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神経症候群（第2版）

—その他の神経疾患を含めて—

VI

XV 頭　　痛

二次性頭痛

感染症による頭痛

飯ヶ谷美峰

XV 頭　　痛

二次性頭痛

感染症による頭痛

Headache attributed to infection

飯ヶ谷美峰

Key words：頭痛，頭蓋内感染症，全身感染症，血液脳関門(BBB)

1. 概念・定義

頭痛は，感染症に罹患した際によくみられる症状であり，6割以上で頭痛を認めるという報告がある[1]．特に，頭蓋内感染症では，初発症状として頭痛を認めることは極めて多い．感染症による頭痛を呈する基礎疾患の症候は様々で，軽度の局所神経症候から重篤な意識障害まで幅がある．

国際頭痛分類第3版beta版では，第2部二次性頭痛の中で，第9章「感染症による頭痛」としてまとめており(**表1**)，一般的な診断基準は，**表2**のとおりである[2]．ここでは，感染症による頭痛を「頭蓋内感染症による頭痛」と「全身性感染症による頭痛」と2つに大別している．また，感染と頭痛の関係を明確にするため，既存の一次性頭痛がある場合，感染によってその頭痛が増悪または慢性化したのか，感染症によって新たに生じた頭痛なのか，区別する基準を示している．さらに，感染に伴って生じた頭痛が，急性か，慢性か，あるいは持続性なのか，という視点で区別し，異なるであろう原因メカニズムと治療アプローチを分類することを促している．

実際の臨床現場では，①初診時の頭痛の臨床的特徴(頭痛の性状，痛みの持続時間や頻度，痛む部位)の評価と，②局所神経徴候や脳症・頭蓋内圧亢進徴候の有無を含めた総合的な臨床像を評価することが重要である．

本稿では，「感染症による頭痛」を生じる原因となる主な感染症について概説していく．

2. 感染症による頭痛を生じる原因

【頭蓋内感染症による頭痛】

1) 細菌性髄膜炎

(1) 疫学：日本における年間発生数は約1,500人であり，75％は小児，25％が成人である．原因菌の約50％は肺炎球菌で，中耳炎，副鼻腔炎，肺炎から派生する．髄膜炎菌は25％で，冬の上気道感染後に生じやすく，気道分泌物を介して人から人へ感染する．

(2) 病因：中耳炎，副鼻腔炎などからの直接波及や，心内膜炎，菌血症による血行性感染，手術や頭部外傷から生じた髄液漏出を介しての拡散などが病因となる．

(3) 病態：硬膜下腔や髄液へ浸潤または，血液中の病原体は側脳室脈絡叢を介して髄液腔に侵入した病原体は，髄液中で急速に増加していく．炎症により血液脳関門(BBB)が損傷されると，透過性が亢進し，血清タンパクが流入，糖輸送が障害される．また，破壊された菌体から生じたサイトカイン，ケモカイン，酸化窒素などのカスケードによる炎症過程の亢進も大きく関与する．炎症の結果，血管炎を生じ脳梗塞を生じることもある．急性頭痛がほとんどであるが，慢性頭痛や持続性頭痛を呈することもある．

(4) 診断：成人の髄膜炎は通常，重篤で，急性の激しい頭痛と悪心嘔吐，意識障害，項部硬

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表1 感染症による頭痛

9.1 頭蓋内感染症による頭痛
- 9.1.1 細菌性髄膜炎または髄膜脳炎による頭痛
  - 9.1.1.1 細菌性髄膜炎または髄膜脳炎による急性頭痛
  - 9.1.1.2 細菌性髄膜炎または髄膜脳炎による慢性頭痛
  - 9.1.1.3 細菌性髄膜炎または髄膜脳炎後の持続性頭痛
- 9.1.2 ウイルス性髄膜炎または脳炎による頭痛
  - 9.1.2.1 ウイルス性髄膜炎による頭痛
  - 9.1.2.2 ウイルス性脳炎による頭痛
- 9.1.3 頭蓋内真菌または他の寄生虫感染による頭痛
  - 9.1.3.1 頭蓋内真菌または他の寄生虫感染による急性頭痛
  - 9.1.3.2 頭蓋内真菌または他の寄生虫感染による慢性頭痛
- 9.1.4 脳膿瘍による頭痛
- 9.1.5 硬膜下膿瘍による頭痛

9.2 全身性感染症による頭痛
- 9.2.1 全身性細菌感染による頭痛
  - 9.2.1.1 全身性細菌感染による急性頭痛
  - 9.2.1.2 全身性細菌感染による慢性頭痛
- 9.2.2 全身性ウイルス感染による頭痛
  - 9.2.2.1 全身性ウイルス感染による急性頭痛
  - 9.2.2.2 全身性ウイルス感染による慢性頭痛
- 9.2.3 その他の全身性感染症による頭痛
  - 9.2.3.1 その他の全身性感染症による急性頭痛
  - 9.2.3.2 その他の全身性感染症による慢性頭痛

Appendix
- A9.1.3.3 頭蓋内真菌または他の寄生虫感染の既往による持続性頭痛
- A9.1.6 その他の感染性頭蓋内占拠性病変による頭痛

A9.3 ヒト免疫不全ウイルス(HIV)による頭痛

[日本頭痛学会・国際頭痛分類委員会(訳):国際頭痛分類 第3版 beta版, p114, p172, 医学書院, 2014. より転載]

表2 感染症による頭痛の診断基準

A. Cを満たす頭痛がある
B. 頭痛の原因となる感染, または感染の後遺症が診断されている
C. 原因となる証拠として, 以下のうち少なくとも2項目が示されている
  1. 頭痛は感染と時期的に一致して発現している
  2. 以下の項目のいずれか一方または両方を満たす
    a) 頭痛は感染の悪化と並行して有意に悪化している
    b) 頭痛は感染の改善または消失と並行して有意に改善または消失している
  3. 頭痛は感染症として典型的特徴をもつ
D. ほかに最適なICHD-3の診断がない

[日本頭痛学会・国際頭痛分類委員会(訳):国際頭痛分類 第3版 beta版, p115, 医学書院, 2014. より転載]

直を呈する. 頭痛は, 髄膜刺激とびまん性脳浮腫, 頭蓋内圧亢進によると考えられる. 成人の起因菌として最も多い肺炎球菌の臨床症候は, 早期から意識障害を呈し, 数時間のうちに巣症状や頻回のけいれん, 昏睡を呈する. 最も致死率の高い起因菌である. 点状出血や紫斑は予後不良の徴候であり, 髄膜炎菌でみられることが多い. 髄液の外観は混濁し, 初圧高値, 多核球優位の著明な細胞増多と糖低下を呈す. 画像所見では, びまん性の脳浮腫, 水頭症, 静脈洞血

栓症などが確認されることがある.

(5) 鑑別診断：脳深部静脈血栓症，くも膜下出血，片麻痺性片頭痛，橋本脳症，巨細胞性動脈炎などと鑑別を要する.

(6) 治療と予後：細菌性髄膜炎を疑った場合，30分以内にエンピリックセラピーとしての抗菌薬を開始すべきである．日本神経治療学会では，①セフトリアキソン(ロセフィン)かメロペネムと，②バンコマイシン，③デキサメタゾンの併用を推奨している．高齢者や消耗性疾患や免疫不全状態であれば，アンピシリンを加えるべきである[3]．死亡率は，10–30％と高く，抗菌薬投与までの時間と死亡率は相関がある．また，肺炎球菌髄膜炎では30％に水頭症，てんかん，脳神経麻痺，認知機能低下などの後遺症が認められる.

＊リステリア菌

高齢者や免疫力の低下した患者や小児における髄膜炎の原因菌として多い．食品を介して感染するが，細菌性食中毒に典型的な急性胃腸炎症状は通常呈さない．髄膜炎，脳炎ともに生じることがあり，脳幹症状を呈しやすい[4]．リステリア髄膜炎の36％では，急性に発症する頸部痛と項部硬直に意識障害を伴うことがある．髄液所見は一般的な細菌性髄膜炎とは異なり，中等度から重度のBBB破壊を伴った著明なリンパ球増多を認める．リステリア脳炎は，急性で激しい全般性の頭痛と，意識障害，けいれん，脳神経麻痺，など様々な神経障害を認め，予後不良である.

2) ウイルス性髄膜炎

(1) 疫学：臨床現場で，最も多く遭遇する髄膜炎の一群である．正確な頻度は不明であるが，診断されたウイルス性髄膜炎の85％はエンテロウイルス属(コクサッキーウイルス，エコーウイルス)によるものと報告されている.

(2) 診断と鑑別診断：発熱頭痛を呈し，項部硬直を認める．髄液所見では単核球優位の軽度～中等度の細胞増多，タンパク増加を認めるが，髄液糖の減少は認めない．原因ウイルスの同定には，髄液抗体検査で，IgM抗体陽性または，2週間後の4倍以上のIgG抗体価上昇で確認する．また，初期には多核球優位の細胞増多を示すことがあり，細菌性髄膜炎との鑑別が必要なことがある．頭部MRIは通常正常，時に軽度の髄膜の増強効果を認めることがある.

20日を超えて，頭痛が持続したり，髄膜刺激徴候があったり，髄液の異常所見がみられる場合は脳血管炎や癌性髄膜炎，慢性肉芽腫性感染症など別の診断を検討すべきである.

(3) 治療：一般に対症療法であるが，細菌性髄膜炎が完全に否定されない場合は，抗菌薬を併用する.

(4) 予後：数日の経過で回復し，入院不要のことも少なくない良性の経過の急性髄膜炎である．細菌性は否定されており，恐らくウイルス性であるが，原因ウイルスは同定されないため，「無菌性髄膜炎」という診断がされていることが多い.

3) ウイルス性脳炎

a. 単純ヘルペス脳炎

(1) 疫学：単純ヘルペスウイルス(HSV)による中枢神経感染症の発病率は1–2/50万人/年で，非常に重篤である.

(2) 病因・病態：まれに一次感染によって生じるが，三叉神経節におけるHSVの再燃とそれに続く側頭葉への拡散で生じる.

(3) 診断：前駆症状として，発熱，倦怠感，筋痛，胃腸症状を呈し，急性に発症，激しい頭部全体の頭痛，項部硬直，悪心嘔吐，昏睡に至る意識障害など，重篤な髄膜脳炎の古典的特徴を備える．二次性全般化けいれんは多く認められ，難治性である．髄液所見は非特異的で，中等度から高度の単核球増多，タンパク増加，髄液糖の軽度減少を認める．オリゴクローナルバンド，抗HSV IgG抗体が陽性である．頭部CT，MRIは，側頭葉病変を認め，出血性となることも多い．髄液のHSV-DNAのPCRは最も鋭敏な診断方法で，感度，特異度はそれぞれ94％，98％である[5].

(4) 鑑別診断：辺縁系症状をきたすその他の疾患として，水痘帯状疱疹ウイルス，サイトメガロウイルス，傍腫瘍性辺縁系脳炎，非ヘルペス性辺縁系脳炎，SLE，などがある.

(5) 治療と予後：早期の集中的な抗ウイルス治療なしには，致死率は75％を超え，後遺症なく回復するのは2.5％のみである．抗ウイルス薬として，アシクロビルを投与する．

b. 水痘・帯状疱疹ウイルス関連中枢神経合併症

(1) 疫学：免疫低下状態の患者では，急性発症の頭痛，項部硬直，昏睡に至る意識障害，けいれんと髄膜脳炎を呈することが知られている．

(2) 診断と鑑別診断：頭部MRIではびまん性の硬膜および軟膜の増強効果を認め，両側性に多発する病巣を認める．髄液所見は著明なリンパ球増多，重度のBBB破壊を認めるが，髄液糖は正常レベルである．

(3) 治療と予後：抗ウイルス薬として，アシクロビルを投与する．水痘・帯状疱疹ウイルスによる中枢神経の細小血管炎は致死率が高く，予後は不良である．

c. ダニ媒介性脳炎

(1) 疫学：ダニ媒介性脳炎は，中央ヨーロッパ(中央ヨーロッパ脳炎)やロシア(ロシア春夏脳炎)を中心に報告されてきたが，1993年以降，日本国内でも発生が報告されている[6]．

(2) 病因：ダニ媒介性脳炎は，フラビウイルス属ダニ媒介性脳炎ウイルス(Tick-borne encephalitis virus: TBEV)を原因とする人畜共通感染症で，マダニを介してヒトやイヌに感染する．

(3) 病態：潜伏期間は7-14日で，中央ヨーロッパ脳炎では，二相性の症状経過を示す．第1期は発熱，筋痛，頭痛を認め，1週間程度で症状は消失するが，解熱後，2，3日後に第2期に入り，けいれん，めまい，感覚障害など多様な神経障害を呈する．致死率は1-2％であるが，神経学的後遺症を10-20％に認める．ロシア春夏脳炎では，発熱，頭痛で発症し，半数は髄膜炎，髄膜脳炎を併発する．致死率は20％と高く，生存した場合も30-40％で神経学的後遺症をきたす[7]．

(4) 診断：検査所見では，白血球増多，赤沈亢進，CRP高値，および髄液細胞数増多を認め，脳波異常やMRI異常所見を認めることがある．

(5) 治療と予後：発症した場合は対症療法のみであるが，免疫グロブリンやステロイド薬が有効なことがある．致死率は1-30％で運動麻痺などの後遺障害を残すことも少なからずある．4類感染症に分類されており，診断した場合は，直ちに保健所への届出義務がある．

4) 脳膿瘍

(1) 病因：感染経路としては，①鼻，耳，副鼻腔，歯など頭蓋部での持続感染から波及，②頭蓋外傷や脳神経外科手術から二次的に感染，③心原性あるいは肺から血行性に波及：感染性微小血栓が飛散するため，通常病巣は多発する．臨床症状や神経放射線画像のパターンは多様で，これらは頭蓋内圧亢進所見を認めない，④特発性(全体の20％)の，4つのカテゴリーに分類される[8]．原因としては，レンサ球菌，黄色ブドウ球菌，各種バクテロイデス属，エンテロバクターなど細菌によるものが多いが，免疫不全者では，アスペルギルス症，ブラストミセス症など真菌によるものや原虫によるものも報告されている．

(2) 病態：基礎疾患として，副鼻腔，耳，顎，歯，肺の感染からの波及によることが多く，髄膜，または動脈組織への直接的な圧迫と刺激，および頭蓋内圧亢進が，頭痛のメカニズムと考えられている．

(3) 診断と鑑別診断：進行性に増悪する頭痛，悪心嘔吐，片麻痺，巣症状と局所けいれんを呈す．発熱がみられることも多い．造影CTまたはMRIでリング状の増強効果を伴う浮腫状の腫瘤を認め，脳腫瘍と鑑別が困難なことがある．膿瘍が破裂した場合には，急激に悪化する頭痛や頸部痛，項部硬直と意識障害を認める．

(4) 治療と予後：治療の基本は排膿ドレナージと抗菌薬投与である．免疫正常者では，感染源となっている感染巣によってエンピリカルな治療を開始する．免疫機能低下患者では，真菌や原虫の可能性も考え，状況に応じて抗真菌薬や抗原虫薬の使用を検討する．

5) 硬膜下膿瘍

硬膜下膿瘍は硬膜とくも膜の間に膿が貯留した状態である．耳，鼻，副鼻腔の感染に起因し，

骨髄炎，神経外科手術から派生して，硬膜下に拡散する．症状は脳膿瘍とは異なり，急性の顕著な頭痛と発熱，項部硬直，片麻痺，意識障害がみられる．

6）結核性髄膜炎

(1) 疫学：結核性髄膜炎は，緩徐に発症し，徐々に増悪する髄膜炎の代表格である．他臓器に感染源を有し，2次的に髄膜炎を併発することがあるが，中枢神経系への感染は，全結核の1％弱である．一方，25％の結核性髄膜炎患者は全身感染の臨床的徴候や病歴を有さない．まれであるが，未治療の場合の致死率は30％と高く，髄膜炎診療では，常に考慮すべき病態である．

(2) 病因・病態：結核感染における頭痛は，通常髄膜炎に伴うものであり，頭蓋内圧亢進を引き起こすような脳実質への波及(粟粒結核)や結核腫による脳占拠性病変形成，閉塞性水頭症によることはまれである．

(3) 診断：初発症状は微熱と頭痛，軽度の項部硬直である．数日から数週間で，脳神経麻痺(III, VI, VII, VIII)や巣症状，けいれんを伴った髄膜脳炎症候群を呈するようになる[9]．MRIでは脳底部の硬膜および軟膜の増強効果と多巣性の高信号域を認め，T1WIでは同部はリング状エンハンスメントが認められる．髄液所見で初圧は正常から軽度高値，重度のBBB障害，髄液糖減少(<40％)，リンパ球優位の著明な細胞増多(≧300/μL)を認める．

(4) 鑑別診断：真菌性髄膜炎，サルコイドーシス，癌性髄膜炎などが鑑別となる．

(5) 治療と予後：治療は，ファーストラインの4種(INH，リファンピシン，ピラジナミド，エタンブトール)が基本である．適切な治療が行われない場合，1，2カ月で致命的となりうる．

7）頭蓋内真菌感染症

(1) 疫学：健康成人で生じることはまれであり，通常，免疫低下状態か，糖尿病，高齢者，長期抗菌薬投与下のリンパ球増殖性症候群の患者で発症する．近年，AIDSに併発する重篤な髄膜炎の起因菌として注目されている．

(2) 病因：中枢神経系における真菌感染では，髄膜炎，血管炎，脳実質障害などが生じうる．症候は一般的に3–4週間かけて発展するが，より緩徐あるいは，より急峻な場合もある．クリプトコッカスはCNSに親和性が高く，真菌性髄膜炎の主要な原因菌である．ほかにアスペルギルス，ムコールがある．

(3) 病態：臨床症状は発熱，進行性の後頭部，および全般性の頭痛と項部硬直，脳神経麻痺，巣症状，精神障害，意識障害である．末期には痙攣や昏睡となる．まれに頭蓋内圧亢進をもたらすような巨大な脳膿瘍を形成することがある．

(4) 診断：髄液所見は，リンパ球優位の細胞増多，重度のBBB障害，髄液糖減少(髄液糖/血糖<40％)を認める．画像所見では，髄膜の血管炎徴候，多発する微小膿瘍，あるいは脳実質内の巨大脳膿瘍など，多彩な所見がみられる．鑑別として，結核性髄膜炎，サルコイドーシスなどがある．

(5) 治療と予後：副作用が少なく，髄液移行性のよいフルコナゾールで治療開始することが多いが，効果が乏しければ，アムホテリシンBとフルオロシトシンの併用投与を行う[10]．

＊Rhinocerebral syndrome

rhinocerebral syndromeは副鼻空や，眼窩，脳を冒す進行性で侵襲的な真菌感染で，進行性の顔面痛と激しい頭痛を呈する．真菌の直接浸潤や血行性に拡散し，眼窩や頭蓋内への拡散によるもので[11]，動脈に浸潤すると，血栓となって，組織壊死を生じる．ムコール症を引き起こす腐生性真菌により，糖尿病患者で認めることが多い．

【全身性感染症による頭痛】

全身性感染症では，発熱や全身倦怠感が全面に出て，通常頭痛は比較的目立たないことが多い．しかしながら，一部の全身性感染，例えば，インフルエンザでは，発熱と並ぶ顕著な症状として頭痛がみられる．ここで髄膜炎を伴っていなければ，全身性ウイルス感染による頭痛と診断する．

全身性感染症が頭痛を引き起こす要因は多様であり，単に発熱や外因性または内因性発熱物

質を介した影響ではないことが示唆されている．頭痛を引き起こすメカニズムとしては，微生物自体の直接作用が含まれる．活性化ミクログリアとマクロファージ，活性化アストロサイトとBBBおよび内皮細胞が，種々の免疫炎症性メディエイターとともに関与すると思われる[2]．

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Oral sumatriptan for migraine in children and adolescents: A randomized, multicenter, placebo-controlled, parallel group study

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Abstract

Objective: The objective of this article is to evaluate the efficacy and tolerability of two doses of oral sumatriptan vs placebo in the acute treatment of migraine in children and adolescents.

Background: Currently, there is no approved prescription medication in Japan for the treatment of migraine in children and adolescents.

Methods: This was a multicenter, outpatient, single-attack, double-blind, randomized, placebo-controlled, parallel-group study. Eligible patients were children and adolescents aged 10 to 17 years diagnosed with migraine with or without aura (ICHD-II criteria 1.1 or 1.2) from 17 centers. They were randomized to receive sumatriptan 25 mg, 50 mg or placebo (1:1:2). The primary efficacy endpoint was headache relief by two grades on a five-grade scale at two hours post-dose.

Results: A total of 178 patients from 17 centers in Japan were enrolled and randomized to an investigational product in double-blind fashion. Of these, 144 patients self-treated a single migraine attack, and all provided a post-dose efficacy assessment and completed the study. The percentage of patients in the full analysis set (FAS) population who report pain relief at two hours post-treatment for the primary endpoint was higher in the placebo group than in the pooled sumatriptan group (38.6% vs 31.1%, 95% CI: −23.02 to 8.04, $p = 0.345$). The percentage of patients in the FAS population who reported pain relief at four hours post-dose was higher in the pooled sumatriptan group (63.5%) than in the placebo group (51.4%) but failed to achieve statistical significance ($p = 0.142$). At four hours post-dose, percentages of patients who were pain free or had complete relief of photophobia or phonophobia were numerically higher in the sumatriptan pooled group compared to placebo. Both doses of oral sumatriptan were well tolerated. No adverse events (AEs) were serious or led to study withdrawal. The most common AEs were somnolence in 6% (two patients) in the sumatriptan 25 mg treatment group and chest discomfort in 7% (three patients) in the sumatriptan 50 mg treatment group.

Conclusions: There was no statistically significant improvement between the sumatriptan pooled group and the placebo group for pain relief at two hours. Oral sumatriptan was well tolerated.

Keywords

Sumatriptan, children, adolescents, migraine

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Background

Migraine is a common and debilitating disorder in children and adolescents. Recently, Abu-Arafeh et al. (1) analyzed prevalence of headache including migraine in children and adolescents in a systematic review of 35 population-based studies of pediatric headache from 23 countries. The review showed that prevalence of migraine in the 3–19 years age group was 1.4%–13.8% (average: 6.0%) in males, and 2.1%–28.4% (average: 9.7%) in females, with the average prevalence of

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migraine of 7.7%. Other reports showed that the mean age of onset of migraine was 7 years for boys and 11 years for girls. Gender ratio changes with age. Migraine prevalence is greater in boys in the 3- to 7-year-old group. In ages 7–11 years, no significant difference in migraine prevalence between boys and girls was found. And at age 15, girls suffer from migraine more frequently (2,3). In earlier studies, diagnosis of migraine was made according to the classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain (International Headache Society (IHS): 1988) (4), and the International Classification of Headache Disorders, second edition (ICHD-II: 2004) (5) used in the trials conducted since 2006. In the Japanese study of adolescents aged 12–15 years (6), overall prevalence of migraine diagnosed according to ICHD-II was 4.8%, with 6.0% in boys and 9.7% in girls.

Establishing the correct diagnosis of migraine is crucial for adequate management. The treatment should be individually tailored and can include nonpharmacological and pharmacological approaches. While nonpharmacological treatment such as avoiding triggers and keeping a regular sleep schedule as well as a well-balanced diet can be helpful, pharmacological treatment of migraine attacks also may be needed.

Currently there is no approved prescription medication in Japan for the treatment of migraine in children and adolescents. The *Japanese Practice Guidelines for Headaches*, first edition (2007), states that ibuprofen and acetaminophen have been considered to be safe and effective for the acute treatment of pediatric migraine (7). Two studies supported the efficacy of ibuprofen and one study supported the efficacy of acetaminophen for the acute treatment of migraine in adolescents (8,9). However, ibuprofen is not licensed for treatment of migraine attacks in children and adolescents in Japan and is used off label.

Triptans are a class of drugs acting selectively as agonists on serotonin 5-$HT_{1B/1D}$ receptors. Sumatriptan, developed by GlaxoSmithKline for treatment of migraine, was the first clinically available triptan. Several studies of sumatriptan nasal spray have demonstrated efficacy and tolerability for acute treatment of migraine in children and adolescents (10–12), whereas the study of oral sumatriptan did not demonstrate clear efficacy (13). This difficulty might be attributed to a higher placebo response rate in children and adolescents as compared to adults (14–16). Several triptans have become available for migraine treatment in adults since 2000 in Japan; however, none of these has been licensed for use in children or adolescents.

The aim of the current study was to evaluate the efficacy, safety and tolerability of oral sumatriptan at doses of 25 mg and 50 mg for the acute treatment of a single migraine attack in children and adolescents. To date, there has been no study of triptan conducted in Japanese children and adolescents.

Methods

Ethical considerations

The study was conducted in accordance with Good Clinical Practice (GCP), Article 14-3 and 80-2 of the Pharmaceutical Affairs Law, all applicable patient privacy requirements, and the guiding principles of the Declaration of Helsinki (Edinburgh 2000, Washington 2002 and Tokyo 2004). The institutional review board/independent ethics committee reviewed and approved the study protocol and patient informed consent form. Written informed consent was obtained from each patient and his or her legal guardian prior to participation in the study.

Study design

This was a multicenter, outpatient, single-attack, double-blind, randomized, placebo-controlled, parallel-group study of two doses of oral sumatriptan vs placebo. This study was conducted from September 28, 2009 to December 3, 2010 in Japan.

Eligible patients were randomized to receive sumatriptan 25 mg, 50 mg or placebo. When randomization was completed, the patients entered a six-week treatment phase during which they could self-treat a single migraine attack according to the treatment arm. Study medication needed to be taken as soon as possible (within 0.5 hours) after the development of a migraine attack associated with grade 3 or more pain (moderate to severe pain) on the five-grade scale. The baseline for each migraine attack was the time the patient took the study medication. A 24-hour pain-free period prior to the onset of headache pain was required to establish that each migraine attack represented a new episode, rather than a recurrence of a previous headache.

Patients

Eligible patients were males and females 10–17 years old without childbearing potential or using adequate birth control having a minimum of a six-month history of migraine with or without aura as defined by ICHD-II criteria; had two to eight migraine attacks monthly for the two months prior to entry into the study; had migraine attacks associated with pain intensity of 3 or more on a five-grade scale that last a minimum of three hours; had shown no response to at least one nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen; were able to distinguish migraine from

other headaches; and were able to read, comprehend, and complete patient diaries.

Patients were ineligible for the study if they had weight <30 kg, ≥15 headache days per month in total (migraine, probable migraine, or tension-type headache), were suffering with retinal (ICHD-II 1.4), basilar (ICHD-II 1.2.6), hemiplegic (ICHD-II 1.2.4 or 1.2.5), or ophthalmoplegic migraine (ICHD-II 13.17); had secondary headaches, a history of cerebrovascular disease or myocardial infarction; signs or symptoms of cardiac ischemia; uncontrolled hypertension, peripheral vascular syndromes; epilepsy or structural brain lesions lowering convulsive threshold, history or manifestations of significant liver or kidney dysfunction were also excluded. In addition, patients were excluded if they used ergot medications in the previous three months for migraine prophylaxis or had changed dose of any other medication for migraine prophylaxis within two months prior to randomization; had taken or planned to take a monoamine oxidase inhibitor anytime within the two weeks prior to entry into the study, or had psychotropic drug, alcohol or substance abuse within the last year.

Blinding and randomization

The investigator informed potential patients and the legal guardians of this study and obtained consent from both. Following this, screening tests and examinations were performed, and if the patient satisfied all eligibility criteria, the investigator (or subinvestigator) completed the registration form and sent it to the randomization center by facsimile. The randomization center ensured that the registration form contained all necessary information and that the patients satisfied all eligibility criteria of the protocol and assigned a randomization number to the patient. For allocation of the participants, a computer-generated list of random numbers was used. The investigator (or subinvestigator) then dispensed the investigational product to the patient according to the computer-generated randomization number. The patients were randomized to sumatriptan 25 mg or 50 mg or placebo in 1:1:2 ratios using random block sizes of four. The sites were trained on how to maintain blind conditions.

Study assessments

To measure efficacy, patients were required to complete diaries at baseline and at regular intervals through four hours post-treatment. Pain intensity was evaluated by using the five-grade categorical rating scale on which no pain, mild, mild to moderate, moderate to severe, and severe pain were scored as 1, 2, 3, 4 and 5, respectively. Date and time of onset, presence of migraine-associated symptoms, such as photophobia, phonophobia, nausea and vomiting were recorded in the diaries.

The primary efficacy endpoint was the percentage of patients who reported pain relief (defined as at least a two-point reduction on the five-grade scale) at two hours post-treatment without previous use of rescue medication.

Secondary efficacy endpoints were the percentage of patients who reported pain relief at time points at 0.5, one and four hours; the percentage of patients who were pain free at 0.5, one, two and four hours post-treatment; the percentage of patients who were free of each of the following symptoms: photophobia, phonophobia, nausea, or vomiting at 0.5, one, two, and four hours post-dose as well as the percentage of patients who used rescue medication from the time of dosing to four hours post-dose. Pain-free was defined as a pain intensity score of "1" (no pain) in patients who had not used rescue medication prior to the assessment. If rescue medication was taken, for subsequent efficacy assessments pain intensity was assumed to be severe and the symptoms were set to be present for the purpose of the data analysis. Rescue medication could include either a single oral dose of an NSAID or acetaminophen, not exceeding the maximum recommended single dose or an antiemetic. Safety evaluation included AEs, laboratory assessments (hematology, blood chemistry and urinalysis), vital signs and electrocardiogram (ECG). Severe adverse events (SAEs) were collected from the time of informed consent up to and including any follow-up contact. AEs were collected from the start of the investigational product until the follow-up contact.

Statistical analysis

Based on the randomization ratio of 1:1:2 (sumatriptan 25 mg, 50 mg and placebo), a total of 140 patients were required to test the hypothesis at the two-sided significance level of 0.05 with 80% power; 166 patients were needed for randomization, assuming a drop-out rate of 15%. Calculations are based on Fisher's exact test. The percentages of patients who would report pain relief at two hours for sumatriptan and placebo groups were assumed as 64% and 39%, respectively, based on the data from a published nasal sumatriptan pediatric trial (9). A pre-defined analysis plan was followed with no interim analysis planned or performed.

The safety population (SP) consisted of all patients who took at least one dose of the investigational product. The full analysis set (FAS) consisted of all patients in the SP who provided any post-treatment efficacy assessment. The per protocol set (PPS) consisted of all patients in the FAS who did not deviate from any major protocol requirements. The last observation

carried forward (LOCF) dataset was defined as the dataset imputed by the LOCF method. Only the post-treatment value was used for the imputation. The observed case (OC) dataset was defined as the dataset without any missing data imputation. The OC dataset was used for a part of the efficacy analysis. These analyses were secondary and aimed to confirm the stability of LOCF results.

SAS® software was also used to perform all calculations. The primary comparison of interest was the percentage of patients who reported pain relief at two hours in the sumatriptan pooled group (pooled across doses) vs placebo groups. The comparison was performed with a significance level of 0.05 (two sided) and based on FAS and LOCF datasets. Other comparisons were two sided and carried out at the significance level of 0.05. However, no adjustment for multiplicity was made since they were secondary comparisons.

The primary efficacy analysis was based on FAS and LOCF datasets. The number and percentage of patients who reported pain relief at two hours were summarized for sumatriptan pooled and placebo groups. The difference in percentages between both groups was calculated along with 95% confidence intervals, and the statistical comparison was made by $\chi 2$ test. The null hypothesis for this study was that there is no difference between sumatriptan pooled and placebo groups in the percentage of patients who report pain relief at two hours. The alternative hypothesis was that there is a difference between sumatriptan pooled and placebo groups in the percentage of patients who report pain relief at two hours.

Secondary analyses were conducted for pain relief, pain free and rescue medication use. The number and the percentage at each assessment time point (0.5, one, two and four hours) or period of "0–4 hours" for rescue medication use were summarized for each treatment (sumatriptan 25 mg, 50 mg, sumatriptan pooled, and placebo). The differences in percentages between each sumatriptan group vs placebo were calculated along with 95% confidence intervals, and the statistical comparisons were made by $\chi 2$ test. Similar analyses as pain relief and pain free were performed for associated symptoms (nausea, vomiting, photophobia and phonophobia). Only patients who had each associated symptom at the treatment were included in the denominator.

Any AEs occurring within the time period that extended from the date of investigational product use up to (and including) the follow-up contact were summarized. The summaries of AEs both by body weight and by age were produced. Summary statistics (*n*, mean, standard deviation, median, minimum and maximum) were provided at each scheduled time point. Also, the number and percentage of patients with data outside normal ranges were tabulated at each scheduled time point. The number and percentages of each urinalysis test result were displayed at each scheduled time point. Summary statistics (*n*, mean, standard deviation, median, minimum and maximum) for vital signs and physical examinations were provided at each scheduled time point. The number and percentages for ECG findings were displayed.

Results

Study population

A total of 178 patients from 17 centers in Japan were enrolled and randomized to an investigational product in double-blind fashion (Figure 1). Of these, 144 patients self-treated a single migraine attack; all provided a post-dose efficacy assessment and completed the study. All 144 patients provided a post-treatment efficacy assessment and were included in the FAS population. Given that all the 144 patients were evaluated for safety and tolerability, the SP and FAS datasets were identical. A total of 136 patients in the FAS population completed the study without any major protocol violations and were included in the PPS population. Eight subjects in the FAS population had major protocol deviations and were therefore excluded from the PPS population (four patients were taking concomitant medication prohibited by the protocol. The other four patients had noncompliance in taking the investigational product).

Demographic and baseline characteristics of the three treatment groups (sumatriptan 25 mg and 50 mg, and placebo) as well as the pooled sumatriptan group are shown in Table 1. Migraine without aura was diagnosed in 76% of the sumatriptan 25 mg group, 85% of the sumatriptan 50 mg group and 79% of the placebo group, respectively. The majority of patients had mild to moderate pain at dosing of investigational product (76% of the sumatriptan 25 mg group, 63% of the sumatriptan 50 mg group and 66% of the placebo group). Average duration of migraine attack of three to 24 hours was the most common across the groups (97% of the sumatriptan 25 mg group, 85% of the sumatriptan 50 mg group and 94% of the placebo group).

Efficacy findings

Pain relief. The percentage of patients in the FAS population who reported pain relief at two hours post-dose (the primary endpoint) was higher in the placebo group than in the sumatriptan pooled group (38.6% and 31.1%, respectively; Figure 2(a)) but failed to achieve statistical significance ($p = 0.345$). The percentage of patients in the FAS population who reported pain

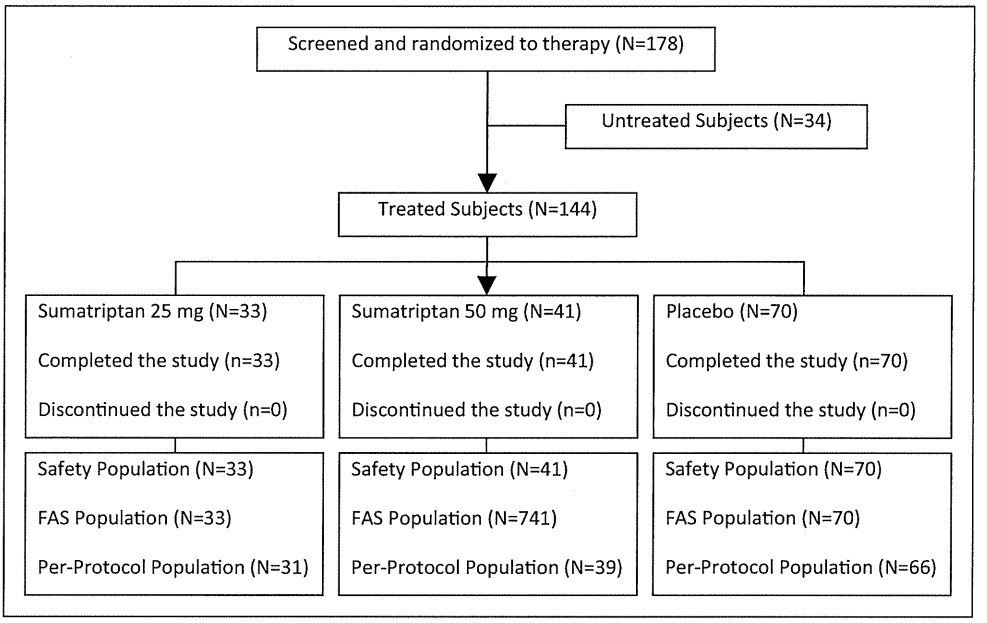

Figure 1. Flowchart of patient disposition.

relief at four hours was numerically higher in the sumatriptan pooled group than the placebo group (sumatriptan pooled: 63.5%, placebo: 51.4%; Figure 2(a)) but failed to achieve statistical significance ($p = 0.142$). Similar results were observed in the PPS population (placebo: 39.4%, sumatriptan pooled: 31.4, $p = 0.331$) and were also seen when analysis by body weight or age was performed (Figure 2(b)).

Pain free. The percentage of patients in the FAS population who were pain free at 0.5, one, and two hours post-dose was numerically higher in the placebo group than in the sumatriptan pooled group. The percentage of patients who were pain free at four hours was numerically higher in the sumatriptan pooled group than in the placebo group (sumatriptan pooled: 50.0%, placebo: 47.1%; Figure 3). Statistical significance was not reached for the sumatriptan pooled group compared to the placebo group ($p = 0.732$).

Associated symptoms. The percentage of patients who were photophobia free at two hours was numerically higher in the sumatriptan pooled group than the placebo group (sumatriptan pooled: 53.6%, placebo: 52.8%). No statistically significant difference was observed between the placebo group and the pooled sumatriptan group for this symptom ($p = 0.950$). The percentage of patients who were phonophobia free at two hours was numerically higher in the placebo group than the sumatriptan pooled group (placebo: 63.6%, sumatriptan pooled: 53.3%). Similarly, a numerically greater percentage of patients was nausea free in the placebo group vs the pooled sumatriptan group (81.0% and 61.1%, respectively). At four hours post-dose, the proportions of patients who had complete relief of photophobia or phonophobia were numerically higher in the sumatriptan pooled group compared to placebo. No statistically significant difference was observed between the placebo group and the pooled sumatriptan group at this time point.

Use of rescue medication. The use of rescue medications was comparable across all treatment groups (12.1%, 14.6%, 13.5%, and 12.9% in the sumatriptan 25 mg, 50 mg, sumatriptan pooled groups and placebo, respectively).

Safety findings

The overall incidence of AEs in each treatment group were 15%, 17%, 16% and 14% in the sumatriptan 25 mg, 50 mg, pooled groups and placebo, respectively. Both doses of oral sumatriptan (25 mg and 50 mg) were well tolerated in this study (Table 2). None of patients reported an SAE or withdrew because of an AE. AE profiles were comparable among treatment groups, with individual as well as pooled active treatment groups showing small increases in overall AE incidence, as was the overall incidence of drug-related AEs over placebo. The most common AEs were somnolence in two (6%) patients with sumatriptan 25 mg and chest discomfort in three (7%) patients with 50 mg. No clear treatment effect was observed in the AE analyses based on age or weight.

Table 1. Demographic and baseline characteristics (SP population).

	Sumatriptan 25 mg (*N* = 33)	Sumatriptan 50 mg (*N* = 41)	Sumatriptan pooled (*N* = 74)	Placebo (*N* = 70)
Age, years				
Mean (SD)	14.5 (2.18)	14.1 (1.96)	14.3 (2.05)	13.9 (2.04)
Age category, *n* (%)				
10–14	12 (36)	22 (54)	34 (46)	41 (59)
15–17	21 (64)	19 (46)	40 (54)	29 (41)
Sex, *n* (%)				
Female	17 (52)	28 (68)	45 (61)	39 (56)
Male	16 (48)	13 (32)	29 (39)	31 (44)
Race, *n* (%)				
Japanese	33 (100)	41 (100)	74 (100)	70 (100)
Height, cm				
Mean (SD)	159.6 (11.33)	156.5 (10.11)	157.9 (10.71)	158.1 (9.89)
Min, max	134, 185	134, 174	134, 185	135, 178
Weight, kg				
Mean (SD)	50.55 (9.934)	47.85 (8.980)	49.06 (9.448)	49.55 (11.868)
Min, max	30.1, 74.0	30.0, 61.7	30.0, 74.0	30.0, 94.0
Migraine type, *n* (%)[a]				
Without aura	25 (76)	35 (85)	60 (81)	55 (79)
With aura	9 (27)	6 (15)	15 (20)	16 (23)
Average number of attacks per month during the past two months				
Mean (SD)	4.3 (1.63)	3.8 (1.93)	4.0 (1.81)	4.2 (1.92)
Min, max	2, 8	2, 8	2, 8	2, 8
Average duration of migraine attack, *n* (%)				
3–24 hours	32 (97)	35 (85)	67 (91)	66 (94)
24–48 hours	1 (3)	1 (2)	2 (3)	1 (1)
48–72 hours	0	5 (12)	5 (7)	3 (4)
Onset age of migraine attacks (years)				
Mean (SD)	10.7 (3.14)	10.0 (3.40)	10.3 (3.28)	9.8 (2.75)
Min, max	5, 15	3, 16	3, 16	2, 14
Pain intensity at dosing, *n* (%)				
Mild to moderate	25 (76)	26 (63)	51 (69)	46 (66)
Moderate to severe	7 (21)	10 (24)	17 (23)	23 (33)
Severe	1 (3)	5 (12)	6 (8)	1 (1)

SP: safety population; Min: minimum; Max: maximum; SD: standard deviation.
[a]Two patients had both migraine types.

Discussion

Children with headaches are usually referred to general pediatrics or neurological clinics; however, this category of patients seems to be underrepresented among the referrals to pediatric neurologists in Japan as compared with other neurologic disorders such as epilepsy syndromes, myopathies and developmental disorders. Migraine is the most frequent primary headache in the outpatient setting because of its severity and associated manifestations.

Accurate diagnosis according to ICHD-II is the first step for migraine treatment. Nonpharmacological treatment such as avoiding triggers, and regular sleep and exercise are recommended for pediatric migraine. If pharmacological treatment is needed, analgesics like ibuprofen and acetaminophen are usually administered. However, even if taken in recommended doses and early in the course of the attack, these medications can be ineffective in severe migraine attacks in some patients.

There is a considerable body of research focusing on pharmacological management of pediatric migraine; however, data from controlled trials are still limited and therefore pharmacological treatment of migraine in children and adolescents is mainly off label (3,7). For acute treatment of migraine, the most rigorously studied agents are ibuprofen, acetaminophen and

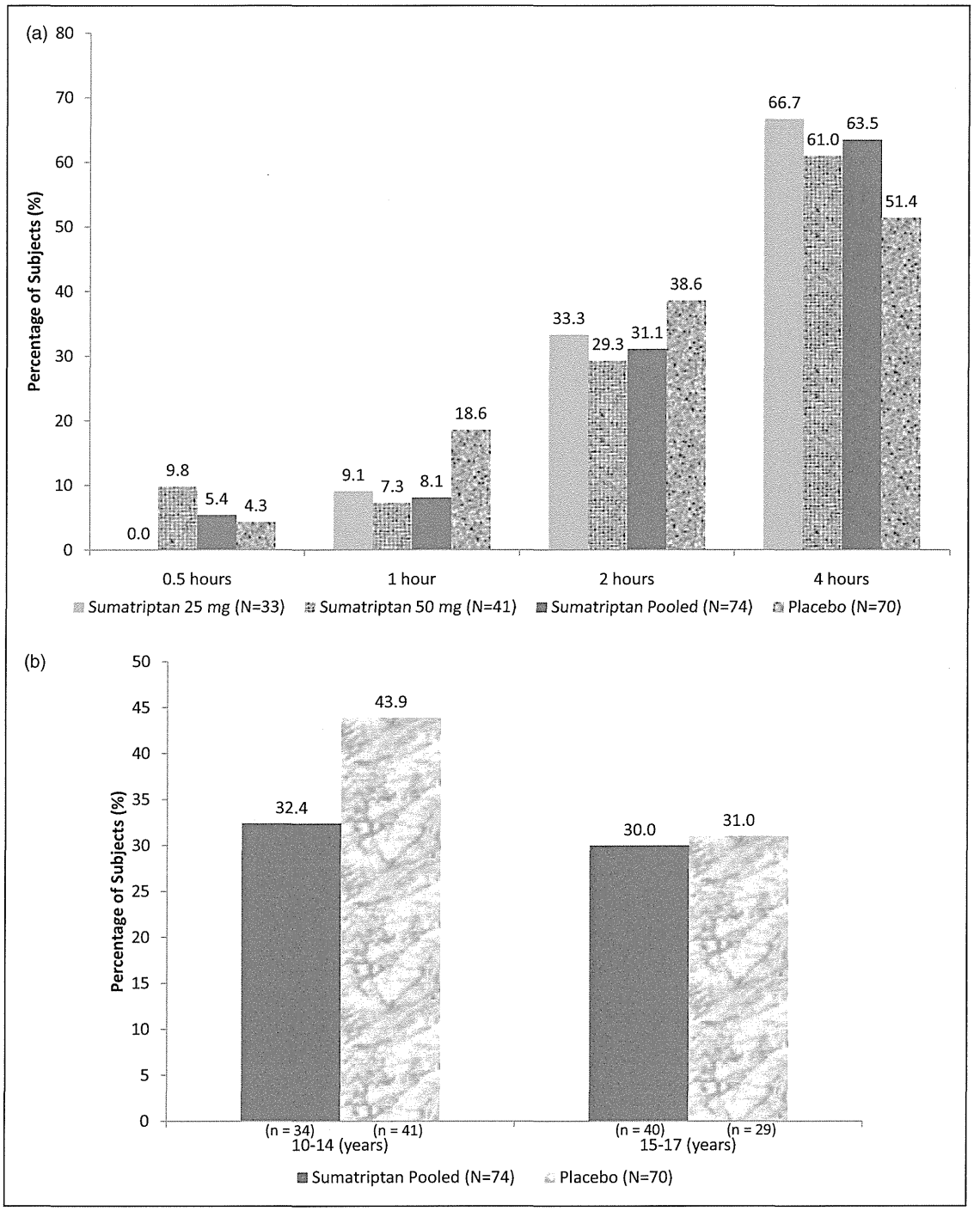

Figure 2. (a) The percentage of patients with pain relief at 0.5, one, two and four hours post-treatment (full analysis set (FAS) population). (b) The percentage of patients with pain relief at two hours post-treatment by age (FAS population).

selected triptans (rizatriptan and almotriptan tablets, sumatriptan and zolmitriptan nasal sprays) (3). In our experience, the efficacy of sumatriptan nasal spray is favorable but the bad taste is not tolerated by some children with migraine, therefore tablet formulation may be preferred by some young migraineurs. However, to date, no study of a triptan has been conducted in children and adolescents in Japan.

This was the first randomized, double-blind, placebo-controlled trial of oral sumatriptan to evaluate its efficacy and tolerability in the treatment of migraine in Japanese children and adolescents. In the current

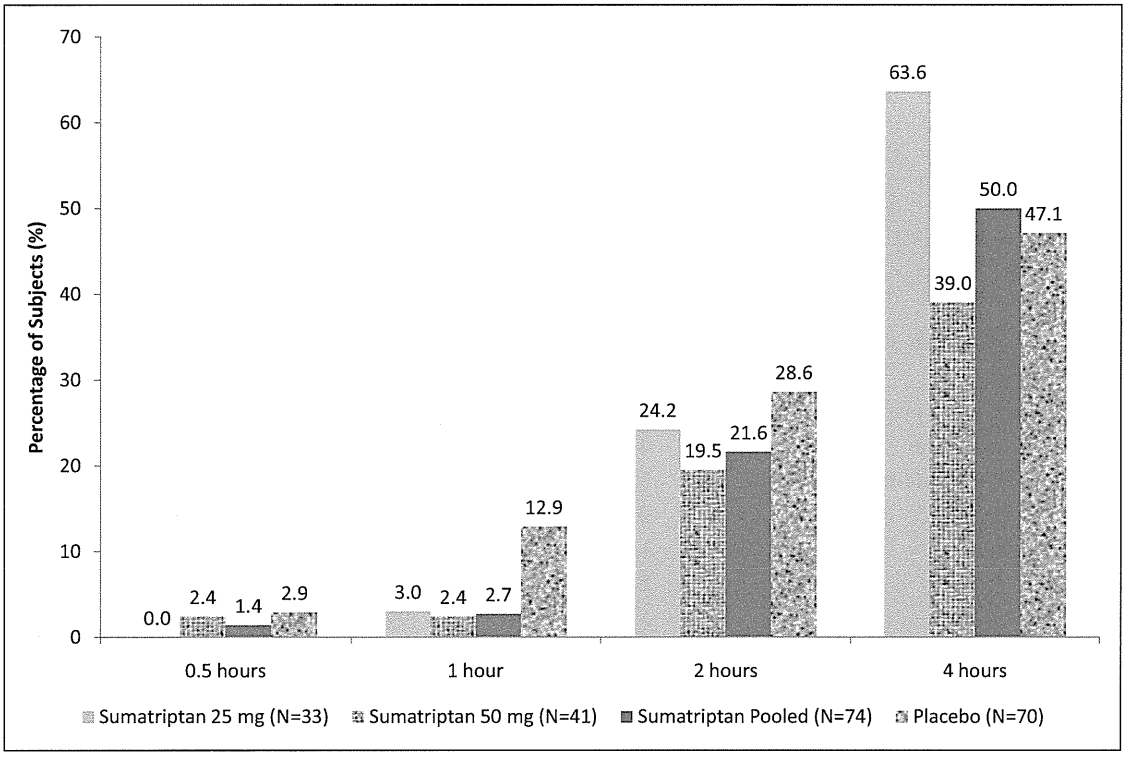

Figure 3. The percentage of patients who were pain free at 0.5, one, two, and four hours post-treatment (full analysis set (FAS) population).

study, patients in the sumatriptan pooled group experienced lower pain relief than in the placebo group at two hours.

The high placebo response in acute treatment of migraine in children and adolescents has been reported in a number of trials (14–16) whereas low placebo response rate was observed in a recent study (17). A parallel-group study design and the use of a four-point pain scale were suggested as the determinants of the high placebo effect (15,16). The placebo response rate in pediatric migraine was shown to be higher than that in adult migraine in the systematic review (15). Factors associated with a lower placebo response rate in children and adolescent trials of acute treatment of migraine were single-center (vs multicenter) trials, and small sample size. Placebo response rate did not depend on age and gender (16).

Our study was a parallel-group multicenter trial from 17 headache centers, and pain relief as a primary endpoint was defined as at least a two-grade reduction on a five-grade scale, which is the same for the sumatriptan nasal spray study that indicated significant efficacy (11). The inclusion of 17 centers might be one of the reasons why this study failed to demonstrate efficacy. However, it was uncertain why pain relief at two hours in the sumatriptan pooled group was lower than that in the placebo group despite the same pain-relief definition as the study for sumatriptan nasal spray. The time to onset of action for sumatriptan nasal spray was 15 minutes. For the sumatriptan tablet, the time was 30 minutes (18). The difference of the time to onset might be one of the reasons why sumatriptan nasal spray is effective but sumatriptan in tablet form is not. A recent oral rizatriptan study has indicated that the rizatriptan was significantly more effective than the placebo and well tolerated for migraine attacks in patients older than 6 years (19). One of the reasons why the study indicated significant efficacy could be the appropriate selection of an outcome measure to evaluate pain intensity. Headache diaries used in the study were completed by the children and also by parents proving assessment of the child's behavior (18). In contrast, headache diaries in our study were filled in only by patients. We used two doses of sumatriptan (25 mg and 50 mg), but did not use 100 mg, because in Japan, 50 mg is the standard dose for adults. Therefore, we used only both 50 mg and 25 mg. However, the use of low-dose sumatriptan (25 mg and 50 mg) might be one of the reasons why this study failed to demonstrate efficacy.

We used a single dose without the option of a repeat dose after two hours because the duration of pediatric migraine is shorter than the duration of adults' migraine. Therefore, we think that treatment by only a single dose is sufficient for Japanese children. Actually

Table 2. Adverse event summary (SP).

	Sumatriptan 25 mg ($N=33$) *n* (%)	Sumatriptan 50 mg ($N=41$) *n* (%)	Sumatriptan pooled ($N=74$) *n* (%)	Placebo ($N=70$) *n* (%)
Subjects with any AE	5 (15)	7 (17)	12 (16)	10 (14)
Subjects with any drug-related AE	4 (12)	5 (12)	9 (12)	4 (6)
Subjects with any SAE	0 (0)	0 (0)	0 (0)	0 (0)
AE				
Blood creatine phosphokinase increased	0 (0)	0 (0)	0 (0)	4 (6)
Protein urine present	0 (0)	2 (5)	2 (3)	1 (1)
Aspartate aminotransferase increased	0 (0)	0 (0)	0 (0)	2 (3)
Urobilinogen urine increased	0 (0)	0 (0)	0 (0)	2 (3)
Blood human chorionic gonadotropin positive	0 (0)	1 (2)	1 (1)	0 (0)
Platelet count decreased	0 (0)	0 (0)	0 (0)	1 (1)
Platelet count increased	1 (3)	0 (0)	1 (1)	0 (0)
Somnolence	2 (6)	0 (0)	2 (3)	1 (1)
Dizziness	1 (3)	0 (0)	1 (1)	0 (0)
Headache	0 (0)	1 (2)	1 (1)	0 (0)
Chest discomfort	0 (0)	3 (7)	3 (4)	0 (0)
Discomfort	1 (3)	0 (0)	1 (1)	0 (0)
Edema	1 (3)	0 (0)	1 (1)	0 (0)
Nasopharyngitis	0 (0)	0 (0)	0 (0)	2 (3)
Acute tonsillitis	0 (0)	1 (2)	1 (1)	0 (0)
Musculoskeletal discomfort	0 (0)	1 (2)	1 (1)	0 (0)
Pain in extremity	0 (0)	1 (2)	1 (1)	0 (0)
Epistaxis	0 (0)	0 (0)	0 (0)	1 (1)
Throat tightness	0 (0)	1 (2)	1 (1)	0 (0)
Nausea	0 (0)	1 (2)	1 (1)	0 (0)
Proteinuria	0 (0)	0 (0)	0 (0)	1 (1)
Flushing	0 (0)	0 (0)	0 (0)	1 (1)

SP: safety population; AE: adverse events; SAE: severe adverse events.

66.7% of subjects treated by placebo in the study achieved pain relief.

We treated one single attack, not three attacks in this trial, because it made study participation easier for Japanese patients; treating three attacks is great burden for the Japanese patients. However, some patients may not respond to sumatriptan in some, but not all, migraine attacks.

The recent sumatriptan and naproxen sodium combination tablets study (17) employed a number of strategies to reduce placebo response rates and improve treatment difference detection, including a definitive primary endpoint (percentage of pain-free patients) that did not require assessing degree of pain; treatment at moderate/severe pain for greater post-treatment pain differentiation; a placebo run-in phase to identify and exclude placebo responders; a selection of subjects with migraines attacks lasting >3 hours to avoid the impact of natural resolution; and site selection emphasizing the pediatric experience for improved communication with adolescents.

Our study did not reach statistical significance on the primary endpoint with the percentage of patients reporting pain relief at two hours port-dose being numerically higher in the placebo group vs the pooled sumatriptan group.

Although analysis of secondary efficacy endpoints in this study generally also did not show a treatment effect, patients in the sumatriptan pooled group experienced numerically higher pain relief; photophobia, phonophobia and were pain free (but had no nausea) compared to the placebo group at four hours post-dose.

The overall incidence of AEs in each treatment group was lower than the rates observed for equivalent doses in previous studies in adults (20). These results

suggested that oral sumatriptan for acute treatment of migraine was well tolerated in children and adolescents. No clear treatment effect was observed in the AEs by age and weight. The results should be interpreted with caution because of the small number of subjects in the subcategories. The results of this study showed that oral sumatriptan was less effective in children and adolescents than in adults. However, a proportion of young migraineurs can benefit from oral sumatriptan at four hours post-dose, but characteristics of this subset of the patient population are not known. Based on the literature, such characteristics of the trial as parallel-group design, the use of outcome measure assessing degrees of pain as well as completion of diaries only by subjects could have contributed to the high placebo response rate.

Further studies to evaluate the efficacy and safety of sumatriptan in children and adolescents are be needed, and these studies should incorporate strategies to minimize placebo response.

Conclusions

There was no statistically significant improvement between the sumatriptan pooled group and the placebo group for the primary endpoint, pain relief at two hours. At four hours post-dose, the proportions of patients who experienced pain relief, were pain free, or had complete relief of photophobia or phonophobia were numerically higher in the sumatriptan pooled group compared to placebo. The most frequently reported AEs were somnolence and chest discomfort in the sumatriptan 25 mg group and the sumatriptan 50 mg group, respectively. No SAEs were reported. Oral sumatriptan was well tolerated for the treatment of migraine in children and adolescents.

Clinical implications

- There was no statistically significant improvement between the sumatriptan pooled group and the placebo group for the primary endpoint, pain relief at two hours.
- At four hours post-dose, the proportions of patients who experienced pain relief, were pain free or had complete relief of photophobia or phonophobia were numerically higher in the sumatriptan pooled group compared to placebo.
- Oral sumatriptan was well tolerated for the treatment of migraine in children and adolescents.

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Conflicts of interest

K. Sato and H. Nishioka are employees of GlaxoSmithKline, the license holder of oral sumatriptan. M. Fujita has been a clinical consultant/advisor to GlaxoSmithKline for this study. F. Sakai has been an investigator in this study.

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短　報

低用量インドメタシンとプレガバリンの併用が有用であった持続性片側頭痛の1例

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要旨：症例は51歳男性である．約3週前より左眼窩から前頭部への頭痛が持続し，頭痛増強時に眼充血，流涙をともなった．神経学的所見，脳MRIは異常なく，インドメタシン（75 mg/日）で頭痛が完全に抑制され，国際頭痛分類第2版から持続性片側頭痛（hemicrania continua; HC）と診断した．インドメタシン減量で頭痛が再燃したので，プレガバリン（150 mg/日）を併用したところ，インドメタシンは25 mg/日まで減量可能で，忍容性も良好であった．HCはインドメタシン反応性頭痛の一つであるが，インドメタシンの連用により，胃腸障害などの副作用で，忍容性が低下し，減量や中止が余儀なくされることがあり，インドメタシンに代わりうる薬剤療法が必要である．

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Key words：持続性片側頭痛，インドメタシン，プレガバリン，忍容性

はじめに

持続性片側頭痛（hemicrania continua; HC）は，国際頭痛分類第2版（International Classification of Headache Disorders 2nd edition; ICHD-2）では「その他の一次性頭痛」に分類され，1日中持続する，連日性で片側性の頭痛で，頭痛増悪時に頭痛側に結膜充血や流涙などの自律神経所見のうち少なくとも1項目がみられ，インドメタシンが著効する慢性連日性頭痛の1型である[1)]．2013年に発表された国際頭痛分類第3版β版（International Classification of Headache Disorders 3rd edition (beta version); ICHD-3β）では，「三叉神経・自律神経性頭痛」に分類されたが，診断基準には大きな変更点はない[2)]．多くのHCはインドメタシンなしでは寛解のない慢性型であるが，インドメタシンの連用により，めまい，胃腸障害などの副作用で，忍容性が低下するので，減量や中止が余儀なくされるばあいは，インドメタシンに代わりうる薬物療法が必要である．今回，われわれは低用量インドメタシンにプレガバリンを併用することにより，良好なコントロールがえられたHCの1例を経験したので報告する．

症　例

患者：51歳，男性
主訴：持続する頭痛
既往歴：28歳；腰椎ヘルニア手術，34歳；声帯ポリープ手術．
家族歴：類症，血族結婚なし．
嗜好歴：煙草；30本/日・30年間，アルコール；ビール350 ml/日．

現病歴：2010年から左眼窩から前頭部にかけての頭痛が持続するようになった．締めつけられる痛みと，ズキズキ，ガンガンする痛みであった．頭痛には変動があり，時に強い痛みとなる．頭痛は完全に消えることはなく，増強時には眼充血，流涙をともなった．市販鎮痛剤や非ステロイド性抗炎症薬が無効で約3週間経過しても改善しないので，当科を紹介受診した．

現症：身長173 cm，体重68 kg，体温36.7℃，血圧115/73 mmHg，脈拍57回/分・整，心音・呼吸音は正常で胸腹部に異常はなかった．左眼窩から前頭部の持続的な痛みがみられた．側頭動脈の腫脹はなかった．項部硬直はなく，他に明らかな神経学的異常はみられなかった．

検査所見：検尿，血液一般，電解質，肝腎機能は異常なく，CRPは陰性で，血沈，甲状腺機能は正常であった．胸部X線，心電図は異常なく，頭部MRI，MRAは正常であった．

経過（Fig. 1）：HCのうたがいとして，インドメタシン（75 mg/日）を開始したところ，4日後に頭痛は消失した．以後3ヵ月間は頭痛がなかったが，50 mg/日への減量で頭痛が再燃し，75 mg/日への再増量で頭痛が消失した．インドメタシンが75 mg/日未満では3ヵ月以上頭痛が継続したと推察さ

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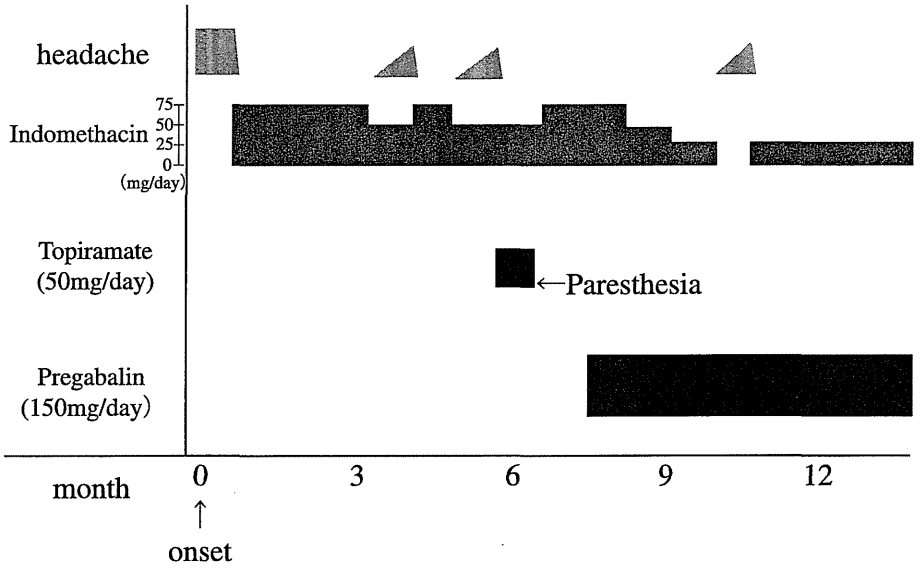

Fig. 1　Clinical course and treatment.
The headache completely disappeared within four days following indomethacin treatment (75 mg/day). His headache recurred after reducing the dose of indomethacin. Thus, the diagnosis of hemicrania continua was established according to the International Classification of Headache Disorders, 2nd Edition. Although the topiramate was effective, it lead to its discontinuation because of paresthesia. After adding pregabalin (150 mg/day) to his treatment regimen, we could reduce the dose of indomethacin from 75 mg/day to 25 mg/day, and the patient tolerated well. On the horizontal axis in the figure, 0 indicates the onset of his headache.

れ，ICHD-2の診断基準[1]から，HCの診断を確定した．ICHD-3βにおいてもHCの診断基準を満たした[2]．インドメタシンの減量により頭痛が出現したので，トピラマート(50 mg/日)を併用したところ，頭痛は軽減したが，錯感覚のため，中止した．かわって，プレガバリン（150 mg/日）を併用したところ，副作用はみられず，頭痛は良好にコントロールされ，インドメタシンを25 mg/日まで減量することができた．その後，約2年にわたりインドメタシン（25 mg/日）とプレガバリン（150 mg/日）の併用で，頭痛は完全にコントロールされ，忍容性も良好であった．

考　察

HCは1984年，Sjaastadによってまれなインドメタシン反応性頭痛として発表され，疾患概念として提唱された．国際頭痛分類の改訂にともない，2004年のICHD-2では「その他の一次性頭痛」の一部として採用され，2013年に発表されたICHD-3βでは「三叉神経・自律神経性頭痛」に分類されたが，その病態はまだ不明な点が多い．

治療量のインドメタシンが絶対的な反応を示すが，海外の報告ではインドメタシンの平均使用量がPeresら[3]，Parejaら[4]，Cittadiniら[5]の報告ではそれぞれ，136.7 mg/日(N＝34)，60.9 mg/日（N＝16），176 mg/日（N＝32）と高用量である．痛みは慢性に持続することが特徴で，82％のHCはインドメタシンなしでは寛解のない慢性型である[5]．HCは長期にわたるインドメタシンの内服治療が必要であるが，その服用量は胃腸障害の危険性と入院率に直線的に相関する．そのため，インドメタシンの減量や代わりうる薬剤療法が必要である．他の有効な治療薬としては，セレコキシブ[6]，ガバペンチン[7][8]，トピラマート[5][8]の報告が多く，Rossiら[9]はHCの治療の第1選択はインドメタシン（25～300 mg/日）であるが，副作用などで服用できないばあいは，第2選択として，セレコキシブ（200～400 mg/日）を選択し，効果がないときはトピラマート(100 mg/日)，ガバペンチン(600～3,600 mg/日)，メラトニン（7～15 mg/日）を挙げている．Porta-Etessamら[6]はインドメタシンで副作用がみられたHC患者5例にセレコキシブ（200～400 mg/日）を使用し，全例で完全寛解がえられている．Spearsら[7]は副作用のためインドメタシンが服用できないHC患者9例に対して，ガバペンチン(600～3,600 mg/日)を投与したところ，4例は完全寛解し，3例は50～80％，1例は10％の疼痛軽減がみられた．1例は無効であった．その他の治療薬として，ピロキシカム，アミトリプチリン，ベラパミルなどの報告例が散見される．

本例はインドメタシン（75 mg/日）で忍容性の低下はなかったが，減量で頭痛が再燃したので，長期のインドメタシン投与の必要性が予想され，今後，副作用が出現する可能性が高いと判断し，他の薬物療法を試みた．近年，選択的COX-2阻害薬の長期間の使用で，心筋梗塞や脳卒中が増加することが報告されており，セレコキシブの長期投与による副作用を考慮し，最初にトピラマートを使用した．有効であったが，