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Full Length Research Paper

Effects of the chemotherapeutic drug (vincristine) in organs and the influence on the bioavailability of two radio-biocomplexes used for bone evaluations in balb/c female mice

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The development of animal model to evaluate the toxicological action of compounds used as pharmaceutical drugs is desired. The model described in this work is based on the capability of drugs to alter the bioavailability of radiopharmaceuticals (radiobiocomplexes) labeled with technetium-99 m (^{99m}Tc). There are evidences that the bioavailability or the pharmacokinetic of radiobiocomplexes can be modified by some factors, as drugs, due to their toxicological action in specific organs. Vincristine is a natural product that has been utilized in oncology. The vincristine effect on the bioavailability of the radiobiocomplexes ^{99m}Tc-methylenediphosphonic acid (^{99m}Tc-MDP) and ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) in Balb/c female mice was evaluated. The fragments of kidney were processed to light microscopy and transmission electron microscopy. The aim of this work was to study at structural and ultrastructural levels the alterations caused by vincristine in organs. One hour after the last dose of vincristine, ^{99m}Tc-PYP or ^{99m}Tc-MDP was injected, the animals were sacrificed and the percentage of radioactivity (%ATI) was determined in the isolated organs. Concerning ^{99m}Tc-PYP, the %ATI (i) decreased in spleen, thymus, lymph nodes (inguinal and mesentheric), kidney, lung, liver, pancreas, stomach, heart and brain and (ii) increased in bone and thyroid. Concerning ^{99m}Tc-MDP, the %ATI (iii) decreased in spleen, thymus, lymph nodes (inguinal and mesentheric), kidney, liver, pancreas, stomach, heart, brain, bone, ovary and uterus. In conclusion, the toxic effect of vincristine in determined organs could be responsible for the alteration of the uptake of the studied radiobiocomplexes.

Key words: Radiobiocomplexes, vincristine, drug interaction, nuclear medicine, oncology.

INTRODUCTION

Although the great relevance of nuclear medicine is well characterized, some authors have reported that other factors, in addition to the disease, can interfere in the bioavailability of a radiobiocomplex (Bernardo et al., 2005).

The lack of knowledge of these factors is undesirable, and the consequences are (i) the possibility of misdiagnosis (misleading information that can either mask or mimic certain disease symptoms) and/or (ii) the repetition of the examination with an increase in radiation dose to the patient (Hladik et al., 1987; Sampson, 1999). Some authors have reported that various synthetic drugs (medications) are capable of altering the bioavailability of different radiobiocomplexes (Hladik et al., 1987; Hesslewood and Leung, 1994; Sampson, 1999). Moreover, other authors have suggested that medicinal plants (natural drugs) can be also associated with the drug interaction with radiobiocomplexes. Santos-Filho et al. (2004) have reported that *Mentha crispa* altered the bioavailability of the $Na^{99m}TcO_4$ and there is an increase of the radioactivity in the thyroid. Moreno et al. (2004) have verified that the *Ginkgo biloba* alters the bioavailability of $Na^{99m}TcO_4$ in rats. Santos-Filho and Bernardo Filho (2005) have demonstrated that *Hypericum perforatum* decreases the bioavailability of the $Na^{99m}TcO_4$ in the bone, muscle and thyroid and increases the bioavailability in pancreas. Passos et al. (2002) have also demonstrated that dietary conditions can also interfere with the bioavailability of radiobiocomplexes. The type of the food seems to contribute to unexpected bioavailability of radiobiocomplex (Capriles et al., 2002; Diré et al., 2003).

The radiobiocomplexes have been in use for many years for diagnosis and therapy of a wide variety of diseases (Saha, 2004). Since a therapeutic drug or a natural product (Hung et al., 1996; Oliveira et al., 1997; Vidal et al., 1998) can also modify (i) the nature of the ^{99m}Tc-radiobiocomplex, (ii) the biochemical milieu to which the radiobiocomplex is exposed or (iii) its capability to bind to blood elements, an unexpected behavior of the radiobiocomplex may be observed in patients under drug therapy. It has been reported that vincristine interferes with the adrenal cortex imaging when this clinical evalua-tion is carried out using ^{131}I-iodomethylnorcholesterol and ^{75}Se-selenomethylnorcholesterol. It is observed an in-crease in the renal retention due to nephrotoxicity of this chemotherapeutic drug (Sampson, 1993; Hesslewood and Leung, 1994; Owunwanne, 1995; Saha, 2004).

Vincristine is a chemotherapeutic drug used in several protocols in oncology. Evidence exists that the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was associated with toxicity as nausea or vomiting, alopecia, peripheral neurologic toxicity, and constipatin (Zinzani et al., 2004). Vincristine is used together with interferon, cyclophosphamide, bleomycin, imiquimod, becaplermin, and laser therapy in the treatment of infantile hemangiomas (Pandey et al., 2008). The vinca alkaloids are cell-cycle-specific agents and, in common with other drugs such as colchicine and podophyllotoxin, block cells in mitosis (Chabner et al., 1996). The biological activities of this drug can be explained by its ability to bind specifically to tubulin and to 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. In addition to their key role in the formation of mitotic spindles, microtubules are involved in other cellular functions such as movement, phagocytosis, and axonal transport. Side effects of the vinca alkaloids, such as their neurotoxicity, may be due to disruption of these functions (McQuairrie, 1987; Chabner et al., 1996).

This drug has a broad spectrum of anti-tumor activity and it is used on the treatment of childish leukemia, solid tumor, Hodgkin disease and other lymphomas (Anderson, 1981; Mareel and De Mets, 1984; Salloum and Schubert, 1996). Such multi-drug-resistant tumor cells display cross-resistance to vinca alkaloids, epipodophyllotoxins, anthracyclines, dactinomycin, and colchicine. Chromosomal abnormalities consistent with gene amplification have been observed in resistant cells in culture, and the cells contain markedly increased the levels of the P-glycoprotein. A membrane efflux pump that transports drugs from the cells Ca2+-channel blockers, such as verapamil, can reverse the resistance of this type. Other membrane transporters may mediate multi-drug resistant, still other forms of resistance to vinca alkaloids involve mutations in tubulin gene that prevent the effective binding of the inhibitors to their target (Chabner et al., 1996).

The introduction of the short half-life technetium-99 m (^{99m}Tc) in 1960 paved the way for convenient method of radiolabelling (Saha, 2004). ^{99m}Tc is the isotope most commonly used in nuclear medicine, because of its nuclear characteristics: emission of gamma radiation of low energy (140keV), short half-life (6 h), absence of beta emission, 100% of decay by isomeric transition to ^{99}Tc. Labeled molecules with ^{99m} Tc are used for visualization of many organs (Saha, 2004; Moraes et al., 2005).

Bone metastases are the commonest contributor to morbidity in cancer patients, especially in those with breast and prostate cancer (Coleman, 1997; Vinã, 2005). Metastatic bone dissemination gives rise to pain, with pain being the most frequent clinical manifestation from bone metastases (Vinã, 2005). Biphosphonates have become an integral tool in the management of malignant bone disease, but they had not demonstrated clinical benefit in men with prostate cancer until recently (Saad et al., 2004). Bone scintigraphy is one the most frequently performed of all radionuclide procedures. Radionuclide bone imaging is quick, relatively inexpensive, widely available, and is invaluable in the diagnostic evaluation of numerous pathologic conditions. The procedure is performed with technetium-99 m-labeled diphosphonates (Love et al., 2003).

It is well established that phosphorous compounds have affinity for hydroxyapatite crystals. Following intra-

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venous injection, the ^{99m}Tc-phosphorus-radiobiocomplex is bound to bone surface probably as a result of adsorption on to the hydroxyapatite crystal (Owunwanne, 1995). ^{99m}Tc-phosphorus-radiobiocomplex also accumulates in infarcted myocardium owing to adsorption onto amorphous calcium phosphate or by complexation with denatured native proteins and other macromolecules. The major pathway of elimination of ^{99m}Tc-phosphorus-radiobiocomplex is through the kidney.

The main uses of these radiobiocomplexes are to the localization of primary bone tumors, metastatic tumors and metabolic bone diseases (Sampson, 1993; Owunwanne, 1995). These radiobiocomplexes are utilized for bone scanning. ^{99m}Tc-PYP has been widely used in the detection of myocardial infarcts. A variety of drug interactions has been documented which affect the bioavailability of the radiobiocomplex and hence could influence the diagnosis of diseases (Hesslewood and Leung, 1994).

With the aim to develop an animal model to study the toxicological effect of drugs and as a patient under chemotherapeutic treatment can be submitted to a nuclear medicine procedure, we decided to evaluate the effect of vincristine on the bioavailability of two radiobiocomplexes used for bone evaluations, the ^{99m}Tc-MDP and the ^{99m}Tc-PYP in female mice.

METHODS

The experiments with the use of animals were conducted in accordance with the ethical protocol established for the *Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro*, and with the Guide to the Care and Use of Experimental Animals (1984). Vincristine (Oncovin, Eli Lilly do Brasil Ltda, Brazil) (0.03 mg, 0.3 ml) was administered by ocular plexus via into female isogenic Balb/c mice (n=15), in three doses with a total interval of 96 h. For the studies in the transmission electron microscopy the fragments of kidney were fixed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.2), added in 0.25% tannic acid. The postfixation was in 1% OsO_4, 0.8% potassium ferricyanide ($K_3Fe(CN)_6$) and 5 mM calcium cloride ($CaCl_2$) in 0.1 M cacodylate buffer. The tissues were dehydrated in acetone and embedded in epon. For light microscopy semithin sections were stained in toluidine blue and observed in optical microscope (Olympus BH2-RFCA, Japan). For transmission electron microscopy (TEM) ultrathin sections were stained in uranyl acetate and lead citrate and observed in transmission electron microscope (EM 906 Zeiss). One hour after the last dose, 0.3 ml of ^{99m}Tc-MDP or ^{99m}Tc-PYP (7.4 MBq) was injected by the same via. In the control group (n=15), vincristine was not administered. To prepare the ^{99m}Tc-MDP or ^{99m}Tc-PYP, ^{99m}Tc, as sodium pertechnetate, recently milked from a ^{99}Mo/^{99m}Tc generator (Instituto de Pesquisas Energéticas e Nucleares, Brazil) was added to a kit of PYP or MDP (Laboratório de Radiofarmácia, INCa, Brazil). The radiochemical control was performed by ascendent chromatography, using paper Whatman n^{o} 1 and 0.9% NaCl solution and acetone as mobile phases. The labeling efficiency was > 95% and the percentage of free pertechnetate was < 5%. After 0.5 h the animals were rapidly sacrificed. The various organs were isolated: pancreas, thyroid, brain, thymus, ovary, uterus, spleen, kidney, heart, stomach, lung, liver, bone and lymph nodes (inguinal and mesentheric), and the radioactivity of the ^{99m}Tc-PYP or ^{99m}T-MDP were counted in a well counter NaI(Tl) (Automatic Gamma Counter, 1272 Clinigamma, LKB, Wallac, Finland). The percentages of radioactivity (% ATI) in the organs were calculated dividing the activity in each organ by the total activity administered. The percentage of radioactivity in each organ was compared between the two groups, control and the treated with vincristine. Statistical analysis was performed by Wilcoxon test ($p < 0.05$).

RESULTS

The effect of vincristine on the uptake of the ^{99m}Tc-MDP in isolated organs from treated and no treated animals is shown in Tables 1 and 2. The results concerning the ^{99m}Tc-PYP are shown in Tables 3, 4 and 5. Table 1 shows the uptake (%ATI) of ^{99m}Tc-MDP in different organs and the analysis of the results reveals a decrease of the uptake in uterus, ovary, spleen, thymus, lymph nodes (inguinal and mesentheric), kidney, liver, pancreas, stomach, heart, brain and bone. Table 2 shows the uptake (%ATI) of ^{99m}Tc-MDP in various organs and the analysis of the results reveals no significant reduction of the uptake in lung and thyroid. Table 3 shows that the uptake (%ATI) of ^{99m}Tc-PYP was decreased in spleen, thymus, lymph nodes (inguinal and mesentheric), kidney, lung, liver, pancreas, stomach, heart and brain. Table 4 shows that the %ATI of ^{99m}Tc-PYP was increased in bone and thyroid. Table 5 shows that the radioactivity of ^{99m}Tc-PYP was not altered in uterus and ovary.

The results in the light microscope observations did not demonstrate alterations in both control and treated animals (Figure 1). The electron micrograph (Figure 2) of control animal kidney shows glomerular capillaries presenting fenestration of the endothelial cells. The fenestrae of the capillaries are bridged by diaphragms. The pedicels are shown around the basal membrane involving the capillary. The electron micrograph of animal treated kidney (Figure 3) displays a glomerular capillary where identified fenestrae of irregular outline, a thickening basal membrane and pedicels is absent.

DISCUSSION

The use of protocols with vincristine is widely used in oncology. Many biological effects of vincristine have already reported (Chabner et al., 1996; McQuarrie, 1987). Interestingly, there is no data in the literature establishing animal model to study the biological effect of pharmaceuticals. Here, we evaluated the action of chemotherapeutic drugs in the interaction with radiopharmaceuticals using Balb/c female mice (Mattos et al., 2001; Gomes et al., 2002a; Gomes et al., 2002b). Besides, an unexpected pattern of radiopharmaceutical distribution provokes a flurry of inquiries regarding the quality of the administered agent. But, the alterations in biodistribution may be related to the chemotherapeutic drug interaction (Mattos et al., 2000; Mattos et al., 2001; Gomes et al., 2002a). Any chemical agent or other

Table 1. Effect of vincristine on the bioavailability of technetium-99m-methylenediphosphonic acid in mice.

Organ	%ATI	
	Control	Treated
Uterus	0.0379 ± 0.0039	0.0104 ± 0.0028 p<0.05
Ovary	0.0179 ± 0.0014	0.0045 ± 0.0011 p<0.05
Spleen	0.0406 ± 0.0013	0.0193 ± 0.0011 p<0.05
Thymus	0.0216 ± 0.0038	0.0083 ± 0.0019 p<0.05
Lymph node inguinal	0.1055 ± 0.0074	0.0062 ± 0.0017 p<0.05
Lymph node mesentheric	0.0528 ± 0.0153	0.0058 ± 0.0008 p<0.05
Kidney	0.4540 ± 0.0252	0.1723 ± 0.0217 p<0.05
Liver	0.2616 ± 0.0184	0.0880 ± 0.0050 p<0.05
Pancreas	0.0225 ± 0.0048	0.0087 ± 0.0017 p<0.05
Stomach	0.1531 ± 0.0142	0.0606 ± 0.0115 p<0.05
Heart	0.1141 ± 0.0146	0.0385 ± 0.0095 p<0.05
Brain	0.2163 ± 0.0311	0.0271 ± 0.0053 p<0.05
Bone	1.1132 ± 0.0584	0.3882 ± 0.0803 p<0.05

Vincristine was administered by ocular plexus via into female mice Balb/c into mice (treated group). The control group did not receive vincristine. After 96hr, ^{99m}Tc -MDP was also injected in both groups of animals. The animals were sacrificed, the organs isolated and the activities (%ATI) determined in each organ. The values are mean ± standard deviation (n=15). The results were compared with the control group, without vincristine, and statistical anallysis were performed (Wilcoxon test, p<0.05).

Table 2. Effect of vincristine on the biodistribution of technetium-99m-methylenediphosphonic acid in mice.

Organ	%ATI	
	Control	Treated
Lung	0.1777 ± 0.0239	0.1770 ± 0.0287
Thyroid	0.0367 ± 0.0039	0.0360 ± 0.0066

Vincristine was administered by ocular plexus via into female mice Balb/c into mice (treated group). The control group did not receive vincristine. After 96hr, ^{99m}Tc-MDP was also injected in both groups of animals. The animals were sacrificed, the organs isolated and the activities (%ATI) determined in each organ. The values are mean ± standard deviation (n=15). The results were compared with the control group, without vincristine, and statistical anallysis were performed (Wilcoxon test, p<0.05).

influence, including a drug, which alters the nature of the biochemical milieu to which tracer is exposed, may result in unexpected behavior of the radiopharmaceutical (Hung et al., 1996; Sampson, 1993).

Vincristine has been used as a component of many chemotherapeutic regimens because of its elative lack of hematologic toxicity. Its mechanism of action is by interfering with microtubule formation and exerts immuno-supressive activity (Mareel and De Mets, 1984; McQuarrie, 1987; Chabner et al., 1996; Salloum and Schubert, 1996). This immunosupressive activity could explain the decrease of the ^{99m}Tc-PYP and ^{99m}Tc-MDP in thymus, spleen and lymph nodes (inguinal and mesentheric). This alteration was related to ^{99m}Tc-MDP (Mattos et al., 1999); it was observed an alteration in uptake in thymus and spleen (Gomes et al., 1998; Britto et al., 1998; Mattos et al., 2000).

The alterations, in the treated animals with vincristine, of the uptake of ^{99m}Tc-PYP and ^{99m}Tc-MDP in kidneys can be due to the capability of this natural compound to produce hyponatremia with abnormal water retention due (probably) to the nonsmotic release of antidiuretic hormome (Chabner et al., 1996) or due to the described nephrotoxicity of vincristine (Hesslewood and Leung, 1994). This alteration was related to ^{99m}Tc-MDP, ^{99m} Tc-DTPA and ^{99m}Tc- DMSA (Gomes et al., 1998; Britto et al., 1998; Mattos et al., 1999; Mattos et al., 2001). The results in the light microscope observations did not demonstrate alterations in both control and treated animals. The electron micrograph of control animal kid-ney shows glomerular capillaries presenting fenestration of the endothelial cells. The fenestrae of the capillaries are bridged by diaphragms. The pedicels are shown around the basal membrane involving the capillary. The electron micrograph of animal treated kidney displays a glomerular capillary where identified fenestrae of irregular outline, a thickening basal membrane and pedicels is absent.

This chemotherapeutic agent is metabolized in liver and the conjugates and metabolites are excreted in the bile. In patients with hepatic dysfunctions (bilirubin greater than 3 mg/dl), a 75% reduction in the vincristine dose is advisable (Anderson, 1981; Chabner et al., 1996). The necessity of this dose adjustment of this vinca

Table 3. Effect of vincristine on the biodistribution of technetium-99m-pyrophosphate in mice.

Organ	%ATI	
	Control	Treated
Spleen	0.3549 ± 0.0463	0.0426 ± 0.0064 p<0.05
Thymus	0.0976 ± 0.0197	0.0095 ± 0.0021 p<0.05
Lymph node inguinal	0.1014 ± 0.0202	0.0184 ± 0.0018 p<0.05
Lymph node mesentheric	0.0324 ± 0.0070	0.0135 ± 0.0018 p<0.05
Kidney	2.6711 ± 0.2475	0.7030 ± 0.1339 p<0.05
Lung	0.3407 ± 0.0242	0.1871 ± 0.0092 p<0.05
Liver	2.9122 ± 0.4501	1.1738 ± 0.0824 p<0.05
Pancreas	0.0622 ± 0.0056	0.0124 ± 0.0028 p<0.05
Stomach	0.3069 ± 0.0617	0.1325 ± 0.0135 p<0.05
Heart	0.8078 ± 0.1098	0.1138 ± 0.0093 p<0.05
Brain	0.4077 ± 0.0863	0.0717 ± 0.0112 p<0.05

Vincristine was administered by ocular plexus via into female mice Balb/c into mice (treated group). The control group did not receive vincristine. After 96hr, ^{99m}Tc-PYP was also injected in both groups of animals. The animals were sacrificed, the organs isolated and the activities (%ATI) determined in each organ. The values are mean ± standard deviation (n=15). The results were compared with the control group, without vincristine, and statistical anallysis were performed (Wilcoxon test, p<0.05).

Table 4. Effect of vincristine on the biodistribution of technetium-99m-pyrophosphate in mice.

Organ	%ATI	
	Control	Treated
Bone	0.0717 ± 0.0081	0.7872 ± 0.1170 p<0.05
Thyroid	0.0141 ± 0.0028	0.0821 ± 0.0213 p<0.05

Vincristine was administered by ocular plexus via into female mice Balb/c into mice (treated group). The control group did not receive vincristine. After 96hr, ^{99m}Tc-PYP was also injected in both groups of animals. The animals were sacrificed, the organs isolated and the activities (%ATI) determined in each organ. The values are mean ± standard deviation (n=15). The results were compared with the control group, without vincristine, and statistical anallysis were performed (Wilcoxon test, p<0.05).

alkaloid could be due to the possible toxic effect of vincristine in the liver and this fact could justify the decrease in the uptake of the ^{99m}Tc-PYP and ^{99m}Tc-MDP in this organ. This alteration was related to ^{99m}Tc -MDP, ^{99m}Tc-PYP, ^{99m}Tc-DTPA and ^{99m}Tc -DMSA (Mattos et al., 1999; Mattos et al., 2001; Gomes et al., 2002a). Rutin increased the uptake of $^{99m}TcO_4Na$ in liver (Bernardo et al., 2004). Rutin is a flavonoid used in conventional and traditional medicine. This substance presents many bio-logical effects, like anti- inflammatory and antispasmodic (Botsaris and Machado, 1999) and has been suggested many pharmacological activities, including myocardial protection and vasodilator (Janbaz et al., 2002).

Side effects of the vinca alkaloids, such as their neurotoxicity, have predictable cumulative effects. Numbness and tingling of the extremities, loss of deep tendon

Table 5. Effect of vincristine on the biodistribution of technetium-99m-pyrophosphte in mice.

Organ	%ATI	
	Control	Treated
Uterus	0.0810 ± 0.0086	0.0811 ± 0.0099
Ovary	0.0294 ± 0.0033	0.0292 ± 0.0029

Vincristine was administered by ocular plexus via into female mice Balb/c into mice (treated group). The control group did not receive vincristine. After 96hr, ^{99m}Tc-PYP was also injected in both groups of animals. The animals were sacrificed, the organs isolated and the activities (%ATI) determined in each organ. The values are mean ± standard deviation (n=15). The results were compared with the control group, without vincristine, and statistical anallysis were performed (Wilcoxon test, p<0.05).

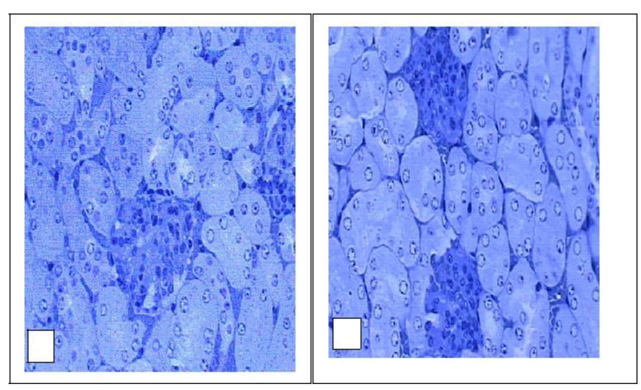

Figure 1. Photomicrographies (x 400) of kidney without alteration in both control and treated group. (A) Control group; (B) treated group.

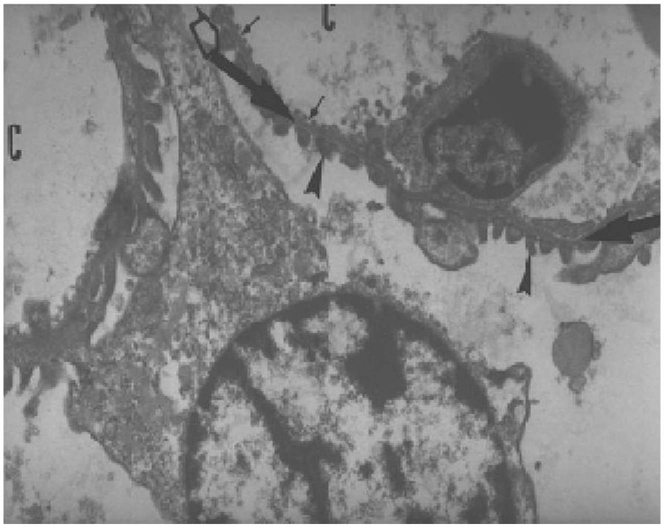

Figure 2. Electron micrograph of control animal kidney that did not receive the chemotherapeutic drug. The glomerular capillaries (C) presenting the fenestrae (small arrows) are observed. The basal membrane (big arrows) surround the capillaries. The pedicels (arrows heads) are showed around the basal membrane; 10.685 X.

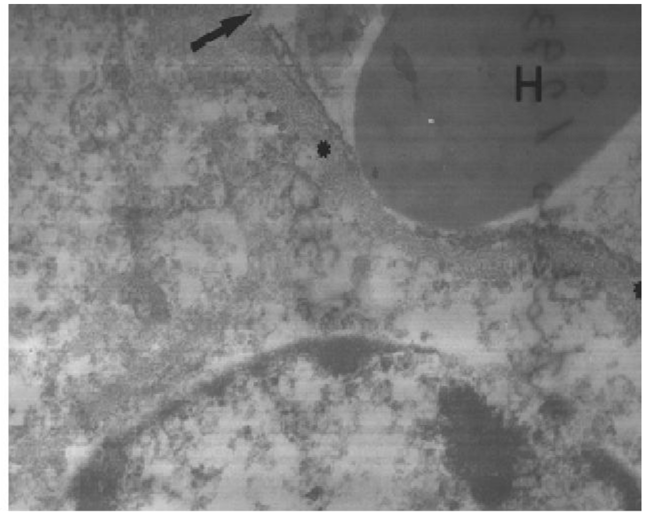

Figure 3. Electron micrograph of kidney of animal treated with the drug. The glomerular capillary is observed containing a red blood cell (H). Fenestrae (arrow) of irregular outline, a basal lamina thickened (asterisks) and absence of pedicels are observed; 29.739 X.

reflexes, and weakness of distal limb musculature constitute the most common and earliest signs. Inadvertent intrathecal vincristine administration produces devastating and invariably fatal central neurotoxicity, with seizures and irreversible coma (Anderson, 1981; McQuaire, 1987; Chabner et al., 1996). These neurological effects could justify the alteration in the fixation of the ^{99m}Tc-PYP and ^{99m}Tc-MDP in brain that is improved by the vincristine treatment.

As bone marrow suppression is the most frequent complications in the protocols with vincristine (Anderson, 1981) this could alter the fixation of the ^{99m}Tc-PYP and ^{99m}Tc-MDP in bone. This alteration was observed to chemotherapic mitomycin-C to ^{99m}Tc-PYP and to ^{99m}Tc-PHY (Gomes et al., 2002a; Gomes et al., 2002b). Cigarette smoke is a complex mixture of chemicals containing more than 4000 different constituents. Some of the compounds identified include pyridine alkaloids, such as nicotine. It was reported that this drug altered the biodistribution of $Na^{99m}TcO_4$ in bone, kidney, lung, spleen stomach, testis and thyroid (Valença et al., 2005).

Ischemic cardiac toxicity and gastrointestinal symtoms have been observed during vincristine therapy (McQuaire, 1987; Chabner et al., 1996). These alterations probably could explain the decreased of the uptake of the studied radiobiocomplexes observed in heart, stomach and pancreas. These results were observed in ^{99m}Tc-MDP and ^{99m}Tc-DMSA (Mattos et al., 1999; Mattos et al., 2001).

In conclusion, the results could be explained by the metabolization and/or therapeutic and immunosupressive action of vincristine. Moreover, as vincristine alters the uptake of both ^{99m}Tc-MDP and ^{99m}Tc-PYP in the bone, it could be necessary to be careful in the interpretation of the examination of patients under this treatment, although our results were obtained with animals. Furthermore, the analysis of the results show that is possible to employ this model to evaluate the toxic effect of pharmaceuticals used by human beings. The effect of this chemotherapeutic drug on the bioavailability with other ^{99m}Tc-radiobiocomplexes is currently in progress in our laboratory.

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