Effect of Prior Radiopharmaceutical Administration on Schilling Test Performance: Analysis and Recommendations

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Previously administered diagnostic and therapeutic radiopharmaceuticals may interfere with performance of the Schilling test for prolonged periods of time. Additionally, presence of confounding radionuclides in the urine may not be suspected if baseline urine measurements have not been performed before the examination. **Methods:** We assumed that a spurious contribution of counts corresponding to 1% of the administered Schilling dose would begin to contribute clinically significant interference. Based on the typical amounts of radiopharmaceuticals administered, spectra of commonly used radionuclides and best available pharmacokinetic models of biodistribution and excretion, we estimated the interval required for 24-hr urinary excretion of diagnostic and therapeutic radiopharmaceuticals to drop below this threshold of significant interference. **Results:** For previously administered ^{99m}Tc-based radiopharmaceuticals and ^{123}I-NaI, the interval required for urinary levels of activity to fall below thresholds of allowable interference are between 2–5 days. For ^{67}Ga-citrate, several ^{111}In compounds, ^{131}I-MIBG and ^{201}Tl-thallous chloride, periods of 12–44 days are estimated. Estimates for ^{131}I-NaI vary greatly between 4 and 115 days, depending on the amount administered, and the degree of thyroid uptake. **Conclusion:** Patients should be interviewed before performing the Schilling test to ensure that interfering radiopharmaceuticals have not been recently administered. The estimates developed in this paper can serve as guidelines for the necessary waiting time between prior radiopharmaceutical administration and the Schilling examination.

Key Words: Schilling test; radiopharmaceuticals

J Nucl Med 1996; 37:1995–1999

The single-isotope Schilling test, introduced over 40 yr ago (*1*), and its current dual-isotope variation, described in 1965 (*2*), remain reliable and useful methods for differentiating the various etiologies of vitamin B12 deficiency (Table 1). Potential causes of error have been previously described, including incomplete urine collection (*3,4*), impaired renal function (*4*), and, in the case of dual-isotope Schilling test, liability of the intrinsic factor (IF)-vitamin B12 bond (*5–7*). Technical blunders, such as poor placement of energy windows, incorrect measurement of samples and erroneous background determination can also cause inaccuracies (*8*).

As demonstrated in this case report, spurious test results may arise during performance of the Schilling examination due to interference from previously administered radionuclides excreted into the urine. Although the true frequency of this occurrence is difficult to define, in a retrospective analysis of 2142 dual-isotope Schilling tests performed during a 10-yr time period in the Grampian Health Board Area in Scotland, interference by previously administered radiopharmaceuticals was suspected in five cases involving three radionuclides (^{67}Ga and ^{75}Se twice each; ^{131}I once) (*3*).

The International Committee for Standardization in Hematology has recommended that immediately before any B12 absorption test, pretest baseline radioactivity measurements should be performed, such as a 12-hr control urine sample in the case of the Schilling test (*9*). As supported by a recent survey of hospitals performing the dual-isotope Schilling test (*8*), it appears that this time-consuming suggestion is not commonly implemented and is recommended in only one (*10*) of three commercial product inserts (*10–12*).

In the following case report, we demonstrate the potential for error during performance of the Schilling test, due to presence of confounding radionuclides remaining in the urine from previous diagnostic examinations. Based on a combination of experimental measurements of radionuclide spectra and analysis of models of radiopharmaceutical excretion, we have quantitatively assessed the effect of previously administered diagnostic and therapeutic radionuclides on Schilling test performance. These data have enabled us to generate guidelines for the recommended interval between radiopharmaceutical administration and the Schilling test to avoid erroneous results as a consequence of residual activity.

CASE REPORT

An 84-yr-old man was admitted to New York Hospital with a chief complaint of urinary retention, secondary to benign prostatic hypertrophy. Concurrent medical problems included exertional angina, anemia and hypercalcemia, secondary to a known parathyroid adenoma. On admittance, the patient was found to have a low serum vitamin B12 level. Dipyridamole myocardial perfusion SPECT study was performed using 118 MBq (3.2 mCi) of [^{201}Tl] thallous-chloride and demonstrated reversible defects in the septum, inferior wall and apex of the left ventricle. Parathyroidectomy and right inguinal hernia repair were successfully performed 3 days later.

A single-isotope Schilling test was administered 7 days after the initial ^{201}Tl administration. Two consecutive 24-hr urine samples were collected and counted 13 days after ^{201}Tl administration. Cumulative 48-hr urinary excretion of ^{57}Co vitamin B12, based on counts in the standard ^{57}Co window (122 ± 42 keV), was 276% of the administered amount, prompting consideration of prior radionuclide administration. The urine and standard were then recounted using a narrow energy window (122 ± 12 keV) in an attempt to eliminate counts from the residual ^{201}Tl emissions (68–80 keV mercury X-rays, 135 keV and 167 keV gamma rays at 94.5%, 22.65% and 10.0% abundance, respectively), and calculated excre-

Received Jan. 3, 1996; revision accepted Jun. 12, 1996.
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TABLE 1
Characteristics of Schilling Test Kits

Method		Single-isotope	Single-isotope	Dual-isotope
Manufacturer		Mallinckrodt (*10*)	Squibb (*11*)	Amersham (*12*)
Nominal activity (μCi)	^{57}Co	0.5	0.56–0.61	0.5
	^{58}Co	–	–	0.8
Shelf-life (days)		180	120	60
Normal*	Urinary free B12	>6–10%‡	≥9%	9–33%
	Urinary bound B12	–	–	8–34%
	Urinary B/F ratio	–	–	0.7–1.2
Malabsorption*	Urinary free B12	≤3%‡	<9%	≤8%
	Urinary bound B12	≤3%‡	<9%	≤8%
	Urinary B/F ratio	–	–	0.6–1.1
IF-Deficiency*	Urinary free B12	≤3%‡	<9%	1–10%
	Urinary bound B12	>6–10%‡	>9%	2–15%
	Urinary B/F ratio	–	–	>1.4†

*Excretion values are according to manufacturers' suggestions for interpretation.
†Some patients with IF deficiency give ratios in the range of 1.2–1.4 (*12*).
‡Values in the 3–5% range are somewhat questionable and usually require further analysis (*10*).
IF = intrinsic factor; B/F ratio = ratio of IF-bound vitamin B12 excretion to free vitamin B12 excretion.

tion decreased to 32.9%. The urine and standard were subsequently recounted using both routine and narrow windows at 25, 34 and 52 days post ^{201}Tl administration in an attempt to exploit the differential decay of ^{201}Tl relative to the longer lived ^{57}Co (3.05 versus 270.9 day half-life). Calculated 48-hr urinary excretion progressively decreased to a plateau value of approximately 10% (Fig. 1).

Materials and Methods

The three stages of our analysis were: (a) choosing a level of interference considered significant to interpretation of the Schilling test, (b) determining the quantity of clinically relevant radionuclides which would contribute this level of significant interference and (c) based on pharmacokinetic models of radiopharmaceutical excretion and biodistribution, estimating at which time postadministration would urinary excretion of diagnostically or therapeutically administered radiopharmaceuticals drop below the selected threshold. Separate estimates were made for the single- and dual-isotope Schilling tests; of the two commercially available single-isotope Schilling test examinations, calculations were based on the Mallinckrodt kit (St. Louis, MO) due to a lower level of activity at expiration (Table 1).

All measurements were performed on two counting systems, the first consisting of a 2-in. end-hole scintillation crystal interfaced to a multichannel analyzer and the second consisting of an integrated scintillation counter with 3-in. end-hole crystal. Energy calibration was performed against known standards, and energy windows for measurement of ^{57}Co and ^{58}Co isotopes were selected based on published recommendations (^{57}Co: 50–200 keV; ^{58}Co: 400-1000 keV) (*13*).

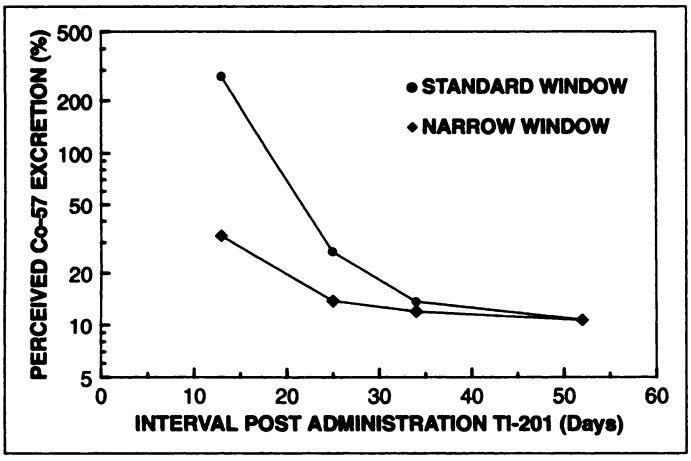

FIGURE 1. Calculated 48-hr urinary excretion of ^{57}Co-vitamin B12 based on counting performed at various intervals after original administration of ^{201}Tl thallous-chloride (semilog plot). Results based on routine and narrow windows are illustrated.

Significant Level of Interference. For interference to be considered clinically significant, we hypothesized that it must change the apparent excretion of cobalt isotopes by at least 1% of the administered activity (^{57}Co-B12 for the single-isotope Schilling test or either free ^{58}Co-B12 or IF-bound ^{57}Co-B12 for the dual-isotope Schilling test). For example, in malabsorption, where absolute levels of free and IF-bound vitamin B12 excretion are decreased, an increase in IF-bound vitamin B12 excretion of greater than 1% will begin to simulate the appearance of pernicious anemia and should therefore be avoided (Table 1). Counting rates in the cobalt windows corresponding to these levels of excretion were calculated based on levels of activity in the clinical kits at expiration. The rates were combined with the sensitivity of the scintillation counters, determined by measurement of 1 ml of dual-isotope Schilling test cobalt standards.

To compare this threshold to counting uncertainty present during typical performance of the single- and dual-isotope Schilling tests, we analyzed inherent stochastic error using a spreadsheet developed for this purpose that calculates the propagation of error at every binary combination of variables (*8*). Estimates were based on the characteristics of our counting systems and the specific activity of the diagnostic test kits at expiration; variables such as percent excretion of the radioactive B12 moieties, total urinary volume, sample volume and counting time were varied to study their effect on counting error, based on the standard formulae for error after addition, subtraction, multiplication and division (*14*).

Contribution of Radionuclides to Cobalt Windows. The second step in our analysis was measuring the contribution of six calibrated, clinically relevant radionuclide sources (^{67}Ga, ^{99m}Tc, ^{111}In, ^{123}I, ^{131}I and ^{201}Tl) to the ^{57}Co and ^{58}Co windows. Accuracy of the dose calibrator, for assaying small quantities of isotopes in the range used in our investigation, was confirmed by measuring linearity of an 8.04 mCi source of ^{99m}Tc as it decayed over the course of 3.5 days. The six clinically relevant radionuclides we studied were diluted to concentrations of approximately 1 μCi/ml of solution and measured in the dose calibrator to within 0.1 μCi

TABLE 2
Pharmacokinetic Parameters for Radiopharmaceutical Excretion

Radiopharmaceutical	α_1	$T_{1/2_1}$ (hr)	α_2	$T_{1/2_2}$ (hr)	α_3	$T_{1/2_3}$ (hr)
^{99m}Tc-pentetate (DTPA)	0.579	1.00	0.421	9.24		
^{99m}Tc-MAG$_3$, normal	1.00	0.417				
^{99m}Tc-MAG$_3$, abnormal (ABN)	1.00	4.17				
^{99m}Tc-MAG$_3$, unilateral renal blockade	0.500	0.417	0.500	120		
^{99m}Tc-succimer (DMSA)	0.250	2.00	0.250	43.2		
^{99m}Tc-glucoheptonate (GHA)	0.350	0.333	0.300	2.40	0.350	88.8
^{99m}Tc-iminodiacetic acid (IDA), normal	0.150	0.100				
^{99m}Tc-iminodiacetic acid (IDA), disease	0.650	0.333				
^{99m}Tc-red blood cell (RBC)	1.00	60.0				
^{99m}Tc-human serum albumin (HSA)	0.0150	6.80	0.0350	31.0	0.950	466
^{99m}Tc-macroaggregated albumin (MAA)	0.250	0.450	0.170	4.50		
^{99m}Tc-DTPA aerosal, fast	0.860	1.67				
^{99m}Tc-DTPA aerosal, slow	0.200	1.67				
^{99m}Tc-phosphates	0.300	0.500	0.300	2.00	0.400	72.0
^{99m}Tc-sestamibi (MIBI), stress	0.100	7.00	0.200	24.0		
^{99m}Tc-sestamibi (MIBI), rest	0.140	7.00	0.170	24.0		
^{99m}Tc-hexamethyl propyleneamine oxime	1.00	4.00				
^{99m}Tc-pertechnetate, thyroid blocked	0.600	4.50	0.400	45.0		
^{99m}Tc-pertechnetate, thyroid not blocked	0.130	3.00	0.160	4.50	0.360	45.0
^{111}In-white blood cells (WBC)	0.962	1680				
^{111}In-platelets	0.650	1680				
^{111}In-DTPA	0.990	1.67	0.0100	168		
^{111}In-chloride	0.300	48.0	0.700	1680		
^{67}Ga-citrate	0.155	30.0	0.755	613		
^{201}Tl-chloride	0.0620	146	0.138	502		
^{123}I-iodoamphetamine (IMP)	0.290	8.00				
^{123}I- or ^{131}I-NAI, blocked	1.00	8.00				
^{123}I- or ^{131}I-NAI, RAIU = 5%	0.950	8.00	0.0500	1920		
^{123}I- or ^{131}I-NAI, RAIU = 15%	0.850	8.00	0.150	1920		
^{123}I- or ^{131}I-NAI, RAIU = 35%	0.650	8.00	0.350	1920		
^{123}I- or ^{131}I-NAI, RAIU = 55%	0.450	8.00	0.550	1920		
^{131}I-metaiodobenzylguanidine (MIBG)	0.360	3.00	0.630	33.6		

(± 10%). This degree of accuracy was deemed acceptable based on the overall assumptions and estimations inherent in the counting and excretion models we employed.

For each preparation, a volume of 10 μl was immediately removed by volumetric pipette and discharged into counting tubes containing 1 ml of buffer solution. The samples were counted for 10 min in each scintillation counter using both cobalt windows. For both the single- and dual-isotope Schilling tests, the amount of each radionuclide contributing the previously determined significant level of interference was noted. The lowest amount based on either gamma counter and, in the case of the dual-isotope Schilling test, either cobalt window, was selected as the most conservative value.

Urinary Radiopharmaceutical Excretion. The final step we addressed was the amount of time necessary for urinary levels of commonly utilized diagnostic and therapeutic radiopharmaceuticals, incorporating the six radionuclides analyzed in this investigation, to decrease below their allowable thresholds. For each radiopharmaceutical, calculation of the interval was based on the amount typically administered, the physical decay of the radionuclide and quantitative kinetic models of radiopharmaceutical biodistribution and excretion.

Excretion functions were obtained for the radiopharmaceuticals used in this study based primarily on the biokinetic models listed in ICRP Publication 53 (*15*), occasionally supplemented by internal data from models developed at the Radiation Internal Dose Information Center in Oak Ridge, TN (data on file) (Table 2). Obsolete radiopharmaceuticals, no longer in common use in either the United States or Europe, were omitted from consideration. Several of the more recently approved radiopharmaceuticals could not be quantitatively analyzed in this manner due to lack of adequate pharmacokinetic models.

For each radiopharmaceutical, an assumed amount of activity administered per procedure was assigned based on published values (*16,17*) and modified according to our own usage and experience. In selected cases, several levels of administered activity for a radiopharmaceutical were analyzed where usage varied significantly for different applications. In other instances, various physiologic states were considered where adequately modeled. The 24-hr urinary excretion of each radiopharmaceutical was calculated sequentially starting one day after administration, continuing until excretion was below levels of interest. The expression for 24-hr excretion of any compound is:

$$U_{24}(t) = \sum_i [\alpha_i \exp(-\lambda_i(t-1)) - \alpha_i \exp(-\lambda_i t)] \exp(-\lambda_p t),$$

where $U_{24}(t)$ = the fraction of administered activity in a 24-hr urine sample at time t; t = the time postadministration (days); α_i = the fractional urinary excretion associated with pathway i; λ_i = the biological removal constant for excretion associated with pathway i (day^{-1}) and λ_p = the physical decay constant of the radionuclide (day^{-1}).

A list of values for α's and T½'s is given in Table 2, where T½ = 0.693/λ.

RESULTS

Measurement of counts per Becquerel in the ^{57}Co and ^{58}Co windows for both cobalt radioisotopes and the six clinically relevant radionuclides appear in Table 3. Based on the mea-

TABLE 3
Count Rate of Various Radionuclides in Cobalt Isotope Windows

Counting System Window		A		B	
		^{57}Co 50–200 keV	^{58}Co 400–1000 keV	^{57}Co 50–200 keV	^{58}Co 400–1000 keV
Background (cpm)	4.9×10^1	5.1×10^1	7.3×10^1	6.4×10^1	
Count-rate efficiency (cpm/Bq)*	^{57}Co	5.20×10^1	3.26×10^{-2}	5.50×10^1	4.65×10^{-2}
	^{58}Co	4.51×10^0	9.92×10^0	4.97×10^0	1.95×10^1
	^{67}Ga	2.8×10^1	6.1×10^{-1}	2.9×10^1	1.0×10^0
	^{99m}Tc	4.6×10^1	1.8×10^{-3}	4.4×10^1	1.4×10^{-2}
	^{111}In	1.7×10^1	1.6×10^{-1}	7.8×10^0	3.3×10^1
	^{123}I	3.3×10^1	2.7×10^{-1}	3.9×10^1	5.9×10^{-1}
	^{131}I	8.8×10^0	2.2×10^0	7.5×10^0	2.6×10^0
	^{201}Tl	3.8×10^1	5.6×10^{-2}	3.9×10^1	8.7×10^{-2}

*Background-corrected.

sured characteristics of our counting systems, levels of stochastic noise inherent in performance of the Schilling test under various test conditions appear in Figure 2.

For both the single- and dual-isotope Schilling tests, the thresholds of interfering activity calculated for each radionuclide, based on the most conservative value from either scintillation counter or cobalt window, are reported in Table 4. For the dual-isotope Schilling test, with the exception of ^{111}In and ^{131}I, interference of radionuclides was greatest in the ^{57}Co window. Based on typical amounts of administered radiopharmaceuticals and models of excretion, the time required for urinary activity to decrease below interfering levels are listed in Table 5. Because of the many combinations of amounts administered and levels of thyroid uptake, data for ^{131}I-NaI are graphed in Figure 3.

DISCUSSION

This case demonstrates the prolonged vulnerability of the Schilling test to interference from diagnostic and therapeutic radionuclides, administered in many-thousand-fold greater amounts. Interfering activity can persist from days to weeks, depending on the amount of radiopharmaceutical administered, the physical half-life of the radionuclide and clearance parameters of the specific radiopharmaceutical. It is often difficult to identify situations of potential interference because referring physicians and staff performing the examination may be unaware of previous imaging procedures that may have taken place elsewhere. Furthermore, by the time that excretion results are calculated and an irregularity is suspected, patients may not be readily available for consultation.

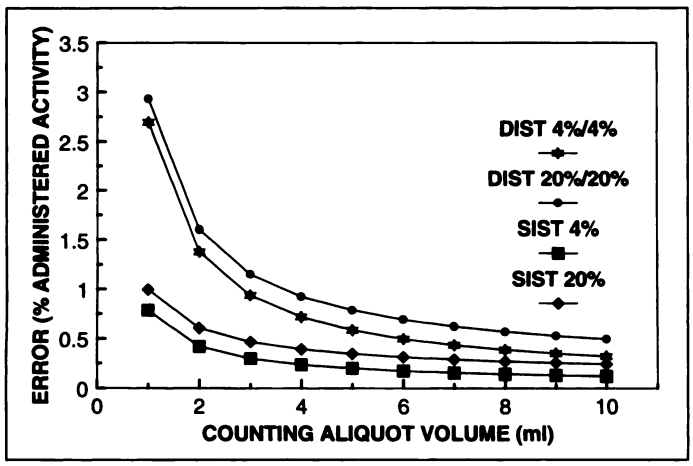

FIGURE 2. Plot of the statistical uncertainty of free B12 excretion for both the single- and dual-isotope Schilling tests as a function of sample volume, based on the characteristics of Counter A, and specific activity of the Schilling test kits at expiration. Calculations have been performed based on a presumed 24-hr urine volume of 1400 ml and a counting time of 10 min at 4% and 20% excretion levels (for the dual-isotope Schilling test, the ratio of IF-bound B12 to free B12 has been set at 1). Values for other counting times (t) can be calculated by multiplying these errors by $\sqrt{10/t}$.

Additionally, in this case, energy resolution of the NaI scintillation detector was insufficient to adequately discriminate between ^{201}Tl and ^{57}Co emissions. Selection of a narrow counting window did not adequately reduce the amount of confounding activity, and 48-hr urinary excretions based on routine and narrow windows remained elevated until the ^{201}Tl in the urinary sample had physically decayed to negligibly low levels. This method of decaying the urine is not optimal in that counting rates and statistic validity of the results will further decrease, and there will be considerable delay before a diagnosis can be made.

Baseline measurements of urinary activity before administration of the Schilling test, as recommended by an expert committee (*9*), would detect interference, but these measurements are not routinely performed nor would they provide information in a cost-effective and timely manner. The simplest and most practical suggestion is that all patients referred for Schilling examinations be systematically interviewed before receiving the radioactive B12 and again on receipt of the test urine, to document, if not prevent, potential interference by recently administered radiopharmaceuticals. When prior radionuclide administration is discovered, it is surprising that no guidelines regarding the necessary waiting period have been previously promulgated.

CONCLUSION

The estimates developed in this paper are useful in determining how much time should elapse between previously performed procedures and the Schilling test. These estimates depend heavily on the assumptions made about the kinetic

TABLE 4
Confounding Levels of Radionuclides (Bq) at 1% Administered Amount Threshold

Radionuclide	Single-Isotope test	Dual-Isotope test
^{67}Ga	2.1×10^2	3.0×10^2
^{99m}Tc	1.3×10^2	1.8×10^2
^{111}In	3.5×10^2	1.0×10^2
^{123}I	1.6×10^2	2.3×10^2
^{131}I	6.9×10^2	7.9×10^2
^{201}Tl	1.6×10^2	2.2×10^2

TABLE 5
Amount Radiopharmaceutical Administered and Recommended Wait (Days)

Radiopharmaceutical*	Specific conditions*	Amount administered		Recommended wait	
		mCi	MBq	SIST	DIST
^{99m}Tc-DTPA	No/flow/flow	2/10	74/370	4	3/4
^{99m}Tc-MAG3	Normal/ABN/URB	2	74	2/3/4	2/3/4
^{99m}Tc-DMSA		2	74	4	4
^{99m}Tc-GHA		20	740	5	5
^{99m}Tc-IDA	Normal or disease	2	74	2	2
^{99m}Tc-RBC		30	1110	5	5
^{99m}Tc-HSA		20	740	5	5
^{99m}Tc-MAA		6	222	3	3
^{99m}Tc-DTPA aerosal	Fast or slow	1	37	2	2
^{99m}Tc-phosphates		20	740	5	5
^{99m}Tc-MIBI	Rest	8	296	4	4
^{99m}Tc-MIBI	Stress	25	925	5	5
^{99m}Tc-HMPAO		15	555	3	3
[^{99m}Tc]pertechnetate	± Thyroid blocked	10–30	370–1110	5	5
^{111}In-WBC		0.5	18.5	25	30
^{111}In-platelets		0.25	9.25	21	26
^{111}In-DTPA		0.5	18.5	12	16
^{111}In-chloride		0.5	18.5	24	29
^{67}Ga-citrate		3/10	111/370	39/44	38/43
^{20}Tl-chloride		3.5	130	33	31
^{123}I-IMP		5.5	204	5	5
^{123}I-NaI	RAIU 0–55%	0.2	7.4	4–5	4–5
^{131}I-MIBG		0.5	18.5	16	16
^{131}I-NAI	RAIU 0–55%	0.01–200	0.37–7400	See Fig.3	

SIST = single-isotope Schilling test; DIST = dual-isotope schilling test. See Table 2 for other abbreviations.

models, amounts of administered activity, specific activity of the test kits at the time of use (we assumed a worst-case scenario of activity at kit expiration), specifics of the counting systems, including energy windows and the somewhat arbitrarily chosen threshold of acceptable interference, though commensurate with levels of uncertainty present during typical performance of the Schilling test. Furthermore, the kinetic models are estimates derived from a variable number of experimental measurements and applied as averages to the population. Their applicability to any individual situation should be considered as approximations, especially at prolonged times after administration when significant individual variation is expected. Rather than absolute limits, these recommendations are intended as general guidelines.

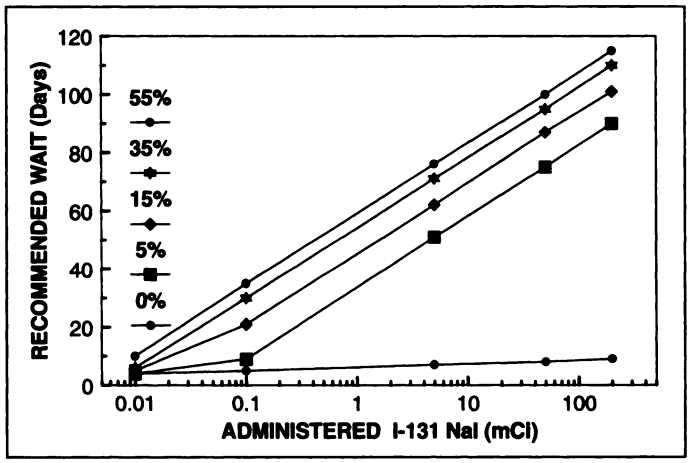

FIGURE 3. Necessary waiting period after administration of various amounts of ^{131}I in patients with thyroid uptake ranging from 0% (blocked) to 55%, based on the single-isotope Schilling test and a threshold of interference of 1% of administered activity. Values for the dual-isotope Schilling test may be slightly shorter but are within two days of the single-isotope test values.

ACKNOWLEDGMENTS

Radionuclides and Dicopac Schilling kits were obtained courtesy of Medi-Physics, Inc., Amersham Health Care, Arlington Heights, IL.

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