FACTORS ASSOCIATED WITH ADVERSE REACTIONS TO COCAINE AMONG A SAMPLE OF LONG-TERM, HIGH DOSE USERS IN SÃO PAULO, BRAZIL

Cleusa P. Ferri [1,3], John Dunn [2], Michael Gossop[3] and Ronaldo Laranjeira [1]

[1]Departamento de Psiquiatria, UNIFESP, Sao Paulo, Brazil

[2]Academic Department of Psychiatry, Royal Free and University College Medical School, Royal Free Campus, London, UK

[3]National Addiction Centre, Institute of Psychiatry, London, UK

Correspondence to: Dr. Cleusa P. Ferri National Addiction Centre, Institute of Psychiatry, 4 Windsor Walk SE5 8AF, London, UK e-mail: c.ferri@iop.kcl.ac.uk

ABSTRACT

Aim. To investigate the frequency of adverse cocaine reactions and associated factors among regular cocaine misusers. **Design, setting and participants.** A cross-sectional survey with 332 cocaine misusers from a range of treatment and non-treatment settings in São Paulo, Brazil. **Measurements.** An interview schedule was translated from English into Portuguese incorporating the Severity of Dependence Scale, the GHQ-28, CAGE and an 8-item questionnaire investigating the frequency of specific adverse cocaine reactions. **Findings.** Patients reported a median of 4.5 different adverse reactions to cocaine. The most commonly described reactions were feeling very hot (84%), shaking uncontrollably (76%) and feeling ill (75%). The least common and most severe symptoms were convulsions or fits (18%) and passing out (21%). Frequency of adverse reactions to cocaine was positively associated with out-of-treatment status, severity of cocaine dependence, ever having injected cocaine, using tranquillisers with cocaine, and GHQ score. **Conclusions.** Adverse reactions to cocaine are common among regular cocaine users. Some of the adverse effects, especially those on the heart and central nervous system, are potentially fatal. Preventive strategies should be developed to reduce the risk of adverse cocaine reactions. The findings are discussed in relation to the type of interventions that might be developed and lines of future research.

Key words: non-fatal overdose, adverse reactions, cocaine, crack cocaine,

INTRODUCTION

It is estimated that 1.7% of the general population in São Paulo, Brazil have at some time used cocaine (around 10% of those aged 18-28 years (Galduroz et al, 2000). Most patients who present to drug treatment services are cocaine users. Until the late 1980s this was predominantly in the form of cocaine powder, but in the early 1990s there was an explosion in the proportion of patients using crack (Dunn et al, 1996, Ferri & Gossop, 1999). Currently, cocaine users in treatment are predominantly young, single, men of low educational attainment, and in relation to the main route of administration, 61% are smoking crack, 37% snorting cocaine powder and 2% injecting it (Ferri et al, 2001). Different from Europe and America, very few patients report having used heroin (Laranjeira et al, 1997).

Cocaine can cause a range of acute adverse effects. Even at low doses some cocaine users report some unpleasant symptoms such as restlessness, palpitations and anxiety. At higher doses more severe signs and symptoms may develop, such as hypertension, tremor, hyperactivity, hyperthermia, hyperreflexia, cardiac arrthymias and convulsions (Benowitz, 1993). Death may be caused by cardiac arrest or infarction and cerebral haemorrhage or infarction (Calaway & Clark, 1994; Davis & Salwell, 1996). Injecting cocaine and smoking it in the form of crack are routes of administration associated with rapid onset of action and the delivery of a bolus of drug to the brain and other organs. These routes are more strongly associated with acute adverse reactions (Pottieger et al, 1992).

In a study of adverse reactions to a range of stimulant drugs (powder cocaine, amphetamines and ecstasy) in an out-of-treatment sample in London (Williamson et al., 1997), 24% of the individuals who had used powder cocaine reported having had a bad experience with the drug, 16% within the last year. The commonest problems were loss of appetite, panic attacks, feeling paranoid and feeling faint. Adverse reactions were more severe among patients who also tended to use stimulants with opiates or benzodiazepines. However, this sample did not include users of crack cocaine. In a study of 294 cocaine and crack users in Brazil, Dunn & Laranjeira (1999) found that 43% reported having experienced severe adverse reaction to cocaine use and 56% had witnessed someone else experience such a reaction. The commonest adverse symptoms reported by patients were fainting or collapsing, palpitations, shaking, anxiety or panic, a sensation of swallowing the tongue, shortness of breath, feeling hot and cold and chest pain. However, risk factors for adverse effects of cocaine use were not examined in this study.

The present study investigates the frequency of acute, adverse reactions to cocaine among a sample of cocaine users in São Paulo, Brazil and also the factors associated with these adverse

reactions. It explores the extend to which adverse reactions are related to the drug itself and its patterns of consumption, to individual characteristics or to the environment surrounding the individual and their cocaine use.

METHODS

Subjects and procedures

The sample comprised 332 cocaine users. The criteria for inclusion were: i) regular cocaine use (at least twice a week for a minimum of 3 months) and ii) recent cocaine use (within the past two months, or within the two-month period prior to admission). Subjects had to meet both criteria. For the non-treatment sample an additional criterion was used: not having sought treatment within the previous year.

Cocaine users were drawn from both treatment and non-treatment settings. The treatment sample consisted of 237 outpatients and inpatients from 12 public and private drug treatment agencies in Sao Paulo, Brazil. A diverse range of drug treatment services was used in an attempt to obtain a broad and heterogeneous sample of cocaine users (Dunn et al, 2001). A snowball sample of 68 cocaine users was obtained by asking patients in treatment to nominate a cocaine using friend or colleague who was not in treatment and who had a broadly similar pattern of use. A further 27 out-of-treatment cocaine users were contacted mainly through non-drug users who knew people who used cocaine within their own social or professional network. In total 95 cocaine users were interviewed from non-treatment settings.

Subjects were given travel and food vouchers in recognition of the time and effort involved in the interview and were only interviewed after informed consent had been obtained. The local medical ethics committee had approved the project.

Measures

Data were collected using a structured questionnaire that had been translated from English and piloted in Brazil. Acute adverse reactions to cocaine were identified by a questionnaire that had been developed in a previous study of the adverse effects of stimulant drugs (Williamson et al, 1997). The symptoms covered by this questionnaire are: feeling ill, being sick, feeling very hot, having difficulty breathing, shaking uncontrollably, afraid of dying, having convulsions/fits and passing out. Each item is scored from 0 to 5 according to the frequency that it has been experienced (never, 1-2 times, 3-5 times, 6-10 time, 11-20 times and more than 20 times). During the interviews, the researchers made sure that patients understood that these symptoms had to have occurred within seconds or minutes of taking cocaine and not at other times

unrelated to cocaine use. The assessment schedule also incorporated three standardised questionnaires: the Severity of Dependence Scale (SDS) to evaluate the severity of cocaine dependence (Gossop et al., 1995; Ferri et al., 2000), the GHQ-28 (General Health Questionnaire) (Goldberg and Williams, 1988) and the CAGE questionnaire (Masur & Monteiro, 1983). All interviewers were trained in the use of these instruments. Information about current drug use refers to the previous month or the month. The treatment sample was asked to report information on the month prior to treatment entry and the community sample on the month prior to interview.

Statistical analysis

Multiple linear regression was performed to investigate the variables associated with acute, adverse cocaine reactions**.** A backward selection procedure, based on the likelihood ratio test, was used.

RESULTS

The mean age of the subjects was 26.5 years (SD 7.8, range 13 to 57) and 90% were male. Only 24% had any secondary or higher education, and 52% were unemployed. The patterns of cocaine use by these subjects is shown in Table 1. Cocaine use had usually started in the late teens and the vast majority had begun using the drug by snorting (85%). Prior to the interview, nearly all subjects had snorted cocaine and most had also smoked it. Large quantities of cocaine (mean=5.2g) were being consumed on an almost daily basis and subjects had been using cocaine for considerable periods of time. Alcohol was the drug most commonly used at the same time as cocaine, followed by cannabis.

Table 1

The frequency of each acute, adverse reaction to cocaine ever experienced by the interviewees is shown in Table 2. The most common and most frequently described symptoms were feeling very hot, shaking uncontrollably and feeling ill, with over three-quarters of patients having experienced each of these at least once. The least common symptoms were passing out and having a convulsion, but even these had been experienced by around a fifth of the sample. The median number of adverse reactions that subjects had experienced was 4.5 (interquartile range 3.0 to 6.0).

Table 2

A multiple regression analysis was conducted to investigate the variables associated with the frequency of adverse cocaine reactions. Fifteen variables were entered into the initial model: gender, age at first cocaine use, length of cocaine use, route of administration (ever injected, ever smoked and ever snorted), amount used on a typical day, frequency of use in the last month, severity of dependence (SDS score), simultaneous use of other drugs (marijuana, alcohol or tranquillisers) with cocaine, positive CAGE, total GHQ score and contact with drug treatment agencies. The dependent variable was the sum of scores from the adverse cocaine reactions instrument. The intercorrelation coefficient alpha for this set of questions was 0.67, and factor analysis, using principal components analysis, revealed a 1 factor solution with an Eigenvalue of 2.5 that accounted for 31% of the variance.

Table 3 shows all variables entered in the initial model and those retained in the final regression equation. Out-of-treatment status, ever having injected cocaine, simultaneous use of tranquillisers and cocaine and higher scores on the GHQ and SDS were all positively associated with more frequent adverse cocaine reactions (β coefficient was 1.78, 2.22, 2.77, 0.44 and 0.25). Age at first cocaine use was inversely related to adverse reactions, as was duration of cocaine use, however, the 95% confidence intervals of the beta coefficients for these variables included zero, indicating that these relationships were not statistically significant.

Table 3

DISCUSSION

The cocaine users in our sample were long term, high-dose users. The majority were using cocaine or a daily or almost daily basis, and their mean daily dose was over 5 grams. Perhaps, not surprisingly, the majority had experienced acute, adverse cocaine reactions, with 50% reporting four or more such symptoms. The most common and frequently reported symptoms were feeling very hot, shaking uncontrollably and generally feeling ill. Serious symptoms such as convulsions and passing out had been experienced by approximately one fifth of subjects. These acute, adverse reactions to cocaine were associated with never having had any contact with treatment services, lifetime injecting of cocaine, simultaneous tranquilliser and cocaine use, greater psychological disturbance and severity of cocaine dependence.

Our sample was drawn from cocaine users in both treatment and non-treatment settings. The finding that out-of treatment status was associated with an increased frequency of adverse

reactions to cocaine is of concern. The occurrence of serious reactions, such as convulsions and loss of consciousness, among this group presents a serious threat to the health of the individual. This population is hard to reach through conventional techniques and, therefore, preventive interventions aimed at reducing the risk or consequences of adverse reactions would need to be undertaken using outreach methods in non-treatment settings. However, measures directed at patients who are in treatment may also have an impact on other users. Most of the cocaine users who were in contact with treatment services in this study had cocaine-using friends who are not in touch with services. Therefore, measures aimed at treatment populations could have an impact on the wider cocaine-using community.

Although the majority of subjects were either smoking or snorting cocaine at the time of interview, a significant minority (20%) had injected the drug at some time during their lifetimes. In the regression analysis, lifetime injection of cocaine was associated with more frequent adverse reactions to cocaine. This finding is understandable, as injection is a route of administration associated with a rapid onset of action and a bolus of drug arriving at the brain and other organs. Likewise, the association between adverse reactions and high levels of cocaine dependence is consistent with clinical observation. The more dependent a patient is, the more out of control their cocaine use is likely to be. Simultaneous tranquilliser use was also found to be associated with adverse cocaine reactions. Why should mixing a sedative drug with a stimulant drug increase the risk of adverse reactions? Clearly the more drugs one takes the wider the range of potential adverse reactions that one might experience and the greater the risk of adverse interactions. Support for this hypothesis is given by the study of Williamson et al (1997) of 158 stimulant users from non-treatment settings. They found that polydrug use, in particular simultaneous administration of stimulants, opiates and benzodiazepines, as well as intravenous administration of stimulants, were more likely to be associated with severe adverse reactions. An alternative explanation for this finding is that cocaine users may have been using tranquillisers to self-medicate adverse reactions associated to cocaine. It is also possible that concomitant tranquilliser use is a marker for polydrug misuse and that it is the effect of taking multiple drugs and their interactions that increases the risk of adverse effects. However, using cannabis and alcohol at the same time as cocaine were not independently associated with acute adverse reactions in our study.

We were surprised that simultaneous alcohol use did not have an independent effect. When alcohol is taken with cocaine it interacts to produce an active metabolite called cocaethylene. This substance has a half-life three times that of cocaine and is more cardio-toxic (McCance et al., 1995). Despite this, the frequency of simultaneous alcohol and cocaine use and the score on the CAGE questionnaire were not associated with the frequency of acute adverse reactions. A

more appropriate measure might have been to ask about the amount of alcohol consumed with cocaine and specifically whether the amount consumed when the adverse reaction occurred was greater than usual.

Our finding that GHQ-28 score, a measure of non-psychotic psychological disturbance, was positively associated with adverse cocaine reactions could have several explanations. Cocaine itself produces symptoms suggestive of psychological disturbance both acutely (e.g. anxiety, restlessness, fear, insomnia, palpitations, difficulty breathing and frank paranoia) and during the withdrawal phase (depression and apathy). Therefore, GHQ score could be indirectly measuring some psychological aspect of cocaine misuse or withdrawal. However, the correlation between the scores on the GHQ and the SDS was not strong (0.31) and the multivariate analysis showed that they acted independently to increase the risk of adverse reactions. Another possibility is that patients who are depressed and anxious are more likely to report adverse symptoms, either because they are more susceptible to them or because they remember them better. Alternatively, for some of the depressed subjects the adverse reaction event may have been a deliberate attempt at self-harm. Depression is the most important factor found to be associated with self-poisoning (Burgess et al., 1998). A study by Rossow & Lauritzen (1999) suggested that there is substantial co-variation between suicide attempts and drug overdose, with polydrug use, poor social functioning and HIV risk behaviour being common risk factors.

It is likely that some adverse reactions may not have been covered by the relatively brief (eight-item) questionnaire used in this study. Consequently, this may have underestimated of the frequency of adverse reactions. A second limitation of the study is the effect of recall on subjects' ability to report adverse reactions. Subjects had been using cocaine for an average of 7.6 years and the reactions they had experienced could have occurred at any time during that period. There are, therefore, issues surrounding the accuracy of recall. However, over 50% of subjects reported having had such a severe reaction to cocaine that they feared they would die. It is likely that such near-death experiences would be remembered.

A problem common to almost all research into acute adverse reactions to drugs of misuse is that information is not collected at the time of the event. The factors assessed at the time of the research interview, which were found to be associated with the frequency of adverse cocaine reactions, may not be directly related to the adverse reactions themselves. A prospective cohort study of cocaine users with frequent and regular follow-up interviews might help in address this problem. However, although adverse cocaine reactions are a common lifetime experience, they may be relatively uncommon over the sort of follow-up periods that are often used in such studies. Even with frequent follow-ups the probability of an adverse reaction occurring a day or

so before the interview would be extremely low. An alternative design would be to use a case-control study. Cases could be subjects who had had a recent adverse cocaine reaction. The circumstances of this event would be investigated in detail. These would then be compared with another occasion within that time period when cocaine had been used but without any adverse reaction occurring. In this design each subject could act as his or her own control.

In this study we have identified five factors that are associated with the frequency of adverse reactions to cocaine. These findings need to be replicated in other countries with different patterns of cocaine use - ideally using other designs. Further research is needed to clarify the basic concept of adverse cocaine reactions. Mapping out the full range of adverse symptoms and accurately measuring their severity would be a useful exercise and could form the groundwork for producing a more comprehensive assessment instrument. This would enable us to arrive at a more reliable, valid and phenomenological definition of acute adverse cocaine reactions. Studies need to focus more on factors that are temporally related to the adverse reactions event. If we are to develop preventive measures it would be useful to find out what cocaine users already know about adverse reactions to cocaine, what they do when they occur and how acceptable and feasible it would be to train them and their close associates in basic intervention techniques.

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Table 1: Patterns of cocaine use and co-morbidity (n=332)

Variable	
Age at 1st use (years) mean (SD) – range	18.8 (6.0) - 8 to 43
Duration of use (years) mean (SD) – range	7.6 (6.0) - 1 to 38
Amount used typical day (grams) mean (SD) – range	5.2(5.2) – 1 to 30
SDS score mean (SD) – range	9.9 (3.8) - 0 to 15
Frequency of use (%)	
1 day per week	11.0
2-3 days per week	19.0
4-5 days per week	26.3
5-7 days per week	43.7
Route of administration (lifetime -%)	
Smoked	83.7
Snorted	97.0
Injected	21.4
Drugs used at same time as cocaine (%)	
Alcohol	78.9
Cannabis	57.2
Tranquillisers	7.1
GHQ-28 score mean (SD) - range	17.4 (6.9) – 0 to 28
CAGE score mean (SD) – range	1.68 (1.50) - 0 to 4

Table 2. Frequency of acute adverse reactions to cocaine (n = 332)

	Frequency with which symptoms experienced (%)					
	Never	1-2	3-5	6-10	11-20	20+
Felt ill	24.7	17.8	13.3	11.7	7.8	24.7
Been sick	45.2	21.1	15.4	4.8	2.7	10.8
Felt very hot	15.7	7.5	13.0	7.8	8.1	47.9
Had difficulty breathing	39.2	13.3	9.9	7.5	5.1	25.0
Shaking uncontrollably	24.4	12.3	10.5	7.2	6.3	39.2
Had convulsions	81.9	11.1	4.2	1.2	0.3	1.2
Afraid of dying	47.3	14.8	8.7	7.2	3.6	18.4
Passed out	79.2	15.1	3.6	1.5	0.3	0.3

Table 3: Variables retained in final regression equation of risk of having ever experienced acute adverse reactions to cocaine.

Variable	β coefficient	95% CI	P
Individual characteristics			
Gender	•	•	•
Comorbidity			
CAGE	•	•	•
GHQ-28	0.44	0.32 to 0.57	0.009
Pattern of consumption			
Time of use			
Age at 1st cocaine use	-0.14	-0.29 to 0.005	0.059
Duration of cocaine use	-0.13	-0.26 to 0.01	0.071
Severity			
Amount	•	•	•
Frequency	•	•	•
SDS	0.25	0.02 to 0.49	0.036
Route of administration			
Ever injected	2.22	0.07 to 4.36	0.043
Ever snorted	•	•	•
Ever smoked	•	•	•
Concomitant drug use			
Cocaine+alcohol	•	•	•
Cocaine+cannabis	•	•	•
Cocaine+Tranquilizers	2.77	0.75 to 4.78	0.007
Environmental			
No treatment contact	1.78	0.46 to 3.11	0.000

Sum of squares=4283.64 F=15.2 $p<0.001$