Commentary

Buprenorphine-associated Deaths in Singapore

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Introduction

Buprenorphine is a thebaine derivative that was developed in the 1970s for pain relief. It was approved for substitution therapy in France in 1996, and in the USA in 2002.

In Singapore, sublingual buprenorphine (2 and 8 mg tablets) has been available since 2002 for the treatment of opioid addiction, under the brand name Subutex. It is registered as a prescription-only medicine, but (at the time of writing of this paper) it is not a controlled drug under the Misuse of Drugs Act (MDA), Chapter 185, Statutes of the Republic of Singapore. Buprenorphine is also available under the brand name Temgesic for the relief of severe pain, as 0.2 mg sublingual tablets or as an injectable form in ampoules.

Concerns About Abuse

Medical practitioners would be aware of the not infrequent reports in the media about the anguish caused by Subutex abuse. For example in November 2003, The Electric New Paper reported Subutex was being sold on the black market at twice the usual price.[1] By July 2006, Channel News Asia carried a report which said that counsellors and ex-Subutex abusers were calling for tighter controls of Subutex.[2] That same month, The New Paper profiled a Subutex abuser in his 30s who had been abusing Subutex for 3 years before he died.[3] The article also reported that the number of Subutex abusers seeking treatment from the Institute of Mental Health had more than doubled, from 510 in 2004 to 1083 in 2005.

Recently, there has been increasing concern about buprenorphine abuse and its related morbidity and mortality. For example, in the July-September 2004 issue of the Epidemiological News Bulletin,[4] a case of a 29-year-old female who developed staphylococcal endocarditis after abusing buprenorphine intravenously was reported. In the October 2005 issue of this journal,[5] 4 cases of parenteral abuse of Subutex resulting in severe upper limb complications were reported.

In a speech on 16 November 2005,[6] Mr Mohamad Maidin, Senior Parliamentary Secretary of the Ministry of Home Affairs spoke of the dangers of Subutex abuse, and that abusers were pounding and dissolving the tablet in hot water and injecting it intravenously, and mixing it with other drugs like midazolam. In March 2006,[7] the Senior Minister of State for Law and Home Affairs Associate Professor (A/P) Ho Peng Kee stated that Subutex abuse first came to the attention of the Central Narcotics Bureau (CNB) in late 2003, and that the CNB was working work with the Ministry of Health (MOH) to explore possible measures to tackle the problem. For example, in a professional circular dated 26 October 2005,[8] the Director of Medical Services (DMS), MOH directed all registered medical practitioners to comply with various requirements on buprenorphine and methadone prescription. These requirements include doctors having the necessary training and resources to manage opiate-dependent patients, and prescribing doctors having to register their prescriptions with a newly established online Central Addiction Registry for Drugs, Singapore (CARDS). Notwithstanding these measures, A/P Ho said that the CNB would keep a close watch on the situation, and that the CNB would make Subutex a controlled drug under the MDA if the need arose.

First Buprenorphine-related Death Detected at the Centre for Forensic Medicine

At the Centre for Forensic Medicine (CFM), Singapore, the first case of a buprenorphine-related death was detected in September 2003. This was a sudden death in a 35-year-old drug abuser, with a hypodermic syringe at the side of the body, later found to contain buprenorphine.

Since then, we felt that there appeared to be an increase in deaths where buprenorphine was detected in a post-mortem blood or urine sample, but we had no real data. Therefore, we conducted a survey of such deaths for a 24-month period from September 2003 (starting from the index case) to August 2005.

Survey Observations

There was a total of 3892 autopsies performed for the period September 2003 to August 2005 – with 1907 and 1985 autopsies in the first and second 12-month periods, respectively. All cases where buprenorphine or norbuprenorphine was present in a post-mortem sample of

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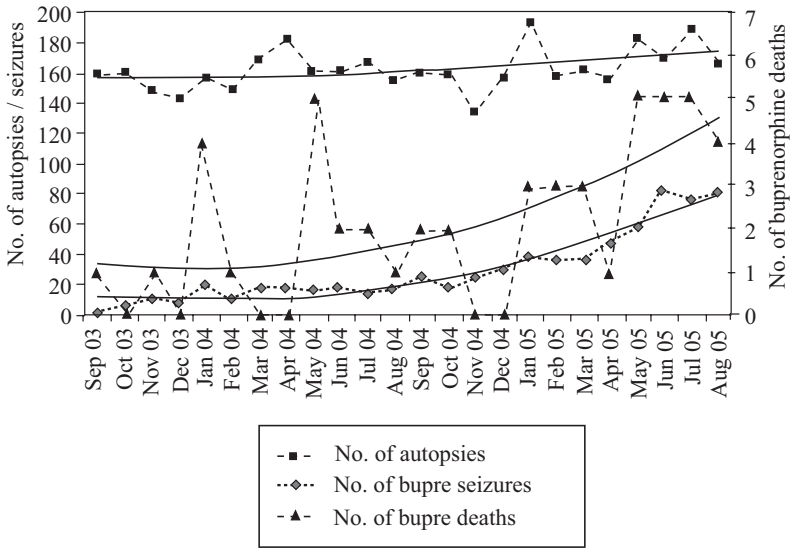

Fig. 1. Monthly autopsies, buprenorphine seizures and buprenorphine-related deaths.

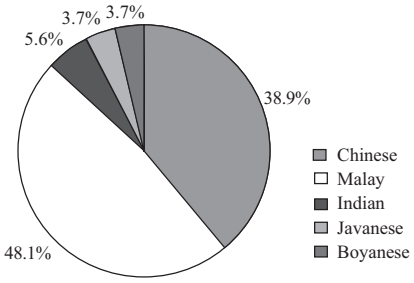

Fig. 2. Racial distribution of cases.

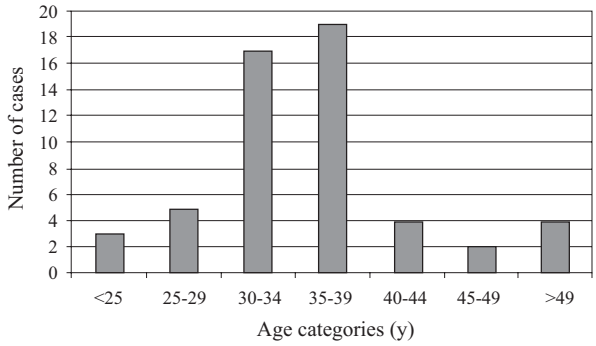

Fig. 3. Age distribution of cases.

blood and/or urine were included in the survey. We termed such deaths as buprenorphine-associated deaths. The term does not necessarily mean that the cause of death (COD) was directly due to buprenorphine.

There was a total of 50 cases of buprenorphine-associated deaths (1.3% of autopsied cases). Of these, 17 occurred in the first 12-month period, and 33 in the second 12-month period. The incidence rate thus nearly doubled in 1 year during the survey period – 9 per 1000 autopsies in the first 12-month period and 17 per 1000 in the second 12-month period. The overall autopsy prevalence for deaths where buprenorphine was detected in post-mortem samples was 13 per 1000.

The monthly distribution of autopsies and buprenorphine-associated cases is shown in Figure 1. The number of drug seizures positive for buprenorphine for the study period is also included.

While the number of autopsies was relatively constant during the study period (at approximately 160 to 180 per month), the number of buprenorphine seizures and buprenorphine-associated deaths showed rising trends. It is also noteworthy that the trend of buprenorphine-associated deaths had increased in parallel with the numbers of buprenorphine seizures analysed by the Centre for Forensic Sciences, Health Science Authority.

All but 2 of the 50 cases involved males. Known drug abusers made up 41% of the cases. Many were unemployed – only 14 (28%) had known occupations. The racial distribution is as shown in Figure 2. The age of the subjects ranged from 16 to 59 years. The mean age was 35.5 years. The age distribution of cases is shown in Figure 3.

Causation of Death

Of the cases where buprenorphine was detected in a post-mortem sample of blood or urine, we further categorised the cases into 3 groups based on the final certified COD as follows:

Table 1. Post-mortem Buprenorphine (BUP) Toxicological Data for Groups 1, 2 and 3

	No. of cases	No. of cases with blood positive BUP level	Mean blood BUP level (ng/mL)	Median BUP level (ng/mL)	Range of BUP levels (ng/mL)
Group 1	13	9	1.64	1.50	0.39 to 3.2
Group 2	22	20	4.69	3.25	0.11 to 17.1
Group 3	15	14	8.76	2.65	0.20 to 68.6

Group 1: sudden death attributed to a natural COD (n = 13);
Group 2: sudden death attributed to an acute mixed drug intoxication (n = 22); and
Group 3: death attributed to some unnatural COD other than the drug (n=15).

An example of a Group 1 type of death would be a sudden death where autopsy indicated that there was significant natural disease, and where the post-mortem buprenorphine level was considered to be below or within the usual therapeutic levels. There were 13 such deaths (26% of the buprenorphine-associated cases).

An example of a Group 2 type of death would be a sudden death where the autopsy findings were normal, and where buprenorphine was detected in the presence of another drug which was capable of causing respiratory depression. There were 22 such deaths (44% of the buprenorphine-associated deaths).

An example of a Group 3 type of death would be a person who say sustained fatal injuries in a fall from a height, and buprenorphine was detected in a post-mortem sample. There were 15 such deaths (30% of the buprenorphine-associated deaths).

Post-mortem buprenorphine toxicological data for the 3 groups is presented in Table 1. In each group, there were cases in which buprenorphine was not detected in the post-mortem blood sample, but buprenorphine or norbuprenorphine were detected in the urine samples.

Comparison was made between the mean buprenorphine blood level in Groups 1 and 2 using the two-tailed unpaired Student's *t*-test. There was no statistically significant difference between the observed difference in blood buprenorphine levels ($P = 0.06$). We interpret this to mean that it cannot be inferred confidently that death was due to buprenorphine just by the drug level detected in a post-mortem blood sample alone. Only after a complete and full autopsy with negative ancillary investigations, taking into account the circumstances in which death occurred and police investigation results, can one confidently say that a death is attributable to buprenorphine use/abuse.

Benzodiazepine Co-use/abuse

The survey also highlights a significant co-use/abuse of benzodiazepines. In this survey, 44 of 50 cases (88%) showed concurrent presence of at least 1 benzodiazepine in the post-mortem blood sample. Midazolam was detected in 26 cases, diazepam 22 cases and nitrazepam 13 cases. Notably, 13 cases had 2 benzodiazepines present in the blood sample, while 2 cases had all 3 benzodiazepines present.

Similarly, other reports note that mortality in buprenorphine-related deaths is in combination with concurrent benzodiazepine use.[9-11]

The safety margin for intravenous buprenorphine is reported to be high.[12,13] However, a large buprenorphine dose is known to cause respiratory depression.[14] Studies on rats have also demonstrated that concurrent use of buprenorphine and benzodiazepine could potentiate respiratory depression in a non-dose dependent manner.[15,16] Our survey indicates the danger of the co-use of buprenorphine and benzodiazepines. Thus, medical practitioners must not be lulled into a false sense of security just because buprenorphine is said to have a high safety margin.

Conclusion

There was a notable 2-fold increase in the incidence of buprenorphine-associated deaths in the two 12-month periods surveyed.

Given the danger of and potential for buprenorphine misuse, medical practitioners must exercise strict clinical practices and administrative controls to prevent diversion of prescribed buprenorphine for illicit use. Patients being treated for opiate dependence with substitution therapy must be warned against the dangers of diversion abuse of buprenorphine and co-abuse with benzodiazepines.

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