Singapore Med J 2012; 53(3) : e57

Indigo carmine-induced hypotension in patients undergoing general anaesthesia

Jeon HJ[1], MD, *Yoon JS*[1], MD, *Cho SS*[1], MD, *Kang KO*[1], MD

ABSTRACT Indigo carmine is a blue dye that is widely applied to localise ureteral orifices. It is generally believed to be a safe, biologically inert substance, and hypotensive reactions are extremely rare. However, we experienced three cases of indigo carmine-induced hypotension within a period of two weeks.

Keywords: hypotension, indigotindisulfonate sodium
Singapore Med J 2012; 53(3): e57–e59

INTRODUCTION

Indigotindisulfonate sodium (indigo carmine) is a blue dye that has been widely used to localise ureteral orifices.[1] Indigo carmine is generally believed to be a safe and biologically inert substance; however, despite its long use for more than nine decades, rare sporadic cases of adverse reactions, such as hypertension, bradycardia, bronchospasm and hypotension, have been reported.[2-8] Here, we report three cases of hypotension associated with intravenous indigo carmine injection in patients undergoing radical prostatectomy within two weeks. These cases occurred after the ingredient supply source had been changed by the manufacturer.

CASE REPORTS

Case 1

A 65-year-old Asian man was scheduled for retrograde radical prostatectomy for prostate cancer under general anaesthesia. His medical history included well-controlled hypertension with a calcium channel blocker. His blood pressure (BP) and heart rate (HR) in the pre-operative admission period were 120–144/67–82 mmHg and 51–58 beats/min, respectively. No history of previous exposure to indigo carmine was reported.

Upon arrival in the operating room, the patient's BP and HR were 178/71 mmHg and 78 beats/min, respectively. Anaesthesia was induced with 120 mg 1% propofol, 40 mg lidocaine and 50 mg rocuronium. After the induction of anaesthesia, a left radial arterial catheter and two 16-G intravenous (IV) lines were placed. During this time, anaesthesia was maintained with sevoflurane and rocuronium. The haemodynamics remained stable after the induction of anaesthesia, with a systolic pressure of 105–138 mmHg and a HR of 56–65 beats/min. Before indigo carmine injection, the patient's BP and HR were 132/56 mmHg and 56 beats/min, respectively. Two minutes after 5 ml of 0.8% indigo carmine (Carmine, Korea United Pharm. Inc, Seoul, Korea) was slowly administered intravenously in 1-ml increments over one minute, the patient's BP rapidly deteriorated to 80/40 mmHg without prior significant blood loss or other surgical events. Electrocardiogram (ECG) and oxygen saturation (SpO_2) maintained a normal sinus rhythm of 62 beats/min and 100%, respectively. The inhalation of sevoflurane was stopped and 100% oxygen was administered. Rapid IV infusion of lactated Ringer's solution followed by 10 mg ephedrine induced the BP to increase to 135/55 mmHg and the HR to increase to 70 beats/min within six minutes. No changes were noted in the patient's ECG, breathing sound, airway pressure, end-tidal CO_2 or skin colour. The surgery was successfully completed approximately 160 minutes after this episode. Throughout the rest of the operation, the patient's haemodynamic condition was stable, without the need for any additional vasopressor support.

Case 2

A 67-year-old Asian man with American Society of Anesthesiologists (ASA) physical status II was scheduled for retrograde radical prostatectomy. The patient's medical history included well-controlled hypertension and fatty liver. Pre-operative laboratory analyses revealed a mild restrictive pattern in the pulmonary function test, but all other laboratory findings were normal. The patient had no known allergy to food or drugs. His BP and HR during the pre-operative admission period were 119–133/73–78 mmHg and 68–84 beats/min, respectively. Initially, his haemodynamics were as follows: BP 156/75 mmHg; HR 98 beats/min; SpO_2 97%. Following the start of the operation, the haemodynamic profiles remained stable, with a BP of 124–102/85–68 mmHg and a HR of 95–85 beats/min for 65 minutes. One minute after 5 ml of 0.8% indigo carmine was administered via an IV bolus, the patient's BP rapidly dropped to 75/56 mmHg without changes in HR (82 beats/min), ECG, end-tidal CO_2 or SpO_2. 15 mg of ephedrine was administered in divided doses. Four minutes after administration of ephedrine, the BP was restored to 145/80 mmHg and the HR was 90 beats/min. Arterial blood gas analysis (ABGA) showed a pH of 7.375, PaO_2 of 171 mmHg, $PaCO_2$ of 38.1 mmHg, HCO_3 of 22.3 mmol/L and

[1]Department of Anaesthesiology and Pain Medicine, Seoul Veterans Hospital, Seoul, Korea
Correspondence: Dr Hee Jung Jeon, Anaesthesiologist, Department of Anaesthesiology and Pain Medicine, Seoul Veterans Hospital, Dunchon 1-dong, Gangdong-gu, Seoul 134-060, Korea. hjjunn@hanmail.net

SaO_2 of 100%. No changes in ECG, breathing sound, airway pressure, end-tidal CO_2 or skin condition were noted. For 175 minutes from the hypotensive event to the end of surgery, BP was maintained at 128–98/82–65 mmHg and the patient did not receive any vasopressors.

Case 3

A 62-year-old Asian man with ASA physical status III was admitted with prostate cancer. The patient had a history of ischaemic heart disease with percutaneous coronary intervention on the middle right coronary artery, hypertension and diabetes mellitus. Pre-operative ECG showed left ventricular hypertrophy with third degree AV block, and a temporary pacemaker was placed one day before surgery. Pre-operative data describing the cardiac enzymes and echocardiogram were within normal ranges. No history of allergy or previous exposure to indigo carmine was reported.

Upon arrival in the operation room, the patient did not complain of any cardiac symptoms and the monitoring data showed a BP of 146/63 mmHg, HR of 69 beats/min and SpO_2 of 95%. A left radial arterial catheter was placed and anaesthesia was induced by administration of 120 mg 1% propofol, 40 mg lidocaine and 50 mg rocuronium. Two 16-G IV lines were placed on the right hand and left external jugular vein. Following the start of the operation, the haemodynamic profile remained stable, with a BP of 98–133/51–66 mmHg and a HR of 62–67 beats/min for 85 minutes. Prior to indigo carmine injection, the patient's BP and HR were 105/52 mmHg and 62 beats/min, respectively. However, within 30 seconds of bolus injection of 5 ml 0.8% indigo carmine, the patient's BP started to deteriorate. The BP decreased to 50/40 mmHg and the HR increased to 90 beats/min without prior significant blood loss or surgical event. Airway pressure, end tidal CO_2 and saturation were maintained within the pre-indigo carmine administration ranges. The inhalation of sevoflurane was stopped and 100% oxygen was administered. Rapid intravenous infusion of lactated Ringer's solution, followed by 30 μg epinephrine and 100 μg phenylephrine was then administered in divided doses. BP was restored to 105/43 mmHg and the HR was 70 beats/min within ten minutes. No changes in ECG, breathing sound, airway pressure, end-tidal CO_2 or skin rash were noted. During the post-indigo carmine period, the patient's haemodynamic conditions were stable, with no adverse events. Postoperative ECG and cardiac enzymes showed no change when compared with the pre-operative data, and they were within normal limits.

DISCUSSION

As the molecular structure of indigo carmine resembles two molecules of 5-hydroxytryptamine (5-HT) arranged as mirror images of each other,[9] indigo carmine-induced hypertension and bradycardia have been reported.[6,8] However, hypotensive reactions related to the administration of indigo carmine dye are extremely rare.[2-5] We observed three cases of indigo carmine-induced hypotension that occurred within two weeks, in which sudden hypotension occurred within two minutes of the administration of indigo carmine, without significant blood loss or surgical event. Systolic BP decreased by 49–55 mmHg in all cases and the HR increased in one case following dye administration. However, other factors such as saturation and airway pressure did not change. Thus, there was a clear temporal association between dye injection and haemodynamic changes. Haemodynamic conditions were stable in the three patients without any event during the pre- and post-indigo carmine periods, and postoperative ECG, cardiac enzymes showed no changes when compared with the pre-operative data, indicating that hypertension or ischaemic heart disease was not likely responsible for the sudden episode of hypotension. However, adverse reactions could be aggravated in patients with ischaemic heart disease.

A study on patients with ischaemic heart disease and hypotension conducted by Owens and O'Brien revealed that coronary ischaemia occurred in a temporally causal relationship with hypotension, suggesting that patients with coronary disease may be susceptible to ischaemic events incurred as a result of low BP caused by excessive hypotensive drug treatment.[10] In two of our patients, BP was easily restored to the pre-indigo carmine level. However, one patient who had a history of ischaemic heart disease received more vasopressors and showed a delayed restoration time, although no changes in the ST segment, ABGA or cardiac enzyme were detected.

It was unclear if the three cases described here occurred by chance or if other factors were involved. We were informed by the pharmaceutical company that the source of ingredients had been changed and that they had stopped supplying the drug. In addition, all drugs containing ingredients from the new source had been collected. Since then, no cases of indigo carmine-induced hypotension have been noted. Upon analysis of samples of indigo carmine from the same lot, all were found to meet the appropriate testing specifications, including sterility and bacterial endotoxin levels.[11]

The cases described by Shir and Raja resemble those reported here. They encountered four cases of indigo carmine-induced hypotension without accompanying cardiac arrhythmia or bronchospasm within six weeks of each other, and the dye used in each case was from the same lot.[2] The three cases of hypotension described here occurred within two weeks of each other, and the dye used in each case was from two different lots. However, both lots were made with ingredients from a new supply source. We did not determine how many patients received indigo carmine-containing ingredients from the new source, but we are certain that more than three patients had received them.

There was no definite explanation for the aetiology of indigo carmine-induced hypotension other than a close temporal correlation with the indigo carmine injection. It has been reported that idiosyncratic anaphylactoid reaction could be the cause of the sudden drop in BP in response to indigo carmine.[4,5]

Anaphylactoid reactions are clinically similar to anaphylaxis, but may occur after the initial exposure to certain drugs, and they have a toxic-idiosyncrastic mechanism rather than an immunologically mediated one. In this study, the three patients had no history of allergy or previous exposure to indigo carmine. Idiosyncratic anaphylactoid reaction could lead to hypotension after indigo carmine. However, the three hypotension cases occurred within two weeks of each other, the dye used in each case was made from a new supply source and no cases of indigo carmine-induced hypotension have been observed since the drug from the new source was recalled. As a result, we cannot rule out drug impurity as a possible cause. Further studies that compare the dyes from the two different sources may help identify the factors responsible for indigo carmine-induced hypotension in susceptible patients.

In conclusion, this report describes three cases of an extremely rare complication of indigo carmine. Since aggravated responses can occur, it is important to be prepared for sudden hypotension, especially for patients with a medical history of cardiac disease.

REFERENCES

1. Song JE, Kim SK. The use of indigo carmine in ureteral operations. J Urol 1967; 98:669-70.
2. Shir Y, Raja SN. Indigo carmine-induced severe hypotension in patients undergoing radical prostatectomy. Anesthesiology 1993; 79:378-81.
3. Naitoh J, Fox BM. Severe hypotension, bronchospasm, and urticaria from intravenous indigo carmine. Urology 1994; 44:271-2.
4. Gousse AE, Safir MH, Madjar S, Ziadlourad F, Raz S. Life-threatening anaphylactoid reaction associated with indigo carmine intravenous injection. Urology 2000; 56:508.
5. Nguyen AC, Kost E, Framstad M. Indigo carmine-induced severe hypotension. Anesth Analg 1998; 87:1194-5.
6. Jeffords DL, Lange PH, DeWolf WC. Severe hypertensive reaction to indigo carmine. Urology 1977; 9:180-1.
7. Satoh K, Sakamoto N, Shinohe Y, Satoh M, Joh S. Indigo carmine-induced bradycardia in a patient during general anesthesia. Anesth Analg 2001; 92:276-7.
8. Ng TY, Datta TD, Kirimli BI. Reaction to indigo carmine. J Urol 1976; 116:132-3.
9. Erickson IC, Widmer BA. The vasopressor effect of indigo carmine. Anesthesiology 1968; 29:188-9.
10. Owens P, O'Brien E. Hypotension in patients with coronary disease: can profound hypotensive events cause myocardial ischaemic events? Heart 1999; 82:477-81.
11. Korea Food and Drug Administration. The Korean Pharmacopoeia, 8th ed. Seoul: Shinil Publishing Company, 2007.