

# Sulfamonomethoxine-Induced Urinary Calculi in Pigs

Wei-Dong Sun, Ke-Chun Zhang, Jin-Yong Wang, and Xiao-Long Wang

**Abstract**—The authors report a case of swine urolithiasis caused by improper administration of sulfamonomethoxine and which was diagnosed by examination of urinary sediments and analyzing the composition of the uroliths. The chemical composition of urinary calculi obtained from affected pigs with urolithiasis was further confirmed as sulfamonomethoxine by fourier transform infrared (FTIR). It is suggested that appearance of typical fanlike or wheat buncy crystals in urinary sediments under observation of light-microscope and determination by FTIR for the crystals are helpful in diagnosing sulfa calculi caused swine urolithiasis.

**Keywords**—Calculi, pig, sulfamonomethoxine.

## I. INTRODUCTION

THERE has been a recent increase in the use of sulfamonomethoxine (SMM) to treat *Toxoplasma gondii*, *Streptococcus*, *Escherichia coli*, *Haemophilus parasuis*, and *Pasteurella multocida* in pigs. The drug is potentially dangerous, with toxic effects relating to crystalline aggregate deposition, formation of calculi, and subsequent obstructive nephropathy. We report a case of SMM-induced calculi that was diagnosed by examination of urinary sediments and analyzing the composition of the uroliths. The chemical composition of urinary calculi obtained from pigs with urolithiasis was confirmed as sulfamonomethoxine by fourier transform infrared (FTIR). FTIR and characteristic fanlike or wheat buncy crystals in urine are useful evidences in diagnosing sulfa calculi. To our knowledge, SMM-induced calculi previously had not been reported in pigs.

## II. MATERIALS AND METHODS

Five Yorkshire-Durox cross-bred castrated pigs within a farrow-to-finish herd with 346 commercial crossbred pigs weighting 45-60 kg were admitted to our animal hospital with uneasiness, inappetance, hyponoia, oliguria, attempting to

Wei-Dong Sun is with the Institute of Nutritional and Metabolic Disorders in Domestic Animals and Fowls, Nanjing Agricultural University, Nanjing CA210095, P R China (e-mail: swd100@sina.com).

Ke-Chun Zhang is with the College of Veterinary Medicine, Nanjing Agricultural University, Nanjing CA210095, P R China (e-mail: ngs@sahvet.gov.cn)

Jin-Yong Wang is with the College of Agriculture, Hebei University of Engineering, Handan CA057150, P R China (e-mail: jyw321@163.com).

Xiao-Long Wang is with the College of Veterinary Medicine, Nanjing Agricultural University, Nanjing CA210095, P R China (corresponding author to provide phone: +86-25-8439 5507; fax: +86-25-8439 8669; e-mail: wangxiaolong888@sohu.com).

urinate, and ataxia. The affected pig's medical history included streptococcal disease and toxoplasmosis, which were diagnosed in the third week and the first week before admission. They were started on a regimen of SMM (50 mg/kg-BW) orally twice a day. At the same time, they were injected SMM (50 mg/kg-BW) once a day after toxoplasmosis was diagnosed.

Urinalysis and Serum clinical biochemistry of pigs with urolithiasis was performed according to the method of Kahn et al [1] and McCurnin et al [2].

Uroliths Uroliths were washed well with distilled water, crushed in a mortar and pestle and dried at 105<sup>0</sup>C. Pellets were prepared by thoroughly mixing 1 mg of finely ground urolith with 100 mg of pure, dry potassium bromide (KBr) in a mortar and pestle. This powder was compressed under a vacuum of 50 kPa for 1.5~2 min at 10 tonnes/cm<sup>2</sup> in a KBr die and press. The pellet was then supported in a holder for scanning. The 4000~400 cm<sup>-1</sup> IR region was scanned with NEXUS 870 FTIR (NICOLET), fitted with a 5 transmittance scale expansion device [3].

## III. RESULTS

Important initial laboratory observations were as follows. (1) The urine was turbid, hypersthenuric (specific gravity 1.032~1.041), acidic (pH 4.8~5.4), and positive for protein (+2~+3). (2) Light microscopic examination of urine sediment revealed a mixed cast of white blood cells and tubular cells (Fig. 1a), and tubular cells (Fig. 1b). Numerous fanlike or wheat buncy crystals in the urine were considered to be typical of sulfa crystals (Fig. 1c). (3) Serum biochemical values were within reference ranges with the exception of increases in blood urea nitrogen levels of 11.6~21.3 mmol/L (reference ranges: 2.86~8.60 mmol/L) and in creatinine levels of 261~438 μmol/L (reference ranges: 88~239 μmol/L). (4) When SMM treatment was stopped, affected pigs received adequate hydration, alkalization of the urine, and increasing water intake. By the 10th day, the patient's values of urine and serum biochemistry levels gradually returned toward the reference ranges.

Several affected pigs were euthanised followed the recommendations of the American Veterinary Medical Association. The primary pathologic changes were urolithiasis and the slight pathologic changes attributable to toxoplasmosis. The smallest calculi (0.05~0.1 cm in size) were found in the cortical zone of the kidneys, while larger

calculi (0.43~0.62 cm in size) were found in the medulla (Fig. 2). Dissection of the bladder and urethra revealed one or more calculi in the bladder and the ureters. The calculi exhibited reticular surfaces, were fragile and easily powdered in hardness, and white to yellow in color (Fig. 3).

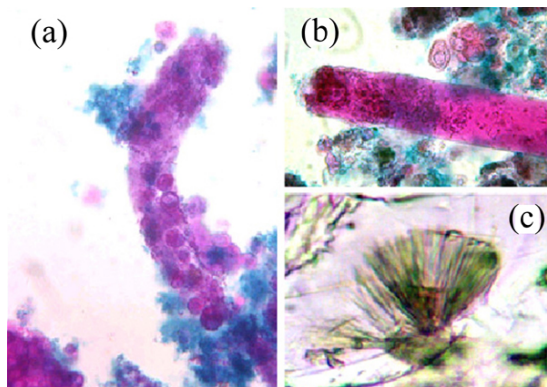


Fig. 1 The results of light microscopic examination results of urinary sediments in pigs (stained by Alcian blue). (a) The mixed cast of WBC and tubular cells; (b) Tubular cells of kidney; (c) Fanlike or wheat buncy crystal of sulfamonomethoxine (SMM)



Fig. 2 Granular uroliths in a section of pig kidney



Fig. 3 Uroliths obtained from the kidney, bladder and ureters of pigs

IR spectra of uroliths were compared with the spectra of pure compounds and mixtures of known composition in the

saddler IR database to confirm the composition of samples as SMM (Fig. 4).

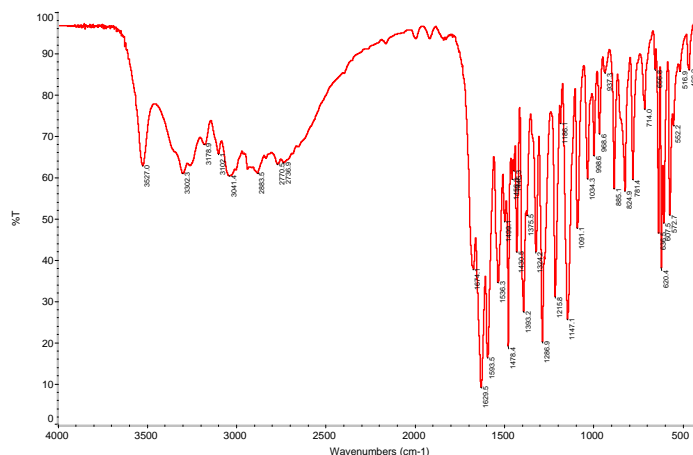


Fig. 4 The FTIR spectrogram of uroliths in pigs

#### IV. MATH

Obstructive urolithiasis has been reported only rarely in neonatal piglets, sows, growing or finishing pigs. The uroliths usually are comprised of uric acid and urate [4], calcium carbonate (calcite) [5], or mixtures of oxalate and carbonate or xanthine and oxalate [6]. Sulfa medications as common antibiotic are used to effectively treat some diseases of animals and human beings. It has long been recognized that the systemic administration of sulfonamides can lead to injury to the urinary tract [7]. The most common and serious toxic reaction relates to obstruction caused by deposition of crystalline aggregates in the renal parenchyma, calyces, pelvis, ureters, and bladder. The cases of obstructing ureteral calculi composed of the sulfamethoxazole-trimethoprim and sulfadiazine-induced obstructive nephropathy were reported [8], [9]. In this case, the reason of the formation of SMM-induced calculi might be related to several factors. (1) The pH value of urine. Sulfa-drugs crystals may develop in acidic urine. Repeated detection of large numbers of sulfa-drugs crystals in fresh urine with low pH value from sick animals should suggested that it is a risk factor for crystalluria. The development of crystalluria depends on the concentration and the solubility properties of the individual sulfa-drugs and their metabolites in the urine, and is more common after parenteral than oral administration. SMM has a relatively low solubility in acidic urine, so that alkalization of the urine can greatly reduce the risk of crystalluria and obstructive calculi. (2) Adverse effects and toxicity. The incidence of adverse reaction depends on the SMM used, the dose and duration of exposure, and the route of administration. Acute toxicity in individuals receiving SMM for the first time is rarely observed; however, if SMM have been previously administered, toxic manifestations may appear within the first 24 or 48 h after institution of therapy. Hypersensitivity reactions are usually encountered after the drugs have been administered for several days to several weeks. (3) Intake of

water. Increasing water intake and therefore increasing the urine volume, with a consequent reduction in the urinary concentration of SMM, reduces calculi formation. In this case, the pigs were fed dry meal, and there was one nipple drinker (1 L/min) per pen which housed 12 pigs. The water originated from a deep pit located on the farm. Affected pigs acutely reduced their water consumption, and in addition the water supply was restricted because of higher temperature around in the farm in the summer. Less severe water deprivation would lead to urine concentration, crystalluria formation, and possibly urolithiasis [5]. (4) Urinary system diseases. In general, urolithiasis is related with the cystitis, pyelonephritis, or vaginal discharge in pigs. Particularly, cystitis caused by persistent *Actinomyces suis*, *Eubacterium suis* and *Corynebacterium suis* colonisation of the bladder leading to necrosis of the uretero-vesicular valves with subsequent ascending infection to the kidney. These factors could provoke the shedding of nephric epithelium, and this condition evidently contributed to changes in kidney function. The cast-off cells also offered convenient sites for calculous nucleation and promoted the occurrence of urolithiasis in pigs.

#### ACKNOWLEDGMENT

The research was supported by the Foundation for Agricultural Innovative Research from Jiangsu Province, China (Grant No. cx(08)135), and supported by the Foundation for University Key Young Teachers from Jiangsu Province, China (Grant No. 2007-2). We thank Dr R.F. Wideman Jr, Professor, Department of Poultry Science, University of Arkansas, Fayetteville, for his help with revising the manuscript.

#### REFERENCES

- [1] C.M. Kahn, S. Line, S.E. Aiello, The Merck Veterinary Manual, 9th ed. Merck & Co., Inc, Pennsylvania, 2005, pp1358-1362.
- [2] D.M. McCurnin, J. M. Bassett, Clinical Textbook for Veterinary Technicians, 6th ed. Elsevier Saunders, St. Louis, 2006, pp184-211.
- [3] R.A. Manning, B.J. Blaney, Identification of uroliths by infrared spectroscopy. Australian Veterinary Journal, 1986, 63: 393-396.
- [4] J. Kakino, R. Sato, Y. Naito, Purine metabolism of uric acid urolithiasis induced in newborn piglets. Journal Veterinary Medical Science, 1998, 60(2): 203-206.
- [5] D. G. Maes, J. Vrielinck, S. Millet, G. P. Janssens, P. Deprez, Urolithiasis in finishing pigs. Veterinary Journal, 2004, 168(3): 317-322.
- [6] J. Smyth, D. Rice, N. Kavanagh, D. Collins, Urolithiasis in weaned pigs. The Veterinary Record, 1986, 119: 158-159.
- [7] L. Weinstein, M. Madoff, C. Samet, The sulfonamides. New England Journal Medicine, 1960, 263: 952-957.
- [8] J. P. Sasson, P. L. Dratch, M. J. Shortsleeve, Renal US findings in sulfadiazine-induced crystalluria. Radiology, 1992, 185: 739-740.
- [9] B. R. Matlaga, O. D. Shah, D. G. Assimos, Drug-induced urinary calculi. Review Urology, 2003, 5(4):227-231.