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Comparison of Population Pharmacokinetic Models for Gentamicin in Spinal Cord-Injured and Able-Bodied Patients

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Population pharmacokinetic models for gentamicin were developed by using data obtained from 29 spinal cord-injured patients and 11 able-bodied control patients. With a one-compartment model, the population parameters were clearance (CL), volume of distribution (V), and their associated variances. Parameter estimates were found by using the computer program NPEM and by the standard two-stage (STS) method. NPEM uses a nonparametric approach incorporating the expectation maximization algorithm to evaluate a joint probability density function at 900 intersections over a bivariate grid. In contrast, the STS method requires conventional assumptions of normality for the underlying distributions. For NPEM, the mean CL was 97.6 ml/h/kg of body weight (coefficient of variation, 33.0% in the spinal cord-injured patients and 67.8 ml/h/kg ± 28.2% in the able-bodied patients; the mean V was 0.31 liter/kg ± 32.3% in the spinal cord-injured patients and 0.23 liter/kg ± 15.8% in the able-bodied patients. For STS, the mean CL was 101.0 ml/h/kg ± 37.5% in the spinal cord-injured patients and 65.0 ml/h/kg ± 33.8% in the able-bodied patients; the mean V was 0.29 liter/kg ± 34.0% in the spinal cord-injured patients and 0.21 liter/kg ± 21.0% in the able-bodied patients. Although the means and variances found by NPEM and the STS method were similar, the NPEM analysis revealed that the distributions of CL and V, even after they were linked to weight, were positively skewed and kurtotic. The cumulative distribution functions for CL ($P < 0.001$) and V ($P < 0.001$) in spinal cord-injured patients were different from those in able-bodied patients. Unique population models are required for the initial dosage selection for spinal cord-injured patients. Future approaches for developing population models should allow the linkage of structural parameters to multiple patient covariates.

Population pharmacokinetic methods are used to study pharmacokinetic processes by analyzing pooled data sampled from some underlying population of interest (1, 5, 12, 15, 19, 28). Population approaches provide mean parameter estimates and allow variances to be partitioned into within-individual and between-individual components. In addition, population approaches allow pharmacokinetic parameters to be linked to informative covariates, and this may further reduce the variance terms in the models. Examples of informative covariates are age, gender, ethnicity, body size, health-disease status or markers, environmental exposures, and genetic characteristics. Properly constructed population pharmacokinetic models are useful for selecting rational dosing regimens of drugs for individual patients.

The standard two-stage (STS) method provides estimates of population parameters in stages (25, 27). In the first stage, ordinary least-squares regression parameters are estimated from data from each individual. In the second stage, population parameters are estimated by pooling the individual estimates. This method, like the computer program NONMEM, which utilizes extended least squares to form mixed-effect population models (1), requires the assumption that the underlying population distributions are normal or will be normal after suitable transformations (19).

Nonparametric, maximum-likelihood approaches to population models have also been developed previously (15, 18). These methods do not require the parametric assumptions of the STS method or NONMEM. NPEM is a computer program which uses a nonparametric approach and the expectation maximization algorithm (3). NPEM can be used to develop one-compartment population models in which each pharmacokinetic parameter can be linked to a single patient covariate (8, 18).

Gentamicin is an aminoglycoside antibiotic that is frequently administered to treat serious gram-negative bacterial infections in spinal cord-injured and able-bodied patients. The use of gentamicin is associated with the occurrence of toxicity involving the kidney, the auditory nerve, and the vestibular apparatus. Therefore, population-specific pharmacokinetic models for optimizing aminoglycoside dosages for spinal cord-injured patients are needed, because the disposition of aminoglycosides in these patients appears quite different from that in able-bodied patients (13, 20, 22–24).

This work was performed in order to develop population-specific pharmacokinetic models for selecting rational gentamicin dosages to treat patients with spinal cord injuries and to compare them with models developed for able-bodied patients. Population models were developed with NPEM and with the STS method.

MATERIALS AND METHODS

Patients and collections. Timed serum gentamicin concentrations were obtained from 29 male patients with spinal cord injuries (17 quadriplegics and 12 paraplegics) and from 11 able-bodied, male patients. None of the patients had a

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diagnosis of life-threatening sepsis, nor was any hemodynamically unstable. Spinal cord injuries were complete and traumatic, and they occurred more than 1 year prior to this study. All subjects were within 15% of their ideal body weight, all had normal renal function, and all were free of ascites, anasarca, and other conditions associated with the redistribution or sequestration of body water. Patients were studied during the daylight hours to minimize circadian variations in gentamicin disposition (4). Each patient gave informed consent for the procedures of the study, and the study protocol was approved by the institutional review board.

Three blood specimens were collected from all patients at the following times: (i) just before a regularly scheduled infusion, (ii) 1/2 h after the end of a 1/2-h infusion, and (iii) at 1.44 estimated half-lives after the second blood specimen. Additional timed specimens were collected from some patients.

Gentamicin assay. The concentration of gentamicin in serum was determined in duplicate by a fluorescence polarization immunoassay (TDx; Abbott Laboratories, North Chicago, Ill.). According to the manufacturer, this assay is sensitive to gentamicin concentrations of 0.27 mg/liter. On the basis of replicate analyses, the interassay standard error (SE) for each concentration in serum (C) may be estimated from the following equation: SE (mg/liter) = $0.2061 - 0.0081\ C + 0.0098\ C^2$.

STS pharmacokinetic analyses. Nonlinear least-squares regression with reciprocal-variance weighting was employed to provide individual estimates of total body clearance (CL) and apparent volume of distribution (V), and this was followed by an STS analysis (27) to give single-compartment, population parameter estimates for spinal cord-injured and able-bodied populations.

NPEM pharmacokinetic analyses. NPEM was used to develop pharmacokinetic models for each population given the pooled data about concentrations in serum. A continuous, joint, bivariate density function was evaluated over a grid of intersections (30 by 30 points) for the pharmacokinetic variates under study. In this case, the variates were CL and V. The user-supplied boundaries for the CL abscissa were 0.0 to 0.24 liter/h/kg of body weight, and for the V abscissa, they were 0.0 to 0.90 liter/kg. In effect, both pharmacokinetic variates were linked (or adjusted) to weight. The program determined the 30 grid points for each abscissa from the roots of an orthogonal polynomial of order 30 in order to accommodate Gauss-Legendre integration (17).

Estimations of the joint density function values were accomplished through a series of iterations involving Gauss-Legendre integration and by using a maximum-likelihood criterion to determine convergence. Output from the program consisted of a matrix of 900 values of the joint density function defined over the CL-versus-V grid. This data matrix was read and analyzed by using a program written for SAS in order to perform numerical, statistical, and graphical analyses of interest. Gauss-Legendre integration was used to find the marginal density functions and cumulative distribution functions for each variate. The mean, median, mode, variance, quantiles, and moments of skewness and kurtosis for CL and V as well as the covariance and correlation between CL and V were calculated by standard numerical techniques (11, 17). The details of these calculations are given in the appendix.

Statistics. Two-sample median tests were used to compare the medians of marginal density functions for CL and V for the two populations. Similarly, the cumulative distribution functions for CL and V were compared by Kolmogorov-Smirnov tests. The size of each statistical test was set at 0.05 for defining significance, but estimates of P values were reported.

TABLE 1. Patient characteristics[a]

Type of patient[b]	Age (yr)	Wt (kg)	Creatinine clearance (ml/min)
Able bodied (11)	44.0 ± 14.1	73.4 ± 9.4	88.1 ± 42.7
Spinal cord injured (29)	39.6 ± 13.3	71.7 ± 15.4	104.5 ± 29.6
Paraplegic (12)	44.1 ± 13.6	73.2 ± 18.6	93.5 ± 34.0
Quadriplegic (17)	36.4 ± 12.5	70.7 ± 13.8	113.0 ± 23.7

[a] Age, weight, and creatinine clearance were not statistically significant different in able-bodied versus spinal cord-injured patients and in paraplegics versus quadriplegics. All data are the means ± standard deviations.
[b] Numbers of patients are in parentheses.

RESULTS

Characteristics of patients are summarized in Table 1. The spinal cord-injured patients did not differ from the able-bodied patients in age, weight, or measured creatinine clearance. Similarly, paraplegics did not differ from quadriplegics in age, weight, or measured creatinine clearance.

The NPEM population pharmacokinetics for spinal cord-injured and able-bodied patients are summarized in Table 2. The median CL of gentamicin was 83.6 ml/h/kg in spinal cord-injured patients, and this was borderline statistically significantly larger than the corresponding value of 61.0 ml/h/kg in able-bodied controls ($P = 0.09$). The median V of gentamicin was 0.27 liter/kg in spinal cord-injured patients, and this was not different from the corresponding value of 0.23 liter/kg in able-bodied patients ($P = 0.14$). Comparison of the cumulative distributions for CL showed that they were different for spinal cord-injured and able-bodied populations ($P < 0.001$). Similarly, the cumulative distributions for V differed for the two populations ($P < 0.001$). Neither the NPEM nor the STS pharmacokinetic parameters for gentamicin in quadriplegics were statistically significantly different from those in paraplegics, and accordingly, these results are not shown.

Table 3 summarizes the population-specific pharmacokinetic parameters obtained by NPEM and the STS method and classified by population type. Mean estimates of CL and V generated by NPEM and by the STS method were not statistically significantly different, although the coefficients of variation were always smaller for the NPEM estimates.

Figure 1 depicts three-dimensional surface plots of the NPEM joint density functions, designated f(CL, V). Values of f(CL, V) are plotted on the ordinates, and those of CL and V are plotted on the abscissas. Figure 2 depicts contour plots of the same joint density functions shown in Fig. 1, except that the viewpoint is from directly above the CL-versus-V grid. For the able-bodied population, CL and V were uncorrelated ($r = 0.08$; $P > 0.05$). For the spinal cord-injured population, CL and V were correlated ($r = 0.62$; $P < 0.01$). Figure 3 depicts plots of the marginal density functions for gentamicin CL, designated f(CL). A marginal density function may be conceptualized as a two-dimensional projection of the integrated joint density function onto a plane perpendicular to the CL-versus-V grid. The solid vertical line indicates the location of the expectation or mean value of the estimated parameter. This value can be incorporated as a

TABLE 2. NPEM summary statistics for gentamicin population models

Type of patient[a]	Parameter	Mean median mode	CV[b] (%)	r	Skewness	Kurtosis
Spinal cord injured (29)	CL (ml/h/kg)	97.6 83.6 66.4	33.0	0.62	0.99	4.82
	V (liter/kg)	0.31 0.27 0.25	32.3		1.21	4.05
Able bodied (controls) (11)	CL (ml/h/kg)	67.8 61.0 89.4	28.2	0.08	−0.11	1.53
	V (liter/kg)	0.23 0.23 0.25	15.8		−0.38	2.23

[a] Numbers of patients are in parentheses.
[b] CV, coefficient of variation.

prior value into a Bayesian dose prediction program. This marginal density function appears bimodal for the able-bodied population, but it would be premature to accept this, given the small number of subjects in the sample. In addition, f(CL) for the able-bodied population is less dispersed than it is for the spinal cord-injured population. Figure 4 depicts plots of the marginal density functions for gentamicin V, designated f(V). As with f(CL), f(V) shows more dispersion for the spinal cord-injured population than for the able-bodied population. Figure 5 depicts the cumulative distribution functions for gentamicin CL and V, designated F(CL) and F(V).

DISCUSSION

The object of population pharmacokinetic analysis is to characterize the location and variation of pharmacokinetic behavior for members of the population of interest. Ideally, this information will be used to ensure that different dosage strategies are developed for those populations that require them. NPEM is a computer program for studying population pharmacokinetics from pooled plasma or measurements of drugs in serum whose pharmacokinetics can be described with one-compartment structural models. NPEM can make use of observational, clinical data which are routinely acquired during patient care.

Victims of spinal cord injuries are exposed to a large number of medications during the immediate postinjury period and over the durations of their lives. The physiopathologic sequelae of spinal cord injuries influence drug disposition and can predispose patients to adverse reactions or therapeutic misadventures unless some form of dosage individualization is performed (20, 21). Therefore, studies to characterize alterations in drug pharmacokinetics or pharmacodynamics in this unique patient population are needed.

These results confirm those of previous works indicating that spinal cord-injured patients have weight-adjusted volumes of distribution for aminoglycosides larger than those of able-bodied patients (13, 24). This finding may be the result of an expanded extracellular fluid volume caused by extravasation of plasma proteins into the interstitial space, a peripheral pooling of blood associated with diminished venomotor tone, and a loss of muscle mass (2, 16, 26).

The finding that spinal cord-injured patients have total body clearances for aminoglycosides larger than those of able-bodied patients has been previously reported (24). This is of interest, since aminoglycoside clearance is considered a reliable index of the glomerular filtration rate (10, 14). Possible explanations for an elevated glomerular filtration rate may be related to reduced afferent and/or efferent arteriolar tone in the glomeruli as a result of a reduced central sympathetic outflow (6). In addition, the greatly increased fluid intake by spinal cord-injured patients to prevent renal infections and stone formation may result in daily diuresis markedly greater than that by able-bodied patients. Therefore, patients with spinal cord injuries require larger weight-adjusted loading and maintenance doses than their able-bodied counterparts in order to achieve and maintain similar aminoglycoside concentration targets in serum for the treatment of serious systemic infections.

The NPEM analysis of gentamicin pharmacokinetics in spinal cord-injured and able-bodied patients was consistent

TABLE 3. Comparison of NPEM and STS population models

Type of patient[a]	Parameter	Results by the following model:			
		NPEM		STS	
		Mean	CV[b] (%)	Mean	CV (%)
Spinal cord injured (29)	CL (ml/h/kg)	97.6	33.0	101.0	37.5
	V (liter/kg)	0.31	32.3	0.29	34.0
Able bodied (controls) (11)	CL (ml/h/kg)	67.8	28.2	65.0	33.8
	V (liter/kg)	0.23	15.8	0.21	21.0

[a] Numbers of patients are in parentheses.
[b] CV, coefficient of variation.

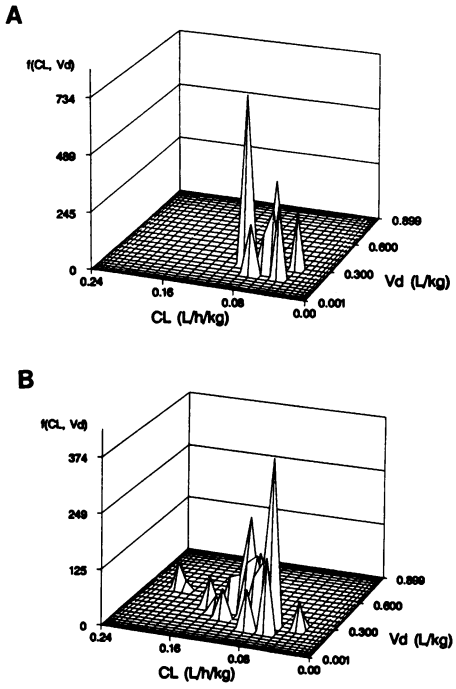

FIG. 1. Three-dimensional surface plots of the joint density functions [f(CL, V)] over the CL-versus-V grid. The boundaries were set at 0.0 to 0.9 liter/kg for V and 0.0 to 0.24 liter/h/kg for CL. Integration of this density function over either abscissa gives the marginal density function for the other abscissa. (A) Able-bodied population; (B) spinal cord-injured population.

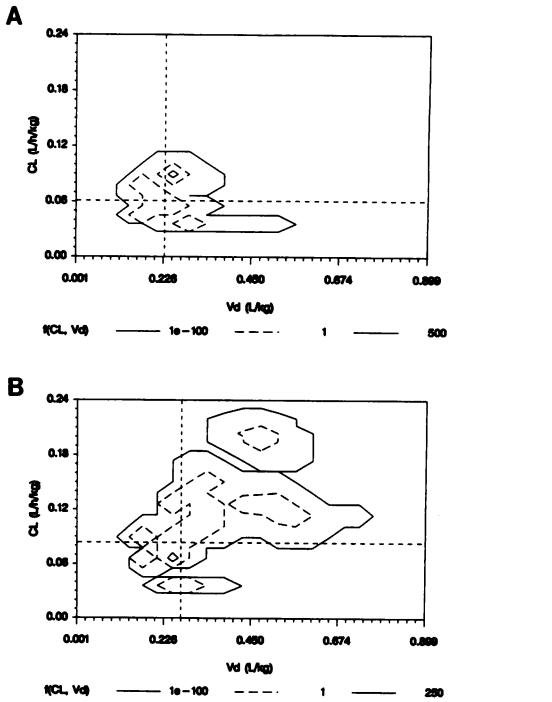

FIG. 2. Contour plots of the joint density functions defined over the CL-versus-V grid. It is clear that the joint density for CL and V is considerably more dispersed in the spinal cord-injured population (B) than it is in the able-bodied population (A). The broken lines indicate the locations of the marginal medians, and their intersection gives the balance point for the joint density.

with the STS analysis, but it provided a more detailed pharmacokinetic description. As shown in Fig. 1 and 2, covariance between CL and V for the spinal cord-injured population is greater than that for the able-bodied population. This is supported by the fact that the correlation coefficient between CL and V was 0.62 in the spinal cord-injured population, whereas it was only 0.08 for the able-bodied population. An examination of Fig. 2 also suggests that the variances of CL and V are heteroscedastic in the spinal cord-injured population and vary directly with their respective values. The variances appear more homoscedastic for the able-bodied population. Figures 3 and 4 show clearly that the dispersion for CL and V in the spinal cord-injured population is greater than that in the able-bodied population.

One of the strengths of nonparametric approaches is that they are not limited by restrictive prior assumptions about the shape of the underlying distributions of the structural parameters. However, it should be noted that NPEM is highly dependent upon the selection of boundaries. NPEM is not robust to poor selection of initial boundaries.

We have shown that NPEM provides the analyst with a powerful tool for nonparametric assessment of interpopulation differences in pharmacokinetic behavior. We are not aware that other investigators have used NPEM for this purpose.

Another application has been studied by researchers who used the expectations and standard deviations of the marginal density functions to form prior models for incorporation into a Bayesian dosage prediction program (7, 9). There was no apparent difference in the predictive performance of an NPEM prior model developed with malnourished patients compared with that of one developed from the same sample by the STS method when each was used to form Bayesian predictions of concentrations in serum in a second sample of malnourished patients (9). On the other hand, there was a difference in predictive performance when an NPEM prior model developed from cholecystitis patients was compared with a prior model developed from appendectomy patients for predicting concentrations in serum in a second sample of cholecystitis patients (7). This supports the premise that different populations will require different prior models for Bayesian dosage selection.

Unless the form of the final NPEM joint density function is bivariate normal before or after transformation, it seems unlikely that NPEM prior models will outperform STS or NONMEM prior models for use in Bayesian dosage prediction programs which assume that pharmacokinetic parameters have Gaussian distributions. It appears to us that, in this case, any possible advantage of describing population pharmacokinetics with a nonparametric model is nullified by using only the expectation (mean) and the standard deviation of the marginals to summarize the entire distribution, unless the marginals are Gaussian. This work and two recent papers have shown that NPEM and the STS method give virtually identical means and standard deviations when used in this manner to analyze the same sets of data (5, 9).

We conclude that NPEM provides prior models which are equivalent to those produced by the STS method and which appear capable of making accurate predictions of pharmacokinetics, provided that the underlying distributions are close to Gaussian in their shape. For populations in which this is not true, linkage of each variate to multiple patient covari-

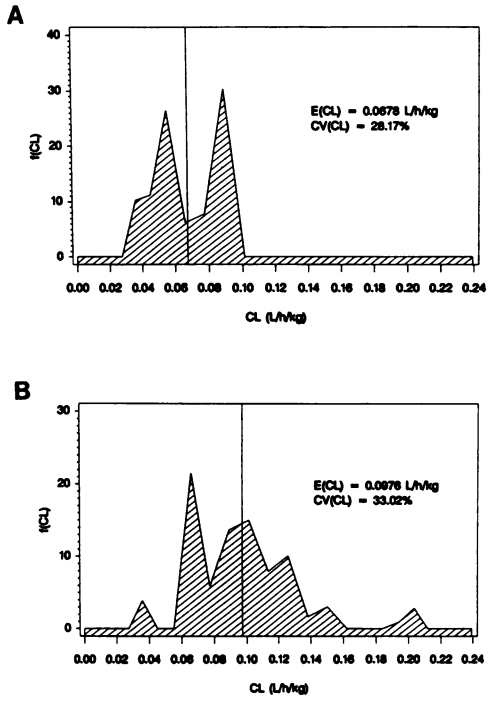

FIG. 3. Marginal density functions for CL. The solid line indicates the location of the expectation (E) or mean value for CL. It should be noted that the distribution is essentially multimodal. Had this analysis been performed by using NONMEM, with a normal distribution assumed, the expectation (mean) and the highest point on the assumed distribution would correspond to a location where, in reality, little or no probability density-mass exists. The NPEM bimodal marginal density function, however, supports serendipity, and NPEM can be used as a hypothesis generating engine. (A) Able-bodied population; (B) spinal cord-injured population.

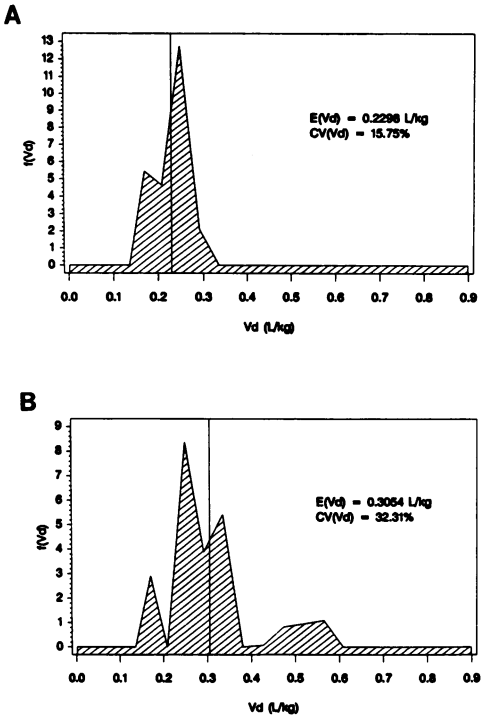

FIG. 4. Marginal density functions for V. The solid line indicates the location of the expectation (E) or mean value for V. (A) Able-bodied population; (B) spinal cord-injured population.

ates may result in unimodal distributions which explain more variation. We suggest that this should be offered in future versions of this novel program. Alternatively, with the aid of NPEM it may be possible to identify patient factors which allow a population to be partitioned into subpopulations whose distributions can be effectively summarized with a mean and a standard deviation for use in conventional Bayesian dosage prediction programs.

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APPENDIX

Calculation of NPEM population parameters. The following formulas were used to find the marginal densities for CL and V [f(CL) and f(V)] and the cumulative distributions for CL and V [F(CL) and F(V)] from the joint density function [f(CL, V)] (11). The 0.25, 0.50, and 0.75 quantiles for the marginal densities of CL and V were interpolated from their respective cumulative distribution functions [F(cl) and F(v)]. The indicated definite integrals were evaluated by Gauss-Legendre integration (Gaussian quadrature), which is accomplished by computing the weighted sums shown below (17).

CL and V are treated as random variables, cl and v are the abscissa points for CL and V, i indexes cl, j indexes v, vwt_j is the

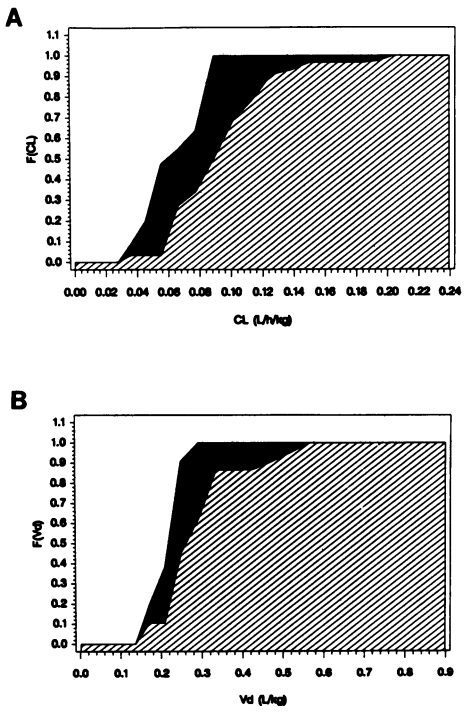

FIG. 5. Cumulative distribution functions for CL and V designated F(CL) and F(V). The border of the solid area indicates the location of the cumulative distributions for the able-bodied population, whereas the border of the striped area indicates the location of those for the spinal cord-injured population. The black area indicates the amount of noncongruence. F(CL) and F(V) for the able-bodied population were different from F(CL) and F(V) for the spinal cord-injured population ($P < 0.001$).

weight needed to integrate v_j by using Gaussian quadrature, and $clwt_i$ serves the same purpose for cl_i. The abscissa points and weights were determined from the coefficients of a Legendre polynomial of degree 30.

Marginal densities were calculated as follows:

$$f(cl_i) = \int_v f(cl, v)\, dv = \sum_j f(cl_i, v_j)\, vwt_j$$

$$f(v_j) = \int_{cl} f(cl, v)\, dv = \sum_i f(cl_i, v_j)\, clwt_i$$

Cumulative marginal distributions were calculated as follows:

$$F(cl_k) = P(CL \le cl_k) = \int_0^{cl_k} f(cl)\, dcl = \sum_{i=1}^{k} f(cl_i)\, clwt_i$$

$$F(v_k) = P(V \le v_k) = \int_0^{v_k} f(v)\, dv = \sum_{j=1}^{k} f(v_j)\, vwt_j$$

The following formulas were used to calculate the expectations (E) and variances (VAR) for CL and V. Exprectations of marginal densities were calculated as follows:

$$E(V) = \int_v v\, f(v)\, dv = \sum_j v_j\, f(v_j)\, vwt_j$$

$$E(CL) = \int_{cl} cl\, f(cl)\, dcl = \sum_i cl_i\, f(cl_i)\, clwt_i$$

Variances of marginal densities were calculated as follows:

$$VAR(V) = E(V^2) - [E(V)]^2$$

$$E(V^2) = \int_v v^2\, f(v)\, dv = \sum_j v_j\, v_j\, f(v_j)\, vwt_j$$

$$VAR(CL) = E(CL^2) - [E(CL)]^2$$

$$\frac{E(CL^2)}{clwt_i} = \int_{cl} cl^2\, f(cl)\, dcl = \sum_i cl_i\, cl_i\, f(cl_i)$$

The following formulas were used to calculate the covariance (COV) and correlation (CORR) between CL and V. Covariance was calculated as follows:

$$COV(CL, V) = \int_v \int_{cl} cl\, v\, f(cl, v)\, dcl\, dv - E(CL)\, E(V)$$

$$= \sum_j \left[\sum_i cl_i\, v_j\, f(cl_i, v_j)\, clwt_i\right] vwt_j - E(CL)\, E(V)$$

Correlation was calculated as follows:

$$CORR(CL, V) = COV(CL, V)/[\sqrt{VAR(CL)}\ \sqrt{VAR(V)}]$$

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