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Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine

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ABSTRACT **Tacrine has been studied in two clinical trials of identical design in patients with probable Alzheimer disease. One trial enrolled patients in the United States, while the other enrolled patients in France. A population pharmacodynamic model has been used to describe the cognitive component of the Alzheimer disease assessment scale (ADASC) using mixed effects nonlinear regression. The model parameters and their population variability and covariance were estimated by using NONMEM. During an observation period of up to 5 months, the rate of disease progression was 6.17 ADASC units/year. The effect of tacrine was described best by a shift in the disease progress curve (−2.99 ADASC units or 177.6 days at a dose of 80 mg/day). The placebo effects associated with tacrine and placebo treatment were similar in magnitude and time course. There was no evidence of tolerance to tacrine but tolerance to the placebo treatment developed during the study. The size of the placebo effect in the French population was 76% larger than in the United States population, and the response to placebo diminished more slowly in the French population.**

Tacrine has been studied in two clinical trials of identical design in patients with probable Alzheimer disease. One trial was in a United States population; the other was in a French population. Disease severity in these trials was assessed by using the cognitive component of the Alzheimer disease assessment scale (ADASC; ref. 1).

We report the results of an analysis of ADASC from these trials based on a nonlinear mixed effects model using NONMEM (2). The design of the trials, methodological aspects of model building and fitting, as well as parameter definition have been reported (3). The general applicability of this type of approach has been recently reviewed (4).

Data

Data from the United States (protocol 970-01) and French (protocol 970-04) studies were provided by the Biometrics Department, Parke–Davis. The following data sets were examined. (*i*) tacal114, all patients in both studies with an ADASC cognitive score on at least one visit. A total of 909 patients with 5253 observations were available. Various subgroups of tacal114 were examined for parameter validation. (*ii*) tacseq114, the subset of patients in tacal114 who were randomized to titration sequence 1—i.e., placebo, 40 mg of tacrine, 80 mg of tacrine. There were 304 patients with 1865 observations of ADASC. (*iii*) tacseq214, the subset of patients in tacal114 who were randomized to titration sequence 2—i.e., 40 mg of tacrine, placebo, 80 mg of tacrine. There were 310 patients with 1740 observations of ADASC. (*iv*) tacseq314, the subset of patients in tacal114 who were randomized to titration sequence 3—i.e., 40 mg of tacrine, 80 mg of tacrine, placebo (970-01). There were 295 patients with 1648 observations of ADASC. (*v*) tacdb14, all patients in both studies with an ADASC cognitive score during the double-blind placebo and active-comparison phases who had completed the active-comparison phase. Only observations made at the end of the double-blind placebo and during the active-comparison phases were included. A total of 315 patients with 1255 observations were available. (*vi*) tacal11, all patients in the 970-01 study with an ADASC cognitive score at any time. A total of 632 patients with 3527 observations were available. (*vii*) Jackknife, 10 subsets of the tacal114 data were created by systematically removing the observations for every 10th individual.

In addition, the influence of the covariates—size, renal function, age, and gender—was explored.

Body size was predicted by using total body weight, ideal body weight (IBW), or height. IBW was calculated from height and gender as follows: Men, IBW (kg) = 52 + 0.75 kg/cm over 152-cm height; women, IBW (kg) = 49 + 0.67 kg/cm over 152-cm height. Tacrine clearance was calculated from the patient's size covariate divided by the mean value for the size covariate in all patients. This mean value was 70 kg for total body weight, 60 kg for IBW, and 165 cm for height.

Predicted creatinine clearance was estimated by the following empirical formula (based on ref. 5):

$$CL_{cre} = (140 - age)/(250 \cdot S_{cre}/11.3) \cdot wt/70.$$

The value is reduced by 10% in women. When age is in years, serum creatinine (S_{cre}) is in mg/dl, and weight (wt) is in kg; the units of clearance are liters/hr. Renal function was calculated as a fraction of a nominal average value of 6 liters/hr. Tacrine clearance was adjusted by multiplying it by renal function.

The potential influence of age and gender on tacrine response was examined by multiplicative scale parameters applied to the tacrine potency parameter β_a.

Results

Model Building. The results of model building described in ref. 3 are summarized in Table 1. The 970-01 and 970-04 patients were distinguished by the application of a protocol scale parameter to certain critical parameters of the model. The protocol scale parameter had a value of 1 for the 970-01 observations and was adjusted to provide the best fit to the 970-04 observations. The parameter that had the largest numerical offset in reducing the objective function was the placebo potency scale factor $F\beta_p4$. The combination of scale parameters that best described the data was based on differences in the baseline disease status, FS_o4, the potency of placebo, $F\beta_p4$, and the apparent elimination half-time of the placebo, $Ft_{1/2,el,p}4$. The improvement in the objective function

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Abbreviations: ADASC, Alzheimer disease assessment scale; IBW, ideal body weight.

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Table 1. Model building and validation

Model description	$N\theta$	ΔObj	Conclusion
Protocol 04 scale factor for tacrine potency (β_a)	12	−2.26	$F\beta_p4$ = 0.8; not different from 1
Protocol 04 scale factor for disease progression (α)	12	−1.61	$F\alpha_4$ = 1.2; not different from 1
Influence of female gender (FSEX) on β_a	12	−0.55	FSEX = 0.9; not different from male
Placebo efficacy (ADDP)	12	−0.51	ADDP = 1.12; not different from 1
Change in β_a per year of age (FAGE)	12	−0.063	FAGE = −0.002; no influence of age
Tacrine tolerance factors (TOL_{50}, TTOLA)	13	−0.059	TOL_{50} = 994 mg/dl, TTOLA = 55 days; no tolerance to tacrine
E_{max} model for tacrine	12	−0.001	E_{max_a} = −230, ED_{50_a} = 6020 mg/day; not better than linear pharmacodynamic model
Clearance corrected using size = IBW	11	0*	Final model
Clearance corrected using size = height	11	0.2	β_a = 3.16; IBW correction slightly better
Clearance not corrected for size	11	2.69	β_a = 3.17; size correction better
Additive population error	11	13.25	Proportional error better
Slope model (T_{eq_a} fixed = 0.001)	10	27.9	Offset model better
No placebo tolerance ($T_{tol,p}$ = 0)	10	53	Placebo tolerance better
All tacrine doses used as if the same unit dose	11	144	Tacrine-related effect exists, which is dependent on dose size
No activity of tacrine (β_a = 0)	9	150	β_a must be nonzero
Covariance of S_o, α, β_a	11	404	Covariance important
No activity of placebo (β_p = 0)	4	†	β_p must be nonzero

$N\theta$, number of model parameters; ΔObj, change in objective function from full model to reduced model.
*Reference objective function value = 22,012.5.
†Model failed to iterate.

was small when scale parameters were estimated for disease progression rate (α) and tacrine potency (β_a).

The objective function was reduced by 53 units with the addition of a single parameter—$t_{1/2,tol,p}$, the half-time of tolerance to placebo. The addition of an $Ft_{1/2,tol,p}$ parameter to distinguish the tolerance half-time in the 970-04 patients produced a further small change of the objective function but not large enough to consider it an important effect.

The influence of age and gender was examined to determine whether they were predictors of response. There was no apparent influence of age or gender on tacrine potency (β_a).

IBW (calculated from height and gender) decreased the objective function when it was used to predict tacrine clearance. Almost the same improvement was obtained from the use of height alone. The objective function was larger when total body weight was used as a predictor of tacrine clearance. No improvement in the fit was obtained by predicting clearance from renal function derived from creatinine clearance.

The variation among individuals was described better by a model that assumed a proportional error function than by an additive error function. When population variability was assumed to be 0 for all parameters, the objective function was substantially larger.

The common parameters for the two groups of patients estimated using the placebo tolerance model ($t_{1/2,tol,p}$) and protocol scale parameters for baseline status, placebo potency, and placebo elimination half-time (FS_o4, $F\beta_p4$, $Ft_{1/2,el,p}4$) are shown in Table 2. The correlation of baseline ADASC score at the start of titration (S_o) with the potency of tacrine (β_a) was 0.31; the correlation of S_o with the ADASC progression rate (α) was 0.37, while the correlation of β_a with α was 0.52.

Validation of Model. The results of models used for validation are shown in Table 1. The validity of the structural model was tested by fixing either tacrine potency (β_a) or placebo potency (β_p) at 0. Both of these models substantially worsened the fit, indicating that there was an association between both tacrine and placebo and the observed change in ADASC. The fit to the model, which proposes an active drug effect on the disease progression rate (slope model), was not as good compared with an effect shifting the disease progression curve (offset model). The effect of tacrine was shown to be related to dose rate by comparing the fit with a model in which all tacrine doses were treated as if they were identical. This fit was substantially worse than the linear model relating tacrine dose to ADASC change. A nonlinear E_{max} model relating tacrine dose to ADASC was no better than a linear model. There was no evidence to support the existence of tolerance to active drug by the tolerance factor model. The efficacy of the placebo response with active treatment was essentially the same as that due to placebo treatment.

Validation of Parameter Estimates. The parameter estimates of the full model were compared with those from subsets of the taca1114 data (Table 3). Removal of the 970-04 protocol observations produced small differences in the estimates of β_a and α. There were substantial differences in the estimates of β_p and placebo elimination half-time. There was also a large increase in the placebo tolerance half-time. This reflects the poor identifiability of these parameters in the model. The differences are unimportant, however, because the other parameters of the model—for example, α and β_a—were stable when different values were obtained from the combined analysis.

When estimates were based only on observations from the time of entering the placebo washout phase after titration in

Table 2. Full data set parameter estimates

Parameter class	Parameter	Estimate	SE	Population CV, %	SE CV
Disease	S_o units	28.7	0.44	37.7	7.8
	α units/year	6.17	1.27	208	141
Pharmaco-dynamic	β_a units/80 mg/day	−2.99	0.67	126	74
	β_p units	−1.42	0.20	128	70
	Delay* days/80 mg/day	177.6	41.7		
Pharmaco-kinetic	$t_{1/2,eq,a}$ days	20.9	6.0		
	$t_{1/2,el,p}$ days	61.0	28.6		
	$t_{1/2,eq,p}$ days	1.58	0.56		
	$t_{1/2,tol,p}$ day	13.5	3.4		
Scale	FS_o4	1.08	0.03		
	$F\beta_p4$	1.76	0.25		
	$Ft_{1/2,el,p}4$	2.78	1.09		
Error	SD ADASC	3.14	0.08		

CV, coefficient of variation.
*Model parameterized using Delay [predicted postponement of disease progression (days) with tacrine at 80 mg/day] as a parameter instead of β_a.

Table 3. Parameter estimates from validation subsets

Parameter	tacal114	tacal11	tacdb114	tacseq114	tacseq214	tacseq314
S_o	28.7	28.6	34.8	29.3	27.9	28.4
α	6.2	4.3	11.4	5.8	5.0	3.8
β_a	−3.0	−2.5	−10.4	−2.8	−3.2	−2.0
β_p	−1.4	−3.2	−2.6	−1.1	−1.2	−1.1
$t_{1/2,eq,a}$	20.9	16.3	114	25.8	16.8	8.2
$t_{1/2,el,p}$	61	6.72	67.2	49.5	35.7	41.7
$t_{1/2,eq,p}$	1.58	6.69	1.55	1.25	0.94	1.10
$t_{1/2,tol,p}$	13.5	320	76.1	20.9	24.3	73.3
FS_o4	1.08	—	0.91	1.05	1.14	1.08
$F\beta_p4$	1.76	—	0.81	1.84	1.68	1.91
$Ft_{1/2,el,p}4$	2.78	—	1.97	1.92	1.74	1.61
Delay	177	212	332	177	232	190

Delay, predicted postponement of disease progression (days) with tacrine at 80 mg/day.

patients who completed the double-blind best-dose phase, there was a marked increased in β_a. This is expected because patients in this group had been selected as responders during the titration phase. The difference in placebo response associated with the French population was no longer marked in this posttitration data set (tacbd14).

Analysis of titration sequence subgroups based on the order of treatments in the enrichment phase did not reveal any marked differences in response to tacrine or placebo except for slower development of tolerance to placebo in patients who received tacrine at 80 mg/day before placebo.

The mean and standard error of the jackknife estimates of the parameters based on 10 subgroups were very similar to the parameter estimates and their asymptotic standard errors estimated from the full data set (Table 4).

Log-Likelihood Profile. The relation between selected parameter estimates and the NONMEM final objective function value was defined by fixing the parameter to values close to the final estimate and reestimating the other parameters of the model. The resulting changes in the objective function values were plotted as a function of the fixed parameter value and a smooth curve interpolated by using a cubic spline.

Confidence Interval for Tacrine Effect. Confidence intervals for the effect of tacrine on ADASC were constructed for the β_a and delay $[(\beta_a)/\alpha]$ parameters by defining a log-likelihood profile for each parameter (Figs. 1 and 2). The effect of tacrine on disease progress can be described in terms of the potency of tacrine, β_a, in producing a vertical shift in the disease progress curve or, in combination with the disease progression rate (α), a delay can be calculated that defines the time that would pass before the disease returns to the same state as at the start of active treatment. For the purposes of defining a confidence interval for this parameter, the model for tacrine effect was parameterized in terms of delay instead of β_a. The value of β_a was then calculated from −delay × α to predict the effect of tacrine at any point in time.

The 95% confidence interval was estimated from the log-likelihood profile at 3.84 units from the minimum (6). The confidence interval for β_a was −4.45 to −1.99 ADASC units·80 mg^{-1}·day^{-1} and for delay it was 120–270 days·80 mg^{-1}·day^{-1}.

Table 4. Jackknife estimates of full-model parameters and their SE

	Jackknife	
Parameter	Mean	SE
S_o	28.6	0.39
α	6.2	1.06
β_a	−3.0	0.80
β_p	−1.4	0.17
Delay	173	55.5
$t_{1/2,eq,a}$	21.2	5.65
$t_{1/2,el,p}$	51.4	32.7
$t_{1/2,eq,p}$	2.27	1.42
$t_{1/2,tol,p}$	12.2	2.61
FS_o4	1.08	0.03
$F\beta_p4$	1.81	0.20
$Ft_{1/2,el,p}4$	2.55	1.12

Delay, predicted postponement of disease progression (days) with tacrine at 80 mg/day.

Discussion

We have developed a model for the time course of ADASC progression in patients with Alzheimer disease and for the effect of active or placebo treatment on ADASC. The model is able to accommodate the actual times of a variety of treatment sequences and does not require that all patients complete all phases of a trial. Important untested assumptions of the model are the independence and additivity of factors predicted to influence ADASC status. These factors include disease progression and treatment with active drug or placebo.

The estimated rate of progression of ADASC from patients who were enrolled in two large clinical trials of tacrine was similar (6.2 units/year) to that estimated from a group of untreated patients over at least a 6-month follow-up period (8.2 units/year; ref. 7). The baseline disease status of 28.7 units can be compared to 23.2 units in the 27 patients used to validate the ADASC scale (1) and 25.1 units at baseline in 30 patients involved in a longitudinal study (7).

The model provides strong evidence for the existence of responses to placebo and active drug. The placebo component of the response associated with active treatment is

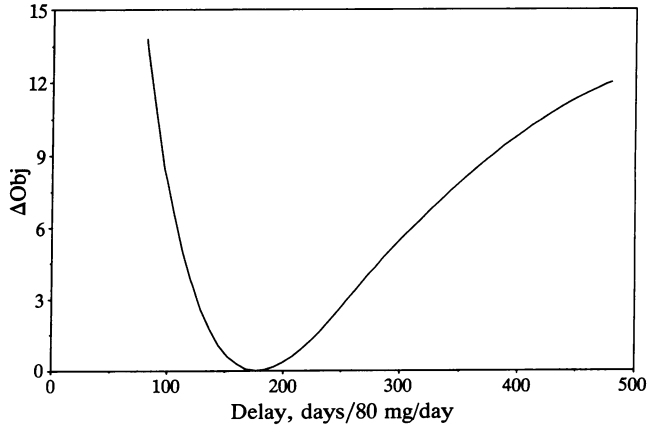

FIG. 1. Log-likelihood profile for the tacrine potency parameter β_a.

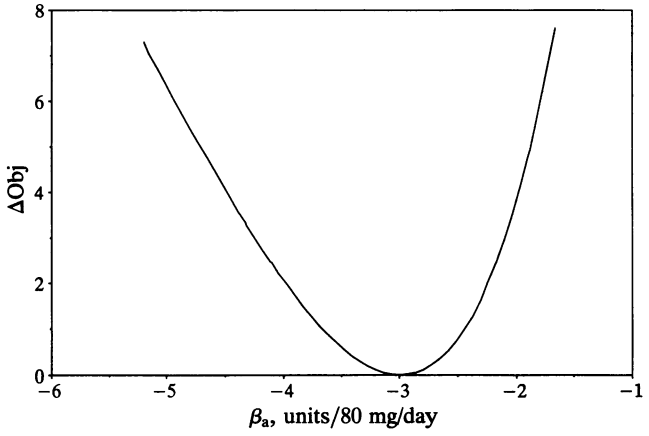

FIG. 2. Log-likelihood profile for tacrine potency parameterized as the delay in disease progression.

indistinguishable in magnitude from the response due to a placebo treatment—i.e., the placebo efficacy of active drug is the same as placebo alone. The response to placebo and to active drug is delayed with respect to the start of treatment.

The delay in onset of tacrine response cannot be due to the time for it to produce inhibition of cholinesterase in the brain because tacrine readily penetrates into the central nervous system and produces rapid effects on cholinesterase activity in animal models (8). The short half-life of tacrine (≈2 hr; ref. 9) also appears to rule out a pharmacokinetic mechanism based on slow accumulation. The 3-week equilibration half-time for the effect of tacrine may be explained by the slow change in the level of a physiological substance that modifies cognitive function.

The slow response to placebo, and subsequent waning of the response, seems reasonable in terms of the expectation of a patient and care giver participating in a clinical trial.

The response to tacrine is best described by an effect on the location parameter of a linear disease progression model. An alternative model based on an effect on the slope of the disease progression model did not fit as well but it should be recognized *a posteriori* that the experimental design cannot be considered adequate to estimate such a type of effect. After due allowance for the delay in tacrine response, the effect appears to be a linear function of tacrine dose rate. There was no suggestion that the effect was approaching a plateau in the dose rate range that was studied.

There was a positive correlation between the baseline disease state, S_0, and both the rate of disease progression and tacrine potency. This implies that patients who initially had worse disease appeared to progress more quickly (if untreated) but also had a better response to tacrine.

The population variability model indicated that there were large intersubject differences in disease progression rate and potency of tacrine and placebo (see Table 1). The distribution of these parameters in the population was described somewhat better by a proportional error model than by an additive model and a lot better than assuming no intersubject variability.

Because the response to tacrine is slow in relation to its half-life in plasma, it seems reasonable to propose that the response may be proportional to the average steady-state concentration of tacrine in the body. This can be predicted from the tacrine dose rate and clearance. Clearance could not be estimated directly, but potential relationships between body size and tacrine clearance were explored. The use of IBW or height as predictors of clearance produced a small improvement in the fit, while total body weight made it worse. Tacrine is eliminated largely by metabolism and it would be reasonable to expect that clearance would be overestimated by total body weight in overweight patients. This may account for the worsening of the fit when total body weight was used to predict clearance. As expected, there was no predictive power associated with using creatinine clearance as a measure of the clearance of active substance. This negative finding also suggests that there would be no difference in the response to tacrine in patients with renal impairment due to associated changes in cholinergic neuronal function or accumulation of an unidentified active metabolite that is renally cleared.

Neither age nor gender was able to predict the potency of tacrine. Other measures such as premorbid smoking history or ethanol use were not tested but could possibly be of predictive value.

It is interesting that there appeared to be quite strong similarities in the rate of disease progression and response to tacrine in the United States trial (970-01) and the French trial (970-04). However, the magnitude of the placebo response appeared to be greater and disappeared more slowly in the French patients. This may reflect differences due to the cultural milieu, which modify the behavioral response to drugs but are independent of pharmacological activity.

The application of a parametric population-based model to the description of two large clinical trials has confirmed the results of previous analyses in establishing that tacrine has an effect distinguishable from placebo (10, 11). Because the population models used the observations from all subjects, without selection on either the basis of response, or tolerance of side effects, or willingness to continue participation in an extended clinical trial, it is likely that the size of the response to tacrine is more typical of what might be expected in clinical use of the drug. The descriptive features of the model also allow some explanation of the time course of the disease and the response to treatment, which may be helpful in evaluating response in individuals and in planning further clinical investigations.

The wide variation in response measured by the population coefficient of variation of the principal structural model parameters and the positive correlation between response to treatment and disease state suggests that the benefit of tacrine to some patients may be greater than the parameter estimates suggest. At the same time, these observations also imply that some patients may be unlikely to show any benefit. The demonstration of a linear dose–response relationship implies that greater benefit might be expected from higher doses if they are tolerated and adjustment of the dose according to IBW may confer some advantage in individualization of treatment.

Whether the benefit of a delay in disease progression of the magnitude predicted by this analysis is important enough to a patient and his/her family in relation to the adverse effects is not addressed. We note, however, that a "minimum target . . . putting them back to where they were six months ago" (G. K. Wilcock, ref. 12) has been suggested as beneficial, and the size of the effect of 80 mg of tacrine per day predicted for ADASC meets this target.

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1. Rosen, W. G., Mohs, R. C. & Davis, K. L. (1984) *Am. J. Psychiatry* **141**, 1356–1364.
2. Beal, S. L. & Sheiner, L. B. (1980) *Am. Stat.* **34**, 118–119.

3. Holford, N. H. G. & Peace, K. E. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 11466–11470.
4. Rowland, M. & Aarons, L. (1992) *New Strategies in Drug Development and Clinical Evaluation: The Population Approach.* (Commission of the European Communities, Brussels), Rept. EUR 13775.
5. Bjornsson, T. D. (1979) *Clin. Pharmacokinet.* **4**, 200–222.
6. Boechmann, A., Sheiner, L. B. & Beal, S. (1990) *NONMEM Users Guide* (NONMEM Project Group, Univ. of California, San Francisco), Part 5.
7. Yesavage, J. A., Poulson, S. L., Sheikh, J. & Tanke, E. (1988)*Psychopharmacol. Bull.* **24**, 531–534.
8. Davis, R. E., Coughenour, L. L. & Gamzu, E. (1991) *Soc. Neurosci. Abstr.* **13**, 487.
9. Forsyth, D. R., Wilcock, G. K., Morgan, R. A., Truman, C. A., Roberts, C. J. C. (1989) *Clin. Pharmacol. Ther.* **46**, 634–641.
10. Department of Health and Human Services, Public Health Service, Food and Drug Administration (1991) *Peripheral and Central Nervous System Drugs Advisory Committee, March 15, 1991* (Transcript: Miller Reporting Company, 507 C Street, N.E., Washington, DC 20002).
11. Davis, K. L., Thal, L. J., Ganzu, E., Davis, C. S., Woolson, R. F., Gracon, S. I., Drachman, D. A., Schneider, L. S., Whitehouse, P. J., Hoover, T. M., Morris, J. C., Kawas, C. H., Knofman, D. S., Earl, N. L., Kumar, V., Doody, R. S. & the Tacrine Collaborative Study Group (1992) *N. Engl. J. Med.* **327**, 1253–1259.
12. Laurence, J. (1991) *The Times* (London), Oct. 3, 1991, p. 13.