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Effect of Antimalarial Drugs on the Bioavailability of the Methylenediphosphonic Acid Labeled with Technetium99m (99mTc-MDP) in *Wistar* Rats

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ABSTRACT

The aim of this work was to study the effect of antimalarial drugs on the bioavailability of ^{99m}Tc-MDP in rats. Mefloquine (MQ) and artemisinin (AM) were administered in two treated groups (T) and sorbitol in control group (C) for 7 days. Then, ^{99m}Tc-MDP was injected in all groups and %ATI was calculated. A significant increase of %ATI in MQ group, from C to T, occurred in spleen (0.35±0.10to0.58±0.13), liver (1.69±0.28to3.31±0.07) and blood (0.79±0.17to2.09±0.53). The %ATI increased si gnificantly in AM group:femur (2.76±0.59to5.98±0.70), liver (1.69±0.28to4.59±0.68), lungs (0.29±0.05to6.22±0.86), spleen (0.35±0.10 to0.86±0.15) and blood (0.79±0 .17 to4.65 ±0.74). A significant decrease of %ATI occurred in MQ group:bladder (0.75±0.07to0.26±0.05), sto ut bowel (2.13±0.34to0.66±0.19), pancreas (0.87±0.24to0.28±0 .18), kidneys (7.00±1.52to3.46±0.62), brain (0.27±0 .08to 0.05±0.01) and also in AM group:bladder (0.75±0.07t o0.30±0.05), stout bowel (2.13±0.34to0.36±0.08), mu scle (2.04±0.39to0.26±0.06), pancreas (0.87±0.24to0.46±0 .12) and kidneys (7.00±1.52to4.35±0.28). These resu lts could be associated to biological effects of antimalarial drugs.

Key words: Drug interaction, radiopharmaceuticals, ^{99m}Tc-MDP, antimalarial drugs, mefloquine, artemisinin

INTRODUCTION

Malaria, once a target for eradication, remains a major threat for human health, especially in sub-Saharan Africa. An estimated 300-500 million clinical cases occur each year, and between one and three million deaths, primarily of children and pregnant women, are attributable to this disease. Every 40 seconds a child dies of malaria, resulting in a daily loss of more than 2000 young lives worldwide. These estimates render malaria the pre-eminent tropical parasitic disease and one of the top three killers among communicable diseases (Miller et al., 2002; Sachs and Malaney, 2002).

Plasmodium falciparum, one of the four malarial parasite species infecting humans, is the most

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lethal *Plasmodia* and still a major cause of the disease burden and mortality in malaria endemic areas. Due to the wide spread drug resistance in combination with poor socio-economic situation in the vast majority of the endemic countries, malaria is today a great global challenge. The efforts to find a suitable drug is, however, progressing (Bremen, 2001; Miller et al., 2002). Mefloquine and artemisinin are both in the top of the best drugs used in the treatment and prophylaxis of *falciparum* malaria multidrug resistant. Mefloquine is active against all forms of malaria parasites including chloroquine or multidrug resistant strains of *P. falciparum.* It is indicated in severe malaria including cerebral malaria, and it ensures both suppression and cure of infections with multidrug resistant *P. falciparum*. It has no effect on gametocytes of *P. falciparum* and it does not eliminate exoerythrocytic (intrahepatic) stages of *P. vivax* (Schwartz et al., 2001). The exact mechanism of action of mefloquine is unknown. It has schizontocidal activity - due to destruction of asexual erythrocyte forms of *P. falciparum and P. vivax*.

However parasite resistance to the actual antimalarial drugs has already reached alarmingly high levels in Southeast Asia and in the African continent, and, therefore, there is a dire need for new drugs in the prophylaxis and treatment of malaria (WHO, 2000). Artemisinin, an ancient Chinese herbal remedy, represents a new class of antimalarials that is effective against drug-resistant *P. falciparum* strains. Chinese researchers isolated artemisinin or qinghaosu in 1972 from *Artemisia annua, L.* (Klayman et al., 1985). This plant has been used in traditional Chinese medicine as a remedy for chills and fevers for more than 2000 years. The drug is present in the leaves and flowers of the plant (van Agtmael et al., 1999). Western interest in this agent began to grow when multidrug resistant *P. falciparum* strains began to spread, especially in Southeast Asia. Many derivatives have been synthesized from dihydroartemisinin, and out of these, artemether, arteether, artesunic acid and artelinic acid are either currently in use or being evaluated for use.

The advent of Technetium-99m (99mTc) provided the first convenient radionuclide for labeling a variety of molecules and cells used as radiopharmaceuticals. Its wide use in nuclear medicine is due to its optimal physical characteristics (half-life of 6 h, gamma ray energy of 140 KeV and resulting minimal dose to the patient), convenient availability from a $^{99}Mo/^{99m}Tc$ generator, and negligible environmental impact (Early and Sodee, 1995; Saha, 1998). In nuclear medicine, these radiopharmaceuticals are employed in the study of blood flow, metabolism, morphology of an organ and to evaluate the drug formulation and drug delivery systems (Chandra, 1998; Perkins and Frier, 1999). According to Hesselewood and Leung (1994), Owunwanne and Collaborators (1995) and Saha (1998), one of these radiopharmaceuticals is the well known methylenediphosphonic acid labeled with ^{99m}Tc (^{99m}Tc-MDP), which is used to perform bone scintigraphy (Owunwanne et al., 1995; Saha, 1998). The ^{99m}Tc-MDP has been used for bone scanning and for the localization of primary bone tumours, metastatic tumours and metabolic bone diseases.

Many authors have been studying the drug interaction as an important factor that can alter the behavior of the radiopharmaceuticals in different organs and tissues of the animal models (Owunwanne et al., 1998; Mattos et al., 1999; Xavier Holanda et al., 2002; Amorim et al., 2003; Britto et al. 2004; Jales-Jr. et al., 2004). Frequently, this phenomenon is responsible for modification of the bioavailability of the radiopharmaceutical (Owunwanne et al., 1995; Hung et al., 1996; Xavier Holanda et al., 2002; Gomes et al., 2002).

Thus, the nuclear medicine practices have increased continually in recent decades. This modality is chosen for its diagnostic qualities and appears to be advantageous in delivering low radiation doses to patients. The evidence that natural and synthetic drug can affect radiolabeling or bioavailability of radiopharmaceuticals in setting of nuclear medicine clinic is already known (Saha, 1998; Gomes et al., 2002; Xavier Holanda et al., 2002; Amorim et al., 2003). These interactions can alter results of nuclear medicine procedures in a patient under chemotherapeutic treatment due to a concomitant disease. This fact may conduce a misdiagnosis or unnecessary exposure to radiation during the repetition of these exams.

The aim of this study was to evaluate the influence of natural and synthetic antimalarial drugs (artemisinin and mefloquine, respectively) on the bioavailability of the radiopharmaceutical methylenediphosphonic acid labeled with technetium-99m (99mTc-MDP) in W*istar* rats.

MATERIAL AND METHODS

The animals weighing on average 230 g, obtained from Biotério do Centro de Ciências da Saúde of Universidade Federal do Rio Grande do Norte, Natal - RN, Brazil, were housed in groups with free access to water and food. Twenty-four animals were used in this experiment and were randomly divided into three groups (two treated groups and one control group) of eight animals each one.

Experiments were performed according to local regulations for animal experimentation (approved by the Ethical Committee for Using Animals of UFRN) and they were sacrificed rapidly in a chamber with ethyl ether. In the first treated group, cloridrate of mefloquine diluted in sorbitol (50mg/10mL; Linha Medicamentos – Rio de Janeiro, Brazil) was administered orally (0.8mL/kg/day) into male *Wistar* rats (n=8; 3 month-old-age), in single dose during 7 days. In the second treated group, *Artemisia vulgaris L.* (prepared from a 10% dye-mother solution and diluted in sorbitol, Laboratório *Herbarium* – Rio de Janeiro, Brazil) was also administered orally (0.4mL/100g/day) into male *Wistar* rats (n=8; 3 month-old-age), in single dose during 7 days. One hour after the last dose was injected, via ocular plexus, 0.1 mL of the ^{99m}Tc-MDP (3.7MBq). The control group (n=8; 3 month-old-age) received 0.8mL/kg/day of the sorbitol solution same way, and also received 0.1mL of the ^{99m}Tc-MDP one hour after the last dose of the sorbitol solution.

To prepare the ^{99m}Tc-MDP, ^{99m}Tc, as sodium pertechnetate, freshly prepared from a ^{99}Mo/^{99m}Tc generator (Instituto de Pesquisas Energéticas e Nucleares, Brazil), was added to a kit of MDP (Liga Norteriograndense Contra o Cancer, Brazil). Each group of 8 rats was quickly sacrificed 60 min after injection of the ^{99m}Tc-MDP. Various organs from the animals were isolated (brain, heart, thyroid, lungs, kidneys, testis, stomach, intestines, pancreas, spleen, liver, abdominal muscle, femur, bladder and a sample of blood) and were put in vials and the radioactivity of the ^{99m}Tc-MDP was counted in a counter NaI (TI), Automatic Gamma Counter-1272, Clinigamma, LKB, Wallac, Finland. The percentages of total radioactivity (%ATI) in the organs were calculated dividing the activity in each organ by the total activity administered. The results were compared with the control group and statistical analyses were performed by Mann-Whitney U test (p<0.01).

RESULTS

Table 1 shows the relationship between the uptake (%ATI) of the ^{99m}Tc-MDP in the group that was treated with mefloquine (n=8) and in the control group (n=8), sixty minutes after administered the ^{99m}Tc-MDP. The analysis of the results showed a significant (p<0.01) increase in the uptake of radioactivity in spleen, liver, muscle and blood. A significant decrease (*p<0.01)* in the %ATI of ^{99m}Tc-MDP occurred in bladder, brain, heart, pancreas, kidneys, stout bowel and stomach. The results also revealed no significant alteration of the %ATI in testis, thyroid, lungs, femur and thin bowel.

Table 2 shows the relationship between the uptake (%ATI) of the ^{99m}Tc-MDP in the group that was treated with artemisinin (n=8) and in the control group (n=8), sixty minutes after administration of the ^{99m}Tc-MDP. The analysis of the results showed a significant (p<0.01) increase in the uptake of radioactivity in spleen, brain, femur, liver, lungs and blood. A significant decrease (p<0.01) in the %ATI of the ^{99m}Tc- MDP was observed in bladder, heart, thin bowel, stout bowel, abdominal muscle, pancreas, kidneys and testis. There was no significant alteration in the %ATI in thyroid and stomach.

Table 1 - Effect of mefloquine on the bioavailability of the ^{99m}Tc-MDP activity in *Wistar* rats, after 60 min administered the ^{99m}Tc-MDP.

Organs	% ATI			
	Control		Treated	
Abdominal muscle	2.047	± 0.397	3.539	± 0.874
Bladder	0.752	± 0.076	0.266	± 0.056
Blood	0.799	± 0.178	2.098	± 0.535
Brain	0.279	± 0.081	0.050	± 0.016
Femur	2.769	± 0.598	3.690	± 1.186
Heart	1.106	± 0.072	0.662	± 0.192
Kidneys	7.007	± 1.523	3.465	± 0.620
Liver	1.697	± 0.281	3.310	± 0.079
Lungs	0.294	± 0.057	0.204	± 0.047
Pancreas	0.871	± 0.244	0.288	± 0.183
Spleen	0.353	± 0.103	0.584	± 0.134
Stomach	6.987	± 0.980	3.886	± 0.851
Stout Bowel	2.131	± 0.341	0.668	± 0.193
Testis	0.497	± 0.082	0.268	± 0.084
Thin Bowel	2.055	± 0.537	2.848	± 0.892
Thyroid	2.555	± 0.664	2.042	± 0.422

Table 2 - Effect of artemisinin on the bioavailability of the ^{99m}Tc-MDP activity in *Wistar* rats, after 60 min administered the ^{99m}Tc-MDP.

Organs	% ATI			
	Control		Treated	
Abdominal muscle	2.047	± 0.397	0.265	± 0.067
Bladder	0.752	± 0.076	0.303	± 0.053
Blood	0.799	± 0.178	4.656	± 0.743
Brain	0.279	± 0.081	0.509	± 0.071
Femur	2.769	± 0.598	5.988	± 0.701
Heart	1.106	± 0.072	0.470	± 0.141
Kidneys	7.007	± 1.523	4.352	± 0.285
Liver	1.697	± 0.281	4.599	± 0.684
Lungs	0.294	± 0.057	6.229	± 0.868
Pancreas	0.871	± 0.244	0.469	± 0.122
Spleen	0.353	± 0.103	0.866	± 0.156
Stomach	6.987	± 0.980	7.352	± 0.990
Stout Bowel	2.131	± 0.341	0.367	± 0.080
Testis	0.497	± 0.082	0.194	± 0.041
Thin Bowel	2.055	± 0.537	0.484	± 0.069
Thyroid	2.555	± 0.664	3.093	± 0.694

DISCUSSION

There is considerable evidence that the biokinetics of radiopharmaceuticals may be altered by a variety of drugs, interaction of drugs (natural or synthetic), radiation therapy, disease states and surgical procedures (Sampson, 1993; Hesselewood and Leung, 1994; Harbert et al., 1996). If unknown, such factors may lead to poor visualization, a requirement to repeat the procedure resulting in unnecessary irradiation of organs or even misdiagnosis (Hojelse et al., 1994; Hung et al., 1996; Saha, 1998). Knowledge of altered bioavailability of the radiopharmaceuticals due to drug interaction definitely helps the physician to avoid misinterpretation of the scintigraphic images and, thus, an incorrect diagnosis and helps to prevent or treat adequately possible adverse reactions to the radiopharmaceuticals (Hladik et al., 1987;

Sampson, 1993). Some drugs enhance the localization of the radiopharmaceutical in the target organ, while others depress the uptake. In some cases, the bioavailability is shifted to other organs (Hladik et al., 1987; Saha, 1998). In addition, the alteration of the bioavailability of a radiopharmaceutical due to the effect of a drug in a specific tissue could aid in identifying the toxicolologic effect of a substance in an organ.

Many authors have reported that various drugs (natural or synthetic) are capable to alter the bioavailability of radiopharmaceuticals. For example, Chen and Collaborators (1994) have reported that gentamicin could cause abnormal renal uptake to be seen on bone scintigraphy using ^{99m}Tc-MDP and the presence of the radiopharmaceutical in the kidneys due to its nephrotoxicity. Santos and Collaborators (1995) have demonstrated that cyclophosphamide was capable to alter the effective half-life of the radiopharmaceuticals ^{99m}Tc-MDP and ^{99m}Tc-pertechnetate. Gomes and Collaborators (1998) have reported that mitomycin-C increased the uptake of the ^{99m}Tc-MDP in thymus, ovary, uterus, heart, stomach, pancreas, kidneys, spleen and lungs. Cronhjort and Collaborators (1998) have observed that the activity bioavailability of the ^{99m}Tc-HDP and ^{99m}Tc-MDP in mice was affected by the phosphate balance and, consequently, could affect the image quality at bone scintigraphy. Mattos and Collaborators (1999) have studied the effect of a chemotherapeutic drug on the bioavailability of the ^{99m}Tc-MDP in different organs isolated from animals treated with vincristine and have shown a decrease of the uptake in uterus, ovary, spleen, thymus, inguinal and mesenteric lymph nodes, kidney, liver, pancreas, stomach, heart, brain and bone. Xavier Holanda and Collaborators (2002) have demonstrated a significant reduction of the %ATI in spleen, femur, kidneys and liver isolated from *Wistar* rats treated with the antileishmanial glucantime on the bioavailability of the ^{99m}Tc-MDP. Amorim and Collaborators (2003) have studied the effect of a natural drug on the bioavailability of the ^{99m}Tc- sodium pertechnetate in various organs isolated from animals treated with *Punica granatum* and Britto and Collaborators (2004) observed significant increase in liver, kidney, bladder, stomach, thyroid and blood of rats treated with tamoxifen on the bioavailability of the ^{99m}Tc-MDP.

Mefloquine and artemisinin are the most effective drugs in the treatment against parasites of the genus *Plasmodium*, mainly *P. falciparum*. Mefloquine is distributed extensively over tissues and is predominantly excreted in the bile and faeces. It is highly protein bound (98%) and may accumulate in erythrocytes (Palmer et al., 1993; Price et al., 1999). It acts on the erythrocytic stage of malarial parasites and it may act by forming toxic complexes with free heme of hemoglobin, which damage membranes of the parasite and interact with other plasmodial components. Mefloquine resistance that leads to treatment failure, results in the preferential transmission of mefloquine-resistant malaria parasites. This accelerates the spread of resistant strains and may increase the incidence of malaria (Price et al., 1999). Thus, the increase in occurrence of drug resistant malaria parasites has necessitated the urgent development of novel antimalarial drugs to control this infection throughout the world. Artemisinin is a promising and a potent antimalarial drug for this. There is increasing acceptance that existing antimalarial drugs should be combined with an artemisinin derivative as protection to the development of resistance (White et al., 1999; White, 2004).

Artemisinin and its derivatives concentrates in parasitized red blood cells (RBCs) and kill all stages of the malaria parasite. For this, it interacts with heme of hemoglobin in RBCs to produce carbon-centered free radicals that alkylate protein and damage the microorganelles and membranes of the parasites (Meshnick and Dobson, 2001).

As mentioned above, the most prominent group of radiopharmaceuticals are the diphosphonates, which are used for scanning the skeleton. Technetium-99m labeled diphosphonates (^{99m}Tc-diphosphonates) such as methylenediphosphonic acid (MDP) has been used for bone scanning and for the localization of primary bone tumours, metastatic tumours and metabolic bone diseases. The uptake of the ^{99m}Tc-MDP in bone reflects bone metabolism and blood flow. The major pathway of elimination of the ^{99m}Tc-diphosphonates is through the kidneys (Saha, 1998; Thrall and Ziessman, 2003).

In this study, the increase observed in the %ATI of the ^{99m}Tc-MDP in femur of rats treated with artemisinin probably represented changes induced by this drug at the site of hydroxyapatite crystal or calcium phosphate deposition (Saha, 1998). A significant increase was also observed in the

%ATI of the ^{99m}Tc-MDP in liver of rats treated with artemisinin and mefloquine, which was probably due to metabolization process of these drugs in this organ. A significant decrease in the uptake (%ATI) of the ^{99m}Tc-MDP in kidneys, bladder and stout bowel of rats treated was observed with mefloquine and artemisinin, which was possibly due to the fact that their conjugates and metabolites were mainly excreted in the urine and in the faeces, respectively (Meshnick and Dobson, 2001; White, 2003; White, 2004). The metabolization and excretion processes and the metabolites produced probably could contribute to a reduction in the uptake of ^{99m}Tc-MDP in these organs (kidney, bladder and stout bowel).

In conclusion, the knowledge about the drugs interaction with the radiopharmaceuticals is very important to secure and safe diagnosis, and the development of biological models to study this phenomenon is highly relevant and desired. Furthermore, these determinations are important as if mefloquine and/or artemisinin have also an effect in the organ (dimension and/or density) in human beings, it could be responsible for artifacts that could induce misdiagnosis. The study of the modifications in the uptakes of the radiopharmaceuticals induced by drugs could be an important tool to evaluate the toxic effect of chemicals.

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RESUMO

Há evidências que algumas drogas usadas para doenças humanas podem modificar a biodisponibilidade de radiofármacos. Nós estudamos o efeito de drogas antimaláricas na biodisponibilidade do ^{99m}Tc-MDP em ratos. Mefloquina (MQ) e artemisinina (AM) foram administradas em dois grupos tratados (T) e sorbitol no grupo controle (C) por 7 dias. Em seguida, ^{99m}Tc-MDP foi injetado em todos os grupos e o %ATI foi calculado. Um aumento significativo do %ATI no grupo da MQ, do controle para o tratado, ocorreu no baço (0,35±0,10 para 0,58±0,13), fígado (1,69±0,28 para 3,31±0,07) e sangue (0,79±0,17 para 2,09±0,53). O %ATI aumentou significantemente no grupo da AM: no fêmur (2,76±0,59 para 5,98±0,70), fígado (1,69±0,28 para 4,59±0,68), pulmões (0,29±0,05 para 6,22±0,86), no baço (0,35±0,10 para 0,86±0,15) e sangue (0,79±0,17 para 4,65±0,74). Uma significante diminuição do %ATI ocorreu no grupo da MQ: na bexiga (0,75±0,07 para 0,26±0,05), intestino grosso (2,13±0,34 para 0,66±0,19), pâncreas (0,87±0,24 para 0,28±0,18), rins (7,00±1,52 para 3,46±0,62), cérebro (0,27±0,08 para 0,05±0,01) e, também, no grupo da AM: bexiga (0,75±0,07 para 0,30±0,05), intestino grosso (2,13±0,34 para 0,36±0,08), músculo (2,04±0,39 para 0,26±0,06), pâncreas (0,87±0,24 para 0,46±0,12) e rins (7,00±1,52 para 4,35±0,28). Estes resultados podem estar associados aos efeitos biológicos das drogas antimaláricas.

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