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Up to date on the use of triptans for child and adolescent migraine: state of the art

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Abstract The introduction of triptans, in the early 1990s, has improved the therapy for acute migraine attack, offering a new quality of life for those patients who suffer from this disabling neurological disorder. Epidemiological data point out that about 10% of school-age children suffer from migraine, with a progressive increase in incidence and prevalence up to the threshold of adulthood. The increase in extent and prevalence of migraine from the years of growth stresses the importance of the application and adjustment of ad hoc therapeutic (either pharmacological or not) and diagnostic measures. Indeed, the peculiar neurobiological and psychological aspects which are typical of an “evolving” organism preclude the use, by simple “transposition” or “proportion”, of the knowledge

acquired from adult-targeted studies. That requires the implementation of studies to analyze the specific responses of children and adolescents to the triptans. To date, the studies on such issues are absolutely insufficient to draw definitive conclusions and indications for the use of triptans for child and adolescent migraineurs.

Key words Migraine • Triptans • Child • Adolescent • Acute therapy

Introduction

Headache is one of the most common disorders occurring in developmental ages. The prevalence of primary headaches ranges from 10% to 20% in school-children, and increases with age: 27%–32% of adolescents (13–14 years of age) experience headache once a month, and 87%–94% suffer headache at least once per year. No sex difference is apparent until age 11 years. Female preponderance begins at about age 12 years, and during and after adolescence the female-male ratio is about 2 to 1 [1]. The prevalence of

migraine also increases with age, and estimates range from 1.2% to 3.2% at age 7 years and 4%–19% at age 15 years [2–5]. Age-related characteristics need to be taken into account in analyzing etiology, diagnosis and treatment of juvenile headache.

Many topics remain to be detected in childhood and adolescence headache [1], and these aspects should be considered in the implementation of trials on drug treatment, because it may help to avoid unexpected results.

The employment of International Headache Society (IHS) [6] criteria has shown limitations of applicability in childhood headache. Modifications to the diagnostic para-

meters have been discussed both for migraine and tension-type headache [7–15]. The suggested changes to IHS criteria for the diagnosis of migraine in children refer to shorter duration, not always unilateral localization, and the variable occurrence of photophobia and phonophobia. Interestingly, over time (even at a brief follow-up period) there is a decreased symptoms overlap and a better fulfilment of IHS diagnostic parameters, stressing the role of increasing age to the better fulfilment of the criteria [15].

A recent follow-up study [15] of patients initially classified as IHS 1.7 (patients who meet all criteria for migraine but one) and 2.3 (patients who meet all criteria for tension-type but one) showed that, after a brief follow-up period (1.5 years), nearly 30% became headache-free, about 20% changed IHS category, and the remaining 50% became migraine or tension-type headache sufferers, as shown by previous outcome studies [16, 17].

The tendency of migraine to spontaneous remission and the clinical phenomenology of the crises during developmental ages should be considered in the analysis and implementation of controlled trials.

A rational drug therapy in children and adolescents requires individualized treatments, recognizing individual (age, comorbid disorders, concurrent medications), developmental (pharmacodynamic, pharmacokinetic, pharmacogenetic) and environmental (diet, obstacles to compliance) factors that can influence disposition and response to treatment. Stage of development markedly influences the absorption, distribution, metabolism and excretion of drugs [18]. Agents that work well in adults may provoke different reactions in children. Safety and tolerability issues need specific attention, not simple transposition from adult to child or adolescent field. The “whole” always differs from the single sum of each part.

Several aspects differentiating children and adolescents from adults should be taken into account in planning a rational drug treatment. Taking into consideration these differential factors is even the *sine qua non* of the implementation of controlled trials on drug responses in children and adolescents.

Triptans in children and adolescents: state of the art

The advent of triptans is considered a revolution in the current approach to acute migraine treatment [19]. The importance of studies on triptans concerns both the efficacy of the drugs and the advancement of our understanding of the pathophysiology of migraine.

Triptans are 5-HT_{1B/1D} agonists. Currently, sumatriptan and zolmitriptan are available, while naratriptan and rizatriptan are not yet available in all countries. The first triptan

to be developed and most extensively used in adults is sumatriptan (GR43175, Imitrex). Triptans have proven effective in adults [20–27], but there are few clear data regarding the use of triptans in pediatric age.

For prepubertal age, data are scanty and relate particularly to sumatriptan, a triptan with a longer seniority of use. In the first balanced double-blind design, Hamalainen et al. [28] failed to prove any significant difference between drug and placebo. Probably children with migraine respond differently from adults to the oral administration of sumatriptan.

A recent trial [29] highlighted a promising response to sumatriptan nasal spray (sumatriptan NS 20 mg). Two hours after medication, a significant pain-free response and relief from associated symptoms was reported. A second study employed a prospective open design on a group of 58 children (mean age, 8.1 years) [30]. Of 376 attacks treated, sumatriptan NS reduced migraine pain in 80% of the cases, nausea in 78%, vomiting in 82%, and phonophobia and photophobia in 63%; there was an overall clinical improvement in 79% of cases. The tolerability overlapped with that observed in adults.

Data relating to the use of triptans in adolescents are, in part, still unclear. The profile studies (balanced double-blind design on 701 patients aged 12–17 years) supplied by the pharmaceutical company with regard to sumatriptan seem quite conservative [31, 32]. No significant efficacy of sumatriptan versus placebo has been observed. Furthermore, the sample showed a significantly lower tolerance than the group of adult patients.

In two recent studies of sumatriptan NS, one a multicentric open-label study [33] and the other a double-blind study versus placebo [34], sumatriptan was superior to placebo with regard to headache response and to the recovery of functional disability 2 hours after medication. The tolerability profiles thereby observed overlapped with those for adults. A recent open-label study [35] on zolmitriptan (Zomig) produced data of efficacy and tolerability which overlapped with those of adults. However, the drug's half-life in adolescents was slightly lower than that in adult patients (3.01 h vs. 3.75 h), probably due to a higher clearance. For this reason, some authors deemed it advisable to use the lowest dosage (2.5 mg) when treating a pediatric population [36]. Another open-label study [37] reported a pain-free headache response 2 hours after medication, entirely overlapping with that already observed in adult subjects.

The occurrence of side effects and the tolerability profile in adolescent patients confirmed the overlap with the same parameters observed in adults. Typical adverse events for sumatriptan (subcutaneous) are hot/burning and pressure sensations, injection site reaction and muscle stiffness [38].

In general we may state that there is a lack of data from clinical trials on the use of triptans in the years of growth. It is also important, as already stated, to have available studies to clarify the pharmacodynamics and pharmacokinetics of triptans in patients in the years of growth. Data from the few available studies highlight that pharmacokinetic mechanisms of triptans in children seem to be different from what has been observed in the adult population. Sumatriptan is mainly metabolized by the enzyme MAO-A (monoamine oxidase A) in the liver [39], but the possible influences of age on the action of MAO-A are not known [28]. In adults, sumatriptan causes neuroendocrine changes (increased plasma growth hormone, possible effects on plasma prolactin) [40, 41], but the neuroendocrine influences in children or adolescents are not known.

The effect of age on pharmacokinetics of zolmitriptan metabolites has been recognized in a recent study on young and elderly adults [42]. The pharmacokinetics of naratriptan in adolescents showed parameters overlapping to those for adults [43].

Studies on subcutaneous sumatriptan [44, 45] showed good efficacy in 64%–84% of patients (6–18 years), but clear data on doses, tolerability and side effects are lacking.

Summing up, in the studies carried out so far and herein analyzed, triptans were effective for reducing migraine pain and symptoms associated with headache pain (e.g. nausea, vomiting, phonophobia, photophobia) and for decreasing the times needed to return to normal activities and for the remission of symptomatology. However, data about the primary efficacy of triptans (i.e. total remission of pain) are not yet sufficient. The tolerability and safety rates are comparable to those observed in adult patients. Side effects are the same in pediatric and adult populations. In light of the results already published in the literature, triptans can be used during pediatric age. However, while waiting for further support, priority use is advised only in those cases in which migraine pain is “hard” or “impossible” to treat with other analgesic drugs. The situation is different in adolescence, for which there are sufficient data suggesting the utility of triptans. It is furthermore advised to give parents and patients precise instructions on the use of triptans, information on the peculiarity of their side effects, and the more general specifications of the drug.

Future directions

Drug treatment in pediatric age should always take into account that age-related differences markedly influence the absorption, distribution, metabolism and excretion of drugs. Recognizing individual (age, comorbid disorders, psychological factors) and developmental (pharmacodynamic, pharmacokinetic, pharmacogenetic) factors that can influ-

ence disposition and response to the treatment is a pressing task, requiring pediatric age goal-directed studies.

Good results for the use of triptans in children and adolescents have emerged from open-label studies, but evidence from placebo-controlled, double-blind, randomized, cross-over trials are absolutely required. Moreover, most data are available only in abstract form.

Clinical trials on pediatric patients are lacking, and the findings are unsatisfactory. There have been no clinical trials testing the efficacy of different triptans. Studies comparing the efficacy of triptans to that of other analgesic drugs with tested efficacy are also needed.

The effect of age in the proband samples should be considered with more attention, because samples usually comprise subjects of pre-pubertal and post-pubertal age.

The presence of “pure” and easily diagnosed migraine according to IHS criteria, instead of mixed types or forms intercalated to (episodic or chronic) tension-type headache, should be carefully assessed, because it may represent factors influencing the efficacy of the triptan.

Analyzing the characteristics of non-responders is another issue to consider in order to understand factors influencing drug efficacy and tolerability. The presence of psychiatric comorbidity should be assessed, also considering the negative implications for the prognosis [46].

Family and school environments, likely secondary gains related to migraine crises, may play an important role in influencing the course of the crises. Issues related to compliance should be carefully analyzed in children and adolescents. Indications for correct triptan intake should be absolutely given.

Another aspect that merits attention is the high rate of response to placebo, because it opens per se the importance of psychological factors in influencing head pain. Moreover, the response rate to placebo (vs. oral sumatriptan) seems to be lower in children [47] than in adolescents [28]. Studies on triptans of established efficacy in adults (most of all rizatriptan) [48–50] are absolutely lacking for child and adolescent patients.

A better comprehension of the biological mechanisms related to the responses to placebo (“how does placebo really work?”) and the likely influence of age on it may help explain the etiopathogenesis of migraine.

In extreme synthesis, the current state of research on the use of triptans for child and adolescent migraine does not lead to definitive conclusions. Many points need further examination towards the objective of giving “the best drug to each patient” according to the individual characteristics. Clearly, that issue assumes particular shadows in children and adolescents, for whom personal characteristics (e.g. biological, psychological) are strictly embedded with the clinical age-related phenomenology of headache crises, in a “crossing-over” of difficult framing and decoding.

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