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Histopathological Comparison of Gentamycin and Amikacin Nephrotoxicity in Rabbits

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Abstract: Gentamycin and Amikacin are 2 of the most important antibiotics of Amynoglycosides family. They are most effective on gram-negative bacteria but one problem limiting their usages is their nephrotoxic effects on kidneys. Regarding to the proved higher wide-spread bactriocidal activity of Amikacin than Gentamycin, researchers were about to compare their nephrotoxocity level so that if Amikacin's lower nephrotoxicity effect can be proved, it will be the choice antibiotic between these two. About 48 rabbits were divided in 3 groups based on time (days 3, 7 and 14). In every group, 6 rabbits were injected by Gentamycin, 6 rabbits were injected by Amikacin and 4 as control group. Injections were done once in a day. About 24 h after the last injection, the rabbits were sacrificed and histopatholgic slides were provided from their kidneys. The slides were examined on the necrosis severity based on some measures (mentioned in the full text). The results after being statistically analyzed ($p<0.05$) showed a remarkable and significant difference between 2 groups so that the Amikacin-induced necrosis was dramatically less than Gentamycin-induced necrosis. So because of Amikacin's higher bacteriocidal effect and less nephrotoxic damage, it can be recommended as a choice drug between these 2 considered antibiotics.

Key words: Gentamycin, nephrotoxicity, amikacin, comparison, infection, treatment, Iran

INTRODUCTION

Aminoglycosides are bactericidal antibiotics that interfere with protein synthesis by causing misreading of the genetic message and stimulation of faulty production of RNA. Gentamycin is an antibiotic belonging to the aminoglycosides and it is widely used in the treatment of gram-negative infections. However, its nephrotoxic action has limited the extent of its use (Mingeot-Leclercq and Tulkens, 1999). This antibiotic is most used for urinary, respiratory, digestive and soft tissues infections. Amikacin is another member of this family which is famous for its wide-spread affections and is almost used in hospitals whose patients have got resistant to other antibiotics of this family. But just like Gentamycin, its nephrotoxicity is a serious problem limiting its usage. This nephrotoxicity occurs as a result of Reactive Oxygen Species (ROS) (Cuzzocrea *et al*., 2002). In veterinary treatment especially in Iran, Gentamycin is the choice drug of this family when aminoglycosides are diagnosed to be taken and vet doctors do not intend to use Amikacin and usage of this drug is not common as much among veterinarians. Regarding to the highest Amikacin's wide-spread influence on different bacterias, researchers are about to prove that if Amikacin-induced nephrotoxicity is dramatically less than Gentamycin-induced one, it will be recommended that Amikacin may be the 1st choice of gram-negative infections treatment so a more effective and less harmful result will be provided.

MATERIALS AND METHODS

This experiment was carried out in Islamic Azad University, Kazeroon Branch in Pathological Department. About 48 rabbits were selected and after being housed under controlled environmental conditions (around 27°C) and being kept in stress-free condition with free access to water and normal diet, they were randomly divided in 3 groups based on time:

Group 1: a-6 rabbits injected intramuscularly by Gentamycin for 3 days (20 mg kg^{-1}), b-6 rabbits injected intramuscularly by Amikacin for 3 days (100 mg kg^{-1}) and c-4 rabbits as control group without any injection.

Group 2: a-6 rabbits injected intramuscularly by Gentamycin for 7 days (20 mg kg^{-1}), b-6 rabbits injected intramuscularly by Amikacin for 7 days (100 mg kg^{-1}) and c-4 rabbits as control group without any injection.

Group 3: a-6 rabbits injected intramuscularly by Gentamycin for 14 days (20 mg kg^{-1}), b-6 rabbits injected

intramuscularly by Amikacin for 14 days (100 mg kg^{-1}) and c-4 rabbits as control group without any injection.

Every group's animals were anesthetized deeply with ether after 24 h of the last injection and both kidneys were excised for histopathological studies and fixed in 10% buffered formalin solution and then placed in fresh fixative solution to pH 7.3 at room temperature for 1 week. After being processed for paraffin embedding and section taking were stained with Hematoxylin and Eosin. These slides were examined by a pathologist with light microscope. In this stage, all the slides were examined for tubular necrosis. The seen differences between level of necrosis and its severity between animals injected by Amikacin and Gentamycin were statistically significant (Kruskal-wallis: $p<0.05$, $df = 4$, $\chi^2 = 44.4$).

RESULTS

In examining the slides by a pathologist some grading levels were provided to be applied on every slide. These levels include:

Level 0 (no necrosis): No tubular necrosis could be seen in the slide.

Level 1 (light necrosis): Average of 1-10 necrosis cells in 10 views of any slide.

Level 2 (medium necrosis): Average of 10-30 necrosis cells in 10 views of any slide.

Level 3 (severe necrosis): Average of >30 necrosis cells in 10 views of any slide.

The kidneys treated by Gentamycin

Three days injections: All the slides of 6 rabbits in this group showed necrosis in medium level.

Seven days injection: The necrosis trend showed a remarkable progress in comparison with the last group. Four slides showed necrosis in level-3 and two of them level-2, so a necrosis with level medium to severe (Fig. 1).

Fourteen days injection: A lot of necrosis was clear in these slides so all of them were graded as severe necrosis (level-3) (Fig. 2).

The kidneys treated by Amikacin

Three days injection: Like Gentamycin, coagulative necrosis was seen in all 6 slides. But their necrosis levels included five level-1 slides and one level-2 slide. So a light to medium level (more tendency to light) was determined.

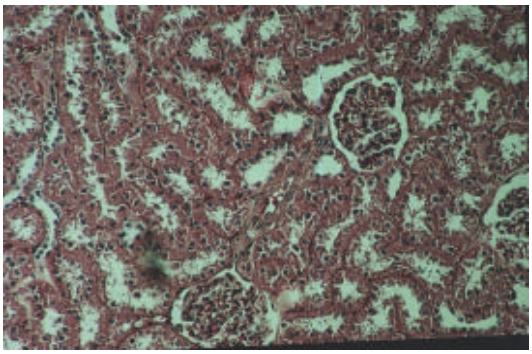

Fig. 1: A slide of a kidney treated by Gentamycin after 7 days injection. A medium to severe coagulative necrosis is obviously seen

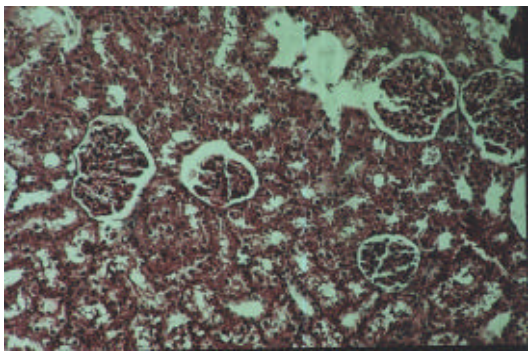

Fig. 2: A view of kidney after 14 days Gentamycin injection. Disorganization of the tissue and severe necrosis are seen in the tubules

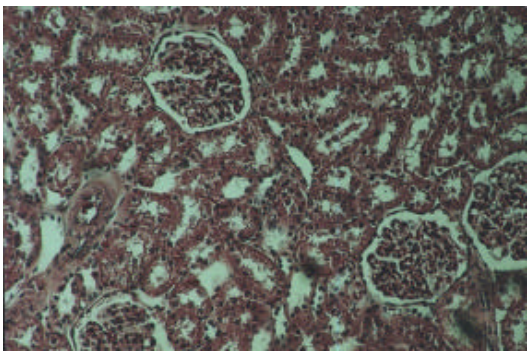

Fig. 3: A view of kidney after 7 days Amikacin injection. Signs of necrosis are clear in the figure but most of the tubular cells have nucleus and do not show coagulative necrosis

Seven days injection: These slides showed a little more necrosis than the last group but was not as much as Gentamycin group. Four slides showed medium level and two slides showed light necrosis (Fig. 3).

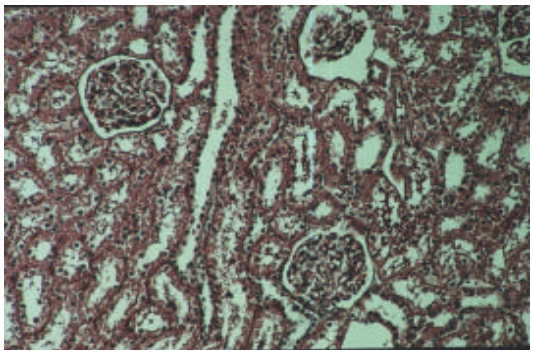

Fig. 4: A kidney's view after 14 days Amikacin injection because of existing nucleuses in most tubular cells, a medium level necrosis was determined for this slide

Fourteen days injection: Changes but not that dramatic were seen compared to the last group. About 4 medium necrosis and 2 severe 1 was indicated (Fig. 4).

DISCUSSION

Amynoglycosides are 1 of the most important families of antibiotics which are used to control bacterial infections, especially gram-negative ones. Among these, Amikacin and Gentamycin are the most common ones. Amikacin is usually used in hospitals and cases which are resistant to other members of this family.

In a study on 1277 pathologic bacteria, it was showed that Amikacin has the good antibacterial activity as Gentamycin, Dibedacin and Tobramycin and also showed the good activity against Kanamycin resistant strains (Kosakai and Oguri, 1975). There is no doubt on lower antibacterial effect of gentamycin in comparison with Amikacin. It has been proved that more than other members, Gentamycin accumulates in the lysosomes of kidney tubular cells and causes apoptosis at clinically relevant doses (Servais *et al*., 2006). So, researchers decided to evaluate the level of nephrotoxicity of Gentamycin and Amikacin to prove that if Amikacin were less nephrotoxic than Gentamycin so in most gram-negative infections researchers would recommend Amikacin as a choice and better drug. The results of this study approved the theory and showed that Gentamycin had more nephrotoxic influence than Amikacin. In the past, different studies have been done to compare nephrotoxicity of different members of aminoglycosides which some of them confirm the findings and some results are against them. In a controlled comparison study, Gentamycin showed more nephrotoxicity than Tobramycin (Schentag *et al*., 1981).

In another study on low-dose nephrotoxocity of Gentamycin, Tobramycin and Amikacin, these antibiotics were respectively more nephrotoxic (Gentamycin> Tobramycin>Amikacin) (Hottendorf and Gordon, 1980). Above all in a typical study on some amynoglycosides, Gentamycin has been considered the most nephrotoxic agent and has had the highest degree of net reabsorption (Smith and Lietman, 1983).

It has been proved that animals with pyleonephritic problems are more susceptible to Gentamycin injections because Gentamycin levels in the cortex and medulla of infected animals were significantly higher than in the normal animals and might have been responsible for the increased toxicity noted in the pyelonephritic animals (Beauchamp *et al*., 1985).

All the given examples prove the findings and between Amikacin and Gentamycin, the former one should be more recommended. On the other hand, in a controlled comparison study of Amikacin and Gentamycin on 174 patients with suspected severe gram-negative infections, the results indicated that Amikacin is effective against severe gram-negative infections and is not more and less ototoxic or nephrotoxic than Gentamycin (Smith *et al*., 1977). Another investigation on some critically ill patients, accumulation of Amikacin and Gentamycin looked similar to each other in the kidneys (French *et al*., 1981). No significant difference between Amikacin and Tobramycin's nephrotoxicity has been reported (Gatell *et al*., 1983).

CONCLUSION

As it can be seen none of these studies do not directly prefer Gentamycin as a less nephrotoxic agent rather than Amikacin and in most cases, the results have been almost identical. So totally it can be concluded that Gentamycin is potentially more nephrotoxic than Amikacin and regarding to Amikacin's more wide-spread antibacterial effects so it is a better choice drug.

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