Double-blind placebo-controlled response test with phenytoin 10% and placebo creams in patients with painful polyneuropathies

Drs. David J. Kopsky,[1] MD & Prof. dr. Jan M Keppel Hesselink,[2] MD, PhD

[1]Institute for Neuropathic Pain Amsterdam, [2]Institute for Neuropathic Pain Bosch en Duin

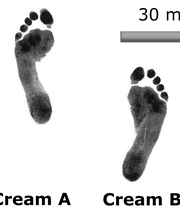
www.neuropathie.nu

Background

Painful polyneuropathy can be very debilitating and affecting the quality of life considerably. Prevalence is between 3 to 7%, mainly caused by diabetes. Painful polyneuropathy is mainly symmetrical, starts in the toes and gradually in time expands up to the knees. The symptoms are numbness, and due to overactivity of the diseased nerves: burning, painful cold, electric shocks, tingling, pins & needles, and/or itch. Most of the patients stop taking oral neuropathic pain medication within 1 year, due to no effect and/or too much side effects. Therefore new treatment modalities are urgently needed.

Fast pain reduction (within 30 minutes) after topical phenytoin application and the symmetrical nature of painful polyneuropathy prompted us to develop a fast response test to identify early responders.[3,4] First we developed a single-blind,[1] followed by a double-blind placebo-controlled response test (DOBRET).[2]

DOBRET



Responders:

- ↓ ≥2 NRS
- Δ ≥1 NRS between A & B in favor of phenytoin 10%

Aim

To evaluate the efficacy and practical use of DOBRET.

Contact information

Institute for Neuropathic Pain
David J. Kopsky, MD
info@neuropathie.nu
+31 6 2867 1847

Material & Methods

From September 2018 to December 2018, data were collected from all patients with painful polyneuropathy who underwent the DOBRET with phenytoin 10% and placebo creams in our Institute for Neuropathic Pain.

Entry criteria: ≤1 difference in baseline 11-point numerical rating scale (NRS: 0 no pain, 10 most pain ever) between both pain areas (mostly left and right foot), with NRS ≥4 at baseline.
The labels of the test tubes (phenytoin 10% and placebo creams) were blinded and renamed with consecutive numbers and as 'A' and 'B' by an independent person. Patients were asked to score their pain in both areas on the NRS prior and 30 minutes after application, where after deblinding followed.

Responders were defined as patients who experienced
(1) within 30 minutes;
(2) ≥2 NRS pain reduction; and
(3) ≥1 NRS difference between the phenytoin 10% cream and the placebo cream area in favor of phenytoin 10% cream. Patients were asked to score their pain in both areas on the NRS prior to the cream applications and again 30 minutes later, where after the two creams were deblinded by the treating physician.
Responders were then prescribed phenytoin 10% cream.

To compare the means of pain reduction after the application of phenytoin 10% and placebo creams on different areas in the same responder, the Wilcoxon signed-rank test was performed (matched pairs).

References

1) Kopsky DJ, Keppel Hesselink JM. Single-Blind Placebo-Controlled Response Test with Phenytoin 10% Cream in Neuropathic Pain Patients. *Pharmaceuticals.* 2018; 11(4).
2) Keppel Hesselink JM, Kopsky DJ, Bhaskar AK. Ethical justification of single-blind and double-blind placebo-controlled response tests in neuropathic pain and N-of-1 treatment paradigm in clinical settings. *J Pain Res.* 2019; 12:345-352.
3) Kopsky DJ, Keppel Hesselink JM. Phenytoin Cream for the Treatment of Neuropathic Pain: Case Series. *Pharmaceuticals*. 2018; 11(2).
4) Keppel Hesselink JM, Kopsky DJ, Bhaskar AK. Skin matters! The role of keratinocytes in nociception: a rational argument for the development of topical analgesics. *J Pain Res.* 2016; 10:1-8.

Results

In total 14 patients were eligible for the DOBRET (50% female).
Age: 5-76 yrs, mean 60.1 yrs (SD: 16.6).
Duration pain: 0.3-20.8 yrs, mean 5.4 yrs (SD: 6.7).

Diagnosis	N
Chronic idiopathic axonal polyneuropathy	5
Chemotherapy induced polyneuropathy	4
Diabetic polyneuropathy	3
Small fiber neuropathy	1
Polyneuropathy due to mixed connective tissue disease	1

Locations	N
Both feet	8
Both feet and lower legs	3
Both feet, lower legs and hands	1
Fingertips	2

Characteristics & Effect	Responders		All patients	
	Ph 10%	Placebo	Ph 10%	Placebo
Pre-treatment NRS (SD)	6.2 (1.5)	6.2 (1.5)	6.0 (1.3)	5.9 (1.3)
Post-treatment NRS (SD)	3.1 (1.1)	4.4 (1.2)	4.2 (2.2)	4.7 (2.0)
Mean % pain reduction (SD)	50.7 (10.3)	28.3 (13.1)	32.1 (31.1)	21.1 (31.8)
MPR30 % (N)	100 (6)	50.0 (3)	50.0 (7)	35.7 (5)
MPR50 % (N)	**66.7** (4)	**16.7** (1)	35.7 (5)	21.4 (3)

Ph: phenytoin, MPR: minimal pain reduction, MRR30: ≥30% MPR, MRR50: ≥50% MPR

In all patients, NRS pain reduction in phenytoin 10% and placebo cream applied areas is 1.8 (SD: 1.7) and 1.3 (SD: 1.7) respectively (p=0.14).

In 6 responders, NRS pain reduction in phenytoin 10% and placebo cream applied areas is 3.1 (SD: 0.3) and 1.8 (SD: 0.4) respectively (p<0.03).

One outlier had unconfirmed small fiber neuropathy and unilateral sciatic pain: 50% reduction in placebo, no effect in phenytoin 10% areas. Without this outlier, the mean percentage pain reduction of the phenytoin 10% and placebo cream applied areas were 34.6% (SD: 30.9) and 18.9% (SD: 31.9) respectively (p=0.012).

Discussion

The DOBRET can be regarded as a selection tool for personalized medicine, because only to responders phenytoin 10% cream will get a prescription. This paradigm reduces unnecessary waiting time, to find an adequate therapy.

The DOBRET can be performed with any suitable topical analgesic, such as amitriptyline, clonidine, ketamine or baclofen.

This first DOBRET, resulting in 6 out of 14 responders. More than one third of the patients had at least 50% pain reduction after phenytoin 10% cream application. This can be translated to a number needed to treat (NNT) of 3.

The current NNT for neuropathic pain treatments is for a capsaicin 8% patch 12.0, capsaicin 0.075% cream 6.6, oral pregabalin 7.0, oral amitriptyline 5.1 and duloxetine 6.8.

The DOBRET will be evaluated in RCTs to explore its predictive capacity. The DOBRET might pave the way for a better understanding of the relation between a clinical syndrome, its pathophysiology and the mechanism of action of the selected active pharmaceutical ingredient in the topical formulation.

Conclusion

The DOBRET is easy to conduct in everyday practice and might become a useful tool in clinical practice as part of a personalized medicine approach for identifying the best topical therapy in patients suffering from painful polyneuropathies.

In future planned RCTs we will explore the value of the DOBRET as a predictive tool selecting sustained responders.

Disclosure

DJK and JMKH are holders of two patent applications:
(1) Topical phenytoin for use in the treatment of peripheral neuropathic pain
(2) Topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain