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DRUG INTERACTION WITH RADIOPHARMACEUTICALS AND THE IMPORTANCE FOR THE RADIATION DOSE TO THE PATIENT

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Abstract

A central aspect of the profession of health physics is to establish practical scientifically based radiation protection standards with the worthy aim of minimizing the detriment while at the same time enhancing the benefits derived from sources of ionizing radiation. The biodistribution or pharmacokinetics of radiopharmaceuticals may be altered by drugs and it can lead to misdiagnosis or the necessity to repeat the examination, increasing the dose to the patient. Vincristine (0.03mg/ml) was administered into female mice. One hour after the last dose, ^{99m}Tc-GHA (7.4 MBq) was administered and the animals (n=15) were sacrificed. The organs were isolated and the percentages of radioactivity (%ATI/g) in the organs were calculated. We calculated the Drug Interaction Factor (DIF) and the Effect Mass Factor (EMF). The results were statiscally significant (Wilcoxon test, $p<0.05$) and have shown that the DIF to ^{99m}Tc-GHA was to thymus 1.70, to pancreas 1.68, to uterus 0.42, to spleen 0.78, to lymph node inguinal 0.55, to kidney 0.45, to heart 0.59. The EMF was to ovary 0.28, to uterus 0.64, to thymus 0.17, to spleen 0.45, to lymph node inguinal 0.24, to kidney 0.80, to liver 0.77, to pancreas 0.61. The effects could be explained by the metabolization and/or therapeutic action of these drug.

1. Introduction

The earliest considerations of radiation effects and protection were built on the principles that a certain specific level of radiation can be incurred by various tissues without apparent ill effect. This in turn logically led to concept of a tolerance dose. More completely and precisely, the tolerance dose was considered to be that level of radiation to which an individual could be continuously exposed without demonstrable ill effect [1].

Hence, drug-radiopharmaceutical interaction will be defined as altered biologic behavior due to tissue response of administered drug. When the modified biologic behavior is desired, the alteration is used for diagnostic intervention or drug therapy monitoring; when it is undesired; it may be due to toxicity or direct interaction. If unknown, the drug interaction with radiopharmaceuticals can lead to misdiagnosis or the necessity to repeat the examination, increasing the dose to the patient [2, 3, 4].

More than 80% of all imaging studies (mostly anatomic) currently use technetium-99m (^{99m}Tc), because it has turned out to be the ideal isotope from various considerations [2, 3, 5, 6]. The biological activities of vincristine can be explained by its ability to bind specifically to tubulin and to block the capability of the protein to polymerize into microtubules [7]. The radiopharmaceutical 99mTc-GHA (glucoheptonic acid) is used to renal study [8]. In this paper we are evaluated the effect of vincristine on the biodistribution of the radiopharmaceutical 99mTc-GHA.

2. Material and methods

Vincristine (Oncovin, Eli Lilly, Brazil LTDA) (0.03 mg, 0.3ml) was administered by ocular plexus via into female isogenic Balb/c mice (n=15), in three doses with a total interval of 96 hours. After 96 hours, the animals were sacrificed, the various organs pancreas, lymph nodes (inguinal and mesentheric), thyroid, brain, thymus, ovary, uterus, spleen, kidney, heart,

stomach, lung, liver and bone were isolated and their mass determined in an analytical balance. The mass of the organs of these animals were compared with the control group, without vincristine. The statistical analysis of the results were performed with Wilcoxon test, $p < 0.05$. To study the vincristine effect in the biodistribution of the radiopharmaceutical, one hour after the last dose, 0.3 ml of ^{99m}Tc-GHA (7.4 MBq) was injected by the same via. In the control group (n=15), vincristine was not administered. To prepare the GHA, ^{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 DMSA (Laboratório de Radiofarmácia, INCa, Brazil). The radiochemical control was performed by ascendent chromatography, using paper Whatman n° 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 hour 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-DMSA and ^{99m}Tc-GHA were counted in a well counter NaI(Tl) (Automatic Gamma Counter, 1272 Clinigamma, LKB, Wallac, Finland). The percentages of radioactivity per gram of tissue (% ATI/g) in the organs were calculated dividing the total activity in each organ by the mass of each organ. The percentage of radioactivity in each organ was compared with the control group. Statistical analysis were performed by Wilcoxon test ($p<0.05$). After that, we have calculated the a Drug Interaction Factor (DIF), dividing the %ATI/g in the organs of the treated animals by the %ATI/g in the organs of the control animals and the and the Effect Mass Factor (EMF), dividing the mass of the organs of the treated animals by the mass of the organs of the control animals.

3. Results

Table 1 shows the relationship between the mass of the isolated organs of the group of mice that was treated with vincristine and the control group (no treated) and the values of the EMF.

Table 1. Effect of vincristine on the mass of different organs from female mice

Tissue	mass (g) control	mass (g) treated	EMF
Lung	0.1446 ± 0.0131	0.1482 ± 0.0167	1.02
Stomach	0.1187 ± 0.0131	0.1223 ± 0.0101	1.03
Heart	0.0858 ± 0.0093	0.0855 ± 0.0119	0.99
Thyroid	0.0135 ± 0.0035	0.0121 ± 0.0035	0.89
Bone	0.0387 ± 0.0082	0.0421 ± 0.0065	1.08
Brain	0.3831± 0.0293	0.3799 ± 0.0162	0.99
Spleen	0.0662 ± 0.0088	0.0300 ± 0.0059	0.45
Thymus	0.0280 ± 0.0055	0.0050 ± 0.0014	0.17
Kidneys	0.1207 ± 0.0122	0.0974 ± 0.0116	0.80
Liver	0.9734 ± 0.0597	0.7545 ± 0.0933	0.77
Ovary	0.0330 ± 0.0087	0.0095 ± 0.0027	0.28
Pancreas	0.0152 ± 0.0022	0.0094 ± 0.0019	0.61
Uterus	0.0453 ± 0.0097	0.0292 ± 0.0069	0.64
Lymph node inguinal	0.0328 ± 0.0062	0.0081 ± 0.0020	0.24
Lymph node mesentheric	0.0312 ± 0.0077	0.0079 ± 0.0023	0.25

The analysis of the results in table 1 shows no significant alteration of the mass of lung, stomach, heart, bone, thyroid and brain and reveals significant ($p < 0.05$) decreasing of the mass of spleen, thymus, kidneys, liver, ovary, pancreas, lymph nodes (inguinal and mesentheric) and uterus. Vincristine was administered into female mice Balb/c ($n = 15$). The animals were sacrificed, the organs isolated and their mass determined. The results were compared with the control group, without vincristine, and statistical analysis were performed (Wilcoxon test, $p < 0.05$). EMF is the effect mass factor.

Table 2 shows the uptake (%ATI/g) of ^{99m}Tc-GHA in the group of the mice that was treated with vincristine and in the control group. The analysis of the results reveals an increase of the uptake in thymus and pancreas, and decreased the uptake in uterus, spleen, lymph nodes (inguinal and mesentheric), kidney and heart. The analysis of the results reveals no significant reduction of the uptake in lung, liver, ovary, stomach, thyroid, brain and bone and shows results of the DIF.

Table 2. Effect of vincristine on the biodistribution of ^{99m}Tc-GHA in mice

%ATI/g	DIF		
Organs	Control	Treated	
Uterus	2.0455 ± 0.1065	0.8692 ± 0.1387	0.42
Ovary	0.9120 ± 0.0802	1.1052 ± 0.1456	1.21
Spleen	0.9999 ± 0.1749	0.7838 ± 0.0815	0.78
Thymus	1.3154 ± 0.3192	2.2366 ± 0.3924	1.70
Lymph node inguinal	6.2145 ± 0.3363	3.4240 ± 0.7052	0.55
Lymph node mesentheric	2.6655 ± 0.1809	1.3971 ± 0.0799	0.52
Kidney	28.4313 ± 2.5731	12.9191 ± 2.6499	0.45
Lung	2.5168 ± 0.0976	2.3914 ± 0.1338	0.95
Liver	0.5023 ± 0.0376	0.6280 ± 0.0712	1.25
Pancreas	1.1370 ± 0.1535	1.9138 ± 0.3079	1.68
Heart	1.2822 ± 0.0827	0.7666 ± 0.1609	0.59
Thyroid	3.8910 ± 0.7460	4.0743 ± 0.7240	1.04
Brain	0.1261 ± 0.0347	0.1169 ± 0.0101	0.92
Bone	0.8991 ± 0.0860	0.8079 ± 0.0689	0.89
Stomach	3.6938 ± 0.4021	3.5615 ± 0.4080	0.96

Vincristine was administered into mice and after 96h ^{99m}Tc-GHA was injected. The animals, the were sacrificed organs isolated and the activities (%ATI/g) determined. The values are averages ($n=15$), Wilcoxon test, $p<0.05$. DIF is the drug interaction factor.

4. 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 factor may lead to poor organ visualization, a requirement to repeat the procedure resulting in unnecessary irradiation of organs of even misdiagnosis [2, 3, 5, 6]. The capability of determined protocols with vincristine to induce long term toxicities, as infertility in males of all ages [7, 9, 10], could also associated with the effect in uterus in our studies to the radiopharmaceutical. As vincristine is a immunosupressive drug [7], this effect could explain

the alteration of the mass of the thymus, spleen and lymph nodes (inguinal and mesentheric), and could explain the alterations in these organs to %ATI/g of the ^{99m}Tc-GHA. This drug can produce hyponatraemia with abnormal water retention due to the non-osmotic rellease of anti-diuretic hormone [7]. This could explain the alterations in uptake in the kidney to the ^{99m}Tc-GHA. Mattos 1999, related the alteration in uptake of ^{99m}Tc-MDP in this organ.

In conclusion, in general, the results could be explained by a direct toxic effect in specific organs, the metabolization and/or therapeutic and immunosupressive action of vincristine. As vincristine is capable to alter, in mice, the mass of many organs, studies are now in progress to evaluate the anatomical characteristics of organs of patients that will be submitted to a protocol with vincristine. Moreover, the fact of the drug interaction can alter the uptake of the radiopharmaceutical in a specific target (organ), unexpected radiation dose in non-target organs is undesired. This is more relevant when this unexpected uptake is in a reproductive organ. Then, we suggest to consider, with special attention, the phenomenon of the drug interaction with the radiopoharmaceutical in the calculation of the radiation dose in organs.

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