Cost-Effectiveness of Thallium-201 versus Technetium-99m-Sestamibi in the Detection of Coronary Artery Disease

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Objectives: The purposes of this study were to demonstrate the applicability of pharmacoeconomic principles in the nuclear medicine market and to compare the cost effectiveness of ^{201}Tl and ^{99m}Tc-sestamibi.

Methods: Cost information was obtained from a South Carolina hospital. Effectiveness data were obtained from the literature.

Results: This research showed that when ^{201}Tl was used either one day before or on the day of calibration it was more cost-effective than ^{99m}Tc-sestamibi for the detection of coronary artery disease; especially when cardiac scheduling was light. This conclusion held for several varying scenarios. Technetium-99m-sestamibi was more cost-effective than ^{201}Tl in the scenarios where patient scheduling was heavy and the ^{201}Tl was used three days post-calibration.

Conclusion: Although the generalizability of these results is strictly limited, this research demonstrates the applicability of pharmacoeconomics to radiopharmaceuticals. These results provide some insight into the efficient use of cardiac imaging agents.

Key Words: cost-effectiveness; ^{99m}Tc-sestamibi; ^{201}Tl; pharmacoeconomics

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Financial access to health care services is one of the most prominent issues in the current political and social environment. Since 1950, health care expenditures have risen from 4.4% of the nation's gross domestic product to 13.9% in 1992 (*1–3*). At current growth rates, health care expenditures are projected to reach 18% of the gross domestic product by the year 2000 (*1*). This trend has shifted much of the focus of health care from clinical and technological issues to economic issues. This is especially true for the pharmaceutical and diagnostic services markets.

This increased attention to health care costs has facilitated the broad application and acceptance of economic analyses by health care practitioners and academicians. A discipline that has emerged as a direct result of this acceptance is pharmacoeconomics. Pharmacoeconomics has been defined as the "description and analysis of the costs of drug therapy to health care systems and society (*4*)."

One of the primary methodological tools employed in pharmacoeconomic research is cost-effectiveness analysis (CEA). CEA is a technique used to provide information that assists a decision-maker in "identifying a preferred choice among possible alternatives (*5*)." The purpose of a CEA is to obtain an economically derived ratio that compares two or more modalities with similar outcomes. The primary characteristic that differentiates CEA from other cost analyses is that the numerator of the ratio represents all relevant marginal costs measured in dollars associated with that particular alternative while the denominator is a measure of physical units. This denominator unit must be the same for all competing alternatives. The resulting ratios present a cost per physical unit. The alternative with the lowest cost per physical unit is considered the most cost-effective alternative. For example, research by Blaufox demonstrated the economic advantages of captopril renogram studies in the differential diagnosis of renovascular hypertension ($3,081 per case detected without a captopril renogram study versus $2,087 per case detected with the captopril renogram) (*6*).

Medical and administrative decision-makers routinely incorporate pharmacoeconomic data when making formulary and therapeutic decisions regarding more conventional pharmaceuticals. If available, it is postulated that this type of pharmacoeconomic information could aid the nuclear medicine practitioner and administrator in a similar manner.

CEA has been used to evaluate the economic impact of drug therapy as well as the economic usefulness of diagnostic services. Patton provides an overview of cost-effectiveness in nuclear medicine and presents a brief review of the use of cost analyses in the discipline (*7*). The primary commonality among the studies reviewed by Patton and those found in an extensive review of the current literature is that these studies compare the costs of nuclear medicine procedures to nothing at all, to other diagnostic procedures, or to

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TABLE 1
Diagnostic Comparability Studies

Author	Citation	Sensitivity	Specificity	Agreement
Villanueva-Meyer, et al.	10	—	—	93%
Taillefer, et al.	17	—	—	89%
Kiat, et al.	16	MIBI:93% ^{201}Tl:80%	MIBI:75% ^{201}Tl:75%	—
Taillefer, et al.	9	—	—	87.2%
Maisey, et al.	11	No significant difference	—	88%
Maddahi, et al.	12	MIBI:89% ^{201}Tl: 90%	—	—
Wackers	14	—	—	>85%

other nuclear medicine procedures. While these studies include the costs associated with the preparation of the radiopharmaceutical, no studies were found that directly compared the cost-effectiveness of competing radiopharmaceuticals. This void does not indicate that cost is not an issue with radiopharmaceuticals; researchers often make reference to cost when discussing the results or implications of their study. However, these comments are usually speculative at best.

The recent introduction of a technetium-based radiopharmaceutical used for cardiac imaging has provided a viable alternative to the standard use of ^{201}Tl. While numerous studies have been conducted to compare the physiological characteristics and clinical applications of ^{201}Tl and ^{99m}Tc-sestamibi, no economic analysis has been conducted regarding these cardiac imaging agents. Minimal references have been made regarding the cost of ^{99m}Tc-sestamibi but no research has substantiated these comments. For example, Taillefer states that advantages of ^{99m}Tc-labeled cardiac imaging agents include the good physical characteristics, the broad availability, and the low cost of ^{99m}Tc (*8,9*). However, no direct cost analysis was presented.

The purpose of this study is two-fold. The first objective is to demonstrate the applicability of pharmacoeconomic research methodologies in the radiopharmaceutical market. The second is to compare the cost-effectiveness of two different products used for the same purpose. This research should provide economic information that may help nuclear medicine departments select cardiac imaging agents.

The present study compares the cost-effectiveness of ^{201}Tl versus ^{99m}Tc-sestamibi. These are two competing agents that are valuable for diagnosing cardiac defects and functioning (*10–14*). To determine cost-effectiveness, it must be shown that each agent produces a similar outcome. One may contend that the outcome of a cardiac study is the set of images. If this was assumed, the CEA would provide comparative ratios of cost per image. However, it has been demonstrated that the images produced by ^{201}Tl and ^{99m}Tc-sestamibi are not of identical quality. The gamma rays of ^{99m}Tc are less attenuated by the soft tissues, providing superior image quality and less scatter when compared to ^{201}Tl. Additionally, the physical characteristics of technetium allow for a higher amount of radioactivity to be administered to the patient, increasing the clarity of the images (*10,11,14–20*). If the focus of a cardiac study is limited to the image itself and the difference in quality and clarity of the images produced by these two agents is clinically significant, then a cost-effectiveness analysis would not be the most appropriate methodology to employ.[1] The application of the alternative methodologies discussed will be left for future research.

We feel that the outcome of a cardiac imaging study is the diagnosis, not the set of images. Therefore, the resulting CEA ratio is the imaging cost per diagnosis. Using this outcome measure, CEA requires that each agent provide information that allows the physician to make the same, correct diagnosis. Several studies have been conducted that compare the use of ^{201}Tl and ^{99m}Tc-sestamibi in cardiac imaging. A review of these studies reveals that the sensitivity and specificity of these agents are very similar (*8–12,14,16,17,20–24*). A summary of some of these studies is presented in Table 1.

Based on this literature, we conclude that ^{99m}Tc-sestamibi and ^{201}Tl provide similar diagnostic information on the presence or absence of coronary artery disease (CAD). This diagnostic comparability increases when protocols include reinjection of ^{201}Tl for resting images (*14,25–27*). Based on this conclusion, the outcome of interest in this study was the detection or ruling out of CAD by the two alternative agents. The CEA ratio is presented here as the cost per case of CAD detected or ruled out ($/study).

METHODS

Cost information for each radiopharmaceutical was obtained from a 450-bed private hospital in South Carolina. These costs were based on 1993 contract year pricing. The costs attributed to ^{201}Tl were based on a one-day, stress-rest protocol where patients were given 2.5 mCi of ^{201}Tl during the stress phase and reinjected 3.5 to 4 hr later with 1.0 mCi. The ^{99m}Tc-sestamibi patients followed a one-day, rest-stress protocol with a resting administration of 10 mCi and a stress-phase, 5 hr later, using an additional 20 mCi.

[1] To satisfy those who would argue this case, one would need to use a different pharmacoeconomic tool such as cost-benefit analysis (CBA) or cost-utility analysis (CUA). These alternative methodologies would not be impossible to conduct on radiopharmaceuticals however, due to the increased assumptions and additional data that would be required, we will make a strong case for the application of CEA.

TABLE 2
Variables Considered for Analysis

Cost Variable	Differential Cost?
Product cost component:	
Kit or bulk product costs	Yes
Kit preparation and quality control time	Yes
Kit preparation materials	Yes, but inconsequential
Decay costs	Yes
Disposal costs	Possibly, but inconsequential
Imaging cost component:	
Nuclear med. tech. time	Yes
Camera time	Protocol dependent
Computer time	No
Patient preparation materials	Yes, but inconsequential
Scheduling and registration	No
Diagnosis component:	
Physician's time	Protocol dependent
Physician's consultation	No
Dictation services	No
Induced cost component:	
Costs associated with adverse effects	No
Costs of repeat tests	No
Costs of induced tests	No
Costs of subsequent treatment	No

Table 2 lists the cost variables considered in this analysis, a brief classification of each variable, and its relevance to this study. The identification of some of these costs follow the research of Stason and Fortess (*28*).

It must be remembered that only the differential costs between ^{201}Tl and ^{99m}Tc-sestamibi are relevant. Costs common to both agents were not included in the final cost-effectiveness calculations. Due to differences in procurement and preparation between the agents, kit costs, kit preparation and quality control time, and decay costs were included in the CEA calculations. Some of these product-related cost variables are common to both agents or are likely to be inconsequential to the final results of this analysis (i.e., costs of syringes and needles). Differential costs that were considered inconsequential to this analysis include kit preparation and quality control materials (syringes, needles, ethanol, hydrochloric acid, and silicone-impregnated quality control strips) and disposal costs.[2]

Based on the hospital's protocols, it was estimated that an additional 10–30 min of patient interaction and preparation time was incurred by the technologists with patients receiving ^{99m}Tc-sestamibi studies when compared to patients receiving ^{201}Tl studies. This differential time was included in the analysis. Based on the protocols, the camera time and computer time for each agent were both very similar. Additionally, patient scheduling and registration were the same for each agent. Technetium-99m-sestamibi studies do require materials in addition to those of ^{201}Tl studies (e.g., milk or chips for gall bladder washout). However, these incidental costs were considered inconsequential.

Costs associated with physician's time and consultation and dictation services were considered the same for both agents.[3]

Although ^{99m}Tc-sestamibi has a more extensive side effect profile than ^{201}Tl, neither results in adverse reactions warranting monetary quantification (*29,30*). The costs associated with induced tests and subsequent treatment are dependent on the diagnosis of CAD. Thus, if ^{99m}Tc-sestamibi and ^{201}Tl demonstrate comparable sensitivity and specificity for the detection of CAD, then these costs would be the same for each agent. Costs of repeated tests would result from misadministration of either agent or from unacceptable tagging efficiency of the ^{99m}Tc-sestamibi kit. One can assume that misadministrations are random occurrences and are not dependent upon which cardiac imaging agent is used (especially when both follow similar protocols, as is the case here). One can also assume that quality control techniques will prevent re-testing due to radiochemical contamination (i.e., free ^{99m}Tc). Based on these assumptions, these variables were not included in the final calculations. Table 3 lists the variables ultimately quantified and included in the CEA calculations.

When evaluating radiopharmaceutical costs, one must consider the source of the product, any regulatory or contractual agreements that may limit its use (kit use efficiency), and any inventory carrying costs (decay costs).

[2] Although it might be argued that the longer storage time resulting from the longer half-life of ^{201}Tl relative to ^{99m}Tc would result in higher disposal costs. We argue, however, that in-house radioactive disposal areas are a fixed cost and unless it is at full capacity, the cost associated with the maintenance of this area will not significantly differ between the disposal of ^{99m}Tc waste and ^{201}Tl waste.

[3] The physician's time could vary between the agents, depending on the protocol. This was not the case with the protocols followed in this hospital.

TABLE 3
Cost Variables and Assumptions

Kit costs (^{99m}Tc-sestamibi cold kit, ^{99m}Tc)
Kit preparation and quality control time (RPh time at $25 and $35 per hr)
Decay costs (Unused ^{201}Tl lost for next day's use)
Kit utilization efficiency (No. of patients per kit or vial)
Nuclear medicine technologist's time (10–30 min per patient at $12–$20 per hr)

A hospital preparing doses in-house can be subject to regulatory or contractual agreements that may restrict the use of a particular product. Of interest here is the practice of patient/kit contractual agreements. Many hospitals that prepare their radiopharmaceutical in-house are limited to six draws from each ^{99m}Tc-sestamibi kit (or three patients per kit for a one-day protocol as in the current study). However, there is usually enough ^{99m}Tc-sestamibi in each kit to prepare at least 10 single doses (five patients per kit). Those hospitals subject to the agreement will experience significantly higher kit costs for ^{99m}Tc-sestamibi scans than those who can achieve maximal kit utilization. In this analysis, the cost of a ^{99m}Tc-sestamibi kit was $315. Following package insert guidelines, the cost of the ^{99m}Tc in a kit reconstituted with 150 mCi (yielding three patients per kit) was $9.00 ($0.06/mCi). The differential pharmacist's time to reconstitute and quality control the ^{99m}Tc-sestamibi kit was estimated to be approximately 20–30 min. However, these activities allow the pharmacist to perform other activities while waiting for the kit to tag and for quality control development. The actual pharmacist time for preparation of a ^{99m}Tc-sestamibi kit is likely to be less than 10 min. Assuming five minutes at $25 per hour, the pharmacist's time cost would be $2.08 per kit. At the other extreme, assuming 10 min at $35 per hour, this cost would be $5.83 per kit. This pharmacist's preparation cost is exclusive to ^{99m}Tc-sestamibi as ^{201}Tl does not require reconstitution and quality control.

Inventory carrying costs can be significant when radiopharmaceuticals are prepared in-house. Once a ^{99m}Tc-sestamibi kit is prepared, it is stable for up to six hours, and any remaining product must be properly disposed. Since ^{201}Tl has a 73-hr half-life, any unused product can be used on subsequent days (up to a six-day expiration from calibration day). However, the unused ^{201}Tl decays 21% every 24 hr. This decay accounts for a significant amount of the inventory carrying costs associated with ^{201}Tl. These carrying costs are not attributable to ^{99m}Tc-sestamibi as it must be prepared daily. The costs for ^{201}Tl used in this analysis are based on a 9.9 mCi vial received one day before the calibration date costing $246.88.

RESULTS

Table 4 summarizes the scenarios under which the cost comparisons were conducted. Table 5 presents the differential costs per study between ^{201}Tl and ^{99m}Tc-sestamibi. The negative values in Table 5 represent situations when the ^{99m}Tc-sestamibi is more cost-effective than the ^{201}Tl under varying scenarios.

As Table 5 illustrates, when ^{201}Tl was used either one day before calibration date or the day of calibration it was much more cost-effective for detection of CAD than was ^{99m}Tc-sestamibi, especially when cardiac scheduling was light (one or two patients). This conclusion held for each scenario. However, when the ^{201}Tl was not used efficiently (i.e., significant loss of activity due to decay) ^{99m}Tc-sestamibi was more cost effective. Technetium-99m-sestamibi was more cost-effective than ^{201}Tl in all scenarios with more than two cardiac patients per day and when ^{201}Tl was used three days post-calibration. When ^{201}Tl was allowed to decay for one and two days post-calibration, the cost-effectiveness results became dependent upon the assumptions. For example, if the ^{99m}Tc-sestamibi kit was used at five per kit, it was more cost-effective (scenarios B and D). However, if the ^{99m}Tc-sestamibi was used at three patients per kit, the ^{201}Tl remained more cost-effective.

DISCUSSION

Maublant et al. conclude that "MIBI may become the agent of choice for the simultaneous evaluation of myocardial perfusion and ventricular function (*20*)." This is a very strong prediction as there is no current evidence supporting this projection. Thallium-201 continues to maintain a significant share of the cardiac imaging market. One might argue that a possible reason for this lack of complete substitution of ^{99m}Tc-sestamibi for ^{201}Tl is of an economic nature. Maublant's prediction was based solely on clinical evidence without regard to economic considerations. This raises the question of whether or not the higher costs of the ^{99m}Tc-sestamibi

TABLE 4
Scenario Assumptions

Scenario	No. of patients per MIBI kit	RPh time	RPh wage	NMT time	NMT wage
A	3	5 min	$25/hr	15 min	$16/hr
B	5	5 min	$25/hr	15 min	$16/hr
C	3	10 min	$35/hr	30 min	$20/hr
D	5	10 min	$35/hr	30 min	$20/hr

TABLE 5
Differential Costs per Study (Cost of ^{99m}Tc-sestamibi/Cost of ^{201}Tl)

No. of patients	Scenario	1 day precal	Day of cal	1 day postcal	2 days postcal	3 days postcal
1	A	227.96	219.00	203.20	183.36	158.03
	B	248.96	240.00	224.20	204.36	179.03
	C	237.71	228.75	212.95	193.11	167.78
	D	258.71	249.75	233.95	214.11	188.78
2	A	94.30	81.88	66.08	43.61	−5.02
	B	104.80	92.38	76.58	54.11	5.48
	C	102.18	89.76	73.96	51.49	2.86
	D	112.68	100.26	84.46	36.07	−13.36
3	A	48.59	36.17	3.09	−36.66	−42.08
	B	55.59	43.17	10.09	−29.66	−35.08
	C	55.84	43.42	10.34	−29.41	−34.83
	D	62.84	50.42	17.34	−22.41	−27.83
4	A	107.26	81.88	66.09	43.61	−13.50
	B	30.99	5.61	−10.18	−32.66	−89.77
	C	115.14	89.76	73.97	51.49	−5.62
	D	37.93	12.55	−3.24	−25.72	−82.83
5	A	66.88	54.45	38.66	−14.92	−65.46
	B	5.87	−6.56	−22.35	−75.93	−126.12
	C	74.38	61.95	46.16	−7.42	−57.61
	D	12.62	0.19	−15.60	−69.18	−119.37
6	A	48.59	36.17	11.74	−10.74	−54.01
	B	55.59	43.17	18.74	−3.74	−47.01
	C	55.84	43.42	18.99	−3.49	−46.76
	D	62.84	50.42	25.99	3.51	−39.76
8	A	66.50	47.60	25.33	2.85	−32.32
	B	30.99	12.09	−10.18	−32.66	−67.83
	C	73.91	55.01	32.74	10.26	−24.91
	D	37.93	19.03	−3.24	−25.72	−60.89
10	A	72.06	54.46	38.66	11.00	−56.41
	B	.05	−6.55	−22.35	−50.01	−117.42
	C	9.56	61.96	46.16	18.50	−48.91
	D	17.90	0.20	−15.60	−43.26	−110.67

have outweighed the advantages of its imaging characteristics. This study provides some insight into this question of cost-effectiveness.

These results show that there was a significant difference between the cost-effectiveness of ^{201}Tl and ^{99m}Tc-sestamibi based on this hospital's pricing contracts and imaging protocols. When ^{201}Tl was used in a timely manner (i.e., within one or two days of receipt), the cost-effectiveness was significant. If the ^{201}Tl was allowed to decay for four days, the ^{99m}Tc-sestamibi became cost-effective as well. The results (i.e., more than two patients per day and two or three days of ^{201}Tl decay) depended more on ^{99m}Tc-sestamibi kit use than on pharmacist and technologist time and wage assumptions.

LIMITATIONS

These results are not generalizable to hospitals receiving their radiopharmaceuticals from outside pharmacies, or those who have drastically different pricing contracts. Also these results could change significantly if the agents were administered via different protocols, that is, if one was administered via a one-day and the other a two-day protocol. In addition, the results found in this study are based on data from a single hospital and do not provide conclusions upon which other hospitals could make decisions. The intent here was to provide an illustration and some insight into how a hospital could begin to investigate this issue internally. We hope future research will provide information that is more generalizable to other institutions.

CONCLUSIONS

When used in a timely manner, ^{201}Tl used in the detection of coronary artery disease was more cost-effective than ^{99m}Tc-sestamibi in the institution studied. Although the generalizability of these results is strictly limited, this research demonstrates the applicability of pharmacoeconomic research methodologies in the radiopharmaceutical market and provides some economic insight into the use of two competing cardiac imaging agents. This type of research should

provide information regarding the selection of cardiac imaging agents for a hospital's nuclear medicine department. These results also provide practitioners with differential costing data that can be used to assess the financial worth of clearer images afforded by ^{99m}Tc-sestamibi.

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