Administration of ^{99m}Tc-DTPA in combination with doxorubicin alters the radiopharmaceutical biodistribution in rats

Original Article

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ABSTRACT

Introduction: Diethylenetriaminepentaacetic acid (DTPA) is a chelating agent used as a radiopharmaceutical compound, ^{99m}Tc-DTPA, for renography. Doxorubicin (DOX) on the other hand is an effective chemotherapy drug used to treat a variety of solid malignancies. Both ^{99m}Tc-DTPA and DOX may be used in close succession in patients undergoing DOX based chemotherapy to evaluate renal function. This study aims to investigate the possible alteration in the biodistribution of ^{99m}Tc-DTPA when given in combination with DOX in rats.

Methods: The study was divided in two arms; a control group (n=10) where ^{99m}Tc-DTPA alone and the experimental group (n=30) where DOX was injected prior to ^{99m}Tc-DTPA administration. The experimental group was further divided into six subgroups (n=5 each) based on the time intervals (4, 8, 18, 36, 72, 96 hours) between DOX and ^{99m}Tc-DTPA administration. In each group, the subjects were sacrificed 2 hours post ^{99m}Tc-DTPA injection, the organs isolated and counted for radioactivity.

Results: The results revealed that the percent total retained dose (%TRD) significantly ($p<0.001$) decreased in urinary tract while significantly ($p<0.001$) increased in liver and biliary tree as compared to the experimental group.

Conclusion: The results of this pre-clinical study put the accuracy of renal scintigraphy in question in patients receiving DOX based chemotherapy. However, human studies are proposed for validity of results with regards to clinical practice.

Key words: Doxorubicin; ^{99m}Tc-DTPA; Radiopharmaceutical; Renography; Total retained dose

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INTRODUCTION

Radio-labeling of acetic Diethylenetriaminepentaacetic acid (DTPA), a chelating agent for heavy metals, with sodium pertechnetate Tc-99m result in the formation of radiopharmaceutical ^{99m}Tc-DTPA. The exclusive renal mode of clearance for ^{99m}Tc-DTPA promotes its utilization in scintigraphy study of kidneys [1-3]. Specifically, the intravenously administered ^{99m}Tc-DTPA is filtered by the renal glomeruli thereby allowing to measure glomerular filtration rate (GFR) [4]. Amongst the various indications of ^{99m}Tc-DTPA in clinics, GFR is measured in cancer patients prior to or following chemotherapy to assess renal function/ toxicity of the chemotherapy drug with suspected nephrotoxicity [5], such as Doxorubicin.

Doxorubicin (DOX) is an anthracycline having a broad spectrum of antineoplastic activity and widely used in the treatment of solid malignancies such as breast cancer, lymphomas, sarcomas and gynecological cancers. The pharmacokinetics (PKs) of DOX has indicated that, after intravenous administration, its levels in the blood reduce radically as it distributes into tissues. Afterward, a slow elimination phase due to renal and biliary clearance and metabolism of the drug follows [6]. DOX can react with several cellular components to induce the antitumor and toxic effects. Specifically, DOX is capable of DNA intercalation and alkylation, interaction with topoisomerase II, inhibition of RNA and DNA polymerase [7-9]. Moreover, DOX can generate reactive oxygen species (ROS) through quinone redox cycling and perturb cellular Ca^{2+} concentrations via both receptor-mediated and redox-mediated pathways [10]. The ability of DOX to increase the plasma concentration of free iron is ascribed to its metal chelating properties [11, 12].

Many have suspected that the biodistribution of radiopharmaceuticals (e.g., ^{99m}Tc-DTPA) may be altered by concurrent administration of chemotherapy drugs. The drug-radiopharmaceutical interactions (DRIs) may arise due to the pharmacologic action of the drug or because of physicochemical interactions between the radiopharmaceutical and the drug such as alteration in the chemical identity of the radiopharmaceutical. Indeed, a considerable body of evidence on such DRIs supports this hypothesis [12-17].

Importantly, the biodistribution of radiopharmaceuticals appears to significantly change by drugs that alter the functional status of the organ. Consequently, the biodistribution of radiopharmaceutical will depend on the organ of interest, chemical class of the drug, given radiopharmaceutical and DRI [18]. Such altered biodistribution of radiopharmaceuticals can significantly impact the interpretation of scintigraphy study and diagnostic imaging accuracy. In extreme manifestations, such imaging results may even compromise the accuracy/utility of nuclear medicine studies. That said, we designed this study to assess the impact of chemotherapy drug on the biodistribution of radiopharmaceuticals. Specifically, the present study aims to investigate the possible alterations in the biodistribution of ^{99m}Tc-DTPA in rats following the administration of DOX.

METHODS

The animals (i.e., Sprague Dawley male rats with a mean age of 6 weeks) were acquired from National Institute of Health (NIH), Pakistan and given free access to food and water. The study was approved by the animal ethical committee of NIH, Pakistan.

National Institute of Health (NIH), Pakistan and given free access to food and water. The study was approved by the animal ethical committee of NIH, Pakistan. Freeze dried kits of DTPA were prepared by Isotope Production Division (IPD) of Pakistan Institute of Nuclear Science and Technology (PINSTECH). Tc-99m was obtained from Mo-99/Tc-99m generators, manufactured by IPD, PINSTECH. Platform for radiolabeling of DTPA kits with Tc-99m, the quality control and bio-distribution of ^{99m}Tc-DTPA in animals was also provided by IPD, PINSTECH.

Doxorubicin Hydrochloride was purchased from Pfizer, Pakistan in injectable form and the reference dose for rats was calculated by finding a dose equivalent to 50 mg/m^2 in humans with the help of "Equivalent Surface Area Dosage Conversion Factors [19]. The dose to be administered came out to be 9.46 mg/kg. The mean weight of the rats used in the study was 55g so that the actual administered dose to each rat was 0.5 mg.

Biodistribution study

The study was divided into two arms; a control group (n=10) where 0.1 mCi of ^{99m}Tc-DTPA alone was injected intravenously into the tail vein of the rats and the experimental group (n=30) where 0.5 mg DOX was injected prior to ^{99m}Tc-DTPA (0.1 mCi) administration. The experimental group was further divided into six subgroups (n=5 each) based on the time intervals (4, 8, 18, 36, 72, 96 hours) between DOX and ^{99m}Tc-DTPA administration. The animals were randomly assigned to each of the time-point groups. Figure 1 illustrates the schematic of all experimental steps involved in this study.

In each group, the rats were sacrificed after two hours of the ^{99m}Tc-DTPA injection, selected organs (i.e., liver, spleen, stomach, intestines, lungs kidneys, femur, bladder, heart, and carcass) were isolated, washed with saline, dried on filter paper and weighed.

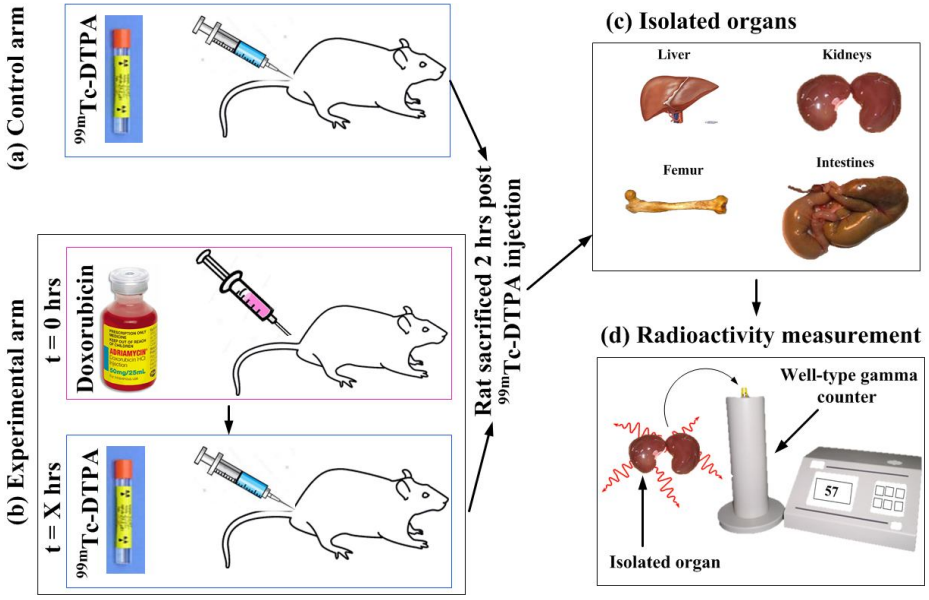

Fig 1. Illustration of the workflow of the study; (a) control arm where ^{99m}Tc-DTPA (0.1 mCi activity/0.02 ml solution of ^{99m}Tc-DTPA) alone was injected in the tail vein of the rats (n=10), (b) experimental arm where DOX (0.5 mg of Doxorubicin/0.25 ml solution) was injected X (=4, 8, 18, 36, 72, 96) hours prior to ^{99m}Tc-DTPA (0.1 mCi) administration in the rat tail (n = 5 in each subgroup), (c) sketch of isolated organs of the rats scarified 2 hrs post ^{99m}Tc-DTPA injection in both arms and (d) activity measurement in isolated organs.

The radioactivity in each organ was counted with well-type gamma counter and expressed as the percent total retained dose (%TRD), as follows

$$\%\ \text{TRD} = \frac{\text{Activity in the given organ}}{\text{Total activity administered}} \times 100$$

The %TRD quantitatively describes the uptake of activity (and thereby the radiopharmaceutical) in a particular organ, normalized by the total activity administered, such that to facilitate the inter-comparison of each organ.

The %TRD for urinary tract was calculated as the sum of %TRD of kidney, bladder, and urine (which was collected in a filter paper). The results from the two groups were analyzed and compared for statistical significance using paired two-tail t-test.

RESULTS

The results of biodistribution study in various isolated organs of rats with particular emphasis on urinary tract and liver for both control and experimental groups are presented herein.

The administered radiopharmaceutical ^{99m}Tc-DTPA is primarily taken up by the kidneys, rapidly passed on to the ureters and bladder and finally eliminated from the body through urine. Consequently, %TRD was calculated for the entire urinary tract plus urine rather than kidneys alone; the results are summarized in Figure 2 which reveal an initial increase followed by a progressive reduction in uptake of ^{99m}Tc-DTPA as the time span between the drug and radiopharmaceutical administration is increased.

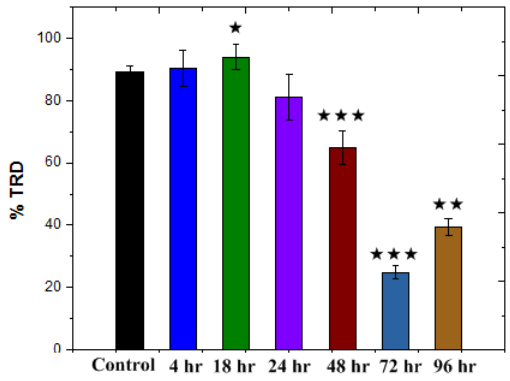

Fig 2. Cumulative mean %TRD of the kidney, urine and bladder in Control (n=10) and Experimental group (n=5 each). Time (in hours) on x-axis shows the gap between administration of DOX (0.5mg DOX/0.25 ml of saline) and ^{99m}Tc-DTPA. The error bar represents standard error. (★ = p value < 0.05; ★★< 0.01; ★★★< 0.001, calculated with two-tail unpaired t-test).

The liver has been believed as the major body compartment for DOX accumulation; thereby liver constitutes an interesting target for % TRD

calculations in our study. The results of %TRD in the liver are illustrated in Figure 3.

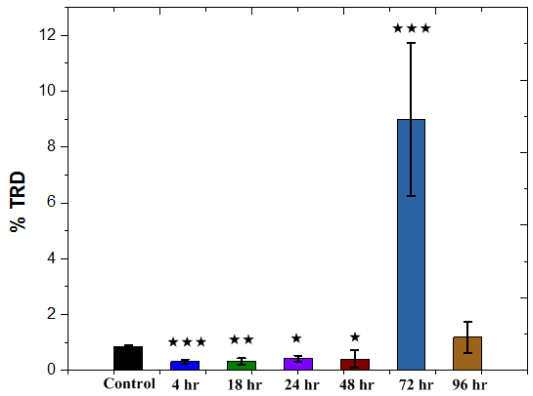

Fig 3. Mean %TRD of the liver in Control (n=10) and Experimental group (n=5 each). Time (in hours) on x-axis shows the gap between administration of DOX (0.5mg DOX/0.25 ml of saline) and ^{99m}Tc-DTPA. The error bar represents standard error. (★ = p value < 0.05; ★★< 0.01; ★★★< 0.001, calculated with two-tail unpaired t-test).

Contrary to the urinary tract, the %TRD in liver increased with the time interval between the drug and radiopharmaceutical administration. In addition, the %TRD for the liver is significantly lower as compared to the urinary tract (Figure 2). The overall activity being excreted via bile can be probed through the %TRD determined collectively for liver, intestines, and stool (Figure 4).

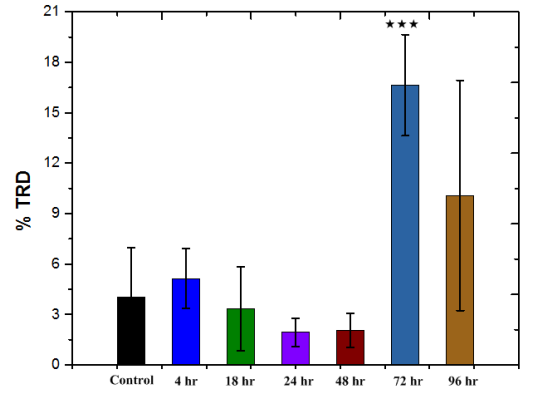

Fig 4. Cumulative mean %TRD of the liver and intestines in Control (n=10) and Experimental group (n=5 each). Time (in hours) on x-axis shows the gap between administration of DOX (0.5mg DOX/0.25 ml of saline) and ^{99m}Tc-DTPA. The error bar represents standard error. (★★★ = p value < 0.001, calculated with two-tail unpaired t-test).

This may also complement the observed increasing trend in %TRD for liver alone. The complete biodistribution data for all oranges has been presented in Table 1.

DISCUSSION

It has been suspected that the PK/biodistribution of radiopharmaceuticals may be altered by various factors such as recent surgery, chemotherapy, radiotherapy, disease states, dialysis, etc. [18]. Indeed, unexpected patterns of radiopharmaceutical biodistribution and poor visualization of organs or even misdiagnosis have been reported [20, 21]. The mentioned factors may cause variations in regional blood flow, metabolism and the binding of the radiopharmaceutical to the blood plasma [22]; subsequently, the distribution, uptake, retention and elimination of the radiopharmaceuticals are altered. That said, it appears essential for the physician to have sufficient knowledge of the altered biodistribution of the radiopharmaceuticals in such cases towards avoiding misinterpretation of the scintigraphy images [16]. To this end, exploring the influence of DRI on the biodistribution of the radiopharmaceutical, as studied here, would be of significant interest.

Various important factors may contribute to the altered biodistribution of ^{99m}Tc-DTPA, as observed here, when it is given in close succession with DOX. For instance, DOX has a mean half-life ~ 30 hours [19, 23] while Tc-99m has an effective half-life ~ 4 hours in humans [24]. The longer half-life of DOX is believed to be due to its extensive binding to plasma proteins (~70%), as opposed to ^{99m}Tc-DTPA (~10%). Further, DOX being lipophilic is widely distributed in tissues by passive diffusion, contrary to ^{99m}Tc-DTPA which requires carrier-mediated transport due to its hydrophilic nature. Moreover, the primary metabolism of DOX occurs in the liver, particularly by the CYP3A4 subfamily of cytochrome P450 liver oxidases; subsequently, the metabolites are unloaded by bile into the stool. A minor part of DOX metabolites is also eliminated via kidneys. Alternatively, ^{99m}Tc-DTPA is not metabolized in the body and quickly gets filtered by the renal glomeruli towards elimination from the body via urine.

Previously, several natural and/or synthetic drugs have been speculated to alter the biological effect of the radiopharmaceutical and subsequently may lead to hyper or hypo uptake of radiopharmaceuticals in the given organ, ultimately causing misinterpretation of results or incorrect diagnosis [25-30]. For instance, vincristine (Mitomycin-C; a frequently used chemotherapy agent) was demonstrated to increase the uptake of ^{99m}Tc-DTPA in spleen [26]. Another study reported that vincristine caused a decrease in the uptake of the Tc-99m labelled methylenediphosphonic acid (^{99m}Tc-MDP; used for bone scintigraphy) in uterus, ovary, thymus, stomach, spleen, liver, kidney, heart and brain [27]. Moreover, with concurrent administration of the same drug (i.e., vincristine), the biodistribution of ^{99m}Tc-phytic acid (^{99m}Tc-PHY; frequently used in hepatic scintigraphy) has been

Table 1: Complete biodistribution data (Mean ±Standard Deviation) for all oranges.

Organs	Control	4 Hours	18 Hours	24 Hours	48 Hours	72 Hours	96 Hours
Liver	0.828 ±0.201	0.311 ±0.075	0.323 ±0.110	0.417 ±0.110	0.407 ±0.310	8.980 ±2.744	1.190 ±0.560
Spleen	0.840 ±0.209	0.075 ±0.024	0.107 ±0.025	0.060 ±0.020	0.087 ±0.047	8.697 ±1.512	1.091 ±0.412
Stomach	1.010 ±0.603	0.318 ±0.115	0.173 ±0.032	0.230 ±0.114	0.227 ±0.133	8.287 ±1.762	0.991 ±0.390
Intestines	3.178 ±1.585	4.581 ±1.067	3.040 ±3.551	1.523 ±0.857	1.640 ±0.871	7.657 ±0.643	1.890 ±0.132
Lungs	0.770 ±0.206	0.074 ±0.017	0.320 ±0.313	0.110 ±0.036	0.327 ±0.312	8.623 ±1.828	0.502 ±0.312
Femur	0.830 ±0.175	0.085 ±0.048	0.107 ±0.031	0.137 ±0.080	0.197 ±0.176	7.463 ±1.831	1.511 ±0.527
Kidneys	2.218 ±0.590	0.665 ±0.132	0.440 ±0.036	0.807 ±0.055	1.170 ±0.554	7.163 ±0.974	10.162 ±0.793
Urine	83.853 ±3.727	70.138 ±6.195	61.710 ±32.109	24.107 ±14.486	4.020 ±3.343	6.730 ±1.057	10.610 ±0.821
Bladder	4.318 ±1.088	19.640 ±4.437	31.810 ±18.142	56.147 ±41.510	59.630 ±5.079	10.877 ±2.538	18.558 ±0.258
Heart	0.865 ±0.134	0.078 ±0.010	0.117 ±0.015	0.197 ±0.144	0.103 ±0.035	7.940 ±2.088	1.049 ±0.882
Carcass	3.018 ±0.662	5.018 ±1.280	1.787 ±0.581	13.953 ±6.143	29.027 ±7.402	9.600 ±1.706	4.216 ±1.021
Blood	0.852 ±0.327	0.553 ±0.573	0.200 ±0.046	2.257 ±1.764	3.752 ±0.640	7.803 ±1.401	2.132 ±0.055
Kidney+Bladder +Urine	89.378 ±1.941	90.443 ±5.892	93.964 ±3.961	81.060 ±7.277	64.820 ±5.536	24.770 ±2.105	39.330 ±2.770
Liver+ Intestines	4.040 ±2.920	5.141 ±1.762	3.361 ±2.510	1.942 ±0.821	2.051 ±1.022	16.637 ±3.180	10.080 ±6.840

documented to increase in lung, spleen, stomach, thyroid and bone, while decrease in thymus and pancreas [28]. Likewise, chloroquine, a precursor for the anti-malarial drug, has shown to significantly increase the uptake of sodium pertechnetate in the blood and liver [25]. Such results have been interpreted on the basis of metabolism, therapeutic action, toxicity and/or immunosuppressive actions of the particular administered drug, eventually affecting the biodistribution of the radiopharmaceutical.

In our study, the % TRD in the urinary tract (Figure 2) is different in all experimental subgroups as compared to the control group. These results indicate that the renal clearance of ^{99m}Tc-DTPA may be changed when DOX was administered prior to the radiopharmaceutical. Particularly, when the time interval between the radiopharmaceutical and DOX was 48, 72 and 96 hours, the renal clearance of ^{99m}Tc-DTPA was significantly less ($p < 0.05$) as compared to the control group. Furthermore, Figure 3 showed a reciprocal relationship of liver %TRD compared to that of the urinary tract. The increase of liver %TRD was maximum ($p < 0.001$) at an interval of 72 hrs (8.98 ±2.74); at this time point, maximum decline in urinary tract %TRD was observed. These findings indicate that the DRI between DOX and ^{99m}Tc-DTPA may alter the biodistribution of ^{99m}Tc-DTPA and may complicate the interpretation of scintigraphy imaging.

The hypothesized DRI is supported by the fact that both DOX and DTPA are metal chelators [24]. Consequently, some quantity of ^{99m}Tc-DTPA may be chelated by DOX [31] and directed away from the kidney system, resulting in a %TRD decline for urinary tract as depicted in Figure 2. Similarly, increased activity in the liver may be explained on the basis of chelation of ^{99m}Tc-DTPA with DOX that draws it in the liver in greater concentrations than the control group. Subsequently, increased excretion of ^{99m}Tc-DTPA in bile is supported by the statistically significant relative increase in %TRD observed in the 72 hours interval subgroup (16.64 ±3.01) as shown in Figure 4.

Decreased renal clearance and increased biliary clearance of ^{99m}Tc-DTPA was not seen at shorter time intervals (e.g. 4 hours) between administration of DOX and ^{99m}Tc-DTPA. Perhaps for shorter time gaps between DOX and ^{99m}Tc-DTPA, DOX extensively binds to plasma protein with limited distribution; the plasma bound DOX would not be capable to interact with ^{99m}Tc-DTPA [32-37]. Importantly, the chemotherapy drug appears capable for altering the physiological status of the given organ or the chemical identity of the radiopharmaceutical [38]. Moreover, a larger number of experimental animals in the subgroups may promote more sensitive measurements and thereby facilitate to observe the argued DRI.

Both DOX and ^{99m}Tc-DTPA show similar PK in rats as compared to humans; therefore, it is expected that the observed trends of altered radiopharmaceuticals in Sprague-Dawley may also provide fairly accurate insights into the behavior of these DRI in humans. Nevertheless, the overall time for drug clearance is expected to be shorter in rats as compared to humans, presumably due to smaller body surface area, faster heart rate and thereby faster blood flow [39-41].

CONCLUSION

The present work was designed to study the influence of DOX on the biodistribution of ^{99m}Tc-DTPA in rats;

significant alterations in the biodistribution of ^{99m}Tc-DTPA were observed. Specifically, the mean activity in rat urinary system decreased significantly ($p<0.001$) while significant increase ($p<0.001$) in liver uptake was observed. The altered behavior was more obvious when the time interval between sequentially injected DOX and ^{99m}Tc-DTPA was 72 hours. These findings indicate that the interpretation of renal scintigraphy study using ^{99m}Tc-DTPA may be complicated in patients receiving DOX based chemotherapy and demands caution for proper assessment. Furthermore, there is a need to thoroughly explore Drug-Radiopharmaceutical interactions by investigating the behavior of other chemotherapy drugs and radiopharmaceuticals that may be used concurrently or in close conjunction to one another in clinical practice.

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