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A Comparison of Three Computer Models for Prediction of Dose in Acute Amitriptyline Overdose

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ABSTRACT: The pharmacokinetics of amitriptyline in overdose have been reported not to fit conventional compartmental models. In this study, the dose-concentration-time relationships of amitriptyline in overdose were modeled with discriminant analysis, with an evolutionary heuristic search program, and with a decision-tree model based on the entropy of uncertainty of classification. The computer models all used the same data from dogs administered treatment (80 mg/kg), toxic (250 mg/kg), or fatal (500 mg/kg) doses directly into the surgically isolated duodenum. All the models achieved a high degree of success (77 to 93%) in assigning records to the high-, low-, or middle-dose groups. Two of the models gave a probability of the assignment. Results of this analysis suggest that blood amitriptyline and nortriptyline concentrations are most useful in estimating dose in acute amitriptyline overdose.

KEYWORDS: toxicology, computers, amitriptyline

The pharmacokinetics of amitriptyline are complex and difficult to model [*1*]. In overdose they become even more so. Pedersen et al. [*2*] have shown that current nonlinear regression models for amitriptyline do not apply in amitriptyline overdose cases. However, successful artificial-intelligence programs have been written for prediction of time interval and response for amitriptyline in overdose cases [*3*]. In this study, two artificial-intelligence programs were compared with a discriminant analysis program for ability to predict dose from blood or plasma amitriptyline and nortriptyline concentrations after therapeutic, toxic, and fatal doses. The programs all used the same data from dogs administered therapeutic, toxic, and fatal doses of amitriptyline.

All programs achieved a high degree of success (77 to 93% correct assignments) in assigning records to the high-, low-, or middle-dose groups. Two of the programs gave a probability associated with the decision.

Methods

Animal Model

To mimic acute ingestion, a single dose of amitriptyline in normal saline was administered directly into the surgically isolated duodenum of dogs [*4*]. Dosages of 80, 250,

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and 500 mg/kg were used to simulate treatment, toxic, and lethal ingestion, respectively. Three animals were used for each dose for a total of nine dogs. Whole blood samples were taken at four sites, the carotid artery, jugular vein, femoral artery, and femoral vein. Samples were collected at predetermined intervals of 0, 15, 30, 45, 60, 90, 120, and 180 min after administration. The matrix of variables for each animal is shown in Fig. 1. Microhematocrits were performed on each sample to assure consistency of the samples.

Amitriptyline Analysis

The analyses of amitriptyline and nortriptyline were performed by high-performance liquid chromatography [5]. The samples were assayed in groups with appropriate quality control to assure a coefficient of variation of no greater than 10%. Samples from previous assays were performed in each new set to assure consistency among analytical results.

Discriminant Analysis

The discriminant analysis software used for this study was SPSS PC+ Version 3.0. Discriminant analysis is a "theory-building" tool. It assists researchers in determining the relationships among variables and the subject's membership in known groups. Discriminant analysis provides researchers with both a visual and numeric picture of the contribution of variable to membership in these groups.

The discriminant-analysis procedure operates in three distinct steps: discriminant, analysis, and classification. During the *discrimination* phase, the program generates a linear combination of weighted variables (discriminant functions) which best differentiate the groups from one another. In the *analysis* phase, the program runs a series of statistical tests which measure the success of the discriminant functions it has generated. In the *classification* phase, the program applies its generated formula for membership in the groups to the subjects, categorizing each of them on the basis of "best fit."

In the discriminant phase, discriminant analysis acts like artificial-intelligence programs. This is when the program generates new variables whose number and nature are determined by the data. To accomplish this, the program flags the subject with a "grouping" or "criterion" code. In this case, the subjects were "grouped" by dosage level (therapeutic, toxic, and lethal). To distinguish between the groups, a set of potentially "discriminating variables" is introduced. In this case, 15 variables were introduced: these

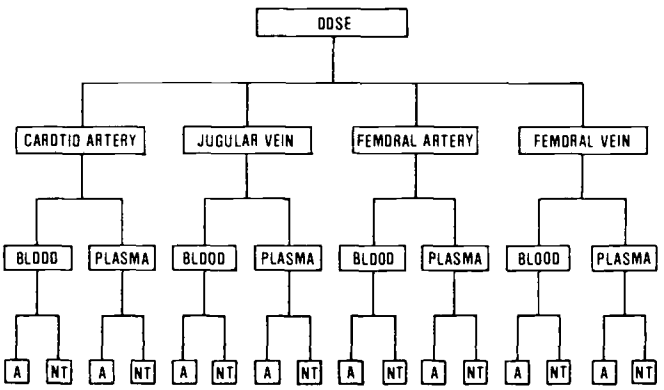

FIG. 1—*Matrix of variables for each animal.*

were the 4 sites at which blood was drawn (carotid artery, carotid vein, peripheral artery, and peripheral vein), 7 times when blood was taken (at 0, 15, 30, 45, 90, 120, and 180 min following injection), and 4 types of blood sample values obtained (amitriptyline in whole blood, nortriptyline in whole blood, amitriptyline in plasma, and nortriptyline in plasma).

The computer program iteratively finds the weighted combination of variables which best differentiates the groups from one another. This is accomplished by testing each combination of weighted variables against a criterion, in this case Wilks' lambda. A stepwise approach was taken. On each iteration, the program identified the most likely contributor to the difference between the groups and entered this variable. Each variable was weighted upon entry to maximize the difference between the groups and weighted again on the same basis as each new variable was added. As each of the 15 variables was considered, previously entered variables were reevaluated. They were retained or removed based on their contribution to the evolving discrimination function. Those which did not significantly improve the ability of the formulae were removed.

In the analysis phase, the program reports the ability of each formula to isolate the groups. It accomplishes this by conducting statistical tests, in this case chi-squares, of the relative strength (power) of the formula. In this instance, the two formulas which produced significant chi-squares ($p < 0.001$) were developed. These formulas are the following:

$$\text{FUNCTION 1} = [(\text{ATW}*0.590\,70) + (\text{NTW}*0.428\,93) + (\text{ATP}*0.298\,96) - (\text{NTP}*0.309\,78) - (\text{TIME}*0.133\,94)]$$

$$\text{FUNCTION 2} = [(\text{ATW}*1.087\,39) + (\text{ATP}*0.720\,18) + (\text{TIME}*0.660\,01) + (\text{NTP}*0.115\,94) - (\text{NTW}*2.042\,90)]$$

where

TIME = time in minutes since acute ingestion,
ATW = amitriptyline in whole blood,
ATP = amitriptyline in plasma,
NTW = nortriptyline in whole blood, and
NTP = nortriptyline in plasma.

A visual representation of these functions is given in Fig. 2 as a "territorial map." As can be seen in Fig. 2, the first formula primarily serves to isolate the fatally dosed cases from those at therapeutic and toxic levels. On this function, the cases with higher dosage levels have higher scores on the function. The value of this function is markedly increased by the amount of amitriptyline or nortriptyline or both in whole blood. The amount of amitriptyline in plasma also raises the value of the function. The value of the function is decreased by the amount of nortriptyline in plasma and the passage of time.

The second formula isolates all three groups from one another. It best isolates those in the therapeutic group from those in the toxic group, for the members of the fatally dosed group are widely dispersed around the zero point. Those cases which were at the therapeutic level have lower scores. This formula is markedly increased by the amount of amitriptyline in whole blood or plasma or both. The passage of time also increases the value of the function. The amount of nortriptyline in whole blood substantially reduces the value of this function.

To classify the subjects into groups, both formulas are used. The case is located in the multidimensional space defined by those formulas mentioned above. The subjects are attributed to that group whose center (centroid) was closest to them. Likelihood estimates

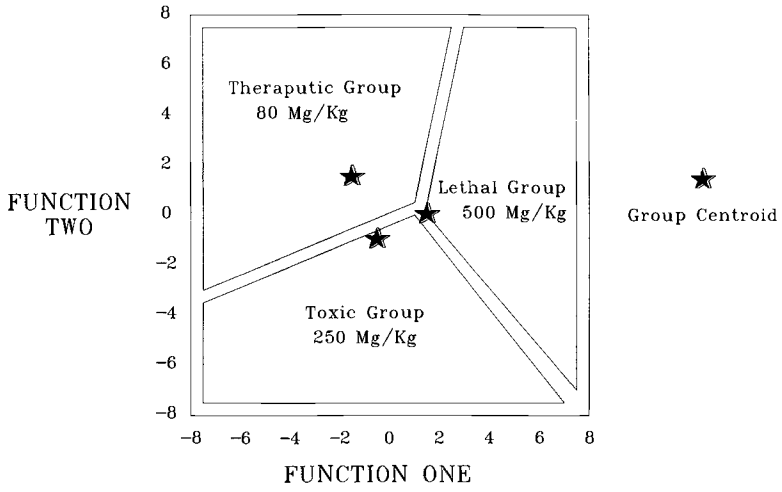

FIG. 2—*Territorial map for discriminant analysis: A = amitriptyline; NT = nortriptyline.*

are provided to the researcher for each subject's inclusion in the most likely and second most likely group. All subjects for which the program had complete data were classified by the program regardless of the likelihood of their placement.

BEAGLE

A knowledge-acquisition program based on a Darwinian evolution model, BEAGLE, written by Richard Forsyth, was purchased from Warm Boot, Ltd, Nottingham, U.K. The program was delivered on a floppy disk and was run on an IBM-compatible PC with 256K memory. BEAGLE is a collection of programs for computer induction of rules from sets of case data. The system applies an inductive algorithm to discover the simplest set of rules that will fit the example case data or training set. Rules are scored according to their performance using chi-square or correlation coefficients. When the target is given as a logical expression (for example, a dose less than 100 mg), the program uses chi-square statistics. When the target expression is an arithmetic calculation, point-biserial correlation coefficients are used. At the end of each generation or survey of the data set, the high-scoring rules are retained and low-scoring rules discarded. They are replaced by mating portions of surviving rules or by mutating surviving rules. After many cycles or generations, the evolved surviving rules are much better at predicting the target than the beginning rules. This process has been termed a bionic evolutionary algorithm generating logical expressions (BEAGLE). The user can review the process as it occurs or at milestones after a given number of generations. For all of the development of rules for estimating dose in this study, 200 generations were used. For rules to estimate time since dose, 500 generations were used.

The rule induction was carried out using a randomly selected subset of the data available from the animal experiments. After records with missing data were removed (the drug concentration was not determined; the animal died; the sample was not obtained; etc.), 209 records remained. For the initial pass, the 209 records were randomly divided into a training set containing 70% of the data (148 records) and a test set with 30% (61 records). The training set is used to induce the rules; the test set is used for validation. In development of the BEAGLE-generated rules, new random selection of training records was made from time to time to ensure that the final rules were not biased by

any incidental characteristics of the training set. A ratio of 70:30 or 40:60 (training set/test set) was used to divide up the records.

The parameters used for the BEAGLE induction of classification rules for dose and their values were dose (80, 250, or 500 mg/kg), site of sampling (carotid artery, jugular vein, peripheral artery, or peripheral vein), time of sampling after a bolus to the stomach (0, 15, 30, 45, 60, 90, 120 or 180 min), blood amitriptyline concentration, blood nortriptyline concentration, plasma amitriptyline concentration, and plasma nortriptyline concentration. In a second phase of rule induction, the amitriptyline/nortriptyline ratio for blood and the amitriptyline/nortriptyline ratio for plasma were added to the parameters. The addition of the ratios produced more complex but also more successful rules.

KnowledgeMaker

The decision tree building program KnowledgeMaker, from KnowledgeGarden, Inc, New York, was used to induce rules for prediction of dose. KnowledgeMaker uses Quinlin's ID3 algorithm to calculate the entropy of the uncertainty of classification. The decision tree is built by minimizing the entropy of classification at each level. If an object can be classified into n different classes, c1 . . . , cn, and the probability of an object being in Class i is $p(ci)$, then the entropy of classification $H(C)$ is

$$H(C) = -\Sigma p(ci) \ln p(ci)$$

To determine how much information there is in knowing the value of one particular attribute, the cases are sorted on the basis of the values of that attribute, and the entropy of each resulting subset, $H(C|aj)$ can be calculated as follows

$$H(C|aj) = -\Sigma p(ci|aj) \ln p(ci|aj)$$

where $p(ci|aj)$ is the probability that the class value is ci when the attribute has the jth value. The attribute having the smallest entropy, and therefore the least uncertainty, provides the most information about classification of the case. In this manner, a decision tree is built up as is shown in Fig. 5. The validity of the decision tree is tested by applying the tree rules to cases which had not been used to build the tree.

Results

Discriminant Analysis

The results of the classification by discriminant function analysis are shown in the upper portion of Table 1 ("Results Reported by Sample"). Classification of a sample as coming from animals with the treatment dose (80 mg/kg), toxic dose (250 mg/kg), or lethal dose (500 mg/kg) was made on the basis of the highest group indicated by the program and the associated probability of being in that group. The success rate for the SPSS discriminant analysis for the three groups is shown in Fig 3. Of the samples from the treatment level (80 mg/kg) dosed animals, 94.7% were correctly classified. Only one sample was misclassified as coming from the lethally dosed (500 mg/kg) animals. Three samples drawn from the treatment-dosed group were classified as coming from the toxic-dosed group. For samples drawn from the toxic-dosed animals (250 mg), animals were correctly placed 67.1% of the time. This represents some improvement over the 33% chance assignment of subjects to groups. Among the misclassified samples, 20% of the samples from the toxic-dosed animals were classified as coming from those in the treatment-dosed group, and 12.9% were classified as coming from those in the lethal-dosed group. Samples drawn

TABLE 1—*Discriminant classification.*

Actual Group	No. of Samples	Predicted Group Membership		
		Therapeutic	Toxic	Lethal
	RESULTS REPORTED BY SAMPLE			
Therapeutic (80 mg/kg)	76	72	3	1
		94.7%	3.9%	1.3%
Toxic (250 mg/kg)	70	14	47	9
		20.0%	67.1%	12.9%
Lethal (500 mg/kg)	63	10	13	40
		15.9%	20.6%	63.5%
	RESULTS REPORTED BY SUBJECT			
Therapeutic (80 mg/kg)	3	3	0	0
Toxic (250 mg/kg)	3	1	2	0
Lethal (500 mg/kg)	3	0	1	2

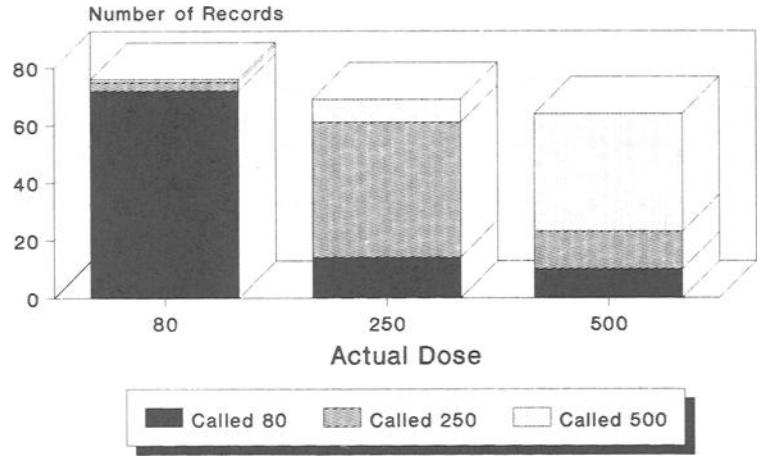

FIG. 3—*Success rate for discriminant analysis classification for groups.*

from the lethal-dosed animals were correctly placed by discriminant analysis 63.5% of the time. Among the misclassified samples, 15.9% were classified as coming from those in the treatment-dosed group and 20.6% as coming from the toxic-dosed group. The trend in error of prediction was toward classifying the toxic dose as a treatment dose and the lethal dose as either a toxic or treatment dose.

In the above classification, each occasion that samples were taken from the subjects was treated as a separate "case." In the second classification analysis, a summary of data on each subject provides the classification results shown in the lower portion of Table 1 ("Results Reported by Subject"). Of note is the fact that, based on the limited number of subjects in this trial, the program has consistently given a conservative classification to each subject. Those in the therapeutic dosage group were all classified as being in the therapeutic group. Two of those in the toxic group were correctly classified and the third

was attributed to the therapeutic group. Likewise, two of those in the lethal groups were correctly classified and the third was attributed to the toxic group.

Discriminant analysis in which the categorical variable was dosage revealed that the sample type (whole blood) and the independent concentrations of amitriptyline and nortriptyline did significantly contribute to the predictability of dosage. The concentration of amitriptyline in whole blood was found to be the primary contributor to the separation of toxic-dosed (250 mg/kg) animals from samples from lethal-dosed (500 mg/kg) animals. Nortriptyline in whole blood was found to be the primary contributor to the classification of samples from treatment-dosed (80 mg/kg) animals from samples obtained from toxic-dosed (250 mg/kg) and lethal-dosed (500 mg/kg) animals. The discriminant-analysis procedure suggests that it may be possible to determine consistently if subjects have received a single therapeutic dose of amitriptyline, based primarily on the relative absence of nortriptyline in whole blood and plasma. The site at which the sample was collected and the type of blood (venous or arterial) evidenced virtually no relationship to the dosage level. Whole blood/plasma ratios were not useful.

The correct and incorrect classifications by dose group for discriminant analysis are shown in Fig. 3.

BEAGLE

The BEAGLE program induced rules for predicting dose with their chi-square scores are shown in Table 2. Although the rules are evolved one at a time, in estimating dose they are used in combination. Table 3 shows the patterns for the rules in combination and the probability associated with each pattern. For example, consider the three rules for classifying the case as a low dose. When all three rules were true in the training set, 57 records, the target was true (dose = 80 mg/kg) in 46 cases. For unknown cases the probability that the dose is low when all three rules are true was 0.81. In the test set, this was correct in 22 out of 26 records which fit this pattern for a success rate of 85%. The same was true in the overall record run.

When all three rules were false, 52 records, the target was never true in the training set. Therefore, the probability that the dose was low is less than 0.01. For the test set, this was correct in 18 out of 18 records. When two out of three rules were false, 26

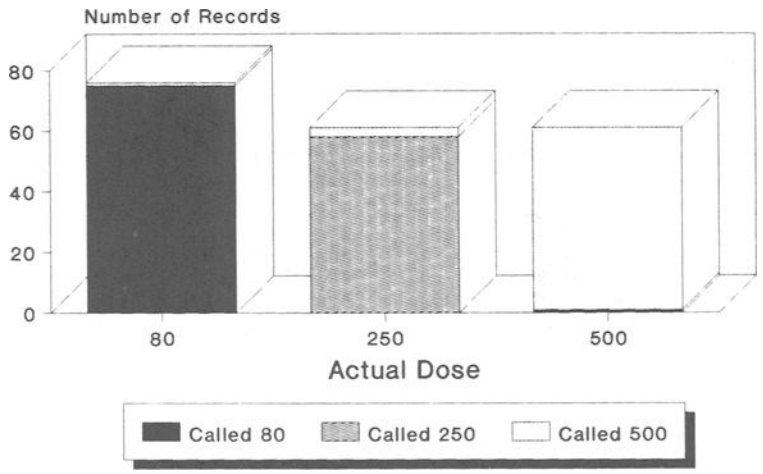

FIG. 4—*Success rate for BEAGLE classification into 80, 250, and 500-mg/kg groups.*

TABLE 2—*BEAGLE rules for dose.*

Rules	Chi-Square Score
TARGET: DOSE = 80 mg/kg	
1. Blood nortriptyline < 200	77
2. Blood amitriptyline ≤ 2118 and blood ami/nor ratio > 0.56	72
3. Plasma amitriptyline ≤ 807 and plasma nortriptyline < 242	70
TARGET: DOSE = 250 mg/kg	
1. Blood nortriptyline ≥ 190 and blood ami/nor ratio < 1.0	57
2. Plasma nortriptyline > 219 and blood amitriptyline ≤ 4942	51
3. Plasma amitriptyline > 833 and plasma amitriptyline > 1002 when plasma ami/nor ratio < 0.38; or plasma amitriptyline < 1002 when plasma ratio > 0.38.	51
TARGET: DOSE = 500 mg/kg	
1. Blood amitriptyline ≥ 3030 and blood ami/nor ratio ≥ 0.69	64
2. Plasma amitriptyline − plasma nortriptyline > 919.5	61
3. Blood nortriptyline > 241.3	47
4. Plasma ami/nor ratio > 0.57 or plasma ami/nor ratio < (time − 10.8)	44

records, the target was only true once in the training set, so the probability for the unknown which fits this pattern being a low dose was 0.06 and 0.09, respectively, and in the test set this was successfully predicted in 10 out of 10 records. In the 209 records run, only 2 out of 101 cases were from the low-dose group when all three rules were false.

Intermediate patterns, 13 records, gave intermediate probabilities of dose = 80 mg/kg, 0.38 and 0.60. When the probability of prediction was between 0.25 and 0.75, the rules are considered unable to classify the unknown. Seven records in the test set were unclassifiable, for an overall success rate in the unquestioned groups of 92% accurate predictions. The correct and incorrect classifications for each dose group by BEAGLE are shown in Fig. 4.

All of the above searches used logical rule induction using chi-square scores to measure the closeness to the target. Searches using numerical targets with correlation coefficients were not as successful. This may be because the attribute to be predicted, dose, is not continuous in this study.

BEAGLE was used with a target of *time*, to induce rules for estimating the time since dose. The rules evolved were weak. Only one had a chi-square score of better than 40. The probability of a positive prediction was at best 0.77, and the success rate on the test set was not significantly better than the prior probabilities. This may be because the sampling time did not approach the half-life of the drug or because both distribution and elimination phases were encountered and the data do not hold any clues to which phase predominates.

KnowledgeMaker

KnowledgeMaker was used to induce rules and to create a decision tree for prediction of dose for just the 1-h or greater records and for a randomly selected training set of 50 cases. The decision tree is shown in Fig. 5. The rules for the set time ≥ 60 min are given

TABLE 3—*BEAGLE rules patterns and probabilities.*

Rule[a] Status				Target True		
Rule	1	2	3 4	Cases	Total Cases	Probability of Target
				TARGET: DOSE = 80 mg/kg		
	0	0	0	2	101	0.02
	0	0	+	1	7	0.17
	0	+	0	0	3	0.09
	0	+	+	2	9	0.24
	+	0	0	1	4	0.27
	+	0	+	1	3	0.34
	+	+	0	2	4	0.47
	+	+	+	67	78	0.85
				TARGET: DOSE = 250 mg/kg		
	0	0	0	12	122	0.10
	0	0	+	4	6	0.62
	0	+	0	0	3	0.08
	0	+	+	0	1	0.16
	+	0	0	13	31	0.41
	+	0	+	3	3	0.83
	+	+	0	14	20	0.68
	+	+	+	23	23	0.97
				TARGET: DOSE = 500 mg/kg		
	0	0	0 0	8	96	0.09
	0	0	0 +	0	3	0.07
	0	0	+ 0	1	30	0.04
	0	0	+ +	0	0	0.30
	0	+	0 0	0	3	0.07
	0	+	0 +	0	0	0.30
	0	+	+ 0	0	8	0.03
	0	+	+ +	7	7	0.91
	+	0	0 0	1	3	0.33
	+	0	0 +	0	0	0.30
	+	0	+ 0	4	8	0.48
	+	0	+ +	1	1	0.65
	+	+	0 0	1	2	0.44
	+	+	0 +	0	0	0.30
	+	+	+ 0	23	27	0.83
	+	+	+ +	18	21	0.83

[a] Rules from Table 2.
[b] 0 means rule false; + means rule true.

in Table 4. KnowledgeMaker uses the entropy of uncertainty of the classification as a measure of the information value of the rule. KnowledgeMaker, like BEAGLE, found that the most useful information was blood nortriptyline and that the critical decision value was around 200 ng/mL. This was followed in value by the ratio of amitriptyline to nortriptyline in blood, with two critical decision points, 1.5 or 0.6. If only records from 1-h or greater were considered, the blood amitriptyline (above or below 2300 ng/mL) or plasma nortriptyline (above or below 1700 ng/mL) were useful. These are the same attributes that BEAGLE evolved and in the same order of significance with very close decision values. Unfortunately, KnowledgeMaker does not print out the probabilities

```
bn ?
  < 199.5
    br ?
      < 1.505
        pa ?
          < 690.5 === low
          >= 690.5
            pa ?
              < 709.5 === high
              >= 709.5 === low
      >= 1.505
        ba ?
          < 1794.5
            bn ?
              < 146.5 === low
              >= 146.5
                site ?
                  partery === low
                  carotid === mid
          >= 1794.5
            site ?
              partery === high
              pvein === mid
              jugular === mid
  >= 199.5
    br ?
      < 0.61 === mid
      >= 0.61
        pa ?
          < 1047.5
            site ?
              jugular === mid
              pvein === mid
              carotid
                br ?
                  < 0.86 === mid
                  >= 0.86
                    ba ?
                      < 4211.5 === high
                      >= 4211.5 === mid
              partery
                bn ?
                  < 203 === high
                  >= 203 === mid
          >= 1047.5
            bn ?
              < 233.5 === low
              >= 233.5
                t ?
                  < 37.5
                    br ?
                      < 0.99
                        ba ?
                          < 5199
                            ba ?
                              < 3711.5 === high
                              >= 3711.5 === mid
                          >= 5199 === high
                      >= 0.99 === high
                  >= 37.5 === high
```

FIG. 5—*KnowledgeMaker decision tree.*

TABLE 4—*KnowledgeMaker rules, time ≥ 60 min.*

Rule 1:	If plasma nortriptyline < 258 and blood amitriptyline < 2380 and plasma amitriptyline < 672, then dose is low.
Rule 2:	If plasma nortriptyline is < 258 and blood amitriptyline is < 2380 and plasma amitriptyline is ≥ 672 and the site is the peripheral artery, then dose is high.
Rule 3:	If plasma nortriptyline is < 258 and blood amitriptyline is < 2380 and plasma amitriptyline is ≥ 672 and the site is the peripheral vein, then dose is low.
Rule 4:	If plasma nortriptyline is < 258 and blood amitriptyline ≥ 2380, then dose is high.
Rule 5:	If plasma nortriptyline is ≥ 258 and plasma amitriptyline is < 1730, then dose is midlevel.
Rule 6:	If plasma nortriptyline is ≥ 258 and plasma amitriptyline ≥ 1730, then dose is high.

that it calculates. The correct and incorrect classifications by KnowledgeMaker by dose group are shown in Fig. 6.

Discussion

The success rates of the three programs were compared based on classification of all 209 complete records. The results are given in Tables 5 and 6. In the first comparison (Table 5), the probability of the classification was ignored. In the second comparison (Table 6), the probability was taken into account and those predictions with a probability of between 25 and 75% were considered unclassifiable or undetermined. While

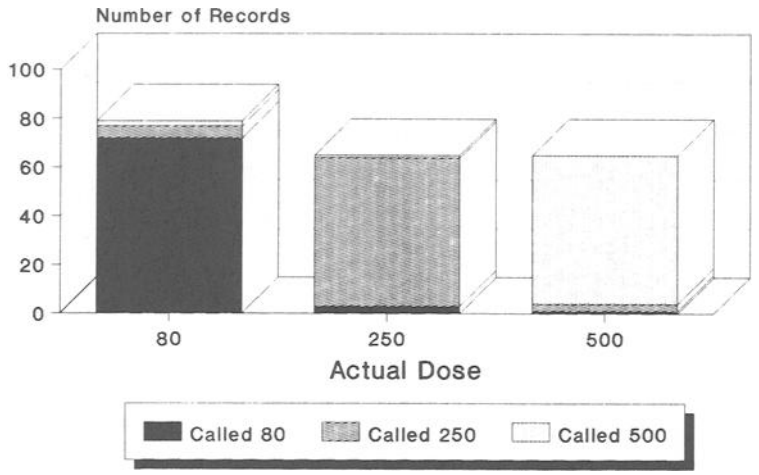

FIG. 6—*Success rate for KnowledgeMaker classification for 80, 250, and 500 mg/kg doses.*

TABLE 5—*Comparison of three methods for prediction of dose, n = 209 cases.*

Method	Correct	Incorrect
BEAGLE	194 (93%)	15 (7%)
KnowledgeMaker	183 (88%)	26 (12%)
SPSS discriminant analysis	161 (77%)	48 (23%)

TABLE 6—*Comparison of three methods for prediction of dose, weighted for uncertainty, undetermined allowed, n = 209 cases.*

Method	Correct	Undetermined	Incorrect
BEAGLE	143 (68%)	49 (23%)	17 (8%)
KnowledgeMaker	169 (81%)	20 (9.6%)	20 (9.6%)
SPSS discriminant analysis	107 (51%)	95 (46%)	7 (3%)

KnowledgeMaker did not reveal the probability, those cases which did not meet the internal criteria for certainty returned a question mark for a diagnosis with this program in the consultation mode.

All of the programs did equally well in assigning a case to the treatment dose group (80 mg/kg) (Figs. 3, 4, and 6). All the programs experienced the greatest difficulty in assigning a case to the toxic group (250 mg/kg). KnowledgeMaker was the most successful in this classification. Discriminant analysis showed more errors in classification of the fatal-dose group (500 mg/kg) than the other two programs.

One of the goals of the animal experiments was to compare the relative values of the whole blood and plasma amitriptyline and nortriptyline measurements [*4*]. Discriminant analysis (Function 1 and Function 2) used all four values plus time in combination, but gave the highest weighting factors to the whole blood amitriptyline or nortriptyline concentrations and lowest to plasma nortriptyline or plasma amitriptyline. From these weighting factors, the whole blood measurements were in general, at least twice as useful in discriminant analysis as the plasma measurements.

With regard to the relative value of whole blood as opposed to plasma measurements, the BEAGLE program found whole blood nortriptyline to be the most useful, based on chi-square scores, followed by whole blood amitriptyline and the ratio of the amitriptyline/nortriptyline concentrations in whole blood. Plasma amitriptyline and nortriptyline was least useful, however the chi-square scores were not greatly different.

In agreement, KnowledgeMaker used the whole blood nortriptyline concentration value as the primary criterion for classification of the dose group, followed by the ratio of the amitriptyline/nortriptyline concentrations in whole blood. At the tertiary branch of the decision tree (Fig. 5), plasma amitriptyline, blood amitriptyline, or blood nortriptyline were used at various points for further classification.

In application of any of these software programs to human case data, the probability of the classification for each individual record or case would have to be read from a table such as that in Table 3 for BEAGLE, based on the laboratory's own case database or based on data from a national registry of human toxicology using representative cases. The classification and the probability of each classification would depend on the amount of data collected and the pattern of the toxicological results for each particular case [*3*].

The extraction of several decision rules by BEAGLE and of a decision tree by KnowledgeMaker from this model of amitriptyline in acute overdose allows the investigation of the extension of this animal model to clinical studies. The next step in this investigation will be to apply the derived decision rules to known cases of amitriptyline acute overdose and compare the success rate with the results of this data analysis.

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