The Treatment of Reflex Sympathetic Dystrophy with Intravenous Regional Bretylium

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Reflex sympathetic dystrophy is a disorder characterized by chronic, refractory, severe pain, usually in a previously injured extremity. The mechanism for the signs and symptoms of reflex sympathetic dystrophy is thought to be an abnormal reflex mediated by the sympathetic nervous system. The exact pathogenesis remains obscure, but probably involves a self-sustaining reflex among sympathetic afferents, sympathetic efferents, and, possibly, sensory afferents, allowing for direct cross stimulation and pain-cycle formation.

In 1974, Hannington-Kiff reported the use of intravenous regional guanethidine for the treatment of causalgia. Since then, there have been numerous clinical reports describing intravenous sympathetic blockade with guanethidine or reserpine for a number of syndromes in which sympathetic tone is implicated in the disease process. These reports have demonstrated beneficial results, at least short term, for most of the patients studied. The beneficial response is attributed to a prolonged sympatholysis with the intravenous regional technique. Unfortunately, guanethidine is not available for intravenous use in the United States. Our experience, and that of others, with intravenous regional reserpine has been less than satisfactory, since patients frequently experience undesirable side effects, including diarrhea, syncope, and prolonged depression.
Furthermore, parenteral reserpine is no longer manufactured in the United States.

Bretlyium tosylate, a quaternary ammonium compound, is an adrenergic blocking agent with actions similar to guanethidine and reserpine. It is approved for intravenous administration by the Food and Drug Administration, and is used in doses of 5–10 mg/kg intravenously as an antiarrhythmic agent for treatment of refractory ventricular dysrhythmias. Its most frequent side effect is hypotension. Bretlyium, guanethidine, and reserpine all produce inhibition of responses to adrenergic nerve stimulation by reducing norepinephrine release. The drugs have several important differences. There are more prominent and prolonged initial sympathomimetic effects with guanethidine compared to bretylium. Bretlyium tends to cause less stimulation of gastrointestinal motility; therefore, there is a lower potential for diarrhea than with guanethidine and reserpine. Reserpine has more central nervous system side effects than guanethidine and bretylium, including sedation and depression, since it is a tertiary amine and crosses the blood-brain barrier. Based upon pharmacologic similarities, we predicted that bretylium would be an effective agent for intravenous regional sympathetic blockade and, possibly, preferable to reserpine should it have a lower side effect liability. A dose of 1 mg/kg was chosen as a safe initial dose for evaluation. Four selected patients are presented to describe the early results we have experienced with intravenous regional bretylium for the treatment of reflex sympathetic dystrophy.

CASE REPORTS

Case 1. A 58-yr-old woman presented with chronic right lower leg pain of 2 yr duration following blunt trauma requiring saphenous vein excision. She had constant pain at rest, and reported severe pain with walking. The light touch of clothing or beddding exacerbated the leg pain. Past failed treatments included nonsteroidal anti-inflammatory agents, oral narcotic analgesics, and trigger point injections into the surgical scars. The patient had marked allodynia and hypesthesia in the entire medial portion of the right lower leg, along with muscle atrophy. She also had evidence of venous stasis, and the right foot was 2.6°C colder than the left foot. A tentative diagnosis of reflex sympathetic dystrophy was made, and a series of intravenous regional sympathetic blocks with bretylium were planned.

After informed consent was obtained, the patient was placed in a supine position with the head slightly elevated. Using 20-gauge intracatheters, venous access was secured in the left hand and right foot. A double tourniquet was placed around the right mid-thigh. The leg was then elevated and tightly wrapped with an Esmarch bandage to the level of the tourniquet. The upper section of the double tourniquet was inflated to 500 mmHg, and the leg was unwrapped and lowered to the guerney. Bretlyium 1 mg/kg with 100 cc of 0.9% lidocaine and 500 units of heparin was injected over 2 min through the right foot intravenous catheter. After 30 min, the tourniquet was deflated. It was reinflated after 10 s and then deflated and reinflated, with subsequently longer deflation times, over a 5-min period. The patient experienced no dizziness or hypotension. She reported excellent pain relief for 7 days following the procedure, then her pain gradually increased and she returned to the clinic 20 days later for the same treatment. Once again, she experienced no adverse side effects from the procedure, and this time she had 25 days of very good pain relief. The patient also reported improvement in her ability to walk. Five days after the pain returned, she had a third treatment, and was pain free at her 7-month follow-up.

Case 2. A 61-yr-old woman was admitted to the pain clinic with right foot pain of 3 yr duration. She attributed the problem to trauma while hiking. The patient had been an ardent long-distance hiker, but became severely incapacitated even with ordinary activity. Prior unsuccessful treatment included decreased weight bearing, nonsteroidal anti-inflammatory agents, local steroid injection, oral steroids, support hose, and warm packs. A diagnostic lumbar paravertebral sympathetic block provided good pain relief for 2 days. On her first visit to our clinic, she complained of chronic pain over the dorsal and lateral aspects of her right foot. Examination revealed dysaesthesia, coolness, and redness to 10 cm below the right knee. Her right foot was mildly erythematous, and was 4.5°C cooler than the left foot. Using the same protocol described in case 1, the patient received an intravenous regional sympathetic block. She tolerated the procedure well without hypotension, dizziness, or other adverse effects. Two hours after the treatment, the right foot was 0.5°C warmer than the left foot. She described almost complete pain relief for 14 days and subjective warmth of the foot during this period of pain relief. As the foot cooled, pain gradually increased. At her second visit, 45 days after the initial block, the right foot was again 4.5°C cooler than the left foot. Because the tourniquet pain with her initial block had been severe, she opted for a trial of oral medication and was placed on guanethidine 5 mg PO TID. It was discontinued after 5 days because she developed diarrhea. Fourteen days later, a second intravenous regional sympathetic block was done. The patient tolerated the procedure well except for transient dizziness during cuff deflation. Prior to the block, the right foot was 2°C cooler than the left foot. Post-treatment, her right foot was 1°C cooler than the left foot. She recorded daily morning right foot temperatures 1–2°C greater than the left foot for 3 days after the procedure, at which time she stopped recording. She experienced good to excellent pain relief for 40 days, and returned after 60 days because the extremity felt cold and the pain was severe. A third intravenous regional sympathetic block was performed. She had very good pain relief for 45 days and managed with slight pain for another 45 days before a repeat block was performed. Since then, the patient has had 6 months of sustained pain relief and improved function, as manifested by her ability to resume short-distance hiking.

Case 3. A 56-yr-old woman presented to the pain clinic with trauma-induced chronic left arm pain of approximately 7 yr duration. Treatments included nonsteroidal anti-inflammatory drugs, narcotic analgesics, prazosin, antidepressants, and benzodiazepines. She also had a first rib resection and surgical sympathectomy 2 yr prior to her first pain clinic visit, and the pain returned 4 weeks after surgery. Since that time, the pain in her left arm has been constant, and she noted persistent weakness in the hand. The examination was remarkable for muscle wasting in the involved extremity, allodynia, hypesthesia, and posturing to protect the hand, which had a shiny appearance and was 3°C cooler than the right hand. An intravenous regional sympathetic block was performed. The double tourniquet was placed around the left arm as high as possible. After exanguination of the forearm, the upper section of the double tourniquet was inflated to 300 mmHg, and bretylium 1 mg/kg with 50 cc of 0.5% lidocaine and 500 units of heparin was injected over 2 min. The deflation technique after 50 min was similar to case 1. She tolerated the procedure well. After treatment, the patient reported complete pain relief for 14 days. The pain gradually returned over the next 7 days to approximately 80% of baseline. She continued her benzodiazepines, antidepressants, and narcotic analgesics during that time, and was started on guanethidine 5 mg PO TID. Guanethidine was stopped after a 2-week trial because of
intolerable dizziness. A second block was repeated 50 days after the first, and provided increased warmth for the first few days and very good pain relief over the next 60 days. The patient also reported improved mobility of her left arm during this period, and was able to reduce her use of narcotic analgesics. She returned to the clinic 70 days after the second block, reporting a gradual return of pain over the preceding 10 days. A third intravenous regional sympathetic block was done, and this was followed by a series of four blocks approximately 50 days apart. At a visit 60 days after the last block, she reported complete pain relief with improved ability to use her left upper extremity, and she had stopped taking narcotic analgesics.

Case 8. A 58-yr-old woman was seen at the pain clinic with a 1-yr history of chronic right foot pain after corrective surgery for an arthritic deviated right great toe. The constant burning pain became worse with weight bearing. On examination, the patient had hyperpathia of the right great toe, second toe, and lateral malleolus, with swelling over the malleolus. Superficial peroneal, saphenous, and posterior tibial nerve blocks at the ankle resulted in excellent but temporary pain relief. A diagnostic right lumbar paravertebral sympathetic block gave complete but temporary pain relief. The diagnosis of reflex sympathetic dystrophy was made, based on the history, physical examination, and response to the lumbar paravertebral sympathetic block. The patient had a bretylium intravenous regional sympathetic block, as described in case 1, resulting in good pain relief for 21 days. Subsequently, she had four additional intravenous regional sympathetic blocks over a period of 7 months, with good to complete pain relief up to 10 weeks. The blocks were repeated when pain returned. The only side effect was transient dizziness after the initial block. The patient was pain free and ambulating normally 7 months after her fifth block. Total duration of treatment, including follow-up, was 15 months.

Discussion

This report presents four selected patients with reflex sympathetic dystrophy who obtained good to excellent pain relief for up to 7 months after treatment with intravenous regional bretylium. In addition, bretylium produced objective signs of prolonged sympatholytic activity (increased skin temperature in case 2) and vastly improved function in all four cases. These clinical effects probably resulted from bretylium's ability to accumulate in adrenergic nerves and block norepinephrine release. For intravenous regional sympathetic blockade, bretylium is an attractive alternative to guanethidine or reserpine as an adrenergic neuron blocking agent. In our early experience, it is as effective as either of the other agents. Furthermore, bretylium appears to have less adverse effects than guanethidine or reserpine. In these four ambulatory patients, who had a total of 19 treatments with 1 mg/kg, the side effects were minimal. Hypotension, the most commonly reported side effect with 5–10 mg/kg of intravenous bretylium, was not a problem in our patients. The overall safety of bretylium has been demonstrated with these larger intravenous dosages for other indications.

Using the intravenous regional method, guanethidine and reserpine have been reported to be effective drugs for treating selected painful peripheral conditions. Based on studies of these agents with long-term follow-up, our initial results with bretylium look promising. On the other hand, certain precautions must be exercised in the interpretation of these results. In a study of tourniquet-induced analgesia, there was good pain relief at 30 min and 24 h after saline intravenously. This finding is supported in a report by Brown, who found that the results with saline were quite comparable to that of reserpine. In the treatment of reflex sympathetic dystrophy, the immediate pain relief from an intravenous regional sympathetic block with bretylium could be explained by tourniquet-induced analgesia, but the long-term improvement probably could not be explained by this mechanism.

We chose to include lidocaine in the treatment combination to minimize the changes from our previous intravenous regional technique, to raise the threshold for tourniquet pain, and to block burning pain on injection of bretylium should it occur. Burning pain on injection of bretylium has not been reported in general usage, but we have not studied this in our patients with reflex sympathetic dystrophy. Lidocaine may contribute to the long-term pain relief when used with sympatholytic drugs in the intravenous regional technique. However, McKain et al., using volunteers, demonstrated that either lidocaine or normal saline in an intravenous regional block produced indistinguishable changes from baseline in average digital skin temperatures during ice-water challenge. This finding suggested the absence of sympatholytic activity of either agent. On the other hand, lidocaine commonly gives prolonged pain relief and objective signs of increased function in stellate ganglion blocks for reflex sympathetic dystrophy.

A comparative long-term parallel study of intravenous regional guanethidine, reserpine, and bretylium is needed. Efficacy, safety, and dose-response curves should be established. The designs must include controls for lidocaine or tourniquet-induced pain relief. For intravenous regional blockade, guanethidine is used in doses of 10–20 mg, and reserpine in doses of 1–2.5 mg. Unfortunately, the therapeutic index of these two drugs, when given intravenously, is low, and the risk of side effects may limit the usefulness of larger doses. Bretylium has been used in dosages of 5–10 mg/kg intravenously to treat refractory ventricular dysrhythmia, but this dose has been associated with hypotension. In our first group of patients, we deliberately used a relatively small dose of bretylium (1 mg/kg) to avoid hypotension. We have recently used doses of 3 mg/kg for intravenous regional sympathetic blockade without immediate adverse effects, but have not had sufficient follow-up to know if this will improve the quality or duration of pain relief, or lead to late-onset side effects, including hypotension.
In summary, we recommend intravenous regional sympathetic blocks with 1 mg/kg bretylium as a rational and effective treatment of reflex sympathetic dystrophy. Use of higher doses may be warranted, but our experience is limited.

REFERENCES


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An Abnormal Epiglottis as a Cause of Difficult Intubation—Airway Assessment Using Magnetic Resonance Imaging

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Many factors can contribute to a difficult tracheal intubation, several of which are readily apparent on physical examination.1-4 In the case described below, the trachea of a patient with an apparently normal physical examination proved difficult to intubate under direct visualization and with a flexible fiberoptic bronchoscope.

Subsequent magnetic resonance imaging (MRI) revealed an elongated epiglottis which had an unusual angulation in respect to the base of the tongue. This airway problem has not been described in the literature, and, yet, we believe that the size and angulation of the epiglottis may be the etiology of some difficult tracheal intubations. This case also illustrates the remarkable ability of MRI to highlight the soft tissue anatomy of the head and neck. Because of this quality, MRI often may be useful when evaluating patients with tracheas that have been or potentially will be difficult to intubate.

REPORT OF A CASE

A 68-yr-old woman (152 cm, 66 kg) was scheduled to undergo a scalene node biopsy for evaluation of enlarged lymph nodes. On physical examination, she appeared healthy. Her neck was long and supple. She had normal temporomandibular joint function and was able to open her mouth well (5 cm). Examination of her mouth revealed full dentition, and the faucial pillars, soft palate, and uvula were visualized directly. The distance between the thyroid notch and the mental protuberance of her mandible was 9 cm. Following induction of anesthesia, ventilation was controlled easily via a mask. The epiglottis was visualized easily, but varying head and neck position, use of straight and curved laryngoscope blades, and

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