The influence of clinical and pharmacological factors on enuresis treatment with imipramine

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1 The aim of this study has been to evaluate the response to imipramine treatment in enuretic children through the use of a series of clinical and pharmacological variables and by applying a multivariate (principal components) analysis technique.

2 The study was carried out on 146 children whose ages ranged from 5 to 14 years, and who received variable doses of imipramine (12.5 to 100 mg day⁻¹).

3 The quantitative variables analyzed were: drug dosage, serum levels of imipramine and its metabolite desipramine, the relationship between them both, the duration of treatment, age and weight.

4 The qualitative variables were: compliance, presence of side-effects, enuretic and/or psychiatric antecedents, intelligence quotient (I.Q.), the existence (or absence) of related pathologies, sex, and the type of enuresis.

5 The response to treatment was quantified by means of the percentage of decrease in frequency of enuresis as compared with the initial frequency.

6 The results obtained show that the variables which are most associated with the reduction of enuresis are, in decreasing order: the dosage of imipramine administered, the duration of treatment, compliance and the level/dose ratio for the sum of the drug and metabolite levels.

Keywords enuresis imipramine serum levels

Introduction

The efficacy of imipramine in the treatment of enuresis has been confirmed in many controlled double-blind studies (Blackwell & Currah, 1973). However, there has been little research done as to those factors which determine a more favourable response to this type of therapy (Klein *et al.*, 1980; Kolvin *et al.*, 1973; Meadow, 1974). Furthermore, the nature of the study, the choice of patients and the data analysis must be taken into consideration when interpreting results, especially if the sample is small. Due to the large

number of both clinical and pharmacological factors to be analyzed and the varied nature of the data, the utilization of complex statistical techniques becomes necessary in order to help clarify the relative importance of those factors which influence the response to a particular pharmacological treatment.

In multiple regression, one of the major difficulties with the usual least squares estimators is the problem of multicollinearity, which occurs when there are near-constant linear functions

of two or more of the predictor, or regressor, variables. Multicollinearities are often, but not always, indicated by large correlations between subsets of the variables and, if multicollinearities exist, then the variances of some of the estimated regression coefficients can become very large, leading to unstable and often misleading estimates of the regression equation. To overcome this problem, various approaches have been proposed: ridge regression, shrinkage estimators, and also approaches based on principal component analysis (Jolliffe, 1986).

The availability of sufficient data from a large population of enuretic children treated with imipramine has allowed us to carry out a multivariate analysis in order to define those clinical and pharmacological variables which exert the greatest influence on the response to this therapy. The results of this analysis are given in this paper.

Methods

The population studied was made up of 146 enuretic children (40 girls, 106 boys) aged 5 to 14 years. They were treated on an outpatient basis at the Child Psychiatry Department of the University Clinical Hospital. In order to be included in the study the patients had to be on imipramine treatment for nocturnal enuresis.

The diagnosis of enuresis was based on clinical criteria, in agreement with DSM-III classification. As diagnostic dichotomic sub-categories we used: Primary-Secondary and Daily-Alternate. Enuresis was considered to be secondary when the child showed nocturnal vesical control for at least 3 months. It was considered daily when the initial frequency of enuresis was at least 5 nights a week.

Pharmacological treatment

The initial prescription of imipramine (12.5–100 mg day⁻¹) was made on the basis of clinical criteria (sub-categories, diagnosis, age and weight) and always for exclusively therapeutic purposes. Later, provided it was necessary, the dosage was altered according to the serum level and/or response observed. In all the cases, the drug was administered daily in a single nocturnal dose.

The duration of treatment varied depending on the outcome. It was necessary to suspend treatment for clinical reasons in two children.

The patients were given no other medication or alternative form of treatment except those necessary for related pathologies (for example,

diabetes, epilepsy . . .). Compliance was monitored by pill counts and serum levels together. When both criteria were discrepant priority was given to serum levels by assuming non-compliance when intraindividually variation of serum level/dose ratio was greater than 20%.

Nuisance side effects were elicited by systematically interviewing parent and child together and were recorded as present or absent in a standard form. The most common were decreased appetite (42%), light sleep (16%), abdominal pains (11%), dry mouth (8%) and headaches (8%).

Serum levels

Monitoring of serum levels of imipramine and its metabolite desipramine was carried out in all patients at least once at steady-state (at least 15 days from the start of treatment and/or change of dosage). The average number of serum levels per patient was 2.3 ± 1.5 . Sampling time was in the morning, approximately 12 h after the prior dose. Blood samples were obtained by venepuncture, transferred immediately to a glass tube without stopper, were centrifuged and serum was separated and frozen (-20°C) until analysis. The method of assay was nitrogen-phosphorus detection gas chromatography. The detection limit was 10 ng ml^{-1} for imipramine and desipramine and had a coefficient of variation of less than 10% for imipramine and 15% for desipramine (Baselt, 1980). The determination of imipramine and desipramine serum levels was carried out by personnel blind to clinical picture and response.

Outcome measures

The response to imipramine treatment was measured monthly as a percentage decrease in the enuresis frequency relative to baseline (this percentage had an average value of $71 \pm 31\%$). A parent (usually the mother) reported on a monthly chart the number of dry nights. The variables analyzed in relation to the outcome of treatment were obtained retrospectively from each patient's clinical record. Their definitions and quantification are shown in Table 1.

Statistical analysis

The relationship between serum levels, other clinical and pharmacological variables and clinical response was investigated by multivariate analysis (principal components) (Belsley *et al.*, 1980; Galindo, 1987; Sandford, 1985).

Principal components regression simply starts

Table 1 Independent variables under study

<i>Variable</i>	<i>Definition (magnitude)</i>
Sex	Male (1) vs Female (0)
Age	years
Weight	kg
Dose	mg kg ⁻¹ day ⁻¹
L/D(Imipramine)	Imipramine serum level-dose ratio
L/D(Desipramine)	Desipramine serum level-dose ratio
L/D(Total)	Total serum level (imipramine + desipramine)-dose ratio
Imipramine/desipramine	Imipramine and desipramine serum levels ratio
Compliance	Compliance (1) vs non-compliance (0)
C _{ss} (Imipramine)	Imipramine steady-state average serum level
C _{ss} (Desipramine)	Desipramine steady-state average serum level
C _{ss} (Total)	Total concentration (imipramine + desipramine) steady-state average serum level
Duration of treatment	days
Number of side effects	0, 1, 2, 3
Enuresis type	PD (3), SD (2), PA (1), SA (0)
First-grade enuretic antecedents	Present (1) vs Absent (0)
First-grade psychiatric antecedents	Present (1) vs Absent (0)
Intelligence quotient	Normal (1) vs Pathological (0)
Related* pathologies	Present (1) vs Absent (0)

*Considered as associated related pathologies were: diurnal enuresis, encopresis, attention deficit disorder, epilepsy, oligophrenia, spina bifida and diabetes.

PD = Primary and daily; SD = Secondary and daily; PA = Primary and alternate; SA = Secondary and alternate.

by using the principal components (new variables, linear combination of the original ones, but non-correlated) of the predictor variables in place of the predictor variables. Since the principal components are uncorrelated, there are no multicollinearities between them, and the regression calculations are also simplified. If all the principal components are included in the regression, then the resulting model is equivalent to that obtained by least squares, so the large variances caused by multicollinearities have not been reduced. However, if some of the principal components are deleted from the regression equation, estimators of the coefficients in the original regression equation are obtained which are usually biased, but which simultaneously greatly reduce any large variances for regression coefficient estimators which have been caused by multicollinearities (Jolliffe, 1986).

Logistic regression (PLR of BMDP) was used in order to establish possible predictors of response (Cox, 1970).

Results

Table 2 shows demographic, clinical and pharmacological characteristics of the study population.

The application of a general linear model procedure showed the existence of a statistically

significant association between the response to treatment and the following independent variables: dose ($r = 0.407$, $P < 0.01$), total serum level ($r = 0.277$, $P < 0.01$), desipramine serum level ($r = 0.237$, $P < 0.01$), age ($r = 0.229$, $P < 0.01$), imipramine serum level ($r = 0.202$, $P < 0.05$), compliance ($r = 0.175$, $P < 0.05$) and duration of treatment ($r = 0.166$, $P < 0.05$).

The analysis of the correlation matrix among all the independent variables showed the presence of collinearity for the following variables: L/D(Imipramine), L/D(Desipramine), C_{ss}(Imipramine), C_{ss}(Desipramine), dose and C_{ss}(Total). This fact was supported by analysis of the last two eigenvalues of the correlation matrix ($\lambda_{18} = 0.0002$, $\lambda_{19} = 0.00014$). Due to this, classical regression techniques have no predictive power since the minimum squared estimates are not stable in the sampling. (Carbonell *et al.*, 1983). As a result we chose to use the technique of the principal components (new variables, linear combination of the original ones, but non-correlated) in order to determine which variables conditioned the response to treatment (Jolliffe, 1986; Sandford, 1985).

The correlation coefficient between the principal components and the response appear in Table 3.

Study of the importance of the original variables in the configuration of the principal components allows us to find indirectly, which of the indepen-

Table 2 Demographic and pharmacological data for the 146 patients

	Mean $\pm$ s.d.		Range
<i>Quantitative variable</i>			
Age (years)	9.0	2.5	5–14
Weight (kg)	30.9	9.3	16–52
Dose (mg kg ⁻¹ day ⁻¹)	1.53	0.52	0.37–3.34
L/D(Imipramine) (1 kg ⁻¹ day ⁻¹ $\times$ 10 ⁻³)	23.3	20.3	0.0–155.0
L/D(Desipramine) (1 kg ⁻¹ day ⁻¹ $\times$ 10 ⁻³)	33.0	41.1	0.0–242.0
L/D(Total) (1 kg ⁻¹ day ⁻¹ $\times$ 10 ⁻³)	56.2	52.4	0.0–5.20
Imipramine/desipramine	1.29	1.36	0.0–5.20
C _{ss} (Imipramine) (ng ml ⁻¹)	35.2	40.7	0.0–416.0
C _{ss} (Desipramine) (ng ml ⁻¹)	46.0	49.3	0.0–275.0
C _{ss} (Total) (ng ml ⁻¹)	81.3	37.7	0.0–486.0
Duration of treatment (days)	137.9	102.3	30–380
<i>Qualitative variable</i>			
	Percentage		
Sex	M (73)		F(27)
Number of side effects	0 (66), 1 (21), 2 (11), 3 (2)		
Enuresis type	PD (81), SD (10), PA (7), SA (2)		
Enuretic antecedents	A (64)		P (36)
Psychiatric antecedents	A (75)		P (25)
Intelligence quotient (I.Q.)	N (95)		Pt (5)
Related pathologies	A (43)		P (57)
Compliance	C (56)		NC (34)

M = male, F = female, P = present, A = absent, N = normal, Pt = pathological, C = compliance, NC = non-compliance.

dent variables analyzed are most associated with the response. The results of this analysis appear in Table 4. Although we tried to establish possible predictors of response, evaluated as a dichotomic variable (0 = no response) (1 = response) among all the independent variables analyzed, the results were not satisfactory (using the Cox regression method as the model (Fox, 1984).

Discussion

The outcome of a pharmacological treatment is conditioned by variables which depend on the patient, the illness and on the particular characteristics of the treatment itself. In our study, the analysis of those variables which most directly affect the antienuretic response has been carried out by means of simple correlation and multivariate analysis. This latter technique became necessary due to a methodologically complex situation: the independent variables were both quantitative and qualitative. Furthermore, some of them are strongly related, thus producing collinearity phenomena (Belsley, 1980). The utilization of two different methodologies could mean obtaining different results since simple correlation analysis takes each variable into account separately, whereas multivariate analysis takes in all the variables and their interrelations.

Table 3 Association between dependent variable (response) and principal components

Principal components	Correlation coefficient multiple	Statistical significance
1	0.25922	$P < 0.05$
2	0.12951	$P < 0.05$
3	-0.01172	NS
4	-0.32302	$P < 0.05$
5	0.04388	NS
6	0.08941	NS
7	0.02321	NS
8	0.13202	$P < 0.05$
9	-0.01991	NS
10	-0.05904	NS
11	0.00944	NS
12	0.15910	$P < 0.05$
13	-0.2635	NS
14	0.07714	NS
15	0.06530	NS
16	-0.13549	$P < 0.05$
17	0.10036	NS

In spite of this, there are no significant discrepancies in the results obtained in our study through both techniques, as can be seen in Table 5.

The results suggest that the enuretic children treated with imipramine show a greater probability of response to this treatment if: they are given an adequate dose of the drug for a long

Table 4 Significant correlation coefficients between patient variables and principal components

Variable	Principal component					
	4	1	12	16	8	2
Age						0.456
Weight						0.430
Dose	0.584					
L/D(Imipramine)				0.499		
L/D(Desipramine)		0.388				
L/D(Total)		0.439		0.316		
Imipramine/desipramine						0.402
Compliance	0.315				0.357	
C _{ss} (Desipramine)		0.398				
C _{ss} (Total)		0.446		0.369		
Duration	0.354		0.392			
Side effects					0.633	
Related pathologies			0.459			
I.Q.			0.486			
Psychiatric antecedents					0.364	

Table 5 Variables significantly associated with the response in decreasing order of importance, by simple regression and multivariate analysis

Simple correlation	Multivariate analysis
1 Dose	1 Dose
2 Total serum level	2 Duration of treatment
3 Metabolite serum level	3 Compliance
4 Age	4 Total serum level
5 Drug serum level	5 L/D(Total) ratio
6 Compliance	6 Metabolite serum level
7 Duration of treatment	7 L/D(Desipramine) ratio
	8 I.Q.
	9 Related pathologies
	10 L/D(Imipramine) ratio
	11 Side effects
	12 Psychiatric antecedents
	13 Age
	14 Weight
	15 Imipramine/desipramine ratio

enough period of time and if they are compliant. The magnitude of total serum level also has a significant influence on the outcome. Earlier studies published by us (Fernández de Gatta *et al.*, 1984) showed that a favourable response was obtained at levels greater than 80 ng ml⁻¹ in a smaller population.

The greater variability of serum levels in patients on the same imipramine dosage, along with the fact that the degree of compliance can be determined by the serum levels (Ereshefsky *et al.*, 1988; Perel, 1988), gives support to the utilization of monitoring drug levels in the treatment of enuresis with imipramine, since it makes it possible to control three of the four variables which are most related to a favourable response to this type of therapy.

Our results also suggest that the response to treatment with imipramine is conditioned neither by the enuresis type, the patient's sex, nor whether there were enuretic antecedents or not. The absence of drug serum level among those variables which are most closely related to the response is significant. This fact supports an adrenergic mechanism for the antienuretic action of tricyclics in view of the inclusion of the total and desipramine serum level among those variables. This fact agrees with the results found by Rapoport *et al.* (1980), in a population of 40 enuretic children.

Nevertheless, the nature of the study, the analysis of the data and the characteristics of the population studied should be considered when interpreting the results. The statistical method-

ology employed is useful for the screening of the data, which enables us to determine those factors which have a marked influence on the results observed. Further study is required for clarification of the mechanisms and the magnitude of the alterations observed since it cannot be clearly established from the data collected here. Moreover the scarce number of similar studies, and the discrepancies found among them, make it difficult for us to compare our results with others

(Jorgensen *et al.*, 1980; Kolvin *et al.*, 1973; Meadow, 1974). Besides, the variables chosen and the methodology used in each study are different.

We conclude that our results, based on a realistic patient population, help to clarify the relative importance of certain factors that affect the clinical response to the pharmacological treatment of enuresis with imipramine.

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