The Effect of Vincristine on the Biodistribution of Technetium-99m DTPA, GHA, and DMSA in Balb/c Female Mice

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Objective: Vincristine has been widely used in various chemotherapeutic protocols in oncology. The purpose of this study was to evaluate the effect of vincristine on the biodistribution of ^{99m}Tc-DMSA, ^{99m}Tc-GHA, and ^{99m}Tc-DTPA in Balb/c female mice.

Methods: Vincristine (0.03 mg, 0.3 mL) was injected into female isogenic Balb/c mice (n = 15), in 3 doses over an interval of 96 h. The ^{99m}Tc-DMSA, ^{99m}Tc-GHA, or ^{99m}Tc-DTPA (7.4 MBq) was administered after the last dose of vincristine. After 0.5 h the animals were killed rapidly. The organs (pancreas, thyroid, brain, thymus, ovary, uterus, spleen, kidney, heart, stomach, lung, liver, bone, and lymph nodes) were isolated and the radioactivity in each organ was counted in a NaI(Tl) well counter. The percentage of radioactivity (%) in each was calculated and compared with the control group. Statistical analysis was performed by Wilcoxon test ($P < 0.05$).

Results: The percentage of ^{99m}Tc-DMSA was increased in the lung, pancreas, heart, thyroid, brain, bone, and lymph nodes (inguinal and mesenteric). The percentage of ^{99m}Tc-GHA was decreased in the uterus, ovary, spleen, thymus, lymph nodes (inguinal and mesenteric), kidney, and heart. The percentage of ^{99m}Tc-DTPA was increased in thymus, lymph nodes (inguinal and mesenteric), ovary, uterus, spleen, kidney, heart, stomach, lung, liver, and bone.

Conclusion: The results could be explained by the metabolization, toxic effect, therapeutic, or immunosupressive action of the studied chemotherapeutic drug.

Key Words: technetium-99m-DMSA; technetium-99m-GHA; technetium-99m-DTPA; vincristine; drug interaction; biodistribution

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The use of radionuclides for medical and basic research applications has continued to grow at a rapid pace. Procedures based on the use of radiotracers for imaging and for radiotherapy have become established clinical modalities. Sometimes, nuclear medicine is described as a triangle with the patient in the center and the biomedical problem, the radiopharmaceutical, and the instruments occupying the 3 corners (*1*,*2*). Nuclear medicine, which applies radioactive tracer technology, has been used for localizing tumors either by a defect of normal function or increased uptake of tracers that is due to increased function in the tumors (*1*,*3*). More than 80% of all imaging studies currently use ^{99m}Tc (*1*–*3*). Unexpected patterns of radiopharmaceutical distribution provoke a flurry of inquiries regarding the quality of the administered agent. The alterations in biodistribution may be related to a therapeutic drug interaction (*4*).

Vincristine is a natural product derived from the periwinkle plant, *Vinca rosea Linn*, described in medicinal folklore in various parts of the world. The vinca alkaloids are cell-cycle–specific agents and block cells in mitosis (*5*). The biologic activity of this drug can be explained by its ability to bind specifically to tubulin and block the ability of the protein to polymerize into microtubules. Through disruption of the microtubules of the mitotic apparatus, cell division is arrested in metaphase (*5*,*6*). Side effects of the vinca alkaloids, such as their neurotoxicity, may be due to disruption of these functions. Such multidrug-resistant tumor cells display cross-resistance to vinca alkaloids, the epipodophyllotoxins, anthracyclines, dactinomycin, and colchicine (*7*). This drug has a broad spectrum of antitumor activity and is used in treating childhood leukemia, solid tumors, Hodgkin's disease, and other lymphomas (*5*,*6*).

It has been reported that many chemotherapeutic drugs can alter the biodistribution of radiopharmaceuticals (*8*). Mattos et al. (*9*), using an animal model, described vincristine as capable of altering the uptake of the ^{99m}Tc-methylenediphosphonic acid (MDP) in many organs. Britto et al. (*10*) reported that this chemotherapeutic drug also alters the biodistribution of ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA). Gomes et al. (*11*) demonstrated that mitmomycin-C also alters the biodistribution of ^{99m}Tc-MDP.

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The accumulation of ^{99m}Tc-DMSA in the kidneys is probably due to its binding to metallothionein, a heavy metal–binding protein, which has approximately 50 mercapto groups per mol. This radiopharmaceutical accumulates mostly in the proximal and distal tubular sites of the cortex and to a lesser extent in the renal medulla, glomeruli, collecting tubules, and blood vessels. Because ^{99m}Tc-DMSA is bound to plasma proteins to a large extent (75%–90%), glomerular filtration is insignificant compared with tubular secretion. This radiopharmaceutical has a slow renal clearance, with 37% of the injected dose excreted within 24 h (*5–7,12*).

Technetium-99m-GHA is used to visualize the kidneys, investigate renal perfusion and morphology, evaluate renal transplants, and image brain tumors and other brain lesions. Technetium-99m-GHA is excreted mainly by the kidneys through glomerular filtration and tubular secretion. Protein-bound ^{99m}Tc-GHA is excreted by tubular secretion, whereas the unbound component is excreted by glomerular filtration. The retention in renal cortex is 10% of the injected dose at 1h, and urinary excretion is 70% within 24 h (*12*). A variety of drug interactions has been documented. These affect biodistribution of the radiopharmaceutical and could influence the imaging procedure outcome (*4,8,10,11*).

Technetium-99m-DTPA is primarily used for renal imaging and for measuring glomerular filtration rate. After intravenous injection it is excreted entirely by glomerular filtration. Technetium-99m-DTPA is used for renal imaging because it has rapid elimination by filtration. Early images of the kidney allow good demonstration of the parenchyma because of the blood supply in the kidney (*12*).

A patient receiving chemotherapeutic treatment can be sent to a nuclear medicine facility for evaluation. We studied the effect of vincristine on the biodistribution of ^{99m}Tc-DMSA, ^{99m}Tc-GHA, and ^{99m}Tc-DTPA in female mice.

MATERIALS AND METHODS

Vincristine (Oncovin; Eli Lilly, Brazil) (0.03 mg, 0.3 mL) was administered through the ocular plexus into female isogenic Balb/c mice (n = 15), in 3 doses over an interval of 96 h. This dose of vincristine is similar to that administered to humans (*5*). These experiments were performed in compliance with guidelines on the use of living animals in scientific investigations (*13*). One hour after the last dose, 7.4 MBq of ^{99m}Tc-DMSA, ^{99m}Tc-GHA, or ^{99m}Tc-DTPA were administered through the ocular plexus. In the control group (n = 15), vincristine was not administered. The radiochemical quality control was performed by chromatography. Labeling efficiency was >95% and the percentage of free pertechnetate was <5%. After 0.5 h the animals were quickly killed. The organs (pancreas, thyroid, brain, thymus, ovary, uterus, spleen, kidney, heart, stomach, lung, liver, lymph nodes [inguinal and mesenteric], and bone) were isolated and the radioactivity of the radiopharmaceuticals counted in a well counter NaI(Tl) (Automatic Gamma Counter, 1272 Clinigamma; LKB, Wallac, Finland). The percentage of radioactivity in the organs was calculated. The percentage of radioactivity in each organ was compared with the control group. Statistical analysis were performed by Wilcoxon test ($P < 0.05$).

RESULTS

The effects of vincristine on the uptake of radiopharmaceuticals in isolated organs from treated and nontreated animals are shown in Tables 1, 2, and 3. Table 1 shows the percentage uptake of ^{99m}Tc-DMSA in the group of mice that was treated with vincristine and in the control group. The results reveal an increased and significant uptake ($P \leqq 0.05$, Wilcoxon test) in lung, pancreas, heart, thyroid, brain, bone, and lymph nodes (inguinal and mesenteric).

Table 2 shows the organs where the percentage uptake of ^{99m}Tc-GHA was decreased after the animals were treated with vincristine and compared with the control group. The results reveal a decreased and significant uptake ($P \leqq 0.05$, Wilcoxon test) in the uterus, ovary, spleen, thymus, lymph nodes (inguinal and mesenteric), kidney, and heart.

Table 3 shows the percentage uptake of ^{99m}Tc-DTPA in the group of mice that was treated with vincristine and the control group. The results reveal an increased and significant uptake ($P \leqq 0.05$, Wilcoxon test) uptake in the uterus, ovary, spleen, thymus, lymph nodes (inguinal and mesenteric), kidney, lung, liver, stomach, heart, and bone.

DISCUSSION

There is considerable evidence that the pharmacokinetics of radiopharmaceuticals may be altered by a variety of drugs, disease states, and surgical procedures. If unknown, such alterations may lead to poor organ visualization, a requirement to repeat the procedure, unnecessary radiation exposure, or even misdiagnosis (*1–4*). It is worthwhile to establish the effects of various drugs on the biodistribution of radiopharmaceuticals.

As vincristine is an immunosuppressive drug (*5,6*), this effect

TABLE 1
Effect of Vincristine on the Biodistribution of Technetium-99m DMSA in Mice

Organ	% Uptake	
	Control (n = 15)	Treated (n = 15)
Lung	0.9470 ± 0.2050	2.2530 ± 0.4946
Pancreas	0.0443 ± 0.0074	0.0943 ± 0.0177
Heart	0.4258 ± 0.0660	0.8077 ± 0.1318
Thyroid	0.0479 ± 0.0143	0.0938 ± 0.0252
Brain	0.0990 ± 0.0240	0.2529 ± 0.0676
Bone	0.2198 ± 0.0400	0.4158 ± 0.0813
Lymph node inguinal	0.0513 ± 0.0149	0.1163 ± 0.0307
Lymph node mesenteric	0.0558 ± 0.0118	0.0888 ± 0.0263
Uterus	0.1644 ± 0.0039	0.1654 ± 0.0020
Ovary	0.1005 ± 0.0229	0.1017 ± 0.0231
Spleen	0.2104 ± 0.0283	0.2230 ± 0.0351
Thymus	0.0718 ± 0.0125	0.0841 ± 0.0200
Kidney	7.5642 ± 0.6362	6.9787 ± 1.0892
Liver	6.1344 ± 1.0150	6.5146 ± 0.6660
Stomach	0.4325 ± 0.0426	0.4759 ± 0.1160

can explain the alteration of the radiopharmaceuticals' biodistribution in lymph nodes. The uptake of ^{99m}Tc-MDP also has been documented in lymph nodes from animals treated with vincristine (*9*).

Gomes et al. (*11*) reported that mitomycin-C increased the uptake of ^{99m}Tc-MDP in thymus, ovary, uterus, heart, stomach, pancreas, kidneys, spleen, and lungs. A similar effect was observed following vincristine in the lung with ^{99m}Tc-DMSA and ^{99m}Tc-DTPA, in the pancreas with ^{99m}Tc-DMSA, and in the heart with all of the radiopharmaceuticals studied.

The alteration of the uptake of ^{99m}Tc-GHA and ^{99m}Tc-DTPA in the kidneys in animals treated with vincristine could be the result of the known nephrotoxicity of vincristine (*8*). Vincristine nephrotoxicity also has increasead the renal retention to other radiopharmaceuticals (*15,16*). We speculate that the capability of this drug to produce hyponatremia with abnormal water retention is probably due to the nonosmotic release of antidiuretic hormone (*5,14*) and could be responsible for the alterations of the uptake of ^{99m}Tc-GHA and ^{99m}Tc-DTPA in the kidneys.

There are no data in the literature that could explain the modifications of ^{99m}Tc-GHA and ^{99m}Tc-DTPA uptake in the uterus and ovaries in the animals treated with vincristine. Azoospermia and increased plasma concentrations of follicle-stimulating hormone have occurred in males that received combination chemotherapy that included vincristine and prednisone with cyclophosphamide or mechlorethamine and procarbazine (*14*). Similarly, we speculate that in females, alterations of ^{99m}Tc-GHA and ^{99m}Tc-DTPA uptake in the uterus and ovaries may occur.

Bone marrow supression is the most frequent complication in the chemotherapy protocols with vincristine (*5,7*). Mattos et al. (*9,17*) have already reported that vincristine is capable of altering the uptake of ^{99m}Tc-MDP in bone. This could explain the alteration of ^{99m}Tc-DMSA and ^{99m}Tc-DTPA uptake in bone that we observed.

TABLE 2
Effect of Vincristine on the Biodistribution of Technetium-99m GHA in Mice

Organ	% Uptake	
	Control (n = 15)	Treated (n = 15)
Uterus	0.0926 ± 0.0048	0.0253 ± 0.0040
Ovary	0.0301 ± 0.0026	0.0105 ± 0.0013
Spleen	0.0662 ± 0.0115	0.0235 ± 0.0024
Thymus	0.0368 ± 0.0089	0.0111 ± 0.0019
Lymph node inguinal	0.2038 ± 0.0110	0.0277 ± 0.0057
Lymph node mesenteric	0.0832 ± 0.0055	0.0111 ± 0.0006
Kidney	3.4316 ± 0.3105	1.2583 ± 0.2581
Heart	0.1100 ± 0.0070	0.0655 ± 0.0137
Lung	0.3639 ± 0.0141	0.3544 ± 0.0198
Liver	0.4890 ± 0.0366	0.4738 ± 0.0537
Pancreas	0.0172 ± 0.0023	0.0170 ± 0.0028
Stomach	0.4384 ± 0.0477	0.4355 ± 0.0499
Thyroid	0.0484 ± 0.0100	0.0493 ± 0.0087
Brain	0.0483 ± 0.0133	0.0444 ± 0.0038
Bone	0.0348 ± 0.0033	0.0340 ± 0.0029

TABLE 3
Effect of Vincristine on the Biodistribution of Technetium-99m DTPA in Mice

Organ	% Uptake	
	Control (n = 15)	Treated (n = 15)
Thymus	0.0103 ± 0.0086	0.0353 ± 0.0024
Lymph node inguinal	0.0141 ± 0.0027	0.0670 ± 0.0056
Lymph node mesenteric	0.0201 ± 0.0074	0.0481 ± 0.0125
Ovary	0.0107 ± 0.0074	0.0475 ± 0.0112
Uterus	0.0204 ± 0.0016	0.1350 ± 0.0098
Spleen	0.0134 ± 0.0068	0.0410 ± 0.0112
Kidney	0.1587 ± 0.0468	0.7891 ± 0.0115
Heart	0.0165 ± 0.0018	0.1632 ± 0.0691
Stomach	0.0334 ± 0.0192	0.2334 ± 0.0142
Lung	0.0272 ± 0.0095	0.4783 ± 0.0181
Liver	0.0668 ± 0.0122	0.3564 ± 0.0102
Bone	0.0162 ± 0.0036	0.1101 ± 0.0311
Pancreas	0.0194 ± 0.0018	0.0130 ± 0.0021
Thyroid	0.0871 ± 0.0123	0.0760 ± 0.0151
Brain	0.0610 ± 0.0132	0.0699 ± 0.0211

CONCLUSION

Our results show: (a) the uptake of ^{99m}Tc-DMSA was increased in the lung, pancreas, heart, thyroid, brain, bone, and lymph nodes (inguinal and mesenteric); (b) the uptake of ^{99m}Tc-GHA was decreased in the uterus, ovary, spleen, thymus, lymph nodes (inguinal and mesenteric), kidney, and heart; and (c) the uptake of ^{99m}Tc-DTPA was increased in the thymus, lymph nodes (inguinal and mesenteric), ovary, uterus, spleen, kidney, heart, stomach, lung, liver, and bone following vincristine therapy. We speculate that these results could be explained by the metabolization and/or therapeutic and immunosupressive action of vincristine. Studies of the effects of this chemotherapeutic drug on the biodistribution with other ^{99m}Tc radiopharmaceuticals are now in progress. The renal examinations of patients that have been conducted in our nuclear medicine department after treatment with vincristine also are being evaluated.

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