COMPLEX REGIONAL PAIN SYNDROME

REFLEX SYMPATHETIC DYSTROPHY SYNDROME

DIAGNOSIS AND THERAPY- A REVIEW OF 824 PATIENTS

(ABSTRACT SUMMARY***)

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OPIATES

Opioids play a major role in management of pain and inflammation in peripheral and central nervous system. The endogenous ligands-opioid peptides (endorphins) are expressed by resident immune cells in peripheral tissues. Depriving the patient of proper pain medication can aggravate the immune system dysfunction. The selection of proper opiates for treatment of CRPS is quite critical. Both opioid agonists and mixed opioid agonist-antagonists have been used for treatment of pain in such patients. Opiates are considered effective in treatment of neuropathic pain. However, due to the complexity and multiple origins of the pain in CRPS, in some patients the opioid agonists are not as effective. Morphine does not consistently reduce the neuropathic pain.

Morphine (0.1-1mg per kg IV) may increase the localization threshold of lesioned limb pressure and may decrease the chronic pain score. Morphine may decrease mechanoallodynia in the diabetic rat, but the effective doses have to be quite high in the range of 2-4mg per kg IV which are too high for human application. Long term use of opioid agonists has the potential of tolerance and dependence,

impairment of physical function, and depression. Yet, 83% of pain specialists have been reported in 1992 to maintain chronic non-cancer pain patients on these medications. This percentage has grown far higher since then: of 824 patients in this study, only 36 (4.3%) had not receive long term opioid agonists therapy. Moreover, the present trend is for poly- pharmacy of opioids in high doses. Such high doses exceed the optimal therapeutic window for analgesia.

The therapeutic window refers to the fact that opiates, similar to anticonvulsants, are most effective in their therapeutic range. Above and below this window they are ineffective.

MORPHINE

The opioid agonists such as morphine, fentanyl, etc, have been found ineffective against the abnormally fluctuating reaction to thermal allodynia (neurovascular instability), while retaining anti-nociceptive activity against painful thermal stimuli (heat hyperalgesia). Long term use of Morphine suppresses many specific functions of the immune system. Both acute and chronic application of Morphine strongly suppress the T-cell immune functions. Morphine may interfere with the development of antibody - antigen immune function. Due to the fact that many cells and organs related to the immune system have shown opiate receptors, Morphine has the potential of directly affecting and altering many immune processes. Morphine may affect and suppress noxious stimulus-evoked fos protein-like immunoreactivity. Morphine and other similar opioid agonists bind to opioid receptors in limbic system (temporal lobe), affecting memory and mood.

Long term application of opioid agonists (e.g. morphine) suppresses the formation of endorphins (Table 2).

Contrary to the common concept, large doses of opiates usually disrupt the natural sleep pattern. It is true that opiates induce excessive sedation in 24 hours. However, the nocturnal sleep pattern is interrupted every few hours due to withdrawal phenomenon , leaving the patient tired and sleepy during the day. The use of proper antidepressants and adherence to the above mentioned therapeutic window help correct this problem.

Endorphins [a] Table 2*

	Endorphins (enkephalins, dynorphin)	Exorphins
Pain relief	Yes	Yes
Antidepressant	Yes	No
Strength	100 x stronger	100 x weaker
Dose release	Microjet	Flooding dosage
Effect on other hormones	Stimulate sex hormones, thyroid hormone	Block secretion of hormones
"Acid rain" effect [b]	No	Yes: flooding the brain temporarily leaving the brain devoid of hormones on withdrawal
Appetite	Increased	Reduced
Sex desire	Increased	Reduced
REM sleep	—	—
Quality of sleep	Increased	—
Duration of effect	Very brief with no significant withdrawal	Prolonged with drastic withdrawal
Sympathetic function	Reduced: warm extremities and normalized BP	Increased during withdrawal: cold extremities, hypertension follows initial hypotension
Effect on endo-BZs	Stimulate more BZs resulting in tranquility	Inhibit ENDO-BZs resulting in withdrawal: anxiety, agitation
Effect on sex hormones and steroids	Increased	Markedly reduced
Effect on limbic system	Stimulate and normalize: better sleep, better memory, better judgment	Inhibit and flood the system: insomnia amnesia, poor judgment
Tolerance	Not known	Strong [c]

a. There are two types of cells in the brain. The nerves, and the glial cells protecting the nerves. The nerve secrete hormones. The glial cells don't. The brain is endocrine gland-controlling behavior with secretion of hormones. Endorphins are powerful hormones controlling pain. Whereas, exorphins (e.g., morphine, Demerol, codeine, and heroin) require large doses (e.g. 10-20 nanogram or billionth of gram). The similarities between endorphins and exorphins end at pain relief. Otherwise they act in a diametrically opposite fashion.

b. Acid rain effect: alcohol as well as exorphins flood the brain cells and hamper their ability to form the dirunal hormones needed for alertness, sleep, tranquility, and antidepressant effects.

c. Apparently the exorphins block the activation of adenylatecyclase, resulting in chronic tolerance.

Table 2*- From:Chronic Pain: Reflex Sympathetic Dystrophy: Prevention and Management. CRC Press, Boca Raton, Florida 1993.

BUPRENORPHINE

The above side effects of long-term treatment with opioid agonists leave the door open to search for more effective opiates. Buprenorphine, an opiate agonist-antagonist, is a strong analgesic without causing dysphoria, or dependence. Sublingual Buprenorphine has been used successfully for detoxification from Cocaine, Heroin and Methadone dependence. Buprenorphine is a Class V narcotic in contrast to Morphine, Methadone or Fentanyl, which are Class II. Within the proper therapeutic window, Buprenorphine (2-6mg/day) and Butorphanol (up to 14 mg/day), act as opioid antagonists by occupying only mu and delta receptors. In higher than therapeutic doses, they fill the Kappa receptors as well, changing said drugs to pure opioid agonists and resulting in problems of rebound and tolerance. Within 2-6mg per day, Buprenorphine occupies mu and delta opioid receptors, but kappa receptor is not occupied and is capable of receiving endorphins. When all 3 opioid receptors are occupied, endorphins cannot bind to them. Consequently, endorphins formation is ceased, leading to dependence and tolerance.

The Harvard group and others have found Buprenorphine to act as an antidepressant leading to "clinically striking improvement in both subjective and objective measures of depression." This is in contrast to the common depressive effect of opioid agonists.

ANTIDEPRESSANTS

Antidepressants, similar to Carbamazepine, block the NMDA receptors and improve cell membrane function. Antidepressants are important in improving the eventual recovery, immune system function, and reduction of mortality and morbidity in chronic pain patients.

Antidepressants possess pure analgesic properties. Examples: Doxepin (Zonalon) topical cream is an excellent topical analgesic for neuropathic pain. The analgesic effect of tricyclics is reversed by Naloxone. The analgesic property makes the therapeutic use of antidepressants essential for treatment of neuropathic pain.

Antidepressants with properly balanced serotonin and norepinephrine (Nor Ep) reuptake inhibition provide maximal analgesia. Antidepressants, similar to Morphine pump, provide naloxone -reversible endorphin type pain relief . Such drugs as desipramine, imipramine and trazodone are superior to mainly serotonin inhibitors such as Mitrazepine (Remeron) and fluoxetine. Remeron is a good hypnotic, but in our patients it has shown no significant analgesic value. On the other hand, Venlafaxine (Effexor) is a weak inhibitor of serotonin and a strong inhibitor of nor ep reuptake-aggravating hypertension and sympathetic vasoconstriction by augmenting norepinephrine function. Venlafaxine has a high profile of adverse drug interaction with P450 and CYP2D6 Isoenzymes inhibitors (which comprise a long list of medications). It is best not to use this drug in CRPS. Buproprion (Wellbutrin) aggravates seizure disorder. Myoclonic jerks (see Movement Disorders) being a common complication of CRPS is aggravated by this drug. Its use is contraindicated in CRPS.

Certain antidepressants such as tricyclics and Trazodone, increase the synaptic serotonin and nor ep concentrations. This balanced phenomenon provides effective analgesia, natural sleep, and antidepressant effect. Trazodone provides analgesic effect in less than 24 hours in contrast with five to seven days for the same effective result with tricyclics. Trazodone does not cause weight gain when compared to amitriptyline(see below).

WARNING

Of the tricyclics, Amitriptyline has been the most widely used analgesic, but it has strong anticholinergic and sedative side effects, and my cause paranoid and manic symptoms. More importantly, it has a tendency to cause weight gain. In our study of 824 CRPS patients, 612 had already been tried on Amitriptyline. In the first year, these patients gained an average of over 7kg, and, in the following year, an additional 3.6kg. Trial of Desipramine or Trazodone did not cause any significant weight gain. Weight gain in a CRPS patient who already has difficulty with ambulation is quite harmful. In addition, tricyclics have adverse cholinergic and muscarinic properties resulting in complications of orthostatic hypotension and ECG changes.

ANTICONVULSANTS

Anticonvulsant treatment is helpful in CRPS for two types of symptoms: 1. Spinal cord sensitization leading to myoclonic and akinetic attacks, and 2. In patients who suffer from ephaptic or neuroma type of nerve damage characterized by stabbing, electric shock, or jerking type of pain secondary to damage to the nerve fibres. In such cases, anticonvulsants, especially Tegretol (non-generic), Depakene, Gabapentin, and Klonopin (non-generic), are quite effective. The ephaptic, causalgic CRPS II is best managed with combination of an effective anticonvulsant, antidepressant, and analgesics.

Clonazepam is effective in control of myoclonic jerks. Decades of experience with Klonopin and Tegretol in neurology have taught the lesson that brand Klonopin and Tegretol are superior to their generic forms (Clonazepam and Carbamazepine) in controlling epileptic seizures. The American Academy of Neurology has recommended that generic antiepileptic drugs not be prescribed. Gabapentin (Neurontin) which is an adjunctive anticonvulsant, provides relief for burning type of neuropathic pain. Similar to Tegretol, Gabapentin is also neuroleptic. Carbamazepine, similar to Mexiletine, is an effective sodium channel blocker. It is far better tolerated than Mexiletine.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

(NSAIDS)

The inflammatory complications of CRPS respond properly to NSAIDS. The beneficial effects of NSAIDS may be related to correcting the immune inflammatory damages in nerve death-be it neuropathic inflammation of CRPS, nerve death due to Alzheimer, or cerebrovascular disease (e.g., benefits from aspirin therapy). In Alzheimer, immune factors such as "membrane attack complex" play a role in nerve death-this may explain the benefits of NSAIDS. Cox inhibitors (e.g., Celebrex or Vioxx) are very helpful for pain relief and detoxification from opioid dependence.

ALPHA BLOCKERS

The alpha-1 blockers Phenoxybenzamine (Dibenzyline) and Hytrin (Terazocin) are effective systemic nerve blocking agents. Forty soldiers suffering from CRPS type II were treated with phenoxybenzamine with excellent results, eliminating the need for sympathectomy. Clonidine in oral, intrathecal, or cutaneous patch forms, Clonidine is quite effective as an alpha-2 blocker. Application of Clonidine patch to the area of original damage in the extremity may aggravate the pain. It is effective when applied topically to paravertebral area in cervical or lumbar region corresponding to the referred pain of sensory nerve roots. After completion of sympathetic nerve block injection, application of Clonidine patch is a complementary treatment and may prevent the need for further invasive nerve block. Another effective alpha-2 blocker, Yohimbine, is not as potent as alpha-1 blockers.