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Pharmacological treatment of attacks in juvenile migraine

Abstract Although migraine is a common complaint in childhood and adolescence, there is a lack of controlled clinical studies regarding treatment. In the young patient, the pharmacological approach should be preceded by setting up non-pharmacological measures which include behavioural intervention. The sole use of symptomatic therapies should be limited to patients who complain of up to four partially or totally disabling attacks, or those who suffer from headache for more than 4 days per month. The therapeutic armamentarium includes non-specific symptomatic drugs, such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), as well as anti-emetics and specific drugs, such as the triptans. Analgesics and NSAIDs are the most frequently used drugs in childhood and adolescence for the symptomatic treatment of migraine attacks of slight or moderate intensity. The first-choice drug for those under 12 years of age is acetaminophen. Among NSAIDs, two double-blind, random-

ized, placebo-controlled studies were conducted for ibuprofen, supporting its efficacy. In the past, ergot derivatives played an important role in the treatment of spontaneous migraine attacks, particularly in adults, but after the triptan revolution their role was strongly confined to a small number of patients. Although they are considered first-choice drugs for moderate and severe migraine attacks in adults, triptans are still under study in migraine patients under 18 years of age. The Health Ministry rules do not approve their use in patients under 18 years. They can only be given legally if the therapeutic plan for their use is previously approved by the Ethics Committee and after informed consent from the patient/parents. Promising results have been obtained, particularly for sumatriptan in nasal spray formulation as well as for zolmitriptan and rizatriptan, showing a high tolerability and safety profile.

Key words Migraine • Analgesics • Triptans

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Introduction

Migraine is a common complaint in children. About 3%–5% of school-aged children experience periodic

attacks of migraine, and this proportion increases to 20% through adolescence. Migraine shows a slight prevalence in males of prepubertal age, then in adolescence there is a shift toward a female preponderance, which is maintained through adulthood [1, 2]. The peculiar character-

istics of juvenile migraine, which emerged from epidemiological studies carried out using the 1988 International Headache Society (IHS) criteria, are reflected in an insufficiently standardized therapeutic approach. This is also due to the lack of well-conducted studies, until the introduction of triptans in the last decade, whose use in childhood and adolescence is limited by ethical problems [3–5].

A fundamental prerequisite for the success of any therapeutic intervention, even in juvenile migraine, is the establishment of a solid patient-physician alliance. This strong relationship requires that the physician reassures and informs patients, if possible, or their parents about the functional nature of the disease and the underlying pathogenic mechanisms.

The registration of the frequency, intensity and duration of the crises in a headache diary is pivotal for the therapeutic plan. The recording of triggering, aggravating or alleviating factors, of the type and quantities of symptomatic drugs used and of their efficacy or side effects is also important for subsequent non-pharmacological strategies and for the choice of the most appropriate drugs [6].

An important point of the diagnostic process, which has implications for the therapeutic intervention, is the identification of the coexistence of more headache forms in the same patient.

General principles

In the young migraineur, the pharmacological approach should be preceded by setting up non-pharmacological measures that include behavioral interventions, such as correct life-style habits or avoidance of certain behavior, the reduction of family or school stressors and the removal of triggering factors, if possible [7]. It may not be possible to eliminate some of the triggering factors (e.g. menstruation, weather changes, weekend), whereas others may be completely or partially removed (e.g. physical fatigue, fasting, some foods). Only if a causal relationship between triggering factors and attack occurrence is clearly recognized and confirmed, can their removal effectively contribute toward reducing the frequency of attacks.

The coexistence of other disorders (comorbidities) should be investigated because their presence can strongly influence the therapeutic choice for migraine crises.

Moreover, drugs used for other diseases should be considered for their potential role as attack triggers and for any drug-drug interactions. In children and adolescents with migraine, psychological aspects and family and school problems should be carefully investigated, because they may contribute toward inducing or sustaining migraine attacks.

The sole use of symptomatic therapies should be limited to patients who complain of up to four partially or totally disabling attacks or those who suffer from headache for more than 4 days per month. The goal of symptomatic treatment is (a) to reduce the intensity and duration of attacks or (b) the complete remission of head pain and accompanying symptoms.

The following main criteria should be followed when adopting a symptomatic strategy:

1. To use a drug with a single therapeutic agent at adequate dosage.
2. To use drug formulations easier to use, such as oral formulations, possibly of pleasant taste, and in particular, effervescent or soluble formulations.
3. To use intramuscular or intravenous formulations only if nausea and vomiting are present.
4. To also use anti-emetics when nausea or vomiting prevail.
5. To adopt adjunctive measures such as lying in bed in a silent and dark room during the most severe attacks.

Drugs for the treatment of migraine attacks

The therapeutic armamentarium includes non-specific symptomatic drugs, such as analgesics and NSAIDs, as well as anti-emetics and specific drugs, such as the triptans. Analgesics and NSAIDs are the most frequently used drugs in childhood and adolescence for the symptomatic treatment of migraine attacks of slight or moderate intensity. Their efficacy is improved if they are taken early, at the beginning of the attack.

The first-choice drug for patients under the age of 12 is acetaminophen. It is well tolerated and has few side effects in the case of sporadic, discontinuous use. They include skin eruptions, gastrointestinal disturbances (nausea, vomiting, abdominal pain), alterations in blood cell count, and liver and kidney dysfunction. The recommended dosage is 15–20 mg/kg per day, which can be repeated up to three times per day if the attack persists [8, 9].

The only study concerning the use of acetaminophen in young migraineurs is that of Hamalainen et al. [10], who compared this drug versus ibuprofen for the acute treatment of migraine in 88 children aged 4–15.8 years and demonstrated that both drugs were more effective than placebo in relieving headache; however, for acetaminophen, the percentage of responders was lower than for ibuprofen.

Acetylsalicylic acid (ASA) should be used only for migraine patients over 12 years of age due to the potential, although rare, risk of Reye's syndrome [11]. No studies have been carried out to investigate the efficacy of ASA in

the treatment of migraine attacks in children and adolescents. The recommended dosage is 5–15 mg/kg per day.

Among NSAIDs, two double-blind, randomized, placebo-controlled studies have been conducted for ibuprofen, supporting its efficacy. In the first study, Hamalainen et al. [10] found that ibuprofen was twice as likely as acetaminophen to abort migraine attacks within the 2-h endpoint. In the second study, Lewis et al. [12] compared the efficacy of a single over-the-counter dose (7.5 mg/kg, p.o.) of children's ibuprofen suspension versus placebo for the acute treatment of paediatric migraine, and showed that ibuprofen was significantly more effective in terms of percentage of responders and improvement of headache severity and nausea. If the dosage of 7.5 mg is the most adequate for children under 10 years of age, the recommended dosage for patients over 12 years is 10 mg/kg. At this dosage, however, there are currently no studies available in the literature on the treatment of juvenile migraine.

Other drugs are nimesulide (100 mg twice a day) in patients over 12 years of age, indomethacin (50–10 mg p.o., or 100–200 mg, p.r.) for patients over 14 years, and ketorolac, for which the recommended dose is 10 mg/day in patients over 16 years. Brousseau et al. [13] compared the effectiveness of intravenously administered ketorolac and intravenously administered prochlorperazine in young migraineurs aged 5–18 years. Intravenous ketorolac showed lower percentages of responders than prochlorperazine (55.2% versus 84.8%). The side effects of NSAIDs were gastrointestinal disturbances, skin reactions, blood cell dyscrasia, and liver and kidney dysfunction. It is important to mention that analgesic and NSAID abuse is a frequent occurrence [14] also in children and adolescents affected by migraine, particularly in those with a high frequency of attacks. The only published report in this regard, however, is that of Symon [15], who described children under 12 years of age with chronic daily headache, evolving from a previous history of episodic migraine without aura and with analgesic abuse. Analgesic abuse is itself responsible for the self-maintenance of attacks and migraine chronicity.

The use of ergot derivatives should be limited to disabling crises resistant to the use of other symptomatic drugs and with a low monthly frequency (1–2 attacks per month) due to the potential risk of abuse. They should always be associated with an anti-emetic because of the frequent associated side effects of nausea and vomiting. These important side effects limit the use of ergot derivatives in childhood and adolescence. However, there is experience in Anglo-Saxon countries, particularly in emergency departments and with inpatient regimens, which demonstrated the efficacy of orally or intravenously administered dihydroergotamine mesylate for the treat-

ment of juvenile migraine attacks, especially for those resistant to other treatments [16]. Dihydroergotamine can be administered orally to subjects over 12 years of age (1–3 mg/day), rectally (2.5–5 mg/day), nasally (1 mg per nostril; maximum daily dose, 2 mg), or intramuscularly (0.25–0.5 mg/day).

Further drugs useful for the treatment of migraine attacks of slight or moderate intensity are the anti-emetics. They also improve gastric stasis, ameliorating the absorption of other symptomatic treatments. Metoclopramide (0.5 mg/kg per day, oral route) has been demonstrated to be significantly effective, but its use is limited by the risk of the occurrence of extrapyramidal symptoms and oculogyric crises [17]. Domperidone (0.3–0.6 mg/kg, oral or rectal route) should be preferred because it does not cross the blood-brain barrier and thus does not induce CNS side effects. The effectiveness of prochlorperazine is supported by a retrospective, open-label study [18] and, as stated previously, by the recent trial conducted versus ketorolac [13]. The intravenous administration route, proposed in the latter study, is limited to the hospital setting and cannot be routinely proposed, particularly in Italy.

Although they are considered first-choice drugs for moderate-to-severe migraine attacks in adults, triptans are still under study in migraine patients under 18 years. The Health Ministry rules do not approve the use of triptans in patients under 18 years. They can only be given legally if the therapeutic plan for their use is previously approved by the Ethics Committee and after informed consent from the patients and their parents. Triptans are indicated, even in children and adolescents, for the treatment of moderate and severe attacks in the presence or absence of prophylactic treatment. They are also indicated for the treatment of less disabling attacks, when analgesics and NSAIDs are inefficacious or partially efficacious and do not relieve accompanying symptoms. Triptans are efficacious for the treatment of both head pain and accompanying symptoms but are inefficacious in migraine aura and tension-type headache.

A controlled study on the oral formulation of sumatriptan, a first-generation drug, versus placebo was carried out on migraine patients between 8 and 16 years of age [19]. The efficacy parameters showed a trend in favour of sumatriptan compared with placebo, without, however, reaching the level of statistical significance. This weaker response in the paediatric age group could be due to differences in pharmacokinetic and pharmacodynamic parameters compared to adults, but these aspects have not been systematically evaluated. The efficacy of sumatriptan, administered subcutaneously, was demonstrated in an open study [20], with slight and transitory side effects, but the use of this administration route was limited by a low compliance in children and adolescents.

The majority of the studies carried out on children and adolescents with migraine were conducted using sumatriptan nasal spray, showing efficacy data similar to those obtained in adults. In a randomized, double-blind, placebo-controlled study [21] carried out on young migraine patients aged between 6.4 and 9.8 years, a significant headache response emerged at 2 h in 88% of patients treated with sumatriptan nasal spray versus 43% of patients treated with placebo. In another randomized, double-blind, placebo-controlled study involving 653 American adolescents, three doses of 5, 10, and 20 mg of sumatriptan nasal spray were compared [22]. The best headache response at 2 h and the greater efficacy on accompanying symptoms was observed for the 20-mg dose. Taste disturbance was the only side effect reported. Rothner et al. [23], in a 1-year open-label study, found that sumatriptan nasal spray was well tolerated and effective in the treatment of migraine attacks in adolescents. Recently, Pakalnis et al. [24] conducted a retrospective chart review to evaluate parental satisfaction in the treatment of childhood migraine with sumatriptan nasal spray. In this study, 100 patients, aged 5–12 years, were identified and the parents were invited to complete a standardized questionnaire; 77% of them reported a good to excellent relief of their child's migraine attacks with sumatriptan nasal spray.

An open-label study [25] indicated that zolmitriptan is efficacious and well tolerated for the treatment of migraine attacks in adolescents complaining of migraine. In this study, doses of 2.5 and 5 mg were compared in a sample of 38 young migraineurs. A headache response was observed at 2 h in 80% of patients, while at 2 h, 66%

of patients were headache-free. No significant side effects were reported in any patient. Regarding rizatriptan, only one study *versus* placebo involving 296 adolescents (12–17 years) is available, and has underlined the good tolerability of the 5-mg dose in this age group [26].

Conclusions

Several studies have been conducted to formulate guidelines for the treatment of migraine attacks in adults based on a broad number of well-conducted studies, particularly for triptans. The recommendations available for children and adolescents are, instead, more empirical and scarcely evidence-supported, due to the limited number of randomized, placebo-controlled studies carried out according to good clinical practice. An aspect which should be noted in this regard is the high placebo response in childhood and adolescence, which can reach 60% and which requires a careful evaluation of study results with respect to the real therapeutic gain obtained.

In children and adolescents affected by migraine, the treatment options should not be limited to pharmacological intervention. They should also include appropriate counselling aimed at reassuring the patients and their parents, explaining the functional disturbance, identifying triggering factors and setting up non-pharmacological strategies. Only with the integration of both pharmacological and non-pharmacological approaches can the best management of migraine in children and adolescents be obtained.

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