Multiple Bier Blocks with Labetalol for Complex Regional Pain Syndrome Refractory to Other Treatments

To the Editor:

Although the Bier block has been used as a treatment for sympathetically-maintained pain (SMP) for many years, the selection of agents remains controversial. Different drug classes have been used, including alpha-adrenergic blockers (guanethidine, reserpine, bretylium), alpha-2 agonists (clonidine), nonsteroidal anti-inflammatory agents (ketorolac, tenoxicam), local anesthetics (lidocaine, prilocaine), and NMDA antagonists (ketamine). To our knowledge the use of labetalol for Bier block has not been reported. We here report a case of complex regional pain syndrome (CRPS) that did not respond to a standard Bier block with bretylium and lidocaine, but responded for 7 years to multiple Bier blocks with labetalol and lidocaine.

Case Report

A 42-year-old man sustained a right fifth metatarsal fracture after a heavy block fell upon his right foot in June 1993. His injury was complicated by osteomyelitis. Following healing, he continued to have persistent sharp, burning pain on the lateral side and dorsum of the right foot. The pain was constantly present, varying in intensity between 7 (0–10 scale) at its worst and 3–4 at its best. The clinical findings were consistent with a CRPS. Before presentation to our service, treatments included seven lumbar sympathetic blocks, each with poor or no pain relief; epidural infusions with bupivacaine and fentanyl, with moderate temporary pain relief; and physical therapy. He had a negative phentolamine infusion test. Multiple oral medication trials, which included opioids (levorphanol, morphine, oxycodone), tramadol and sodium channel blockers (IV lidocaine), failed to relieve his pain.

At presentation, his medications included amitriptyline 100 mg daily, clonidine 0.2 mg po three times daily, clonazepam 0.5 mg po three times daily, gabapentin 900 mg po three times daily, and dextromethorphan 90 mg po three times daily. He had no pending litigation, drank alcohol socially, and smoked for 20 years.
On physical examination his right foot was mottled, mildly swollen, colder than the left, and had excessive sweating and dystrophic changes of the skin. Significant cold allodynia and pinprick-induced hyperalgesia were present on the lateral and dorsal surfaces. Strength was normal, with mild limitation in range of motion secondary to pain. He walked with crutches and was unable to bear weight on the foot, except for the duration of pain relief gained with Bier block.

In contrast to a Bier block with bretylium 120 mg and lidocaine, which did not bring him pain relief except for the short duration of local anesthetic, Bier blocks with the combination of labetalol (20–40 mg) and lidocaine (100–200 mg) gave him complete pain relief for 7 to 10 days. During the past seven years, he has received this block 158 times. Initially, the blocks were performed once each month; during the last 5 years, he has undergone this procedure every two to three weeks. Medical and vascular evaluations have identified no contraindications to these serial Bier blocks. Other treatments, including a spinal cord stimulation trial, have been proposed, but the patient refused because he was satisfied with the current treatment.

In order to determine whether the effect of Bier block was mediated through A beta fiber conduction block, the patient consented to an ischemic tourniquet block of the right foot, with no medication administered; this caused an exacerbation of pain and allodynia. In addition he underwent a Bier block with normal saline and lidocaine (without labetalol) in a blind manner to test the effects of lidocaine alone and a possible placebo effect. This procedure provided him with only minimal pain relief for a few hours, as compared to more than 7 days for the combination of lidocaine and labetalol.

Comment

Sympathetically-maintained pain (SMP) may or may not be present in patients with CRPS. The treatment of SMP with a Bier block using guanethidine has been used clinically for many years. Guanethidine’s site of action is on noradrenergic ganglionic synapses. Guanethidine is transported across the sympathetic nerve membrane by the same mechanism that transports norepinephrine itself. After uptake, guanethidine replaces norepinephrine, causing a gradual depletion of norepinephrine stores in nerve endings. It has been suspected that repeated Bier blocks with guanethidine might cause permanent damage to the noradrenaline reuptake system, as guanethidine accumulates in nerves for a prolonged time. The clinical effect of guanethidine in cases of SMP has been reported to last days to weeks, but others failed to observe a long-term pain relief.

Reserpine has also been used for Bier block in cases of SMP. This is a false precursor for dopamine and norepinephrine in the nervous system. Injectable guanethidine and reserpine are not clinically available in the USA and bretylium has been used instead. Initially, bretylium releases norepinephrine from sympathetic ganglia and terminal endings of postganglionic adrenergic neurons. Subsequently, the drug inhibits the release of norepinephrine from adrenergic nerve endings and blocks its reuptake. Bretylium was found effective in the treatment of CRPS.

For our patient, the standard bretylium combined with lidocaine did not provide significant pain relief. Ischemic tourniquet block caused an exacerbation of pain, and, therefore, it is unlikely that the pain relief during his numerous Bier blocks was caused by A beta conduction block. Administration of normal saline and local anesthetic alone did not provide long-lasting pain relief. Phentolamine infusion and lumbar sympathetic blocks were ineffective.

There are very few reports about the use of drugs with nonselective beta-blocker properties (propranolol) or with combined alpha and beta-blocker potency (labetalol) for CRPS pain. Several patients with causalgia were successfully treated with propranolol. Successful use of IV and PO labetalol for pain was reported in one patient with algodystrophy, a term synonymous with CRPS. Labeltalol was also given into the epidural space for treatment of pain in gynecologic cancers. The efficacy of epidural labetalol in pain control was attributed to membrane stabilizing activity (also known as quinidine-like effect or local anesthetic activity), and to beta-blocking effect. However the use of labetalol in the Bier block was never reported.
Labetalol is a competitive antagonist of alpha-1 receptors as well as beta-1 and beta-2 receptors. Labetalol’s affinity for alpha-receptors is 10 times less than that of phentolamine, but labetalol is alpha-1 selective. Its beta blocking potency is 3 times lower than that of propranolol. The ratio of beta- to alpha-adrenergic blocking potency of labetalol is 3:1 with oral administration and 7:1 with parenteral administration.

It is not clear by which mode of action labetalol provided pain relief in our patient. Beta-1 receptors are located in presynaptic adrenergic nerve terminals, whereas beta-2 and alpha-1 receptors are not present in peripheral nerves. Alpha-1 receptors are present on postsynaptic effector cells, especially smooth muscle, and under the pathological condition of SMP, they can be expressed on the peripheral nociceptors. Therefore, a possible explanation of labetalol’s efficacy in this patient could be related to the fact that labetalol’s beta-1 presynaptic effect inhibits the reuptake of norepinephrine into adrenergic nerve terminals. The inhibition of norepinephrine uptake by labetalol suggests a mechanism somehow similar to that of guanethidine and bretylium, and may account for labetalol’s longer lasting analgesic properties. Nevertheless the alpha-1 blocking effect may also provide pain relief by blocking the ongoing activity in peripheral sensitized nociceptors.

Another possible explanation might be the local anesthetic activity of labetalol, also known as “membrane stabilizing” effect. This action is the result of sodium channel blockade. The local anesthetic blockade is usually not evident after systemic administration because the plasma concentration is too low. During the Bier block, the concentration of labetalol in the treated extremity is significantly higher, making it possible for labetalol to be clinically effective as sodium channel blocker without eliciting systemic side effects. However, this action alone is unlikely to account for long-lasting pain relief.

In summary, this case illustrates the successful and unusual use of labetalol with Bier blocks for CRPS refractory to conventional treatment. The case supports the safety of repeated treatment with Bier blocks in patients with CRPS and also demonstrates a lack of tolerance to this treatment modality.

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References


Burst Ketamine to Reverse Opioid Tolerance in Cancer Pain

To the Editor:

Long-term opioid therapy is commonly administered for the management of severe cancer pain.\(^1\) Increasing doses of opioids are titrated against effects until analgesia is achieved or intolerable adverse effects occur.\(^2\) Opioid tolerance, which refers to the phenomenon by which repeated doses of opioids produce decreased effects or increasingly larger doses are required to maintain the previous effect, also may occur, but this phenomenon is really less clear in the clinical setting than in experiments because there are other driving forces able to produce a decrease in the analgesic response. Indeed, disease progression, reduced opioid responsiveness due to changing pain mechanisms or patient-related factors, and development of tolerance each may contribute to the increasing dose requirements seen in patients receiving long-term opioids, and are hardly distinguishable.\(^3\) Rapid opioid escalation, due to either the worsening of the pain condition or the development of tolerance, is a negative prognostic factor for the development of adverse effects, and suggests limited opioid responsiveness.\(^4\)

In the clinical setting, occasional patients develop a hyperexcited state during opioid dose escalation, which is worsened rather than improved by further dose increments. In escalating opioid doses rapidly, the development of tolerance and hyperalgesia should be suspected, as higher doses of opioids may stimulate rather than inhibit the central nervous system. There may be multiple mechanisms, responsible for this.\(^5\)

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been reported to improve analgesia in patients with uncontrolled pain receiving high dose of opioids administered by different routes. Possible explanations for the reduced morphine requirements during and following ketamine administration include an additive analgesic effect or reversal of opioid tolerance. Improvement of analgesia in cancer patients is commonly achieved by administering doses in the range of 40–3200 mg daily, intravenously or subcutaneously. However, previous reports have never focused on the possibility that tolerance may be reversed in patients taking high doses of opioids, using a pulse protocol, rather than a continuous administration that does not allow any distinction between the analgesic effect and reversal of tolerance. Experimental studies have shown that single doses of a NMDA antagonist may reduce hyperalgesia but not enhance morphine antinociception.\(^6\) With this aim, we developed an open-label protocol, from which we report the first surprising case.

Case Report

A 72-year-old woman with metastatic breast cancer was admitted at a Pain Relief and Palliative Care Unit for back pain radiating to the legs due to lumbar metastases. Pain was aching and exacerbated with movement. She had received several courses of chemotherapy, external radiotherapy, and monthly cycles of pamidronate. During three years, she had received oral morphine first, which was slowly increased up to 800 mg daily. Due to the need to rapidly escalate her morphine dose, which induced some cognitive disturbances, she was switched successfully to methadone 90 mg daily. In the subsequent months, the methadone dose was increased progressively up to 80 mg three times a day. A progression of bone and hepatic metastases was demonstrated by vertebral MRI and abdominal ultrasound.

Considering the relatively high doses of methadone and the further need to increase the dose due to uncontrolled pain, we proposed to start periodic bursts of intravenous ketamine in doses of 100 mg daily for two days in an attempt to improve analgesia, but above all, to reduce or reverse the development of tolerance. In the two days after ketamine doses, the methadone was decreased from 240 mg to 180 mg daily. Pain control was optimal and the patient was discharged home.

The doses of methadone were maintained at the same level for the following month. One month after, she was proposed a further trial in