi itkee
lapsi voi pahoin
lapsi oksensi
lapsi menee pitkälleen
päätsärky ohi
lapsi nukahti

Jos lapsi nukahti, olipa päätsärky poissa heräämisen jälkeen?
Miten hyvin lääke mielestäsi auttoi?
Rastita sopiva vaihtoehto.

<table>
<thead>
<tr>
<th>Erinomainen</th>
<th>Hyvä</th>
<th>Kohtalainen</th>
<th>Huono</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lääke 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lääke 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lääke 3</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Tuliko tutkimuslääkkeistä mitään sivuvaikutuksia?

Lääke 1

Lääke 2

Lääke 3

Saiko lapsi jotakin muuta lääkettä?

Lääkkeen 1 jälkeen
  □ Ei
  □ Kyllä Lääkkeen nimi __________________________
          Antoaika __________________________

Lääkkeen 2 jälkeen
  □ Ei
  □ Kyllä Lääkkeen nimi __________________________
          Antoaika __________________________

Lääkkeen 3 jälkeen
  □ Ei
  □ Kyllä Lääkkeen nimi __________________________
          Antoaika __________________________