

## Subutex® abuse presenting to the emergency department: a case series

### 濫用「據悉」到急症室求診的個案系列

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**Introduction:** Subutex® (sublingual buprenorphine hydrochloride) tablets are prescribed to alleviate symptoms of opiate withdrawal in addicts undergoing a cessation programme. Although Subutex® is safe and effective, parenteral abuse is an emerging phenomenon. A variety of complications may present due to the different areas that patients inject themselves. **Aim:** We present a case series of four patients who presented to the emergency department following complications of Subutex® abuse. The complications included deep venous thrombosis, limb ischaemia and epidural abscess with osteomyelitis of the spine. **Discussion:** Sublingual buprenorphine was launched in Singapore in 2002. It is currently the preferred alternative to methadone for treating opiate dependency locally. Despite safeguards, instances of abuse of buprenorphine exist. These medications can be passed or sold to others not on a cessation programme. Two of the 4 patients in this series obtained Subutex® illegally. Parenteral abuse of Subutex® is of grave concern. In Australia and France, between 23-37% of Subutex® users have abused it in this fashion. **Conclusion:** Subutex® abuse is not uncommon in Singapore. Complications especially from parenteral use can occur and may result in serious morbidity. A high index of suspicion among physicians must be maintained in patients with unusual limb infections, ischaemia or venous thrombosis. Tighter regulations on prescription and consumption of Subutex® may be useful in preventing these complications, in addition to increasing public awareness and education of the risks of parenteral abuse for patients on cessation programme. (*Hong Kong j.emerg.med.* 2007;14:163-168)

**簡介：**「據悉」(舌下服用的鹽酸丁丙諾啡)藥片是處方給癮君子於戒毒療程中舒緩鴉片製劑戒除時的症狀。雖然「據悉」是安全和有效的，但其注射的濫用卻有興起的現象，並因病者注射自己不同的部位而呈現多樣的併發症。**目的：**現呈報4名病者因濫用「據悉」後呈現併發症到急症室求診的個案系列。併發症包括深層靜脈血栓、肢體缺血、硬膜外膿腫及脊椎骨髓炎。**討論：**舌下服用的丁丙諾啡於2002年在新加坡啟用，它是現時當地治療鴉片毒癮較美沙酮更受歡迎的選擇。儘管有防範措施，丁丙諾啡的濫用例證依然存在；這類藥物可轉交或售與非戒毒療程的人士。在系列4名病者中，2人是經非法途徑取得「據悉」的。注射「據悉」的濫藥問題是值得嚴重關注，在澳洲和法國，大約23-37%的「據悉」用家曾利用這種方式濫藥。**總結：**在新加坡，濫用「據悉」是普遍的，特別是注射性的可引致併發症及嚴重的病態。對於患有不尋常肢體感染、缺血或靜脈血栓的病者，醫師應保持高度懷疑。提高公眾的警覺性，教育戒毒療程病者有關濫用注射的風險，及更嚴謹的規例管制「據悉」的處方和服用，或有助防止這類併發症的發生。

**Keywords:** Buprenorphine, intravenous substance abuse, substance-related disorders

**關鍵詞：**丁丙諾啡、靜脈注射藥物濫用、有關濫藥的疾病

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## Introduction

Subutex® (sublingual buprenorphine hydrochloride) tablets are prescribed to alleviate symptoms of opiate

withdrawal in addicts undergoing a cessation programme. It is currently the preferred drug of choice for treating opiate withdrawal due to its effectiveness and fewer adverse effects.<sup>1,2</sup>

Although Subutex® is safe and effective, parenteral abuse is an emerging phenomenon.<sup>3-5</sup> A variety of complications may present due to the different sites into which patients inject themselves.

We present a case series of four patients who presented to the emergency department following complications of Subutex® abuse. Local complications included deep venous thrombosis, limb ischaemia, and abscess over injection sites. Systemic complications involved epidural abscess and osteomyelitis of the spine.

#### ***Patient 1***

A 30-year-old Malay female presented in February 2006 with sudden onset of left lower limb swelling with pain and fever (Figure 1). Clinically, she had evidence of deep venous thrombosis which was confirmed on duplex ultrasonography. She admitted injecting Subutex® into her left femoral vein. She was commenced on anticoagulation but subsequently she defaulted follow-up.

#### ***Patient 2***

A 35-year-old Chinese male developed left hand pain and numbness after injecting his radial artery with Subutex® in May 2006. Clinically, he had developed left hand ischaemia with absent pulses up to the brachial artery (Figures 2 & 3). Duplex ultrasonography confirmed acute thrombosis of the brachial artery. He underwent successful thrombolysis but subsequently discharged himself against medical advice and defaulted follow-up.

#### ***Patient 3***

A 40-year-old Malay male presented in May 2006 with complaints of fever and lower back pain. He initially denied any intravenous drug use but needle marks were seen over both his arms. Clinically he had a positive straight leg raising test. No neurological deficit was detected. He was admitted for a presumed diagnosis of epidural abscess which was confirmed on magnetic



**Figure 1.** Left lower limb swelling extending to upper thigh caused by deep venous thrombosis of the femoral vein.



**Figure 2.** Needle marks as a result of intravenous drug use.

resonance imaging (MRI) of the spine (Figure 4). This was surgically drained and the patient was treated with a prolonged course of intravenous antibiotics.

#### *Patient 4*

A 60-year-old Indian male complained of multiple painful skin lesions over both arms and legs in June 2006 (Figures 5a & 5b). Clinically, he had multiple abscesses over the upper limbs and popliteal fossa with needle marks over the areas. He was admitted for

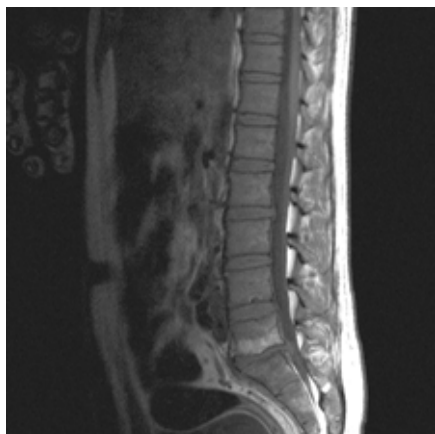
incision and drainage of these abscesses but he discharged himself against medical advice the following day.

#### **Discussion**

Sublingual buprenorphine was launched in Singapore in 2002. It is currently the preferred alternative to methadone for treating opiate dependence.<sup>3</sup> Despite



**Figure 3.** Left hand digital ischemia from brachial artery thrombosis following accidental intraarterial injection.



**Figure 4.** MRI spine showing osteomyelitis of the lumbar spine with epidural abscess over the L5-S1 region.



(a)



(b)

**Figure 5.** Abscess formation seen over the skin of both right and left biceps region following injection with contaminated needles.

safeguards, instances of abuse of buprenorphine exist.<sup>4,5</sup> These medications can be passed or sold to others not on a cessation programme. Two of the 4 patients in this series obtained Subutex® illegally.

Parenteral abuse of Subutex® is of grave concern. In Australia and France, between 23-37% of Subutex® users have abused it in this fashion.<sup>4,6</sup> This is primarily due to the main mechanism of action of buprenorphine which has a partial agonist effect on the  $\mu$ -opioid receptor and is hence able to produce euphoria and opioid-like effects. Abusing it intravenously gives addicts a quicker onset of 'highs'.

To date in Singapore, two case series documenting patients with upper limb and vascular complications following Subutex® abuse have been published. This trend of abuse is likely to increase locally, as demonstrated in this series, and may present in a wide variety of ways.<sup>7,8</sup>

The general complications of intravenous drug abuse and needle sharing habits are transmission of hepatitis B and C, and the human immunodeficiency virus. Unique characteristics of Subutex® abuse include the pharmacodynamic synergistic effects on respiratory depression as well as the more common features of cellulitis, non-healing wounds as well as vascular complications. These are proposed to be a result of the excipients in the preparation of Subutex®, which is meant to be administered sublingually, causing chemical irritation to the vessel wall resulting in poor healing and increased infective and thrombosis rates. The effect of Subutex® on the vessel wall has not been studied but the excipients which act as binders to buprenorphine are likely to precipitate local inflammation causing thrombosis or intimal weakening, leading to either vessel occlusion or pseudoaneurysm formation after several injections. This effect can be aggravated by hot or warm injections as a result of the preparation methods as well as inadequate sterility techniques of injection.<sup>8</sup>

Local infections result from the use of contaminated preparations and needles. Common bacteria involved are skin organisms such as *Staphylococcus* and

*Streptococcus*. These infections present in a myriad of ways from simple cellulitis to necrotising fasciitis, which can be life threatening. Delayed presentation may result in increased severity of the infection.<sup>7-12</sup> Treatment of such infections usually requires extensive debridement and may result in loss of tissues and poor functional outcome. Complex reconstructive procedures may be required to restore function, and amputation is occasionally required to control the infection.

Limb ischaemia or venous thrombosis occurs when a large vessel is injected, either deliberately or inadvertently. The drug itself or other constituents of the tablet cause inflammation, vasospasm and thrombosis. Incompletely dissolved constituents form micro-emboli, which lodge in the microcirculation, causing widespread end-organ ischaemia. Venospasm and venous thrombosis result in outflow obstruction and may cause the acute compartment syndrome. Intermittent decrease in the arterial vasospasm and opening of collateral vessels can precipitate a reperfusion injury, which translates to significant swelling and compartment syndrome. Treatments with antiplatelet drugs, vasodilators, anticoagulation, corticosteroids, thrombolysis, thrombectomy and hyperbaric oxygen therapy have all been tried. Fasciotomy may be required to relieve compartmental pressure. Failure to salvage limbs is frequently attributed to delayed presentation for fear of prosecution and widespread damage to the microcirculation from micro-emboli.<sup>7,8</sup>

Pulmonary complications of injection drug abuse include pulmonary infections, interstitial pneumonia, pulmonary vascular diseases, septic embolisation and pneumothorax, among others.

The risk of community acquired pneumonia is higher in this group of patients compared to the general population.<sup>13</sup> This has been attributed to several factors including:

1. Impairment of macrophage activity and mucociliary clearance
2. Aspiration pneumonia or lung abscess following

stupor from drug intoxication

3. Haematogenous spread of bacteria which subsequently infect the lung

Organisms commonly involved include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Staphylococcus aureus*.<sup>14</sup> Antibiotics should be targeted against these bacteria.

Apart from structural valvular lesions, a number of factors uniquely predispose patients who use injection drugs to infective endocarditis. These include:

1. Transient or permanent endothelial damage to the tricuspid valve following injection of particulate matter along with drugs.<sup>15</sup>
2. Cumulative subclinical damage of the tricuspid valve following repetitive use of injection drugs.
3. Simultaneous injection of bacteria or fungi present on the surface of the skin, in the drug itself, in diluents, fillers, or filters used to reconstitute and prepare drugs for injection.<sup>16</sup>

*Staphylococcus aureus* is the most common cause of infective endocarditis in intravenous drug users, followed by streptococci and enterococci.<sup>16,17</sup> The vast majority of right-sided endocarditis (predominantly involving the tricuspid valve) occur in this group of patients although left-sided disease is more common overall.<sup>15</sup> These patients with infective endocarditis frequently present acutely, without heart murmur in those with isolated tricuspid valve involvement or stigmata of infective endocarditis.<sup>17</sup> However, blood cultures are usually positive in drug abusers with infective endocarditis.<sup>16</sup> This emphasises the need for a high degree of suspicion for infective endocarditis as well as highlights the importance of obtaining blood cultures prior to the administration of antibiotics in these patients.

Epidural abscess of the spine threatens the spinal cord by both physical compression as well as vascular infarction of the spinal cord. Complications such as motor dysfunction and sensory problems or even paralysis may occur if this is left untreated. The diagnosis is frequently delayed as the initial

presentation may be back pain alone or radicular symptoms. The clinical triad of fever, back pain and neurologic deficit is not present in most patients. Early presentations are usually subtle and atypical presentations are not unusual. Intravenous drug abusers belong to a high risk group and hence this medical emergency, which may require urgent surgical decompression and drainage of the abscess as well as intravenous antibiotics, must be suspected in such patients when they present with fever and back pain.

## Conclusion

Subutex® abuse is not uncommon in Singapore. Complications especially from parenteral use can occur and may result in serious morbidity. A high index of suspicion among physicians must be maintained in patients with unusual limb infections, ischaemia or venous thrombosis.

Tighter regulations on prescription and consumption of Subutex® may be useful in preventing these complications, in addition to increasing public awareness and education of the risks of parenteral abuse for patients on cessation programme.

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