Letters to the Editor

Use of Carrier in the Preparation of Iodine-123 HEAT

TO THE EDITOR: We recently described the preparation in high radiochemical and chemical purity of microcurie quantities of [^{123}I]- and [^{125}I]-2[β-(iodo-4-hydroxyphenyl)ethylaminomethyl]tetralone or -iodoHEAT, an alpha-1 receptor imaging agent (*1*). This reaction entailed the electrophilic aromatic substitution of 2-[β-(4-hydroxyphenyl)ethylaminomethyl]tetralone (HEAT) by the I^+ cation. All yields were expressed as a percent of the original activity added. Reaction of HEAT With 1 mCi Na[^{125}I] and chloramine-T followed by ethyl acetate extraction gave 80–90% of the radioactivity in the organic layer. After extraction, HPLC was employed to obtain pure [^{125}I]HEAT in ~60% overall yield. In contrast, the same reaction with 1 mCi and 25 mCi Na[^{123}I] gave, upon extraction alone, yields of 40–80% and <3%, respectively. Here we report reaction conditions that give, after extraction and HPLC, about a 50% yield of [^{123}I]HEAT that exhibits no significant loss of specific receptor binding.

RadioiodoHEAT was prepared by the reaction of HEAT·HCl (10 μl, 2 mg/ml in 13.5 m*M* HCl), sodium radioiodide in 0.1 N NaOH, and aqueous chloramine-T (20 μl, 0.34 mg/ml) in 1*M* pH 7.6 phosphate buffer (200 μl) (*1*). To optimize yields when preparing millicurie quantities of [^{123}I]HEAT, the reaction mixture was maintained at a pH of 7.3–7.6 by the addition of 1*M* KH_2PO_4, the Na[^{123}I] (25 mCi in 0.1 N NaOH, 2.5 × 10^5 Ci/mmol, Nordion International, Inc., Kanata, Ontario, Canada) was dried under a jet of nitrogen, and carrier NaI (0.75 μg; >99.99%, Aldrich Chemical Co., Milwaukee, WI) was added.

Empirical physico-chemical equations can be used to explain the effects of added carrier and reaction volume on reaction yield. The absolute disintegration rate ("activity") of an isotope, −dN/dt, can be expressed as

$$-dN/dt = \lambda N,$$

where λ is the decay constant and N is the original number of radioactive atoms present. Rearranging this equation and using the relationship $\lambda = 0.693/t_{½}$ where $t_{½}$ is the half-life of the isotope expressed in sec, the number of atoms can be calculated by

$$N = dN/dt \times t_{½}/0.693.$$

Using this equation with the appropriate half-life and 1 mCi = 3.7 × 10^7 Bq or transformations per second (t/sec)

$$N = 3.7 \times 10^7 \text{ t/sec} \times 4.8 \times 10^4 \text{ sec}/0.693$$
$$= 2.6 \times 10^{12} \text{ atoms per mCi.}$$

Similarly, there are 2.8 × 10^{14} atoms in 1 mCi [^{125}I]. Thus, there are 100 fold fewer iodide atoms in the reaction with 1 mCi Na[^{123}I] than there are with 1 mCi Na[^{125}I] or, expressed as a ratio, there is 1 atom of [^{123}I] or [^{125}I] for every 14,000 or 129 molecules HEAT, respectively (Table 1). Fewer collisions between $[^{123}I]^+$ and HEAT give rise to a correspondingly lower product yield. Addition of 0.75 μg NaI to the reaction mixture reduces the N_{HEAT}/N_I ratio from 14,000:1 to 12:1 thereby greatly increasing the possibility of both I^+ and $[^{123}I]^+$ interactions with HEAT and, as a result, radiochemical as well as chemical yields are greatly improved.

TABLE 1
Relative Amounts of Reagents

Reagent	N* (molecules)	N_{HEAT}/N_I
1 mCi Na[^{123}I]	2.6 × 10^{12}	4,000
25 mCi Na[^{123}I]	6.5 × 10^{13}	550
1 mCi Na[^{125}I]	2.8 × 10^{14}	129
0.75 μg NaI	3.0 × 10^{15}	12
20 μg HEAT·HCl†	3.6 × 10^{16}	

* N = 6.02 × 10^{23} molecules/mole × weight of reagent/gram molecular weight.
† 331.82 g/mol.

The volume of 0.1 N NaOH present with 25 mCi Na[^{123}I] can increase the reaction volume from 250 μl up to 650 μl. Even with added carrier, where the N_{HEAT}:N_I ratio is about four times larger than in the 1 mCi [^{125}I] reaction, fewer collisions between reactants occur and the radiochemical yield is significantly reduced. Use of dried Na[^{123}I] alleviates this problem.

Theoretically, the no-carrier-added radioiodinated HEAT can be assumed to have the specific activity (SA) of the radioiodine (SA[^{123}I] = 2.5 × 10^5 Ci/mmole; SA[^{125}I]) = 2.2 × 10^3 Ci/mmole) because the HPLC step separates the product from all by-products. Assuming complete conversion of I^- to I^+ for both species, the theoretical specific activity of the final product from the reaction of 25 mCi [^{123}I] (1.08 × 10^{-10} mole) with 0.75 μg NaI (4.98 × 10^{-9} mole) should be

$$SA_{product} = 2.5 \times 10^5 \frac{\text{Ci}}{\text{mmol}} \times \frac{1.0 \times 10^{-10} \text{ mol } [^{123}\text{I}]\text{HEAT}}{5.09 \times 10^{-9} \text{ mol } ([\text{I}]\text{HEAT} + [^{123}\text{I}]\text{HEAT})}$$
$$= 5.3 \times 10^3 \text{ Ci/mmol.}$$

Trace amounts of iodine and bromine in the reagents will cause the actual specific activities of both the no carrier-added and carrier-added [^{123}I]HEAT to be less, by the same extent, than the theoretical value and the optimal amount of added NaI carrier may vary slightly as the source of reagents is changed. Nevertheless, the specific activity of the carrier-added product should be about 2.5 times that of no-carrier added [^{125}I]HEAT prepared with the same reagents.

Since less than 2% of the [^{123}I] added to the no-carrier-added reactions is retained by the reaction vessel after extraction and removal of both layers, the decrease in yield is not caused by binding of the iodide ion to the reaction vessel.

This reduction in the specific activity of the carrier-added versus no-carrier-added [^{123}I]HEAT could cause a correspond-

ing reduction in its specific binding to alpha-1 receptor sites; however, we observed that, in rats, the thalamus/cerebellum and frontal cortex/cerebellum activity ratios were the same, within experimental error (n = 4), for both the no carrier-added and the carrier-added [^{123}I]HEAT. Owing to the shorter half-life and higher energies of [^{123}I] compared to [^{125}I], this reduction in specific activity does not exclude such radiopharmaceuticals from use in nuclear medicine.

Although this paper describes the synthesis of a single radiopharmaceutical, the principles discussed above should be applicable to the syntheses of other radiopharmaceuticals using isotopes with high specific activities and, as a result, low numbers of molecules.

Acknowledgments

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Reference

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Pediatric Brain Imaging with Technetium-99m-HM-PAO and SPECT

TO THE EDITOR: Garty et al. (*1*) published a review on pediatric imaging with emphasis on nuclear medicine, magnetic resonance imaging (MRI) and other radiological procedures, mainly computed tomography (CT). Under the subsection cerebral vascular diseases, on clinical applications in the central nervous system, little reference is made to new radiopharmaceuticals now widely available. The importance of a technetium-99m (^{99m}Tc) tracer to study regional brain perfusion with single photon emission computerized tomography (SPECT) is in our opinion underestimated. Technetium-99m HM-PAO has been used in clinical routine in Europe since 1985 mainly to investigate patients with cerebrovascular disease (*2*). Its normal distribution in vivo was described for normal man. Its regional brain distribution (on SPECT studies) correlates well with the anatomic localization of structures where higher and lower perfusion rates are expected (*3*). The Food and Drug Administration (FDA) has recently approved its introduction in the U.S.A. as a brain perfusion radiotracer to study cerebrovascular disease.

We have found that [^{99m}Tc]HM-PAO/SPECT investigation of the brain perfusion in pediatric patients with cerebrovascular disease adds an important and objective parameter to the definition of the underlying pathophysiology.

References

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2. Ell PJ, Hocknell JML, Jarritt PH, et al. A ^{99}Tc^{m}-labelled radiotracer for the investigation of cerebral vascular disease. *Nucl Med Commun* 1985; 6:437–441.
3. Costa DC, Ell PJ, Cullum ID, Jarritt PH. The *in vivo* distribution of ^{99}Tc^{m}-HM-PAO in normal man. *Nucl Med Commun* 1986; 7:647–658.

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REPLY: We would like to thank Drs. Costa and Ell for their letter regarding the clinical capabilities of [^{99m}Tc]HM-PAO and SPECT in pediatric patients. We are in total agreement with the authors' comments and will no doubt see a significant increase in the number of [^{99m}Tc]HM-PAO studies being performed in children now that this radiopharmaceutical has been approved by the FDA for routine clinical use in the United States.

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Correction: Radioisotope Penile Plethysmography: A Technique for Evaluating Corpora Cavernosal Blood Flow During Early Tumescence

In the article by Schwartz, Graham, Ferency, et al, "Radioisotope Penile Plethysmography: A Technique for Evaluating Corpora Cavernosal Blood Flow During Early Tumescence," (*J Nucl Med* 1989;30: 466–473), an error occurred on p. 470. In the second column, second paragraph, the sentence reading "The change in volume ranged from 16 ml to 18 ml (mean 43.4 21.5) *should read* ". . . ranged from 16 ml to 65 ml (mean 43.4 ml)."