Case report / Artykuł kazuistyczny

Occurrence of peripheral edema in patients treated with sublingual naloxone: a case report

Występowanie obrzęku obwodowego u pacjentów leczonych naloksonem podawanym podjęzykowo: opis przypadku

Sina Radparvar

Southern California Permanente Medical Group, Sylmar, USA

Alcohol Drug Addict 2022; 35 (3): 245-248
DOI: https://doi.org/10.5114/ain.2022.120785

Abstract

Introduction: Sublingual Naloxone combined with Buprenorphine in various formulations has been approved for treatment of opioid use disorder. Despite its low bioavailability, Naloxone can reach systemic circulation and cause adverse effects. Peripheral edema has been reported as a side effect of Buprenorphine/Naloxone but not as a side effect of Naloxone in post-marketing data as well as other reports elsewhere.

Case description: A case report is presented which includes a patient that experienced bilateral peripheral edema related to Buprenorphine/Naloxone combination. After the patient was switched to monotherapy with Buprenorphine by itself, the side effects resolved.

Commentary: Naloxone given in sublingual formulation may have oral bioavailability despite previous reports. After reaching systemic circulation,

Streszczenie

Wprowadzenie: Nalokson podawany podjęzykowo w połączeniu z buprenorfiną, w różnych preparatach, został zatwierdzony do leczenia zaburzeń związanych z używaniem opioidów. Pomimo niskiej biodostępności nalokson może dotrzeć do krążenia ogólnoustrojowego i wywołać niepożądane skutki. Obrzęki obwodowe jako działanie niepożądane buprenorfiny/naloksonu, ale nie samego naloksonu, zgłaszano po wprowadzeniu preparatu do obrotu (w danych postmarketingowych), jak również w innych doniesieniach.

Opis przypadku: Opisano przypadek pacjenta, u którego jako działanie niepożądane leczenia kombinacją buprenorfiny i naloksonu wystąpił obustronny obrzęk obwodowy. Działania niepożądane ustąpiły po wprowadzeniu u pacjenta monoterapii buprenorfiną.

Komentarz: Pomimo wcześniejszych doniesień nalokson podawany podjęzykowo może mieć doustną biodostępność, a po dotarciu do krążenia ogólnoustrojowego – powodować działania niepożądane.

Correspondence to/Adres do korespondencji: Sina Radparvar, Southern California Permanente Medical Group, 12669 Encinitas Avenue, Sylmar, California 91342, USA, phone: +1 818-838-7709, e-mail: sina.radparvar@gmail.com

Authors' contribution/Wkład pracy autorów:

No ghostwriting declared./Nie występuje zjawisko *ghostwriting*.

Submitted/Otrzymano: **04.05.2022** • **Accepted/Przyjęto do druku:** **06.07.2022**

Naloxone has potential for causing side effects. Peripheral edema may be caused by Naloxone's role in antagonising the endogenous opioid system resulting in capillary permeability.

Keywords: Naloxone, Peripheral edema, Adverse effects.

Obrzęki obwodowe mogą być spowodowane rolą naloksonu w antagonizowaniu endogennego układu opioidowego, co skutkuje przepuszczalnością naczyń włosowatych.

Słowa kluczowe: nalokson, obrzęki obwodowe, działania niepożądane.

Introduction

Suboxone is a combination product containing Buprenorphine (a partial opioid agonist) and Naloxone (an opioid antagonist). It is a synthetic opioid used for treatment of opioid use disorder and chronic pain syndrome. The combination product containing Buprenorphine/Naloxone has been regarded as safer compared to the single entity Buprenorphine. This is due to the Naloxone component which is thought to be "activated" only if dissolved and used intravenously antagonising the mu (μ) receptors in the brain. This is the reason behind combining Naloxone with Buprenorphine in the combination product to prevent overdose and diversion.

The recognised side effects of Buprenorphine/Naloxone combination are often attributable to the partial opioid agonist Buprenorphine component of the medication and include nausea, vomiting, constipation, headache, abdominal pain and hyperhidrosis [1]. Peripheral edema is listed as a side effect of Buprenorphine/Naloxone combination without specified rate but not listed as a side effect for single agent Buprenorphine in post-marketing analysis [1].

Naloxone which is an opioid antagonist is thought to have low oral bioavailability in healthy subjects. The oral availability of Naloxone in healthy subjects has been studied at various doses. The mean oral absolute bioavailability of Naloxone in one study was less than 2% at doses ranging from 5 mg to 120 mg [2]. However subsequent studies have casted doubt on this assumption with at least one study showing significant absorption of sublingual Naloxone (92.7%) in patients prescribed the combination Buprenorphine/Naloxone products [3]. In addition, these patients were found to have significant quantifiable concentrations of Naloxone in the urine toxicology testing [3].

The case presented herein is a patient who developed peripheral edema 3 weeks after initiation of Buprenorphine/Naloxone combination. The patient's edema resolved after a switch was made to single agent Buprenorphine.

Case description

A 32-year-old male with a history of gastroesophageal reflux disease and opioid use disorder was initiated on Suboxone (Buprenorphine/Naloxone) at starting dose of 8 mg sublingual per day with dose titration over one week. He was stabilised on the medication at a dose of 24 mg sublingual per day. His only other medication was Pepcid 20 mg orally per day. After 3 weeks of treatment, the patient reported lower extremity edema bilaterally but more on the right lower extremity. There were no changes of edema with position per patient report. Physical examination was remarkable for pitting edema grade 2 (3-4 mm depth) on the right and grade 1 (2 mm) on the left. The edema was located over the dorsum of the feet and in the pretibial areas bilaterally. There were no changes in skin temperature, colour or texture. Systemic evaluations including complete blood count, urinalysis, electrolytes, creatinine, blood sugar, thyroid stimulating hormone and albumin were all within normal limits. Given the acute nature of onset of edema and slight right-sided predominance, Wells criteria [4] were used to determine the probability of deep venous thrombosis (DVT). The patient was determined to have Wells score 0 thus blood D-dimer test was used as first step in the diagnosis of DVT since patient had low pre-test probability. D-dimer testing was negative. Next, a search in drug data base was conducted looking for potential medication side effects as the cause of peripheral edema. The search indicated peripheral edema as a possible medication side effect due to Buprenorphine/Naloxone [1] but did not reveal Pepcid as a potential cause [5]. Finally, the inactive ingredients of the Buprenorphine/Naloxone Film formulation that the patient was taking were identified and

researched drug databases to rule out as a potential secondary cause of edema. Per US Food and Drug Administration website [6], the inactive ingredients include Polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavour, citric acid, FD&C yellow No. 6 and white ink. None of these agents at the low concentrations within the film formulation was found to be a potential source for peripheral edema [7-13]. The patient's edema was thought to be related to Naloxone. Buprenorphine/Naloxone combination was discontinued and the patient was started on Buprenorphine monotherapy 24 mg sublingual per day. After two weeks, the patient's edema was resolved.

■ Commentary

Recent research shows that Naloxone when used sublingually is absorbed and reaches systemic circulation [3]. In addition, the research also shows that patients prescribed the combination product Buprenorphine/Naloxone have significant quantifiable concentrations of Naloxone when urine drug screening is performed [3]. After reaching the circulation, Naloxone can cause side effects reported by patients taking combination products including peripheral edema. Drug-induced peripheral edema caused by Naloxone may be under recognised and misdiagnosed. The mechanism for this side effect has not been fully elucidated though it is hypothesised that Naloxone in the systemic circulation may be involved in modulation of local edema via the endogenous opioid system. Naloxone is a competitive antagonist of mu, kappa and sigma receptors with higher affinity for the mu (μ) receptors [14]. Multiple studies using various opioid agonists and Naloxone have explored the role of endogenous opioid system in the modulation of inflammatory reactions and microvascular leakage in animal models [15-17]. Multiple opioid receptors including mu, kappa and delta have been shown to participate in the inflammatory response regulation by the endogenous opioid system [18].

Studies in animal models have shown involvement of the endogenous opioid system in the physiological response to local injury, resulting in microvascular leakage in the inflamed tissues. [15]. This may explain the mechanism by which Naloxone can cause peripheral edema via precapillary arteriolar vasodilation (vasodilatory edema) or increased capillary permeability (permeability edema).

Further research in this area is needed to determine the exact mechanisms behind Naloxone-induced peripheral edema. In addition, other side effects reported by patients on combination Buprenorphine/Naloxone but not on single agent Buprenorphine may be attributed to the Naloxone component. These include anxiety, headache, diaphoresis and mood changes. Further research may also be needed in this area.

Conflict of interest/Konflikt interesów

None declared./Nie występuje.

Financial support/Finansowanie

None declared./Nie zadeklarowano.

Ethics/Etyka

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, Uniform Requirements for manuscripts submitted to biomedical journals and the ethical principles defined in the Farmington Consensus of 1997.

Treści przedstawione w pracy są zgodne z zasadami Deklaracji Helsińskiej odnoszącymi się do badań z udziałem ludzi, ujednoliconymi wymaganiami dla czasopism biomedycznych oraz z zasadami etycznymi określonymi w Porozumieniu z Farmington w 1997 roku.

References/Piśmiennictwo

1. Buprenorphine/Naloxone: Adverse effects. *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 28.03.2022).

2. Smith K, Hopp M, Mundin G, Bond S, Bailey P, Woodward J, et al. Low absolute bioavailability of oral naloxone in healthy subjects. *Int J Clin Pharmacol Ther* 2012; 50(05): 360-7. DOI: https://doi.org/10.5414/cp201646.
3. Strickland DM, Burson JK. Sublingual absorption of naloxone in a large clinical population. *J Drug Metab Toxicol* 2018; 09(02). DOI: https://doi.org/10.4172/2157-7609.1000240.
4. Palanisamy D, Omkumar A. A study on the effectiveness of wells criteria for diagnosing deep vein thrombosis: a prospective observational study. *Int Surg J* 2021; 8(2): 569. DOI: https://doi.org/10.18203/2349-2902.isj20210365.
5. Pepcid: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed 28.03.2022).
6. *Indivior UK Ltd. SUBOXONE® (buprenorphine and naloxone) sublingual film, for sublingual or buccal use CIII Initial U.S.* Approval: 2002. [package insert]. U.S. Food and Drug Administration website. Revised September 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022410s020s022lbl.pdf (Accessed: 18.06.2022).
7. Polyethylene oxide: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
8. Hydroxypropyl methylcellulose: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
9. Maltitol: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
10. Acesulfame potassium: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
11. Lime extract: Adverse effects. *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
12. Citric acid: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
13. Sodium Citrate: Adverse effects. In: *DRUGDEX Evaluations. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health;* 2022. https://www.micromedexsolutions.com/ (Accessed: 18.06.2022).
14. Helm II S, Trescot AM, Colson J, Sehgal N, Silverman S. Opioid antagonists, partial agonists, and agonists/antagonists: The role of Office Based detoxification. *Pain Physician* 2008; 11(2): 225-35. DOI: https://doi.org/10.36076/ppj.2008/11/225.
15. Planas ME, Rodriguez L, Sanchez S, Pol O, Puig MM. Pharmacological evidence for the involvement of the endogenous opioid system in the response to local inflammation in the rat paw. *Pain* 1995; 60(1): 67-71. DOI: https://doi.org/10.1016/0304-3959(94)00090-2.
16. Sacerdote P, Bianchi M, Panerai AE. Involvement of β-endorphin in the modulation of paw inflammatory edema in the rat. *Regul Pept* 1996; 63(2-3): 79-83. DOI: https://doi.org/10.1016/0167-0115(96)00014-6.
17. Taylor BK, Peterson MA, Roderick RE, Tate J, Green PG, Levine JO, et al. Opioid inhibition of formalin induced changes in plasma extravasation and local blood flow in rats. *Pain* 2000; 84(2): 263-70. DOI: https://doi.org/10.1016/s0304-3959(99)00212-2.
18. Romero A, Planas E, Poveda R, Sánchez S, Pol O, Puig MM. Anti-exudative effects of opioid receptor agonists in a rat model of carrageenan-induced acute inflammation of the paw. *Eur J Pharmacol* 2005; 511(2-3): 207-17. DOI: https://doi.org/10.1016/j.ejphar.2005.02.004.