

Complications Relating to Intravenous Buprenorphine Abuse: A Single Institution Case Series

Andy KS Yeo,¹MBBS, Chung-Yip Chan,²MBBS, MRCS (Edin), MMed (Surg), Kok-Hoong Chia,²MBBS, FRCS (Edin), FAMS

Abstract

Introduction: We present a retrospective descriptive study of cases admitted to Tan Tock Seng Hospital from March 2005 to October 2005 with complications of Subutex abuse. **Clinical Picture:** A total of 8 patients were studied. Of the 8, 7 were male and one was female. Their complications consist of the following: arterial pseudoaneurysm (2), arterial pseudoaneurysm with infective venous thrombus (1), infective venous thrombus (1), venous thrombus (2), and arterial spasms (1) and sympathetic dystrophy (1). **Treatment:** For the patient who presented with buprenorphine-associated neuropathy, non-operative treatment with analgesics was given. Conservative medical therapy involving deep venous thrombosis treatment was instituted for the patient with deep venous thrombosis. Repair, restorative bypass and embolectomy surgery were performed for patients who had severe embolic/thrombotic complications. One of the patients who received the above surgery required amputation of his lower limb. **Outcome:** Of the 8 patients, 4 were treated medically, 3 required surgery and 1 required amputation. Their recoveries were uneventful. Of the 8, 1 absconded and was not followed up with. **Conclusion:** Parenteral injection of buprenorphine can cause a wide range of vascular complications from simple vascular irritation to severe infective thrombosis and pseudoaneurysms requiring limb amputations. Non-sterile preparation of an injected substance or non-sterile injection sites and the repeated punctures of major vessels are possible culprits in those who are seen to have acute infection of injection sites.

Ann Acad Med Singapore 2006;35:487-91

Key words: Femoral vein, Heroin, Pseudoaneurysm, Thrombus

Introduction

Buprenorphine, more commonly known as Subutex (Reckitt Benckiser Pharmaceuticals), has been released in Singapore since 2002. Initially marketed as an opiate substitute to help addicts wean off their dependence, it has another formulation, Suboxone, which additionally contains naloxone as an active ingredient. Subutex is used to initiate weaning off dependence and its use is followed by Suboxone for maintenance (FDA Talk Paper, TC02-38, Oct 8 2002, <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01165.html>). Its mechanism of action is mainly as a partial agonist on the μ -opioid receptor and as an antagonist at the κ -opioid receptor (http://www.fda.gov/cder/drug/infopage/subutex_suboxone/default.htm). The action of buprenorphine and methadone on opioid receptors, and their ability to produce euphoria and opioid-like effects, creates potential for abuse of these drugs.

In recent months, a noticeable number of patients have presented with complications related to parenteral injections of these drugs. The femoral vein at the groin is a favoured site due to its accessibility and relative ease of injection. This, and the inadvertent puncture of the adjacent femoral artery and nerve, has led to various complications that require medical and surgical intervention. This paper seeks to address the range of presentation and treatment modalities, as well as to explore the possible reasons for the propensity of Subutex, a sublingual preparation, to cause vascular complications when used in a parenteral route.

Materials and Methods

This is a retrospective descriptive study of cases admitted to Tan Tock Seng Hospital from March to August 2005. The details of each case were gathered from clinical notes, investigation reports and records of intervention and treatment. Bedside and telephone interviews were carried

¹ Singapore General Hospital, Singapore

² Department of General Surgery, Tan Tock Seng Hospital, Singapore

Address for Reprints: Dr Chia Kok-Hoong, Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

Table 1. Demographics

Serial no.	1	2	3	4	5	6	7	8
Age (y)	33	26	41	33	37	30	46	34
Gender	M	M	M	M	M	F	M	M
Race	M	M	M	M	M	M	C	P
Duration of Subutex (months)	-	15	8	8	(30)	10	12	6
Previous abuse history	-	Heroin	Heroin	Heroin	Heroin IV	Heroin IV	Nil	Heroin

Gender: M: male, F: female

Race: M: Malay, C: Chinese, P: Pakistani

Demographic details of Patient 1 were incomplete, clinical data were obtained from his admission notes.

out for details of patients' history of abuse for all patients except Patient 5 who was lost to follow-up. A journal search on Pubmed was employed in the literature research for this paper. The following keywords were used in the search: parenteral, drug, abuse, complications, buprenorphine and femoral.

Results

A total of 8 patients were found to have complications resulting from buprenorphine injection into the groin. There were 7 males and 1 female, with a mean age of 35 years (range 26-46). Table 1 shows the demographics of the 8 patients (Table 1).

Case History

Patient 1: Mr JBK, a 33-year-old Malay male, has a 4- to 5-year history of drug abuse and had previously completed rehabilitation for heroin abuse. He admitted to injecting himself in the groin with Subutex. He presented with profuse bleeding from the right groin and hypotension. Emergency surgery revealed a right superficial femoral artery pseudoaneurysm extending up to the external iliac artery. Multiple punctures were noted over the superficial femoral artery, common femoral artery and femoral vein. The pseudoaneurysm was debrided and repaired primarily. Postoperatively, he complained of severe right limb pain. He was diagnosed with acute limb ischaemia with mottling up to the proximal thigh that required an amputation above the right knee. He recovered well postoperatively.

Patient 2: Mr YBM is a 26-year-old Malay male with a history of heroin abuse and, like Mr JBK, had completed rehabilitation 5 years ago. He started abusing Subutex 15 months prior to his admission. His method of preparation was to crush the tablets before mixing them in boiled water, and reuse the needles and syringes 2 to 3 times for parenteral administration. He presented with symptoms of right groin pain and swelling. On examination, he was found to have a pulsatile groin mass. An urgent duplex scan showed a

pseudoaneurysm of the right common femoral artery. Extensive debridement and excision of the pseudoaneurysm was carried out, and reconstruction was performed with a rifampicin-soaked PTFE (polytetrafluoroethylene) graft bypassed from the external iliac artery to the superficial femoral artery via a subcutaneous tunnel away from the contamination. He recovered well postoperatively (Fig. 1).

Patient 3: Mr HS is a 41-year-old manual labourer. He was a heroin abuser in the past, and underwent rehabilitation from 1988 to 1993. Recently, he picked up the habit of Subutex abuse from his friends. The belief he had about Subutex was that it was a legal drug for abusers as it was obtained from doctors. His period of abuse lasted 8 months, during which he used clean new needles every time. He would crush the tablets and mix it in water before injecting into various sites. He was puncturing his right femoral vessels for 3 days before he presented to us with right groin pain and swelling extending down to his right foot, associated with fever. Multiple groin abscesses were noted on computed tomography. Duplex ultrasound was then done in view of the proximity of the abscesses to the femoral vessels. This showed a small right common femoral artery pseudoaneurysm as well as deep vein thrombosis of the superficial femoral vein. Right groin exploration was performed and intraoperative findings showed a small proximal superficial femoral artery pseudoaneurysm with surrounding necrotic tissue and purulent venous thrombus in the vein with 2 venous puncture sites. The infected thrombus was removed and the wound was debrided. The venotomy site was repaired primarily. The pseudoaneurysm was not repaired as it was small and had been sealed up by scar tissue. His postoperative recovery was uneventful.

Patient 4: Mr ASBM is a 33-year-old Malay male working as an odd job labourer. He has a long history of drug abuse, ranging from sleeping tablets to heroin. He first heard of Subutex in 2000 when he was introduced to it by his friends. At that time, he had already been off heroin for 3 years. After 3 months of sublingual Subutex, he converted to



Fig. 1. The postoperative groin wound of Patient 2. A PTFE rifampicin soaked graft was bypassed laterally to the infected area.



Fig. 2. His right forearm was mainly affected by his complications of injection. A mottled appearance can be seen extending up to his elbow on his volar side.



Fig. 3. A close up of the mottled appearance of the skin.

intravenous administrations. He was on Subutex for a total of 8 months, usually injecting himself in both groins. He prepared the formulation by dissolving the tablets in hot water without prior crushing. He reused the needle 2 to 3 times and used the occasional alcohol swab whenever he could afford it. He presented to us with right groin pain and right lower limb swelling. Duplex scan showed a right deep venous thrombus and he was treated medically. No pseudoaneurysm was seen.

Patient 5: Mr ZBM is a 37-year-old Malay male working as a security officer. He has a history of heroin abuse from 1998 to 2000, which he both smoked and injected. He first started on Subutex in 2002 when he tried it sublingually for 2 days before going to parenteral administration. He occasionally mixed Subutex with midazolam. Usually, he would be with friends when injecting but no sharing of needles occurred. He would clean the site with a wet tissue

and inject, sometimes using the needle for a second time. Dilution resulted by crushing and mixing the tablet in hot water. He was seen in January 2005 for right lower limb thrombosis involving the entire right common femoral vein, for which treatment was instituted. However, he was subsequently discharged against advice. He presented again in August 2005 with fever and lower limb pain. An infected venous thrombus was suspected in view of his history of drug abuse but he again absconded before any investigations and treatment commenced.

Patient 6: Ms HBO is a 30-year-old Malay female with a short history of parenteral heroin abuse spanning several months. She was introduced to Subutex by her boyfriend, and would melt it in boiling water and mixed it with midazolam before parenteral injection. She would reuse the needle 2 to 3 times, soaking it in warm water each time, but did not share her needles. She presented in June 2005 with right calf pain and swelling after injection of Subutex into the said area. She was diagnosed with a right calf abscess, and this was debrided. The large wound subsequently required a split skin graft for coverage. She was referred to the Institute of Mental Health for rehabilitation but defaulted on treatment. She presented again in September 2005 with left lower limb deep venous thrombosis affecting the external iliac and common femoral vein. Anticoagulation therapy with warfarin was instituted.

Patient 7: Mr TAL is a 46-year-old Chinese male who does not have a previous history of drug abuse. He has been on Subutex for the past year, and would divide and crush the tablet before mixing it with water. The drug was injected without site cleansing and his most recent site was through the medial mid-humeral level of his right upper limb. He presented with right upper limb numbness over

the radial aspect of his arm and forearm for 2 weeks with the pain worsening in the last few days. On examination, his right arm was mottled from a level distal to the elbow (Figs. 2 and 3). As there was no acute injury to arterial circulation of his upper limb, he was treated non-operatively with analgesics for possible reactive neuropathy and/or sympathetic dystrophy to the injected substances.

Patient 8: Mr YK is a 34-year-old odd job labourer with a history of heroin smoking. He has been in rehabilitation twice but claimed to be off drugs for 10 years. Recently his friends introduced him to Subutex as a “legal” form of drug abuse. He would clean his puncture site with water before injecting a mixture of 1–2 mg Subutex with midazolam, crushed and mixed with hot water. His complication arose when he injected into his left radial artery, developing symptoms of left hand erythema and subsequent cyanosis and pain over all his fingers. Duplex of his upper limb arteries did not show any arterial or venous thrombosis. Clinical impression was that of possible end arterial spasms. Intravenous flolan (epoprostenol) treatment was instituted in an attempt to relieve the spasms.

Discussion

The clinical problem arising from Subutex abuse is a recent phenomenon. This case series is presented to highlight the serious vascular and neurological complications resulting from parenteral Subutex abuse, and to heighten awareness of its devastating effects.

Subutex is a sublingual preparation and excipients of the tablet formulation are as follows: monohydrated lactose, mannitol, maize starch, povidone excipient K30, citric acid, sodium citrate and magnesium stearate. Preparation forms exist in 0.4 mg, 2 mg and 8 mg tablets and are sublingual in their routes of administration. A wide range of complications can occur after Subutex abuse, depending on the site of injection. These range from subcutaneous abscesses to arterial and venous pseudoaneurysms and thrombosis. Past reviews have shown complications to be mainly cellulitis and non-healing wounds.^{1,2} It is possible that buprenorphine was meant to be administered as a sublingual preparation and some of the current excipients in the preparation of Subutex may have caused a chemical irritation to the vessel wall resulting in poor healing and increased infective and thrombosis rates. A report of parenteral abuse of buprenorphine in France between 1998 and 2003 did not include a single vascular complication but ranged from soft tissue infection to bacteraemia and its complications.³ It also has pharmacodynamic synergistic effects on respiratory depression,⁴ not to mention the general complications of intravenous drug abuse and needle sharing habits which include transmission of hepatitis B and C, and human immunodeficiency virus.

A hypothesis for the vascular complications suffered by the patients in this series is related to the components of the Subutex tablet. Originally a sublingual preparation, some of the excipients could have acted as binders to buprenorphine. By direct parenteral injection, its effect on the vessel wall is yet unknown as this has not been previously studied. Our proposed theory is that it could have precipitated enough local inflammation to cause thrombosis or intimal weakening, leading to either vessel occlusion or pseudoaneurysm formation after several injections. Medically required arterial punctures with similar syringes have not been known to cause pseudoaneurysms. Even for procedures requiring femoral cannulation and catheterisation, pseudoaneurysms of the artery range from 0.07% to 0.11% of the patients studied.^{5,6} Hot or warm injections due to their preparation method could have aggravated the situation further. This, coupled with inadequate sterility techniques of injection, led to the majority of these patients presenting with infective complications which required salvage surgery.

A profile of the Subutex abuser has been previously studied and several factors such as an impulsive state, depression and under-dosing were identified as high-risk indicators for drug abuse of buprenorphine treatment.⁷ From the interviews of the above patients, most of them appeared to have completed rehabilitation or been off physiological addiction for a period of time before they started on Subutex. Unlike other countries, drug trafficking and smuggling laws in Singapore have been strictly enforced to the degree of capital punishment being meted out. However, the status of Subutex as a legal drug appeals to the psychological addiction of addicts. Local costs from general practitioners range from \$20 to \$22. Interviews with patients have revealed that half a tablet of 4 mg Subutex can be found for \$18 in the black market with prices reaching \$100 per 8 mg tab.

In the US, the Secretary of Health and Human Services of the Department of Health is the approving body for commencing Subutex treatment for patients (<http://www.fda.gov>). The latest professional circular from the Ministry of Health (21/2005) provides guidelines on the number of patients each General Practitioner is allowed to follow up on, and also makes provisions for a centralised reporting system (Central Addiction Registry for Drugs, CARDS) to track patients who would be on treatment. Furthermore, dispensing physicians would be required to attend an 8-hour course before they are certified. Tackling the problem is multi-pronged. Greater education and awareness of physicians to this current issue is needed, preferably from a central source. Guidelines on dispensing as well as a register would aid in monitoring if abusers were obtaining Subutex from multiple sources. Restricting dispensing to certain sources will also help but what is

required is comprehensive education of the entire medical community to ensure that addicts with complications are picked up early and reported to the relevant authorities. In penal law (Part IV, Regulation 19 of Misuse of Drugs Regulation), a physician is required to report details of a suspected drug abuser to both the Director of Medical Services as well as to the Director of the Central Narcotics Bureau. Many parenteral drug abusers have probably slipped past this net and would relapse again after their rehabilitation, and possibly present again with more and more severe complications, and even death. Studies in France and Australia^{8,9} have found that up to 40% of patients on Subutex treatment are parenterally abusing it. These figures are probably underreported and the extent of the problem locally cannot be underestimated.

Banning of Subutex can be considered a quick fix to the solution. However, consideration should be given to the use of Suboxone as an alternative with lower potential for abuse, which has also been promising in the outpatient treatment of opiate dependence.^{10,11} If there is greater awareness of the situation in the medical circle, coupled with an increased availability and knowledge of Suboxone, the current Subutex abuse issue may be somewhat controlled.

REFERENCES

1. Warner RM, Srinivasan JR. Protean manifestations of intravenous drug abuse. *Surgeon* 2004;2:137-40.
2. Del Giudice P. Cutaneous complications of intravenous drug abuse. *Br J Dermatol* 2004;150:1-10.
3. Cazorla C, Grenier de Cardenal D, Schuhmacher H, Thomas L, Wack A, May T, et al. Infectious complications and misuse of high-dose buprenorphine. *Presse Med* 2005;34:719-24.
4. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 2005;44:661-80.
5. Wang YQ, Wang Y, Cai BN, Liu WH, Chen SL, Dong JZ, et al. Clinical analysis of 1,400 cases of coronary artery angiography without heparin. [Chinese] *Di Yi Jun Yi Da Xue Xue Bao* 2005;25:1429-31.
6. Demirbas O, Batyraliev T, Eksiz Z, Pershukov I. Femoral pseudoaneurysm due to diagnostic or interventional angiographic procedures. *Angiology* 2005;56:553-6.
7. Fontaa V, Bronner C. Persistent injecting practices in subjects on methadone or buprenorphine maintenance therapy. A study of 600 cases [French]. *Ann Med Interne (Paris)* 2001;152 Suppl 7:59-69.
8. Guichard A, Lert F, Calderon C, Gaigi H, Maguet O, Soletti J, et al. Illicit drug use and injection practices among drug users on methadone and buprenorphine maintenance treatment in France. *Addiction* 2003;98:1585-97.
9. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? *Addiction* 2005;100:197-205.
10. Gowling L, Ali R, White J. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2006;19:CD002025.
11. Bell J, Byron G, Gibson A, Morris A. A pilot study of buprenorphine-naloxone combination tablet (Suboxone) in treatment of opioid dependence. *Drug Alcohol Rev* 2004;23:311-7.