

DIS News

College of Health Professions and Biomedical Sciences
Drug Information Service

Literature Highlight: Safety of Enteral Naloxone for the Reversal of Opiate-Induced Constipation in the Intensive Care Unit

Opiate-induced constipation has been reported in 83% of patients in intensive care units (ICU) and is considered to be dose-related. Naloxone is an opioid antagonist that has been shown to treat opioid-induced constipation when given orally in patients receiving chronic opioid therapy; however, the opiate withdrawal and analgesic reversal reported in previous studies is a concern. Additionally, the safety of its use has not been studied in patients in the ICU. A prospective, observational trial studied the safety of enteral naloxone for opiate-induced constipation in patients in the ICU.

Twenty-four patients in the ICU receiving both naloxone and an opiate drug were followed for five consecutive naloxone doses or until they were taken off of either drug. Patients were excluded from analysis if they were paralyzed, had an extubation scheduled within 24 hours, had known cirrhosis, acute hepatitis, or known portal hypertension, or were not assessed using the Richmond agitation-sedation scale (RASS). The naloxone injectable solution was administered enterally. Patients received a mean dose of 3.6 ± 0.9 mg of naloxone every eight hours. Blood pressure, mean arterial pressure, heart rate, respiratory rate, presence of pain, fentanyl dose, propofol dose, and midazolam dose were evaluated at -2, -1, 0, 1, 2, and 4 hours of the naloxone dose. The primary endpoint was change in the RASS score. Changes in blood pressure, MAP, heart rate, respiratory rate, pain, and medication doses were also evaluated.

There was an increase in bowel movements in the 24 hours after naloxone administration ($p=0.0396$); however, there were no significant changes in RASS score, heart rate, mean arterial pressure, respiratory rate, or presence of pain. Additionally, there were no significant changes in pain medication doses after

naloxone administration. Limitations included the observational, non-controlled study design, the small sample size, the differences in the timing of data collection, and the inability to assess efficacy due to lack of controlling for potential confounders.

SUMMARY: Enterally administered naloxone may be considered safe for use in ICU patients with opiate-induced constipation. Future studies are needed to assess the efficacy of naloxone in ICU patients.

Arpino PA, Thompson BT. Safety of enteral naloxone for the reversal of opiate-induced constipation in the intensive care unit. J Clin Pharm Ther 2009;34:171-175.

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We welcome any comments and suggestions for future newsletter topics.

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Dysport®: a new competitor for Botox®

A new competitor of botulinum toxin type A (Botox®) was approved by the FDA on April 29, 2009. AbobotulinumtoxinA (Dysport®) is indicated for the treatment of cervical dystonia and the temporary improvement of moderate to severe glabellar lines in adults less than 65 years of age.¹ AbobotulinumtoxinA suppresses the release of acetylcholine presynaptically, which causes long-term neuromuscular blockade. It is injected intramuscularly every 12 weeks (the interval may be longer depending on the patient's response) and causes specific muscle paralysis, which relieves sustained muscle contractions and decreases facial lines by inhibiting muscle movements during frowning, worrying, or squinting.² The potency units are unique to abobotulinumtoxinA so it cannot be directly interchanged with other botulinum toxins.¹

In a prospective, randomized, double-blind, placebo-controlled clinical trial of 158 patients, abobotulinumtoxinA (500 U) showed significantly better reduction in glabellar lines compared to placebo using a four-point photographic comparison scale.³ The onset for abobotulinumtoxinA was 24 hours for 15% of patients and 48 hours for 35% of patients. The median time to onset was three days, and the median length of effect was 85 days. There was a higher incidence of ocular events in the treatment group (6.7%) versus the placebo group (5.7%) including ptosis, blepharospasms, dry eye, eyelid dysfunction, ocular hyperemia, and blurred vision.³

A double-blind, randomized, parallel-group study evaluated the effects of abobotulinumtoxinA versus botulinum toxinA in 62 women between 18 and 55 years old with moderate to severe glabellar lines.⁴ Patients were divided into two equal groups and received five injections of either botulinum toxin A or abobotulinumtoxinA. There was a significantly higher number of patients who showed improvement at 16 weeks in the botulinum toxin A group versus the abobotulinumtoxinA group (53% vs. 28%; $p=0.04$). The botulinum toxin A group also reported feeling more attractive and satisfied than the abobotulinumtoxinA group. There were no significant

differences in the incidence of adverse effects. The authors concluded that botulinum toxin A has a longer duration of action than abobotulinumtoxinA. The results were obtained in mostly Caucasian females, and the injection sites were altered from the recommended sites, which limits the generalizability of these results.⁴

A randomized, placebo-controlled, crossover study evaluated the differences in efficacy between botulinum toxin A (100 U), low dose abobotulinumtoxinA (300 U), or higher dose abobotulinumtoxinA (400 U) in 54 patients over 18 years of age with cervical dystonia.⁵ The patients received all three treatments in a random order. The injections were performed every 16 weeks, unless the patient had not returned to baseline, then the time between injections was lengthened. Both strengths of abobotulinumtoxinA produced significantly better improvement on both the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Tsui scale (a clinical scale grading the amplitude and duration of both sustained and spasmodic movements) compared to botulinum toxin A ($p=0.006$). The number of adverse events was significantly higher with both doses of abobotulinumtoxinA compared to botulinum toxin A ($p<0.01$). Dysphagia was reported most often with all treatments (17.6% for botulinum toxin A vs. 33-36% for abobotulinumtoxinA). Dysphonia, asthenia, neck weakness, prolonged pain at injection site, and dry mouth were also reported. The authors concluded that abobotulinumtoxinA was more effective than botulinum toxin A for cervical dystonia but it had a higher incidence of adverse effects. Limitations of this study include the small patient population and possible crossover effects.⁵

There have been reports of abobotulinumtoxinA spreading beyond the intended site of injection, resulting in systemic symptoms of botulism poisoning including asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties.¹ AbobotulinumtoxinA has already been approved in 76 countries around the world and has been in use for

19 years;² however, the FDA is requiring a risk evaluation and mitigation strategy (REMS) for abobotulinumtoxinA to determine if the benefits outweigh the risks.¹

Dysport® appears to be more effective than Botox® for the treatment of cervical dystonia. It is also effective for the treatment of glabellar lines, although the duration of effect may be shorter than the duration of effect for Botox®. Treatment with Dysport® should be carefully monitored, because of the possibility of migration of the abobotulinumtoxinA beyond the site of injection.

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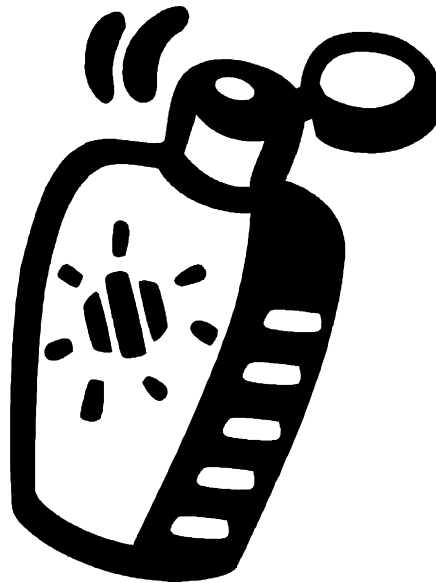
Treatment Options for Vitiligo

The recent death of Michael Jackson brought new attention to a rare skin disorder called vitiligo, which affects about 1-4% of the world's population.¹⁻⁶ It is a progressive disease that usually begins early in life.^{4,5,7} The cause is uncertain, but genetic, immunological, and environmental factors may play a role.^{2,6} The melanocytes become dysfunctional, resulting in a reduced amount of melanin in the skin leading to hypopigmentation.^{1,4,6} The pigment of the skin, typically affecting the area around body orifices (eyes, mouth, nipples, nostrils, genitalia), slowly becomes lighter over time, leading to permanent white patches.^{2,4,5} Because of the detrimental cosmetic nature of vitiligo, quality of life can be greatly diminished, resulting in emotional distress.^{2,7,8} Psychological counseling should be offered for all patients and their family members to help them cope with the disease and complications of certain treatments.⁷

There are many treatment options available to help with skin repigmentation; however, most are only moderately effective (51-63% success rate).⁴ A combination of photochemotherapy and phototherapy is the most common treatment;² however, some European guidelines recommend a topical steroid or pimecrolimus as first-line.⁷ Psoralen and khellin, which increase melanocyte sensitivity and activate melanocytes, are the photochemotherapeutic agents used most in practice. Phototherapy utilizes narrow band ultraviolet rays to stimulate inactive melanocyte activity.^{2,4,7,9} The success rates of the combination therapy is highest in younger patients.⁹ Adverse effects include phototoxic reactions, blistering, hyperpigmentation, and erythema.^{2,5} Vitamin D₃ analogues, such as calcipotriol, may also be used to stimulate the growth of melanocytes, but further research is needed before a recommendation can be made. The success rate is greater when used with phototherapy.^{2,4,7}

Topical corticosteroids are recommended for patients with new-onset vitiligo to help minimize further depigmentation; however, they should only be used for a trial period of two months due to the increased risk of adverse events including skin atrophy.⁷ Systemic corticosteroids, such as low-dose prednisolone or methylprednisolone, are used to slow

the progression of the disease. Using lower doses minimizes the adverse events seen with corticosteroid use. Topical immunomodulators, such as tacrolimus or pimecrolimus, are newer treatments recommended for symmetrical vitiligo. They are considered an alternative to topical steroids because they can be used long-term with fewer side effects.^{6,7} Immunomodulators suppress cytokines that promote inflammation. Combining these



agents with phototherapy has a synergistic effect, but may also increase the risk of skin cancer.⁶

Surgery, including tattooing, grafting, or transplantation, should be reserved for patients with stable vitiligo (no new lesions or extension of the lesion in the past 12 months).⁷ Several of these procedures may need to be done to see a desired response. One drawback to surgery is scarring; however, the success rate is higher than with other treatments (87-95%).^{4,6}

Other less commonly used therapies that help in repigmentation include *Ginkgo biloba*, laser therapy, and phenylalanine or Placentrex®.^{2,3,5,6} The leaves of *Ginkgo biloba* have immunomodulatory and anti-inflammatory properties.³ It is typically used as monotherapy; however, when combined with topical steroids, repigmentation occurs faster.^{3,5} Excimer laser therapy uses a wavelength of 308 nm to help target the areas affected by the disease and spare healthy skin.^{4,6} Head and neck areas respond the best; however, this somewhat less effective than phototherapy. Compared to photo-

chemotherapy and phototherapy treatment, the excimer laser costs more and patient compliance is an issue, making it a less desirable treatment option. Phenylalanine and Placentrex® (extract of human placenta) promote melanin synthesis and migration of melanocytes to depigmented skin cells from healthy ones and have resulted in relatively good repigmentation rates.^{4,6}

Another treatment option is depigmentation. This is typically reserved for extreme cases (patients with >50% of the skin surface area affected or extensive depigmentation on the face or hands). It may also be used in patients who do not wish to try repigmentation strategies and fully understand the permanence.⁷ Monobenzyl ether of hydroquinone (MBEH) and 4-methoxyphenol (4MP) effectively induce depigmentation within four months; however, it may take up to a year for the full effect, and repigmentation may recur in some areas treated.^{1,7} Depigmentation is highly controversial, particularly in individuals with dark skin because it results in the appearance of an albino (like Michael Jackson). This procedure also leaves the patient extremely sensitive to the sun.¹

Vitiligo is a rare but serious skin problem that can result in a decreased quality of life and extensive emotional problems. There are many options available to treat the physical symptoms of vitiligo; however, their success rates are moderate at best. Therefore, it is also important to incorporate psychological counseling to help these patients cope with their changing appearance.

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