A MATHEMATICAL MODEL FOR PAROXETINE ANTIDEPRESSANT EFFECT TIME COURSE AND ITS INTERACTION WITH PINDOLOL

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INTRODUCTION

The problem of the delay of onset of therapeutic benefits is approximately the same for all available antidepressants. Selective 5-HT reuptake inhibitors (SSRIs) block monoamine uptake within hours of administration, but their full clinical effect does not appear until 2-4 weeks after treatment onset. Pindolol, a betablocker with weak partial 5-HT_{1A} receptor agonist activity has been shown to decrease the delay of action of SSRIs. Howewer, the optimal dosing schedule of pindolol remains controversial.

OBJECTIVES

To develop a new class of PK-PD models in order to describe the time course of the effect (clinical score) of SSRIs and to simulate the influence of pindolol on paroxetine clinical response in order to define the optimal dosing schedule.

MATERIALS AND METHODS (1)

Set-point model for kinetics of SSRI action :

• The model is based on the concept of homeostatic control mechanisms, in which SSRIs exert their antidepressant effect by increasing the transduction set-point of the postsynaptic 5-HT_{1A} receptor and pindolol increases the rate of feedback mechanisms.

• This model is described by the following set of differential equations :

$d\theta/dt = K_T.(\varphi^{\gamma} - \theta)$ $\quad \theta(0) = \theta_0$ = set-point

$d\varphi/dt = K_F\,[1 + h(PL))\,(\theta - \theta_0[1 + f(I)])$ $\quad \varphi(0) = \varphi_0$

Where :

θ = postsynaptic 5-HT_{1A} receptor transduction level — **φ = feedback signal**

h (PL) =Hill model for pindolol effect — **f (I) = Hill model for SSRI effect**

K_T = rate constant associated with the variation of T — **K_F = rate constant for feedback signal**

γ = amplification factor

• The kinetics of SSRI and pindolol cerebral concentration were described as a zero-order input in a single compartment, with a first-order elimination rate constant, respectively K_I and K_{PL} associated with drug elimination. So, the SSRI cerebral concentration as a function of time t, was described as follows :

$I/I_{50} = (R_I/K_I)\,(1 - e^{-KIt})$ **where R_I is the single parameter related to SSRI dosing rate**

In the same way, pindolol cerebral concentration was described as follows:

$PL/PL_{50} = (R_{PL}/K_{PL})\,(1 - e^{-KPLt})$ **where R_{PL} is the single parameter related to pindolol dosing rate.**

• The transduction set point is lower in depressed patients (θ_0<1) than in healthy subjects (θ_0 = 1). In a treated patient, the SSRI increases the transduction signal by increasing the set-point.

• The clinical response to paroxetine (assessed with the MADRS scale) is related to transduction θ by a Hill-type model.

Estimation of the parameters in a specific example :

• The study used to estimate the parameters was a double-blind, randomized, placebo-controlled, parallel groupe study performed in 80 outpatients with major depression (1). All patients received paroxetine (20 mg once a day) plus either pindolol (2.5 mg three times a day) or matching placebo for 6 weeks.

• The parameters were estimated by non-linear regression (WLS) using the data reported in the clinical trial (1). The objective function to be minimised was based on the comparison between the proportions P_i of treatment responders observed at several time points t_i and the expected proportions π_i estimated by population simulation based on the model and the experimental conditions in (1).

• The goodness-of-fit was assessed by a predictive check.

Simulations for assessing the impact of dosing rate :

• The score simulations on the MADRS scale with different doses of paroxetine and pindolol for a single typical individual, were performed using ADAPT II software. The parameters of the model were set to the mean values estimated from the data of the study by Tome (1) .

RESULTS

• The parameter values estimated by non-linear regression are presented in Table I.

• The predictive check is illustrated in figure 1 and 2. Since no lack-of-fit arises, the model and the parameter values are compatible with experimental data.

• The simulated clinical score of a typical patient treated with paroxetine associated with 3 different doses of pindolol are illustrated in Fig 3. The time required to achieve a clinical response decreases when the dose of pindolol increases : this time is about 18 days without pindolol, 13 days with pindolol 1.5 mg/day, 9 days with pindolol 7.5 mg/day and 5 days with pindolol 37.5 mg/day. Pindolol does not increase paroxetine efficacy since, at steady state, the MADRS score obtained with paroxetine alone or with paroxetine plus pindolol at different dosing rates, leads to the same value.

Table I : Estimates of the parameters of the set-point model after fitting to the data of Tome study (1)

Parameter	Value
θ_0	0.47 (fixed)
φ_0	1.25
K_T (d^{-1})	10 (fixed)
K_F (d^{-1})	0.06
s	0.30
K_I (d^{-1})	1.2
R_I (d^{-1})	3.5 (for 20 mg/d)
K_{PL} (d^{-1})	3.33
R_{PL} (d^{-1})	2.23 (for 7.5 mg/d)
Sm_I	0.92
Sm_P	2.7

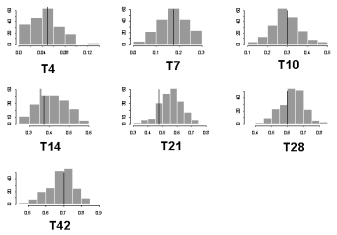

Fig.1 : Predictive check of the set-point model. The histograms show the predictive distribution of the proportions of responders at day 4, 7, 10, 14, 21, 28, 42 in patients treated by paroxetine 20 mg/d. The vertical lines show the observed proportion in the study by Tome (1).

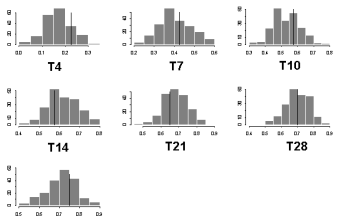

Fig.2 : Predictive check of the set-point model. Same as fig 1 but patients treated by paroxetine 20 mg/d AND pindolol 7.5 mg/d.

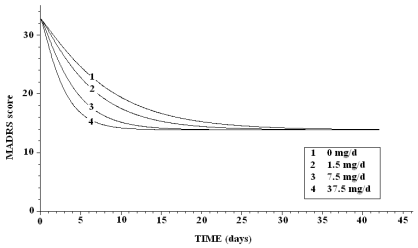

Fig 3 : simulation of the time course of the clinical score (MADRS) of a typical patient treated by paroxetine (20 mg/day) alone or associated with pindolol at 3 dosing rates (1.5 mg/day, 7.5 mg/day and 37.5 mg/day)

DISCUSSION

Properties of the set-point model :

• The general properties of the model are (i) no effect when no drug is given, (ii) SSRIs and pindolol reach a maximal effect at high dose, (iii) no effect of SSRIs and pindolol in healthy subjects because the score decreases marginally when $\theta > 1$, (iv) at steady state, after treatment with a SSRI, θ is restored to the value of healthy subjects, (v) pindolol reduces the delay of action of SSRIs but does not increase their maximal efficacy and has no antidepressant effect by itself.

• A simple indirect response model for transduction would lack two important features. (1) it could not describe the effect of pindolol. Indeed, the action of pindolol would have to be described either by increasing the rate of production or by decreasing the rate of elimination of the response, resulting in an increase of the equilibrium level, *i.e.* an antidepressant effect. (2) a simple indirect response model could not accommodate an oscillatory behaviour of the response *i.e.* fluctuations in the level of mood.

Extrapolations based on the model :

• The simulated MADRS score obtained after treatment with paroxetine alone (20 mg/d) or paroxetine (20 mg/d) + pindolol (7.5 mg/d) are in accordance with the experimental scores observed in several clinical trials.

• The model suggests that a fivefold increase of pindolol dosing rate compared with the usual dose would result in a mean reduction of 4 days in the delay of action of paroxetine.

• The model has also been fitted to the data of a clinical trial with fluoxetine (data not shown).

• The model may be suitable for clinical trial simulation.

REFERENCE: Tome MB et al.. Paroxetine and pindolol : a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *Int. Clin. Psychopharmacol.* 12 : 81-89 (1997).