Intravenous Reserpine for Treatment of Reflex Sympathetic Dystrophy

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ABSTRACT: The efficacy of reserpine in relieving the pain of reflex sympathetic dystrophy was tested in 25 patients—21 with upper extremity and four with lower extremity involvement. Injection of the drug relieved the acute signs and symptoms in the upper extremity in 12 of 17 patients. Four patients with quiescent reflex sympathetic dystrophy of upper extremities had prophylactic injection at the time of reconstructive surgery; they had no flare of symptoms. Relief was obtained in the four cases of lower extremity dystrophy. Our patients had no significant side effects. The drug is confined to the extremity by a pneumatic tourniquet as used for intravenous regional anesthesia. After the extremity is exsanguinated and the cuff is inflated, 1 mg of reserpine diluted to 50 ml with normal saline is injected intravenously into the upper extremity. In the lower extremity, 2 mg of reserpine diluted to 100 ml is injected. The tourniquet is removed after 15 minutes. The procedure is safe and can be done in an office setting.

TREATMENT OF PAIN is difficult because we do not completely understand its neurophysiology. In some instances after an injury to an extremity, a particular pain syndrome—reflex sympathetic dystrophy—develops. It varies in severity and often has devastating effects on the patient.[1]

Various terms have crept into general usage to describe the cause and intensity of reflex sympathetic dystrophy. An incomplete injury to a peripheral nerve may produce *causalgia*, which is the most severe form; as the Greek derivation indicates, it is perceived as a burning pain. *Minor causalgia* and *mimo causalgia* were terms introduced to identify the syndrome when it was not the result of nerve injury.[2,3] Lankford and Thompson[4] reclassified minor causalgia as involving a purely sensory nerve. *Minor* and *major traumatic dystrophy* describe the intensity of the syndrome when it develops after an injury that does not involve damage to a peripheral nerve. *Sudeck's atrophy* is a posttraumatic dystrophy with bone involvement shown on roentgenograms. The *shoulder-hand syndrome* is a reflex sympathetic dystrophy that involves the entire upper extremity. It often follows a visceral disturbance such as a heart attack, but it may develop after a fracture to the shoulder.

The cause of this pain syndrome remains elusive when peripheral nerves are damaged. Because interruption of the sympathetic nervous system relieves the pain, an abnormal autonomic reflex has been postulated. Livingston[5] in 1943 postulated that continuing pain fiber stimulation causes abnormal activity in the "internuncial pool of the spinal cord," resulting in increased sympathetic function.

The "gate" theory of pain was proposed by Melzack and Wall[6] in 1965. They theorized that special cells in the substantia gelatinosa of the dorsal column of the spinal cord modulate sensory input and that the large myelinated afferent fibers of the peripheral nerve "closes the gate" whereas the smaller C fibers "opens the gate." Thus a mild stimulus transported along the C fibers can be perceived as intense pain. This concept does help explain why the patient's perception of pain is out of proportion to the stimulus.

Sympathetic blockade by a local anesthetic agent is the accepted diagnostic test for reflex sympathetic dystrophy. A single block may be therapeutic and relieve the pain, but usually several blocks are required. If the pain syndrome is only temporarily relieved, surgical sympathectomy should be done.[7-9]

In 1974 and 1977, Hannington-Kiff[10,11] reported the use of intravenous guanethidine for peripheral sympathetic blockade to relieve the pain of reflex sympathetic dystrophy. The injection technic is the same as that used for intravenous regional anesthesia, but this alternative treatment is not available in the United States because of restrictions by the Food and Drug Administration in the use of guanethidine. Our interest was stimulated by the case report of Gorsky,[12] who used intravenous reserpine instead of guanethidine to obtain a beneficial sympatholytic effect in a patient with Raynaud's phenomenon. Since we began this study, Miller[13] has reported his results with reserpine.

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using the injection technic of Hannington-Kiff, in treating reflex sympathetic dystrophy involving the feet.

This report presents our initial experience using intravenous reserpine to relieve the pain of reflex sympathetic dystrophy in upper and lower extremities.

PHARMACOLOGY

Reserpine is one of more than 20 alkaloids derived from *Rauwolfia serpentina.* Reserpine has a tranquilizing and sedating effect on the central nervous system and has been used to treat hypertension because it depresses adrenergic nerve activity and reduces cardiac output.[14]

The site of action in the peripheral nervous system is the nerve ending, where reserpine blocks the function of the catecholamine granules,[15] thereby effecting a depletion of norepinephrine stores and inhibiting its synthesis. These granules are synthesized in the nerve cell body and are transported along the axon to the nerve terminal. In rabbits, five to seven weeks are required for the terminal granules to be fully replenished.[16]

MATERIALS AND METHODS

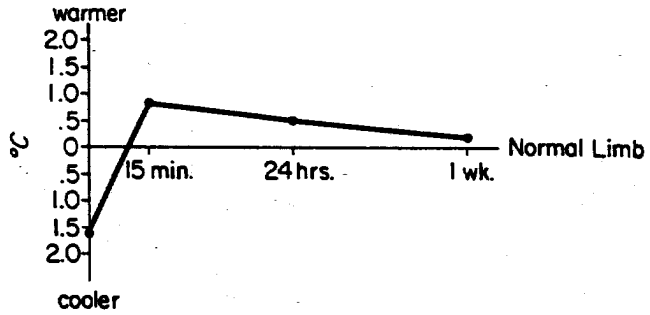
Twenty-five patients (13 men and 12 women) with the clinical diagnosis of reflex sympathetic dystrophy were given injections of reserpine according to our protocol. The first injection for this study was given on Aug 24, 1978, and the last on July 27, 1979. Follow-up has ranged from four to 15 months.

Twenty-one of the patients had reflex sympathetic dystrophy in the upper extremity (Table 1). Causalgia from an incomplete injury to a mixed peripheral nerve was diagnosed in two patients. Causalgia as the result of an injury to a purely sensory nerve was found in six patients. After the reserpine block relieved the pain syndrome in two patients with mimo causalgia, its underlying cause was determined to be deQuervain's disease. Seven patients had major traumatic dystrophy, and four had minor traumatic dystrophy.

As a subgroup, four of the 21 patients with upper extremity involvement were categorized as having quiescent reflex dystrophy. Their treatment and results will be discussed separately from those of the other 17 patients.

TABLE 1. Causes of Reflex Sympathetic Dystrophy (25 Patients)

Cause	*Upper Extremity*	*Lower Extremity*
Causalgia		
Mixed nerve	2	2
Sensory nerve	6	
Mimo causalgia		2
Traumatic dystrophy		
Major	7	2
Minor	4	
Total	21	4



Change in skin temperature (listed in centigrade) after injection of reserpine.

In the lower extremity, causalgia as the result of an incomplete sciatic nerve injury was diagnosed in two patients. Two other patients had major traumatic dystrophy after crush injuries to the foot.

Technic and Dosage

With the patient comfortably positioned supine on an examining table, a pneumatic tourniquet is placed on the arm or leg. A vein, usually on the dorsum of the hand or foot, is cannulated. The extremity is then exsanguinated with an Esmarch's rubber bandage, and the tourniquet is inflated to the appropriate level.

Next the reserpine is rapidly injected. For the upper extremity, 1 mg of reserpine is diluted in 50 ml of normal saline; for the lower extremity, 2 mg of reserpine is diluted in 100 ml of normal saline. One of us (J.S.G.) includes adjuvant lidocaine (Xylocaine) at a 0.1% dilution to alleviate the burning sensation that may accompany the injection. The tourniquet is released after 15 minutes.

In patients with quiescent dystrophy, the drug may be injected during operation, after the pneumatic tourniquet is inflated. If regional intravenous anesthesia is used, the reserpine can be mixed with the anesthetic at the time of the block.

RESULTS

The reserpine block produced beneficial results in 12 of the 17 patients who had the acute symptoms of reflex sympathetic dystrophy in the upper extremity (Table 2). Results were classified as beneficial, equivocal, or no effect. A "beneficial" result was rather dramatic, in that each patient had complete relief of the pain as soon as the tourniquet was removed. The patient would then voluntarily use the hand and allow it to be manipulated for examination.

TABLE 2. Results of Reserpine Block in 21 Patients With Acute Reflex Sympathetic Dystrophy

Result	*Upper Extremity*	*Lower Extremity*
Beneficial	12	4
No effect	4	
Equivocal	1	
Reinjection	1	3

Four patients were unimproved, but no patient's condition was worse after the injection was given. The result in one patient with causalgia from an incomplete median nerve injury was considered equivocal. This person was relieved of the burning pain in the hand but continued to have paresthesias that we thought were the result of the incomplete nerve injury.

One of the failures was in a patient who had temporary benefit for about two weeks, after which the symptoms rapidly recurred. A second injection provided relief for five days, followed by another sudden return of symptoms. Stellate sympathetic blockade produced complete relief for only several hours. Surgical sympathectomy was deferred by this patient.

Reconstructive hand surgery was indicated for a special group of patients with quiescent reflex dystrophy. The first of these patients had a flare of symptoms after operation, but a single postoperative reserpine block produced relief. Thereafter, the other four patients had prophylactic intravenous reserpine block at the time of reconstructive surgery of the hand, without flare.

The four patients with lower extremity pain had beneficial results after the first injection, though three of them had a second injection six weeks to three months later to relieve recurrence (Table 2).

As a result of the vasospastic component, most of the involved extremities were cooler than the opposite normal ones. After the injection, the involved limb was warmer than the uninvolved one. This was evident when the tourniquet blush had resolved at 30 minutes, and was still evident 24 hours after the injection. By one week after injection, the temperatures of the two extremities were equal.

To substantiate this impression, we recorded skin temperatures at selected loci on the six most recent patients by means of an infrared thermometer (Micron M-25, Mikron Instrument Company, Wykoff, New Jersey). The involved extremity of one patient was 1 C warmer than the uninvolved one before injection. That difference increased to 2.9 C at 30 minutes after injection, and one week later the involved extremity was again 1 C warmer. Before injection, the other five involved extremities averaged 1.6 C cooler (range, 0 to 3 C cooler) than the corresponding uninvolved limbs. Thirty minutes after injection the involved extremities averaged 0.8 C warmer (range, 0 to 1.4 C warmer). After 24 hours, the treated limbs were warmer by an average of 0.5 C, and one week later the average was 0.3 C warmer (Figure).

These data indicate that the vasospastic component is relieved by the reserpine, and the skin temperature returns to that of the uninvolved limb.

DISCUSSION

Before Hannington-Kiff[10,11] introduced a new approach to the treatment of reflex sympathetic dystrophy, the only way of relieving this debilitating pain syndrome was either by sympathetic ganglion blockade or sympathectomy, both of which carry a risk that had to be accepted. Reserpine has been shown to effectively inhibit the adrenergic nerve ending. It has been used intra-arterially to treat vasospastic disorders by producing vasodilatation.[17-20]

A high concentration of the drug is confined to the extremity by the intravenous block technic. The 15 minutes during which the tourniquet is inflated is apparently sufficient to allow tissue fixation of the drug, though that conclusion is not proven.

When the tourniquet was released, our patients had no significant side effects. Some had transient episodes of facial flushing and a feeling of warmth, and two patients noticed a peculiar taste that they could not exactly characterize. In no instance were these side effects considered detrimental, nor did they require observation or delay the patient's returning home. No effect on blood pressure was noted. Intra-arterial injections of reserpine of from 1.0 mg to as high as 6.0 mg produced no significant side effects other than consistent flushing.[17,18] We did not have the experience reported by Abrams et al,[19] whose patients, four hours after intravenous injection of 1 mg of reserpine, had abnormal sensations of warmth, nasal congestion, facial flushing, and fall in diastolic blood pressure.

Similar to our experience, Tindall et al[20] noted that their patients had a burning sensation in their hands and fingers when reserpine was injected, but they considered that response to be nonspecific because it could be elicited by injecting physiologic saline. Lidocaine (Xylocaine) mixed with the diluted reserpine will relieve this pain without affecting the end result.

Reserpine has a known physiologic response. A double-blind study with intra-arterial reserpine injections showed that when injected into the extremity the drug rapidly causes obvious vasodilatation and flushing.[20] Persons with reflex sympathetic dystrophy have well known emotional lability. Our experience with one patient who had intravenous saline placebo without effect and later a successful reserpine block convinced us that a study comparing reserpine to placebo would not be in the best interests of our patients.

Although the extremities were painful, our patients allowed exsanguination with Esmarch's rubber bandage without complaint. They tolerated the tourniquet pressure as well as any other patient would. Each patient was told that the tourniquet would be uncomfortable, and each accepted the situation.

The traditional approach to diagnosing and treating reflex sympathetic dystrophy has been to relieve the sympathetic input by ganglionic blockade with a local anesthetic. Surgical sympathectomy has been the de-

finitive treatment. Inhibiting the adrenergic nerve ending yields the same beneficial effect without exposure to serious risk.

We have been pleased with our initial results, as presented in this report. This relatively simple procedure will dependably relieve the pain experienced in reflex sympathetic dystrophy.

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