Clinical Report

Hypertension and pulmonary oedema associated with ketamine administration in a patient with a history of substance abuse

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Cocaine use, frequently associated with other substance abuse, is becoming more common in the pregnant patient. These patients are more likely to experience peripartum complications. A case of hypertension and pulmonary oedema in such a patient, possibly triggered by ketamine, is reported. A tumultuous course in the intensive care unit was resolved when the patient's hypertension and sympathetic reactivity were successfully treated with barbiturates. A number of factors supported a diagnosis of barbiturate withdrawal in this patient, its onset also was related temporally to ketamine administration. Hypertension should be considered a sign of acute barbiturate withdrawal. If a history of cocaine use, particularly crack cocaine, is elicited, one should suspect multiple substance abuse and be especially cautious when administering ketamine.

L'usage de la cocaïne, fréquemment associé à l'abus d'autres substances toxicogènes, se retrouve de plus en plus fréquemment chez les femmes enceintes. Celles-ci sont sujettes à des complications pendant la période qui entoure l'accouchement. On rapporte ici un cas d'hypertension et d'œdème pulmonaire chez une cocaïnomane. La situation orageuse consécutive à l'accouchement se poursuit aux soins intensifs et ne se calme que lorsque l'hypertension et la réactivité sympathique sont contrôlées par l'administration de barbituriques. Plusieurs facteurs favorisent le diagnostic de retrait barbiturique chez cette patiente dont le début coïncide avec l'administration de kétamine. L'hypertension doit être considérée comme un signe de retrait barbiturique. Si l'anamnèse rapporte l'utilisation de cocaïne, particulièrement sous forme de crack, on doit toujours suspecter une polytoxicomanie et exercer la plus grande prudence à l'égard de la kétamine.

Key words

ADDICTION: cocaine;
ANAESTHESIA: obstetrical;
ANAESTHETICS, INTRAVENOUS: ketamine;
COMPLICATIONS: hypertension, pulmonary oedema;
WITHDRAWAL SYNDROME: barbiturate.

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Substance abuse among pregnant women is becoming more prevalent. Random urine toxicology studies have demonstrated illicit drug use in 10–25% of patients.¹ This population is at increased risk for increased perinatal morbidity and mortality.

Cocaine use, in particular, can present numerous problems.² It is particularly concerning because, in comparison with previous drug epidemics, more women of child-bearing age appear to be affected by cocaine use.³ In a recent study, 11.8% of newborns tested positive for cocaine.⁴ Adverse outcomes associated with cocaine use include statistically significant increased incidences of low birth weight infants, prematurity, abruptio placentae, placenta previae and perinatal death.⁵ Apart from the increased demands on the obstetrician and perinatologist,

the anaesthetist will also encounter these patients, often on an emergency basis, as there is an increased incidence of fetal distress requiring caesarean section.⁶ Further, patients will often deny or under-report substance abuse.^{1,4,6-8} so that a high index of suspicion is warranted. Some characteristics may be helpful in identifying those at risk. In one group, mothers at highest risk for cocaine use were poorly educated, black women without a partner.⁹ The following is a description of pulmonary oedema after ketamine administration in a patient who gave a history of crack cocaine use. Also associated temporally with the use of ketamine was the onset of a severe course of labile systemic hypertension, apparently as part of a barbiturate abstinence syndrome. Hypertension has not been previously mentioned as a characteristic sign of barbiturate abstinence.^{10,11}

Case report

A 39-yr-old black woman, gravida 7, para 5, presented approximately 12 hr post-partum for elective tubal ligation. Her pregnancy had been complicated by two episodes of preterm labour. One week before delivery the patient had been hospitalized for tocolytic therapy with magnesium sulfate and then oral terbutaline. She was discharged home after five days and returned in labour two days later. The subsequent spontaneous vaginal delivery had been uncomplicated. Her baby was known to be a viable 35-wk-old male infant, with one and five minute Apgar scores of 8 and 9 respectively.

The patient's past medical history included intermittent untreated hypertension (in the nonpregnant state), history of rheumatic fever and childhood asthma (inactive for many years). Blood pressure measurements throughout pregnancy were normal. The patient had a history of cigarette smoking in the recent past and a history of crack cocaine use which she denied in the past year.

On arrival in the OR for the tubal ligation, she was anxious but cooperative. Noninvasive blood pressure was 140/70 mmHg and heart rate 90 beats per minute. She had been fasting for nine hours and had been given 30 ml sodium bicitrate immediately preoperatively, as well as ranitidine 50 mg *iv* one hour before surgery. Subarachnoid block was chosen as the anaesthetic. The patient was placed in the sitting position and 75 mg lidocaine in 7.5% dextrose without epinephrine was injected through a 25-gauge Quinke-type needle at the L₃₋₄ interspace via the midline approach. The patient tolerated the procedure well and was immediately placed supine. She was noted to have a T₈ block level to pinprick, with some patchiness in the periumbilical region. Because of minor discomfort during incision, she was given 50% nitrous oxide in oxygen by mask. Fentanyl 50 µg was given twice and midazolam 2 mg administered gradually. At

all times the patient demonstrated a haemoglobin oxygen saturation of greater than 97%. The surgery proceeded uneventfully until strong traction at the surgical site was required.

At that time, because she complained of pain, ketamine 30 mg plus 20 mg was given *iv*. Within ten minutes the blood pressure had increased to 220/110 mmHg. The patient became tachypnoeic and the decision was made to intubate the trachea. Therefore nitrous oxide was discontinued and 100% O₂ was administered for two minutes. The surgery was halted, and rapid-sequence induction was performed with thiopentone 200 mg and succinylcholine 80 mg while applying cricoid pressure. At laryngoscopy, a large amount of pink froth emerged from the laryngeal inlet, which was, nonetheless, easily visualized. There was no sign of other secretions in the pharynx to suggest aspiration of stomach contents. Following quick suctioning and intubation of the trachea, froth poured from the tracheal tube. Haemoglobin oxygen saturation decreased from 98% to 89%, 10 cm PEEP was instituted and the lungs were ventilated with 100% O₂. Intermittent suctioning was performed as tolerated. Haemoglobin oxygen saturation returned to 95%.

An arterial line was inserted and the patient was transferred to the Intensive Care Unit (ICU) following expeditious completion of the surgical procedure. Although the blood pressure returned to normal following administration of the thiopentone it was elevated again on arrival in the ICU. A pulmonary artery catheter was inserted. Pulmonary artery pressure was 45/28 with a cardiac output of 4.6 L · min⁻¹. Pulmonary capillary wedge pressures were in the range of 12–15 mmHg. Pulmonary vascular resistance was calculated to be 214 dynes · sec · cm⁻⁵.

The patient experienced a stormy course over the next several days. Chest radiograph was consistent with diffuse pulmonary oedema. She exhibited extremely labile hypertension and was intermittently tachycardic. Mean arterial pressures ranged from 50 to 200 mmHg in the space of one hour. Any sensory disturbance (e.g., touching the skin, adjusting bed position) would cause the patient's blood pressure to soar, with coincident decrease in PaO₂. Arterial pressures as high as 300 systolic were recorded with diastolic pressures reaching 202 mmHg. Phentolamine boluses were used initially but were inadequate in controlling these hypertensive episodes. Moderate to high dose infusions of labetalol and sodium nitroprusside were used to control her blood pressure. She was given lorazepam and morphine to assure sedation and analgesia. Vecuronium was infused to prevent desaturation caused by fighting the ventilator.

Investigations into the aetiology of the patient's hypertension and pulmonary oedema were undertaken. Ec-

lampsia was considered unlikely in the absence of any premonitory blood pressure elevation or proteinuria. Renal ultrasound was normal. Echocardiogram showed normal left ventricular function, left ventricular hypertrophy, normal left atrial size, a normal aortic valve, and a possibly thickened mitral valve. Right-sided pathology was not noted in this technically compromised study. Phaeochromocytoma investigation, including serum and urinary catecholamine evaluation, was negative. A toxicology screen sent shortly after surgery was positive for "barbiturates other than phenobarbital" and "opiates," and was negative for cocaine. These results were consistent with the drugs which had been administered during anaesthesia.

Over the first 48 hr the patient's blood pressure continued to be very labile. An inspired oxygen fraction > 0.6 with PEEP of 15–20 cm H_2O was required to obtain an adequate PaO_2 . On the third day the results of a toxicology screen from the baby showed traces of barbiturate.

The patient was given pentobarbital 100 mg *iv* with dramatic results. Her blood pressure stabilized with continued *iv* pentobarbital administration and all anti-hypertensive agents were discontinued. The patient was then given a loading dose of *iv* phenobarbital to achieve a therapeutic serum level and the pentobarbital was discontinued. Her general condition improved rapidly and the trachea was extubated on the fifth postoperative day. Occasional hypertension still occurred but was easily controlled with small doses of labetalol. Oral phenobarbital maintenance therapy was instituted.

Further history obtained from the patient and the family revealed that she had been drinking 1–1½ quarts beer/week and had also been using "crack" cocaine up to several weeks before delivery. The patient did not admit to using any form of barbiturate. She did seek counseling and was discharged home taking metoprolol, clonidine and a tapered dosing schedule of phenobarbital.

Discussion

This is a complex case of an acute hypertensive crisis apparently triggered by the use of ketamine in a young woman with a history of cocaine use. There are a number of possible contributing factors which deserve comment. Pink frothy sputum of the volume exhibited in this patient is reminiscent of that seen in negative pressure pulmonary oedema.¹² Although the aetiology of this phenomenon is multifactorial¹³ the precipitating event can be identified as a discrete episode of upper airway obstruction. While this cannot be completely ruled out, it was not observed in this case.

A contributing factor in the development of pulmonary oedema is the presence of increased pulmonary capillary hydrostatic pressure. Given the patient's history of co-

caine use, she may have been predisposed to developing such conditions. "Crack" cocaine, or "freebase," is the alkaloid derivative of cocaine hydrochloride which is inhaled into the lungs. Cocaine has been shown to cause pulmonary vasoconstriction^{14,15} which is consistent with its known action of blocking presynaptic reuptake of norepinephrine. Pulmonary artery medial hypertrophy has been shown at autopsy in some freebase cocaine smokers.¹⁶

Presumably, the development of cocaine-induced vascular medial hypertrophy is similar to that seen in cor pulmonale in which the stimulus to hypertrophy is vasoconstriction in response to hypoxia. Chronic exposure to hypoxia (or crack) may lead to pulmonary hypertension. There have also been reports of pulmonary vascular hypertrophy in *iv* drug abusers in association with embolized foreign particulate matter.^{17,18} Many, 25–60%, of cocaine freebase users complain of respiratory symptoms including cough, chest pain, dyspnoea, and bloody or black sputum.^{19,20} Although this patient was asymptomatic, she may well have suffered enough exposure to crack cocaine to develop a hyperreactive pulmonary vasculature.

Ketamine is a potent sympathomimetic.²¹ There is at least one report of pulmonary hypertension and pulmonary oedema caused by intravenous ketamine,²² in a patient with coronary artery disease. The effects were reversed by administration of fentanyl. In a patient whose pulmonary vasculature was rendered hyperactive by chronic cocaine use, such an effect may be easier to achieve and more difficult to reverse. Even in normal patients ketamine has been noted to produce increased pulmonary artery pressures, increased pulmonary vascular resistance, and secondarily an increase in right ventricular stroke work.^{23–25} This patient's calculated pulmonary vascular resistance was in the high normal range in the ICU, but its initial value, while under the influence of ketamine, is unknown.

The above may help to explain the patient's early course. The persistence of systemic and pulmonary hypertension, with associated hypoxaemia, tachycardia and diaphoresis is more of a puzzle. Despite all attempts at pharmacological control with traditional vasodilators the patient's blood pressure continued to remain elevated with marked exacerbations in response to even the slightest stimulus such as touching the skin. This despite receiving regular doses of lorazepam and morphine for sedation. The puzzle appeared to be solved when it was discovered that the patient's child had traces of barbiturate in his serum. Since the infant had been delivered 12 hr. before the administration of thiopentone to the mother, the barbiturate could only have been transferred to the fetus as a result of maternal ingestion of the substance

before delivery. The subsequent administration of pentobarbital to the patient resulted in prompt resolution of her elevated blood pressure and associated symptoms. It seems that the patient had been experiencing a drug abstinence syndrome which was successfully treated with barbiturates. Alcohol withdrawal was considered. However, it is unlikely because she had not exhibited withdrawal symptoms during her previous five-day hospitalization for preterm labour. Withdrawal from alcohol is usually manifest within 48 hr.²⁶

Nonetheless, if this indeed represents a barbiturate abstinence syndrome, it is different from existing reports. Sullivan and Selkers¹⁰ described the major signs and symptoms of barbiturate abstinence as seizures and delirium which appeared 24–115 hr after cessation of the drug. This patient may have exhibited a degree of delirium, but there was no evidence of seizure activity during periods when the muscle relaxant was allowed to wear off for neurologic assessment. Other usual abstinence symptoms described by patients include anxiety, involuntary twitching, weakness, dizziness, visual perception distortion, nausea and vomiting, and postural hypotension. Our patient was too sick to give a subjective report. Janacek *et al.*¹¹ described restlessness, nausea, and perspiration. Nonetheless, hypertension, which was the predominant sign in this patient, is not mentioned by any of these authors.

Does this case represent an atypical case of barbiturate abstinence? Certainly there are a number of confounding factors, including the patient's concomitant cocaine use, her recent delivery, and the administration of ketamine. What role did the administration of thiopentone play in this patient? Fukuda *et al.*²⁷ showed in the isolated rabbit pulmonary artery model that thiopentone increased the responsiveness of alpha receptors to norepinephrine. Perhaps this was another contributing factor in the initiation of hypertension and pulmonary oedema in this patient although, in retrospect, it appears that these signs were present before thiopentone administration.

Clearly, there are a number of potential drug interactions and pathophysiological processes that need clarification in this case. Regardless, some summarizing statements can be made.

- 1 More patients are presenting for anaesthesia, especially on the obstetric ward, who have a history of illicit drug use. It is prudent to maintain a high index of suspicion for multiple substance abuse when the history of drug use, especially cocaine, is elicited.⁹
- 2 Crack cocaine use may predispose to the development of pulmonary artery hypertension and pulmonary oedema. The use of ketamine in such a patient should be undertaken with caution.
- 3 Hypertension should be considered as a possible com-

ponent of the barbiturate abstinence syndrome in addition to the signs and symptoms already described.

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