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The Serum Digoxin Test and Digoxin Toxicity: A Bayesian Approach to Decision Making

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SUMMARY The clinician may often be uncertain about the presence of digoxin toxicity. This uncertainty is particularly important when the clinician must make initial therapeutic decisions about continuing or discontinuing digoxin. We describe a method that helps to clarify the role of the serum digoxin test in decreasing the uncertainty surrounding the diagnosis and treatment of toxicity. The relation between the test and toxicity was first determined in our patient population. An approach to the interpretation of the test based on the likelihood ratio was then developed by combining our data with selected data from the literature. The relation between the pretest risk of toxicity (the estimated risk of toxicity in the population under investigation before the test result is known) and the predictive value of the test was established. This relation was also used to analyze the importance of the degree of elevation of the test. The appropriate threshold probability for institution of treatment of toxicity was then determined by an interview technique. The test was able to make the patient's probability of toxicity cross the threshold probability for treatment of toxicity for an intermediate range of pretest risk. Our analysis suggests that the serum digoxin test may have a critical effect on therapeutic decisions and can be best considered as contributing to the spectrum of risk.

THE DILEMMA of the diagnosis and treatment of digoxin toxicity is faced by many clinicians. No diagnostic test can definitely confirm the presence of toxicity. Given this uncertainty, discontinuing digoxin is beneficial when toxicity is present but may be harmful if toxicity is absent; failing to discontinue digoxin may be disastrous when toxicity is present.

The value of the serum digoxin test in resolving this dilemma has been questioned.¹ The magnitude of the problem is indicated by studies that report a prevalence of toxicity on admission to the hospital of

up to 20%, with significant morbidity and mortality.²⁻⁶ This study was designed to clarify the role of the test in decreasing the uncertainty surrounding the diagnosis and treatment of toxicity.⁷

The premise of this analysis is that the value of a laboratory result is determined by its ability to influence the diagnostic or therapeutic decision making process. The serum digoxin test can sometimes critically influence this process. The test result is best viewed as part of a spectrum of risk for toxicity.

Methods

The charts of all patients who had a serum digoxin test ordered at Kaiser Foundation Hospital, Los Angeles, California, from April 1 to April 21, 1977 were requested for review. All patients had received Lanoxin (Burroughs-Wellcome). During the 3-week study period, 110 tests on 66 patients were evaluated.

Electrocardiographic Data

All ECGs or rhythm strips obtained subsequent to the day before the initial test were interpreted by one of the investigators. The ECGs were divided into the

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TABLE 1. *Clinical and Laboratory Data for 17 Patients with Electrocardiographic Evidence of Digoxin Toxicity and 49 Patients Without* Digoxin Toxicity*

Datum or laboratory determination†	Value in patients with possible digoxin toxicity‡		Value in patients without digoxin toxicity‡		Significance
Individual serum digoxin (ng/ml)	1.90 ± 1.32	(30)	0.99 ± 0.71	(80)	$p < 0.001$
Mean age (years)	70 ± 9	(17)	67 ± 12	(48)	NS
Sex (% male)	11/17 (65%)		33/49 (67%)		
Mean weight (kg)	63.8 ± 11.4	(14)	67.3 ± 14.8	(40)	NS
Mean daily digoxin dose (mg)	0.223 ± 0.065	(15)	0.219 ± 0.077	(45)	NS
Individual serum potassium	4.45 ± 0.79	(83)	4.22 ± 0.71	(190)	NS
Individual serum creatinine	1.70 ± 1.37	(57)	2.17 ± 1.91	(127)	NS
Individual blood urea nitrogen	32.98 ± 21.46	(43)	39.71 ± 23.57	(105)	NS
Cardiac diagnoses					
Coronary artery disease	13/17 (76%)		34/47 (72%)		
Congestive heart failure	9/17 (53%)		28/47 (60%)		
Died	3/17 (18%)		2/47 (4%)		

*Digoxin toxicity based on ECG criteria only, as defined by Beller.² (Probable digoxin toxicity is combined with definite digoxin toxicity and reported as probable digoxin toxicity because of lack of sequential ECGs in some cases.)

†All laboratory values recorded on day of serum digoxin concentration test or 1 day before.

‡Mean ± SD; figures in parentheses denote number of values.

categories of definite, possible, or no digoxin toxicity, based on Beller's criteria, without knowledge of the test or clinical parameters.² Beller's criteria consist of taking patients with arrhythmias suggestive of toxicity and observing the effect of discontinuing digoxin administration. Toxic patients will convert to their baseline rhythm or to a nontoxicity-associated rhythm. Nontoxic patients with an arrhythmia will continue to have a toxicity-associated arrhythmia despite the discontinuance of digoxin. Because we did not have sequential ECGs for some patients, definite and possible toxicity were combined in a category of possible digoxin toxicity (tables 1 and 2, fig. 1).

Clinical Data

All patient charts were reviewed by a research assistant or clinical pharmacist who recorded age, sex, weight and cardiac diagnoses. Medication records were reviewed to determine the dose and time of digoxin administration.

Laboratory Data

All determinations of blood urea nitrogen, serum creatinine, and serum potassium were performed by standard laboratory techniques. Multiple tests in one patient were treated as separate entries in calculations. The individual test results were compared by the unpaired *t* test.

A Gammacoat ¹²⁵I digoxin radioimmunoassay kit for the quantitative determination of digoxin levels in serum of plasma (Clinical Assays, Inc.) was used for all determinations. From April 1 to April 22, 1977, 30 determinations were made for each digoxin pool. The low-range pool showed a coefficient of variation of 2.3%, the medium-range pool 1.1%, and the high-range pool 0.3%.

Literature Survey

Twenty-two articles cited by Ingelfinger and Goldman and two recent articles were reviewed, with six studies indicating prevalence of disease and degree of test abnormality analyzed in detail (table 3).^{1-6, 8-22}

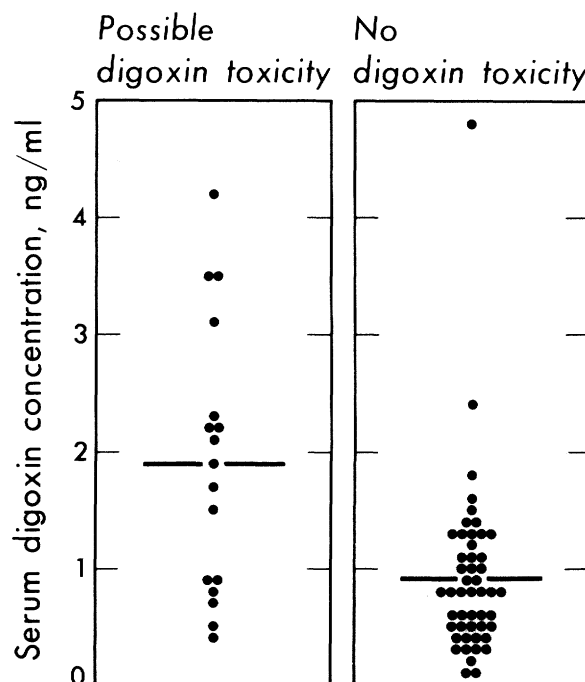


FIGURE 1. Horizontal lines indicate patient mean serum digoxin test values for 17 patients with possible digoxin toxicity and 49 patients without evidence of toxicity. No digoxin toxicity: 0.92 ± 0.74 ng/ml (range 0.1–4.8 ng/ml). Possible digoxin toxicity (by Beller's criteria): 1.90 ± 1.15 ng/ml (range 0.4–4.2 ng/ml²).

TABLE 2. *Rhythm Disturbances in 17 Possibly Toxic Patients and Six Nontoxic Patients with Cardiac Arrhythmias*

Rhythm disturbance	Possibly toxic patients	Nontoxic patients with arrhythmia
Multifocal ventricular ectopic complexes	4/17	3/6
Unifocal ventricular ectopic complexes, but > 5/min	2/17	2/6
Ventricular bigeminy or trigeminy	4/17	0
Ventricular tachycardia	4/17	1/6
Nonparoxysmal atrioventricular junctional tachycardia (> 80/min)	1/17	1/6
Atrioventricular dissociation with ventricular rate exceeding atrial rate	1/17	0
Atrial fibrillation with ventricular response < 50/min if accompanied by ectopic ventricular beats	1/17	1/6
Paroxysmal atrial tachycardia with atrioventricular block	2/17	0
Sinoatrial exit block or sinus arrest	2/17	0

Probabilities — Definitions and Calculations

Definitions were adopted from McNeil et al.,²³ Lusted,²⁴ Keeney and Raiffa,²⁵ Pauker and Kassirer,²⁶ and Weinstein et al.²⁷ (appendix 1). The probability of digoxin toxicity is the frequency with which the disease occurs in a population. The probability of a disease is denoted by $P[D]$ and reads "P of D." The probability of not having toxicity is denoted by $P[\bar{D}]$. The pretest risk, $P[D]$, is the estimated risk of toxicity in the population under investigation before the serum digoxin test result is known. The probability that a patient has toxicity (D) given that a test is within a specified range (R) is an example of a conditional probability. This conditional probability is denoted by $P[D | R]$, where the vertical bar is read "conditional upon," or simply "given." The conditional probability that a patient has toxicity given a test result > 2 ng/ml (T+) is denoted by $P[D | T+]$ and ≤ 2 ng/ml (T-) is denoted by $P[D | T-]$. $P[D | T+]$ is an example of posttest risk and is the estimated known risk of toxicity in the population under investigation after the treatment is known. The posttest risk is also called a posterior probability of disease because it is determined after the result of the test is known.

The likelihood ratio has a numerator that is the probability of a test result (R) in patients with disease (D) and a denominator that is the probability of the same test result in patients without disease (\bar{D}). The likelihood ratio, L, is

$$L = \frac{P[R | D]}{P[R | \bar{D}]}$$

Bayes' formula can be used to define the posterior probability of disease, $P[D | R]$, as a function of the prior probability of disease $P[D]$, and the likelihood ratio, L, for the observed test result.

The traditional form of Bayes' formula,

$$P[D | R] = \frac{P[D] P[R | D]}{P[D] P[R | D] + (1 - P[D]) P[R | \bar{D}]}$$

can then be written in a slightly modified but mathematically equivalent form:

$$P[D | R] = \frac{P[D]}{P[D] + (1 - P[D])/L}$$

From this equation the posterior probability of disease was estimated for the pretest risk $P[D]$ and the likelihood ratio.

For each study subjected to detailed analysis, the value of $P[D | R]$ was computed for test results that fell in each of the 1-ng/ml ranges from 0–0.99 ng/ml, 1.0–1.99 ng/ml, 2.0–2.99 ng/ml and ≥ 3.0 ng/ml (table 4, fig. 2). A family of curves could then be generated showing the posterior probability of disease as a function of prior probability. Each curve represents a different test result and its corresponding likelihood ratio. These curves illustrate the extent to which the predictive value of the test depends on the prior probability of disease and the likelihood ratio.

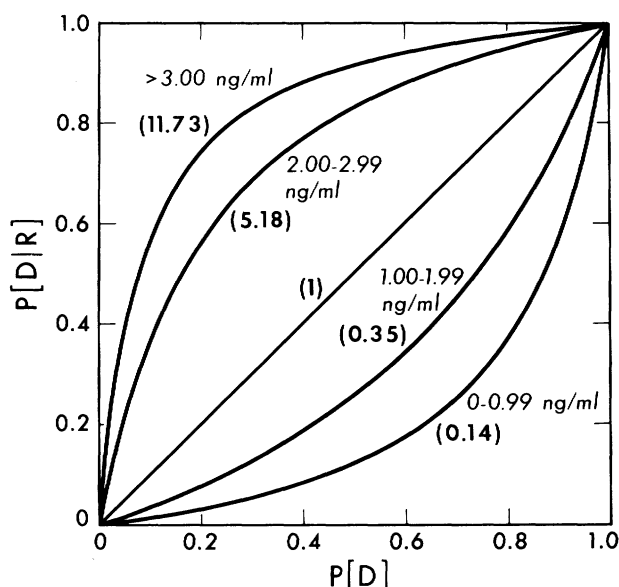


FIGURE 2. Posterior probability of digoxin toxicity (posttest risk, or $P[D | R]$) as function of pretest risk ($P[D]$) for test outcomes indicated. Curves are based on empirical values of the likelihood ratios (L) associated with test outcomes (table 4) using the likelihood ratio formulation of Bayes' theorem. Greater degrees of test elevation are associated with larger likelihood ratios and with increased disease probability compared to pretest risk. Conversely, test elevation < 2.0 ng/ml is associated with likelihood ratio of less than unity and with modest reduction in disease probability compared to pretest risk. Boldface numbers in parentheses are likelihood ratios.

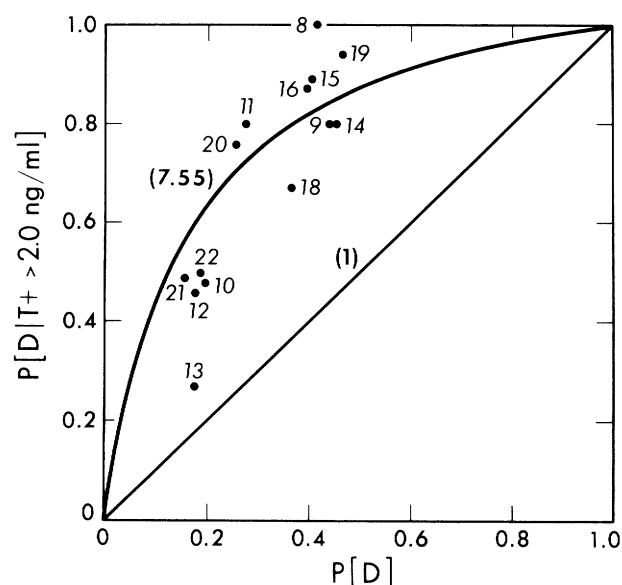
TABLE 3. Study Population Summary

Study	Digitalis toxicity		Significance	Method to diagnose digoxin toxicity	Study group description
	No Serum digoxin (ng/ml)	Yes			
Beller et al. ²	1.0 ± 0.05	2.3 ± 1.6	$p < 0.005$	Cardiac criteria. Possibly toxic group.	931 patients admitted from August 1969 to April 1970; 135 patients taking digoxin, digitoxin, or digitalis leaf up to 48 hours before admission (Boston City Hospital).
Carruthers et al. ³	1.21 ± 1.22	2.76 ± 0.69	NS: $p < 0.1$, > 0.05	Nausea, vomiting and arrhythmias that resolved on withdrawal of digoxin. No possibly toxic group.	101 patients taking routine digoxin maintenance therapy with emergency admission to general medical ward from March 1972 to June 1973 (Belfast City Hospital).
Evered and Chapman ⁴	1.38 ± 0.77	3.36 ± 1.20	$p < 0.001$	Nausea, vomiting and arrhythmias that resolved on withdrawal of digoxin. No possibly toxic group.	108 patients taking routine oral digoxin maintenance therapy, admitted consecutively by six physicians (General Infirmary, Leeds).
Huffman et al. ⁵	0.95 ± 0.52* 1.49 ± 0.46†	3.32 ± 1.23	Significantly different at 95% level.	Cardiac criteria of Beller. ² Possibly toxic group.	1200 patients admitted with test ordered; 143 patients taking maintenance digoxin dose for 1 week between July 1971 and June 1973 (Univ. of Kansas Medical Center).
Waldorff and Buch ⁶	1.0 ± 0.6	2.3 ± 0.6	$p < 0.001$	Cardiac criteria of Beller. ² Possibly toxic group of 4 patients reported, but excluded here.	711 patients admitted from February to July 1976; 101 patients taking digoxin (Diakonissestiftelsen Hospital, Copenhagen).
Park et al. ¹⁷	1.1 ± 0.1	3.8 ± 0.5	$p < 0.005$	Cardiac criteria of Beller. ² No possibly toxic group.	129 adult patients admitted to medical ward from January to May 1972, for whom serum digoxin test requested; other randomly obtained medical patients taking maintenance digoxin dose (Univ. of Cincinnati Medical Center).

*Group 1 defined as not toxic, in congestive heart failure.

†Group 2 defined as not toxic, not in congestive heart failure.

Single values for $P[D|T+]$, obtained from the literature, were calculated for test results > 2.0 ng/ml and compared with the curve derived for the studies



reviewed in detail (table 3, fig. 3).² Likelihood ratios were then plotted for the midpoint of each 1-ng/ml range (fig. 4). This allows the clinician to estimate the likelihood ratio associated with a specific test result.

Utilities — Definitions and Calculations

Five cardiologists from Stanford Medical Center were interviewed. They were initially shown a list of rhythm disturbances acceptable for consideration of digitalis intoxication according to the criteria of Beller. They were then asked to select the specific

FIGURE 3. Curve shows posterior probability of digoxin toxicity (posttest risk, or $P[D|T+]$, with $T+ > 2.0$ ng/ml) as a function of pretest risk $P[D]$ for test outcome > 2.0 ng/ml. The curve is based on the empirical value of the likelihood ratio (L) of 7.55 associated with test outcome (table 4) using the likelihood-ratio formulation of Bayes' theorem. Superimposed on the curve are individual points obtained from other studies in the literature. Italicized numbers refer to study in the bibliography from which the data were derived; boldface number in parenthesis is likelihood ratio.

TABLE 4. *Comparative Values of Likelihood Ratio Obtained For Serum Digoxin Concentration (SDC) Test Outcomes**

SDS outcome (ng/ml)	Study	P[R D]†	P[R D]‡	Likelihood
0-0.99	Evered and Chapman ⁴	0 (0/22)‡	0.41 (35/86)	0.14
	Carruthers et al. ³	0 (0/13)	0.50 (44/88)	
	Park et al. ¹⁷	0 (0/21)	0.63 (68/108)	
	Waldorff and Buch ⁶	0 (0/7)	0.54 (45/83)	
	Eraker and Sasse (present study)	0.35 (6/17)	0.61 (30/49)	
	Weighted mean values	0.075 (6/80)	0.54 (222/414)	
1.0-1.99	Evered and Chapman ⁴	0.090 (2/22)	0.41 (35/86)	0.51
	Carruthers et al. ³	0 (0/13)	0.35 (31/88)	
	Park et al. ¹⁷	0.14 (3/21)	0.27 (29/108)	
	Waldorff and Buch ⁶	0.29 (2/7)	0.42 (35/83)	
	Eraker and Sasse (present study)	0.18 (3/17)	0.35 (17/49)	
	Weighted mean values	0.125 (10/80)	0.353 (146/414)	
2.0-2.99	Evered and Chapman ⁴	0.27 (6/22)	0.13 (11/86)	5.18
	Carruthers et al. ³	0.77 (10/13)	0.091 (8/88)	
	Park et al. ¹⁷	0.29 (6/21)	0.083 (9/108)	
	Waldorff and Buch ⁶	0.57 (4/7)	0.012 (1/83)	
	Eraker and Sasse (present study)	0.24 (4/17)	0.020 (1/49)	
	Weighted mean values	0.375 (30/80)	0.072 (30/414)	
≥ 3.0	Evered and Chapman ⁴	0.64 (14/22)	0.058 (5/86)	11.73
	Carruthers et al. ³	0.23 (3/13)	0.057 (5/88)	
	Park et al. ¹⁷	0.57 (12/21)	0.019 (2/108)	
	Waldorff and Buch ⁶	0.14 (1/7)	0.024 (2/83)	
	Eraker and Sasse (present study)	0.24 (4/17)	0.020 (1/49)	
	Weighted mean values	0.425 (34/80)	0.036 (15/414)	
> 2.0	Evered and Chapman ⁴	0.91 (20/22)	0.19 (16/86)	4.89
	Carruthers et al. ³	1.00 (13/13)	0.15 (13/88)	6.77
	Park et al. ¹⁷	0.86 (18/21)	0.10 (11/108)	8.42
	Waldorff and Buch ⁶	0.71 (5/7)	0.036 (3/83)	19.76
	Eraker and Sasse (present study)	0.47 (8/17)	0.040 (2/49)	11.53
	Beller et al. ^{2§}	0.71 (24/34)	0.15 (14/96)	4.84
	Huffman et al. ⁵	0.84 (27/32)	0.036 (3/84)	23.63
	Weighted mean values	0.788 (115/146)	0.104 (62/594)	7.55

*See text for description of criteria for entry into table 3.

†See appendix 1 for definitions.

‡Numbers in parentheses denote number of patients.

§For test, T+ defined as test > 1.7. Defines D (digitalis toxicity) as including patients taking either digoxin (93 patients), digitalis leaf (27 patients), or digitoxin (nine patients).

arrhythmia usually associated with the best overall outcome and the worst overall outcome. For example, the worst overall outcome arrhythmia might be ventricular tachycardia. This selection was done because cardiologists use different thresholds for discontinuing digoxin, depending on the seriousness of the arrhythmia, and provides a sensitivity analysis as to the effect of different arrhythmias.

A hypothetical case was presented to the cardiologists:

Assume that you are taking care of a 50-year-old male patient who has been taking digoxin for years and is admitted to the cardiac care unit with the worst digoxin-toxicity associated arrhythmia. You have to make two decisions. Is the arrhythmia due to digoxin cardiac toxicity (tox or no tox)? Will you stop the digoxin administration (cont or discont)? We will assume that you will employ other appropriate measures for treatment of the patient and arrhythmia in all cases.

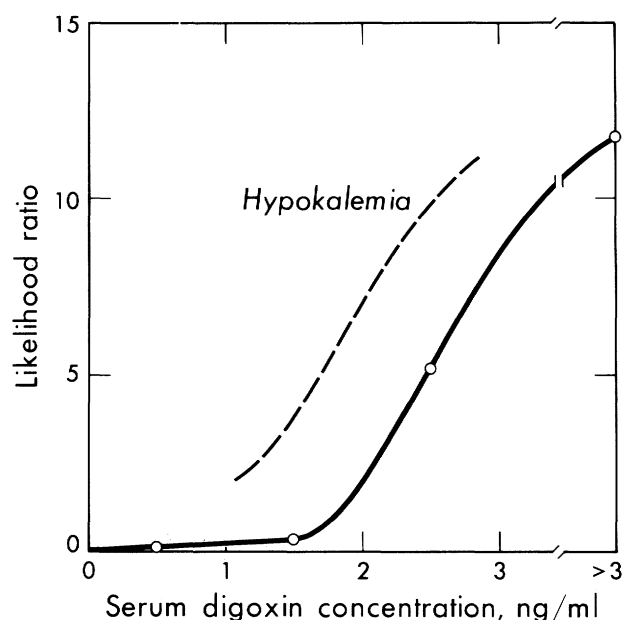


FIGURE 4. The solid line shows estimated relationship between midpoints of serum digoxin concentration ranges (ng/ml) and likelihood ratio (table 4). A higher digoxin concentration is associated with a higher likelihood ratio. The dashed line shows theoretical effect of underlying hypokalemia. Because underlying hypokalemia is associated with increased myocardial sensitivity to digoxin, the curve is shifted upward.

Consideration of morbidity, mortality and financial costs of both treatment and disease status was encouraged (tables 5 and 6).

The clinical decision tree in figure 5 displays the structure of the clinical situation. By convention, the choice nodes are represented by squares and chance nodes by circles. The decision tree identifies alternative actions that might be taken when the patient is initially evaluated. The primary aim of the decision tree is to help the cardiologist think clearly about the available actions and their temporal relationships.²⁷

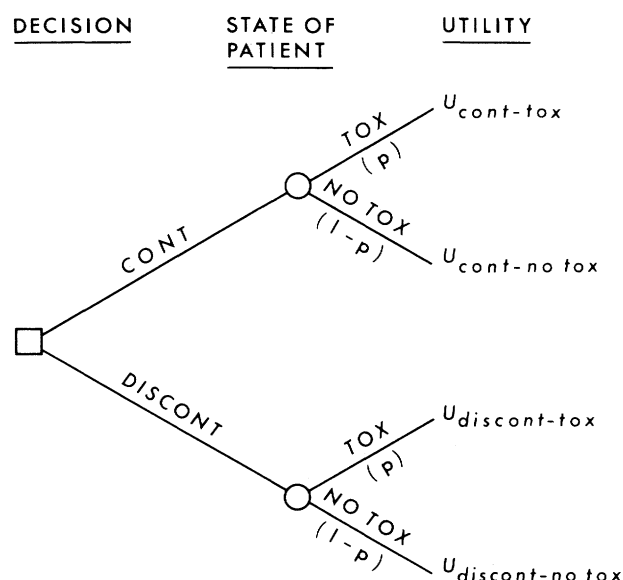


FIGURE 5. Decision tree showing treatment-toxicity outcomes of continue or discontinue digoxin for patients who either do or do not have digoxin toxicity.²⁷ The square node is a decision point; the circular nodes denote a chance happening.

When the patient with possible digoxin toxicity is evaluated, the cardiologist must decide between continuing and discontinuing digoxin. Because the decision must be made without complete knowledge of the patient's disease status, the choice node must precede the chance node at which the true state of the patient is revealed. Stopping digoxin in a nontoxic patient with sinus rhythm may not be harmful, but patients with arrhythmias and taking digoxin may be subjected to significant morbidity and mortality if it is discontinued.^{28, 29} One study indicated disastrous implications of continuing digoxin administration in a patient with underlying digoxin toxicity.³⁰

Initially, the cardiologist considers only the worst overall outcome; for example, ventricular tachy-

TABLE 5. Utility Data on Treating Hypothetical Patient With or Without Worst Arrhythmia and Threshold Probability for Treatment of Disease

Cardiologist	Worst outcome arrhythmia	Utility*		Threshold probability for disease treatment
		Discontinue digoxin— toxicity present	Discontinue digoxin— no toxicity present	
1	Ventricular tachycardia	0.99	0.9	.0917
2	Ventricular tachycardia	0.9	0.7	0.25
3	Ventricular tachycardia	0.99	0.98	0.0198
4	Ventricular tachycardia	0.7	0.9	0.125
5	Ventricular tachycardia	0.99	0.99	0.01

*Utility reflects indifference probability for comparison of intermediate outcome with continue digoxin—toxicity present (utility = 0) and continue digoxin—no toxicity present (utility = 1).

TABLE 6. *Utility Data on Treating Hypothetical Patient With or Without Best Outcome Arrhythmia and Threshold Probability for Treatment of Disease*

Cardiologist	Best outcome	Utility*		Threshold probability for disease treatment
		Discontinue digoxin— toxicity present	Discontinue digoxin— no toxicity present	
1	Nonparoxysmal atrioventricular junctional tachycardia (> 80/min)	0.95	0.9	0.0952
2	Atrioventricular dissociation with ventricular rate exceeding atrial rate	0.6	0.4	0.50
3	Unifocal ventricular ectopic complexes, but > 5/min	0.5	0.4	0.545
4	Atrial fibrillation with ventricular response < 50/min if accompanied by ectopic ventricular beats or Mobitz type I (Wenckebach) 2nd-degree atrioventricular block†	0.5	0.6	0.308
5	Paroxysmal atrial tachycardia with atrioventricular block	0.8	0.9	0.0139

*Utility reflects indifference probability for comparison of intermediate outcome with continue digoxin—toxicity present (utility = 0) and continue digoxin—no toxicity present (utility = 1).

†Cardiologist selected two arrhythmias to have equal probability of having the best overall outcome.

cardia. Classic utility theory, as developed by Von Neumann and Morgenstern, is then used to determine the relative significance of the four possible treatment-toxicity outcomes: $U_{\text{discont-tox}}$, $U_{\text{discont-no tox}}$, $U_{\text{cont-tox}}$, and $U_{\text{cont-no tox}}$. The cardiologist needs to explicitly consider strengths of preference among these four possibilities. The first step is to rank all outcomes from best to worst.

By the axioms of utility theory, we set the utility of the best outcome as 1 and the utility of the worst outcome as 0. Utility is without dimension.

Next, the cardiologist must determine the placement of the two intermediate treatment-toxicity outcomes between 0 and 1. (fig. 6). The midpoint of the scale is defined as equivalent to a gamble, giving a 50% chance of the best outcome and a 50% chance of the worst. If the intermediate outcome, for example, discontinue-toxicity, is preferred to an even gamble, it is placed closer to the best outcome and might be



FIGURE 6. *Determination of the indifference probability for a lottery between the best outcome and the worst outcome and an intermediate outcome for certain. We asked each cardiologist to initially select the worst overall arrhythmia from Beller's article; for example, ventricular tachycardia.² For this worst overall arrhythmia, they then order from 1–4 possible treatment-toxicity outcomes. The cardiologists then estimate the probability q required for the best outcome of a lottery between the best outcome (1) and the worst outcome (4) that would result in indifference to the intermediate outcome for certain.*

given a value close to 1. The cardiologist would then have given the intermediate outcome of discontinue-toxicity the value p (where p is an indifference probability between 0 and 1). This indicates indifference between this outcome and a gamble giving a p chance of the best outcome and a $(1 - p)$ chance of the worst outcome. Then p is the utility of the intermediate outcome. In a similar manner, the cardiologists were then asked to consider the best overall outcome arrhythmia, to order the four possible treatment-toxicity outcomes, and to assign utilities to the intermediate treatment-toxicity outcomes.

Threshold Probabilities — Definition and Calculation

Pauker and Kassirer²⁶ described a clinically useful mathematical relationship to help the physician decide whether or not to treat a patient who may or may not have a disease. The benefit of discontinuing digoxin is limited to patients who have digoxin cardiac toxicity. This benefit may be expressed as the difference between the utility of discontinuing digoxin in patients who have toxicity and the utility of continuing digoxin in patients who have toxicity:

$$\text{Net Benefit (B)} = U_{\text{discont-tox}} - U_{\text{cont-tox}}.$$

The adverse effects of treatment can be applied to treated patients both with and without the disease (fig. 6). The cost of treatment in patients who have the disease is incorporated into the utility of the uppermost branch ($U_{\text{discont-tox}}$).²⁶ Therefore, the cost of treatment applies to patients who do not have the disease. This cost is expressed as the difference between the utility of continuing digoxin in patients who do not have toxicity and the utility of discontinuing digoxin in patients who do not have toxicity:

$$\text{Net Cost (C)} = U_{\text{cont-no tox}} - U_{\text{discont-no tox}}.$$

After determination of the net benefit and net cost, the threshold probability for treatment of toxicity can be determined (appendix 2).

Results

Clinical and Laboratory Results

When the patients with possible digoxin toxicity were compared with those without digoxin toxicity (table 1), the only significant differences between the two groups were in the individual and mean serum digoxin concentrations. For the 49 patients without evidence of toxicity, the mean test value was 0.92 ± 0.74 ng/ml (range 0.1–4.8 ng/ml) (fig. 1). For the 17 patients with possible digoxin toxicity, the mean test value was 1.9 ± 1.15 ng/ml (range 0.4–4.2 ng/ml). Eighteen percent of the patients with possible digoxin toxicity died, compared with 4% of the patients without toxicity. Table 2 is a list of the electrocardiographically documented rhythm disturbances in the 17 patients with possible toxicity and in six patients in the nontoxic group with arrhythmias.

Literature Survey Results

In order to have enough patients to use the likelihood ratio approach, our data were combined with data from a literature review. Of the 24 articles reviewed, six (table 3) indicated a correlation between the test and digoxin toxicity and allowed calculation of the prevalence of disease.^{2-6, 17} One article that did not report statistical significance in which $p < 0.10$, but > 0.05 , was included in the analysis.⁸ In two studies, both cardiac and noncardiac symptoms were used for diagnostic criteria.^{3, 4} Three studies did not report a possibly toxic group.^{3, 4, 17} One study used the ordering of a test as a basis for inclusion of patients.⁵ Another study also used the ordering of a test as a basis for inclusion, but used additional randomly obtained medical patients on a maintenance dose of digoxin.¹⁷

Calculation of Likelihood Ratios

To determine the likelihood ratio for a test value of 1.0–1.99 ng/ml, see figure 1. For the patients with toxicity (D), three of 17 patients had a test result of 1–1.99 ng/ml. The $P[R|D]$ for this range is then 3/17, or 0.18. Seventeen of 49 patients who did not have toxicity (\bar{D}) had a test result of 1–1.99 ng/ml. The $P[R|\bar{D}]$ for this range is then 17/49 or 0.35. The likelihood ratio for our data associated with a test result in the range 1–1.99 is then

$$L = \frac{P[R|D]}{P[R|\bar{D}]} = \frac{0.18}{0.35} = 0.51.$$

Individual Patient Application

For the weighted mean test range of 1.0–1.99 ng/ml, the likelihood ratio is $L = 0.35$ (table 4). The likelihood ratio can then be used to determine the relationship between any estimated pretest risk, $P[D]$ and the posttest risk of disease, $P[D|R]$. Beller² found

that the prevalence of digitalis intoxication at hospital admission in 135 consecutively digitalized patients was 0.23. Assume that the only clinical information available was that the patient had been taking digoxin; the best estimate of pretest risk for toxicity would be $P[D] = 0.23$. If this patient had a test result of 1.5 ng/ml with an associated $L = 0.35$, we can calculate the posttest risk of toxicity by the modified version of Bayes' formula:

$$P[D|R] = \frac{P[D]}{P[D] + (1 - P[D])/L} = \frac{0.23}{0.23 + (1 - 0.23)/0.35} = 0.095.$$

The importance of obtaining pretest information from the history and physical examination is emphasized by the Bayes' theorem approach. Beller found that anorexia was the only noncardiac manifestation of toxicity that was significantly different between toxic and nontoxic patients.² Seventeen of 28 definitely toxic patients (61%) had anorexia and only 21 of 83 nontoxic patients (25%) had anorexia when initially screened. Assume that the prior risk of toxicity in our population of patients taking digoxin was $P[D] = 0.23$. We would like to estimate the probability of toxicity given the presence of anorexia, that is, $P[D|\text{anorexia}]$.

$$L = \frac{P[\text{anorexia}|D]}{P[\text{anorexia}|\bar{D}]} = \frac{0.61}{0.25} = 2.44$$

$$P[D|\text{anorexia}] = \frac{0.23}{0.23 + (1 - 0.23)/2.44} = 0.42$$

To combine the presence of anorexia with the digoxin test result to determine the posttest risk of toxicity, we make an assumption called conditional independence. Let us assume that the presence of anorexia and the test result are conditionally independent, given toxicity and nontoxicity. This implies that the presence of anorexia does not influence the probability of obtaining a specific test result. That is,

$$P[\text{anorexia}, R|D] = P[\text{anorexia}|D] \cdot P[R|D].$$

This assumption permits us to multiply two individual probabilities to yield the joint probability of disease. Combining the above examples, suppose we want to know the probability of toxicity in a patient taking digoxin with anorexia and a test result of 1.5 ng/ml. If $P[D] = 0.23$ and $P[D|\text{anorexia}] = 0.42$, then for a test result of 1.5 ng/ml:

$$P[D|\text{anorexia}, R] = \frac{0.42}{0.42 + (1 - 0.42)/(0.35)} = 0.20.$$

If the test result came back 2.5 ng/ml with an associated $L = 5.18$ (table 4), then the revised posttest risk of toxicity, $P[D|\text{anorexia}, R]$, would be 0.79. To avoid unnecessary assumptions about conditional independence, the conditional probabilities of the joint occurrence of the test result and clinical state,

(anorexia, R), would be required. Weinstein et al. reported that these data are rarely available in medical applications; however, the assumption of conditional independence usually provides a good first approximation for estimation of probabilities.²⁷

Evaluation of the degree of pretest risk associated with cardiac manifestations of toxicity is more difficult, given the many arrhythmias listed by Beller as suspicious for toxicity,² and requires a comparison of rhythm disturbances in nontoxic and toxic patients. Data from our study and one other study³¹ indicate that the arrhythmias that are most predictive of toxicity are ventricular bigeminy or trigeminy, with $L = 2.00$, and ventricular tachycardia, with $L = 1.60$. Assuming $P[D] = 0.23$, the joint probabilities for disease are $P[D | \text{ventricular bigeminy or trigeminy}] = 0.38$ and $P[D | \text{ventricular tachycardia}] = 0.32$. Jelliffe et al.³² proposed another way to help the clinician to estimate pretest risk. This estimate is based on known data of the dosage regimen taken, the patient's weight, renal function and the pharmacokinetic behavior of the drug. A family of curves allows estimation of posttest risk from pretest risk according to the degree of test elevation.

Degree of Test Elevation by 1.0 ng/ml Intervals

By varying the range of pretest risk, $P[D]$, from 0 to 1 in the modified Bayes' theorem, we can generate a curve relating posttest risk to pretest risk according to the degree of test elevation. Figure 2 has a diagonal line corresponding to a likelihood ratio of 1 ($L = 1$). If a test result for an individual patient were to have an associated likelihood ratio of 1, there would be no difference between the pretest risk of toxicity on the horizontal axis and the posttest risk, or revised estimate of risk after knowing the test result, on the vertical axis. For a likelihood ratio of 1, a pretest risk of 0.23 would have an associated posttest risk of 0.23. The test result has added no new information. The family of curves relating posttest risk to pretest risk according to the degree of test elevation based on the value of the mean likelihood ratios in table 4 indicates a gradation of risk that depends on the degree of test abnormality. The greater the spread of test result and the higher the likelihood ratio above 1, the greater the relative merit of the test result as a predictor of disease. Conversely, a likelihood ratio of less than 1 results in a decreased probability of disease compared with pretest risk. The risk noted for the test result showing 2.0–2.99 ng/ml with $L = 5.18$ increases for test results showing ≥ 3.0 ng/ml with $L = 11.73$. Conversely, a test within the range of 1.0–1.99 ng/ml with $L = 0.35$ confers a modest reduction in posttest risk compared with pretest risk, and this reduction is successively greater for the test results within the range of 0–0.99 ng/ml with $L = 0.14$. We can begin with an estimation of pretest risk on the horizontal axis. By assuming conditional independence, this estimate may be revised to take into account clinical information. The posttest risk of toxicity for a given test result can then be estimated on the vertical axis.

Test Elevation of > 2.0 ng/ml

The curve relating posttest risk to pretest risk shows a considerable increase in posttest risk associated with the test level > 2.0 ng/ml with $L = 7.55$ (fig. 3). Additional data points from other studies in which both pretest and posttest risk of digoxin toxicity could be computed for a test > 2.0 superimposed upon the curve derived from studies reported in table 3 for tests > 2.0 ng/ml. For most studies, there is a moderately close correspondence.

Likelihood Ratios Associated with a Specific Test Result

A higher digoxin concentration is associated with a higher likelihood ratio (fig. 4). We can speculate about the effects of underlying disease on the likelihood ratio, although these data are not available from our study. For example, if the patient had underlying hypokalemia there would be increased myocardial sensitivity to digoxin,^{33, 34} and the curve in figure 4 would be shifted upward.

Utility Data and Calculation of Threshold Probability for Treatment

All five cardiologists agreed that the arrhythmia usually associated with the worst outcome is ventricular tachycardia (table 5). There was no agreement as to the arrhythmia usually associated with the best outcome (table 6). All cardiologists agreed that for both the best and the worst arrhythmia, the most preferred of the four possible outcomes was to continue digoxin when there was no toxicity and that the least preferred was to continue digoxin when there was toxicity.

We now examine the particular set of expressed preferences for cardiologist 1. First, cardiologist 1 chose the best outcome (cont-no tox), which was placed at the upper end of the utility scale and assigned a value of 1. Next, the least preferred outcome (cont-tox) was placed at the lower end of the scale and assigned a value of 0. Cardiologist 1 placed the intermediate outcome (discont-tox) much closer to the best treatment-toxicity outcome than to the worst treatment-toxicity outcome. By placing the p (discont-tox) at the value 0.99, the cardiologist was indicating indifference between this intermediate outcome and a gamble, giving a 0.99 chance of the best outcome (whose value is one) and a $(1 - p)$ or 0.01 chance of the worst outcome (whose value is 0). The utility of discontinuing digoxin in the presence of toxicity was then 0.99. By similar methods, the utility for the third intermediate outcome (discont-no tox) was found to be 0.9. By definition, we have:

$$\text{Benefit (B)} = U_{\text{discont-tox}} - U_{\text{cont-tox}} = 0.99 - 0 = 0.99$$

$$\text{Cost (C)} = U_{\text{cont-no tox}} - U_{\text{discont-no tox}} = 1.0 - 0.9 = 0.1$$

$$B/C = 0.99/0.1 = 9.9.$$

The threshold probability of cardiologist 1 for treatment of digoxin toxicity was

$$T = \frac{1}{B/C + 1} = \frac{1}{9.9 + 1} = 0.0917.$$

This implies that cardiologist 1 would require a probability of 0.0917 of digoxin toxicity before discontinuing digoxin administration. Combining the data for all five cardiologists for the worst-outcome arrhythmia, which was ventricular tachycardia, the mean T was 0.054 ± 0.051 (range 0.01–0.25) (table 5). Although the cardiologists did not agree on the best outcome arrhythmia, by combining the data, the mean T was 0.292 ± 0.236 (range 0.0139–0.545) (table 4).

Resolution of study results into intervals of 1.0 ng/ml (fig. 2) provides evidence that the degree of test elevation can be important in determining the probability of toxicity. The distribution of likelihood ratios demonstrates that risk depends on test levels. For the cardiologist with a threshold probability of treatment $T = 0.01$, the test would probably have little effect on the initial therapeutic decision. The posterior probability that the patient has toxicity is almost always greater than the threshold probability for discontinuing digoxin.

For the cardiologist with $T = 0.25$, the test result could clearly shift the therapeutic decision. If the pretest risk of toxicity was estimated to be 0.2, a test result in the range of 2–2.99 ng/ml would result in a posterior probability of disease of 0.56. Because this is above the threshold probability for treatment, the correct therapeutic decision would be to discontinue digoxin. By contrast, a test result in the range of 1.0–1.99 ng/ml would result in a lower posterior probability of 0.08. Because this is below the threshold probability for treatment, the optimal therapeutic decision would be to continue digoxin. The value of the test in altering the treatment decision occurs over an intermediate range of pretest risk.

Figure 7 shows the theoretical shift above or below the threshold curve for continuing or discontinuing digoxin, depending on the test level. (This curve is not derived from our data.) For example, if the pretest risk of toxicity is 0.4, a test of 3.0 ng/ml results in discontinuation of digoxin. In contrast, a test of 1.0 ng/ml results in continued digoxin administration.

Discussion

Complex therapeutic decisions must be based on both the likelihood of the diagnosis of disease and the benefits and costs of treatment. This study supports the capacity of the digoxin test to influence the likelihood of disease in a given population for an intermediate range of pretest risk. Although we supplemented our relatively small sample size with additional studies from the literature, our results should not be applied to other populations, such as children or acute post-operative patients. When the benefits and costs of treatment are considered for a given population, the test can critically shift the optimal therapeutic decision.

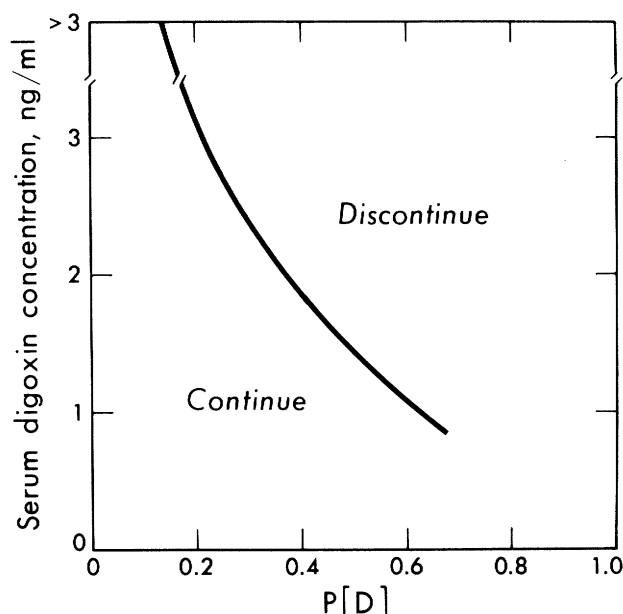


FIGURE 7. Theoretical relationship between pretest risk, $P[D]$, and serum digoxin concentration. This curve is not derived from our data and is theoretical. After clinically estimating the pretest risk of toxicity, the decision to continue or discontinue digoxin may be shifted above or below the threshold curve by the digoxin test level.

An assumption of this analysis is that an entity called digitalis cardiac toxicity exists and can be diagnosed. This is the basis for Beller's criteria, which indicate that arrhythmias characteristic of digoxin toxicity exist and disappear when digoxin is discontinued. The clinical situation, however, is that digoxin is one of many factors that can create anorexia, nausea and arrhythmias. This is the basis for the requirement of Ingelfinger and Goldman that studies addressing the value of the digoxin test in the diagnosis of toxicity study patients with similar toxic manifestations.¹ The required data for a Bayesian analysis of the serum digoxin test are straightforward, but often they were not available in the literature. Unfortunately, the results of carefully conducted trials are often reported so as to obscure the important relations of degree. An alternative basis for an analysis of this type might be the diagnosis of an underlying arrhythmia caused by any combination of agents such as hypokalemia, hypoxia, hypermagnesemia, hypercalcemia or digitalis. The data base allowing these issues to be addressed must be developed.

Ingelfinger and Goldman¹ indicated that, on the basis of their analysis, the literature was inadequate to determine the value of the test. Although our study met most of the proposed criteria, in order to have sufficient data for the analysis, we drew from studies with a potentially suspect data base. This variability may be reflected in the observed range of likelihood ratios, but we do not believe that this significantly detracts from our analysis and approach. Several articles that meet most of the criteria proposed for investigation have also supported the usefulness of the test in the diagnosis of toxicity.^{31, 35} Criteria proposed

for investigation of the usefulness of the test in the diagnosis of toxicity met by this study are: study of patients with similar toxic manifestations, definition of criteria for digoxin toxicity, selection of representative patients, description of study population, and control concentrations from patients with symptoms that suggested digoxin toxicity.¹

Weinstein et al.²⁷ suggested the practical limitations of utility assessment in the clinical setting.²⁷ The first problem is that utility estimates obtained under one condition may not apply when conditions for eliciting utilities are altered. For example, a cardiologist with patients who have serious complications from digitalis toxicity at the time of interview may express preferences different from those of a cardiologist with patients who do not have digitalis toxicity. Second, utilities are expressions of preferences among outcome states which the decision maker may not have clinically experienced. Third, some persons may react negatively to the concept of gambling, which may inhibit utility assessment. Finally, the person who obtains the utilities may consciously or unconsciously bias the person whose preferences are being elicited.

These limitations may account for some of the differences in threshold probabilities for treatment of toxicity. Although there is considerable diversity associated with the utilities attached to the treatment-toxicity outcomes, not everyone will agree on utility assessments. How the cardiologist reacts to a given test level will obviously depend on how concerned he or she is about the problem. The test result may effect the initial therapeutic decision to discontinue digoxin for one cardiologist but not for another. Unlike probability assessments, utility assessments have no external validity. If the individual cardiologist believes them and understands their implication up to the limits of past and current experiences, those utility assessments are "correct."²⁷

This analysis is oriented toward the practicing clinician because he or she is usually responsible for making diagnostic and treatment decisions. We assume that the clinician will have some awareness of the patient's preferences and attitudes toward risk and will incorporate these into the utility assessment.

Bayes' theorem shows that the posterior probability of disease depends on the likelihood of the test result in patients with and without the disease as well as on the prior probability of disease. It also indicates that some patients are very sensitive to digoxin and may develop toxicity at low serum levels. We have indicated that the pretest risk for toxicity at the time of admission in one representative study was 0.23.² One implication of the Bayesian approach is that different medical centers should adjust their diagnostic probabilities based on the prevalence of disease in the populations they serve.²⁷ Another implication is the importance of obtaining pretest information from the patient history and physical. The assumption of conditional independence allows us to combine the pretest risk with clinical data to calculate a joint probability for disease.

Decision analysis provides a model for thinking explicitly about the role of the test result in the management of a patient's clinical problem. Our analysis suggests that one should abandon altogether the concept of a positive or negative test result that can unequivocally diagnose digoxin toxicity. The test result can best be considered as contributing to the definition of a spectrum of risk. The rational combination of clinical criteria and drug level should result in optimal therapeutic decisions.

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Appendix 1

Definitions and Symbols

D = set of patients with disease (digoxin toxicity by Beller's criteria²).

\bar{D} = set of patients without disease.

R = set of patients with test result falling within a specified range.

T+ = set of patients with test result > 2 ng/ml.

T- = set of patients with test result ≤ 2 ng/ml.

P[D] = prevalence of disease or pretest risk, or D/(D + \bar{D}).

P[D | R] = probability that a patient has a disease given a test result falling within a specified range (posterior probability of disease).

P[R | D] = true-positive rate for the test or probability of a test result falling within a specified range given the presence of disease in a patient.

P[R | \bar{D}] = false positive rate for the test or probability of a test

result falling within a specified range given the absence of disease in a patient.

L = likelihood ratio for the presence of disease associated with an abnormal test.

$U_{\text{discont-tox}}$ = utility of discontinuing digoxin in a patient with an arrhythmia caused by digoxin cardiac toxicity (fig. 5).

$U_{\text{discont-no tox}}$ = utility of discontinuing digoxin in a patient who may or may not have an arrhythmia but does not have digoxin cardiac toxicity

$U_{\text{cont-tox}}$ = utility of continuing digoxin in a patient with an arrhythmia caused by digoxin cardiac toxicity

$U_{\text{cont-no tox}}$ = utility of continuing digoxin in a patient who may or may not have an arrhythmia but does not have digoxin cardiac toxicity

Indifference probability = the probability required for the best outcome of an uncertain lottery between the best and the worst outcome that would make the physician indifferent to the intermediate outcome for certain. The best and worst outcomes are determined by having the physician rank from 1 to 4 the utilities of the four possible outcomes listed above (fig. 6)

Appendix 2

For those unfamiliar with the methods used to make these calculations, a brief summary is provided.

Assigning numerical values to probabilities and utilities of each outcome makes it possible to calculate the worth, or expected value of each outcome. The contribution of each of the outcomes to the value of a particular course of action is equal to the product of the utility of that outcome and the probability of its occurrence. The expected value of each decision course is calculated by summing the products of the probability and utility of each outcome. For example, the expected value of the option to discontinue digoxin (EV_{discont}) is equal to $(p)U_{\text{discont-tox}} + (1 - p)U_{\text{discont-no tox}}$. The expected value of the option to continue digoxin (EV_{cont}) is equal to $(p)U_{\text{cont-tox}} + (1 - p)U_{\text{cont-no tox}}$. Applying the principles described above, one should select the course of action with respect to discontinuing or continuing digoxin with the higher expected value. When the expected value of discontinuing digoxin is equal to the expected value of continuing digoxin, the physician should be indifferent to choosing either course. Indifference exists when $EV_{\text{discont}} = EV_{\text{cont}}$.

Substituting the equations given allows one to derive an expression containing a probability value at which the physician should be indifferent to discontinuing or continuing digoxin administration. This probability value at the indifference point is derived as $EV_{\text{discont}} = EV_{\text{cont}}$.

Therefore, $(p)U_{\text{discont-tox}} + (1 - p)U_{\text{discont-no tox}} = (p)U_{\text{cont-tox}} + (1 - p)U_{\text{cont-no tox}}$.

Solving for p (the probability at the indifference point),

$$p = \frac{U_{\text{cont-no tox}} - U_{\text{discont-no tox}}}{U_{\text{discont-tox}} - U_{\text{cont-tox}} + U_{\text{cont-no tox}} - U_{\text{discont-no tox}}}$$

Substituting B (benefit) and C (cost) for the utilities in the equation, and substituting T for p, we obtain the equation described by Pauker and Kassirer relating benefits and costs to the threshold probability²⁶: $T = \frac{C}{B + C}$.

This can be further simplified to $T = \frac{1}{B/C + 1}$.

If the probability of toxicity for a given patient exceeds T, EV_{discont} exceeds EV_{cont} , and discontinuing digoxin would be the preferred course of action. If the probability of toxicity for a given patient is less than T, EV_{cont} exceeds EV_{discont} , and the digoxin should be continued.

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S A Eraker and L Sasse

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