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Case Report

Erectile Dysfunction as Rare Side Effect in the Simultaneous Intrathecal Application of Morphine and Clonidine

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We report on the case of a 52-year-old man who presented with a history of chronic neuropathic pain treated with intrathecal application of morphine for many years. In spite of significant dose escalation, considerable pain relief had not been achieved. Ziconotide had been tried but not only did it not provide pain relief, but it also caused severe side effects in this patient. A combination of morphine and clonidine was delivered by a programmable pump, slowly increasing the clonidine rate over several weeks. For ease of transition and minimization of hospitalization, which was a special concern to this patient, combining clonidine and morphine was chosen over monotherapy with hydromorphone, with both possibilities being described as equal alternatives in the literature. Considerable pain relief was achieved during week 2 at a clonidine dose of 0.040 mg/d, thereby decreasing the visual analog score (VAS) from 10 to 4. Yet, after developing erectile dysfunction and relative hypotension soon after beginning clonidine treatment, the patient decided not to continue with the combined application of morphine and clonidine. Treatment was therefore switched back to the former monotherapy with morphine. Thereafter, erectile dysfunction disappeared and blood pressure returned to habitual high levels. Although common in systemic application, erectile dysfunction caused by the intrathecal application of clonidine has not been described yet in the literature. In this patient, this rare side effect decisively impaired life quality, subjectively outweighing the considerable pain relief which could be achieved after formerly inefficacious treatment. Further and prospective investigation might be needed to estimate the connection of erectile dysfunction to intrathecal application of clonidine.

Key words: intrathecal, erectile dysfunction, morphine, chronic pain, drug pump

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Intrathecal drug application is a well-established method for the treatment of chronic pain syndromes. The use of morphine is common and considered a first line therapy (1-3) with tolerable side effects (4,5). Several other substances, including bupivacaine, clonidine, midazolam, hydromorphone, and ziconotide are in clinical use. For some of these substances, data on their therapeutic effect and side effects are not yet comprehensive. We report on a patient with a chronic pain syndrome due to diabetic polyneuropathy who developed erectile dysfunction during the intrathecal application of morphine and clonidine.

Methods

A 52-year-old man presented with intractable pain despite the intrathecal application of morphine. His medical history included hypertension and since 1983, insulin-dependent diabetes mellitus with complications, namely polyneuropathy with bladder dysfunction and erectile dysfunction. With testosterone

treatment since 2007, a normal erectile function was achieved.

The patient's pain history began in his youth with complaints of lumbago while exercising and while wrestling on a serious level. His current complaints developed in 1996. The patient complained of a burning pain in both legs, a lancing pain in the coccygeal region, and a persistent pain diffusely spread over the whole body. Depending on stress and weather, the pain intensity was rated 7-10 on the VAS. Neither physiotherapy nor psychotherapy yielded a pain relieving effect.

Medical therapy began with transcutaneous application of fentanyl and was changed to intrathecal application of morphine in 2004 after the patient developed dermal reactions from the transcutaneous delivery. The applied dose increased swiftly until a drug holiday in 2007, yet oral analgesics did not produce satisfying pain relief afterwards. The intrathecal application of morphine was therefore continued, seeing a swift dose escalation. A few months into the ziconotide trial, the patient developed burning sensations all over his body without experiencing substantial pain relief. Therefore, the trial was ended. As well as pruritus and increased sweating, paresthesia and limb pain are considered adverse effects of ziconotide, yet are not seen frequently (6). Most frequently dizziness, nausea, a confused state, and nystagmus are reported.

A physical examination showed an awake, oriented, cooperative, obese patient with a Karnofsky score of 70% and an absence of fever, headache, or meningism. Cranial nerves were grossly intact. Upper and lower limbs showed no pareses and muscle tone was within normal limits. The patient was able to walk without assistance, using a wheelchair for distances beyond a few steps. Sensation was intact to light touch throughout. No tremor was present.

Second line options in medical therapy were changing to hydromorphone, adding bupivacaine, or adding clonidine (1). Informed consent was given for the application of morphine and clonidine, which was chosen for a seamless transition and shorter hospitalization, the latter being very important for the patient. Furthermore, while most of our patients are being treated with morphine alone, our department had more clinical experience adding clonidine than bupivacaine. After the scheduled replacement of the implanted programmable pump, the application of clonidine began, slowly increasing the daily clonidine dosage in weekly steps of 33 µg while decreasing the morphine accordingly.

Results

In the course of treatment, the patient's pain intensity decreased from a 10 to 4 rating on the VAS in week 2 after therapy onset at a clonidine dose of 66 µg/d (Fig.1). At the same time, the patient reported new erectile impotence. During this time testosterone blood levels were normal, and blood sugar levels showed continuing good control of the known insulin-dependent diabetes mellitus. Blood pressure did not drop below normal levels.

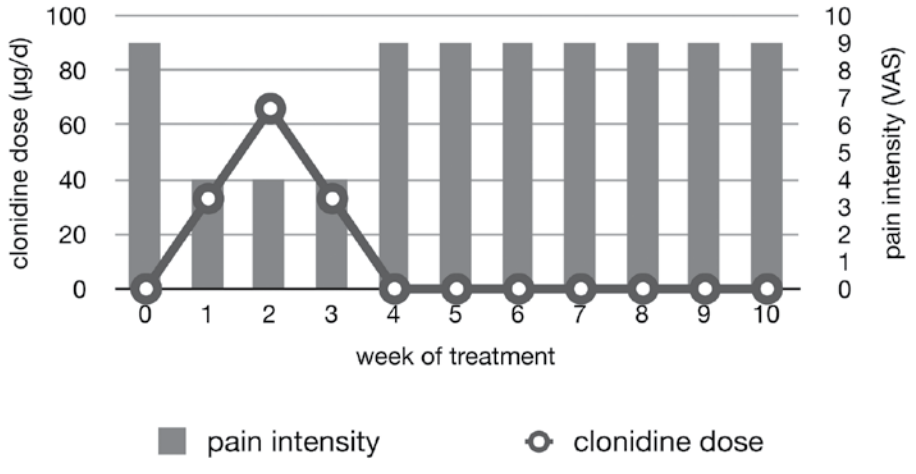

Fig. 1. *Course of clondine dose and pain intensity*

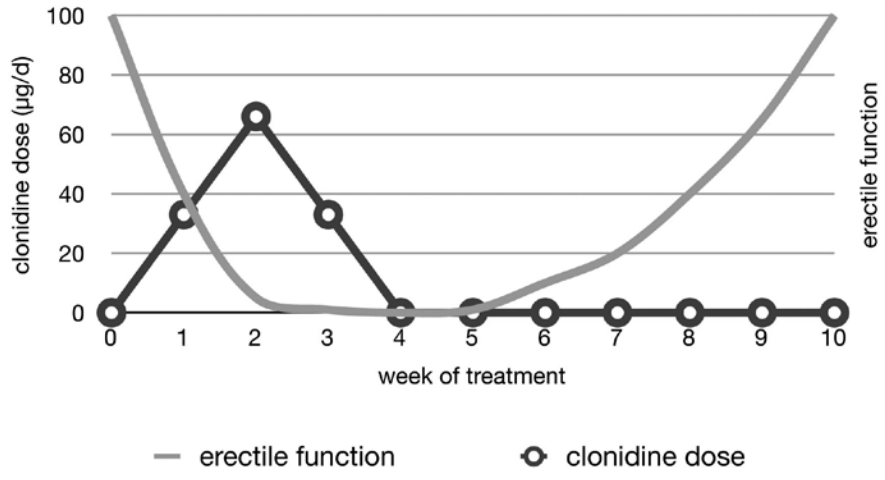

Fig. 2 *Course of clonidine dose and erectile function*

The patient therefore decided to discontinue the therapy with morphine and clonidine and to return to the single drug therapy with morphine. Pain intensity swiftly returned to formerly known levels, and within a few weeks normal erectile function returned (Fig. 2).

Discussion

At our institution, 6 patients were given therapy which included the intrathecal application of clonidine; 2 of them were men. Neither of them complained of erectile dysfunction.

In the systemic application of clonidine a decline of libido and potency are known and common side effects, seen in up to 10% of patients treated (7). The available literature mostly deals with the intrathecal application of clonidine in its use for spinal anesthesia during obstetrics, where hypotension, sedation, and lowering of heart frequency are described (8,9). In pain therapy, clonidine is expected to increase the analgesic effect of morphine when added (10). The dosage range is from 47 to 850 µg/d (1,10,11). Reports on the development of erectile impotence under intrathecal application of clonidine in men could not be found in PubMed, whereas sexual dysfunction is described in the animal model (12,13).

In this patient, experiencing sexual dysfunction during intrathecal application of clonidine was of high clinical relevance. Use of a phosphodiesterase-5-inhibitor might have alleviated the problem, but was not desired by the patient. The phenomenon led to the discontinuation of a therapeutic regime through which good pain relief had been achieved after formerly unsatisfying results. This single case obviously does not allow to differentiate between coincidence and causal connection. A multitude of other causes are imaginable, yet with endocrine and cardiovascular remaining without substantial deviations, the course in this patient suggested an on-off-effect of clonidine application and is to be noted.

Conclusion

We conclude that erectile dysfunction has to be taken into consideration when indicating an intrathecal application of clonidine. In patients already being treated with intrathecal clonidine or being considered for this therapy, specific history-taking and prospective evaluation is necessary to support a causal link between intrathecal application of clonidine and the developing of erectile dysfunction.

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