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Acute Reduction of Glomerular Filtration and Renal Plasma Flow by Telazol in Laboratory Swine

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The goal of this retrospective study was to determine whether having added tiletamine–zolazepam to an anesthetic cocktail of ketamine and xylazine (KX) during an ongoing series of studies of renal function in domestic pigs changed baseline renal hemodynamics. Group A (10 pigs) had been anesthetized with KX, group B (25 pigs) was anesthetized with tiletamine–zolazepam combined with KX (TKX), and group C (10 pigs) was anesthetized with KX. Measurements of baseline glomerular filtration rate (GFR; inulin clearance), effective renal plasma flow (eRPF; para-aminohippuric acid clearance), and mean blood pressure (BP) were made during three 15-min urine collection periods. GFR and eRPF were lower in group B (TKX) than in groups A and C (KX only) by 34% to 40% and 39% to 49%, respectively. BP did not differ between the 3 groups. GFR and eRPF in groups A and C were not different from each other. These findings suggest that adding tiletamine–zolazepam to an anesthetic cocktail can cause an acute decline in GFR and eRPF independent of arterial BP in laboratory swine.

Abbreviations and Acronyms: BP, blood pressure; eRPF, effective renal plasma flow; GFR, glomerular filtration rate; KX, ketamine and xylazine; PAH, para-aminohippuric acid; TKX, telazol with ketamine and xylazine

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Introduction

Telazol was developed in the late 1960s at Parke-Davis Laboratories and consists of a combination of tiletamine, a dissociative anesthetic and NMDA receptor antagonist, and zolazepam, a benzodiazepine tranquilizer.[1] While the prescribing information for tiletamine–zolazepam clearly states that it is for use only in dogs and cats, tiletamine–zolazepam has been used in a wide variety of species including an expansive list of farm animals, wild animals, laboratory animals, and even endangered species.[1]

Before the introduction of tiletamine–zolazepam into our protocol we were engaged in a series of experiments to understand how shock wave lithotripsy and percutaneous nephrolithotomy affect renal structure and function in swine. During these studies, we were asked by our veterinary staff to add tiletamine–zolazepam to our initial anesthetic mixture of ketamine and xylazine (KX) to assure rapid-onset anesthesia with good muscle relaxation.[1] We changed our anesthetic protocol to include telazol with KX (TKX), but over the course of the next year we observed highly variable, and often uniformly low, measurements of both baseline and after shock wave lithotripsy and percutaneous nephrolithotomy treatment values of glomerular filtration rate (GFR) and effective renal plasma flow (eRPF), which defied explanation. A subsequent literature search revealed that tiletamine–zolazepam can be nephrotoxic in some species.[2,3] This finding coupled with our growing concerns about the quality of our clearance data led us to remove tiletamine–zolazepam from our anesthesia protocol and to resume the use of the original KX cocktail, which we use to this day.

We suspected that the TKX cocktail was altering renal function/renal hemodynamics during our experimental protocol beyond what we normally observed with KX alone, so we initiated a retrospective study to compare baseline renal clearance data between pigs that had received KX alone and pigs that had received the TKX cocktail. We chose to only look at baseline clearance values because shock wave lithotripsy and percutaneous nephrolithotomy treatment by themselves alter renal function, which could confound our analysis of posttreatment data.

Our measurements of renal function/renal hemodynamics are based on the renal clearance of infused exogenous tracers, a methodology that has been used for almost 100 y. Among these the clearance of inulin (for GFR) and the clearance of para-aminohippuric acid (PAH) (for renal plasma flow) are considered the 'gold standard' for measuring kidney function.[4] Inulin is a long-chain fructose polymer that is freely filtered and not reabsorbed or secreted by the cells in the kidney and is viewed as a nearly ideal substance to measure the plasma filtration rate taking place in the glomerulus. PAH, on the other hand, is freely filtered and actively (and almost completely) secreted into the urine by the kidney and is used to estimate plasma flow through the kidney. The renal clearance of these tracers (in milliliters per minute) is calculated by measuring the urine concentration of the tracer/arterial concentration of that same tracer and then multiplying that value by the urine flow rate from timed urine collections.

Materials and Methods

Animal procedures. The selection criteria for this retrospective study included using only pigs obtained from the same supplier (Hardin Farms, Danville, IN) and being of the same strain (*Sus domesticus*, Yorkshire × Landrace), age (7 to 9 wk),

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sex (female), and of similar weight (10 to 17.7 kg). The pigs also had to be free of previous or current infections, free of evidence of respiratory distress during the experimental protocol, and had not been involved in any previous surgeries. Using these selection criteria, we were able to identify 25 healthy pigs to include in our group of animals exposed to TKX (group B) over the year it was used. Applying the same selection criteria, we identified 10 pigs that had been studied just before the start of TKX usage (group A) and another 10 pigs from the period just after we had discontinued use of TKX (group C). Group A pigs were chosen starting with the last pig used before switching to TKX and working backward until 10 pigs were identified that met our selection criteria. Likewise, group C pigs were chosen starting with the first pig used after we resumed use of the KX cocktail and working forward until 10 acceptable pigs were identified. We limited the number of pigs in groups A and C to help control for drift in health status over time in the pigs, and for other experiment-related changes such as an alteration in the manufactured lots of inulin (Sigma-Aldrich, St. Louis, MO) or PAH (Sigma-Aldrich, St. Louis, MO), and for any changes in technical staff. We analyzed only the baseline clearance measurements (pre-experimental manipulation) of renal function and blood pressure (BP) for each pig since all the procedures conducted on the pigs to that point were identical and preceded any further surgical or experimental manipulations.

The surgical and animal treatment protocols used to assess renal function changes were carried out in accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the IACUC of the Indiana University School of Medicine. The design of the experiments and all surgical procedures employed during the experiments followed methods used in previously published studies.[5–7] The pigs were injected with a combination of either ketamine (15 to 20 mg/kg) and xylazine (2 mg/kg), or with TKX (0.02 to 0.04 mL/kg), which provided 2 to 4 mg/kg tiletamine–zolazepam (1 to 2 mg/kg tiletamine, 1 to 2 mg/kg zolazepam), 1 to 2 mg/kg ketamine, and 1 to 2 mg/kg xylazine. Once the pigs were unconscious, they were intubated and then maintained on isoflurane anesthesia (2% to 4%). Both flanks of each animal were shaved, and the pigs were placed supine on a surgical table. Respirations were spontaneous. Pigs were covered with a warming blanket to maintain body temperature. A catheter was placed in an ear vein for the infusion of isotonic saline at a rate of 1% body weight per hour and for infusion of inulin and PAH. Next, catheters were placed in a femoral artery, for BP monitoring and blood collection, and in both ureters for timed urine collections. The ureter catheters were tied in place with suture so that no urine leaked around the catheters. Additionally, all surgical incisions were closed with sutures to prevent tissue desiccation and fluid loss. Once the inulin and PAH infusions had approached steady-state concentrations, three 15-min urine collections were obtained. Blood samples were collected at the beginning and end of each urine collection interval. Normally, the time between the injection of TKX or KX cocktail until all surgical procedures were completed and vital signs were stable enough to start renal clearance measurements was 1.5 to 3 hours.

Renal clearance analysis. The concentrations of inulin and PAH in the collected urine and plasma were determined colorimetrically[8,9] and were used to calculate the clearances of inulin (for GFR) and PAH (for eRPF). These individual values were averaged over the entire collection period to arrive at a single estimate of renal function for each kidney. Total GFR and eRPF for each pig were calculated by adding the values for both kidneys together.

Data analysis. All of the figures show data expressed for each pig (filled circles) for the combined clearance periods.

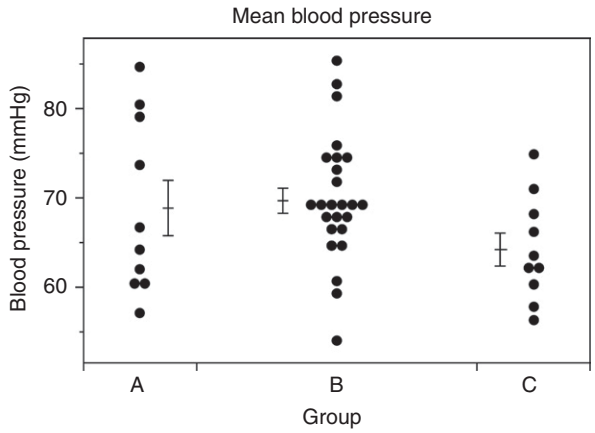

Figure 1. Mean BP measured in group A (n = 10), group B (n = 25), and group C (n = 10). Each circle represents the average BP measured during the clearance period in one pig. The error bars adjacent to the circles indicate the mean and 1 SEM for that group.

For statistical calculations, the mean values for each pig were averaged to arrive at an overall mean ± SEM (shown as a black line with error bars in the figures) for all of the pigs in each group. One-way ANOVA with the Tukey–Kramer honestly significant difference method for post hoc comparisons was used to compare the baseline values for each variable between each of the 3 groups of pigs. Two-sided P values <0.05 were considered to indicate a significant difference for these values. In addition, linear regression analysis was done to determine whether there was any relationship between BP and GFR or eRPF, with P values <0.05 indicating a significant difference.

Results

Linear regression analysis (data not shown) did not show any relationship between BP and GFR or eRPF for all pigs in the study, or for group B pigs alone (GFR, P = 0.71 and P = 0.36; eRPF, P = 0.15 and P = 0.79). Mean BPs between the groups (Figure 1) were similar at the time the urine and blood samples were taken, and averaged 68.9 ± 3.1 mmHg in group A, 69.7 ± 1.4 mmHg in group B, and 64.2 ± 1.9 mmHg in group C (P = 0.16).

GFR was significantly lower (by 34% to 40%) in group B than in groups A or C (P = 0.0035 and P = 0.0002, respectively, Figure 2). GFR averaged 20.8 ± 1.6 mL/min in group A, 13.7 ± 0.8 mL/min

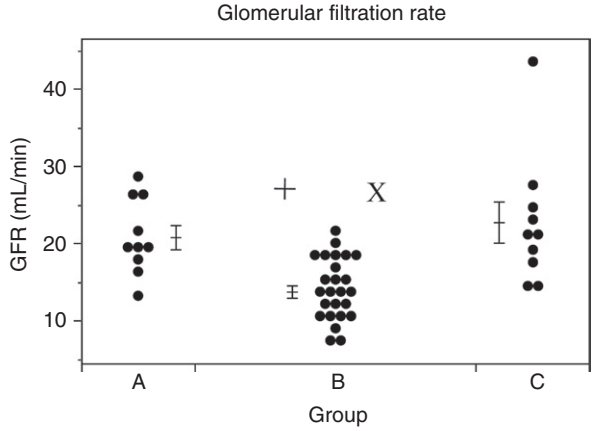

Figure 2. GFR measured in group A (n = 10), group B (n = 25), and group C (n = 10). Each circle represents the average GFR during the clearance period in one pig. The error bars adjacent to the circles indicate the mean and 1 SEM for that group. +, P = 0.0035 comparing group A to group B; X, P = 0.0002 comparing group B to group C.

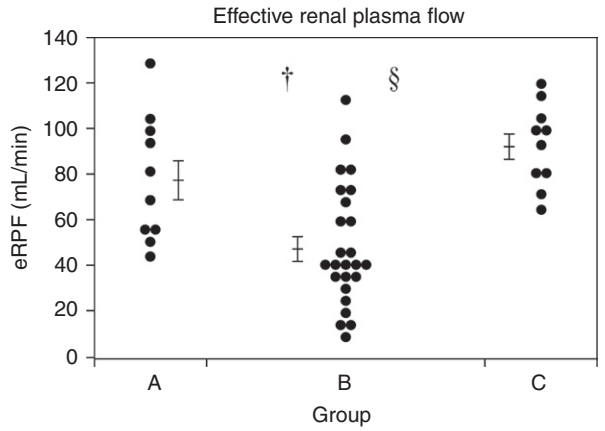

Figure 3. eRPF measured in group A (n = 10), group B (n = 25), and group C (n = 10). Each circle represents the average eRPF during the clearance period in one pig. The error bars adjacent to the circles indicate the mean and 1 SEM for that group. †, P = 0.0076 comparing group A to group B; §, P < 0.0001 comparing group B to group C.

for group B, and 22.7 ± 2.7 mL/min in group C. GFR was not significantly different between groups A and C (P = 0.70).

Likewise, eRPF was significantly lower (by 39% to 49%) in group B than in groups A or C (P = 0.0076 and P < 0.0001, respectively, Figure 3). eRPF averaged 77.4 ± 8.6 mL/min in group A, 47.3 ± 5.4 mL/min in group B, and 92.1 ± 5.5 mL/min for group C. eRPF was not significantly different between groups A and C (P = 0.40). Interestingly, there is a rather large spread in the data shown for group B in Figure 3. While the overall mean eRPF is significantly lower in group B compared with the other groups, at least 6 eRPF values in group B pigs are distributed within 1 SEM or above that of group A. This is more than what was observed in group B pigs related to GFR (Figure 2) and could suggest a possible difference in the effect that TKX has on eRPF compared with GFR.

Discussion

As mentioned above, we added tiletamine–zolazepam to our anesthetic cocktail of KX on the recommendation of our animal care veterinarians for approximately 1 y, but subsequently returned to KX alone after we became concerned about the effects that tiletamine–zolazepam may be having on renal function in our swine. Our analysis of the data obtained from animals in groups A and C (KX alone) and group B (TKX) suggests that tiletamine–zolazepam reduced both GFR and eRPF when added to our anesthetic cocktail. While this statement holds true for GFR and almost all pigs when it comes to eRPF, 6 pigs appeared to maintain normal eRPF after TKX injection (Figure 3). This observation is puzzling but could indicate natural variability in the response to tiletamine–zolazepam when it comes to eRPF. Alternatively, this observation could indicate that a threshold must be reached before a decline in eRPF is initiated. In any case, our retrospective analysis cannot explain this result.

A decrease in eRPF and GFR can be the result of a fall in BP, as a loss of fluid driving pressure interferes with normal renal blood flow and filtration. Intriguingly, a significant acute decline in systolic BP has been observed in pigs after receiving tiletamine–zolazepam.[10] However, a BP difference was not observed in our pigs, as the mean BPs (Figure 1) during the urine collection periods were comparable between all groups.

The decline in GFR and eRPF that we observed in group B seems unrelated to reduced BP, so what other factors might be involved? When tiletamine–zolazepam was added to our anesthetic cocktail, the pigs in that group experienced an overall fall in GFR and eRPF. Moreover, this effect followed from only a single dose of TKX, and it began in as little as 1.5 to 3 h after injection. Since these animals had no prior exposure to tiletamine–zolazepam, it seems unlikely that the pigs were having a hypersensitivity reaction to one or both drugs in tiletamine–zolazepam. Moreover, this effect occurred in a relatively short timeframe (minutes) and suggests that increased vascular tone and/or decreased glomerular capillary permeability were driving the change in hemodynamics rather than drug-induced renal tubular necrosis, which requires hours to days to disrupt GFR and eRPF.[11] Interestingly, both tiletamine and zolazepam are known to take several minutes to reach high concentrations in the blood after intramuscular injection. Zolazepam takes 65 min to reach its maximum concentration while tiletamine requires only 32 min to reach its maximum in swine.[12] Our renal collections did not begin until 90 min or more after TKX injection, so the concentration of both drugs would have peaked before our collections of urine and blood began. Moreover, both drugs should have remained at high concentrations throughout our collection period, as the plasma half-lives for zolazepam and tiletamine in swine are 8.4 and 3.7 h, respectively.[12]

What mechanisms could account for such a rapid change in renal function/renal hemodynamics, as the effect must have occurred soon after the injection of the TKX? As mentioned above, tiletamine is an NMDA receptor antagonist. NMDA receptors are widely expressed in the CNS and have also been found in the kidneys of several mammalian species. So far, NMDA receptors have been identified in rats, mice, the opossum kidney cell line, and the Madin-Darby canine kidney cell line.[13,14] We suspect that these receptors will also be found in pig kidneys. Experiments by Deng and colleagues showed that when renal NMDA receptors were stimulated, renal blood flow and GFR increased within minutes after stimulation.[15] This effect occurred even if the treated kidneys were denervated, which suggests that renal NMDA receptors can operate independently of renal nerves and are normally found on cells in the kidney. Deng and colleagues also showed that inhibition of NMDA receptors by glycine antagonists or NMDA channel blockers significantly reduces renal blood flow and GFR.[15]

Our experience with TKX is not the first time that tiletamine–zolazepam, whether alone or part of an anesthetic cocktail, has been found to alter renal function in laboratory animals.[2,3] Brammer and colleagues reported that tiletamine–zolazepam given alone increased BUN and serum creatinine in New Zealand white rabbits within 2 d after injection, and these blood markers continued rising through day 6 when the experiment was terminated.[2] Doerning and colleagues later reported that tiletamine was the likely cause of the observed change in BUN and creatinine.[3] In addition to the complications listed above, tiletamine–zolazepam usage has been linked to a number of adverse effects in healthy animals and, because it is primarily excreted by the kidneys, it should be used with caution in animals with renal dysfunction.[16,17]

Our data do not allow us to determine that only a single component of TKX caused the changes in renal function that we are reporting in this study. Even so, it seems reasonable to suspect that tiletamine is responsible since it impaired renal function in rabbits.[3] It is also conceivable that ketamine worked synergically with tiletamine to depress renal function in our pigs since ketamine is also an NMDA channel blocker.[18] In addition to not being able to link an individual component of TKX to

the decline in renal function in our analysis, neither could we determine how long the functional decline persists, or if there is a threshold dose for this effect in swine. Another limitation to our study concerns the use of only female pigs. While we do not have any reason to suspect that male pigs will behave differently from female pigs when it comes to the response to TKX, additional studies with male pigs will need to be done before we can be certain that all pigs respond the same to TKX exposure.

Perhaps the most troubling aspect of our analysis, if it is confirmed, is the potential impact that the extralabel use of tiletamine–zolazepam may have on any study involving swine. If the outcome of a particular experiment could be altered by an acute change in renal function, conclusions drawn from those experiments could be invalid. Because of this concern, we advise investigators to carefully reevaluate their data in light of our findings if tiletamine–zolazepam was part of their experimental protocol.

Conclusions

In conclusion, our findings suggest that tiletamine–zolazepam should not be used for anesthetic induction in swine for studies of renal function and/or renal hemodynamics because of its apparent ability to cause acute, bilateral reductions of GFR and RPF. Whether this effect is transient, long-lasting, or permanent, and whether it is also associated with tissue injury in swine remain to be determined. In addition, we think that further studies are needed to confirm our findings and to determine the long-term safety of tiletamine–zolazepam in swine.

Conflict of Interest

The authors have no conflicts of interests to declare.

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