European Review for Medical and Pharmacological Sciences 2012; 16(4 Suppl): 110-112

Magnetic resonance imaging contrast agent related pulmonary edema: a case report

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Abstract. – Gadobutrol is a contrast agent often used during magnetic resonance imaging (MRI). The agent has several side effects, some of which can be serious. It has extremely rare life-threatening systemic complications, which can lead to bronchospasm, hypersensitivity reactions and cardiovascular arrest. However, there is no data available on the development of noncardiogenic pulmonary edema following use of gadobutrol. This paper examines the case of a 37-year-old male patient reported to have developed noncardiogenic pulmonary edema after intravenous injection of gadobutrol during MRI.

Key Words:
Contrast agents, Gadobutrol, Magnetic resonance imaging, Noncardiogenic pulmonary edema.

Introduction

Gadobutrol has a safety profile comparable to other Gadolinium-based MRI contrast agents (MRI-ca)[1]. The agent is often preferred as it provides superior quality MRI conditions[2]. Its plasma half-life is about 90 minutes. After intravenous (i.v.) administration, its plasma level rapidly peaks within minutes, and it is then excreted renally[3].

Although side effects are similar to other gadolinium-based agents, these are usually a mild or moderate[4]. The most common are headache, dizziness and nausea. Dyspnea, urticaria, and anaphylactic reactions rarely occur[4]. In adults, gadolinium-based MRI-ca related hypersensitivity reactions are seen in 0.07% of patients. Seventy-four percent of these reactions are mild[5]. Very rarely, severe anaphylaxis can be encountered[6]. Reactions can occur rapidly (< 1 hour), or slowly (> 1 h)[6]. Acute reactions usually manifest themselves as anaphylaxis. In such situations, fast and effective treatment can be life saving[6]. Although gadolinium related reactions are well known, there are no available information about gadolinium attributable pulmonary damage. This paper presents a case of noncardiogenic pulmonary edema, developed after i.v. injection of gadobutrol during MRI.

Case

A 37-year-old male patient with a complaint of lumbalgia was admitted to our Neurology Clinic. During the spinal MRI procedure, intravenous gadobutrol was given by cephalic vein (solution Gadovist, Bayer Schering Pharma AG, Germany) (14 ml).

Following injection of the MRI-ca, the patient developed severe dyspnea, cyanosis, and loss of consciousness. Nasal oxygen was initiated. Methylprednisolone (i.v. 125 mg) was administered and the patient was transferred to the intensive care unit (ICU). He had no prior history of MRI-ca exposure, drug allergies, atopy or systemic disease. He was unconscious upon arrival to the ICU and had bradypnea, cyanosis, and absent arterial pulsation.

Airway patency was rapidly secured by tracheal intubation and connected to a manuel bag-valve system with oxygen at a rate of 10 L/min. Although monitored heart rate was 110 BPM, there were no pulses at peripheral arteries and arterial blood pressure could not be measured. External cardiac compression was started. Adrenaline 1 mg i.v. was given. An arterial blood gas analysis was pH 7.16; $PaCO_2$: 69 mmHg; PaO_2: 24 mm Hg.

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To correct cardiovascular collapse, fluid replacement and dopamine (10 µg/kg/ min) infusion was started. Approximately 1500 ml of fluid infusion was given over a 15 minute period. Following inotropic support, an intraarterial line was placed and the blood pressure was recorded as 65/27 mmHg and the peripheral arterial saturation was 77%. Cardiac compressions were terminated and the patient was connected to mechanical ventilator on SIMV mode. The ventilator parameters were adjusted as follows: FiO_2: 100%; frequency: 16/dk; PEEP: 5 cm H_2O; and tidal volume: 7 ml/kg.

Despite the maximally used dose of dopamine and 4 mg of adrenaline, invasive blood pressure value was not high enough. Staff administered a 10 µg/min infusion of noradrenaline (8 µg/mL). The ECG showed sinus rhythm and T wave inversions in the inferior and lateral leads. Transthoracic echocardiogram showed normal left ventricule and valve function. Diffuse rales were heard during pulmonary auscultation.

A chest radiograph showed an increase in pulmonary vascularity (Figure 1). Biochemical laboratory values were measured in the blood as follows: CK: 303 U/L; CK-MB: 88 U/L; troponin I: 11.4 ng/ml; Ca: 6.9 mmol/L; WBC: 31.7 K/uL; and NEU: 30.1 K/uL. Serum potassium was 2.4 mmol/L and a potassium infusion was initiated. Subsequent values indicated 2 mmol/L and 1.6 mmol/L and the concentration of potassium in the infusion was increased. Arterial blood gas after one hour on 100% oxygen indicated the chest radiograph showed significant improvement and the t-wave inversion reversed. CVP was 11 cmH_2O, and there was no urinary output detected within the first hour of ICU admission. After one hour, urine output started at a rate of 110 ml/h, and increased over several hours to an average rate of 300-400 ml/h. FiO_2 was 100% at the end of the first hour. The result of blood gas analysis at first hour with 100% FiO_2 as follows pH: 7.25 mmHg, PaO_2: 122 mmHg $PaCO_2$: 53 mmHg. FiO_2 was gradually reduced according to the values of repeated blood gas tests.

Four hours after ICU admission, with 60% FiO_2, the results obtained as pH: 7.31, PaO_2: 275 mmHg, $PaCO_2$: 43 mmHg, HCO_3: 21.7 mmol/L. Dopamine and noradrenaline infusions were tapered off as arterial blood pressure stabilized at around 130/75 mm Hg. Control chest X-rays showed almost recovery (Figure) and T wave inversion in ECG returned to normal. Recovery of the patient based on respiratory and hemodynamic parameters necessitated changing the mode of ventilation to CPAP. The patient was extubated after 12 hours in the ICU. The control values of serum cardiac markers (such as creatine kinase myocardial band [CK-MB] and troponin I) gradually decreased. A day after admission, the patient was transferred to the Cardiology Service and observed for three days for complications. He was discharged without sequelae.

Discussion

Gadobutrol can have serious side effects, such as dyspnea, anaphylactic reactions and excessive hypotension, but these are very rare[7]. Despite evidence of anaphylactic shock through the use of

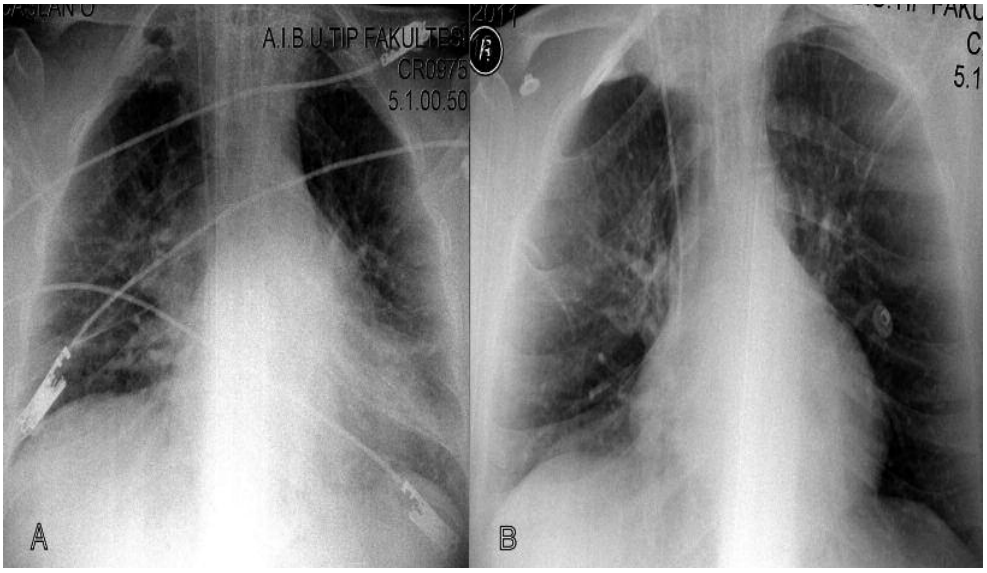

Figure 1. Chest roentgenogram. ***A,*** The image shows increased pulmonary vascularity. The X ray obtained 30 min after ICU admission. ***B,*** The X ray after 12 hours of ICU admission.

gadobutrol as reported in the literature, we found no reports of the development of pulmonary edema with this agent. Therefore, this paper represents the first case of this complication. Pulmonary edema is generally seen in two different forms; noncardiogenic and cardiogenic[8]. Noncardiogenic pulmonary edema (NCPE) is leakage of fluid as a result of increased microvascular permeability[9]. How MRI contrast agents cause pulmonary edema is not known. It has been suggested that it is the result of widespread endothelial damage induced by activation of the complement system, or as a direct irritant effect of the drug in the lung[1,8,9].

Gadobutrol has been used worldwide in approximately 5.7 million patients between 1998 and 2010. Of these, 1175 have developed side effects. Serious reactions were reported in 309 cases. These are cardiac and respiratory arrest, anaphylactoid shock, and nephrogenic systemic fibrosis[7]. Forstinga et al[10] published an observational study of 14,299 patients. Results of the study showed nausea and vomiting to be the most frequent side effect (0.31%), followed by urticaria (0.08%), and other skin lesions (0.07%). Only two patients (0.01%) presented serious side effects, one of which was anaphylactic reaction, while the other was swelling and itching of the throat.

In our case, rapid development of dyspnea and cyanosis immediately after administration of i.v. gadobutrol suggests NCPE. Rales were present in the lungs, the PaO_2/FiO_2 rate was less than 200, there was increased pulmonary vascular congestion on chest X-ray, and there was rapid response to treatment; all supporting NCPE. Gadobutrol associated skin lesions have rarely been reported[4,10]. In our patient, excessive hypotension, despite the lack of skin lesions, suggests severe anaphylactic reaction. The patients' diagnosis was anaphylactic shock with noncardiogenic pulmonary edema and provides the first case in the current literature.

In this case, severe hypokalemia was observed. There is no information that gadobutrol may cause this situation. However, in an *in vitro* study, hERG (human Ether-a-go-go) mediated dose-dependent inhibition of potassium current has been reported[11]. We observed hypopotassemia rather than hyperpotassemia, which usually accompanies acidosis. This phenomenon can be explained by inhibition of potassium current. This effect can also be thought to play a role in observed ECG changes in the patient. We suggest that the raised values of serum cardiac markers were the result of cardiac massage, because of normal ventricular wall motion in transthoracic echocardiography.

In conclusion, anaphylactic shock with noncardiogenic pulmonary edema after the use of gadobutrol is presented in this paper. As this is the first case in the literature, we suggest anaphylactic shock and noncardiogenic pulmonary edema must be kept in mind during MRI. Additionally, as in this case, accompanied hypopotassemia requires analysis and should be investigated in terms of gadobutrol attributable arrests, and, in particular, hERG mediated potassium current inhibition.

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