Radioiodine-induced kidney damage and protective effect of amifostine: An experimental study

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Abstract

Background: Ablative radioiodine-131 (131I) therapy is used in the standard treatment procedure of thyroid carcinoma and procedures using 131I represent the majority of Nuclear Medicine therapeutic procedures. The principal route of 131I excretion after the administration of 131I is the urine. Amifostine is an organic thiophosphate ester prodrug and the kidney concentrations of the active metabolite WR-1065 are about 100 times higher than tumour concentrations. To our knowledge, there is no published data in literature presenting acute effect of radioiodine on renal tissue during high dose I-131 radioiodine treatment (RIT). Additionally, it is not known whether amifostine takes role in this process.

Materials and methods: In this study, 50 healthy female Wistar albino rats, weighing 200–250 g and averaging 16 weeks old were utilised. The rats were randomly divided into ten groups. 1- Sham group (n=5), 2- Amifostine group (n=5): rats pretreated with 1 cc amifostine (200 mg/kg) by intraperitoneal injection, 3- Radioactive iodine first day group (RI-1) (n=5): rats treated with 1 cc oral 185 MBq radioactive iodine-131 and sacrifice performed after 1st day, 4- Amifostine + Radioactive iodine first day group (A+RI-1) (n=5): rats pretreated with amifostine (200 mg/kg) by intraperitoneal injection and rats treated with 5mCi radioactive iodine-131 and sacrifice performed after 1st day. 5- Radioactive iodine third day group (RI-3) (n=5), 6- Amifostine + Radioactive iodine third day group (A+RI-3) (n=5), 7- Radioactive iodine fifth day group (RI-5) (n=5), 8- Amifostine + Radioactive iodine fifth day group (A+RI-5) (n=5), 9- Radioactive iodine seventh day group (RI-7) (n=5) and 10- Amifostine + Radioactive iodine seventh day group (A+RI-7) (n=5). The renal cast formation and tubular damage are evaluated by a pathologist in a blinded manner.

Results: Ablative radioiodine-131 therapy induced renal tubular damage was significantly higher in the radioactive iodine fifth day group (RI-5) when compared with the Sham group (p=0.01) and Amifostine group (p=0.01).

Conclusions: A marked ablative radioiodine-131 induced renal toxicity was seen at fifth day of the therapy after a single RIT application and the main histopathological change was tubular damage. Amifostine have protective effects against ablative radioiodine-131 therapy and this effect is significant at fifth day of the therapy. Hippokratia. 2012; 16 (1): 40-45

Key words: amifostine, radioiodine therapy, renal toxicity

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Ablative radioiodine-131 (131I) therapy is used in the standard treatment procedure of thyroid carcinoma and procedures using 131I represent the majority of Nuclear Medicine therapeutic procedures. The 131I activities administered during therapeutic procedures for thyroid cancer may vary from patient to patient according to the patients' pathological anatomy. The limiting factor in this approach is choice of the maximum permissible activity based on the absorbed dose to the patient’s bone marrow and the other organ toxicity. The principal route of 131I excretion after the administration of 131I is the urine (about 80–90% of the activity is excreted in the first 48 hours). Because of renal excretion of this radiopharmaceutical, renal toxicity is the limiting factor, although pharmacological intervention using cationic aminoacids and amifostine may help in reducing this problem.

Amifostine is an organic thiophosphate ester prodrug and must be activated by alkaline phosphatase to convert into an active sulfhydryl compound (WR-1065). The kidney concentrations of the active metabolite WR-1065 are about 100 times higher than tumour concentrations, which forms the basis for the selective protection of healthy tissue. Previous reports have recently shown that amifostine can ameliorate functional renal damage in rat kidneys.

To our knowledge, there is no published data in literature presenting acute effect of radioiodine on renal tissue during high dose I-131 radioiodine treatment (RIT). Additionally, it is not known whether amifostine takes role in this process. To clarify these obscure we examined
Materials and methods

Experimental protocol

The experimental protocol was approved by the Ethical Committee. In this study, 50 healthy female Wistar albino rats, weighing 200–250 g and averaging 16 weeks old were utilized. The rats housed at the Animal Care and Research Unit were used for this study. Food and tap water were available ad libitum. In the windowless animal quarter automatic temperature (21±1°C) and lighting controls (12 h light/12 h dark cycle) were performed. Relative humidity ranged from 55% to 60%. All animals received human care according to the criteria outlined in the ‘Guide for the Care and Use of Laboratory Animals’ prepared by the National Academy of Sciences and published by the National Institutes of Health.

Despite that experimental models on acute or chronic side-effects of the radioactive iodine treatment are limited a single high dose radioactive I-131 ablation therapy model in rats was chosen in the present study. Rats in radioactive iodine groups received 185 MBq (5 mCi) I-131.

The rats were randomly divided into ten groups:
1. Sham group (n=5): rats pretreated with 1 cc 0.9% NaCl solution without radio-ablation.
2. Amifostine group (n=5): rats pretreated with 1 cc amifostine (200 mg/kg) by intraperitoneal injection.
3. Radioactive iodine first day group (RI-1) (n=5): rats treated with 1 cc oral 185 MBq radioactive iodine-131 and sacrificed performed after the 1st day.
4. Amifostine + Radioactive iodine first day group (A+RI-1) (n=5): rats pretreated with amifostine (200 mg/kg) by intraperitoneal injection and rats treated with 185 MBq radioactive iodine-131 and sacrificed performed after the 1st day.
5. Radioactive iodine third day group (RI-3) (n=5): rats treated with 1 cc oral 185 MBq radioactive iodine-131 and sacrificed performed after the 3rd day.
6. Amifostine + Radioactive iodine third day group (A+RI-3) (n=5): rats pretreated with amifostine (200 mg/kg) by intraperitoneal injection and rats treated with 185 MBq radioactive iodine-131 and sacrificed performed after the 3rd day.
7. Radioactive iodine fifth day group (RI-5) (n=5): rats treated with 1 cc oral 185 MBq radioactive iodine-131 and sacrificed performed after the 5th day.
8. Amifostine + Radioactive iodine fifth day group (A+RI-5) (n=5): rats pretreated with amifostine (200 mg/kg) by intraperitoneal injection and rats treated with 185 MBq radioactive iodine-131 and sacrificed performed after the 5th day.
9. Radioactive iodine seventh day group (RI-7) (n=5): rats treated with 1 cc oral 185 MBq radioactive iodine-131 and sacrificed performed after the 7th day.
10. Amifostine + Radioactive iodine seventh day group (A+RI-7) (n=5): rats pretreated with amifostine (200 mg/kg) by intraperitoneal injection and rats treated with 185 MBq radioactive iodine-131 and sacrificed performed after the 7th day.

At the time of sacrifice, the rats were anesthetized with 10 mg/kg xylazine and 50 mg/kg ketamine and then left nephrectomy was performed.

Kidney Histology

The rat kidneys were fixed in buffered neutral 10% formaldehyde for 24 hours. The tissues were cut sagitally and half of each kidney was sampled and they were subjected to alcohol processing for 12 hours. Five micrometer thick sections were obtained from the paraffin embedded tissues. The hematoxylin–eosin stained slides were evaluated 2 times under light microscope (Olympus BX51, Japan) by a pathologist in a blinded manner. The glomeruli, tubuli, interstitium and the vessels were evaluated. As the only visible damage was seen on the tubules, the tubular damage was evaluated semi-quantitatively as 0: none, 1: mild, 2: moderate, 3: severe. There were also intraluminal protein casts in some of the tubules of some of the kidneys and the casts are counted in 10x objective in 10 consecutive fields and the sum is divided into 10 to get the mean value of the tubular casts.

Statistical Analysis

The results are expressed as mean ± standard deviation. The histopathologic data were submitted to non-parametric and parametric tests. Pearson’s chi-square test was used to compare the number of patients with acute tubular damage. Groups’ comparisons were done by one-way ANOVA because data showed normal distribution. A post hoc Bonferroni statistical analysis was used. p values below 0.05 were considered as statistically significant.

Results

The renal cast formation and tubular damage are summarized for each group in Table 1. Ablative radioiodine-131 therapy induced renal tubular damage was significantly higher in the radioactive iodine fifth day group (RI-5) (Figure 3a) when compared with the Sham group (p=0.01) (Figure 1) and Amifostine group (p=0.01). Renal tubular damage was not significant in the Amifostine + Radioactive iodine fifth day group (A+RI-5) (Figure 3b) when compared with the Sham group (p=0.06) and Amifostine group (p=0.06).

Ablative radioiodine-131 therapy induced renal tubular damage was not significantly higher in the radioactive iodine seventh day group (RI-7) (Figure 4a) when compared with the Sham group (p=0.06) and Amifostine group (p=0.06). Renal renal tubular damage was not significant in the Amifostine + Radioactive iodine seventh day group (A+RI-7) (Figure 4b) when compared with the Sham group (p=0.86) and Amifostine group (p=0.86).

According to the scoring of pathological changes in the kidney, renal tubular damage scores were 1.40 ± 0.60 in the Radioactive iodine first day group (RI-1) and
Figure 1: Normal histology of a kidney from control group (HEx100)

Figure 2: The kidney of the 3rd day non-treated group showed near to normal histology with mild dilation of the tubules and mild vacuolisation in the tubular epithelium (HEx100).

Figure 3a: There is moderate damage to the tubules of the 5th day non-treated group with dilated tubules and desquamated epithelial cells leaving the basement membranes of some of the tubules naked. (HEx100).

Figure 3b: Epithelial desquamation and the tubular dilatation are not as prominent in the treatment group kidney of 5th day as in the non-treated kidney of the same group (HEx100).

Figure 4a: The tubular damage of the 7th day of non-treated group is similar with the non-treated kidney of the 5th day (HEx100).

Figure 4b: The tubular damage of the 7th day of treated kidney has relatively milder damage (HEx100).
Discussion
The main findings of our study were as follows: 1) a marked ablative radioiodine-131 induced renal toxicity was seen at fifth day of the therapy after a single dose of 185 MBq; 2) the main histopathological change was tubular damage whereas cast formation was not seen at significant levels; 3) amifostine have protective effects against ablative radioiodine-131 therapy and this effect is significant at fifth day of the therapy; 4) these protective effects against ablative radioiodine-131 induced renal toxicity were also seen in seventh day of the therapy.

The principal route of $^{131}$I excretion after the administration is the renal excretion and renal toxicity is the limiting factor$^{6,7}$. However, to the best of our knowledge, there is no published data in the literature presenting acute effects of ablative radioiodine-131 on renal toxicity and also acute and early protective role of amifostine on renal damage. In our study a marked ablative radioiodine-131 induced renal toxicity was seen at fifth day of the therapy after a single dose of 185 MBq.

The human sodium iodide symporter (hNIS) is a transmembrane protein that mediates the active transport of iodide in the thyroid gland$^{12}$. Following cloning of NIS, NIS expression has been detected in a broad range of nonthyroidal tissues, suggesting that iodide transport in these tissues is conferred by the expression of functional NIS protein. Spitzweg et al$^{13}$ examined functional hNIS expression in kidney. The NIS has been found in the kidney primarily in the distal tubular system, with less in the proximal tubules and none in the glomeruli$^{13}$.

In our study the main histopathological change was tubular damage whereas cast formation was not seen at significant levels.

Table 1: The renal cast formation and tubular damage are summarized for each group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cast formation (mean±SD)</th>
<th>Tubular damage (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham group</td>
<td>0.40±0.40</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>Amifostine group</td>
<td>0.20±0.20</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>RI-1 group</td>
<td>4.40±2.22</td>
<td>1.40±0.60</td>
</tr>
<tr>
<td>Amifostine +</td>
<td>0.20±0.20</td>
<td>0.60±0.40</td>
</tr>
<tr>
<td>RI-3 group</td>
<td>1.40±0.51</td>
<td>1.20±0.20</td>
</tr>
<tr>
<td>Amifostine +</td>
<td>1.00±1.00</td>
<td>1.00±1.00</td>
</tr>
<tr>
<td>RI-5 group</td>
<td>3.40±1.40</td>
<td>1.60±0.24</td>
</tr>
<tr>
<td>Amifostine +</td>
<td>1.80±0.66</td>
<td>1.40±0.24</td>
</tr>
<tr>
<td>RI-7 group</td>
<td>2.00±0.49</td>
<td>1.40±0.24</td>
</tr>
<tr>
<td>Amifostine +</td>
<td>0.60±0.40</td>
<td>1.00±0.31</td>
</tr>
<tr>
<td>RI-7 group</td>
<td>0.00±0.00</td>
<td>1.00±0.31</td>
</tr>
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$^{0.60 ± 0.40}$ Amifostine + Radioactive iodine first day group (A+RI-1) (p=0.1). Renal tubular damage scores were 1.20±0.20 in the Radioactive iodine third day group (RI-3) (Figure 2) and 1.00±1.00 Amifostine + Radioactive iodine third day group (A+RI-3) (p=1.00). Renal tubular damage scores were 1.60±0.24 in the Radioactive iodine fifth day group (RI-5) and 1.40±0.24 Amifostine + Radioactive iodine fifth day group (A+RI-5) (p=1.00). Renal tubular damage scores were 1.40 ± 0.24 in the Radioactive iodine seventh day group (RI-7) and 1.00 ± 0.31 Amifostine + Radioactive iodine seventh day group (A+RI-7) (p=1.00).
ity related with multiple mechanisms. Normal tissues have higher alkaline phosphatase activity in the plasma membrane, higher interstitial pH and better vascularity when compared with tumor cells that are relatively hypovascular and have lower interstitial pH. In our study amifostine have protective effects against ablative radiodine-131 therapy and this effect is significant at fifth day of the therapy. Additionally, this protective effect against ablative radiodine-131 induced renal toxicity is persisting on the seventh day of the therapy.

Amifostine is rapidly cleared with a half-life of less than 1 minute and more than 90 percent within 6 minutes from the plasma compartment after administration and that have demonstrated by pharmacokinetic studies in patients. These findings point out that after entrance of amifostine into the plasma, rapid metabolism and distribution occurs in the tissues whereas the metabolic products (WR-1065 and WR-33278) excrete slowly15,16.

Ionizing radiation (radiotherapy and radionuclide therapy) and chemotherapy agents activates several cytoplasmic signal transduction pathways involving Tyr kinases, protein kinase C, ERK-1/2, ceramide, and Ca2+ homeostatic mechanisms17,18. Protective effect of amifostine on acute and chronic toxicities associated with radiation (radiotherapy and radionuclide therapy) and chemotherapy has been studied in several studies. Caloglu et al19 mentioned that amifostine have significant protective effects against radiation-induced late nephrotoxicity. The main histopathological findings were interstitial fibrosis and proximal tubular damage. Interstitial degeneration and atrophy were less common in the amifostine + radiotherapy group than in the radiation group20. In another study, pretreatment with amifostine protected against nephrotoxicity induced by both single and repeated doses of cisplatin without affecting the antitumor effects of cisplatin21.

Additionally, amifostine exerts a direct protective effect at the site of maximum cisplatin toxicity and significantly reduces the severity of nephrotoxicity22. There is no agreement in the literature concerning the renoprotective effect of amifostine. Brizel et al23 demonstrated that the incidence and severity of acute and chronic xerostomia that develops during the radiotherapy of head and neck cancer can reduced after daily administration of amifostine without compromising the efficacy of the radiation. Uzunoglu et al24 reported that cisplatin induced nephrotoxicity was not protected by amifostine, furthermore, their findings suggested that application of amifostine before chemotherapy may enhance nephrotoxicity histopathologically25. In our study, the findings suggest that amifostine has protective effect on radioiodine induced renal damage, and these results support previous literature observing protective effects of amifostine on kidney damage.

The limitation of the present study is that our results include the findings of the experimental animal study suggesting that amifostine therapy might be beneficial in preventing against ablative radiodine-131 therapy. When choosing an animal model clinicians must consider the extent of similarity between the anatomy, physiology, and regulation of gene expression between two species26. Additionally, the rat is the most used animal model for experimental studies of nephrotoxicity27. Although based on these experimental results, further investigations are warranted and additional human studies are required to clarify the role of acute and chronic effects of ionizing radiation and protective role of amifostine.

In conclusion, these findings point out that renal toxicity was seen after radiodine-131 treatment, and also the protective effects of amifostine was observed on renal cast formation and tubular damage after ablative radiodine-131 therapy. To the best of our knowledge, there is no published data in the literature about acute and early protective role of amifostine on renal damage.

Conflicts of Interest: None

References
13. Spitzweg C, Dutton CM, Castro MR, Bergert ER, Goellner JR,


