Effect of Dopamine on Excretory Urographic Image Quality and the Prevention of Contrast-Induced Nephropathy in Dogs

Jihye CHOI1), Heechun LEE1), Dongwoo CHANG1), Kichang LEE1), Kidong EOM1), Youngwon LEE2), Mincheol CHOI1) and Junghee YOON3)*

1)College of Veterinary Medicine, Seoul National University, Seoul 151–742 and 2)College of Veterinary Medicine, Chungnam National University, Taejon 305–764, Republic of Korea

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ABSTRACT. The effect of low dose dopamine on the excretory urographic image quality and contrast media-induced nephropathy in normal dogs (experiment 1) and the dogs with decreased renal function (experiment 2) were assessed. In experiment 1, the dogs with decreased renal function were induced by gentamicin overdose. In each experiment, animals were divided into 3 groups. In group 1, only contrast medium (iohexol) was administered. In group 2, contrast medium plus intravenous fluid (0.9% saline) were administered. And in group 3, contrast medium plus intravenous fluid and low dose dopamine were administered. Investigated parameters included intrarenal resistive index (RI), serum BUN and creatinine concentrations, contrast medium elimination time and radiographic image quality. In experiment 1, RI of group 1 increased at 80 min after contrast medium administration (p<0.05), but RI of group 3 decreased at 48 and 72 hr (p<0.05). Serum BUN concentration of group 1 was higher than that of group 2 and 3 (p<0.05); in radiographic examination, contrast medium elimination time decreased in group 2 and 3, but image quality of group 2 was inferior to that of group 3. In experiment 2, image quality of group 3 only provided adequate visualization of renal structures. The formula of contrast medium plus low dose dopamine was found to provide good nephrogram and pyelogram image quality without supplemental contrast medium, and to protect renal tubules from prolonged exposure to concentrated contrast medium.

KEY WORDS: canine contrast-induced nephropathy, dopamine, excretory urography.

Excretory urography is a good diagnostic modality to assess the renal function, however, in risk conditions such as dehydration, diabetes mellitus, congestive heart failure and preexisting renal disease, it may cause the contrast media induced nephropathy [2, 3, 5, 7, 16, 21, 22]. The etiology and pathophysiology of contrast media induced nephropathy are not manifested and just five mechanisms such as decrease of renal perfusion, direct renal tubular injury, altered glomerular permeability, intraluminal obstruction and immunologic reaction, have been proposed [3, 5, 7]. Various prophylactic treatments such as fluid, mannitol, furosemide and dopamine, have been attempted in many studies, but the effects of these methods have been controversial [2, 7, 11, 19].

In renal disease, contrast media for optimal image must be administered in double or threefolds of normal dosage and in this condition more risk factors to iatrogenic renal damage may exist [1]. The method which can produce optimal image with low dose contrast media even in renal disease is pursued.

Low dose dopamine stimulates D1-like and D2-like dopamine receptors selectively and causes vasodilation, increase of the renal blood flow, natriuresis and diuresis [4, 23]. But there have been many arguments about the prophylactic effect of dopamine for nephrotoxicity of contrast media [12, 26].

The previous studies mainly investigated the hemodynamic change of dopamine against contrast media induced nephropathy in human not in animal, and there were no attempts to assess the image quality of excretory urography with dopamine. The present study was performed to clarify the dopamine effect on contrast media induced nephropathy, to evaluate the urographic quality with low dose dopamine in normal and in animals with preexisting renal disease condition, and to establish revised protocol for excretory urography with minimal nephropathic complications and maximal image quality in small animal radiographic studies.

MATERIALS AND METHODS

Experimental animals: Twenty eight mature, clinically healthy, mongrel dogs were used. Nineteen dogs with normal renal function were allotted in experiment 1 and 9 dogs with experimental renal impairment were allotted in experiment 2. In Experiment 1, clinically healthy on the basis of the CBC, radiography, ultrasound and urine analysis, dogs weighing 1.5–6.0 kg were utilized for dopamine effect on excretory urography in normal kidney. The dogs were provided with water and food ad libitum. Every dog was divided into 3 groups. Eleven dogs in group 1 were undergone the excretory urography with only radiocontrast media, four dogs in group 2 with radiocontrast with 0.9% saline and four dogs in group 3 with radiocontrast plus dopamine diluted in 0.9% saline. In Experiment 2, gentamicin sulfate (Gentamicin®, Daesung Microb. Lab., Korea) was given in 35 mg/kg doses, sevenfold of normal dosage.
intramuscularly for 7 days to induce the acute renal impairment. The experimentally induced renal impairment was determined by serum creatinine and BUN concentration. When the concentrations of serum creatinine and BUN were out of upper limit of normal range (creatinine > 1.6 mg/dl, BUN > 27 mg/dl), excretory urography was performed. The dogs were provided with water and food ad libitum. Every dog was divided into 3 groups by the criteria like experiment 1 and each group involved 3 dogs.

Excretory urography: Group 1 was the control group in experiment 1 and 2, and there was no prophylactic treatment for excretory urography. Iodinated radiocontrast medium, iohexol 300 mgI/ml (Omnipaque®, NYCOMED, U.S.A.), was administered in 850 mgI/kg dose intravenously. The radiographic images were obtained by Toshiba IME-12A (Toshiba Corporation Medical System Division, Tokyo, Japan) at 5, 15, 30, 60 and 80 min after injection. In Group 2, all the animals received 0.9% saline intravenously at a rate of 2 ml/kg/hr beginning 30 min before the contrast injection as the prophylactic treatment for excretory urography and then contrast medium, iohexol 300 mgI/ml in 850 mgI/kg dose was given intravenously. The saline infusion was continued during and for another 6 hr after excretory urography. In Group 3, dopamine (Dopamin®, Kwangmyung, Korea) was diluted in 0.9% saline and low dose dopamine was used as prophylactic treatment. Dopamine was infused in renal doses, 5 µg/kg/min, from 30 min before urography and for 6 hr after the procedure. Excretory urography was performed using iohexol in 850 mgI/kg dose like groups 1 and 2.

Radiographic image investigation: The time that nephrogram and pyelogram began, whether the contrast medium was eliminated 80 min after contrast medium administration, and whether the quality of image was enough for diagnosis were investigated.

Intrarenal vascular resistive index (RI): Ultrasound examinations were performed with a Toshiba SSA-260A unit (Toshiba Corporation Medical System Division, Tokyo, Japan) using 7 MHz electronic phased-array sector probe. The overall gain was setting on 76 and the depth of observation was 4 cm. Anatomic sites of pulsed-Doppler interrogation were interlobar artery along the border of the medullary pyramids or arcuate arteries at the corticomedullary junction. These vessels were visualized by color-flow Doppler ultrasonographic imaging. The RI was calculated for each animal as an average value obtained from three-to-five similarly-appearing wave forms from three distinct vessels. The RI was measured by ultrasonographic unit internal calculation software before contrast medium injection and at 1, 1.3, 24, 48 and 72 hr after contrast medium injection.

Serum chemistry: Blood samples were obtained from jugular vein. BUN, creatinine, ALT, AST, ALP, total protein and glucose were measured with Selectra 2 (Merck, U. S. A.). The samples were collected before and 1, 12, 24, 48 and 72 hr after contrast medium injection.

Statistical analysis: The results were analyzed using Student t-test and Kruskal-Wallis test.

RESULTS

Experiment 1: In the radiographic images, the mean beginning time of nephrograms of all groups was 0 min and the mean beginning time of pyelograms was 28.1 ± 12.2 min in group 1, 15.0 ± 9.1 min in group 2 and 7.5 ± 5.0 min in group 3. In group 1, contrast medium eliminated from kidney at 80 min except one dog but in group 2, contrast media were eliminated in three of four dogs and in group 3, contrast media were not remained in all dogs at 80 min (Fig. 1). The quality of image was graded into 4 levels (Table 1, Fig. 2).

In group 1, intrarenal vascular resistive index (RI) did not change 1 hr after contrast medium injection but there was statistically significant increase of intrarenal vascular RI after 80 min (P<0.05). In groups 2 and 3, there were no significant changes of RI immediately after injection but in group 3 there were significant decreases of intrarenal vascular RI 48 and 72 hr after contrast medium administration (P<0.05, Fig 3). These RI values of all groups were in normal range (0.65 ± 0.05). But RI of group 1 was increased and RI of groups 2 and 3 were decreased according to time.

There were no significant changes of serum BUN and creatinine concentrations before and 1, 12, 24 and 48 hr after contrast medium injection. Radiocontrast-induced nephropathy was not induced after contrast study, but 72 hr after radiocontrast media administration, serum BUN concentration of group 1 was higher than that of group 2 and that of

Fig 1. Radiographs at 80 min after contrast medium administration in experiment 1. A, group 1; B, group 2; C, group 3.
Experiment 2: In the radiographic images, the contrast images of all groups could not achieve the good quality for diagnosis of renal anatomic and functional abnormalities compared with those of normal groups. Especially in groups 1 and 2, only nephrograms were identified with conventional contrast dose (Fig. 4). The quality of images was divided in 4 grades (Table 2). The elimination of contrast medium were delayed in groups 1 and 2 compared with time in group 3.

In groups 1 and 2, RI was not changed after contrast medium injection but in group 3, RI was decreased significantly at 1 hr temporarily (P<0.03, Fig. 5).

In serum BUN and creatinine concentration, there was no significant change in 3 groups.

DISCUSSION

In normal kidney, nephrographic phase begins at 10-30 seconds after contrast media injection. That means that renal parenchyma has normal function. In pyelographic phase, the pelvic recesses and the proximal ureter was observed [3]. Contrast agents for excretory urography are highly osmolar and highly charged and these characteristics are believed to contribute to nephrotoxicity, allergic reactions, vomiting and cardiovascular complications such as bradyarrhythmias, tachyarrhythmias, and hypotension [6, 21]. Among these complications, contrast media induced nephropathy has been reported to be one of the most com-

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Table 1. Grades of X-ray images in experiment 1

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<th>Group 1</th>
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a) +: Only nephrogram shown.
b) ++: The pelvis found by contrast medium following nephrogram.
c) +++: The renal pelvis and the shape of renal recess imaged indistinctly following nephrogram.
d) ++++: The renal pelvis and renal recesses identified distinctly following nephrogram.

Fig. 2. Excretory pyelograms of 3 groups in normal renal function. In group 1 (A) and group 3 (C), renal recesses were fairly but in group 2 (B), the contour of renal recesses was identified indistinctly.

Fig. 3. The intrarenal vascular resistive index (RI) of 3 groups in experiment 1 (▲ group 1, ● group 2, ■ group 3).
mon causes of acute renal failure acquired in the hospital [5, 16, 21]. Contrast media induced nephropathy may be identified as an acute impairment of renal function by radiographic contrast materials. If alternative etiologies for renal impairment are excluded, nephrotoxicity is usually identified clinically by an increase in the serum creatinine concentration, as an increase more than 50% of baseline within 24 hr after the administration of the contrast agent [2, 7, 19, 21].

Despite considerable number of studies, the mechanism producing contrast media induced nephropathy remains uncertain. But, five etiologies, such as failure of renal perfusion, change of renal glomerular permeability, direct injury to renal tubule, intraluminal obstruction, and immunologic reaction have been proposed [3, 5]. Altered glomerular permeability is related with the proteinuria by a modest impairment of the tubular reabsorption of low molecular weight proteins and with small increase in the excretion of the urinary enzymes, and then the direct tubular injury is developed [9, 24]. Schiantarell et al. [20] proposed that oxalate deposition and calcium oxalate crystalluria play a role in the intraluminal obstruction. Immunologic mechanism, hypersensitive reaction to contrast media, has been proposed to develop the nephropathy [7]. Failure of renal perfusion is related to a biphasic renal blood flow after contrast injection [7, 11]. Hypertonicity is a silent feature of all contrast agents used for excretory urography and this property may be central to its hemodynamic activity like transient increase in the total renal blood flow with vasodilation followed by prolonged decrease with vasoconstriction [5, 7, 11]. Contrast media induced nephropathy appears to be due to medullary ischemia caused by decreased renal blood flow resulting from an imbalance of vasodilative and vasoconstrictive factors [14, 15, 18, 19]. Ischemia causes alteration in vascular membrane structures, leading to an aggregation of red blood cells in the medullary vessel, which will further compromise medullary oxygenation and predispose to contrast media induced nephropathy.

These actions provide a foundation for several prophylactic efforts to prevent or reduce contrast media induced nephropathy, including hydration and the administration of furosemide, mannitol, calcium channel blockers, dopamine, atrial natriuretic peptide and theophylline [2, 19, 25]. The etiology and pathophysiology of contrast media induced nephropathy have not made clear, so optimal prevention from contrast media induced nephropathy in high risk

### Table 2. Grades of radiologic images in experiment 2

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![Fig. 4. Excretory urographs of 3 groups in renal impairment. In group 1 (A) and group 2 (B) only nephrograms were performed but in group 3 (C) the pyelogram was shown and the renal recess could be identified.](image)

![Fig. 5. Intrarenal vascular resistive index according to time after contrast injection in experiment 2 ( ▲ group 1, ● group 2, ■ group 3).](image)
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patients has not been yet well defined [25]. It has already been shown that dehydration potentiates the vasoconstrictive effects of contrast media and some investigators have attempted to reduce the likelihood of contrast media induced nephropathy by pretreatment with volume expansion or diuresis [17, 21]. Intravenous fluid could be beneficial before the administration of contrast agents by correcting plasma volume depletion [2, 8, 18], but Charles et al. proposed that hydration with intravenous saline before and after the procedure was not related to the development of nephropathy [3]. Mannitol with efficacy in preventing or reducing the severity of ischemic renal insufficiency in humans is also controversial [2]. In previous study, furosemide in conjunction with fluids alleviates medullary hypoxia and protects tubules from ischemic injury by reducing oxygen demand imposed by active sodium reabsorption [2, 25], but Richard et al. demonstrated that furosemide accelerates the contrast media induced nephropathy by ischemic injury [18].

Low dose renal dopamine infusion is commonly used in an attempt to prevent or treat renal dysfunction by stimulating renal dopamine receptors leading to vasodilation and a subsequent improvement in renal function [13]. This administration rate, a dose of 3–5 μg/kg/min is often called 'renal dose' or 'low-dose' dopamine and is thought to minimize the spillover stimulation of α- and β-adrenergic receptors [12]. Weisberg et al. found that low dose dopamine did not prevent the contrast media induced nephropathy [26], but Hans et al. proposed that dopamine treatment protected renal function from worsening by contrast media [10]. Dopamine is the endogenous precursor of norepinephrine that stimulates β₁-receptors and dopamine receptors [4]. Dopamine receptors are located at various regions within the kidney including the vasculature, sympathetic nerve terminals innervating different sites, juxtaglomerular cells and renal tubules [23]. The biological effects of dopamine are mediated through at least five genetically distinct dopamine receptors, D₁, D₂, D₃, D₄ and D₅. These are classified into two major families as D₁-like receptors which include D₁ and D₃, and D₂-like receptors which include D₂, D₃ and D₄ based on the stimulation and inhibition of adenyl cyclase, respectively [23]. Selective agonists of D₁-like receptors cause hypotension, increase in renal blood flow and glomerular filtration rate as well as increase in urinary excretion of sodium and water, whereas D₂-like receptor agonists produce hypotension, bradycardia, a decrease in afterload, and vasodilatation in certain vascular beds [23]. Dopamine at 3–10 μg/kg/min dosage increases cardiac output with little change in heart rate or blood pressure whereas at high infusion rates, 10–20 μg/kg/min, stimulates α- and β-adrenergic receptors and lead to increase in cardiac contractility, heart rate and blood pressure [4, 23].

In this study, the image quality and prophylactic effect using low dose dopamine were mainly investigated. In experiment 1, the rates of contrast excretion in groups 2 and 3 were faster than that in group 1. It meant that in only contrast medium administered condition the renal tubule exposed to concentrated contrast medium longer and prophylactic treatment with fluid or dopamine might lower the possibility to induce renal injury. On the radiographs, group 1 and group 3 showed definite pyelogram compared with group 2. In group 2, the pretreatment of fluid diluted the contrast material in blood stream so contrast could not reach the concentration to form the image of kidney. But in group 3, despite using fluid as pretreatment for urography as in group 2, low dose dopamine causes the vasodilation of renal vessels and the increase of renal blood flow, so the image could maintain good quality. RI of group 1 increased significantly 80 min after contrast medium injection, but RI of group 3 were decreased at 48 and 72 hr and it suggested that dopamine caused vasodilation. The serum BUN concentration in group 1 was significantly higher than in groups 2 and 3 (P<0.05). It is, however, considered that contrast media induced nephropathy did not occur in group 1 with normal dose excretory urography. In experiment 2, images of group 1 was not distinct enough for diagnosis on the contrary of normal group, it is thought that was because the dose of contrast media for optimal image must be administered in double or threefold of normal dosage especially when serum creatinine concentration is higher than 4 mg/dl [1]. But in group 3, the image, not optimal, was adequate to diagnose the urinary abnormalities without additive contrast administration. RI of group 3 at 1 hr after contrast medium injection was decreased temporarily (P<0.03), but there was no significant change in BUN and creatinine concentration. All RI values of group 1 were in normal range, but there was a tendency that RI of group 1 increased. It was caused by vasoconstrictive activity of contrast medium and in groups 2 and 3, the prophylactic treatment prevented this complication of contrast medium.

Although there was no significant increase of serum creatinine concentration in healthy kidney group and renal impairment group, dopamine improved the quality of image and promoted the elimination of contrast media in both groups. So, it was thought to prevent the renal tubules from exposing to the concentrated contrast medium for a prolonged period. In addition, there is no need to increase the dose of contrast media in renal impaired group to obtain proper radiographic contrast images. Although there was no clear evidence of dopamine effect on contrast media induced nephropathy, it provided the possible prophylactic effect on vasoconstriction which has been considered as the main mechanism of contrast media induced nephropathy. Therefore, low dose dopamine diluted in 0.9% saline was thought to be the proper formula for excretory urography in patients with preexisting renal disease.

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REFERENCES


