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Gentamicin and Phenylbutazone Nephrotoxicity in a Calf

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Abstract: The frequent use of nonsteroidal anti-inflammatory drugs in combination with gentamicin poses the additional risk of nephrotoxic renal failure. A six weeks old and dead Holstein calf with history of pneumonia and administration of gentamicin and phenylbutazone was referred to Department of Pathobiology, Faculty of Veterinary Medicine, University of Shahrekord. At necropsy, severe bilateral hydronephrosis and renal papillary necrosis, cranioventral consolidation of lung and hemorrhagic linear erosions on the mucosal folds of abomasum were seen. Histopathological examination of renal sections revealed decreased thickness of renal cortex and medulla, tubular epithelial vacuolation and necrosis, infiltration of mononuclear inflammatory cells, interstitial fibrosis and tubular dilation. In the abomasum, numerous focal mucosal hemorrhages and necrosis and abomasitis were seen. Fatty degeneration and necrosis of hepatocytes were observed in liver sections. To our knowledge, there is no report about naturally occurrence of nephrotoxicity due to use of gentamicin and phenylbutazone together in calf and in this case report, the authors describe gross and histopathological characteristics of this nephrotoxicity in the affected animal.

Key words: Nephrotoxicity, gentamicin, phenylbutazone, calf

INTRODUCTION

Gentamicin (GM) is one of the most important of the aminoglycoside antibiotics used widely for the treatment of serious and life-threatening infections and whose clinical use is limited by its nephrotoxicity (Ekor *et al*., 2006). There are numerous studies about experimental nephrotoxicity induced by gentamicin and different agents used to reduce its nephrotoxicity (Ali, 2003; Atessahin *et al*., 2003; Parlakpinar *et al*., 2005; Pedraza-Chaverri *et al*., 2003).

The frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with gentamicin poses the additional risk of nephrotoxic renal failure (Hosaka *et al*., 2004). Oral and gastrointestinal tract erosions and ulcers, renal medullary crest necrosis and vascular thromboses have been reported in phenylbutazone treated horses (Collins and Tyler, 1984; Gunson and Soma, 1983; MacKay *et al*., 1983; Read, 1983). There are few experimental studies about nephrotoxicity induced by phenylbutazone in the rat (Owen and Heywood, 1983, 1986).

To our knowledge, there is no report about naturally occurrence of nephrotoxicity due to use of gentamicin and phenylbutazone together in calf and in this case report, the authors describe gross and histopathological characteristics of this nephrotoxicity in the affected animal.

MATERIALS AND METHODS

A six weeks old and dead Holstein calf with history of pneumonia and administration of gentamicin and phenylbutazone was referred to Department of Pathobiology, Faculty of Veterinary Medicine, University of Shahrekord. After gross studies, tissue samples were taken from kidneys, liver, lung, heart and abomasum of the animal for histopathological studies. They were fixed in 10% neutral buffered formalin, processed and embedded in paraffin. Sections of 5 μm thickness were cut, stained with haematoxylin and eosin and examined microscopically.

RESULTS

At necropsy, severe bilateral hydronephrosis and renal papillary necrosis (Fig. 1), cranioventral consolidation of lung and hemorrhagic linear erosions on

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the mucosal folds of abomasum (Fig. 3) were seen. The most of renal lobes were as thin walled (2 to 3 mm thick), Fig. 2 and urine filled sacs (Fig. 1 and 2).

Histopathological examination of renal sections revealed decreased thickness of renal cortex and medulla (Fig. 4), tubular epithelial vacuolation and necrosis, infiltration of mononuclear inflammatory cells, interstitial fibrosis and tubular dilation. In the abomasum, numerous

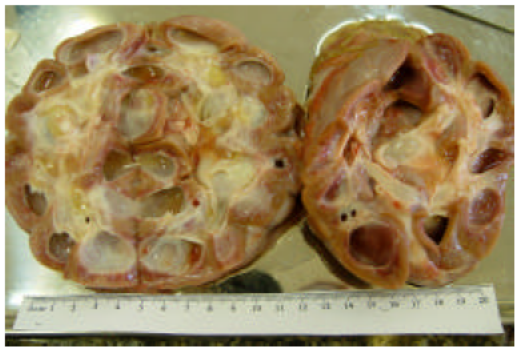

Fig. 1: Severe bilateral hydronephrosis and renal papillary necrosis

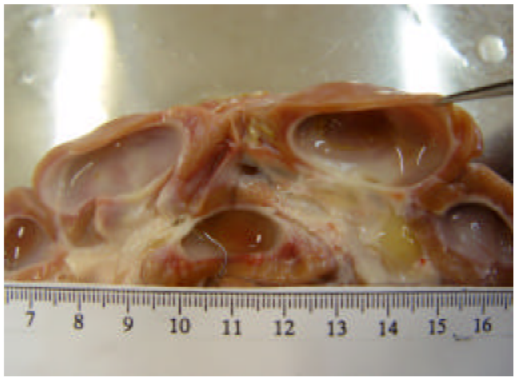

Fig. 2: Renal lobes are seen as thin walled (2 to 3 mm thick) sacs

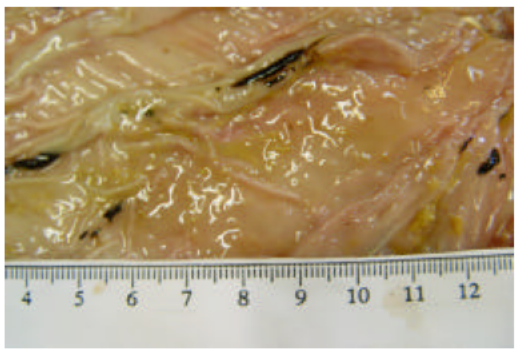

Fig. 3: Hemorrhagic linear erosions on the mucosal folds of abomasum

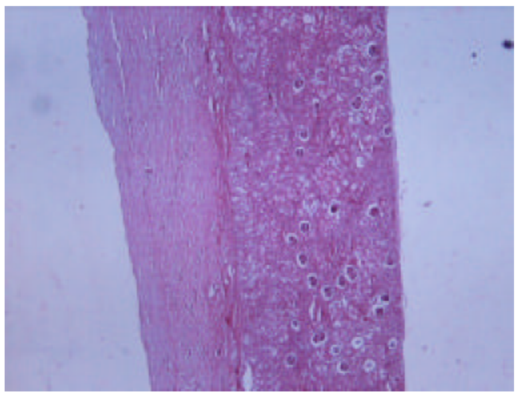

Fig. 4: Severe decreased thickness of renal cortex and medulla (H and E, ×92.5)

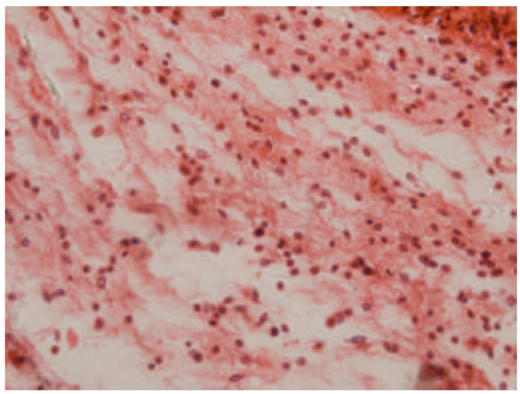

Fig. 5: Infiltration of lymphocytes, plasma cells and macrophages in the tunica submucosa adjacent to the mucosal erosion of abomasum (H and E, ×370)

focal hemorrhages and necrosis of surface and glandular epithelium and infiltration of lymphocytes, plasma cells and macrophages especially in the underlying tunica submucosa were seen (Fig. 5). Midzonal and centrilobular fatty degeneration and necrosis of hepatocytes and severe hemorrhages were observed in liver sections.

DISCUSSION

In this study, severe bilateral hydronephrosis and renal papillary necrosis were observed in the affected case. There was no cause of severe bilateral hydronephrosis such as congenital malformations, calculi and neoplasms on the post mortem examination of the lower urinary tracts. According to the case history and pathological examination, these lesions were ascribed to the gentamicin and phenylbutazone administration.

Treatment with gentamicin and NSAID is known to result in nephrotoxicity and the exact mechanism is still not completely understood. Gentamicin induced nephrotoxicity is a well documented event involving some functional and cellular mechanisms such as glomerular

lesions that interfere with glomerular hemodynamics and altered tubular transport, with the injury ranging from solely functional alterations to necrosis of proximal tubular cells (Hosaka *et al*., 2004). Experimental evidences suggest that generation of reactive oxygen species play an important role in GM nephrotoxicity (Ekor *et al*., 2006; Kuhad *et al*., 2006; Parlakpinar *et al*., 2005).

The main mechanism of action of non-steroidal anti-inflammatory drugs is the inhibition of cyclooxygenase (COX), the enzyme involved in prostaglandin synthesis and their nephrotoxicity is linked to this inhibition (Giovanni and Giovanni, 2002). Two different isoforms of COX have been shown to exist. COX-1 is the main enzyme responsible for the synthesis of renal vasodilator prostaglandins, while COX-2 participates predominantly in the inflammatory process (Hosaka *et al*., 2004; Giovanni and Giovanni, 2002). Nonselective NSAIDs such as phenylbutazone inhibit both cyclooxygenase and nephrotoxicity of them has been well documented (Brideau *et al*., 2001; Harris, 2006; Morton *et al*., 2005). Necrosis of interstitial cells in renal medulla or cyclooxygenase inhibition result in decreased prostaglandin production and lead to decreased vascular perfusion, vasoconstriction and eventually to ischemic renal papillary necrosis (Brix, 2002).

In this case, the hemorrhagic linear erosions of abomasum may be caused by the nonselective inhibition of phenylbutazone. In addition to the role of COX-1 in the renal circulation, it is involved in other physiologic functions such as maintenance of gastric mucosal integrity (Morton *et al*., 2005).

The present results may indicate that phenylbutazone aggravates gentamicin nephrotoxicity in the calf. More studies are needed to reach a definite conclusion about it.

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