Abstract: Neuropathic pain results from a dysfunction of the peripheral nerves or, less commonly, of the central nervous system. Common causes include diabetes, herpes zoster, acquired immune deficiency syndrome (AIDS), demyelinating lesions, vascular pathology, and mechanical pressure on the nerve body (ex. compression and entrapment syndromes), neoplasms, etc. An increasing number of drug treatments is becoming available for the neuropathic pain. Current treatments for the neuropathic pain are: antidepressants, anticonvulsants, opioids, topical drugs, and non-pharmacological therapies.

Keywords: neuropathic pain, pharmacological treatment, combination therapy

Rezumat: Durerea neuropată este generată de disfuncții ale nervilor periferici și mai puțin frecvent de alterarea funcționalității sistemului nervos central. Cele mai frecvente cauze ale durerii neuro-pate sunt: diabetul, infecția cu virusul zoster, infecții cu HIV, leziunile demielinizante ale SNC (scleroza multipla), patologia vasculară cerebrală (stroke-ul), compresiunile mecanice asupra nervilor, neoplasmele, etc. Actualmente există o plăț largă de metode farmacologice și nefarmacologice acceptate în tratamentul durerii neuropate. Terapia farmacologică a durerii neuropatice include: antidepresive, anticonvulsivante, opioizi, și medicamente cu acțiune topicală.

Cuvinte cheie: durere neuropată, tratament, terapie combinată

Recent specialized literature data estimate that 1.5-8% of the general population is suffering from neuropathic pain. (1). Neuropathic pain common causes are: diabetes, alcoholism, post-chemotherapy, HIV infection, zoster herpes, trigeminal neuralgia, multiple sclerosis etc. Diabetes is the most frequent cause of the neuropathic pain. (1). Half of the neuropathic patients develop a certain form of diabetic neuropathy. Its prevalence is increasing along with the age and diabetes length. Pain often occurs at the beginning of the diabetic neuropathy.

Neuropathic pain fundamentally differs from the nociceptive pain, by the fact that the lesions that bring about it are placed in the nervous ducts (central and/or peripheral) that normally lead to this form of sensitiveness.

Nociceptive pain supposes the activation of the intact pain nervous ducts by the nociceptive stimuli

Neuropathic pain management

The treatment of the neuropathic pain involves the use of a large range of therapeutic agents, including antidepressants, anticonvulsants, opioids, topical drugs, and non-pharmacological therapies. Half of the patients do not respond to the properly lead treatment (2). Regarding the patients with refractory neuropathic pain, agents combined therapy and synergic mechanisms may be tried (3), as well as the implantation of neuromodulation devices, medullar stimuli or interpolated pumps with topic medication release. (4)

Antidepressants

Literature data support the fact that antidepressants are the most efficient drugs in neuropathic pains (5). Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine, imipramine and maprotiline) in doses of 30-200 mg are the most efficient in the postherpetic neuralgia and diabetic neuropathy. (5). These drugs, used for many years in the neuropathic pain, act by blocking the noradrenaline reuptake in synapses, on the pain descending line. Although tricyclic antidepressants are efficient in the neuropathic pain, their use on large scale is still limited taking into account their side effects, such as anticholinergic ones and reduced tolerance in many patients, especially in the elderly. Thus, these drugs may produce, especially in the elderly; dizziness, sedation, orthostatic hypotension, mouth dryness, constipation, being counter indicated in the patients with glaucoma, prostatic hypertrophy, cardiac conducting disorders. If old patients use them, the medium doses are recommended: of 25 mg/day (6.).

Serotonin-norepinephrine reuptake inhibitors (SNRI) proved to be more efficient than the selective serotonin reuptake inhibitors (SSRIs), in the treatment of the neuropathic pain. The most efficient are: Venlafaxine 225 mg/day, respectively Duloxetine 60 mg/day. The European Guide on Neuropathic Pain Therapy recommends the SNRI antidepressants as a second line of treatment (2), having in view their efficiency, despite the better safety profile of the tricyclic antidepressants.

Anticonvulsants

Beside antidepressants, certain anticonvulsants are considered of first intention in the neuropathic pain

AMT, tome II, no. 2, 2008, page 231
treatment. Carbamazepine, whose main action mechanism is to reduce the conductance of sodium channels and the inhibition of the ectopic discharges was the first antiepileptic used in the treatment of the neuropathic pain. Carbamazepine proved to be efficient along with time in the treatment of the trigeminal neuralgia, in the pain of the “ghost limb”, being less efficient in the generalized painful neuropathies. Gabapentine, an analogue of GABA, which was initially used in the treatment of the complex partial crises; today, it is used in the neuropathic pain treatment, having a non linear pharmacokinetic profile and requiring slow titration. The initial doses are of 300mg/day (or even more reduced in the elderly), reaching doses of even 900-3600mg/day, according to the individual reactivity of the patient. Pregabaline, just like gabapentine, modulates the subunits α2-δ of calcium channels, reducing the glutamate, noradrenalin and P substance release, being a drug with multiple actions; anticonvulsant, anxyolitic and analgesic in the neuropathic pain.

Having a linear pharmacokinetics, titration is made rapidly, the efficient dose in the neuropathic pain being between 300-600 mg/day. Due to the anxyolitic effect, it improves the sleep and, implicitly the quality of the patients’ life.

Opioids

Opioids treatment in the neuropathic pain is controversial in the last 10-15 years. The European Guides recommend their use, as a second line of treatment. The main disadvantages of the opioids are: low tolerability if used for a long period of time and the occurrence of the addiction phenomenon (dependence). The most used drugs of the opioids class, efficient in the neuropathic pain are: Tramadole and Oxycodone (2007).

Tramadole acts by inhibiting the norepinephrine reuptake and serotonin releasing in the synaptic cleft (resembling with the tricyclic antidepressants).

Its active metabolite (+) M1 is linked by the μ-opioids receptors. The benefic effect of Tramadol in the neuropathic pain is the serotonergic modulation from pain transmission. It is well tolerated, but it may have side effects: sleepiness, constipation, headaches and orthostatic hypotension. It must be used carefully in association with medication that increases the level of serotonin, existing the risk for the occurrence of the serotonergic syndrome. The treatment starts with 50 mg/day, the dose increasing gradually up to an average dose of 150-200 mg/day. Maximum of efficiency will be obtained ½ weeks after therapy initiation. The opioid effect is reduced, it does not develop any tolerance, and it may be used in the chronic treatment.

Oxycodone is a semi-synthetic opioid, thebain derived; it is a strong agonist on the μ-opioids receptors. There are oral preparations with prolonged releases, the efficient dose in the neuropathic pain being of 40 mg/day. (2007). Opioids most significant side effects are: nausea, constipation, dizziness, sleepiness.

Topic agents:

Capsaicin under the form of ointment, topically applied, acts by releasing the P substance at the level of the sensorial fibres. It proved its efficiency by local administration in the postherpetic neuralgia and diabetic neuropathy. The disadvantage is that it generates the sensation of burnt on the administration place, especially in the first week of treatment. Topic administration under the form of plasters of lidocaine 5% proved to be efficient in the postherpetic neuralgia and in other focal neuropathies (7).

Combined therapy

Recent studies proved the benefic effect of the combined therapy, between classes of drugs with synergic effects. The most benefic seems to be the combination between gabapentin and one opioid (oxycodo-na). The analgesia obtained by the combination of the two drugs, was better than that obtained by monotherapy with only one of them. These clinical observations are supported by the action mechanisms of these drugs. The pharmacological studies proved that gabapentin stimulates the synthesis of κ and μ opioids receptors at spinal level (2). Oxycodona acts on κ receptors, the antinociceptive effect being more expressed on the spinal opioids μ receptors. Thus, we can explain the benefic effect of the association between two medications in the neuropathic pain.

Non-pharmacological therapy of the neuropathic pain

Today, there are a few non-pharmacological methods in the treatment of the neuropathic pain. The transcutaneous electric nerve stimulation (TENS) may be useful in some forms of neuropathic pain. Other methods of electric nerve stimulation, respectively the electromagnetic neuronal stimulation are being experimented. In the case of the patients who do not respond to the classic medication treatment in the neuropathic pain, one may try the implantation of neuromodulators or stimulators at spinal level or at the level of the peripheral nerves.

CONCLUSIONS

- Today, there is an increase of the number of drugs approved in the treatment of the neuropathic pain.

- The combined therapy between an opioid agent (oxycodone) and gabapentin, seems to be the most efficient. This observation is supported by vast clinical studies made on patients with neuropathic pain who do not respond to monotherapy with different classes of drugs.

- The patients with neuropathic pain are exposed to a multitude of chronic disorders, comorbidities, antialgic medication abuse, that incur substantially increased costs towards the patients with other types of painful symptoms. The neuropathic pain has a great impact on the quality of the patients’ life, bringing about secondary sequelae of the type of depression,
sleep disorders, deterioration of the physical and psychological functions.

**BIBLIOGRAPHY**