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REVIEW

Rat models of colistin nephrotoxicity: previous experimental researches and future perspectives

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Abstract

Colistin is an old antibiotic, which is abandoned decades ago because of high nephrotoxicity rates. However, it is reintroduced to clinical medicine due to lack of newly discovered antibiotics and is still widely used for the treatment of resistant gram-negative infections. Discovering mechanisms to reduce nephrotoxicity risk is of significant importance since exposed patients may have many other factors that alter kidney functions. Several agents were evaluated in animal models of colistin nephrotoxicity as a means to prevent kidney injury. Considerable heterogeneity exists in terms of reporting colistin dosing and experimental designs. This issue leads clinicians to face difficulties in designing studies and sometimes may lead to report dosing strategies inadequately. Here, we present a review according to animal models of colistin nephrotoxicity using data gathered from previous experiments to draw attention on possible complexities that researchers may encounter.

Keywords Animal model · Colistin · Nephrotoxicity

Introduction

Polymyxins are a separate class of antibiotics discovered in 1950s for the treatment of gram-negative infections [1]. Various forms used in different countries include polymyxin B and colistin (polymyxin E). Although they have similar chemical structures and mechanisms of action, pharmacokinetics and pharmacodynamics differ considerably between two forms. Colistin was removed from the market because of significant nephrotoxicity [2]. Yet, lack of newly discovered antimicrobial agents lead to reintroducing colistin to the clinical practice. Colistin is now used as the last-line treatment of resistant gram-negative bacterial infections including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Infections with these species comprise a considerable percent of mortality in critically ill patients. This explains why colistin is still widely used despite significant nephrotoxicity risk.

Most of previous animal models were performed using colistin rather than polymyxin B. Here, we present literature data regarding to animal models of colistin nephrotoxicity most of which were designed to test efficiency of various agents against kidney injury.

Colistin formulations

Various colistin formulations are available in clinical practice. Colistimethate sodium (CMS) is a nonactive prodrug and following administration it converses to the active form—colistin—endogenously [3]. Although different brands of CMS from various parts of the world have similar elemental compositions, they lead to different exposures to the microbiologically active formed colistin [4]. A more important issue is reporting the administered colistin dose. There is an extensive variability between studies in terms of reporting colistin dosing, and inconsistency with current dose conversion recommendations was determined in 29% of papers [5].

One milligram of colistin base is contained in 2.4 mg of CMS, and CMS has a potency of 12,500 IU/mg. Use of international units rather than milligrams was highly suggested to use correct dosing and avoid confusion [6]. However,

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confusion still may exist since there are many formulations and units [7]. Dosing information is expressed in terms of colistin base in some countries. Clearly, there is a multiplicity in expressing colistin doses around the world. This issue was discussed at the "First International Conference on Polymyxins" in 2013 by international leaders in the field and the "Prato Polymyxin Consensus" was released [8]. Experts concluded that the major problem relating to colistin dosing was because of confusing terminology used in articles published in journals, and they recommended that an equivalence between the two primary conventions (e.g., 1 million IU is equivalent to approximately 30 mg of colistin base activity) should be provided in the "Materials and methods" section. It was stated that in other parts of the article (e.g., Introduction, Results, Discussion), authors and journals should cease reporting doses in terms of milligrams of CMS, and colistin doses should be expressed in terms of the primary convention used in the region of the world where the study was performed (i.e., number of IU or milligrams of colistin base activity).

Great care is needed while reporting doses and formulations used in studies. For instance, in several papers, it was suggested that colistin was prescribed to rats in a dose of 450.000 IU/kg/day. The formulation they used is actually CMS, rather than colistin and the dose 450.000 IU/kg/day equals to 36 mg/kg/day of CMS. If the dose is to be expressed for colistin, it should be 15 mg/kg/day which equals to 36 mg/kg/day of CMS. This may lead to mistakenly prescribe 2.4 times the intended colistin dose. Similar confusions lead to patient death and alerts were given to prevent serious medication errors [9].

Mechanisms of nephrotoxicity

CMS is filtered by glomerulus and secreted by tubules. It is predominantly cleared by the kidneys. However, most of colistin that is generated by CMS endogenously that is filtered into tubular urine is reabsorbed [3]. Indeed, the fraction of filtered colistin that undergoes reabsorption is comparable to, or greater than, the fractional reabsorption of filtered water, consistent with the reabsorption of colistin involving a carrier-mediated process.

In rats administered colistin (sulfate) intravenously twice daily for 7 days, the ratio of the average concentration of colistin in kidney homogenate to that in plasma after the final dose was 65.7. The ratios for kidney were substantially higher than those for the heart, lung, liver, spleen, and muscle. Immunostaining studies of sections of rodent kidneys from animals treated with polymyxin B have shown that accumulation occurs predominantly in the renal cortex, and more specifically within proximal tubular cells [10] where transporters that have tendency to bind polymyxins reside [3].

Since colistin has cationic polypeptides, it interacts with anionic structures in tubular cell membrane leading to increased permeability and cell lysis. This mechanism also represents the antimicrobial activity of the drug. Cationic molecules inside the drug lead to detachment of bacterial membrane via interacting with anionic lipopolysaccharide molecules in the outer membrane of gram-negative bacteria [11]. Other mechanisms of nephrotoxicity include apoptosis [12, 13], altered nitric oxide balance [14, 15], mitochondrial dysfunction [16], and oxidative stress [17, 18]. In proximal tubular cell culture colistin downregulated P-glycoprotein expression in proximal tubular epithelial cells and caused nephrotoxicity [19]. Using P-glycoprotein inducers altered nephrotoxicity. Megalin, an endocytic receptor expressed at the apical membranes of proximal tubules and mediates nephrotoxicity of aminoglycosides, was also studied in colistin exposed mice, and megalin knockout mice treated with colistin were free of renal tubular injury while megalin-replete proximal tubule epithelial cells exhibited signs of injury [20]. In addition, colistin-induced nephrotoxicity was prevented using silastatin, an agent that blocks megalin. Coadministration of megalin ligands and colistin resulted in urinary *N*-acetyl-β-D-glucosaminidase (NAG) excretion [21]. These findings highlighted the role of tubular transport mechanisms on colistin-induced nephrotoxicity.

Based on these observations, many agents with antioxidative effects were used experimentally to prevent nephrotoxicity following colistin administration [15, 17, 18, 22–33].

Animals

Previous researches were performed using various mice strains, Wistar rats or Sprague-Dawley rats. There is no data to suggest particular genre of animal to use while performing study about colistin nephrotoxicity. More sophisticated methods are needed to analyze blood biochemistry in mice since much lower amount of blood is gathered. Because Wistar rats have better vasculature, studies about stroke or ischemic conditions are better performed in these types of rats [34]. Wistar rats also have more superficial glomeruli [35]. The significance of these structural differences in terms of designing colistin nephrotoxicity model is not studied.

In researches where rats were used, almost all animals were male while authors used female Sprague-Dawley rats in a study [29]. On the other hand, studies differed for animal gender where mice were used. There is no clear data to support use of a particular gender of animal. Although female mice are generally more resistant to ischemic acute kidney injury than males, they are more prone to develop acute kidney injury following *cisplatin* administration [36]. Animal age is another factor that may affect kidney injury. For instance, ischemic acute kidney injury is affected by the animal age in

mice. Yet, animals with similar ages should be used in colistin nephrotoxicity model [36].

Differences between animals in terms of activity and behavior may also be of particular importance in nephrotoxicity models. Mice are more active during the night so they consume more water at the dark period of light-dark cycle. So, mice housed under 12:12-h light-dark cycle are more volume depleted in the afternoon than in the morning [36]. Although this is the case for particularly ischemia experiments, the same may be valid for nephrotoxic injury models. Ideally, weights of animals should be evaluated in a daily basis. Equal total volumes should be prescribed to all groups to better prevent effects of volume disturbances on organ functions. Rate of metabolism of an animal's system can also induce or minimize toxicity [37].

Route of administration and dosing

Since oral bioavailability of colistin is very poor [38], it is administered parenterally. Complications may be observed following parenteral drug administration including local irritation, pain, infection, and damage to the surrounding tissue. Every route has its particular advantages and drawbacks [37]. Intramuscular administration can lead to muscle necrosis and inflammation of the nerves. It is also hard to use and needs experience. Asepsis is critical if intravenous route is to be used to prevent possible septicemia. Agents may precipitate following mixing with blood and cause vascular occlusion. Jugular venous catheter may be required for repeated intravenous drug delivery.

The most frequently used route of administration in previous colistin nephrotoxicity models was intraperitoneal. Intraperitoneal administration is simple and does not require sedation; however, care should be taken against peritonitis development. Although it is easy to deliver drugs intraperitoneally, accuracy of administration is not clear. Materials can be injected in gastrointestinal tract, subcutaneously, retroperitoneally, or into the bladder [39]. Preliminary dosing strategies maybe helpful in both determining colistin dose and also dose and timing of the drug which is used for the prevention.

Based on dosing used in previous researches, it seems that Sprague-Dawley rats are more susceptible to renal injury of colistin compared to Wistar rats. The most frequently used amount of CMS was 300.000 IU/kg/day for the former [14, 32], while higher doses were needed for the latter rats [28].

Previous reports showed that the dose used in preliminary study maybe low that no kidney injury can be established histologically. The dose can also be high leading to altered vital signs of animals. Although nephrotoxicity is a well-known side effect of colistin, neurotoxicity may also be subtle leading to dose reductions in experimental models. Keirstead et al. observed decreased motor activity, cyanosis, and cold extremities in rats following intravenous colistin administration in their preliminary work [40]. This observation leads to authors to change the route of administration and use colistin subcutaneously. Dosing strategies used in experimental colistin nephrotoxicity models is presented in (Table 1).

Volume of total drug to be administered is of significant importance. Total volume administered should be kept minimum to avoid hypervolemia. General suggestions for volume and sites of routes are as follows [41]: intraperitoneally 10 mL/kg, intravenous up to 5 mL/kg (bolus) (tail or saphenous vein), intramuscular maximum of 0.05 mL/kg per site (triceps, quadriceps, dorsal lumbar, semimembranosus, semitendinosus muscles), and subcutaneous maximum of 5 mL/kg per site (intrascapular, neck, shoulder, flank). Smaller volumes over multiple injection sites minimize adverse reactions and can be used in subcutaneous or intramuscular drug administration. It is possible to give colistin within these cut-off levels for maximal volume of materials to be administered.

Duration of treatment and determination of nephrotoxicity

Animal models are of significant importance since they let researchers clarify disease pathogenesis using methods that are not suitable to perform on human subjects. However, experiments should have reproducibility and validation criteria should be better used when designing an experiment on animal models. For instance, to study a diabetic nephropathy in mice, one should know that there are functional and histopathological properties expected to be observed [42].

Kidney biopsy is not routinely performed for patients under colistin treatment. Up to now, models were set on the basis of administering colistin in a daily basis resulting with biochemical and histological signs of nephrotoxicity.

Colistin nephrotoxicity is dose dependent and is reversible following drug cessation [43]. Studies in human reveal that median time to acute kidney injury is 3 days [44]. It is also suggested that nephrotoxicity occurs in the first 5 to 7 days of drug commencement [45]. Colistin was administered for 6 to 14 days in different experiments. Histological findings of nephrotoxicity were established in all these papers while some of them revealed abnormalities in biochemical markers of kidney injury. In the study of Hakim et al., colistin did not exert histologically detectable kidney damage following 15 days of administration [46]. However, they used CMS in a dose of 300,000 IU/kg/day intramuscularly, a dose that was significantly lower than the dose used in more recent experiments performed in Wistar rats. In addition, how histological examination was evaluated and graded was not reported in detail.

Experimental studies showed that serum creatinine is not sensitive enough to show toxicity especially in first days of

Table 1 Data according to previous experimental protocols about animal models of colistin nephrotoxicity

Reference	Animal	Route	Dosing	Duration	Preventive	Biochemical Evaluation			Anesthesia	Preliminary study	PK study
						Blood	Urine	Tissue			
Edrees et al. [30]	Male Wistar rats	Intraperitoneal	300,000 IU/kg/day CMS	6 days	Curcumin (oral)	SCr, urea, uric acid	Not studied	MDA, NO, TNF-α, IL-6, caspase-3 expression CAT, GSH, Bcl-2 expressions brain GABA levels	Not reported	No	No
Ceylan et al. [15]	Male Wistar rats	Intraperitoneal	300,000 IU/kg/day CMS	10 days	NAC (30 min prior to CMS)	SCr	NAG	SQS, apoptosis, total oxidant and antioxidant status, eNOS, SOD2, MMP3	Ketamine-xylazine	Yes	No
Sivanesan et al. [31]	Female Swiss mice, and male Sprague-Dawley rats	Subcutaneous	Colistin sulfate; cumulative dose of 84 mg/kg	1 day (14 mg/kg every 2 h)	Gelofusine (simultaneously IP)	Not studied	Not studied	SQS	Isoflurane	Yes	Yes
Yousef et al. [32]	Male Sprague-Dawley rats	Intravenous	Colistin sulfate cumulative dose of 36.5 mg/kg	7 days	Melatonin 20 min prior to colistin	SCr colistin	NAG colistin	SQS, SOD colistin	Not reported	Yes	Yes
Yousef et al. [33]	Male Sprague-Dawley rats and PTC culture	Intravenous	Colistin sulfate cumulative dose of 36.5 mg/kg	7 days	ascorbic acid 20 min prior colistin	SCr colistin	NAG colistin	SQS colistin	Not reported	Yes	Yes
Dai et al. [18]	C57BL/6 mice	Intraperitoneal	Colistin sulfate 18 mg/kg/day	7 days	Baicalein (oral) 2 h prior to colistin	SCr and BUN	Not studied	SQS and oxidative stress biomarkers caspase-9 and caspase-3 activities, TNF-α, IL-1β	Sodium pentobarbital	No	No
Dai et al. [17]	Adult Kunming mice	Intravenous	Colistin sulfate 15 mg/kg/day	7 days	Lycopene (oral) 2 h prior to colistin	SCr and BUN	Not studied	SQS oxidative stress biomarkers caspase-3, caspase-9, and HO-1	Not reported	No	No
Arslan et al. [27]	Male Wistar rats	Intraperitoneal	480,000 IU/kg/day CMS	7 days	Luteolin, 4 h prior to CMS	Not studied	Not studied	SQS TUNEL assay	Ketamine-xylazine	No	No
Ghlissi et al. [28]	Male Wistar rats	Intramuscular	300,000 and 450,000 IU/kg/-day CMS	7 days	Vit. E, astaxanthine, and olive oil by oral gavage	SCr and GGT	Not studied	Histological analysis, oxidant and antioxidant parameters	Ketamine	No	No
Ozkan et al. [14]	Sprague-Dawley rats	Intraperitoneal	300,000 IU/kg/day CMS	6 days	Grape seed proanthocyanidin extract (GSPE) by oral gavage	SCr and BUN	Not studied	SQS oxidant and antioxidant parameters; TUNEL assay for apoptosis; immunohistochemical analysis for iNOS, eNOS, caspase-3, caspase-1, and calpain 1.	Ketamine-xylazine	No	No
Ozyilmaz et al. [29]	Female Sprague-Dawley rats	Intraperitoneal	300,000 IU/kg/day CMS	6 days	NAC	BUN, SCr TNF-alpha	SCr	Oxidant and antioxidant parameters	Ketamine-xylazine	No	No

BUN blood urea nitrogen, *CAT* catalase, *CMS* colistimethate sodium, *eNOS* endothelial nitric oxide synthase, *GABA* gamma butyric acid, *GGT* gama-glutamyl transpeptidase, *iNOS* inducible nitric oxide synthase, *MDA* malondialdehyde, *MMP* matrix-metalloproteinase, *NAC* N-acetylcysteine, *NAG* N-acetyl-β-D glucosaminidase, *SCr* serum creatinine, *SOD* superoxide dismutase, *SQS* semiquantitative score, *TUNEL* terminal deoxynucleotidyl transferase dUTP nick end labeling

treatment [27]. Various urinary kidney injury biomarkers started to increase in day 2 in Wistar rats following the first subcutaneous colistin dosing in the study of Keirstead and colleagues [40]. Urine was collected from animals following housing in metabolic cages for 6 h of a 24-h cycle. Authors performed an extensive analysis of up-to-date urinary biomarkers including kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Sensitivity of serum creatinine for the diagnosis of kidney injury in colistin-treated rats was 88.8%, while KIM-1 and alpha-glutathione S-transferase showed 100% predictive sensitivity. One of the conclusions authors made was that these urinary kidney injury biomarkers are highly sensitive and can be used to differentiate between polymyxin analogs with varying nephrotoxicity.

Ghlissi and colleagues concluded that plasma cycstatin C is more reliable than plasma creatinine to establish kidney injury and urinary NGAL was the most sensitive marker according to their research [47]. Yet, authors stated that histopathologic assessment remained the most accurate method to detect nephrotoxicity.

Most previous reports still reveal that histological evaluation is the most sensitive way of determining kidney injury since many authors could not observe a significant increase in serum creatinine and urinary biomarkers were not measured in most of them. Semiquantitative score (SQS) is the most frequently used histological scoring system in previous experimental studies on colistin nephrotoxicity. Histopathological evaluation is performed as grade 1, mild acute tubular damage with tubular dilation, prominent nuclei, and a few pale tubular casts; grade 2, severe acute tubular damage with necrosis of tubular epithelial cells and numerous tubular casts; and grade 3, acute cortical necrosis/infarction of tubules and glomeruli with or without papillary necrosis. The grades are scored as grade 1 = 1, grade 2 = 4, and grade 3 = 10. The percentages of the kidney slices affected are scored as $< 1\% = 0$, 1 to $< 5\% = 1$, 5 to $< 10\% = 2$, 10 to $< 20\% = 3$, 20 to $< 30\% = 4$, 30 to $< 40\% = 5$, and $\geq 40\% = 6$. The overall score is calculated as the product of percentage score and grade score. Finally, a semiquantitative score (SQS) for renal histological changes is assigned as follows: SQS 0 = no significant change (overall score, < 1); SQS + 1 = mild damage (overall score, 1 to < 15); SQS + 2 = mild to moderate damage (overall score, 15 to < 30); SQS + 3 = moderate damage (overall score, 30 to < 45); SQS + 4 = moderate to severe damage (overall score, 45 to < 60); and SQS + 5 = severe damage (overall score, 60).

SQS seems to be convenient and applicable for nephrotoxicity determination and grading in animal models of colistin nephrotoxicity. Ideally, electron microscopic evaluation should be routine part of the histological evaluation to increase sensitivity for detection of renal injury.

Designing control groups and efficient preventive agents

Previous researches were set as to have usually four groups as follows: group 1 = colistin, group 2 = preventive agent + colistin, group 3 = preventive agent and, group 4 = control group. Sodium chloride (0.9%) is usually administered to control groups. Preventive agents were given usually 20 min to 4 h prior to colistin (Table 1). Experiments can be designed in more than four groups with different dose ranges [24], while the protocol was set in three groups in several papers [14, 29].

Although many studies established the protective roles of various agents against colistin nephrotoxicity, only few searched pharmacokinetic interactions between the agent used for prevention and colistin. This issue may be of considerable value to identify unpredictable drug toxicity or colistin underdosing. This is discussed in some of previous papers. Sivanesan and colleagues determined the nephrotoxicity via only SQS without measuring kidney injury markers in blood or urine samples [31]. However, they used rats also to search how the protective agent (gelofusine) affects colistin pharmacokinetics. They extensively studied pharmacokinetic parameters including clearance, volume of distribution, elimination half-life, area under the curve, urinary recovery of the unchanged colistin, renal clearance, and plasma protein binding. It was concluded that gelofusine significantly lowered the accumulation of colistin in kidneys of mice and its administration did not alter colistin pharmacokinetics in rats. In the study of Yousef et al., authors found a significant pharmacokinetic interaction between ascorbic acid and colistin despite ascorbic acid reduced colistin exposure of renal tubules [33].

Anesthesia

Previous studies in colistin nephrotoxicity frequently used ketamine and xylazine for anesthesia (Table 1). Anesthesia is used only prior to sacrification in many of these researches. Type of anesthesia maybe of importance if blood is to be taken days before sacrification. For instance, isoflurane has been shown to have nephroprotective effects. Use of isoflurane anesthesia in the middle of the experiment for drawing blood may exert nephroprotective effects in the remaining time of the protocol [48].

Wei and colleagues reported mortality following ketamine-xylazine anesthesia and authors stated that phenobarbital may lead to mortality occasionally if the dosage is not well controlled [49].

Yet, in these experiments, type of anesthesia was of significance value to provide enough time for surgical procedures without compromising organ functions and vital signs. This is not the case in colistin nephrotoxicity models. Currently,

ketamine and xylazine seem to be enough for anesthesia in colistin nephrotoxicity models.

Conclusion

Much work is needed in the field of colistin nephrotoxicity. Previous preclinical study designs in acute kidney injury were criticized for lack of reproducibility and transparency (no mortality reports), reporting only positive outcomes and no documentation that the investigators were fully blinded to treatment groups and statistical power [50]. These considerations should also be taken into account prior to designing an experimental study about colistin nephrotoxicity. Several authors were able to design colistin nephrotoxicity model more than once with similar experimental protocols [24, 33].

It seems that colistin will still be used for a considerable length of time particularly in critically ill patients since it has no alternative. So, special approaches that may alter nephrotoxicity rates even mildly should be established. Animal studies are important in understanding pathophysiological pathways of human diseases. However, well-described standardized validation criteria must be set to allow reproducibility, reduce cost, and stop time-wasting. There is no validation on methods of developing experimental colistin nephrotoxicity model. Yet, it seems prudent to perform a preliminary research to determine the most ideal colistin dosing strategy for particular routes of administration. Although histology is indispensible for assessing nephrotoxicity, next-generation urinary biomarkers are quite sensitive and applicable. Authors should comply with recommendations in terms of reporting colistin dosing [8].

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