

Pharmacokinetics of α_1 -Antitrypsin Replacement Therapy in Severe Congenital Emphysema

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OBJECTIVE: α_1 -antitrypsin (AAT) deficiency is a codominant autosomal genetic disorder that predisposes a patient to chronic obstructive pulmonary disease and emphysema. Specific treatment is systemic, consisting of intravenous infusion of AAT. The protocol currently recommended by the Spanish Registry is infusion of 180 mg/kg every 21 days. The objective of this study was to assess the pharmacokinetic behavior of AAT and estimate the level of protection, defined as the percentage of time that the AAT plasma concentration was above the assumed protective threshold of 50 mg/dL with the usual protocol and with other alternative ones.

MATERIAL AND METHODS: Plasma concentrations at 4 times were analyzed for 9 patients to profile the pharmacokinetics of AAT. The data were fitted to a single compartment open model with the WinNonlin software package. The duration of protection was estimated by simulating the evolution of AAT plasma activity over time according to the model constructed based on data recorded in the study.

RESULTS: Five men and 4 women (mean weight, 69 kg; range, 59-84 kg) were given a mean AAT dose of 12.06 g (range, 11-15 g). The mean (SD) volume infused was 516.67 (88.17) mL.

The half-life of AAT was 8.7 days and the volume of distribution was 127.6 mL/kg. The currently recommended treatment protocol (180 mg/kg every 21 days) gave a level of protection of 67% (considering 60 mg/dL to be protective threshold) or 76% (for a threshold of 50 mg/dL). Protection values for the alternative protocol of 120 mg/kg every 14 days were 82% and 100%, respectively. For the alternative protocol of 60 mg/kg every 7 days, protection was 100% for both thresholds.

CONCLUSIONS: Profiling the pharmacokinetic behavior of AAT has enabled the coverage time to be assessed for several treatment protocols. The regimen of 120 mg/kg every 14 days had the most appropriate profile.

Key words: *Emphysema. α_1 -antitrypsin. Pharmacokinetics. Duration of protection. Replacement therapy.*

Farmacocinética de la alfa-1-antitripsina utilizada en el tratamiento sustitutivo del enfisema congénito grave

OBJETIVO: El déficit de alfa-1-antitripsina (AAT) es una enfermedad genética autosómica codominante, que predispone a enfermedad pulmonar obstructiva crónica y enfisema. El tratamiento específico consiste en la administración intravenosa sistemática de AAT. La pauta de tratamiento actual recomendada por el Registro Español es de 180 mg/kg cada 21 días. El objetivo de este trabajo ha sido evaluar el comportamiento farmacocinético de la AAT y estimar el grado de cobertura, definido como el porcentaje de tiempo que la concentración plasmática de AAT se sitúa en valores superiores a 50 mg/dl, valor considerado como protector, de la pauta de tratamiento habitual y otras pautas alternativas.

MATERIAL Y MÉTODOS: El análisis farmacocinético de la AAT se realizó mediante el ajuste de 4 pares de valores concentración/tiempo, de 9 pacientes, a un modelo farmacocinético monocompartimental abierto empleando el paquete informático Win-Nonlin. La estimación del tiempo de cobertura se efectuó mediante la simulación de la evolución de la actividad plasmática de la AAT, en función del tiempo, según el modelo propuesto y los valores de los parámetros obtenidos en el estudio.

RESULTADOS: Los pacientes presentaban las características demográficas siguientes: 5 varones y 4 mujeres, peso medio de 69 kg (intervalo, 59-84 kg) y dosis media de AAT por infusión de 12,06 g (intervalo: 11-15 g). El volumen medio (\pm desviación estándar) de infusión fue de 516,67 \pm 88,17 ml.

La vida media de la AAT fue de 8,7 días, y el volumen de distribución de 127,6 ml/kg. La pauta de tratamiento actual (180 mg/kg cada 21 días) presentó un porcentaje de cobertura del 67% (considerando que 60 mg/dl es el valor protector) o del 76% (para 50 mg/dl), y los porcentajes para la pauta alternativa de 120 mg/kg cada 14 días fueron del 82 y el 100%, respectivamente. Para 60 mg/kg cada 7 días fue del 100% en ambos casos.

CONCLUSIONES: La caracterización del comportamiento farmacocinético de la AAT ha permitido evaluar el tiempo de cobertura de las diversas pautas de tratamiento y establecer como más adecuada la de 120 mg/kg cada 14 días.

Palabras clave: *Enfisema. Alfa-1-antitripsina. Farmacocinética. Tiempo de cobertura. Tratamiento sustitutivo.*

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Introduction

α_1 -antitrypsin (AAT) deficiency is an autosomal genetic disorder that can cause chronic liver disease in childhood and early progressive panacinar emphysema. The genes are inherited as 2 codominant alleles and the variant most often responsible for the disease is the Z allele.^{1,2} AAT is an inhibitor of proteolytic enzymes such as neutrophil elastase and the molecule also has anti-inflammatory and proinflammatory properties.² The activity of AAT in homozygous ZZ patients is 35% below the lower limit of normal. This creates an imbalance in the capacity of AAT to neutralize elastase in such patients, accelerating the destruction of the elastic fibers in the lung and leading to early-onset emphysema.^{1,2}

Although other mechanisms may also contribute to emphysema, AAT replacement therapy comprising intravenous administration of the molecule purified from the plasma of healthy human donors has been available since 1987, based on the antielastase properties of the molecule.¹ Biochemical and clinical indicators of the effectiveness of AAT therapy include plasma concentrations of AAT greater than 50 mg/dL—considered the minimum protective threshold³—throughout the dosing period. There should also be evidence that the functional capacity of AAT remains once the drug has been administered and that progression of emphysema is slowed, so reducing morbidity and improving survival. Finally, there should also be evidence that it can be safely administered.⁴

The current dosing regimen recommended by the Spanish Registry,⁵ an organization that monitors the disease, consists of administration of 180 mg/kg every 21 days, although treatment regimens with dosing every 7, 14, and 28 days have been tried in other countries. The limited commercial availability of the drug up until very recently has hindered studies to characterize its pharmacokinetic profile. Studies to optimize the dosing regimen based on pharmacokinetic data are therefore also lacking.

The aim of this study was to assess the pharmacokinetic behavior of AAT and to estimate the level of protection, that is, the percentage of time during which the plasma concentration of AAT is above 50 mg/dL, under the current recommended treatment regimen (180 mg/kg every 21 days), and the alternative regimens of 120 mg/kg every 14 days and 60 mg/kg every 7 days.

Material and Methods

Patients

The study included 9 ZZ phenotype patients with severe AAT deficiency who were receiving AAT replacement therapy in stable conditions (more than 6 months of prior therapy) and who regularly attended the pulmonology service of the Hospital Universitario Vall d'Hebron in Barcelona, Spain.

Samples

At least 4 serum samples were extracted to obtain pairs of AAT concentrations at a time between 0.5 hours and 1

hour, and then 7, 14, and 21 days after administration of AAT.

AAT Analysis

Pharmacokinetic analysis. The pharmacokinetic analysis of AAT was done by fitting the pairs of concentration-time points to a single compartment open pharmacokinetic model. The parameters estimated from the model were biological half-life, maximum concentration, volume of distribution, clearance, dose-normalized area under the concentration-time curve, and mean residence time. Experimental data were fitted to the pharmacokinetic model with the WinNonlin version 1.1 software package using a nonlinear iterative regression algorithm.

Estimated time of protection. The duration of protection was estimated by simulating the course of the AAT plasma concentration as a function of time, in accordance with the proposed pharmacokinetic model and the values of the parameters obtained for the patients included in the study (WinNonlin version 1.1). The percentage of time with protection was the ratio of time when the concentration of AAT was above 50 mg/dL and 60 mg/dL to total time. The estimate was made for the following predefined therapeutic regimens: 180 mg/kg every 21 days, 120 mg/kg every 14 days, and 60 mg/kg every 7 days.

Ethical Considerations

The study protocol was submitted to the clinical ethics committee of the Hospital Universitario Vall d'Hebron and approved on March 31, 2005.

Analytical Techniques

Plasma concentrations of AAT were determined by kinetic nephelometry with rabbit anti-human AAT antibody in the BN-II nephelometer (Dade Behring, Marburg, Germany).

Results

The 9 patients included in the study—5 men and 4 women, with a mean weight of 69 kg (range, 59–84 kg)—received a mean dose of 12.06 g of AAT (range, 11–15 g) in each infusion. The mean (SD) volume of the infusion solution was 516.67 (88.17) mL.

The values of the pharmacokinetic parameters are shown in the Table. The mean half-life of AAT was 8.7 days and the mean volume of distribution was 127.6 mL/kg. The mean values obtained were introduced in the simulation model to yield the plot shown in the Figure. For the current recommended therapeutic regimen (180 mg/kg every 21 days), the percentage time of protection was 67% (for 60 mg/dL as the protective threshold) or 76% (for 50 mg/dL as the threshold). For the alternative regimen of 120 mg/kg every 14 days, the percentage times of protection were 82% (60 mg/dL) and 100% (50 mg/dL). The estimated percentage time of protection for the regimen of 60 mg/kg every 7 days was 100%, regardless of which protective threshold was used (50 mg/dL or 60 mg/dL).

The pharmacokinetic data for AAT are limited and mostly come from initial studies with the first licensed

preparation of plasma AAT. The plasma half-life in these studies was 4.5 days or 120 hours,^{6,7} slightly lower than the half-lives reported in this study. No previous data are available on the volume of distribution or clearance.

Discussion

AAT was licensed for therapeutic use in the United States of America in 1987 to treat AAT deficiency after it had been shown that high plasma concentrations were attained, that the antielastase activity in serum and bronchoalveolar wash improved, and that these 2 observations were strongly correlated.⁸ Currently, 2 AAT preparations are available in Spain for intravenous administration—Prolastin® (QF Bayer) and Trypsone® (I. Grifols). Both preparations have similar characteristics in that they have good safety profiles, with few adverse reactions and no reports of virus or prion transmission.⁹

The dosing regimens used for AAT replacement therapy have not been clearly established. Periods between dosing of 7, 14, 21, and 28 days have all been used. When elastase is not present, AAT behaves like an inert molecule and does not make any substantial contribution to plasma osmolarity or undergo appreciable glomerular filtration, so it does not cause renal damage. Excess AAT is therefore considered harmless in the first few hours after intravenous administration with the 21- or 28-day regimens.¹⁰ The first regimen to be used was 60 mg/kg every 7 days, but the difficulties associated with long-term weekly dosing led to tests with longer periods between dosing. In 1999, the Spanish Registry recommended the regimen of 180 kg/kg every 21 days, and this regimen has been used in Spain ever since.¹¹

The clinical efficacy of intravenous administration of purified AAT in patients with specific deficiency has been assessed in a number of studies.¹²⁻¹⁷ Markers of clinical efficacy that have been used include change in forced expiratory volume in 1 second, carbon monoxide diffusing capacity, decrease in infections and mortality, and loss of pulmonary density measured by computed axial tomography.

According to biochemical assays, the concentration of AAT in plasma remained above the protective threshold for the entire period between doses with the regimen of 60 mg/kg every 7 days.¹⁸ In another study that used the same dosing regimen, a minimum

TABLE I
Pharmacokinetic Parameters of α_1 -Antitrypsin in the Study Population*

Parameter	Mean	95% CI
AUC/D, mg×h/L	807.6	626.4-988.9
Biological half-life, h	208.8	188.6-228.9
Maximum concentration, mg/L	2746.6	1966.9-3526.4
Clearance, mL/h/kg	0.420	0.356-0.484
MRT, h	301.2	272.1-330.3
Volume of distribution, mL/kg	127.6	100.9-154.3

*AUC/D indicates dose-normalized area under the concentration-time curve; MRT, mean residence time; CI, confidence interval.

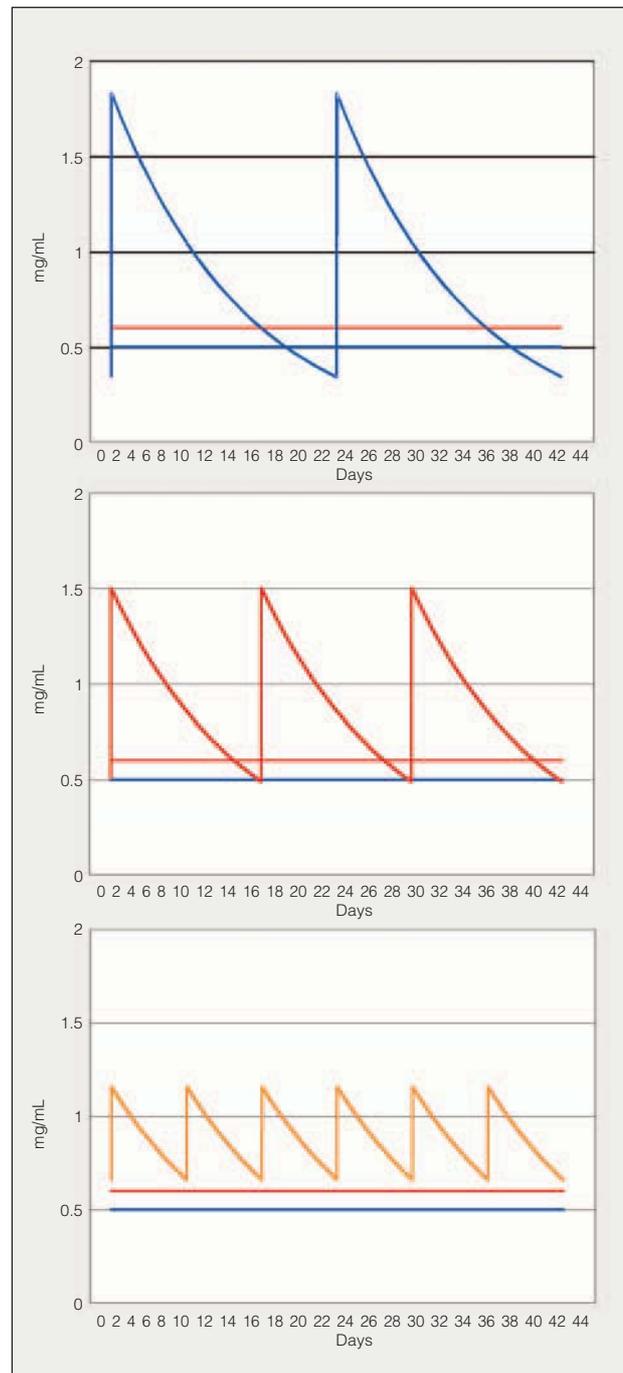


Figure. Simulation of change in plasma activity of α_1 -antitrypsin over time for different dosing regimens.

concentration of 80 mg/dL was obtained throughout the dosing period.⁸ A study of 120 mg/kg every 14 days in 23 patients suggested that this regimen is not sufficient to maintain plasma concentrations of AAT above 70 mg/dL to 80 mg/dL,¹⁹ although the levels were above 50 mg/dL for the entire dosing period in all patients. The same findings have been reported for a regimen of 120 mg/kg every 14 days, whereas with the 250 mg/kg

dose every 28 days, protective levels were observed for 25 days of the dosing period (89%).²⁰ The data obtained in our study are essentially in line with those findings: the only treatment regimens that guarantee full protection with levels above the 50 mg/dL protective threshold are those with time between dosing of 14 days or less.

Study of the pharmacokinetic behavior of AAT therefore suggests that the most suitable therapeutic regimen would be 120 mg/kg every 14 days. This regimen has the longest interval between dosing while ensuring that the levels of AAT are kept above the protective threshold for the entire period. If it is not possible to increase the frequency in certain individuals, it should be remembered that 24% of the period between doses lacks protection with the current dosing regimen of 180 mg/kg every 21 days. On the other hand, decreasing the period between doses to less than 14 days could allow smaller effective doses of AAT to be administered.

Another interesting aspect of optimizing AAT therapy is the possibility of tailoring the doses according to the pharmacokinetic response of each patient. Adaptation of the treatment to each patient in an individualized regimen could also permit, in addition to a better plasma concentration-time profile, use of lower doses of AAT, so reducing the cost of treatment.

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