

Severe Upper Limb Complications from Parenteral Abuse of Subutex®

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Abstract

Introduction: Subutex® is a sublingual formulation of buprenorphine that is used to treat opioid dependency. It may be abused parenterally with disastrous consequences. **Clinical Presentation:** We present 4 cases of parenteral abuse of Subutex® resulting in severe upper limb complications. **Treatment:** Two vascular complications were treated with combinations of anticoagulants, vasodilators, brachial plexus block and iloprostol. One severe hand abscess required surgical debridement, and 1 median nerve injury required neurolysis. **Outcome:** All patients had a poor outcome. Both patients with vascular complications required multiple amputations, the patient with a thenar abscess had severely impaired thumb function, and the patient with median nerve injury has ongoing neuralgic pain, numbness and thenar weakness. **Conclusion:** The incidence of complications of parenteral abuse of Subutex® is increasing in Singapore. These complications have a poor outcome despite adequate management, and are best prevented by education or legal means.

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Key words: Buprenorphine, Gangrene, Intravenous substance abuse, Median neuropathy, Soft tissue infections

Introduction

Subutex® (sublingual buprenorphine hydrochloride) tablets are prescribed by licensed physicians to alleviate symptoms of opiate withdrawal in addicts undergoing a cessation programme. It is increasingly used instead of methadone in cessation programmes, as it is effective, well tolerated and has fewer side effects.¹⁻³ In Singapore, according to Institute of Mental Health figures, over 4000 patients were prescribed buprenorphine in 2004. Although the dispensation and use of Subutex® is theoretically safe, we have recently encountered 4 cases of severe upper limb complications from parenteral abuse, all presenting within the first few months of 2005.

Case Reports

Case 1

A 55-year-old male presented with a large thenar abscess. His entire thenar eminence was intensely swollen, extremely

tender, red and warm. There were 3 other indurated subcutaneous swellings on his forearm along the line of his cephalic vein (Fig. 1). During surgical debridement, a large, multiloculated abscess was found within the thenar muscles, which were gangrenous and required complete excision. Cultures grew *Staphylococcus aureus*, and he was treated with intravenous cloxacillin followed by oral augmentin. He initially denied, but later admitted to being a chronic intravenous drug abuser, and having injected Subutex® into his left thenar eminence. As all his thenar muscles were excised, he has lost palmar abduction and opposition of the thumb, impairing his ability to pinch and grasp. He declined further reconstructive surgery.

Case 2

A 48-year-old male on an opiate cessation programme injected Subutex® twice into his radial artery at the right wrist. He presented 12 hours later with an intensely swollen, ischaemic hand (Fig. 2). There were injection marks at the

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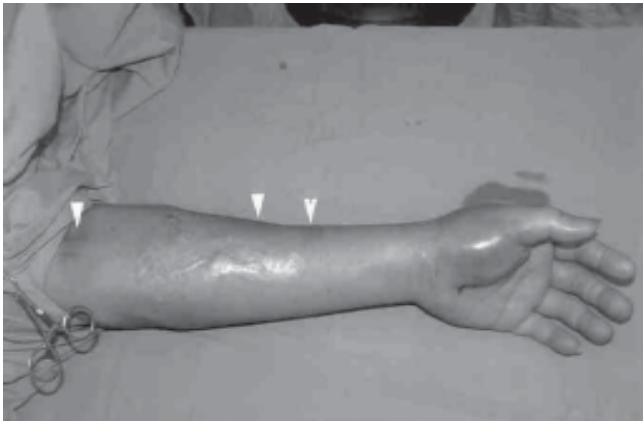


Fig. 1. Case 1, thenar intramuscular abscess. Several smaller subcutaneous abscesses are present along the line of the cephalic vein and in the cubital fossa (arrows).



Fig. 3. Case 2, 2 weeks after injecting Subutex® into the radial artery. Dry gangrene of the tips of the thumb, index, middle and ring finger.

right wrist overlying the radial artery. The radial pulse was palpable proximal to the wrist crease but not beyond. The ulnar pulse was palpable, but Allen's test showed markedly delayed capillary refill from both radial and ulnar arteries. He was treated with intravenous dextran, oral pentoxifylline, nifedipine and aspirin. An axillary brachial plexus block with marcain was given for vasodilation and pain relief. The thenar and first dorsal interosseous muscle compartments were decompressed with fasciotomies. The colour and capillary return of the hand initially improved over 3 days and he was discharged on oral medications. However, his thumb, index, middle and ring fingers gradually turned gangrenous over the next month (Fig. 3). These were amputated once the gangrene had fully demarcated – the fingers at the proximal interphalangeal joint and the thumb at the interphalangeal joint.

Case 3

A 23-year-old male presented initially with severe unilateral left upper limb oedema with no history of trauma.



Fig. 2. Case 2, 24 hours after injecting Subutex® into the radial artery. There is fixed patchy mottling of the palmar skin similar to a “trash foot”, due to micro-emboli. The tips of the thumb, index, middle and ring fingers are dusky, but the little finger is spared. This pattern may be due to an incomplete palmar arterial arch with separate supply from the ulnar artery to the little finger. Injection marks can be seen along the course of the radial artery at the wrist (arrows). Thenar fasciotomy has been performed.



Fig. 4. Case 3, 2 months after injecting Subutex® into the brachial artery. There is wet gangrene of all the fingers, with blistering and fixed discoloration of the skin of the hand and forearm.

Investigations revealed a subclavian vein thrombosis and he was treated with warfarin. He presented 2 months later with ischaemia distal to the mid-forearm and dry gangrene of all the digits of the left hand (Fig. 4). He admitted to having injected a Subutex® solution into his brachial artery because he could not find a vein. He initially refused amputation and absconded, but presented again 3 months later with sepsis and wet gangrene of the digits. All digits on his left hand were amputated at the level of the proximal phalanx. Following this, he again injected Subutex® into his left brachial artery, resulting in worsening ischaemia from the level of the mid-forearm distally. He was given intravenous iloprostol and prophylactic antibiotics, but his forearm turned gangrenous, requiring a below-elbow amputation.

Case 4

A 22-year-old male with a history of intravenous heroin abuse presented a month after attempting to inject dissolved Subutex® into a volar vein in his left wrist. He had burning pain, paraesthesia and numbness of the thumb, index and middle fingers. He later developed paralysis of the thenar muscles. Examination showed a complete loss of sensation of the thumb, index and middle fingers and severe atrophy of the thenar muscles. Nerve conduction studies and electromyography showed denervation of the thenar muscles and no conduction across the median nerve at the wrist and carpal tunnel. He had not recovered sensation or thenar motor function after 2 months. Surgical exploration revealed scarring of the median nerve proximal to the carpal tunnel. One month after undergoing microsurgical neurolysis, he continues to have neuralgic pain, numbness and thenar weakness.

Discussion

Parenteral abuse of Subutex® is an emerging phenomenon in Singapore. In the first 3 months of 2005 alone, we saw 4 cases with severe upper limb complications. In contrast, we had seen none in the preceding 3 years. Since its launch in 2002, sublingual buprenorphine has become a popular alternative to methadone for treating opiate dependence in Singapore. Although safeguards for dispensing buprenorphine for outpatient use exist, the system can still be abused. Take-away Subutex® increases the risk of deliberate or accidental overdose by the patient. These medications could also be passed or sold to others who are not on a cessation programme. Three of the 4 patients in this series obtained Subutex® illegally. Of greater concern is the potential for parenteral abuse of Subutex®. Sublingual formulations are easier to dissolve compared to oral formulations, and abusers may perceive it to be safer to inject. Parenteral abuse of Subutex® is already a problem in Australia and France, where surveys have found that between 23% and 37% of those who use Subutex® had used it intravenously.^{4,6}

Upper limb complications from parenteral abuse of intravenous or oral formulations of drugs such as heroin, benzodiazepines and methadone are well documented in the literature. These consist of infections of varying severity,⁷ vascular complications including superficial thrombophlebitis, deep venous thrombosis and critical limb ischaemia⁸ and compartment syndrome.⁹ In previously reported series, patients tended to be chronic intravenous drug abusers, usually in their 20s to 30s. In this series, patients were also chronic intravenous drug abusers, but on average were older, with 2 patients above 45 years old.

There are few reports of such complications arising from buprenorphine abuse in the literature, probably because

this drug has only been widely available in the last few years. To date, these problems have rarely been encountered in the local population. However, as this series demonstrates, parenteral abuse of buprenorphine is a problem locally, and may result in any of the previously described complications.

Unsafe preparation and injection using contaminated needles may cause local infections. These range from cellulitis to life-threatening necrotising fasciitis. Implantation of microorganisms into deeper planes may result in severe multi-planar, multi-tissue infections, particularly in the hand, where numerous different tissues are packed closely together. The bacteria involved are usually skin flora such as *Streptococcus* or *Staphylococcus*, but unusual organisms may be encountered.⁷ Delay in presentation results in increased severity of the infection. Treatment of such infections requires extensive debridement, resulting in loss of tissues and a poor functional outcome. Complex reconstructive procedures may be required to restore function, and amputation may occasionally be required to control the infection.

Limb ischaemia occurs when a large artery is injected, either deliberately or inadvertently. The drug itself or other constituents of the tablet causes inflammation, severe vasospasm, and thrombosis. Incompletely dissolved constituents form micro-emboli, which lodge in the microcirculation, causing widespread scattered end-organ ischaemia. Venospasm and venous thrombosis result in outflow obstruction and acute compartment syndrome.⁹ Intermittent decrease in the arterial vasospasm and opening of collateral vessels may result in reperfusion injury, which can also cause significant swelling and compartment syndrome. Treatment with antiplatelet agents, vasodilators, anticoagulation, corticosteroids, intravenous dextran-40,⁸ intravenous iloprost (a prostaglandin analog),^{10,11} thrombolysis,^{12,13} thrombectomy, and hyperbaric oxygen therapy¹⁴ have all been tried. A fasciotomy may be required to relieve compartment pressure. There is a high failure rate of about 25% in one large series.⁸ However, numerous individual case reports or small case series have documented successful revascularisation with more aggressive methods including thrombolysis and thrombectomy.¹⁰⁻¹³ Reasons for failure may include delayed presentation and widespread damage to the microcirculation from micro-emboli. In the absence of infection, amputation should be delayed until the level of dry gangrene is fully demarcated. Onset of infection (wet gangrene) requires immediate amputation to a level above the infection.

Inadvertent damage to the median nerve is a rare complication of parenteral drug abuse that has not been previously reported. This may be due to direct trauma or extravasation of the injected solution. Varying degrees of nerve injury ranging from temporary neuropraxia to fibrosis

or destruction of nerve fibres may potentially occur. In the case described, there was total loss of nerve function due to perineurial and intraneurial scarring. This was probably caused by an inflammatory reaction to Subutex® injected around and into the nerve. In the absence of recovery on close follow-up with serial clinical examination and neurophysiological studies, surgical exploration and neurolysis may be required, as in the case described. Reconstruction with nerve grafts may be required if there is no recovery following neurolysis, or in the presence of more severe nerve injury.

For fear of legal prosecution, patients usually present late, are not forthcoming, and may give confusing histories to explain their complications. Parenteral drug abuse should be considered in patients with unusual upper limb infections that are inconsistent with the history, or with sudden onset of unexplained upper limb ischaemia or nerve palsy. A close examination may reveal thrombosed superficial veins and puncture marks at the sites of injection.

Treatment of complications of parenteral Subutex® abuse taxes public resources and had a poor outcome in our series. This may be due to delayed presentation, non-compliance with outpatient treatment following discharge from hospital, and continued parenteral drug abuse. These complications can be prevented by tighter regulations on the prescription and consumption of Subutex®. Preventative measures include a central registry to monitor drug prescription and prevent doctor hopping for Subutex®, and mandatory consumption in the presence of medical personnel.⁴ Greater public awareness and education regarding the dangers of parenteral abuse of Subutex® for patients on cessation programmes should also help decrease the incidence of such complications.

REFERENCES

1. Davids E, Gastpar M. Buprenorphine in the treatment of opioid dependence. *Eur Neuropsychopharmacol* 2004;14:209-16.
2. Eder H, Fischer G, Gombas W, Jagsch R, Stuhlinger G, Kasper S. Comparison of buprenorphine and methadone maintenance in opiate addicts. *Eur J Addict Res* 1998;4 (Suppl)1:3-7.
3. O'Connor PG, Oliveto AH, Shi JM, Triffleman EG, Carroll KM, Kosten TR, et al. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am J Med* 1998;105:100-5.
4. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? *Addiction* 2005;100:197-205.
5. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. *Addiction* 2001;96:267-72.
6. Vidal-Trecan G, Varescon I, Nabet N, Boissonnas A. Intravenous use of prescribed sublingual buprenorphine tablets by drug users receiving maintenance therapy in France. *Drug Alcohol Depend* 2003;69:175-81.
7. Simmen HP, Giovanoli P, Battaglia H, Wust J, Meyer VE. Soft tissue infections of the upper extremities with special consideration of abscesses in parenteral drug abusers. A prospective study. *J Hand Surg* 1995; 20B:797-800.
8. Funk L, Grover D, De Silva H. Compartment syndrome of the hand following intra-arterial injection of heroin. *J Hand Surg* 1999;24B: 366-67.
9. Treiman GS, Yellin AE, Weaver FA, Barlow WE, Treiman RL, Gaspar MR. An effective treatment protocol for intraarterial drug injection. *J Vasc Surg* 1990;12:456-66.
10. Gouny P, Gaitz JP, Vayssairat M. Acute hand ischemia secondary to intraarterial buprenorphine injection: treatment with iloprost and dextran-40 – a case report. *Angiology* 1999;50:605-6.
11. Andreev A, Kavrakov T, Petkov D, Penkov P. Severe acute hand ischemia following an accidental intraarterial drug injection, successfully treated with thrombolysis and intraarterial Iloprost infusion. Case report. *Angiology* 1995;46:963-7.
12. Tisnado J, Bartol DT, Cho SR, Vines FS, Beachley MC, Fields WR. Low-dose fibrinolytic therapy in hand ischemia. *Radiology* 1984;150:375-82.
13. Silverman SH, Turner WW Jr. Intraarterial drug abuse: new treatment options. *J Vasc Surg* 1991;14:111-6.
14. Adir Y, Halpern P, Nachum Z, Bitterman H. Hyperbaric oxygen therapy for ischaemia of the hand due to intra-arterial injection of methadone and flunitrazepam. *Eur J Vasc Surg* 1991;5:677-9.