Use of Sublingual Nitrates for Management of Limb Ischemia Secondary to Inadvertent Intra-Arterial Buprenorphine/Naloxone (Suboxone®) Film Injection

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Multiple case reports have signaled a rise in buprenorphine abuse in the US, particularly among inmates. We present the case of limb ischemia secondary to accidental intra-arterial buprenorphine/naloxone film injection successfully treated with sublingual nitroglycerin. A 39-year-old man with history of intravenous drug use presented sudden severe left-hand pain since three days prior to evaluation. Pain was preceded by self-injection of dissolved buprenorphine/naloxone sublingual film onto the affected arm. An arteriogram suggested severe vasoconstriction in the absence of frank thrombosis. Patient was initially treated with continuous heparin infusion and nifedipine. Forty-eight hours later, due to poor response, sublingual nitroglycerin was added to therapy. Digits regained color, sensation, and pain resolved within 15 minutes of administration of sublingual nitroglycerin. The presence of acute limb ischemia caused by prolonged vasospasm is a very rare complication. A normal angiogram should raise suspicion regarding vasospasm as the mechanism of ischemia, and prompt nitroglycerin therapy. [*P R Health Sci J 2020;39:278-280*]

Key words: Suboxone, Buprenorphine, Naloxone, Intravenous drug user, Limb ischemia, Nitroglycerine

Multiple case reports have signaled a rise in buprenorphine abuse in the US, particularly among inmates (1). In addition to the deleterious effect of this type of addiction, inadvertent injection of dissolved buprenorphine/naloxone film into the arterial circulation rather than the venous circulation can lead to severe complications. This action may compromise arterial patency and endothelial structure, resulting in acute limb ischemia. It is estimated that accidental intra-arterial injections are found in 1:3,500-1:56,000 patients visiting the emergency department (2). This condition presents a therapeutic challenge due to its rarity and lack of established guidelines. We present the case of limb ischemia secondary to accidental intra-arterial buprenorphine/naloxone film injection successfully treated with sublingual nitroglycerin.

Case Presentation

A 39-year-old man with history of intravenous drug use (IVDU) presented sudden onset of severe left-hand pain, most prominent over the first three digits, since three days prior to evaluation. Pain occurred 45 minutes after self-injection of dissolved buprenorphine/naloxone sublingual film onto the affected arm. He noted associated pallor, paresthesia, flushing, and worsening bluish discoloration of the skin. Clinical examination revealed a clean injection site mark at the radial side of the distal left forearm. There was delayed capillary refill and decreased two-point discrimination over the first three digits of the left hand. Motor strength and radial pulse were normal. He denied shortness of breath, palpitations, chest pain, fever or chills. An arteriogram revealed significant distal narrowing of the arterial lumen of digital arteries of the first two fingers of the left hand; other digital arteries were normal (Image 1). These findings were suggestive of severe vasoconstriction in the absence of thrombosis. Erythrocyte sedimentation rate (ESR) was mildly elevated at 46 mm/h and C-reactive protein (CRP) was 15 mg/dL. Toxicology screen was positive for opioids; negative for cocaine. Assays for rheumatoid factor, antinuclear antibodies (ANA), antineutrophil cytoplasmic autoantibody (ANCA), and extractable nuclear antibodies (ENA) were negative. Complement C3 and C4 levels were normal.

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Patient was initially treated with continuous heparin infusion to maintain a partial thromboplastin time (PTT) between 46 to 70 s, and intravenous nifedipine titrated to maximum dose of 90mg. Forty-eight hours later, there was no significant improvement. However, there were no signs of compartment syndrome, new or worsening neurologic deficits. At this point, sublingual nitroglycerin was added to therapy. Digits regained color, sensation, and pain resolved within 15 minutes of administration of sublingual nitroglycerin. Seven days later, he was discharged with low dose aspirin regime, but was ultimately lost to follow up.

Discussion

Buprenorphine/naloxone hydrochloride (Suboxone®) preparations are indicated for management of opioid addiction. This formulation consists of a film for sublingual administration. It contains magnesium stearate, talcum, hydroxypropyl methylcellulose, silica, and amidon compounds, which make it indissoluble and unsuitable for intravenous use (3-6). Buprenorphine/naloxone sublingual films are primarily comprised of gelatinous compound hydroxypropyl methylcellulose that gives it a thick consistency when mixed with water. Given this substance has varying solubility depending on temperature, along with improper filtration methods (e.g. cigarette filters and cotton), particle deposits within the vessel may lead to vascular occlusion. Schneider et al. reported two patients with necrotic livedoid lesions caused by amidon deposits with histological evidence of direct cytotoxic effects of this product. Similarly, a prospective data collection identified 30 cases of necrotic cutaneous lesions after injection of filtered buprenorphine solution (3).

Local injection site thrombosis followed by downstream thromboembolic events has been described as a major mechanism of ischemia secondary to intra-arterial drug injections (7). Repeated arterial puncture may lead to endothelial inflammation and dysfunction, further promoting thromboembolic phenomena and particle deposits that compromise microvascular flow (4,8). Frequent endovascular injuries attenuate endothelial nitric oxide (NO) release, which results in inappropriate vasoconstriction (8). NO has vasoprotective effects on the endotelial wall which help maintain critical physiological functions such as vasodilation, anticoagulation, optimized leucocyte adhesion, smooth muscle proliferation, and antioxidative capacities (9).

There are no guidelines for management of limb ischemia secondary to intra-arterial buprenorphine/naloxone injection. Nevertheless, intravenous heparin is generally accepted as initial therapy to prevent clot propagation and preserve collateral circulatory flow (10). Adjunctive therapies, such as daily low dose aspirin, analgesics, calcium channel blockers, prostacyclin analogs, and invasive procedures such as direct thrombolysis of the affected artery have been reported.

Figure 1. Angiographic study demonstrating 1st and 2nd digits with markedly reduced distal flow of digital arteries, suggestive of severe vasoconstriction. No evidence of frank thrombosis.

Our patient did not respond to intravenous heparin along with high-dose of aspirin and nifedipine. However, sublingual nitroglycerin provided almost immediate clinical resolution of limb ischemia. This suggests the mechanism of ischemia was arterial vasospasm. There are no head-to-head trials regarding the use of calcium channel blocker over nitrates for the treatment of vasospastic acute limb ischemia.

After an extensive literature review, we found multiple reports of vasospastic acute limb ischemia secondary to cocaine, ergotamine, amphetamine and lysergic acid (11-12); however, response to vasodilator therapy was inconsistent. We did find documented cases of successful use of nitroglycerin in neonate patient with peripheral ischemia following cannulation (13).

The presence of acute limb ischemia caused by prolonged vasospasm is a very rare complication of this type of drug use. A normal non-occlusive arterial angiogram should raise suspicion regarding vasospasm as the mechanism of ischemia, and prompt nitroglycerin therapy.

Conclusion

Sublingual nitroglycerin seems a reasonable and effective therapy to prevent limb loss in acute limb ischemia secondary to intra-arterial buprenorphine/naloxone injection. Patients with history of IVDU should be educated regarding the possible complications of the inappropriate use of this drug. Finally, we did not find any other published case in which nitroglycerin had been successfully used in a patient such as ours.

Resumen

Varios informes de casos han señalado un aumento en el abuso de buprenorfina en los EE. UU., particularmente entre los confinados. Aquí presentamos el caso de isquemia de extremidad secundario a inyección accidental de buprenorfina/naloxona intraarterial que fue tratada exitosamente con nitroglicerina sublingual. El paciente presentó con dolor súbito, y severo, en la mano izquierda desde tres días antes de la evaluación. El dolor fue precedido por la auto inyección de una película sublingual de buprenorfina/naloxona licuada. Una arteriografía sugirió vasoconstricción severa en ausencia de trombosis franca. El paciente fue tratado con infusión continua de heparina y nifedipina. Cuarenta y ocho horas más tarde, se añadió nitroglicerina sublingual a la terapia provocando recuperación instantánea del color, sensación y dolor de la extremidad. La presencia de isquemia aguda de extremidades causada por vasoespasmo prolongado es una complicación muy rara, y debe ser tratada con vasodilatadores prontamente.

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