

Reducing harm from injecting pharmaceutical tablet or capsule material by injecting drug users

PERRINE ROUX^{1,2,3}, M. PATRIZIA CARRIERI^{1,2,3}, LENNEKE KEIJZER⁴ & NABARUN DASGUPTA⁵

¹INSERM, U912 (SE4S), Marseille, France, ²Université Aix Marseille, IRD, UMR-S912, Marseille, France, ³ORS PACA, Observatoire Régional de la Santé Provence Alpes Côte d'Azur, Marseille, France, ⁴Study Lead at Apothicom, Paris, France, and ⁵Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, USA

Abstract

Background. It has long been known that drug users may use a variety of pharmaceutical preparations by injection, many of which are not intended for intravenous administration (e.g. buprenorphine, methylphenidate, oxycodone). The introduction of tablet fillers such as talc or starch, in the blood circulation may cause, besides local injection site complications, pulmonary emboli. To reduce the harmful consequences of injecting such solutions, drug users have been encouraged to use filters. This research studied the effectiveness of an injection drug user syringe filter (IDUSF) in eliminating these particles. **Methods.** Generic buprenorphine and methylphenidate (Ritaline®), both containing talc, are frequently diverted for use by injection in France. The aim of our laboratory-based study was to compare the effectiveness of an IDUSF (Sterifilt®, filter pore size = 10 µm) versus no filtration, at reducing the number of particles in solutions of dissolved generic buprenorphine and Ritaline®. **Results.** Compared with a non-filtered solution drawn up through a 30G needle, filtering of the generic buprenorphine solution eliminated approximately 85% of all particles between 1 and 5 µm in diameter and 97% of particles between 5 and 18 µm. In the Ritaline® solution, these values were two-thirds and 95%, respectively. **Conclusion.** Preliminary results indicate that IDUSF are effective in significantly filtering out large particles, which are responsible for major harms like pulmonary emboli. One strategy for alleviating these consequences is to promote the implementation of IDUSF in harm reduction programs, accompanied by training of social workers, peers and drug users. [Roux P, Carrieri MP, Keijzer L, Dasgupta N. Reducing harm from injecting pharmaceutical tablet or capsule material by injecting drug users. *Drug Alcohol Rev* 2011;30:287–290]

Key words: filter, buprenorphine, methylphenidate, talcosis, filler.

Introduction

The availability of syringe exchange programs and opioid substitution treatment has contributed to a dramatic decrease in the incidence of HIV infection among injecting drug users (IDUs) [1,2]. Despite widespread access to harm reduction programs, injecting drug use remains a high-risk practice, as the sharing of paraphernalia can lead to hepatitis C virus transmission, and unsafe injection practices can lead to serious local and systemic bacterial infections and other complications [3,4]. Moreover, drug users may inject oral pharmaceutical formulations which are not intended for intrave-

nous administration (e.g. methadone, buprenorphine, methylphenidate, oxycodone [5–8]). Generally, tablets are crushed or capsules opened, the resulting powder is mixed with water, and the suspension is injected. Most tablets contain insoluble fillers (starch, talc, cellulose), which are introduced into the peripheral veins and first circulate to the lungs, where they can obstruct fine capillaries. In addition to complications at the injection site, such as vascular problems and granuloma formation [9], some systemic complications can occur [10]. Many studies of IDUs over the past 40 years have provided alarming evidence of severe morbidity, for example, from pulmonary emboli [11–14]. In 1978,

Perrine Roux PharmD, PhD, M. Patrizia Carrieri PhD, Lenneke Keijzer MSc, Nabarun Dasgupta MPH, Researcher. Correspondence to Dr Perrine Roux, ORS PACA/InsermU912, 23 rue Stanislas Torrents, 13006 Marseille, France. Tel: +33 (0)496102878; Fax: +33 (0)496102899; E-mail: perrine.roux@inserm.fr

Received 13 March 2010; accepted for publication 12 November 2010.

Smith *et al.* [15] stated that 'It seems likely that we will continue to see lung disease develop due to this abuse'. Today, talc, starch and other fillers are still used in most pharmaceutical tablets. Adverse pulmonary effects of drug injection still occur [16] and little effort has been made to reduce associated harms for drug users.

One of the most implicated fillers in harms is talc and, to a lesser extent, starch [14,17]. Injected talc can induce 'pulmonary talcosis', a pulmonary arterial hypertension in association with the presence of foreign material [18]. Injected talc particles are first trapped in the small blood vessels in the lung, which respond with inflammation and formation of granular lesions (granulomas) that can lead to fibrosis and block blood flow through the lung [19,20]. This causes high pressure in blood vessels which enter the lung (pulmonary hypertension) which adversely affects the heart (*cor pulmonale*) and can be fatal [21–23].

In France, increased access to buprenorphine (Subutex®) in sublingual formulation as opioid substitution treatment has contributed to major public health outcomes such as a reduction in both HIV and overdoses among drug users [24]. Its wide availability and low prescribed doses have, however, been associated with an increased risk of diversion by injection [25,26]. Indeed, the fact that bioavailability of buprenorphine by intravenous use is eight times higher than that of the sublingual route [27], patients who are underdosed may inject buprenorphine in order to rapidly obtain an increased effect [28]. Although generic formulations of buprenorphine are diverted as is Subutex®, the risks induced by its intravenous use are potentially higher, as a result of the presence of talc among tablet fillers. Talc is also present in methylphenidate tablets (Ritaline®), which are also diverted by injection. To date, no in-depth study has been carried out on the extent to which these practices cause pulmonary damage.

To reduce the harmful consequences of injecting pills which are not intended for intravenous administration, drug users have been encouraged to use filters. They commonly use a piece of cigarette filter or cotton [29]. These filters are not sterile; they are often manipulated and kept for later use and compose a perfect growing environment for bacteria. Furthermore, they are often sold or exchanged, becoming transferring agents for hepatitis C infections [30]. Moreover, they are not efficient in eliminating insoluble particles from solutions [31].

Injection drug user syringe filters (IDUSF) have been specifically conceived to replace makeshift filters. Three IDUSF are currently available: the Compet AG syringe filter, the 'Filter syringe' and the Sterifilt®. They are not designed to sterilise solutions, but to promote

single use of filters and to eliminate particles of over 10 microns (extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions) in accordance with the European Pharmacopeia concerning injectable preparations. Some commercial syringe filters (Sartorius Syringe Filter, Millex-Millipore) have also been shown effective in removing particles [32] and in filtering out bacteria for those with a pore size of 0.22 µm. The problem, however, is that some of these microfilters also retain more active compound [31,32] and may thus be kept by IDUs for later use. Although this retention can be prevented by using a preliminary coarse filter and by adding one to three additional rinses to the preparation process [32], the context in which drugs are used, especially in the street scene, can be a barrier to the use of extra rinses.

A major disadvantage of small pore size filters is that they risk being blocked by fillers, especially if solutions containing cornstarch or similar fillers are heated. For IDUSF, a preliminary coarse filter can prevent this even without adding rinses to the process: by placing a cotton filter underneath the syringe filter.

The aim of our study was to assess the effectiveness of Sterifilt® with a pore size of 10 µm compared with no filtration, in terms of particle reduction in solutions containing dissolved generic buprenorphine or Ritaline®.

Methods

Solutions were prepared using 8 mg buprenorphine or 10 mg Ritaline® solid oral formulations. At the time of this research, all sublingual generics available in France (Arrow, Biogaran and Mylan) came from the same factory and contained the same ingredients. Tablets were, without prior crushing, dissolved in 1 mL sterile water at room temperature, as done in the French street scene. A particle counter (Liquid Syringe Sampler 3000A/HIAC/ROYCO) was used to count the number of particles found within specific size ranges. The sample dilution factor was 1/10 000.

Results

Compared with a non-filtered solution drawn up through a 30G needle, filtering of the generic buprenorphine solution eliminated approximately 85% of all particles between 1 and 5 µm in diameter and 97% of particles between 5 and 18 µm (Table 1). In the Ritaline® solution, these values were two-thirds and 95%, respectively (Table 2).

Limitations

A limitation of this study is that the counter cannot discriminate between different types of tablet fillers and

Table 1. Particle count^a in a buprenorphine solution after filtration with Sterifilt® (BupSF) and without filtration (BupNF)

Particle size (µm)	BupNF	BupSF
0.99–2.45	33 229	5 545
2.94–4.89	6 724	265
5.38–7.34	5 488	202
7.82–9.78	3 448	125
10.27–12.71	2 404	62
13.19–15.15	1 267	31
15.64–18.08	556	0

^aSolution was prepared using an 8 mg buprenorphine tablet in 1 mL of sterile water with a sample dilution factor of 1/10 000.

Table 2. Particle count^a in a Ritaline® solution after filtration with Sterifilt® (RitaSF) and without filtration (RitaNF)

Particle size (µm)	RitaNF	RitaSF
0.99–2.45	114 151	44 969
2.94–4.89	32 438	2 508
5.38–7.34	16 791	966
7.82–9.78	9 011	382
10.27–12.71	6 581	374
13.19–15.15	3 637	148
15.64–18.08	2 827	179

^aSolution was prepared using a 10 mg Ritaline® tablet in 1 mL of sterile water with a sample dilution factor of 1/10 000.

that the results of particle size were given only according to the capacity of the counter. In addition, in regard to the fact that the Sterifilt® data have not been compared to alternative filters, the findings cannot provide information in regard to comparative effectiveness between filters. Moreover, no direct assessment of loss of active drug through filtration has been done in this study. Further studies should be designed to better address these issues.

Discussion

Preliminary results indicate that IDUSF are effective at filtering out large particles, which are responsible for major harm in drug users. The European Pharmacopeia states 'intravenous infusion of particles larger than the internal diameter of capillaries (>5 µm) be clinically significant because the particles may increase the risk of foreign particle embolism'. The use of IDUSF, with a cost of 0.17 USD per Sterifilt® and a high retention of particles with a diameter >5 µm, may help limit the complications related to frequent pharmaceutical tablet

injection. IDUSF are harm reduction tools with potential benefits to drug users in the community, as well as for drug-dependent prison inmates [33]. The great medical expense of treating filler-related complications, such as pulmonary disease, also suggests a societal benefit of investing in prevention efforts. Pharmaceutical companies should provide accurate and accessible information about the composition of fillers in pharmaceutical products and adapt compositions in order to reduce injection-related harms.

Even if deaths from pulmonary complications due to injecting practices have been documented in case reports since 1950, further studies are needed on the effects of fillers. These should include studies on potential diversion of pharmaceutical products and an active surveillance of cases of pulmonary complications in IDUs. Meanwhile, the implementation of IDUSF and microfilters in harm reduction programs should be promoted and accompanied by the training of drug workers and health professionals.

Conflict of interest

Apothicom has developed and distributes since 2004 an injection drug user syringe filter (IDUSF), the Sterifilt®. A comparative study conducted by Jennifer Scott in 2008 [31] has shown the effectiveness of the Sterifilt® in reducing the amount of particles, and in retaining very little drug (heroin, 6-MAM, morphine). In France many injectors of Subutex® use Sterifilt® to filter: when talc-containing generics of Subutex® became available in the French pharmacies in 2008, Apothicom asked researchers of a public research institute to conduct a new study on the filtering capacity of the Sterifilt® with these pills. Lenneke Keijzer works at Apothicom and has participated in this study. All other authors have no conflict of interest.

References

- [1] Des Jarlais DC, Arasteh K, Perlis T, *et al.* Convergence of HIV seroprevalence among injecting and non-injecting drug users in New York City. *AIDS* 2007;21:231–5.
- [2] Emmanuelli J, Desenclos JC. Harm reduction interventions, behaviours and associated health outcomes in France, 1996–2003. *Addiction* 2005;100:1690–700.
- [3] Bassetti S, Battagay M. Staphylococcus aureus infections in injection drug users: risk factors and prevention strategies. *Infection* 2004;32:163–9.
- [4] Ditzen A, Ehrlich R, Monecke S. Disseminated cutaneous and pulmonary abscesses in an injecting drug user caused by a Pantone-Valentine leucocidin-positive, methicillin-susceptible Staphylococcus aureus strain. *Eur J Clin Microbiol Infect Dis* 2008;27:1013–15.
- [5] Hind CR. Pulmonary complications of intravenous drug misuse. 1. Epidemiology and non-infective complications. *Thorax* 1990;45:891–8.

- [6] Glatt MM. The changing British drug scene. *Lancet* 1969;2:429–30.
- [7] Showalter CV. T's and blues. Abuse of pentazocine and tripeleminamine. *JAMA* 1980;244:1224–5.
- [8] Rosenblum A, Parrino M, Schnoll SH, *et al.* Prescription opioid abuse among enrollees into methadone maintenance treatment. *Drug Alcohol Depend* 2007;90:64–71.
- [9] Del Giudice P. Cutaneous complications of intravenous drug abuse. *Br J Dermatol* 2004;150:1–10.
- [10] Pare JP, Cote G, Fraser RS. Long-term follow-up of drug abusers with intravenous talcosis. *Am Rev Respir Dis* 1989;139:233–41.
- [11] Butch AJ, Yokel RA, Sigell LT, Hanenson IB, Nelson ED. Abuse and pulmonary complications of injecting pentazocine and tripeleminamine tablets. *Clin Toxicol* 1979;14:301–6.
- [12] Sieniewicz DJ, Nidecker AC. Conglomerate pulmonary disease: a form of talcosis in intravenous methadone abusers. *AJR Am J Roentgenol* 1980;135:697–702.
- [13] Farber HW, Falls R, Glauser FL. Transient pulmonary hypertension from the intravenous injection of crushed, suspended pentazocine tablets. *Chest* 1981;80:178–82.
- [14] Lamb D, Roberts G. Starch and talc emboli in drug addicts' lungs. *J Clin Pathol* 1972;25:876–81.
- [15] Smith WR, Glauser FL, Dearden LC, *et al.* Deposits of immunoglobulin and complement in the pulmonary tissue of patients with 'heroin lung'. *Chest* 1978;73:471–6.
- [16] Shlomi D, Shitrit D, Bendayan D, Sahar G, Shechtman Y, Kramer MR. Successful lung transplantation for talcosis secondary to intravenous abuse of oral drug. *Int J Chron Obstruct Pulmon Dis* 2008;3:327–30.
- [17] Johnston WH, Waisman J. Pulmonary corn starch granulomas in a drug user. Light and electron microscopic study of a case. *Arch Pathol* 1971;92:196–202.
- [18] Abraham JL, Brambilla C. Particle size for differentiation between inhalation and injection pulmonary talcosis. *Environ Res* 1980;21:94–6.
- [19] Arnett EN, Battle WE, Russo JV, Roberts WC. Intravenous injection of talc-containing drugs intended for oral use. A cause of pulmonary granulomatosis and pulmonary hypertension. *Am J Med* 1976;60:711–18.
- [20] Marschke G, Haber L, Feinberg M. Pulmonary talc embolization. *Chest* 1975;68:824–6.
- [21] Bainborough AR, Jericho KW. Cor pulmonale secondary to talc granulomata in the lungs of a drug addict. *Can Med Assoc J* 1970;103:1297–8.
- [22] Robertson CH Jr, Reynolds RC, Wilson JE 3rd. Pulmonary hypertension and foreign body granulomas in intravenous drug abusers. Documentation by cardiac catheterization and lung biopsy. *Am J Med* 1976;61:657–64.
- [23] Kringsholm B, Christoffersen P. The nature and the occurrence of birefringent material in different organs in fatal drug addiction. *Forensic Sci Int* 1987;34:53–62.
- [24] Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. Buprenorphine use: the international experience. *Clin Infect Dis* 2006;43 (Suppl 4):S197–215.
- [25] Roux P, Villes V, Blanche J, *et al.* Buprenorphine in primary care: risk factors for treatment injection and implications for clinical management. *Drug Alcohol Depend* 2008;97:105–13.
- [26] Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. *Addiction* 2001;96:267–72.
- [27] Brewster D, Humphrey MJ, McLeavy MA. The systemic bioavailability of buprenorphine by various routes of administration. *J Pharm Pharmacol* 1981;33:500–6.
- [28] Vidal-Trecañ 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.
- [29] Thiede H, Hagan H, Murrill CS. Methadone treatment and HIV and hepatitis B and C risk reduction among injectors in the Seattle area. *J Urban Health* 2000;77:331–45.
- [30] Hahn JA, Page-Shafer K, Lum PJ, *et al.* Hepatitis C virus seroconversion among young injection drug users: relationships and risks. *J Infect Dis* 2002;186:1558–64.
- [31] Scott J. Safety, risks and outcomes for the use of injecting paraphernalia. Bath: University of Bath, Scottish Government Social Research, 2008.
- [32] McLean S, Bruno R, Brandon S, de Graaff B. Effect of filtration on morphine and particle content of injections prepared from slow-release oral morphine tablets. *Harm Reduct J* 2009;6:37.
- [33] Finlinson HA, Colon HM, Negron J, Robles RR. Designing an experimental HIV/HCV intervention to promote the safe re-use of drug preparation materials by injection drug users in Puerto Rico. *Harm Reduct J* 2008;5:14.