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INFLUENCE OF ANTIPYRETIC DRUGS ON THE LABELING OF BLOOD ELEMENTS WITH TECHNETIUM-99m

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Acetaminophen (AAP), acetylsalicylic acid (ASA) and dipyrone (DIP) are antipyretic and analgesics drugs that have wide use in health sciences. Some drugs can modify the labeling of blood elements with technetium-99m (^{99m}Tc). This work has evaluated the effect of AAP, ASA and DIP on the labeling of the blood elements with ^{99m}Tc. Blood was incubated with different concentrations of the drugs before the ^{99m}Tc-labeled process. Plasma (P), blood cells (BC), insoluble (IF-P, IF-BC) and soluble (SF-P, SF-BC) fractions were separated and percentage of radioactivity (%ATI) in each fraction was determined. Data have shown that the antipyretic drugs used in this study did not significantly modify the fixation of ^{99m}Tc on the blood elements when the experiments were carried out with the doses usually used in human beings. Although the experiments were carried out with rats, it is possible to suggest that AAP, ASA or DIP should not interfere with the procedures in nuclear medicine involving the labeling of blood elements with ^{99m}Tc.

Keywords: Acetaminophen – acetylsalicylic acid – dipyrone – blood elements – Technetium-99m

INTRODUCTION

Acetaminophen, acetylsalicylic acid and dipyrone are antipyretics and analgesics of wide use and share in common several pharmacological actions of therapeutics interest. The antipyretic and analgesic actions of these drugs are based on inhibition of cyclooxygenase that is a enzyme responsible for the prostaglandin synthesis and some autacoids [6, 9, 10, 32]. Acetylsalicylic acid and dipyrone present also antiinflammatory action by the same mechanism of their antipyretic and analgesics actions [2, 3, 39], while acetaminophen exhibits little or no antiinflammatory properties [33]. However, acetylsalicylic acid and dipyrone can present a number of adverse effects at therapeutics doses as: (i) respiratory alkalosis with increased Na^+, K^+ and bicarbonate excretion [26, 29]; (ii) gastric ulceration, erosive gastritis, gastrointestinal hemorrhage and exacerbation of peptic ulcer symptoms [7, 25]; (iii) decreased urate excretion [18] and (iv) increased bleeding time, alterations in leukocyte and platelet

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count [15, 21]. On other hand, the therapeutic use of acetaminophen is associated to: (i) erythematous or urticarial skin rash and [31] (ii) neutropenia and thrombocytopenia [8] and (iii) immunosuppression and hepatotoxicity [24].

The labeling efficiencies of blood elements with technetium-99m (^{99m}Tc) can be influenced by medicines [1, 23, 28, 35] or labeling conditions [4] and the presence of disease may be missed and/or underestimated [36].

Thus, data have shown that some drugs can modify the labeling of blood elements as red blood cells with ^{99m}Tc (^{99m}Tc-RBC) and alter the results obtained in the daily routine procedure in nuclear medicine laboratories [11, 14, 16]. High labeling yields and good *in vivo* stability of the *in vitro* labeling procedure give superior images, while *in vivo* labeling is more convenient and thus, quite widely used. In addition to pool imaging and other uses in nuclear cardiology, applications of ^{99m}Tc-RBC have also included diagnosis of deep vein thrombosis, gastrointestinal bleeding, hepatic hemangiomas and splenic reticuloendothelial system [4, 5, 23].

The aim of this work was to investigate the *in vitro* effects of acetaminophen, acetylsalicylic acid and dipyrone on the labeling of blood elements with ^{99m}Tc.

MATERIALS AND METHODS

Animals

Adult male Wistar naive rats (3–4 months of age, body weight 250–350 g) were housed, five per cage, in an environment controlled room with inverted light/dark cycle conditions (12 h light/12 h dark; lights on at 6:00 a.m.), for an acclimatization period of at least 3 weeks. Animals had free access to water and food and ambient temperature was kept at 25 ± 2 °C. Experiments were conducted in accordance with the Department Committee of Animal Care.

Drugs

Acetaminophen and dipyrone were purchased from Medley Indústria Farmacêutica (Brazil) and acetylsalicylic acid was purchased from Bayer (Brazil).

Study protocol

An *in vitro* technique employed to label RBC described elsewhere [4] was used with minor modification. Heparinized whole blood was withdrawn from Wistar rats. Samples of 0.5 ml were incubated with 100 µl of acetaminophen, acetylsalicylic acid or dipyrone at different caffeine concentrations (10, 20, 100 and 10 000 µg/ml) for 1 h at room temperature. A sample of heparinized whole blood was incubated with NaCl 0.9% (Reagen, Rio de Janeiro, Brazil) as a control. Then, 0.5 ml of stannous

chloride (1.2 µg/ml) (Sigma Chemical Co., St. Louis, USA) was added and the incubation continued for another 1 h. After this period, ^{99m}Tc (0.1 ml), as sodium pertechnetate, recently milked from a ^{99}Molybdenium/^{99m}Technetium generator (Instituto de Pesquisas Energéticas e Nucleares, Comissão Nacional de Energia Nuclear, São Paulo, Brazil), was added and the incubation continued for another 10 minutes. These samples were centrifuged and plasma (P) and blood cells (BC) were separated. Samples (20 µl) of P and BC were precipitated with 1 ml of trichloroacetic acid (TCA) 5% and soluble (SF) and insoluble fractions (IF) were separated. The radioactivity in P, BC, IF-P, SF-P, IF-BC and SF-BC were determined in a well counter (Clinigamma, gamma counter, LKB, Wallac, Finland). After that, the percentage of radioactivity (%ATI) was calculated, as previously described [4].

Statistical analysis

Data are reported as means ± SE of %ATI were compared between the treated and control groups by one-way analysis of variance-ANOVA, followed by Bonferroni post test with a $p < 0.05$ as significant level. InStat Graphpad software was used to perform statistical analysis (GraphPad InStat version 3.00 for Windows 95, GraphPad Software, San Diego California, USA).

RESULTS

The results in Table 1 show the percentage of radioactivity (%ATI) in blood cells (BC), plasma (P), insoluble and soluble fractions of plasma (IF-P and SF-P) and insoluble and soluble fractions of the blood cells (IF-BC and SF-BC) from whole blood treated with different concentrations of acetaminophen. The data presented in this table show that the treatment with this drug does not significantly ($p > 0.05$) modify the uptake of ^{99m}Tc by blood elements.

Table 2 shows %ATI in BC, P, IF-P, SF-P, IF-C and SF-C from whole blood treated with different concentrations of acetylsalicylic acid. The data presented in this

Table 1
Effect of acetaminophen on the labeling of blood elements with ^{99m}Tc

AP (µg/ml)	%ATI					
	BC	P	IF-P	SF-P	IF-C	SF-C
0	97.8 ± 0.7	2.2 ± 0.7	72.3 ± 4.3	27. ± 4.3	85.6 ± 4.7	14.4 ± 4.7
10	98.4 ± 0.5	1.6 ± 0.5	66.3 ± 4.9	33.7 ± 4.9	83.2 ± 4.4	16.7 ± 4.4
20	98.6 ± 1.3	1.4 ± 1.3	64.5 ± 7.0	33.5 ± 7.0	85.5 ± 3.5	14.5 ± 3.5
100	99.0 ± 0.4	1.0 ± 0.4	65.8 ± 5.4	34.2 ± 5.4	80.7 ± 3.2	19.3 ± 3.2
1000	98.3 ± 0.6	1.7 ± 0.6	62.6 ± 7.6	37.4 ± 7.6	82.6 ± 5.1	17.4 ± 5.1

Table 2
Effect of acetylsalicylic acid on the labeling of plasma proteins with ^{99m}Tc

AS (μg/ml)	%ATI					
	BC	P	IF-P	SF-P	IF-C	SF-C
0	97.8 ± 0.7	2.2 ± 0.7	72.3 ± 4.3	27.7 ± 4.3	85.6 ± 4.7	14.4 ± 4.7
10	97.7 ± 0.3	2.3 ± 0.3	70.3 ± 5.0	29.7 ± 5.0	86.1 ± 4.9	13.9 ± 4.9
20	98.3 ± 0.3	1.7 ± 0.3	68.9 ± 4.4	31.1 ± 4.4	85.3 ± 5.4	14.7 ± 5.4
100	97.1 ± 0.8	2.9 ± 0.8	71.5 ± 4.3	28.5 ± 4.3	84.6 ± 5.4	15.4 ± 5.4
1000	95.4 ± 1.3	4.6 ± 1.3	69.7 ± 8.4	30.3 ± 8.4	82.0 ± 7.4	18.0 ± 7.5

Table 3
Effect of dipyrone on the labeling of plasma proteins with ^{99m}Tc

DP (μg/ml)	%ATI					
	BC	P	IF-P	SF-P	IF-C	SF-C
0	97.8 ± 0.7	2.2 ± 0.7	72.3 ± 4.3	27.7 ± 4.3	85.6 ± 4.7	14.4 ± 4.7
10	96.1 ± 1.0	3.9 ± 1.0	75.2 ± 3.3	24.8 ± 3.3	73.4 ± 1.5*	26.6 ± 1.5*
20	95.4 ± 0.3	4.6 ± 0.3	76.3 ± 1.7	23.6 ± 1.7	85.7 ± 5.5	14.3 ± 5.5
100	94.7 ± 1.7	5.3 ± 1.7	74.1 ± 2.2	25.9 ± 2.2	92.6 ± 1.4	7.4 ± 1.4
1000	94.1 ± 1.3	5.9 ± 1.3	84.6 ± 1.4	15.4 ± 1.4	93.3 ± 1.3*	6.7 ± 1.3*

* $p < 0.05$.

table show that the treatment with this drug also does not significantly modify the uptake of ^{99m}Tc by blood elements.

Table 3 shows the %ATI on BC, P, IF-P, SF-P, IF-BC and SF-BC from whole blood treated with the various concentrations of dipyrone. The data presented in this table indicate that the treatment with this drug does not modify in important way the uptake of ^{99m}Tc in blood elements. However, at lowest and highest concentrations (10 and 1000 μg/ml) a slight alteration ($p < 0.05$) of the %ATI in insoluble (IF-BC) and soluble (SF-BC) fractions of blood cells was observed.

DISCUSSION

Therapeutic drugs can modify the nature or amount of the ^{99m}Tc-radiopharmaceutical bound to blood elements and result in unexpected behavior of the radiopharmaceutical [22, 23, 37, 42]. Thus, the evaluation of the influence of drugs on fixation of ^{99m}Tc in blood elements are important. However, the data from these studies are relatively scarce and the effects of pharmacologically active agents on the diagnostic by radiopharmaceuticals can be evaluated.

The data obtained in this work show that acetaminophen, acetylsalicylic acid and dipyrone at concentrations used (10 up to 1000 μg/ml) did not modify the fixation of ^{99m}Tc in the blood elements (Tables 1, 2 and 3). The lowest effective plasma concentrations of acetaminophen and acetylsalicylic acid were 10 and 150 μg/ml, respectively [20]. Toxic concentrations of acetaminophen were higher than 300 μg/ml [20] while toxicity of acetylsalicylic acid in human is obtained with 200 μg/ml [20]. It was verified [40] that the maximum plasma concentration of dipyrone in humans was about 13.4 μg/ml at an oral dose of 480 mg after 1 up to 1.5 hours of administration. Thus, the results obtained in this work showed that these drugs in the plasma concentrations applied in humans did not alter the uptake of the ^{99m}Tc.

Acetaminophen has been described to induce haematologic and hepatocellular oxidative stress [43]. On the other hand, this drug has been shown to inhibit the leukocyte myeloperoxidase antimicrobial system and, under certain experimental conditions, can act as an antioxidant inhibiting the myeloperoxidase-hydrogen peroxide-nitrite mediated modification of low density lipoprotein [13] and can reduce lipid peroxidation associated with decreased progression of atherosclerosis [12]. However, these possible effects of acetaminophen have not affect the fixation of ^{99m}Tc on red blood elements under conditions studied in this work.

Several effects of acetylsalicylic acid have been associated to antioxidant properties [38, 44]. However, other authors have showed that when this drug is given orally, its main metabolite is the salicylic acid that presents antioxidant effect higher than acetylsalicylic acid [19]. Thus, the absence of effect of acetylsalicylic on uptake of ^{99m}Tc by red blood cells may be related to its short antioxidant effect.

The data presented in Table 3 indicate that dipyrone at the lowest and highest concentrations used (10 and 1000 μg/ml, respectively) may modify the fixation of the ^{99m}Tc on in insoluble and soluble fractions of blood cells proteins (IF-BC and SF-BC). However, in intermediary concentrations (20 and 100 μg/ml), dipyrone did not alter the fixation of ^{99m}Tc on blood elements as shown in Table 3. Thus, the data we obtained showed that dipyrone in the plasma concentrations applied to humans as therapeutic doses could not alter the uptake of the ^{99m}Tc.

The agranulocytosis induced by dipyrone may involve metabolic activation to reactive intermediates by hypochlorite formed by myeloperoxidase in activated neutrophils [27, 41]. In addition, it was observed that dipyrone radicals formed by peroxidase action cause GSH, NADH or arachidonate oxidation and in this process reactive oxygen species are produced [17]. Thus, the little influence of dipyrone on the fixation of ^{99m}Tc on cell protein fractions observed at the lower and the higher concentrations used may be related to production of free radicals.

Another possibility that may explain the possible dipyrone effect on fixation of ^{99m}Tc on plasma protein fractions is the competition between this drug and the radionuclide for the same binding site. This hypothesis is based on other data that suggested that the labeling of blood elements with ^{99m}Tc should be altered by some drugs or extracts of plants [16, 30, 34].

In conclusion, the data presented in this work showed that acetaminophen, acetylsalicylic acid and dipyrone in concentrations usually found in the plasma of humans did not modify the labeling of blood elements with ^{99m}Tc in rats.

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