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Quantitation of Iodine-124 Contamination in Iodine-123 Radiopharmaceuticals: Characterization of a Second Dose Calibrator

TO THE EDITOR: We previously described a simple method to quantitate iodine-124 (^{124}I) contamination in iodine-123 (^{123}I) radiopharmaceuticals (*1*), supplying at that time a graph and characterization constants suitable for use with the dose calibrator manufactured by Capintec (Model CRC-10). We cautioned in that article, however, that these results were not appropriate for use with dose calibrators of different design nor with sample containers and Pb shields constructed at variance with those used to collect the data.

We have now characterized a second dose calibrator (RADCAL, Model 4045). Using the Pb shield provided for the moly breathrough test, the measured constants were found to differ very little from those reported in (*1*); T3 = 0.00663, T4 = 0.366 and D = 0.547. For convenience of the RADCAL users, the correct curve for the ^{124}I contaminant assay is shown (solid line) for comparison with that for the Capintec instrument (dashed line). Over the range shown, the curves differ by no more than 0.21 percent ^{124}I. Hence, for the purpose of assaying I-124 contamination, the two instruments and associated moly breathrough shields are seen to be essentially identical.

It is not surprising that the radiations of ^{123}I and ^{124}I produce comparable responses in these two instruments since they are of the gas ionization chamber type and have quite similar well dimensions. We caution again, however, that these curves and constants may not be appropriate for use with other dose calibrators, especially those that use NaI scintillation detectors because of their considerably different energy response functions.

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Adverse Reactions to Technetium-99m Methylene Diphosphonate

TO THE EDITOR: The published incidence of adverse reactions to [^{99m}Tc]MDP is low. Reported reactions in the United States indicate an incidence of 0.5 per 100.000 in 1984 (*1*). A publication from the United Kingdom covering the

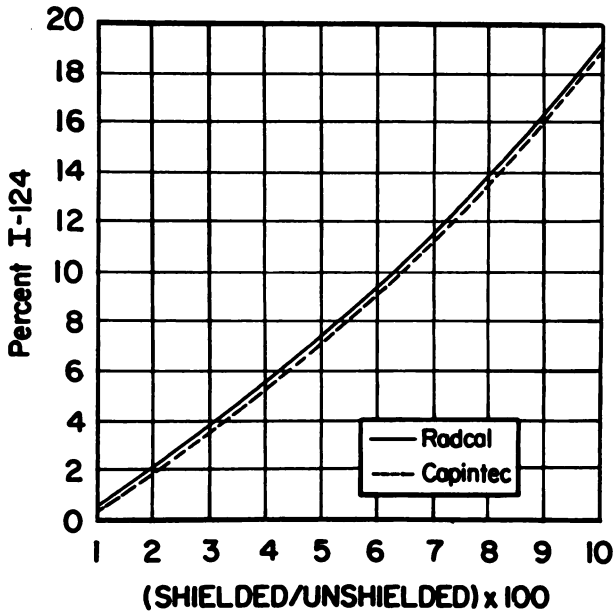

FIGURE 1
Curves for assay of percent ^{124}I contamination with two radionuclide dose calibrators. "Shielded" refers to dose calibrator readings of a vial containing ^{123}I radiopharmaceutical taken while within the moly breathrough shield with the instrument set to assay ^{123}I; "unshielded", to readings without use of the shield. Curve points were determined by the method of Reference (*1*).

period between 1977 and 1983 estimated an incidence between 1 per 1,000 and 1 per 10.000 of adverse reactions to radiopharmaceuticals (*2*). Nearly half of the more recent reports in the United Kingdom concerned reactions to [^{99m}Tc] MDP and the authors estimated that they were notified of <10% of the events including the trivial reactions. After encountering such a reaction, we attempted prospectively to determine the incidence in our bone scan patients.

A 56-year-old female came for an initial bone scan because of a painful left knee, probably arthritis. Her medical history included bilateral hip dysplasia and Parkinson's disease. She did not take medication. Approximately 30 min after intravenous administration of 654 MBq technetium-99m (^{99m}Tc) methylene diphosponate (MDP) (Solco Nuclear, Birsfelden, Switzerland) the patient experienced severe headache with photophobia, nausea, dizziness and sensation of warmth. She had not had those symptoms before and rarely had headache. The symptoms gradually disappeared 2 hr after onset. She reported these complaints when she returned for imaging 4 hr after administration. No therapy was given. There were no late manifestations in the days after the examination.

After this event every patient who came for bone scan to our department was asked for complaints in the interval between injection and imaging. Four patients out of 400 reported, only when asked, transient and moderate headache, dizziness and nausea ~30 to 60 min after injection. Late reactions did not occur. Two of these patients had carcinoma of the breast. One patient used the oral anticoagulant acenocoumarol and the other patient took no medication. The third patient had carcinoma of the lung and used ibuprofen. The fourth patient had probably reflex sympathetic dystrophy and used naproxen. None of the five patients with reactions had

previously received diphosphonate compounds. Other patients injected from the same vial developed no symptoms. Pyrogenic and nonsterile reactions were excluded. According to the package insert the kit did not contain additives except tin and MDP. The temporal relationship between [^{99m}Tc]MDP injection and these symptoms is suggestive for a reaction to the radiopharmaceutical. Those patients with reactions have not returned for a second bone scan.

Few data are available on the nature of the reactions to [^{99m}Tc]MDP. The most common reaction seems to be a skin rash 2 to 24 hr after injection (*2,3,4*). Our patients, however, did not show cutaneous manifestations. Ramos-Gabatin et al. (*4*) described a case with a certain similarity to our patients, the symptoms consisted of nausea, headache, cough, myalgias and fever. It was discovered that the patient had a similar but milder reaction one month earlier when an initial bone scan was performed. Spicer et al. (*3*) reported a case with a mucocutaneous reaction and also a more severe reaction following repeated [^{99m}Tc]MDP injection. In neither report was there evidence of previous sensitization to the radiopharmaceutical. Both authors stated that an allergic response was responsible for these reactions which is very likely in the case of a late mucocutaneous reaction (*3*) but is very difficult to establish with certainty even by skin testing (*4,5*). The symptoms in our patients may also be explained by nonimmunologic histamine release such as probably occurs in reactions to radiographic contrast media (*5*).

An important question is how to deal with a repeat bone scan in those patients with a reaction from a previous injection of [^{99m}Tc]MDP. It is likely that there is cross reactivity to several diphosphonate compounds from different manufacturers (*4*). Technetium-99m pyrophosphate may be a safe substitute as a bone imaging agent as has been shown in two patients (*3,4*). Alternatively, repeated administration of [^{99m}Tc]MDP may be considered after pretreatment with antihistamines and corticosteroids which is a recommended strategy in cases of a previous reaction to radiographic contrast media (*5*).

The reported incidence of adverse reactions to radiopharmaceuticals may not only be biased by failure to report reactions but also because moderate symptoms are ignored or not associated with radiopharmaceutical administration. The present report suggests that mild adverse reactions to [^{99m}Tc]MDP occur more frequently than officially documented. Possibly repeated injections may cause reactions of increasing severity. More awareness and registration of any adverse reactions is needed.

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Kinetics of Interstitially Administered Monoclonal Antibodies for Purposes of Lymphoscintigraphy

TO THE EDITOR: We read with interest the article "Kinetics of Interstitially Administered Monoclonal Antibodies for Purposes of Lymphoscintigraphy" by Wahl, Geatti, Liebert, et al. (*1*). They report little difference in clearance rate between intact IgG and IgM monoclonal antibodies from a subcutaneous injection site in mice.

We (*2*) and others (*3*) have found a significant difference in clearance rates from a subcutaneous injection site between indium-111- (^{111}In) labeled IgG and IgM monoclonal antibodies. Our study showed that in rabbits maximum clearance from the injection site occurred by 24 hr postinjection, with IgG antibody clearing more rapidly (86%) than IgM antibody (66%). The study by Halpern et al. (*3*) also showed that in mice ^{111}In-labeled IgM antibody cleared much slower from a subcutaneous injection site than IgG antibody.

There are a number of differences between our study and that of Wahl et al. which may explain these results. First, there may be differences in clearance rates between different subclasses of IgG antibodies. Our study compared IgG_1 monoclonal antibody with IgM whereas the study by Wahl et al. compared IgG_{2ak} antibody with IgM. Second, there may even be differences in clearance rate between different antibodies of the same isotype and subclass. For example, we have found differences in hepatic uptake and clearance rates between different ^{111}In-labeled IgG_1 antibodies. There may also be species differences in clearance rates. Our study used a rabbit model to study the clearance of subcutaneously injected murine antibodies whereas the study by Wahl et al. used a mouse model. However, it should be noted that the study by Halpern (*3*) also used a mouse model. Finally, although both ^{111}In- and iodine-131- (^{131}I) labeled antibodies are referred to in the "Methods" section of the paper by Wahl most of the data reported in the "Results" section pertain to ^{131}I-labeled antibodies. However they report no significant difference in clearance from a subcutaneous injection site at 6 hr postinjection between ^{111}In- and ^{131}I-labeled antibodies. In our study we found that clearance is very similar between ^{111}In-labeled IgG and IgM antibodies up to 4 hr postinjection with much more marked differences observed at later time points.

It appears that further study may be necessary to fully understand the clearance kinetics of different isotypes and subclasses of monoclonal antibodies from a subcutaneous injection site.

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