INVITED COMMENTARY

The Potential Role of Generator-Produced Radiopharmaceuticals in Clinical PET

Many articles over the last 15 y have suggested that radioisotope generators provide a desirable alternative to cyclotrons for the production of short-lived positron-emitting radionuclides (*1–3*). It has also been suggested that the availability of generator-derived radionuclides is very important for PET studies and now allows use of the procedure at facilities that are remote from production sites, thus making the on-site cyclotron no longer essential for patient examination by PET.

A list of generators producing positron emitting daughter radionuclides is presented in Table 1. Several of these generators have been suggested as systems with potential for clinical applications; of these systems, the $^{82}Sr/^{82}Rb$, $^{68}Ge/^{68}Ga$, $^{62}Zn/^{62}Cu$, and $^{122}Xe/^{122}I$ have been most widely studied.

^{82}Rb (as Rb^+) was the first new drug application-approved positron emitting radiopharmaceutical; it gained approval by the Food and Drug Administration on December 29, 1989. The $^{82}Sr/^{82}Rb$ generator is a microprocessor-controlled, self-contained infusion system (*4*) with a replaceable column. The generator was initially marketed by Squibb Diagnostics; currently only the infusion system is available from CTI (Knoxville, TN) and the column is sold separately by Bracco Diagnostics. The major use of this generator has been in myocardial perfusion studies, in which ^{82}Rb (as Rb^+) acts as an analog of potassium. It has also been used to study blood–brain barrier changes in patients with brain tumors and Alzheimer's-type senile dementia (*5*). To date, approaches to produce a neutral lypophilic rubidium complex that could be used for other applications has met with limited success. Krohn et al. (*6*) performed preliminary evaluations of complexes with longer-lived tracers; however, the chemistry places serious constraints when used with a 76-s radionuclide.

The $^{68}Ga/^{68}Ge$ generator produces ^{68}Ga as either Ga-ethylenediaminetetraacetic acid or gallium in 1 *N* HCl (*7*). Many reports in the literature have described the development of ^{68}Ga radiopharmaceuticals (*7–9*), and techniques have been developed to label blood constituents (*10*) as well as proteins, peptides, and antibody fragments (*11–13*). Over the past few years, only a very limited number of patient studies have used this generator; with perhaps the largest number applying the simplest ^{68}Ga radiopharmaceutical (gallium citrate), which on administration produces gallium-transferin. This approach has been used by Schuster et al. (*14–18*) to measure pulmonary transcapillary escape rate (PTCER) in various disease states.

The $^{122}Xe/^{122}I$ generator and its applications have been discussed by the Berkeley group (*19*). Mathis et al. (*20*) have described an automated generator system that allows the remote preparation of a series of iodinated radiopharmaceuticals. This is a major accomplishment, because ^{122}I has a half-life of only 3.6 min. The Berkeley group suggests that ^{122}I radiopharmaceuticals have potential for accelerator-free PET studies in various applications, including brain and heart perfusion. Unfortunately, their description of the generator was published in 1986 (*20*), and only a limited number of applications have since appeared in the literature. A limitation of ^{122}I is that the production of ^{122}Xe requires proton energies of 65–43 MeV, but new resources and commercial facilities have been commissioned in the United States that are capable of operating with high-intensity100 MeV proton beams (*22*). This technological advance, in combination with a fast automated labeling system for the synthesis of ^{122}I radiopharmaceuticals, may well make the clinical use of this generator a possibility.

The article by Haynes et al. (*23*) in this issue of the *Journal of Nuclear Medicine,* discusses the performance of an automated $^{62}Zn/^{62}Cu$ generator that is currently in clinical trials using the perfusion agent ^{62}Cu-pyruvaldehyde-bis(n4-methylthiosemicarbazone (PTSM). The $^{62}Zn/^{62}Cu$ generator was first described by Robinson et al. (*24*) in 1980, and improved generators have been described by several groups (*23,25,26*). The automated system described by Haynes directly produces the radiotracer copper-PTSM, which has been validated as a flow tracer in the brain, heart, kidney, and tumor. The generator described could provide other radiopharmaceuticals, including ^{62}Cu-diacetyl-bis(n4-methylthiosemicarbazone) (ATSM), a promising hypoxia tracer (*27,28*). At present, there are 6 clinical trials of copper-ATSM either underway or currently being evaluated at Washington University Medical Center, St. Louis, MO. At Washington University, however, instead of using ^{62}Cu from a generator, ^{60}Cu (*29*) directly produced in the cyclotron is used. Five copper radionuclides have been used in nuclear medicine (Table 2), and our group has discussed the use of ^{60}Cu, ^{61}Cu, and ^{64}Cu (*30*). Although ^{60}Cu has a very high positron energy and several high-energy γ-rays, high-

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TABLE 1
Generators Producing Positron Emitters Daughter Radionuclides

Parent	Parent half-life	Parent decay mode (%)	Daughter	Daughter half-life	Daughter decay mode (%)	γ MeV (%)
^{44}Ti	48 y	EC (100)	^{44}Sc	3.92 h	β^+(88), EC(12)	0.375 (22)
^{52}Fe	8.27 h	β^+(57), EC(43)	^{52m}Mn	21.1 min	β^+(98), EC(2)	1.43 (100)
^{62}Zn	9.13 h	β^+(18), EC(82)	^{62}Cu	9.8 min	β^+(98)	1.17 (0.5)
^{68}Ge	278 d	EC(100)	^{68}Ga	68 min	β^+(88), EC(12)	1.08 (3.5)
^{82}Sr	25 d	EC(100)	^{82}Rb	76 s	β^+(96), EC(4)	0.78 (9)
^{118}Te	6.0 d	EC(100)	^{118}Sb	3.5 min	β^+(75), EC(25)	1.23 (3)
^{122}Xe	20.1 h	EC(100)	^{122}I	3.6 min	β^+(77), EC(23)	0.56 (18.4)
^{128}Ba	2.43 d	EC(100)	^{128}Cs	3.8 min	β^+(51), EC(49)	0.44 (27)

quality PET images have been obtained using this radionuclide.

The ^{62}Zn/^{62}Cu system described in the article by Haynes et al. (*23*) would be economically feasible if a ^{62}Cu tracer (PTSM, ATSM, or another complex) proves to be as clinically useful as FDG. Without this routine clinical need, it is likely that the majority of copper radiopharmaceutical studies will be performed with one of the directly produced nuclides listed in Table 2.

We have compared the costs described for the ^{62}Zn/^{62}Cu generator described by Haynes et al. (*23*) with our own costs for the cyclotron-produced copper thiosemicarbazones. The authors envision that the generator would be delivered on a weekly basis, and so all imaging with ^{62}Cu would occur on a single day. Therefore, the best comparison for us to make is with the cyclotron production costs of ^{61}Cu. This isotope has a 3.35 h half-life, and a single irradiation early in the day would provide enough ^{61}Cu to image patients throughout the day. Therefore a comparison with the ^{62}Cu generator is fair.

The yield (*29*) of the ^{61}Ni(p,n)^{61}Cu reaction is 7.62 mCi/μA/h; we estimate that production of 400 mCi should be sufficient for an entire day's use. This translates to an irradiation cost of approximately $550. Preparation and work-up of the target combined with the preparation of the final radiopharmaceutical (in this case, Cu-ATSM) and subsequent analysis costs approximately another $250. So our final (nonoptimized) cost for production of enough [^{61}Cu]ATSM to last an entire day is approximately $800, which compares well with the costs of the ^{62}Cu generator. However, we feel that the authors may have underestimated the true costs of production and use of the generator. For example, our analysis includes radionuclidic evaluation of each sample on a germanium detector—this would correspond to a breakthrough analysis on each batch of ^{62}Cu eluted from the generator.

There is a problem with this model, however. By having the isotope available on only a weekly basis, it means that some patients would have to wait for up to 6 d before an imaging procedure could be completed. In many cases this is not desirable, and, for this reason, we favor the use of cyclotron-produced ^{60}Cu. This isotope has a 23.7 min half-life, and we are able to produce enough isotope for a single dose of [^{60}Cu]ATSM with a short irradiation (typically less than 30 min). As stated earlier, we currently have 6 human protocols approved for the evaluation of this tracer in both oncology and myocardial ischemia; as a result, on average we currently produce this radiopharmaceutical twice a week. The cost of production of a single dose of [^{60}Cu]-ATSM is estimated to be approximately $450. Our costs for production of this radiopharmaceutical are higher on a per batch basis than those for [^{61}Cu]ATSM, despite the shorter irradiation costs (approximately $150), because of the inclusion of stringent quality control procedures. In our opinion, the convenience of having such a tracer "on demand" outweighs the costs of scheduling and delaying diagnosis.

TABLE 2
Copper Radionuclides Used in Nuclear Medicine

Nuclide	Half-life	Decay model	Mode of production
^{60}Cu	23.7 min	93% β^+ 7% EC	^{60}Ni(p,n)^{60}Cu
^{61}Cu	3.347 h	60% β^+ 40% EC	^{61}Ni(p,n)^{61}Cu
^{62}Cu	9.74 min	β^+	^{62}Zn-generator
^{64}Cu	12.70 h	EC 43% 38% β^- 19% β^+	^{64}Ni(p,n)^{64}Cu
^{67}Cu	58.5 h	β^-	Spallation

CONCLUSION

The role of generators in the future of clinical PET remains unclear. If copper thiosemicarbazones prove to be as useful as predicted, then demand for copper radionuclides will increase. This would clearly be good news for the ^{62}Zn/^{62}Cu generator, but it would also make the production and local distribution of cyclotron-produced isotopes such as ^{61}Cu more commercially appealing. On a final note: although generators hold potential for PET imaging at sites removed from cyclotrons, one should also consider that the current price of a ^{82}Sr/^{82}Rb infusion system is approximately $62,000 and columns are needed on a monthly basis at an additional $25,000 each. Similarly, the price of a ^{68}Ge/^{68}Ga generator that produces non–pharmaceutical-grade ^{68}Ga is approximately $50,000. Whether

these high prices are the result of low demand or costs that are not discussed by Haynes et al. (*23*) is uncertain.

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