Pharmacokinetics of C1-inhibitor protein in patients with acute myocardial infarction

Objectives: C1-inhibitor protein (C1-INH) purified from pooled human plasma is used for the treatment of patients with hereditary angioedema. Recently, the beneficial effects of high-dose C1-INH treatment on myocardial ischemia or reperfusion injury have been reported in various animal models and in humans. We investigated the pharmacokinetic behavior of C1-INH in patients with acute myocardial infarction to calculate the amount of C1-INH required for optimal efficacy.

Methods: Twenty-two patients received an intravenous loading dose, followed by 48 hours of continuous infusion of C1-INH. Changes in the endogenous production of C1-INH were evaluated in 16 control patients with acute myocardial infarction. A 2-compartment model was used to estimate the fractional catabolic rate constant (FCR), transcapillary escape rate constant (TER), and extravascular return rate constant (ERR) of C1-INH. Software designed to analyze and fit measured data to unknown parameters in a system of differential equations was used to fit the experimental data against the 3-parameter model.

Results: With fixed TER and ERR values (0.014 h^{-1} and 0.018 h^{-1}, respectively), 20 of the 22 cases yielded well-determined FCR values, and simultaneous fitting resulted in a median FCR of 0.011 h^{-1} (95% confidence interval, 0.010 to 0.012 h^{-1}) versus 0.025 h^{-1} as reported in healthy control patients. Simultaneous estimation of TER, ERR, and FCR demonstrated weakly defined TER and ERR values, whereas the median FCR value remained unchanged. The use of a 2-compartment model resulted in a significantly better fit compared with the 1-compartment model. Physiologic explanations are offered for discrepancies in the literature.

Conclusions: Dose calculation of C1-INH in patients treated with massive doses of C1-INH requires turnover parameters that differ from those found in healthy subjects, possibly because of suppression of continuous C1-INH consumption by target proteases. (Clin Pharmacol Ther 2002;72:498-504.)

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C1-inhibitor protein (C1-INH), a protein of approximately 104 kd, regulates the classical activation pathway of the complement system.[1] Patients with hereditary angioedema (HAE), in whom there is a congenital

lack of C1-INH, have attacks of uncontrolled complement activation that may lead to life-threatening laryngeal obstruction or swelling of the gastrointestinal mucosa.[2] Depending on the severity of the edematous attack, treatment of patients with HAE usually consists of one or more bolus injections of C1-INH purified from pooled human plasma.

Other diseases in which complement inhibition might have beneficial effects are being explored, and the administration of C1-INH has been investigated in patients with sepsis,[1] rheumatoid arthritis,[3] and B-cell lymphoproliferative disorders.[4] Recent studies in various animal models have shown reduction of myocardial ischemia or reperfusion injury after high-dose C1-INH therapy.[5-8] To investigate the effects of C1-INH in patients with acute myocardial infarction, we recently performed a dose-escalating pilot study.[9] Patients were given an initial loading dose of C1-INH, followed by

continuous infusion during the next 48 hours. Comple-
ment inhibition in this study proved to be strongly
dose-dependent and necessitated accurate Cl-INH dos-
age control. However, Cl-INH was apparently elimi-
nated more slowly than expected from available data of
patients with HAE. Therefore we decided to study the
pharmacokinetics of Cl-INH in patients with acute
myocardial infarction receiving high doses of this in-
hibitor.

METHODS

Twenty-two patients (12 men and 10 women; median
age, 60.5 years) with acute myocardial infarction were
admitted to the Intensive Coronary Care Unit, Univer-
sity Hospital Maastricht, The Netherlands. After in-
formed consent was obtained for patients to participate
in an open-label pilot study, treatment with Cl-INH
was started 6 hours after the onset of symptoms by
means of 3 different dosage schemes as follows: an
initial loading dose of 50 U/kg body weight, followed
by a continuous infusion of 1.25 $U \cdot kg^{-1} \cdot h^{-1}$; an
initial loading dose of 100 U/kg body weight, followed
by a continuous infusion of 1.25 $U \cdot kg^{-1} \cdot h^{-1}$; or an
initial loading dose of 100 U/kg body weight, followed
by a continuous infusion of 2.00 $U \cdot kg^{-1} \cdot h^{-1}$ during
the next 48 hours. Loading doses were infused at a rate
of 250 U/min. The administered amounts were chosen
in an effort to reach concentrations between 200% and
300% of normal. No presumptions were made about
reaching steady-state conditions. Cl-INH (Cetor; CLB,
Amsterdam, The Netherlands) was purified (>95%)
from human plasma according to good manufacturer's
practice guidelines and was tested for viral safety and
clinical efficacy. The lyophilized protein was reconsti-
tuted in water before administration.

Blood samples were collected before administration
of the loading dose and at 1, 3, 6, 9, 12, 15, 18, 24, 36,
48, and 72 to 96 hours after the start of loading dose
administration. Clotting was prevented with ethyl-
enediaminetetraacetic acid (EDTA), and plasma sam-
ples obtained by immediate routine centrifugation were
stored at −70°C until further analysis.

Changes in endogenous Cl-INH production after
acute myocardial infarction were assessed by measur-
ing the course of plasma Cl-INH in 16 control patients
with acute myocardial infarction who did not receive
Cl-INH. These patients were admitted to the Depart-
ment of Cardiology, VU University Medical Center,
Amsterdam, The Netherlands.[10] Blood samples were
collected at admission and at 2, 6, 12, 24, 36, 48, 60,
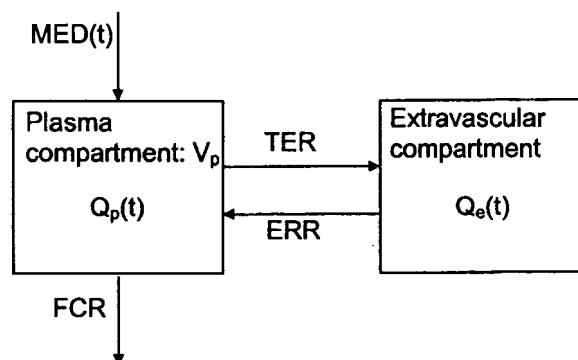and 72 hours thereafter. After centrifugation, plasma

Fig 1. Two-compartment model. $Q_p(t)$, Amount of Cl inhib-
itor (Cl-INH) in plasma (in units) at time t; $Q_e(t)$, amount of
extravascular Cl-INH (in units) at time t; V_p, plasma volume;
Med(t), input function of Cl-INH; TER, transcapillary escape
rate constant; ERR, extravascular return rate constant; FCR,
fractional catabolic rate constant.

was collected and stored in aliquots at −70°C until
assays were performed.

Cl-INH concentrations were determined with the use
of a commercially available functional assay based on
a chromogenic assay (Berichrom Cl inhibitor assay;
Behringwerke AG, Marburg, Germany). Values were
expressed in units per liter, with 1 unit equal to the
activity of Cl-INH in 1 mL of pooled plasma obtained
from healthy donors. The specific activity of Cl-INH
was 3.8 U/mg protein.

A 2-compartment model, as described in Fig 1, was
used to estimate individual pharmacokinetic parameters
of Cl-INH. Time-related changes in plasma and ex-
travascular Cl-INH pools are given by the following
equations:

$$dQ_p(t)/dt = MED(t) - (FCR + TER) \times Q_p(t) \quad (1a)$$
$$+ ERR \times Q_e(t)$$

$$dQ_e(t)/dt = TER \times Q_p(t) - ERR \times Q_e(t) \quad (1b)$$

in which $Q_p(t)$ and $Q_e(t)$ are the plasma and extravas-
cular pools, respectively, expressed in units at time t,
MED(t) is the input function of Cl-INH, FCR is the
fractional catabolic rate constant (per hour) for the
elimination of Cl-INH from the plasma, TER is the
transcapillary escape rate constant (per hour) of Cl-
INH for extravasation of Cl-INH to the extravascular
compartment, and ERR is the extravascular return rate
constant (per hour) for the return of Cl-INH from the
extravascular compartment to plasma.

Equation 2, used as an initial condition, presents
steady-state conditions for the amount of Cl-INH in the
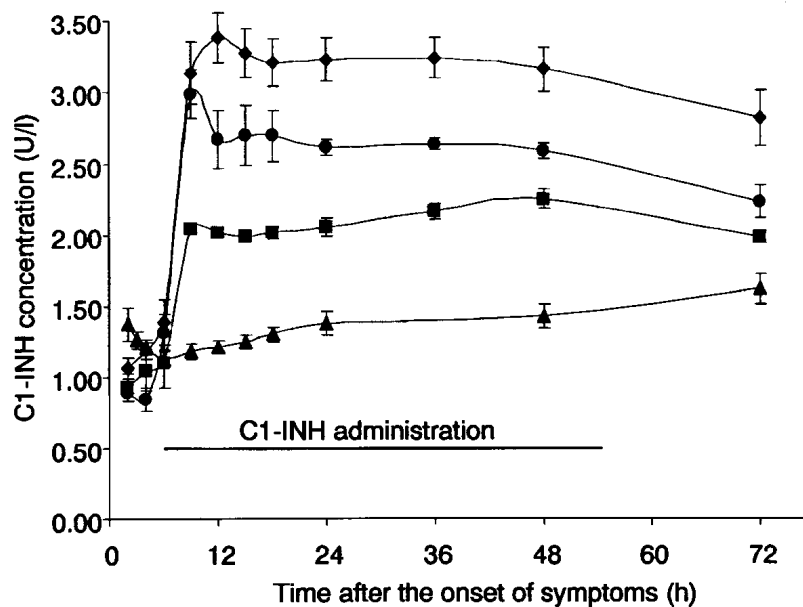extravascular compartment at time 0. $Q_p(0)$ is known

Fig 2. C1-INH plasma curves of 3 infusion groups and control patients (mean with standard error). Group 1 *(squares)*: Loading dose, 50 U/kg; infusion rate, 1.25 U $\cdot$ kg^{-1} $\cdot$ h^{-1} (n = 6). Group 2 *(circles)*: Loading dose, 100 U/kg; infusion rate, 1.25 U $\cdot$ kg^{-1} $\cdot$ h^{-1} (n = 5). Group 3 *(diamonds)*: Loading dose, 100 U/kg; infusion rate, 2.00 U $\cdot$ kg^{-1} $\cdot$ h^{-1} (n = 11). Control patients *(triangles)*: No C1-INH administered (n = 16).

by measurement of the C1-INH plasma concentration at time 0 (ie, before C1-INH administration).

$$Q_e(0) = [TER/ERR] \times Q_p(0) \qquad (2)$$

All plasma concentrations were converted to total amounts in units by multiplying the concentrations in units per liter by the individual plasma volume in liters. Plasma volume was calculated from the initial increase in C1-INH concentration after administration of the loading dose.

A software package called spIds,[11] developed for estimation of unknown parameters in time-dependent dynamic systems,[12] was used to solve the system defined by the differential algebraic equations 1a and 1b and the initial condition given by equation 2. It uses the algebra package Maple V (Waterloo Maple Inc, Ontario, Canada) to derive variational equations from the differential equations. These variational equations are then used in the process by combining them with the initial differential equations. The Levenberg-Marquardt method was used to minimize the total sum of squared discrepancies between calculated and measured values of Q_p. A confidence interval (CI) at a user-defined level α (ie, .05) is calculated for each estimate. The program also gives a detailed analysis of the reliability and interdependencies of the parameters. This is used to

evaluate whether each parameter independently contributes to a significant decrease in the total sum of squares. Thus we can verify whether the use of a 2-compartment model is to be preferred over a 1-compartment model.

RESULTS

Fig 2 shows mean plasma C1-INH concentrations for the 3 patient groups with different dosage schemes and for the control patients. A clear dose-concentration profile is visible in the 3 groups that received C1-INH therapy. A decrease in C1-INH is shown in the group of control patients in the first 6 hours after the onset of symptoms, and a slow but continuing increase in C1-INH concentration after 6 hours can be noted in the same group.

Fig 3 demonstrates the mean observed and fitted C1-INH plasma concentration curves, as well as the calculated extravascular C1-INH pool, for each dosage group. After a rapid increase caused by the loading dose, a plateau phase is visible for the duration of the infusion. When the infusion was stopped, a gradual decline in the plasma concentration was seen, while the extravascular pool continued to increase, albeit with diminishing speed. The latter finding indicates that no steady-state conditions were reached.
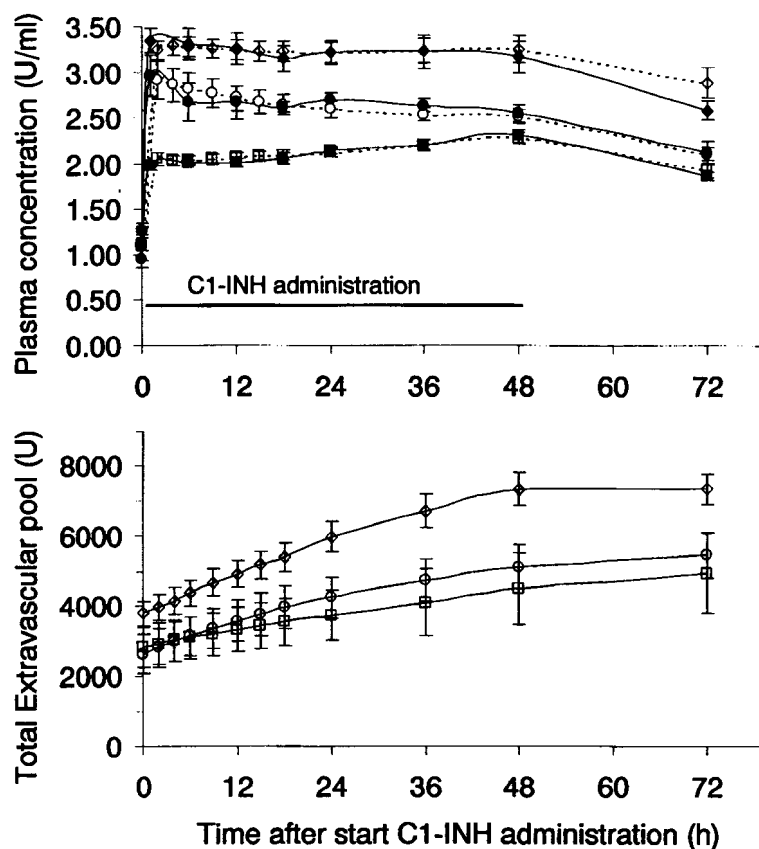
Fig 3. Time course of C1-INH plasma concentration and extravascular content after treatment (mean with standard error [n = 22]). *Upper panel,* Plasma concentrations (in units per milliliter) in group 1 *(squares),* group 2 *(circles),* and group 3 *(diamonds). Solid lines,* Measured C1-INH plasma concentrations; *dotted lines,* fitted C1-INH plasma concentrations. *Lower panel,* Calculated extravascular C1-INH pool (in units) in group 1 *(squares),* group 2 *(circles),* and group 3 *(diamonds).*

On the basis of plausible fixed TER and ERR values ($0.014 \; h^{-1}$ and $0.018 \; h^{-1}$, respectively; see Discussion section), the FCR for individual patients was estimated. The results listed in Table I demonstrate that 20 of the 22 cases had well-determined FCR values, with CIs of less than 55%. The 2 cases with CIs greater than 100% both underwent sampling for only a short period of time (<30 hours) because of difficulties with blood sampling (not drug-related). Simultaneous fitting of the remaining 20 patients with fixed TER and ERR values yielded the same FCR as the calculated median (0.011 h^{-1}), but this value was better defined (Table I).

Estimation of all 3 parameters resulted in almost the same FCR value, $0.012 \; h^{-1}$ (CI, 0.002 to 0.022 h^{-1}). The TER and ERR values were $0.021 \; h^{-1}$ (CI, −0.018 to 0.060 h^{-1}) and $0.019 \; h^{-1}$ (CI, −0.055 to 0.093 h^{-1}), respectively, but the large CIs indicate that no precise TER and ERR values could be determined.

DISCUSSION

Recovery of C1-INH

From the plasma volumes and individual body weights listed in Table I, a median plasma volume of 48 mL/kg body weight was calculated. Comparison with the normal plasma value of 41 mL/kg (corrected for sex, weight, and age)[13] showed an apparent incomplete recovery (85%) of C1-INH, probably caused by consumption of C1-INH in the acute phase. This finding is supported by the initial decrease in C1-INH in control patients (Fig 2).

Validation of model used

On the basis of the independency of the parameters (data not shown), adding a second compartment to the model caused a significant reduction in the total sum of squares. This means that, although the data obtained lack extravascular measurements, the use of a

Table I. Results of 2-compartment model on patients with acute myocardial infarction

Patient no.	Sex	Age (y)	Body weight (kg)	V_p (mL)	FCR and 95% CI (h^{-1})*
1	F	74	75	2953	0.009 (0.005 to 0.013)
2	M	51	107	5144	0.009 (0.008 to 0.010)
3	M	60	85	4474	0.007 (0.005 to 0.009)
4	M	58	105	4953	0.005 (0.003 to 0.007)
5†	F	55	55	2500	0.900 (−0.470 to 2.270)
6	F	38	71	3170	0.011 (0.010 to 0.012)
7	M	61	88	3411	0.012 (0.009 to 0.015)
8	F	46	60	2970	0.003 (0.002 to 0.004)
9	F	70	56	2857	0.011 (0.008 to 0.014)
10	M	57	75	5068	0.010 (0.005 to 0.015)
11	M	40	78	3000	0.021 (0.017 to 0.025)
12	M	51	80	4420	0.010 (0.006 to 0.014)
13	M	63	70	3784	0.017 (0.012 to 0.022)
14	F	83	64	2795	0.016 (0.014 to 0.018)
15	F	78	73	3106	0.016 (0.011 to 0.021)
16	M	59	70	3590	0.025 (0.021 to 0.029)
17†	F	74	58	2929	0.002 (−0.004 to 0.008)
18	M	61	100	6329	0.017 (0.010 to 0.024)
19	M	61	82	4059	0.007 (0.004 to 0.010)
20	M	68	93	4769	0.009 (0.007 to 0.011)
21	F	57	96	3254	0.012 (0.005 to 0.019)
22	F	68	87	3750	0.011 (0.009 to 0.013)
Median (n = 20)		60.5	77	3500	0.011 (0.008 to 0.014)

V_p, Plasma volume; FCR, fractional catabolic rate constant; CI, confidence interval; F, female; M, male.
*Simultaneous fit of 20 patients (fixed transcapillary escape rate constant [0.014 h^{-1}] and extravascular return rate constant [0.018 h^{-1}]): FCR = 0.011 h^{-1} (95% CI, 0.010 to 0.012 h^{-1}). Individual fit of 20 patients (estimation of all 3 parameters): FCR = 0.012 h^{-1} (95% CI, 0.002 to 0.022 h^{-1}).
†Sampling period <30 hours; therefore patient's data were excluded from calculations.

2-compartment model still results in a better fit of the plasma curves compared with a 1-compartment model.

TER and ERR values

The choice of plausible fixed values for TER (0.014 h^{-1}) and ERR (0.018 h^{-1}) in this study was based on an overview of data on the behavior of circulating proteins in humans.[14] These data, in most cases obtained from turnover studies of radiolabeled proteins, show an average extravasation rate of about 1.4% of the plasma pool per hour for proteins with a molecular weight exceeding 100 kd. Moreover, it was found that the extravascular pool of such proteins is somewhat smaller than the plasma pool, as also follows from the equilibrium relation E/P = TER/ERR = 0.78, where E/P is the extravascular pool/plasma pool ratio.

The fact that no precise TER and ERR values for C1-INH could be determined is mainly caused by the lack of extravascular measurements. The small number of observations (2 or 3) made after the end of infusion enlarges the imprecision of TER and ERR because it is primarily this last part of the plasma curve that expresses these values.

Estimation of FCR: Comparison with data from literature

Table II presents an overview of C1-INH turnover studies in healthy subjects and in patients with various diseases. Apart from this study, all studies used single intravenous bolus injections of C1-INH. With the exception of the study of Kunschak et al,[15] in which the total observation time was limited to 24 hours, C1-INH concentrations were measured for at least 72 hours.

In a number of these studies[15-17] the apparent disappearance rate constant (k_d) rather than the true fractional catabolic rate constant for the disappearance of C1-INH from plasma was determined. For instance, Brackertz et al[16] found a biphasic disappearance of injected C1-INH in control subjects and reported a plasma half-life of 64 hours for the final slow disappearance phase from 3 to 8 days after injection. However, the corresponding apparent disappearance rate constant $k_d = (\ln 2)/64 = 0.011$ h^{-1} also incorporates the return of extravascular C1-INH to plasma, which suggests that the FCR would be even lower than 0.011 h^{-1}.

Another situation occurred in the study of Kunschak

Table II. Data from literature on human C1 inhibitor turnover

Reference	Subjects	C1-INH preparation	k_d (h^{-1})	FCR (h^{-1})	TER (h^{-1})	ERR (h^{-1})	TER/ERR = E/P	Method
Brackertz et al[16] (1975)	Controls (n = 3) Hereditary angioedema (n = 3)	Iodine label	0.011 0.010	— —	— —	— —	— —	Exponential fit (k_d from second phase)
Quastel et al[18] (1983)	Controls (n = 9) Hereditary angioedema (n = 5)	Iodine label	— —	0.025 0.035	— —	— —	0.60 1.26	Matthews (2-compartment model) or Nosslin (non-compartmental model)
Woo et al[3] (1985)	Controls (n = 10) Rheumatoid arthritis (n = 13)	Iodine label	— —	0.025 0.028	— —	— —	— —	Matthews (2-compartment model)
Melamed et al[4] (1986)	LPD (n = 5)	Iodine label	—	0.053	—	—	1.54	Matthews (2-compartment model)
Waytes et al[17] (1996)	Hereditary angioedema (n = 6)	Concentrate	0.015	—	—	—	—	Half-life estimation over 72 h
Kunschak et al[15] (1998)	Hereditary angioedema (n = 10)	Concentrate	0.018 0.029	— —	— —	— —	— —	$t_{1/2}$ activity $t_{1/2}$ antigen (k_d first phase)
This study	Acute myocardial infarction (n = 22)	Concentrate Concentrate	— — —	0.011 0.012 0.015	0.014 0.021 —	0.018 0.019 —	0.78 1.11 —	2-Compartment fit: TER, ERR (fixed) TER, ERR (free) Corrected for endogenous production

C1-INH, C1 inhibitor; k_d, apparent disappearance rate constant; TER, transcapillary escape rate constant; ERR, extravascular return rate constant; E/P, extravascular pool/plasma pool; LPD, lymphoproliferative disorder; $t_{1/2}$, half-life.

et al,[15] who reported half-lives of 37.8 to 24.0 hours for the initial disappearance phase of C1-INH in patients with HAE, corresponding to k_d values of 0.018 to 0.029 h^{-1}. These values are indeed higher than the true FCR, because C1-INH is not only catabolized but also extravasating during the first 24 hours after a bolus injection.

Overall, Table II shows that an FCR value of 0.025 h^{-1} was obtained in healthy subjects and that higher values are obtained in patients with various diseases that cause consumption of C1-INH as a result of complement activation, such as HAE, rheumatoid arthritis, and various forms of leukemia.

Possible explanations for discrepancies in FCR values

A first explanation for the relatively low FCR value could be a considerable increase in endogenous production of C1-INH in the days after acute myocardial infarction. Such acute phase reactant-like behavior of C1-INH could compensate for the extra consumption of C1-INH as a result of complement activation during the first 24 hours after acute myocardial infarction. However, the course of C1-INH plasma levels in the control patients did not support this explanation, given that levels initially decreased rather than increased (Fig 2),

suggesting increased consumption and not increased synthesis.

Furthermore, increased endogenous production of acute phase reactants usually starts after more than 24 hours, and Fig 2 indeed shows that C1-INH plasma concentrations in control patients are increasing slightly in the days after acute myocardial infarction. On the basis of data from these patients, it was estimated that this slow increase corresponded to an average increase in C1-INH synthesis of 17 U/h. When this production was added to equation 1a, it was found that the FCR changed only marginally to 0.015 h^{-1} (CI, 0.013 to 0.017 h^{-1}) (Table II).

Another explanation for the discrepancy between healthy subjects and patients with acute myocardial infarction could be that continuous consumption of C1-INH caused by complex formation with activated proteases and subsequent rapid removal of complexes from plasma is a main determinant of C1-INH elimination in healthy subjects. If it is assumed that the disappearance of functional C1-INH proceeds via 2 almost equally contributing pathways, (1) inactivation resulting from complex formation and (2) slow hepatic removal of C1-INH with an FCR value of about 0.011 h^{-1}, it is clear that in studies that used lower doses the

combination of 2 removal pathways could be mistaken for a higher FCR value.

An obvious difference between the other studies mentioned in Table II and this study is that we used bulk amounts of C1-INH instead of trace amounts of radiolabeled C1-INH. Patients with HAE are usually treated with doses of 1000 U. In contrast, the patients with acute myocardial infarction in this study received total doses of as much as 20,000 U. At these high doses, disappearance as a result of complex formation will play only a relatively minor role, as compared with hepatic removal of functional C1-INH. This could reveal the observed FCR value of 0.011 h^{-1}.

A similar low FCR value was found by Quastel et al[18] for a dysfunctional C1-INH protein, Ta. They reported that C1-INH Ta scarcely binds to C1. This too supports the idea of the important role of continuous C1-INH disappearance from plasma as a result of complex formation. The defective complex formation of Ta blocked one of the two pathways, thus decreasing the speed of disappearance and revealing the true FCR.

In conclusion, pharmacokinetic data for C1-INH were estimated in patients with acute myocardial infarction receiving high doses of this inhibitor. The obtained FCR value (0.011 h^{-1}) is lower than that previously found (0.025 h^{-1}). Saturation of the normal steady-state kinetics of C1-INH may explain this finding. These data may help to design further clinical trials with this anti-inflammatory drug.

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