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Analgesic Onset of Action or Onset of Relief in Neuropathic Pain

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Time to onset of relief is quite important for chronic neuropathic pain patients, we learned recently. In 2015 we developed a new topical analgesic formulation to treat localized neuropathic pain, based on the mother of all anti-epileptics, phenytoin. [1] Our findings provoked us to look into the established terms: 'action of onset' and 'action of relief'. It seems that those two concepts are often regarded as identical. Action of onset however seems more popular, as more literature can be identified in PubMed based on the keyword combination 'onset of action' (more than 20.000 hits) compared to ' onset to relief' (less than 4000 hits). This indicates a dominance of a pharmacologically driven definition (onset of action) over a patient-centered one (onset of relief).

Many of the pain patients we see in our clinic for neuropathic pain, complain about unwanted side effects and tolerability issues of their prescribed medication (gabapentoids, opioids, antidepressants). They also point out that it often takes quite some time before they notice the first pain relief. Such late onset of action is linked to the fact that various analgesics such as amitriptyline, pregabalin and gabapentine generally need a step by step increase of dose, in order to reduce tolerability issues.

During the development steps of phenytoin cream, our patients informed us of its quick 'action of onset' after application, mostly within a time-frame of 15-20 minutes. This triggered us to develop a single-blind response test based on placebo and active cream, in order to identify responders during their first visit to our clinic. [2] We could thus reduce the chance that patients, after an initial placebo response of some weeks, eventually end up as non-responders to the cream. This test is easy and takes only a minute to conduct. We first document the baseline Numeric (Pain) Rating Scale (NPRS) score of two localized area's (for instance both feet). Patients then receive a fingertip unit (0.5 gram) placebo to rub in on one foot, followed by phenytoin cream to apply on the other foot. After 10-20 minutes, we evaluate the NPRS at both sites. We define a responder as those patients noticing a difference of at least 30% pain reduction or 2 points reduction on the NPRS between placebo and the active cream, or if the patient clearly states there is a real meaningful difference in pain noticeable between the two localizations.

We found that especially patients suffering from localized burning pain due to neuropathy, where pain is felt in the skin, are particularly clear responders to phenytoin cream. Once identified as a responder, patients receive a prescription for phenytoin cream. Based on the experience during the response test, they have gained confidence in this topical therapy, due to its quick action of onset. In case of chronic pain syndromes, such quick action of onset is quite helpful for maximizing compliance. In case of topicals, in the absence of systemic side effects, tolerability issues are rare and thus not leading to patients dropping out of therapy early.

During this process, we thus had opportunities to discuss with patients what they experienced as time to onset of action (notable analgesia). We came to realize that the terminology used, 'action of onset', is not a patient centered concept. A patient centered concept would be 'action to notable pain relief'. Patients report that a decrease of 2 points on the NRS compared to baseline, or a decrease of around 25% in general is notable and relevant, of course experienced in a short time frame of maximal 30 minutes.

Onset of action

'Onset of action' is often defined based on a biochemical or physiological read out. For instance, in the development of asthma drugs time to onset of action can be defined as 'time to 15% increase of Forced expiratory volume in 1 second (FEV1). [3]

In pain studies, we can find definitions based on statistics, for instance time to onset of action x is defined as: 'mean percentage pain reduction for active analgesia first significantly differentiated from placebo at x minutes.' [4] In certain papers 'onset of action' is used synonymously to 'onset of pain relief', for instance as the first study day on which a patient reported > 1-point reduction in pain relative to baseline. [5] If, however, such period of time is measured in days rather than in hours, we can ask ourselves whether patients would notice such 1 point difference after many days, as an onset of notable pain relief. One (1) point decrease in pain intensity reached in 10 minutes might be notable and relevant for a patient, but 1 point decrease after 3 days might be quite debatable and perhaps not notable.

Onset of relief

Onset of relief should not be defined based on statistics alone. For instance, to define time to onset of relief based on a statistical difference of one point on the NPRS between placebo and an analgesic does not need to be meaningful for the patient. In a pooled analysis based on 2 pivotal studies of the effects of a controlled release gabapentine, time to onset of pain relief was defined as the first of two consecutive days with significantly ($P < 0.05$) greater percent reduction in the NRS score from baseline in the active group compared with the placebo group. [6] More such examples can be found in literature. For instance, the time period to reach a 50% reduction in the original pain severity was used as a parameter for evaluating the time for onset of pain relief. [7] Or, in a migraine study, onset of relief was defined as the earliest time point at which a statistically significant difference in pain relief compared with placebo was achieved and maintained through 2 hours after dosing. [8]

Given the above it seems important to realize that time to 'onset of action' can be something quite different from time to 'onset of notable pain relief'. In pain studies of the future it is recommended to use a patient-centered variable, and not a numerical-statistical decrease of a pain score.

Conflict of interest

The author is one of the patent holders of two patents related to repurposing of phenytoin: topical phenytoin for use in the treatment of peripheral neuropathic pain and topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain.

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