

# Simple approach to predict the maximal effect elicited by a drug when plasma concentrations are not available or are dissociated from the effect, as illustrated with chondroitin sulfate data

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The analysis of the relationship between the pharmacologic response of a drug and its dose or its plasma concentrations is essential to determine the adequate dosage to use, to evaluate the benefits and the risks of dosage adjustment, to compare its potency with that of other drugs, and to predict the repercussions on the effect of drug-drug interactions. The analysis of the changes of the response as a function of the plasma concentrations of a drug allows prediction of the maximal effect ( $E_{max}$ ) elicited by the drug and the concentration eliciting 50% of  $E_{max}$  ( $EC_{50}$ ). Estimation of  $E_{max}$  and  $EC_{50}$  with the  $E_{max}$  model<sup>1</sup> is simple whenever the relationship between response and plasma concentrations is direct (ie, the relationship depicts a hyperbola).

The  $E_{max}$  model does not allow analysis of the effect-concentration relationship of every single drug, since there are drugs that are not absorbed such as cholestyramine and colestipol, drugs generating low to undetectable plasma concentrations such as alendronate, drugs rapidly degraded to compounds with lower molecular weight, such as hyaluronic acid, chondroitin sul-

fate, and glucosamine, drugs originating many active metabolites such as antipsychotic agents, and drugs eliciting an effect that is measurable after a long period of exposure, such as hormones, antidepressants, alendronate, chondroitin sulfate, and the like. Under all these circumstances, the analysis of the effect-concentration relationship with the  $E_{max}$  model may be difficult or impossible. Furthermore, for the venue of gene therapy, with the use of recombinant proteins and other natural products, the method to assay the plasma concentrations of the active compound may be less accessible and make more difficult the calculation of  $E_{max}$  and  $EC_{50}$ .

This study aimed to put forward a simple approach to assess  $E_{max}$  when the plasma concentrations of the active moiety are not available, when the kinetics and the time course of the dynamics are dissociated, when multiple active compounds are present, when several drugs are used to reach the same goal, when there is a cumulative effect as a function of time, and when an effect is to be assessed in the absence of drug therapy. The proposed method is not a substitute for the  $E_{max}$  method but may be an alternative approach in situations where the  $E_{max}$  method cannot be applied.

The approach proposed to estimate  $E_{max}$  was validated by analyzing the pharmacologic response to chondroitin sulfate in patients with knee osteoarthritis from the data reported by Morreale et al<sup>2</sup> and Pavelka et al.<sup>3</sup> Chondroitin sulfate is a slow-acting drug for the treatment of osteoarthritis, characterized by a slow onset of action over 2 or 3 weeks and with a maximal effect being attained several months later, an effect that persists after cessation of therapy.<sup>4</sup> Chondroitin sulfate is a sulfated glycosaminoglycan that is rapidly

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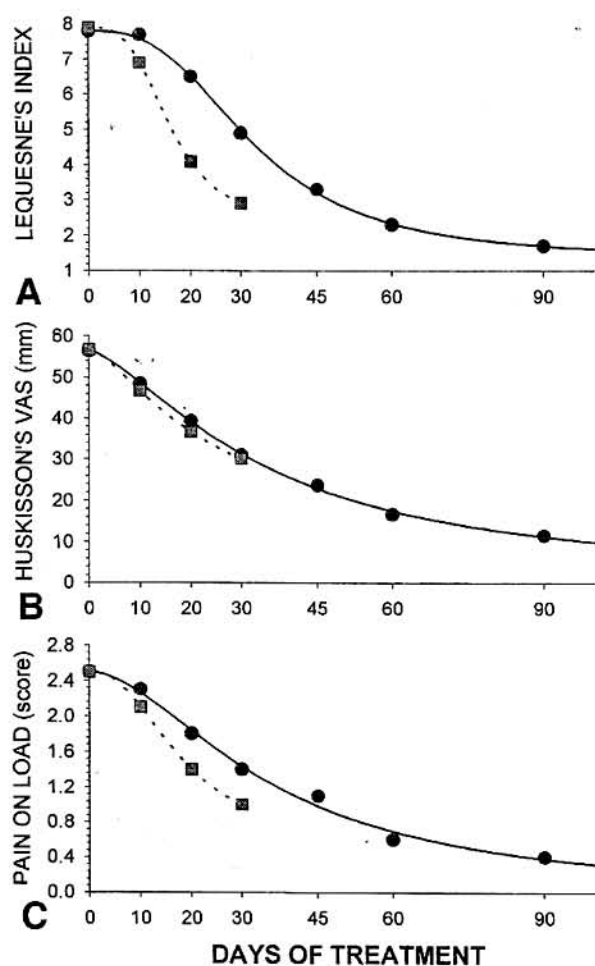
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**Fig 1.** Average observed and predicted algofunctional (A, index of Lequesne et al<sup>10</sup>) and antialgesic (B, VAS of Huskisson et al<sup>11</sup>; C, pain on load) scores in response to oral chondroitin sulfate 1200 mg/d for 90 days (n = 74) and diclofenac sodium 150 mg/d for 30 days (n = 72) in patients with knee osteoarthritis. Data from Morreale et al.<sup>2</sup>

degraded during its absorption and by an extensive first-pass metabolism; the active moiety remains unknown.<sup>5,6</sup> The assay of chondroitin sulfate and its derivatives in plasma has allowed the estimation that in man the half-life of total chondroitin sulfate is around 15 hours<sup>7,8</sup> (ie, steady state is attained in 3-4 days); however, approximately 3 to 6 months is required to obtain the maximal effect.<sup>4</sup>

The proposed approach is based on the fact that in the absence of tolerance the pharmacologic response will increase as a function of time until it reaches the maximal effect. Graphic representation of the changes of the pharmacologic response as a function of time

**Table I.** Predicted pharmacodynamic parameters of chondroitin sulfate given at dose of 1200 mg/d for 90 days (n = 74) and diclofenac sodium given at dose of 150 mg/d for 30 days (n = 72) to patients with knee osteoarthritis (original data from Morreale et al<sup>2</sup>)

	Chondroitin sulfate	Diclofenac sodium
Index of Lequesne et al <sup>10</sup>		
E <sub>0</sub> (score)*	7.8 ± 0.4	7.9 ± 0.4
E <sub>max</sub> (score)	6.4	5.7
E <sub>max</sub> /E <sub>0</sub> (×100)	82	72
T <sub>50</sub> (d)	33	16
γ	2.8	3.3
VAS of Huskisson et al <sup>11</sup>		
E <sub>0</sub> (mm)*	56.4 ± 1.9	56.7 ± 2.2
E <sub>max</sub> (mm)	56	43
E <sub>max</sub> /E <sub>0</sub> (×100)	99	76
T <sub>50</sub> (d)	35	22
γ	1.5	1.5
Pain on load		
E <sub>0</sub> (score)*	2.5 ± 0.1	2.5 ± 0.1
E <sub>max</sub> (score)	2.5	1.9
E <sub>max</sub> /E <sub>0</sub> (×100)	100	74
T <sub>50</sub> (d)	36	18
γ	1.8	2.3

E<sub>0</sub> is the baseline value at the day of entry into the trial; E<sub>max</sub> is the predicted maximal effect after single or multiple administrations of a drug; T<sub>50</sub> is the time required to achieve 50% of E<sub>max</sub>; γ is an exponential for sigmoid effects.  
\*Values are mean ± standard error of the mean.

elicits a hyperbola defined by a modified Hill equation<sup>9</sup> as follows:

$$E = E_0 + \frac{E_{\max} \cdot T^\gamma}{T_{50}^\gamma + T^\gamma}$$

where E<sub>0</sub> is the baseline value of the effect being measured at the day of entry into the trial, E<sub>max</sub> is the predicted maximal effect after single or multiple dosing of a drug and reflects the difference between E<sub>0</sub> score and the score predicted at the peak effect, T is the time at which the effect is measured, γ is an exponential for sigmoid effects, and T<sub>50</sub> is the time required to achieve 50% of E<sub>max</sub>. When the pharmacologic effect is measured after multiple dosing, a prerequisite for this approach is the use of a fixed dose.

In a randomized, double-blind, parallel group study, Morreale et al<sup>2</sup> treated 74 patients with knee osteoarthritis with 400 mg of chondroitin sulfate 3 times a day for 90 days and 72 patients with 50 mg of diclofenac sodium 3 times a day for 30 days. The authors assessed treatment efficacy with the "algofunctional" index of Lequesne et al<sup>10</sup> and pain with the 100-mm visual analog scale (VAS) of Huskisson et al,<sup>11</sup> as

**Table II.** Effect of dose on functional and antialgesic effect of chondroitin sulfate administered for 90 days to 35 patients per group with knee osteoarthritis

	<i>Chondroitin sulfate</i>			
	<i>Placebo</i>	<i>200 mg</i>	<i>800 mg</i>	<i>1200 mg</i>
Index of Lequesne et al <sup>10</sup>				
$E_0$ (score)*	12.2 ± 0.4	11.8 ± 0.4	11.0 ± 0.4	11.4 ± 0.4
$E_{max}$ (score)	3.3	5.3	7.7	7.1
$E_{max}/E_0$ (×100)	27	45	70	62
$T_{50}$ (d)	10	45	50	40
$\gamma$	1.1	1.0	1.0	1.1
VAS of Huskisson et al <sup>11</sup>				
$E_0$ (mm)*	71 ± 2	70 ± 2	70 ± 2	69 ± 2
$E_{max}$ (mm)	16	25	51	45
$E_{max}/E_0$ (×100)	23	36	73	65
$T_{50}$ (d)	5	24	25	20
$\gamma$	0.6	0.4	0.7	0.5

Original data from Pavelka et al.<sup>3</sup>

\*Values are mean ± standard error of the mean.

patients with the same characteristics, algofunctional and antialgesic effects of chondroitin sulfate appear similar to those predicted for diclofenac sodium, although the time to elicit an effect ( $T_{50}$ ) is longer with chondroitin sulfate than with diclofenac sodium. In patients with more severe osteoarthritis,<sup>3</sup> the  $E_{max}$  predicted by chondroitin sulfate suggests that the baseline values of algofunctional and pain parameters can be reduced by as much as 70%; in these patients, a reduction of the pain to 50%  $E_{max}$  will be achieved more rapidly than will an amelioration of the algofunctional response. It should be noted that  $T_{50}$  was not shortened by doses greater than those needed to elicit  $E_{max}$ . The use of the modified  $E_{max}$  model confirms that in patients with knee osteoarthritis the predicted  $E_{max}$  is greatest with a daily dose of 800 mg.

The values of  $\gamma$  were more sensitive to the severity of the disease, as defined by the baseline score values, and to the parameter considered than were  $E_{max}$  and  $T_{50}$ . The severity of the disease diminished the value of  $\gamma$ , suggesting that chondroitin sulfate should elicit an effect more readily in severe cases of osteoarthritis even if  $T_{50}$  is longer. It is of note that for any of the parameters assessed the value of  $\gamma$  estimated with the use of placebo was not modified by increasing dosages of chondroitin sulfate, even if the  $T_{50}$  of placebo was approximately one fourth the  $T_{50}$  estimated with chondroitin sulfate. The values of  $\gamma$  estimated with chondroitin sulfate treatment were similar to those obtained with diclofenac sodium, suggesting that  $\gamma$  is determined predominantly by the severity of disease rather than by the drug or its dosage.

Simulations with the data generated by the modified  $E_{max}$  model for chondroitin sulfate and diclofenac sodium suggest that the time to reach 90% of  $E_{max}$  depends on  $T_{50}$  and  $\gamma$  values. When  $\gamma$  is  $\geq 1.4$ , it is possible to predict that 90% of  $E_{max}$  will be reached after  $\leq 5$ -fold  $T_{50}$  (ie, after approximately 180 days of treatment for the patients described by Morreale et al<sup>2</sup>). On the other hand, when  $\gamma$  is  $\leq 1.4$ , 90% of  $E_{max}$  will be reached after  $\geq 5$ -fold  $T_{50}$  (ie, after around 1 year of treatment for the patients described by Pavelka et al<sup>3</sup>). These simulations may have practical implications for the design of an experimental protocol, in the sense that in patients with less severe disease and a  $\gamma > 1.4$   $E_{max}$  will be accurately predicted with measures of response for 3 or 4 months, but longer periods of data collection may be required for patients with a more severe osteoarthritis.

These observations suggest that the severity of the disease will affect the response to chondroitin sulfate, but not all symptoms will respond equally. This information is probably well known by the physician who does simple dose-response analysis; however, the advantage afforded by the use of the modified  $E_{max}$  model is the ability to quantify differences in response and, in addition, be able to predict accurately  $E_{max}$ , the time required to achieve  $E_{max}$ , and  $\gamma$ . Moreover, the ability to model the changes of response as a function of time allows abnormal responders to be more accurately defined. Finally, the knowledge of the efficacy of a drug and the time to achieve a selected effect is of practical use for the physician and the patient in selection of the drug and the dosages to use, as well as the need to use concomitant medication.

well as with the 4-point ordinal scale of pain on load at days 0, 10, 20, 30, 45, 60, and 90.

To further validate the proposed model, we have analyzed the results reported by Pavelka et al.<sup>3</sup> concerning a prospective, randomized, double-blind, dose-effect study comparing placebo with the antialgesic effect of 200, 800, and 1200 mg/d of chondroitin sulfate given over a period of 3 months to 140 patients with knee osteoarthritis.

$E_{max}$  and  $T_{50}$  values of chondroitin sulfate and diclofenac sodium were calculated by using a subroutine written in FORTRAN for the computer program WinNonlin (Scientific Consulting Inc, Apex, NC).

In patients with knee osteoarthritis treated with chondroitin sulfate and diclofenac sodium, the baseline scores of the index of Lequesne et al.,<sup>10</sup> the VAS of Huskisson et al.,<sup>11</sup> and pain on load decreased progressively as a function of time (Fig 1). The changes in the measured scores as a function of time were well described by the modified  $E_{max}$  sigmoid model. The coefficient of correlation ( $r^2$ ) between the measured effect and the predicted effect was >0.99, the estimated standard error was <15%, and the coefficient of variation for predicted scores ranged between 0% and 16.4%, supporting the accuracy of the approach.

The predicted  $E_{max}$  suggests that chondroitin sulfate can decrease the baseline values of the parameters assessed by 82% to 100%. The value of  $T_{50}$  was approximately 35 days for all three parameters assessed (Table I). The efficacy of chondroitin sulfate was similar to that predicted for diclofenac sodium, but the  $T_{50}$  was twice as long.

The effect elicited by various doses of chondroitin sulfate and placebo on functional status and pain, as assessed by the index of Lequesne et al.<sup>10</sup> and the VAS of Huskisson et al.,<sup>11</sup> is depicted in Fig 2. The predicted functional and antialgesic maximal effect of 1200 mg daily of chondroitin sulfate was not superior to the response elicited by 800 mg daily (Table II). It is worth noting that the  $T_{50}$  for the index of Lequesne et al.<sup>10</sup> was twice as long as the  $T_{50}$  estimated for the VAS of Huskisson et al.<sup>11</sup>

The values of  $\gamma$  varied according to the parameter considered and according to the values for chondroitin sulfate and diclofenac sodium (Table I) (ie, these values were greater for the prediction of the index scores of Lequesne et al.<sup>10</sup> than for the prediction of the VAS of Huskisson et al.<sup>11</sup>). In addition, the values of  $\gamma$  appear to be greater in patients with less severe osteoarthritis. For instance, in patients treated with 1200 mg of chondroitin sulfate with a baseline Lequesne et al.<sup>10</sup> index score of 7.8 and a Huskisson et al.<sup>11</sup> VAS of 56.4,<sup>2</sup> esti-

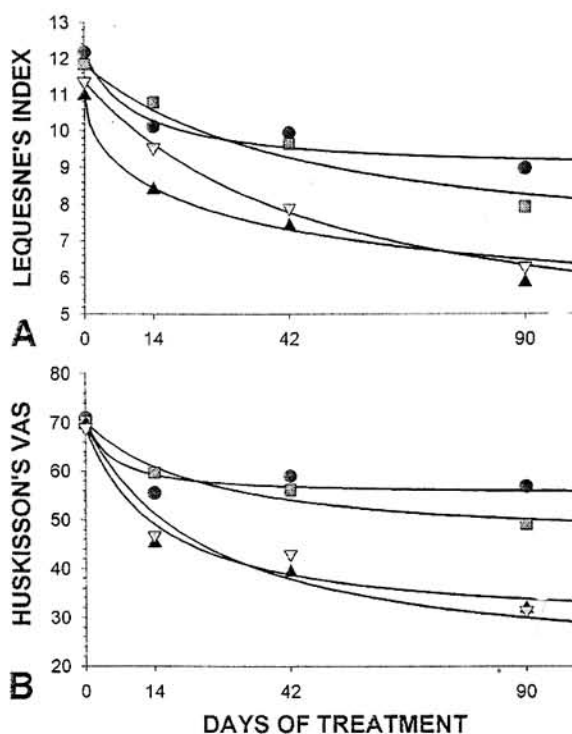


Fig 2. Observed and predicted effect of 200, 800, and 1200 mg daily of chondroitin sulfate compared with placebo on average algofunctional (A, index of Lequesne et al.<sup>10</sup>) and antialgesic (B, VAS of Huskisson et al.<sup>11</sup>) responses in patients (n = 35 per group) with knee osteoarthritis treated for 90 days. Data from Pavelka et al.<sup>3</sup>

mated  $\gamma$  values were 2.8 and 1.5, respectively; on the other hand, in patients with more severe osteoarthritis treated with the same dose of chondroitin sulfate with a baseline Lequesne et al.<sup>10</sup> index score of 11.4 and a Huskisson et al.<sup>11</sup> VAS of 69,<sup>3</sup> estimated  $\gamma$  values were 1.1 and 0.5, respectively. The  $\gamma$  values for placebo were the same as for active treatment. The dosage of chondroitin sulfate did not influence the value of  $\gamma$ .

#### INTERPRETATION AND IMPLICATIONS OF THE DATA GENERATED

The approach proposed allowed us to predict the changes in functional and antialgesic effects of chondroitin sulfate as a function of time and provided values for  $E_{max}$  and  $T_{50}$ . In patients with knee osteoarthritis of moderate severity,<sup>2</sup> it may be predicted that chondroitin sulfate can reduce baseline pain and algofunctional values by >80% ( $E_{max}$ ): in addition, for these patients it will take approximately 35 days to achieve 50% of  $E_{max}$  for any of the parameters assessed. In

The modified  $E_{max}$  approach may be applied to situations in which the plasma concentrations of the active moiety are not available, as, for instance, to evaluate and quantify the effect of placebo. Other situations in which the modified  $E_{max}$  model may be useful include the assessment of the effect of diet on plasma cholesterol or triglyceride values or on blood glucose levels or to quantify the response of drugs that are not absorbed, such as the bile acid-binding resins cholestyramine (INN, colestiramine) and colestipol, or inhaled corticosteroids for asthma. The modified  $E_{max}$  approach may also be an useful tool to quantify the response resulting from several concomitant interventions, where the effect may not be associated with the plasma concentrations of a specific drug. For instance, when drug therapy is added to a diet, the effect may not be clearly associated with the plasma concentrations of the drug. The proposed modified  $E_{max}$  approach will be equally useful to quantify the effect of several drugs given to treat a pathologic condition such as diabetes, hypertension, myocardial ischemia, heart failure, hyperlipoproteinemia, and the like. With the increment in the number of drugs of biologic origin, which are sometimes difficult to measure or to differentiate from endogenous compounds, the analysis of the effect as a function of time may represent a useful alternative to classical methods.

When the effect is measured regularly over long periods of time and analyzed as a function of time, the presence of a counterclockwise hysteresis may not be a limitation to the modified  $E_{max}$  approach. A clockwise hysteresis that is the result of homeostatic reactions, as may happen with the use of antihypertensive agents, will not distort the predictions when the effect is measured over long periods of time, for instance, once weekly for several weeks. The limitations of the analysis of the effect as a function of time will be apparent when the pharmacologic response is measured over a short period of time (ie, for several half-lives of the drug after its administration). When the effect is documented over short periods of time, the response will increase as a function of time, attain a maximal effect, and decrease thereafter (ie, it does not depict a hyperbola). When the effect is measured over limited periods of time, the maximal effect will be reached sooner or later in the presence of a clockwise hysteresis or a counterclockwise hysteresis, respectively.

In summary, the analyses of the effect as a function of time may be an alternative approach to predict the  $E_{max}$  of a drug; meanwhile it is given over extended periods of time and at a unique dosage regimen. This

approach will not provide information about the potency of a drug but rather on the time required to elicit 50% of  $E_{max}$ , the parameter associated with the potency of the drug. The accuracy of the predictions will depend on the reliability and number of observations used to estimate  $E_{max}$ ,  $T_{50}$ , and  $\gamma$ . Early observations are required to define adequately  $T_{50}$  and  $\gamma$ , and late observations will be needed to characterize  $E_{max}$ .

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