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Identification of Responders for Pain Treatments: Did we find the Holy Grail?

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ABSTRACT

Recent focus in pain research is to phenotype and genotype patients with the aim to better target therapies. Until now, no major breakthroughs are presented in this field. The pathophysiology of pain due to polyneuropathy partly may reside in the skin. Polyneuropathy is usually symmetrical, and the same holds true for pain intensity in both feet. Therefore, topical analgesics present an interesting treatment option.

To avoid treatment delay after consultations we developed a quick response evaluation. Responders can be fast identified through a single-blind or a double-blind placebo-controlled response tests (SIBRET or DOBRET), when a patient has 2 areas of comparable pain intensity as it is often seen in polyneuropathy. On one area placebo cream and on the other area an active cream will be applied. A responder is defined based on 1) response within 30 minutes, 2) a difference of at least 2 points on the 11-point numerical rating scale in favor of the active cream. This diagnostic tool for identifying an optimal analgesic treatment has proven to be fast and simple in our hands.

INTRODUCTION

Genetic profiling and qst evaluation: current limitations

At the 17th World Congress on Pain, held in Boston in September 2018, many scientists focused on stratifying pain patients in order to be able to match the right therapy to the right subgroup. The techniques currently being focused on are quantitative sensory testing (QST), genomic profiling, and channel profiling in the skin. QST is used to phenotype patients with neuropathic pain, testing the function of several nerve fibers in the skin that conduct sensory qualities such as heat, cold, pressure and touch. By combining data of thousands of patients, researchers have defined 3 sensory phenotypes: thermal hyperalgesia, mechanical hyperalgesia, and sensory loss [1]. However, QST has a limited scope as it can only predict partially treatment effects for a few drugs [2].

Genetic profiling has yet not lead to any positive pain trial. One recent trial, for example, showed that 8 patients, who were heterozygous carriers of the Nav1.7 R1150W polymorphism, responded better to the selective Nav1.7 blocker TV-45070, though the trial was not positive on its primary endpoint [3].

Identifying subgroups and the promise of individualized medicine

The current interest in treatments that work better in some patient subgroups encourages researchers and physicians to find other ways to identify responders. Techniques to personalize pain medicine, characterized as fast, clear and cheap,

would be very welcome. Moore et al. have already pointed out that personalized medicine is needed especially in non-cancer pain, where differences in underlying pathophysiological mechanisms of pain generation may occur even in one disease entity [4]. For any treatment, a profound clinical response is confined to a relatively small proportion of patients [4]. Moore et al. state that at present we cannot identify responders before treatment [4]. The problem of predicting the right therapy is possibly solved with the placebo-controlled response test.

Topical treatments as an inroad to personalized pain treatment: development of response tests

At the Institute for Neuropathic Pain in the Netherlands, we have developed a response test to identify responders to phenytoin cream or to any other compounded cream containing co-analgesics such as baclofen, ketamine or amitriptyline.

The development of the response test began with the application of an active analgesic cream on the area of localized neuropathic pain. When the patient reported a pain reduction of 2 points on the 11-point numerical rating scale (NRS), they were labeled as a responder and a prescription was provided. Analgesic creams however are prone to a large placebo effect. Thus, further development led to the single-blind placebo-controlled response test (SIBRET). This test is suitable for symmetrical polyneuropathy, affecting both lower legs and/or feet with the same level of pain intensity. This type of polyneuropathy is very common, for example in painful diabetic neuropathy and chronic idiopathic polyneuropathy.

The patient applies a placebo cream on one area (e.g. right foot), and phenytoin cream on the other area (e.g. left foot). If within 30 minutes the patient experiences a difference in pain intensity of 2 points on the NRS between the 2 areas in favor of the phenytoin cream, the patient is identified as a responder, and will be prescribed phenytoin cream (figure 1). This is a fast and cost effective way of selecting responders and affirms that the tested cream is the correct treatment for the patient. Non-responders will be invited to repeat the SIBRET with another analgesic cream. Further development has led to the double-blind response test (DOBRET), with which any bias of the treating physician is ruled out.

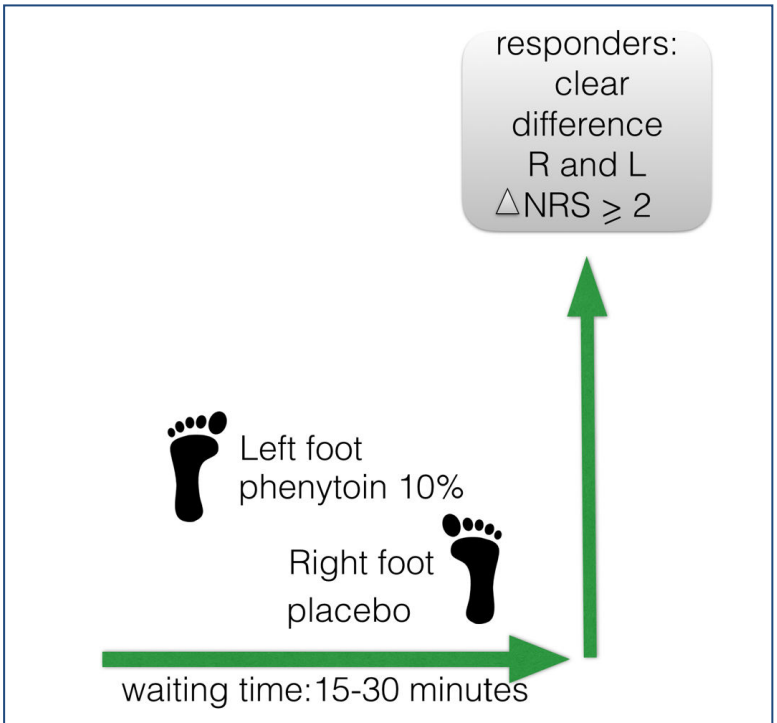

Figure 1: DOBRET: a double-blind response test, where we apply active cream on one foot and control cream on the other feet, ask the patient to evaluate after 309 minutes and subsequently we break the blind to analyze whether the patient was a responder

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Value of response test to enrich populations in randomized controlled trials (rct's)

The response test could also result in positive clinical trials for topical analgesics, enriching the trials with responders on the SIBRET or the DOBRET. More pragmatic trials are urgently required in order to study analgesics in responder groups. One example is the enriched enrolment, randomized withdrawal (EERW) pain trial. Currently we are preparing such trials in 2 academic centers in the Netherlands. First, in the open label phase, responders are selected and treated for 8 to 12 weeks. Thereafter, patients will be randomized in a double-blind fashion to a placebo and active arm. The common used primary endpoint is the time to exit: the duration of the analgesic effect. Patients in the placebo group are expected to experience more pain. The time to this point (e.g. 2 points difference on the NRS, compared with the baseline entering the double blind phase) is called time to exit. This innovative trial design, if properly constructed and conducted, is entirely appropriate in the context of chronic pain to explain whether a treatment is efficacious, and to pragmatically support decisions over its use.[4] In the near future we will use both the SIBRET and the DOBRET to include initial responders in our trials on phenytoin cream. The EERW trial design in particular will elucidate the value of the response test for a longer period of time.

CONCLUSION

Using SIBRET or DOBRET can help to identify responders and to exclude placebo-responders. This simple design has great value, both in clinical practice as well as for designing RCT's. In clinical practice, it helps to directly identify responders and prescribe the correct topical analgesic, for instance based on a compounded cream containing co-analgesics such as baclofen, amitriptyline or phenytoin. In RCT's it helps enriching the population, and thus creating a stronger instrument for evaluating the efficacy in the selected population.

DISCLOSURE

The authors are holders of two patents: 1) topical phenytoin for use in the treatment of peripheral neuropathic pain and 2) topical pharmaceutical composition containing phenytoin and a (co-) analgesic for the treatment of chronic pain. The authors report no other conflicts of interest in this work.

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