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ITR Newsletter

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Society of Toxicology Annual Meeting and ToxExpo 2014

The B & I Group (Biology and Zoology Research Center and ITR Canada) will be present at the 53rd Society of Toxicology Annual Meeting and ToxExpo held at the Phoenix Convention Center in Phoenix, Arizona on March 23-27 2014.

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SOT POSTERS

Acute Kidney Injury Biomarkers following Low-Dose Gentamicin Treatment of Rats

The use of biomarkers as part of the preclinical assessment of kidney injury is now a well established goal. Published analysis of multiple datasets from the toxicology industry has convincingly identified a panel of urine and serum biomarkers which correlate with drug induced kidney injury. Several biomarkers have been shown to be superior to blood urea nitrogen (BUN) and serum creatinine at detecting renal injury. The present study correlates histopathologic evidence of kidney damage with urinary and serum biomarkers after very low dose regimens of Gentamicin.

Experimental procedures

Male Sprague-Dawley rats received daily subcutaneous injections of Gentamicin sulfate for 15 days at dose levels of 5, 15, and 50 mg/kg/day. Urine samples were collected over 16 hours for biomarker assessment at multiple timepoints (Pre-Tx, Days 4, 10, and 16). Blood was also collected at the end of a fasting period and serum preserved. A panel of biomarkers was tested in urine (Albumin, B2M, clusterin, cystatin C, KIM-1, NAG, NGAL, OPN, RBP) and serum (BUN, creatinine, and cystatin C). Kidney histology was assessed on days 4 and 16.

Results

Increased excretion of urinary biomarkers was observed on Days 10 and 16 of gentamicin treatment, and was associated with histologic changes on Day 16. Serum and urine creatinine and BUN remained unchanged over the treatment period.

Conclusions

As previously reported, creatinine and BUN levels were insensitive to low levels of acute kidney injury. Increased urine excretion of a group of biomarkers was associated with histopathological findings despite the normal values of creatinine and blood urea nitrogen. These biomarkers are candidate diagnostics and potential surrogates to histological evaluation of acute kidney injury.

Sildenafil Induced Changes in Auditory Brainstem Response in Mice

Auditory brainstem response (ABR) recording in animals is a useful method to investigate ototoxicity of chemicals. Several animals, including rabbits, guinea pigs and rats, are used to investigate ototoxicity. The phosphodiesterase 5 inhibitor sildenafil was reported to induce sudden hearing loss in humans. We used mice in this study to induce hearing loss by small amounts of chemicals and investigated the ototoxicity of sildenafil by ABR recording. B6C3F1 male and female mice were administered 20 mg/kg/day of sildenafil for 2 weeks and then 40 mg/kg/day for an additional 2 weeks. ABR was recorded from 6 male and 6 female mice under isoflurane anesthesia every week during the administration period. Acoustic clicks were delivered through an inner-type earphone, 1000 responses to repetitive stimuli at a rate of 20 Hz were averaged and analyzed for 10 msec. The stimulus intensity was delivered between 20 and 90 dB sound pressure level (SPL). After 7 days of sildenafil administration, a slight increase in amplitude of wave I or II was observed sporadically. This slight change was considered to be a precursory phenomenon of subsequent hearing changes. Then, after 21 days of sildenafil administration (7 days after increasing to 40 mg/kg), the ABR threshold shift rose up to 60 dB SPL and decreased in amplitude, suggesting hearing dysfunction by sildenafil treatment. After 28 days of sildenafil administration, the ABR threshold returned to a normal level; however, the amplitude of waves I and II with 90 dB SPL was rather increased abnormally and the wave pattern was deformed. At this dose level, we could not reveal the effects of sildenafil on the latency of ABR or histopathological changes in the cochlea. These results suggest that sildenafil affects auditory function in mice. Further dose-finding trials would be required.

Comparison of the Expression of ALP Isoenzymes in Serum among Five Animal Species Used in Toxicity Studies

Alkaline phosphatase (ALP, EC 3.1.3.1.) in serum is measured frequently in toxicity studies. ALPs exist widely in the whole body and are highly expressed in the liver, bone, small intestines, kidney and placenta in humans. ALP in serum is the sum of that transferred into the blood stream from organs and tissues. ALP isoenzymes in serum are important items for the evaluation of organ toxicity, but they have not yet been well-examined in experimental animals. In this study, a human serum ALP isoenzyme analysis kit (AlkPhor System, Jokoh Co., Ltd., Tokyo, Japan) for polyacrylamide gel disk electrophoresis was applied to mice, rats, guinea pigs, rabbits and dogs, and the expression of ALP isoenzymes in serum was compared among them. As a result, bone ALP was commonly observed in all animal species examined and it decreased with age. Liver ALP was also common in all animal species. It had less activity in untreated animals, but it remarkably increased in the cholestasis model. Intestinal ALP and high molecular weight intestinal ALP were detected only in rats and decreased by fasting. Intestinal-type ALP was specific to guinea pigs and hardly observed in untreated animals. High molecular weight ALP was specific to rabbits and was low in untreated animals. Atypical ALP was specific to dogs and was identified as bone-type ALP corresponding to the human variant bone ALP isoenzyme. Corticosteroid-induced ALP was also specific to dogs, increased with age, and showed individual differences. As stated above, a total of eight ALP isoenzymes were identified in serum among five animal species. Bone and liver ALPs were common to 5 animal species while the others were found in specific animal species with characteristic nature. The present results strongly suggest that analysis of ALP isoenzymes in serum of animal species used in toxicity studies is important to evaluate toxicities.

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