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Onset of action in placebo-controlled migraine attacks trials: A literature review and recommendation

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Abstract

Background: Migraine patients want acute treatment to provide complete relief of the migraine attack within 30 minutes. Traditionally, "speed of onset of effect" is evaluated by estimating the time-point for first statistical separation of drug and placebo. The estimated onset of effect can be a few percent difference of patients being pain free in very large randomised, controlled trials. This difference, however, can be clinically irrelevant.

Methods: Placebo-controlled randomised, controlled trials with pain freedom results from 30 min to 2–4 hours were retrieved from the literature. For each time-point, the therapeutic gain (drug minus placebo) (TG) was calculated. Therapeutic gain for being pain free of 5% was chosen for the definition of "onset of action", since this is approximately 1/3 of the 16% TG and 1/4 of 21% of TG for sumatriptan 50 mg and 100 mg, respectively.

Results: A total of 22 time-effect curves based on randomised, controlled trials were analysed. Based on the "onset of action" of 5% pain freedom, the evaluated drugs and administration forms can be classified as follows: i) Early time to onset, $\leq$30 min (three randomised, controlled trials); ii) medium time to onset, 60 min (nine randomised, controlled trials); iii) delayed time to onset, 90–120 min (10 randomised, controlled trials).

Conclusion: Only three non-oral administration forms with a triptan (subcutaneous sumatriptan and nasal zolmitriptan) resulted in an "onset of action" at $\geq$30 min; in the future, early onset of action should be a priority in the development of new drugs or new administration-forms for the treatment of acute migraine attacks.

Keywords

Migraine, clinical trials, onset of action, triptans, lasmiditan, gepants

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Introduction

For the last two decades, the primary efficacy parameter in randomised, controlled trials comparing drugs for the treatment of migraine attacks with placebo has been pain freedom at 2 hours (1–3). Previously, it was headache relief (a decrease of headache from moderate or severe to none or mild) after 2 hours (4). The 2-hour time-point was chosen as the approximate time for maximum plasma concentration (C_{max}) of most triptans in humans (5) and as a clinically meaningful early outcome.

The 2-hour pain freedom has been the standard parameter in placebo-controlled and comparative acute drug randomised, controlled trials, and in systematic reviews (4,6,7), meta-analysis (8), and Cochrane Reviews (9,10).

The patients, however, want early, complete relief of all migraine symptoms, without recurrence and without adverse events (11–13). In two studies, the patients chose complete relief of migraine as early as 30 minutes, no adverse events, and no recurrence as their major priorities (14,15). Accordingly, one of the attributes of an optimal agent for the treatment of migraine attacks was described in 2007 as "an almost immediate onset of action" (16). The speed of onset of the

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treatment effect on migraine attacks has, however, only been evaluated in few randomised, controlled trials (e.g. 17,18), in one pharmacokinetic study (19), and systematic reviews (4,20,21). Traditionally, "speed of onset of effect" has been investigated by evaluating early statistically significant differences of pain freedom (or headache response) of active drug versus placebo. Alternatively, in a few comparative RCTs of two drugs, time-to-events analysis (22,23) has been used to evaluate which of the drugs resulted in an earlier effect within 2 hours (24,25).

The estimation of the onset of effect as the first time-point of a statistically significant difference can in our view sometimes be misleading from a clinical point of view. This addresses the issue of statistical, significant differences versus clinically relevant differences. In an abstract of a large randomised, controlled trial comparing intranasal zolmitriptan 5 mg (n = 935) and placebo (n = 933) for speed of onset it was stated: "Significantly higher pain-free rates were obtained with zolmitriptan nasal spray, compared with placebo, from 15 minutes post dose onward ($p < 0.005$)" (17). The therapeutic gain (verum minus placebo) for pain free at 15 min was (zolmitriptan 1.4% minus placebo 0.4%) 1.0% (95% CI: 0.1– 2%) (17). This statistically significant difference is only due to the large number of patients (n = 1868). A 1% absolute difference for pain freedom between zolmitriptan and placebo is, however, clinically irrelevant.

The time-to-event analysis can preferably be used to compare the time-effect curves of two active drugs. A hazard ratio for drug A being more likely than drug B to result in an effect in the next few minutes can be calculated; for example, 62% for rizatriptan 10 mg versus naratriptan 2.5 mg (23,25). This time-to-event analysis gives no information on the onset of effect. Primarily, it was a concept for analysing triptans with more or less fast absorption. The calculation of the hazard ratio also depends on the final clinical response after 2 hours (23).

Currently, there is no consensus on how to evaluate the "onset of action or the speed of response", taking also the clinical relevance of the response of onset of action into account.

The aim of this review is to provide a basis for such a consensus by reviewing the early part of the time-effect curves for the pain freedom response after oral, and in a few cases non-oral, administration of triptans, lasmiditan (a 5-HT_{1F} receptor agonist), and the oral CGRP receptor antagonists telcagepant, rimegepant and ubrogepant. Based on the experience gain from this review we suggest an, in our view, clinically relevant therapeutic gain that should determine the time-point at which a clinically relevant onset of action is present in migraine attack trials. In addition, the aim is also to provide the clinician with an easy-to-remember figure for onset-of-effect that can be used when they judge controlled clinical trials of migraine attack treatment. We propose a 5% therapeutic gain for pain free as the cut off value for defining a clinically relevant onset of the treatment of migraine attacks in randomised, controlled trials.

Methods

We hand-searched the literature for placebo-controlled RCTs in which moderate to severe migraine headaches were treated with triptans, lasmiditan, telcagepant, rimegepant and ubrogepant for pain freedom results prior to and after 2 and 4 hours. Reference lists in the following references were searched (4–6,8–10,16,26,27). In a few cases, we found more extensive information on pain free results in the GSK Trial Registry (28).

Oral sumatriptan 50 mg or 100 mg are standard doses for the treatment of migraine attacks (5,8). After administration of sumatriptan 50 mg 100 mg, the therapeutic gains (active drug minus placebo) for pain freedom at 2 hours are 16% and 21%, respectively (9). We applied a cut-off difference for a relevant difference as a therapeutic gain of 5% for pain freedom. This value is approximately 1/3 of the therapeutic gain of sumatriptan 50 mg (16%) and 1/4 of the therapeutic gain of sumatriptan 100 mg (21%).

For each time-point from 10–20 min, 30 min, 60 min, 90 min, 2 h, and 4 h, the therapeutic gain (therapeutic gain in percentage) with 95% confidence intervals (CI) was calculated (29) in order to construct the time-effect-curves for pain freedom. Only statistically significant differences, regardless of relevance, are shown in Table 1. We used large single placebo-controlled randomised, controlled trials data from systemic reviews and meta-analyses.

In the few cases in which the results for RCTs in which two doses of the same active drug were investigated, the time-to-onset of action of these doses were compared.

Results

The time-to-onset of action, defined as a therapeutic gain $\geq$5% for pain freedom in 22 dose-response curves, are shown in Table 1 and Table 2. Subcutaneous sumatriptan 6 mg has the earliest therapeutic gain $\geq$5% (8%) after 20 min in one randomised, controlled trial (30). For intranasal zolmitriptan 5 mg, the therapeutic gains were $\geq$5% after 30 min in two randomised, controlled trials (both 5%) (17,18), whereas in one randomised, controlled trial with intranasal zolmitriptan the therapeutic gain was $\geq$5% (12%) after 60 min (31). For intranasal sumatriptan 20 mg,

Table 1. "Onset of action", therapeutic gain (TG) > 5% for pain freedom (PF) of up to 2 hours of systemic and oral triptans. Only statistically significant therapeutic gains (effect after active drug minus effect after placebo (Pl)) are presented with 95% confidence intervals in parentheses. The first therapeutic gains with onset of action are presented in bold.

Drug and dose (Ref)	Number of patients	TG for PF, 10–20 min	TG for PF, 30 min	TG for PF, 60 min	TG for PF, 90 min	TG for PF, 2 h
Intranasal zolmitriptan and sumatriptan.						
Zolmitriptan (Z) 5 mg (31)	Z (n = 464) Pl (n = 451)		4% (2–8%)	**12% (7–16%)**		27% (21–32%)
Zolmitriptan (Z) 5 mg (17)	Z (n = 935) Pl (n = 933)	15 min: TG = 1% (0.1–2%)	**5% (3–8%)**	13% (10–17%)		22% (18–26%)
Zolmitriptan (Z) 5 mg (18)	Z (n = 235) Pl (n = 226)		**5% (1–9%)**	18% (12–24%)		30% (23–37%)
Sumatriptan (S) 20 mg (9)	S (n = 891) Pl (n = 488)			**10% (5–14%)**[b]		21% (17–25%)
Optinose nasal sumatriptan (OS) 22 mg (40)	OS (n = 108) Pl (n = 104)					**17% (5–28%)**
Oral and subcutaneous sumatriptan.						
Almotriptan (A) 12.5 mg (20)	A (n =721) Pl (n = 355)		2% (0.2–3%)	**5% (2–8%)**	14% (10–18%)	21% (16–26%)
Rizatriptan (RZ)10 mg (6)	RZ (n = 2046) Pl (n = 1249)		2% (0.1–2%)	**9% (7–11%)**	19% (17–21%)	31% (28–34%)
Eletriptan (E) 40 mg (32,33)	E (n = 726) Pl (n = 524)			**6% (4–8%)**		22% (1–26%)
Sumatriptan (S) 50 mg (9)	S (n = 3922)[c] Pl (n = 2525)[c]			3% (1–5%)		**16% (14–18%)**
Sumatriptan (S) 100 mg (9)	S (n = 4017)[c] Pl (n = 2554)[c]			**6% (4–7%)**		21% (20–24%)
Subc. suma-triptan (S) 6 mg (30)	S (n = 734) Pl (n = 370)	20 min **8% (5–10%)**	30 min 15% (12–18%)	60 min 39% (34–44%)		
Zolmitriptan (Z) 2.5 mg (34)	Z (n = 475) Pl (n = 241)			**5% (1–9%)**		21% (15–26%)
Zolmitriptan (Z) 5 mg (34)	Z (n = 475) Pl (n = 245)			**7% (2–11%)**		20% (14–26%)
Naratriptan (N) 2.5 mg (25,39)	N (n = 340) Pl (n = 209)				**6% (1–11%)**	9% (2–14%)
Frovatriptan (F) 2.5 mg (41–43)	F (n = 670) Pl (n = 426)					**7% (4–10%)**

[a]The 5% pain freedom is approximately 1/3 of 16 % (therapeutic gain for sumatriptan 50 mg after 2 hours) and 1/4 of 21% (therapeutic gain for the 100 mg dose) and was chosen as a reasonable clinically relevant difference for onset, see discussion in text.
[b]After 60 min: S (n = 320) and Pl (n = 179).
[c]number of patients at one hour.

Table 2. "Onset of action" , therapeutic gain (TG) > 5% for pain freedom (PF) up to 2 hours of lasmiditan (a 5-HT1F receptor agonist) and three gepants (CGRP receptor antagonists: Telcagepant, rimegepant and ubrogepant). Only statistically significant therapeutic gains (effect after active drug minus effect after placebo (Pl)) are presented with 95% confidence intervals in parentheses. The first therapeutic gains with onset of action are presented in bold.

Lasmiditan.						
Drug and dose (Ref.)	Number of patients	TG for PF, 10–20 min	TG for PF, 30 min	TG for PF, 60 min	TG for PF, 90 min	TG for PF, 2 h
Lasmiditan (LA)100 mg (35)	LA (n = 1035) Pl (n = 1063)			3% (0.8–6%)	**9% (6–12%)**	12% (8–15%)
Lasmiditan (LA) 200 mg (35)	LA (n = 1046) Pl (n = 1063)			**9% (6–11%)**	15% (11–18%)	17% (13–21%)
Oral gepants						
Telcagepant (T) 280/300 mg (37,38)	T (n = 669) Pl (n = 348)				**8% (4–11%)**	17% (12–23%)
Rimegepant (RI) 75 mg (44)	RI (n = 537) Pl (n = 535)					**8% (3–12%)**
Rimegepant (RI) 75 mg ODT (36)	RI (n = 669) Pl (n = 683)				**8% (4–11%)**	10% (7–15%)
Ubrogepant (UB) 25 mg (45)	UB (n = 435) Pl (n = 456)					**6% (1–12%)**
Ubrogepant (UB) 50 mg (45)	UB (n = 464) Pl (n = 456)					**7% (2–12%)**

Note: See Table 1 for the choice of therapeutic gain for 5% pain freedom for defining the "onset of action".

the therapeutic gain was 10% after 60 min (9). In seven oral time-effect-curves the therapeutic gain was ≥5% after 60 min: almotriptan 12.5 mg, (therapeutic gain- = 5%) (20), rizatriptan 10 mg (therapeutic gain = 9%) (6), eletriptan 40 mg (therapeutic gain = 6%) (32,33), sumatriptan 100 mg (therapeutic gain = 6%) (9), zolmitriptan 2.5 mg (therapeutic gain = 5%) (34), zolmitriptan 5 mg (therapeutic gain = 7%) (34), and lasmiditan 200 mg (9%) (35). In three oral time-effect curves, the therapeutic gain was ≥5% after 90 min: Lasmiditan 100 mg (therapeutic gain = 8%) (35), rimegepant (orally dissolving tablets) 75 mg (therapeutic gain = 8%) (36), telcagepant 280/300 mg (therapeutic gain = 10%) (37,38), naratriptan 2.5 mg (therapeutic gain = 6%) (25,39). In seven time-effect curves, the therapeutic gain was ≥5% after 2 h: Nasal powder inhaled sumatriptan 22 mg (therapeutic gain = 17%) (40), sumatriptan 50 mg (therapeutic gain = 16%) (9), frovatriptan 2.5 mg (therapeutic gain = 7% (41–43), rimegepant 75 mg (therapeutic gain = 8%) (44), ubrogepant 25 mg (therapeutic gain = 6%) (45), and ubrogepant 50 mg (therapeutic gain = 7%) (45).

Doubling the dose of oral sumatriptan and oral lasmiditan increased the therapeutic gain for pain freedom after 2 h (see Tables 1 and 2). For both drugs, the higher dose had an earlier "onset of effect" than the lower dose. "Onset of effect" was 60 min for sumatriptan 100 mg and 120 min for sumatriptan 50 mg; for lasmiditan 200 mg and 100 mg, "onset of effect" was 60 min and 90 min, respectively (Table 2).

Discussion

New drugs like triptans (4,5,8–10), gepants (rimegepant and ubrogepant) (36,44,45), and ditans (lasmiditan) (35) have been developed in the last 30 years for the pharmacotherapy of acute migraine attacks. These new drugs have primarily been evaluated for efficacy at 2 hours, a time-point near the T_{max} for several of these drugs (5,35,36). The primary efficacy measure 2 hours after oral administration of the drugs has been either headache relief (a decrease from moderate or severe headache to none or mild) or pain freedom at 2 hours, as recommended by the International Headache Society (IHS) (1–3,8).

Patients primarily want complete relief of all migraine symptoms as early as 30 min, without adverse events, and no recurrence (14,15). The early aspects of treatment of migraine attacks have only been evaluated in few randomised, controlled trials; for example, two RCTs (17,18), in one pharmacokinetic study (19), and three systematic reviews (4,20,21).The speed of onset of the drug effect on migraine attacks has been investigated by evaluating early statistically significant differences of pain freedom (or headache relief) of active drug versus placebo. A statistically significant *p*-value is, however, not *per se* a useful outcome for evaluating the clinical relevance of an early effect in an RCT. Intranasal zolmitriptan 5 mg resulted in a significant pain free difference after 15 minutes ($p < 0.05$), but the therapeutic gain was only 1% (17), a clinically irrelevant difference.

This statically significant (but clinically irrelevant) result in a very large RCT (n = 1868) demonstrates, in our view, the need for defining one relevant pain-free response that can be used to evaluate "onset of action" of drugs in acute RCTs for migraine. After evaluating the 22 RCTs presented in Table 1 and Table 2, we suggest that the time-point at which the therapeutic gain (active drug minus placebo) for pain freedom is ≥5%, and statistically significant, should be the time-point for "onset of action". The choice of 5% is arbitrary. We used the therapeutic gain for pain freedom at 2 hours for two standard clinical doses, oral sumatriptan 50 mg (therapeutic gain = 16%) and sumatriptan 100 mg (therapeutic gain = 21%), as the basis for suggesting a clinically relevant outcome. The five percentage therapeutic gain for pain freedom was chosen. This number reflects approximately 1/3 of 16% (therapeutic gain for 50 mg sumatriptan) and 1/4 of 21% (therapeutic gain for 100 mg sumatriptan) (9).

The "onset of action" based on ≥5% therapeutic gain (TG) for pain free in 22 RCTs with oral, intranasal and subcutaneous administration of triptans, gepants and an oral ditan, are shown in Table 1 and Table 2. Only for subcutaneous sumatriptan 6 mg (T_{max} = 10 min) was the TG, 8% (95% CI: 5–10%) at 20 min, greater than 5% before 30 min. Intranasal zolmitriptan 5 mg (intranasal absorption accounts for 70% of the total exposure to zolmitriptan in the first hour post-dose (17)) resulted in "onset of action" at 30 min, see Table 1.

When evaluating the results for oral drugs, it is noteworthy that early results are often not available, in most cases probably because the RCTs were not designed to evaluate the early time-effect curves up to 2 hours. The magnitude of the therapeutic gain for pain freedom at the first time-point ≥5% is in most cases only marginally higher than 5%, indicating that an unknown statistical effect at the prior time-points, if present, is most likely less than 5%.

In the oral RCTs presented in Table 1 and Table 2, "onset of action" was observed after 60 min in seven RCTs (5%, 9%, 6%, 6%, 5%, 7%, 9%), after 90 min in four RCTs (6%, 9%, 8%, 8%), and after 120 min in five RCTs (16%, 7%, 8%, 6%, 7%). As would be expected because of our choice of 5% TG for "onset of action", the TGs for onset for oral drugs are, with the exception of TG = 16% for oral sumatriptan 50 mg (9), just above the 5% (6–9%).

The time to "onset of action" of these oral drugs depends most likely not only on the speed of absorption of these drugs but also on the maximum effect, which is usually determined as TG for pain free at 2 hours, before any rescue medication is allowed. The therapeutic gain for pain freedom after 2 hours increased with doubling the dose: From 16% (sumatriptan 50 mg) to 21% (sumatriptan 100 mg), see Table 1, and from 12% (lasmiditan 100 mg) to 17% (lasmiditan 200 mg), see Table 2; "onset of action" of the higher doses of these two drugs are in both cases earlier than the lower ones, see Table 1. This is most likely due to a simple effect of E_{max} at 2 hours on time-to-onset: An increase in E_{max} will result in a steeper early time-effect curve, allowing early relevant separation from the placebo curve. This is illustrated for lasmiditan 100 mg and 200 mg in Figure 1. This interpretation of the possible relationship between E_{max} and the time-point of "onset of action" is supported by the results of oral zolmitriptan 2.5 mg and 5 mg: at 2 hours, the TGs for pain freedom were 21% (2.5 mg) and 20% (5 mg) and for both doses the "onset of action" occurred after 60 min (Table 1).

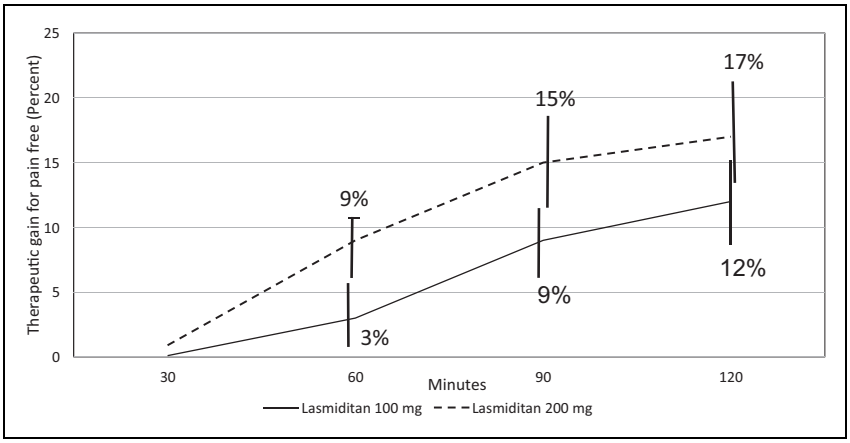

Figure 1. Therapeutic gain (pain freedom for lasmiditan minus pain freedom of placebo) for up to 2 hours for oral lasmiditan 100 mg and 200 mg (35). Note that therapeutic gain for lasmiditan 200 mg is above 5% after 60 min, whereas this is first the case therapeutic gain for 100 mg after 90 min.

When evaluating time-effect curves, for example, for two drugs for migraine attack treatment one should, in addition to using a fixed, clinically relevant criterion for difference between drug and placebo, also evaluate whether there is a difference of E_{max} of the two drugs, which could influence the result.

Conclusion

Patients want early relief from the symptoms of migraine attacks. With the current available treatment options, it is unrealistic to fulfil the optimum wish of patients, which is complete relief of all migraine symptoms within 30 minutes (14,15). Even with the most quickly acting drug, subcutaneous sumatriptan 6 mg, the effect on pain freedom after 30 min is observed in only a minority of patients, 17% (TG = 15%), see Table 1. In these circumstances, we suggest that a therapeutic gain of 5% pain freedom for an oral drug could be a suitable difference from placebo when judging when a clinically relevant response for onset of action has been observed in a randomised, clinical trial.

Using this definition for onset of action, the currently reviewed treatments can be classified in three groups concerning time to "onset of action"; for details, see Table 1 and Table 2:

(I) Early time to onset (≤30 min): Subcutaneous sumatriptan 6 mg, and intranasal zolmitriptan 5 mg (two RCTs).
(II) Medium time to onset (60 min): Intranasal zolmitriptan 5 mg (one RCT), oral almotriptan 12.5 mg, oral eletriptan 40 mg, oral sumatriptan 100 mg, oral zolmitriptan 2.5 and 5 mg, oral lasmiditan 200 mg, and intranasal sumatriptan 20 mg.
(III) Delayed time to onset (90–120 min): oral sumatriptan 50 mg, oral naratriptan 2.5 mg, oral frovatriptan 2.5 mg, oral rizatriptan 5 mg, intranasal Optinose (sumatriptan) 22 mg, oral lasmiditan 100 mg, rimegepant 75 mg, oral ODT rimegepant 75 mg, oral telcagepant 280/300 mg, and oral ubrogepant 25 and 50 mg.

Clinical implications

- Onset of antimigraine effect should not be judged solely on a statistically significant effect.
- Onset of action should be estimated as relevant difference between active drug and placebo.

Declaration of conflicting interests

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