Biochemical and hematological alterations associated with intravenous administration of double doses of non-ionic contrast media in anesthetized dogs

Papuc Ionel*, Lacatus Radu, Purdoiu Robert Cristian and Pavaloiu Alexandra Nicoleta

Veterinary Medicine Faculty, University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Calea Mănăștur 3-5, Romania.

Accepted 10 May, 2013

To monitor the effects of a double dose of non-ionic contrast agent administered intravenously (iv) to anesthetized dogs, on the major functions and the biochemical and hematological parameters, two non-ionic contrast agents were tested (Optiray 350 and Ultravist 370) on two lots of 15 adult male and female dogs. The administered dose was 7 ml/kg and the recommended dose was 3.5 ml/kg. Several biochemical and hematological parameters were determined at 15, 60 min and 24 h after administration of contrast agents. Blood urea nitrogen (BUN) and bilirubin (BILI) had a statistical significance at F < 0.05 in values measured after 15 min, and statistical significance at p < 0.001 were obtained for aspartate aminotransferase (AST) and BILI. Statistical significance at F < 0.05 for the parameters measured after 60 min were BILI and AST, and statistical significance of values at p < 0.001 was obtained for the same parameters. Within 48 h of substance administration, the values of the tested parameters came back within physiological limits. Administration of contrast substance in double dose did not produce changes in pulse, body temperature and respiratory rate.

Key words: Non-ionic contrast medium, dog, blood chemical analysis, administration, intravenous.

INTRODUCTION

Adverse reactions to contrast agents range from a mild inconvenience, such as itching associated with hives, to a life-threatening emergency. Renal toxicity is a well-known adverse reaction associated with the use of intravenous contrast material. Other forms of adverse reactions include delayed allergic reactions, anaphylactic reactions, and local tissue damage (Thomas and Maddox, 2002).

Complications from radiographic contrast media depend on variety of factors, including the route of administration, chemical composition of the substance and the patient's underlying condition. The mechanical effect of needle placement is also a consideration (Paithanapagare et al., 2008). The selection of contrast medium has a crucial role in radio diagnostic examination. The ideal contrast preparation should be minimal neurotoxic, should be pharmacologically inert, miscible with cerebrospinal fluid and radio opaque at an isonotic concentration (Widmer and Blevins, 1991). A number of other studies consistently reported a lower incidence of contrast-induced nephropathy where non-ionic, iso-osmolar contrast media were used, regardless of the route of N-acetylcysteine administration (Baker et al., 2003; Azmus et al., 2005; Ye et al., 2012). The association of such a contrast medium with reduced contrast-induced nephropathy incidence was well
demonstrated (Soehardy, 2004; Hernandez et al., 2009; Ye et al., 2012).

In our study, we worked with two contrast substances: Optiray 350 (producer Tyco Healthcare Canada) and Ultravist 370 (producer Schering AG - Germany), which are non-ionic contrast substances with a low osmolality. The osmolality of a particular contrast agent is determined by the number of osmotically active particles formed when it is dissolved in solution. Ionic agents dissociate into ions when dissolving in water and contain an iodinated benzene ring. As a result, ionic agents have a higher osmolality than blood. Non-ionic agents do not dissociate into separate particles when dissolved in water; their osmolality is therefore one half that of ionic agents (Thomas and Maddox, 2002). It is concluded that unlike ionic contrast media, non-ionic contrast agents appear to have less inhibitory effects on blood clot formation and thus, it might be associated with a higher risk of thromboembolic complications during coronary angiography (Hwang et al., 1989).

High-osmolar ionic contrast media are more cytotoxic than low-osmolar non-ionic contrast media to gallbladder epithelial cells (Ju et al., 2002). A low-osmolar, ionic contrast medium, has a greater anticoagulant effect than a low-osmolar, non-ionic contrast agent (Kurisu and Tada, 1992). Some studies demonstrated that a higher incidence of contrast-induced nephropathy occurred most often in subjects that have used a low-osmolality ionic contrast medium (for example, iomeprol) (Ye et al., 2012).

The goal of our study was to track the effects of biochemical and hematological changes and modification of physiologic function when double doses of non-ionic contrast substance were administrated intravenously (iv) in anesthetized dogs.

MATERIALS AND METHODS

The study was conducted on a total of 30 adult dogs of different breeds and sexes and an average weight of 20 kg. The animals were divided into two lots of 15 individuals. The study monitored the biochemical and hematological changes induced by administration of a double dose of non-ionic contrast substance (Optiray 350 - group I, Ultravist 370 - group II), with the normal dose administered to dogs for the two substances studied being between 3 to 3.5 ml/kg. We also followed the influence of the dose on the major physiological functions and observed if this dose was life-threatening. Before substance administration, patients underwent 24 h food diets, water was administered ad libitum. Each patient was examined clinically; the non-ionic substance dose was 7.0 ml/kg intravenously. Before administration, patients were subjected to neuroleptanalgesia with xylazine and ketamine (xylazine 1 to 2 mg/kg im bw; Ketamine 10% 0.06 to 1 ml/kg im bw) (products manufactured by Animal Health GMP, Netherlands). We also monitored heart rate, body temperature and respiratory rate after 10 min, 1 and 24 h. Blood samples were collected and analyzed after 15, 60 min and 24 h after substance administration. Non-ionic contrast substances used were administered intravenously in bolus, in the cephalic vein. The biochemical and hematological parameter measurement was performed with the help of the Clinical biochemistry analyzer by Diatron LTD, USA.

Statistical analysis

The changed parameter values in the two lots, following administration of contrast substance were statistically calculated using the mean and standard deviation. To check the variance equality of the two groups, the F test was applied for each parameter change. The Student t-test was used for comparison between the mean changed parameters in the two substances studied. Statistical processing was performed with Microsoft Excel 2010 software (Microsoft).

RESULTS

The results obtained from biochemical analysis of the 15 cases in lot I to which Optiray 350 was given were subjected to statistical calculation, using the mean and standard deviation. After 15 min, after administration of Optiray 350 in lot I, increases in alkaline phosphatase (ALP) 152 ± 3 IU/L, normal value ranging from 12 to 121 IU/L, gamma glutamyl transferase (GGT) 14 ± 1, 65 IU/L values normally ranging from 2 to 10 IU/L, increases in blood urea nitrogen (BUN) 41 ± 3.87 mg/dl normal value ranging from 8 to 30 mg/dl, increases in aspartate aminotransferase (AST) 81 ± 4.97 IU/L value normally ranging between 16 to 54 IU/L and elevated total bilirubin (BILI) 0.76 ± 0.042 mg/dl normal value ranging from 0.1 to 0.3 mg/dl [reference values after Vaden et al. (2009)], were found. The remaining biochemical parameters did not change. Also, there were no reported changes in either the serum protein electrophoresis; values obtained were within normal limits. At the hematological exam, the values obtained were within normal limits except mean corpuscular hemoglobin concentration (MCHC), this parameter showed a slight increase up to 1.5 g/dl from the maximum allowed value (normal value 32 to 36 g/dl).

After 60 min from the administration of Optiray 350, increases in ALP 162 ± 4.23 IU/L, GGT 13 ± 2.24 IU/L, BUN 36 ± 4.47 mg/dl, AST 76 ± 9.65 IU/L and increases in BILI 0.73 ± 0.080 mg/dl, appeared. Regarding the hematological parameter values, in 60 min after administration of Optiray 350, a slightly higher number of red blood cells (RBC) with an average of 0.07 units (normal value 5.8 to 8.5 10^12/l) and an increase in hemoglobin (HGB - normal value 14 to 19.1 g/dl) and mean corpuscular hemoglobin concentration (MCHC - normal value 32 to 36 g/dl) with an average of 0.5 units to the maximum permitted levels, were identified.

In 48 h from Optiray 350 administration, both the mean of the biochemical parameters as well as the mean of the hematological parameters was within the reference interval. In group II, after receiving a double dose of the
non-ionic contrast substance Ultravist 370, after 15 min, ALP 154 ± 3.76 IU/L, GGT 13 ± 2.51 IU/L, BUN 30 ± 2.27 mg/dl, AST 92 ± 4.17 IU/L and 0.68 ± 0.07 BILI mg/dl were increased. At 60 min after a double dose of Ultravist 370, ALP 161 ± 3.63 IU/L, GGT 12 ± 1.46 IU/L, BUN 37 ± 3.48 mg/dl, AST 62 ± 3.59 IU/L and BILI 0.68 ± 0.04 mg/dl were still elevated.

Hematological parameters showed no significant increase, after 15 min we observed an increase in MCHC with an average of 0.99 units to the maximum, and after 60 min after a double dose of Ultravist 370, we noticed slight increases of RBC, with an average of 0.1 units, and of HGB and MCHC with an average of 0.8 units. Values obtained in serum protein electrophoresis showed no changes.

Analyses carried out 48 h after dosing a double dose of Ultravist 370 showed no significant changes, the average values of measured parameters returned to normal limits. To check the variance equality of the two lots, the F test was applied for each parameter change. After statistical processing, we applied the Student t-test, comparing the equality of average values obtained between the two lots. The t-test statistical significance was p < 0.05. Among the parameters measured at 15 min, BUN and BILI had a statistical significance at F < 0.05, and statistical significance at p < 0.001 was obtained for AST and BILI. Among the parameters measured at 60 min, statistical significance (F < 0.05) was found for AST and BILI, and statistical significance at p < 0.001 was determined for AST and BILI. When it came to the values measured after 24 h, F < 0.05 was obtained for BILI, and statistical significance at p < 0.5 was obtained for PAL, at p < 0.001 for BUN and p < 0.01 for AST.

**DISCUSSION**

After the study, in 23% (7 patients) we found mild feelings of discomfort, pain during administration, skin reactions such as hives or erythema and vomiting, symptoms that disappeared a few hours after administration, not being life threatening. Biochemical changes were reported both at 15 and 60 min after administration of contrast substance in both groups studied. Determined biochemical changes were found only in ALP, GGT, BUN, AST, BILI, showing moderately increased values. Rising of total serum ALP is determined by component isoenzymes. The most common isoenzymes are the liver isoenzymes which is increased in cholestasis, but without modification values in cellular damage or necrosis, bone isoenzymes with high values in bone remodeling and corticosteroid-induced isoenzymes produced in liver being specific only for dogs.

Gamma-glutamyltransferase is an enzyme found in different type of tissues, especially in kidney, pancreas and intestinal mucosa, but has an important role in hepatic diseases. GGT value is high in cholestasis or biliary necrosis, the mechanism of increase GGT serum value in this affection is not well known, but could be due to increase GGT production or release of GGT from cells membranes.

Blood urea nitrogen is the final product of protein metabolism and is produced in the liver through urea cycle. BUN is tested for modification of renal function and is also a marker of liver function or liver insufficiency. High level of AST most commonly indicates either hepatocellular or muscle injury. Because red blood cells contain also AST, therefore high level of AST could be found in intravascular hemolytic disease. Serum bilirubin may be increased in prehepatic icterus, hepatic icterus or in posthepatic icterus.

Statistical calculation for AST and BILI values obtained 15 and 60 min after administration of contrast substance (p < 0.001) shows the direct link between changes in parameters and the contrast substance. In 24 h, the statistical significance at p < 0.5 was shown for ALP, at p < 0.001 for BUN and p < 0.01 for AST. Moderate increase of ALP and GGT correlated with a slight increase of BILI were indicating a possible cholestasis and biliary reactivity due to the metabolism of the contrast substances, the values exceeded the maximum limit by only a couple of units. Increased urea correlated with increased GGT appeared due to the effect of the active substance on the kidney caused by mild intravascular hemolysis, mild cholestasis and a possible acute tubular reaction. Increased urea did not produce morphological changes on the kidney, biochemical examination conducted one week after administration of contrast showed normal levels of urea, and radiological and ultrasound examination did not show changes in the renal parenchyma.

Administration of contrast substance in bolus correlated with the low osmolarity of the substances can cause a possible intravascular hemolysis which can lead to increased AST and MCHC. Relative increase in hemoglobin and red blood cells indicated a possible splenic contraction reaction to the contrast substance. The electrophoresis of serum proteins did not change from the normal values for both substances studied.

Non-ionic contrast substances, when properly administered, are not painful, the optimal dose of Optiray 350 is 3.5 ml/kg and the optimal dose of Ultravist 370 is 3 ml/kg. Double doses of contrast substance increases metabolism time, therefore, in radiological examinations, the image quality does not change, and there are no life-threatening effects. Biochemical and hematological changes induced by administered contrast substances returned to physiological values after 48 h. The products tested had excellent neural tolerance and a minimal influence on the cardio-respiratory system.
Conclusion

The effect of non-ionic contrast substances on the liver and kidneys were minimal, no morphological or functional changes were noticed in a week after substance administration.

ACKNOWLEDGEMENT

This work was supported by CNCSIS-UEFISCSU, project number PNII-IDEI 847/2007.

REFERENCES


