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Editorial comment

From patient observation to potential new therapies—Is old spironolactone a new analgesic?

Eija Kalso*

Institute of Clinical Medicine, University of Helsinki, Pain Clinic, Helsinki University Central Hospital, P.O. Box 140, 00029 HUS, Finland

1. Introduction

In this issue of the *Scandinavian Journal of Pain* Heinrich Wernze and Thomas Herdegen [1] report that spironolactone shows beneficial long-term effects on pain, mood, and quality of life in 50% of the 31 fibromyalgia patients they treated with spironolactone for 12 months. This review addresses two questions: why would spironolactone be effective in reducing fibromyalgia-related symptoms and what is the role of case series in modern medicine.

2. Fibromyalgia

Fibromyalgia is a common pain syndrome with a point prevalence of 1–5%. The majority of fibromyalgia patients are female. The syndrome is often preceded by local pain problems such as headache, neck and back pain, which then develop to widespread pain. Sleep disturbance and obesity are also related to fibromyalgia, which often coincides with other symptoms or diseases such as migraine, asthma, and irritable bowel disease. Anxiety and depression are common co-morbidities with fibromyalgia as is the case with other chronic pain conditions. The pathophysiology of fibromyalgia is slowly being revealed. Dysfunction of the stress axis and descending pathways of endogenous pain inhibition, aberrant brain networks and peripheral small fibre neuropathy [2] have been shown to be related to fibromyalgia.

The treatment of fibromyalgia consists of exercise, physiotherapy, and pharmacological management. However, the available analgesics are not effective in most patients. A recent report based on meta-analyses using at least 50% pain relief as the outcome suggested an NNT of about 10 for pregabalin and duloxetine, the two drugs for which individual patient data are available [3].

3. Why would spironolactone relieve fibromyalgia-associated symptoms?

Spironolactone dose-dependently blocks both mineralocorticoid and androgen receptors and it is a progesterone receptor agonist. The mechanism by which spironolactone could cause significant pain relief and improvement of sleep, cognitive function, emotional wellbeing, and quality of life in fibromyalgia is unclear. A few hypotheses, however, are available.

One possibility is that spironolactone had a significant pain relieving effect, which then resulted in improvements in other measures. It has been shown that a large effect, at least 50% reduction in pain, has significant secondary positive effects on sleep, mood and function [3]. What is the evidence for spironolactone having analgesic effects?

The currently available literature suggests that spironolactone has no antinociceptive effects in acute thermal models of pain [4]. However, a mineralocorticoid antagonist eplerenone has been reported to reduce pain behaviour in neural inflammation when applied locally to the dorsal root ganglion but not after systemic administration [5]. In this zymosan-induced model the expression of mineralocorticoid receptors was increased in the neurones and satellite glia were activated. Both the activation of satellite glia and the excitability of the small-diameter sensory neurones were reduced by local eplerenone [5].

Activation of the mineralocorticoid receptors promotes classical inflammation [6] leading to the production of metabolites of oxidative stress and proinflammatory cytokines. It could be postulated that stress, due to adverse life events or chronic local pains, can activate the mineralocorticoid receptors leading to increased inflammation in various tissues including the nervous system. Obesity and other proinflammatory factors could then further enhance the activation of this proinflammatory pathway. Blocking of the minneralocorticoid receptors could thus have positive effects on many of the mechanisms that have been indicated as promoting the development of fibromyalgia.

Also the emotional wellbeing of the patients in the case series of Wenze and Herdegen [1] was improved. In addition to being a consequence of decreased pain intensity it is also possible that blocking of central mineralocorticoid receptors by spironolactone may have had more direct effects on e.g. anxiety [7]. In mice, streptozotocin-induced diabetes was shown to increase anxiety-like behaviour, which was less responsive to diazepam than in normal mice [8] whereas mineralocorticoid receptor antagonists showed anxiolytic-like effects. In man, spironolactone has been reported to increases the circulating levels of deoxycorticosteroids and progesterone [9], whose neurosteroid metabolites enhance

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* Corresponding author. Tel.: +358 9455243.
E-mail addresses: eija.kalso@helsinki.fi, eija.kalso@hus.fi

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GABAergic transmission [10]. These neurosteroids can have various neuropsychiatric effects [11].

In the case series by Wenze and Herdegen [1] spironolcatone was administered as an add-on medication to the fibromyalgia patients of whom some were using opioids. The consumption of analgesics, including opioids, was remarkably reduced during spironolactone administration. Interestingly, spironolactone has recently been shown to significantly enhance the efficacy of morphine induced antinociception and to increase morphine concentrations in the central nervous system probably by inhibiting P-glycoprotein [4].

4. What does this study tell us?

The idea of testing spironolactone in fibromyalgia originates from the clinical observation that spironolactone administered during the luteal phase in women with premenstrual syndrome achieved a marked improvement in mood and headache. The authors then tested the drug in 31 fibromyalgia patients who had not responded to previous attempts to alleviate their symptoms. Thirty-one patients started the treatment with spironolactone, 16 of these stopped the treatment due to lack of efficacy whereas 15 continued on the medication for 12 months.

The patients consented to comply with a written instruction of all modalities of treatment and the off-label use of spironolactone, which has been approved in the indications of primary and secondary hyperaldosteronism.

Fibromyalgia was adequately diagnosed using the American College of Rheumatology diagnostic criteria. The patients were assessed at 4–6 weeks, 6 months, and 12–14 months using relevant tools such as the fibromyalgia impact questionnaire FIQ and a validated German self-report multidimensional mood questionnaire BSKE. In addition, non-validated questionnaires considered relevant were used, adverse effects were monitored, and biochemical tests for electrolytes and kidney and liver function were performed. At the endpoint the patients were asked about the global impression of improvement and improvement in health related quality of life, and several other measures.

Results are reported as descriptive statistics compared with baseline. The 15 patients out of the 31 showed remarkable average improvement in the large battery of tests. The treatment was also well tolerated. The results of this case series would have been stronger had the 16 patients who stopped the treatment due to lack of efficacy been followed using the same protocol as the responder group. In order to control for the effect of therapeutic interaction, the patients who did not continue on spironolactone should have been seen by the treating physician as often as the spironolactone-treated patients.

5. Case series need to be standardized

Clinical observations are an important source for new potential therapeutic indications for old drugs or other therapies. Pregabalin is the only drug that was registered with neuropathic pain as its main indication. Most of the drugs used to manage neuropathic pain, such as amitriptyline, were used for other indications. It was only because of clinical observations that tricyclic antidepressants were considered efficacious in chronic pain, too. Now we know, that amitriptyline has many other pharmacological effects that can explain their efficacy in alleviating neuropathic pain.

A recent carefully documented case report described the efficacy of cetuximab in cancer-related treatment resistant neuropathic pain [12]. Cetuximab had no beneficial effect on cancer but it consistently relieved neuropathic pain. Once it was obvious that cetuximab had no effect on cancer, the patient was given low doses of the drug as a control analgesic. As cetuximab is a MAP kinase inhibitor the authors concluded that cetuximab most likely relieved pain via this mechanism [13].

Case series can open new possibilities for the management of pain, which is difficult to treat. In order to test the hypothesis, the observation has to be recorded using a standardized protocol and relevant outcomes. If possible, patients receiving standard treatments should be followed using the same protocol. It is important to have the patient's informed consent if the treatment is used off label.

6. Conclusion and implications

Compared with the available therapies this case series indicates very good efficacy for spironolactone in fibromyalgia as half of the patients benefited and adverse effects were few. It is important to execute a large randomized and controlled trial, which should preferably include three arms: spironolactone, an inactive control (placebo), and an active control (e.g. duloxetine or pregabalin). It would be important to collect enough "biomarker" data to clarify which patients are likely to respond should the controlled trial confirm the promises this case series suggests.

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