MÆDICA - a Journal of Clinical Medicine

UPDATES IN CLINICAL MEDICINE

High-Concentration Capsaicin Patch (Qutenza) – A New Step in Treatment of Neuropathic Pain

Ana COBZARU, MD

Department of Neurology, University Hospital Bucharest

The diagnosis and the management of neuropathic pain still remain challenging. The main reason for these is the variety of underlying mechanisms of neuropathic pain. Different treatment regimens are needed for different pain mechanisms, thereby a mechanism based treatment approach would result in efficient analgesia. It is worth to mention that the pain system is not static and the changes occur in a dynamic, step-up way, from periphery to central and somewhat unpredictable manner whenever the system was activated.

Ectopic nerve activity has been involved in many positive phenomena (spontaneous, ongoing or paroxysmal pain, primary hyperalgezia/allodynia), characteristic of neuropathic pain and could be due to: (1) increased expression of voltage-gated sodium channels and secondary lowering action potential threshold or/and (2) abnormal expression and function of various receptor proteins family such as the transient receptor potential cation channel subfamily V member 1 (TRPV1), also known as the capsaicin receptor and the vanilloid receptor 1.

TRPV1 is located on subtypes of peripheral nociceptive endings (mostly C and some Aδ fibers) and is a polymodal receptor being sensitive to noxious heat (> 43°C), acidosis (pH between 5 and 6) and to different chemical agents ("endovanilloids" – anadamine, arachidonic acid metabolites, ethanol and a variety of pungent compounds such as capsaicin). After a nerve injury, TRPV1 is downregulated on affected nerve fibers but upregulated on intact C-fibers. This kind of expression of TPRV1 and additional sensitization to heat by intracellular signal transduction lead to spontaneous activity induced by normal body temperature, if the threshold of TPRV1 is reduced below 38°C. Clinically patients experience heat hyperalgesia in addition to burning pain. The loss of function (defunctionalization) of these nociceptors would be expected to produce pain relief if they are spontaneously active or hypersensitive.

Capsaicin can induce loss of function of TRPV1 receptors by multiple mechanisms: (1) inactivation of voltage-gated Na^+ channels, (2) direct pharmacological desensitization of plasma membrane TRPV1 receptors, (3) overwhelming of intracellular Ca^{2+} buffering capacity with subsequent cytoskeleton breakdown and interruption of fast axonal transport by activation of calcium-dependent proteases, and (4) at concentrations far in excess of those required to activate TRPV1, capsaicin can also induce

Address for correspondence:
Ana Cobzaru, MD, Emergency University Hosptital, Neurology Clinic, 169, Splaiul Independentei, Bucharest.
E-mail: cobzarica@yahoo.com

alteration in mitochondria function by directly inhibiting electron chain transport. Loss of mitochondrial function may render affected nerve processes unable to maintain plasma membrane integrity and thus cause collapse of nerve endings to the depth. Because of the high selectivity of capsaicin for the TRPV1 receptor and the selective expression of TRPV1 in nociceptive sensory nerves, other skin sensory nerve endings may remain intact and functional (Aβ fibers which convey tactile and proprioceptive stimuli as well as a subpopulation of C fibers and the majority of Aδ fibers, which are primarily responsible for mediating pin-prick) even with pronounced defunctionalisation and reduction of cutaneous nociceptors.

A high-concentration capsaicin 8% patch (Qutenza™) was recently approved in the EU and USA for post-herpetic neuralgia and painful HIV associated neuropathy.

The capsaicin 8% patch is designed to rapidly deliver capsaicin into the skin while minimizing unwanted systemic or environmental exposure of capsaicin to patients and healthcare providers. Phase 1 studies suggested that a single 60-min patch application was adequate to induce nociceptor defunctionalization, as measured by reversible reduction in intra-epidermal nerve fibres (ENFs), marked by the structural nerve marker protein gene product (PGP) 9.5 immunostaining, and small, reversible alterations in cutaneous nociceptor function. Phase 3 studies demonstrated efficacy for 12 weeks against PHN and painful HIV associated neuropathy.

The primary adverse effects seem to be local, transient, application site reactions, mainly pain and erythema. Transient increases in arterial pressure associated with the pain experienced during the application procedure were observed during clinical trials.

Treatment of neuropathic pain is still difficult because of complexity and of variety of underlying mechanisms. Qutenza has earned an important place in treatment of peripheral neuropathic pain in those cases where there are symptoms or signs of peripheral sensitization and of ectopic nerve activity.

References

1. **Anand P, Bley K–** Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011; 107:490-502
2. **Baron R, Binder A, Wasner G –** Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9:807-819
3. **Backonja M, Wallace MS, Blonsky ER, et al. –** NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol* 2008; 7:1106-1112
4. **Simpson DM, Brown S, Tobias J. –** Controlled trial of high-concentration capsaicin patch for treatment of painful HIV. *Neurology* 2008; 70:2305-2313.