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Research Article

Pharmacokinetic/Dynamic Correlation of Pulmonary and Cardiac Effects of Fenoterol in Asthmatic Patients After Different Routes of Administration

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Pulmonary and cardiac effects of the β_2-adrenergic drug fenoterol were studied in 27 asthmatic patients using an integrated pharmacokinetic/dynamic (PK/PD) approach. Airway resistance (R_f), intrathoracic gas volume (IGV), heart rate, and plasma levels were monitored after placebo, injection (12.5 and 25 μg), nasal instillation (400 μg), inhalation (200 and 400 μg), and infusion (200 μg/180 min with or without loading dose). The pharmacokinetics were best described by an open three-compartment model with a terminal half-life of 200 min ($\gamma = 0.23 \pm 0.08$ L/hr), a volume of distribution at steady state of 1.9 ± 0.8 L/kg, and a clearance of 0.86 ± 0.32 L/hr/kg, with 14 and 9% absorbed after nasal and pulmonary administration, respectively. For the noninhalation regimens, a PK/PD correlation linked the concentration in the shallow pharmacokinetic compartment to the investigated effects via an E_{max} relationship, resulting in three to five times higher EC_{50} values (concentration necessary to achieve half-maximal effect) for the heart rate than for the β_2-mediated effects on IGV and R_f. In contrast, pulmonary effects after inhalation could not be incorporated into the correlation, indicating that these effects are induced locally after inhalation. Intrapatient variability for EC_{50} and E_{max} was approximately 90%.

KEY WORDS: fenoterol; pharmacokinetic/dynamic correlation; lung function; side effects, antiasthmatics.

INTRODUCTION

Fenoterol is a highly active β_2-adrenergic drug. When given as aerosol, it produces an immediate and retained bronchodilatation (1) with higher pulmonary effects, but also cardiac side effects, than terbutaline and salbutamol (2,3).

Integrated pharmacokinetic/pharmacodynamic (PK/PD) correlations have emerged as powerful tools for describing and predicting drug effects for a variety of drugs, including antiasthmatics (4). Complementing clinical and pharmacological studies, it was desirable to apply this approach to the detailed characterization of pulmonary effects and cardiac side effects of fenoterol. Different routes of administration such as iv bolus injection, infusion, nasal administration, and inhalation were included to obtain a more complete PK/PD profile with the final goal of evaluating inhalation therapy with respect to the systemic and local contributions.

MATERIALS AND METHODS

Subjects

Twenty-seven inpatients of the University Clinic of Bochum who were under fenoterol treatment for the management of chronic obstructive lung disease for an average length of 10 years (range, 1–16 years) were randomly assigned to three groups. For group 1 (7 male/4 female, 64 ± 12 years old, 73 ± 11 kg), group 2 (6 male/2 female, 58 ± 10 years, 79 ± 22 kg), and group 3 (6 male/2 female, 53 ± 16 years, 75 ± 14 kg), analysis of variance (ANOVA) did not reveal any significant differences ($P_{age} = 0.194$; $P_{weight} = 0.732$, $P_{sex} = 0.835$).

Drug Administration and Sample Collection

All patients restrained from fenoterol inhalations the night before the study. Each of the three groups received fenoterol in different dosages and forms of administration in a placebo-controlled, randomized (Latin square) crossover study which was approved by the Medical Ethical Committee of the University Hospital of Bochum. Group 1 received placebo (injection of phosphate-buffered saline), two puffs of fenoterol aerosol (Berotec; total dose, 400 μg), an iv injection of 12.5 μg of fenoterol (0.5 ml of Partusisten intrapartal), and an infusion (Partusisten infusion solution, 200 μg/240 min) with a prior loading dose of 12.5 μg. Group 2 received

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placebo, one puff of fenoterol aerosol (200 μg), an iv injection of 25 μg, and an infusion (200 μg/180 min) with a prior loading dose of 25 μg. Placebo, infusion (200 μg/180 min without loading dose), inhalation (400 μg), and nasal administration (400 μg) were studied in group 3. Heart rate and lung function were monitored at 10 min prior to dosing and at 0, 1, 3, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180, and 240 min after dosing. Blood samples were taken accordingly, and plasma was stored at −20°C. For the evaluation of the lung function, airway resistance (R_f) and intrathoracic gas volume (IGV) were determined with a constant-volume body plethysmograph (Body Test, Jaeger, Würzburg, Germany) during quiet breathing. Each data point was the mean of five plethysmograph flow signal readings. All pharmacodynamic parameters were expressed as percentages of baseline values.

Determination of Fenoterol Plasma Levels

Fenoterol plasma levels were determined with a published radioimmunoassay procedure (5).

Data Analysis

The statistical analysis of the area under the effect–time curves was generally performed for a 4-hr observation period within the individual groups using the ANOVA module of SYSTAT (Systat Inc., Evanston, IL). For multiple comparisons, the selected significance level ($P < 0.05$) was adjusted by the method of Bonferroni (p/number of comparisons). All pharmacokinetic and pharmacodynamic data were fitted to the relevant equations using the nonlinear curve-fitting program MINSQ (Micromath Scientific Software, Salt Lake City, UT). The model selection criterion (MSC) of MINSQ, a modification of the Akaike information criterion, was used to select the most appropriate model (highest MSC).

Pharmacokinetic Analysis

A compartmental analysis for individual patients was employed, as intercompartmental rate constants were needed for the PK/PD correlation. A three-compartmental model with central elimination was most suitable for the iv bolus data (see Results). This model was also applied to the remaining data to allow the application of a uniform pharmacokinetic model for the PK/PD correlation. The following equations or combinations were used.

Injection

$$C_t = D(A * e^{-\alpha t} + B * e^{-\beta t} + C * e^{-\gamma t}) + C_o * e^{-\gamma t} \quad (1)$$

with D being the dose, A, B, and C the dose-corrected hybrid constants, and α, β, and γ the disposition rate constants. C_o, the experimentically determined residual fenoterol concentration (mean of $t = -10$- and 0-min values, 51 ± 49 pg/ml), was incorporated into the model under the assumption that the terminal phase had been reached. This could be justified from placebo data (see Fig. 2).

Infusion

$$C_t = k_o \left[\frac{A}{\alpha} * (1 - e^{-\alpha t}) + \frac{B}{\beta} * (1 - e^{-\beta t}) + \frac{C}{\gamma} * (1 - e^{-\gamma t})\right] + C_o * e^{-\gamma t} \quad (2)$$

Here, k_o represents the infusion rate.

Postinfusion

$$C_t = k_o \left[\frac{A}{\alpha} * e^{-\alpha t} * (e^{-\tau*\alpha} - 1) + \frac{B}{\beta} * e^{-\beta t} * (e^{-\tau*\beta} - 1) + \frac{C}{\gamma} * e^{-\gamma t} * (e^{-\tau*\gamma} - 1)\right] + C_o * e^{-\gamma t} \quad (3)$$

with τ being the length of the infusion.

Nasal and Inhalative Route

$$C_t = E\left[\frac{k_a(k_{21} - k_a)(k_{31} - k_a)}{(\alpha - k_a)(\beta - k_a)(\gamma - k_a)} * (e^{-k_a t}) + \frac{k_a A}{(k_a - \alpha)} * e^{-\alpha t} + \frac{k_a B}{(k_a - \beta)} * e^{-\beta t} + \frac{k_a C}{(k_a - \gamma)} * e^{-\gamma t}\right] + C_o * e^{-\gamma t} \quad (4)$$

with K_a being the absorption rate constant and k_{21} and k_{31} the transit rate constants. E represents a fusion term containing the volume of distribution (V_d), the dose (D), and the fraction absorbed (F): $E = D * F/V_d$). Microconstants were calculated from the hybrid constants A, B, C, α, β, and γ (6).

The study design was suboptimal for the pharmacokinetic analysis. As the patient conditions did not justify a prolonged treatment-free sampling period after infusion, the terminal elimination phases were determined from iv bolus (group 1 and 2) and nasal administration (group 3). For group 2, all other parameters were determined from simultaneous fits of iv bolus and infusion data. For group 3, the remaining hybrid constants were obtained from infusion data, alone. Infusion data of group 1 were excluded from the pharmacokinetic analysis, as the bolus loading dose in conjunction with the missing postinfusion phase did not allow any reliable pharmacokinetic estimates. The absorption rates for nasal and pulmonary administration were determined from Eq. (4) using the previously determined pharmacokinetic parameters of individual patients. This was done to reduce the number of parameter estimates and the related pitfalls in multiparameter fitting.

The areas under the concentration time curve (AUC_∞), corrected for residual fenoterol, the total-body clearance (CL), the volume of distribution of the central compartment (V_d), and the volume of distribution at steady state ($V_{d_{ss}}$) were calculated by standard methods (6). The fraction absorbed after inhalation and nasal administration was determined from the AUC ratio between nasal (or inhalation) and corresponding iv bolus regimens. This method was feasible, as the oral bioavailibility of fenoterol is very low, 1.5% (7).

Pharmacokinetic-Dynamic Analysis

Several compartmental (parametric) PK/PD models were tested for correlating pharmacokinetic and dynamic data (see Results). As these differed in the definition of the effect compartment (central, peripheral, or hypothetical effect compartment; see Results), various equations had to be derived which describe the time course of drug concentration in these effect compartments. As an example, the concentration–time course in the shallow peripheral compartment (compartment X_{P1} in Scheme I) after nasal administration of fenoterol was calculated from the previously determined pharmacokinetic parameters (Table I):

$$C_e = \frac{FD}{V_d}\left[\frac{k_a k_{21}(k_{31} - k_a)}{(\alpha - k_a)(\beta - k_a)(\gamma - k_a)} * e^{-k_a t} + \frac{k_a k_{12}(k_{21} - \alpha)}{(k_a - \alpha)(\beta - \alpha)(\gamma - \alpha)} * e^{-\alpha t} + \frac{k_a k_{12}(k_{31} - \beta)}{(k_a - \beta)(\alpha - \beta)(\gamma - \beta)} * e^{-\beta t} + \frac{k_a k_{12}(k_{31} - \gamma)}{(k_a - \gamma)(\alpha - \gamma)(\beta - \gamma)} * e^{-\gamma t}\right] \quad (5)$$

C_e was correlated with the pharmacodynamic effects (E) via a sigmoid E_{max} function (8):

$$E = E_0 - \frac{E_{MAX} * C_e^N}{(EC_{50}^N + C_e^N)} \quad (6)$$

Here E_{max} is the maximal response, E_0 is the pharmacodynamic baseline value, EC_{50} the pseudo-steady-state drug concentration causing 50% of E_{max} (8), and N the slope factor, which was set to 1 if not otherwise stated. Nasal instillation, infusion, and injection data were fitted simultaneously, allowing only one EC_{50} for the three groups. However, E_0 and E_{max} were allowed to differ among the groups to adjust for group differences.

RESULTS

Plasma concentration–time curves after iv bolus administration of 12.5 and 25 μg fenoterol (Fig. 1) were best described by an open three-compartment model with central elimination (MSC = 6.5 for a three-compartmental model; MSC = 3.2 for a two-compartment model). The iv infusion data are shown in Fig. 2. The pharmacokinetic parameters resulting from the analysis of the iv data are listed in Table I. ANOVA analysis of the dose-standardized AUCs of the different iv regimens (12.5–225 μg) did not reveal significant differences ($P = 0.189$; power to detect 30% differences at α of 0.05, 64%). Linear regression of the individual dose-normalized AUCs resulted in a slope indistinguishable from zero: AUC = −1 (±7.3) * dose + 1250 (±120).

Table I. Pharmacokinetic Parameters[a]

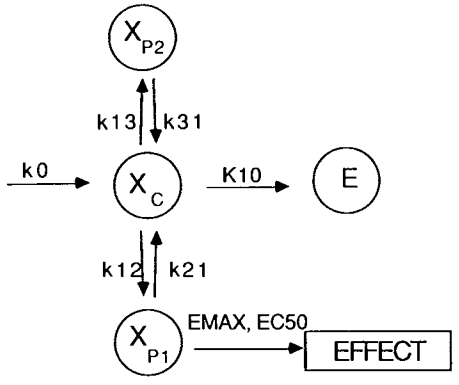
Parameter	Mean	SD	Range
α (L/hr)	45	29	20–137
β (L/hr)	4.0	1.7	1.8–7.2
γ (L/hr)	0.23	0.08	0.07–0.38
k_{31} (L/hr)	0.43	0.16	0.18–0.82
k_{21} (L/hr)	12	10	3.7–40
k_{12} (L/hr)	21	21	6–89
k_{13} (L/hr)	7.3	4.1	4.5–16
Cl (L/hr/kg)	0.87	0.32	0.30–2.3
V_d (L/kg)	0.11	0.08	0.03–0.31
$V_{d_{ss}}$ (L/kg)	1.9	0.8	0.7–4.1
$k_{a(inh)}$ (L/hr)	1.4	0.7	0.8–6.2
$k_{a(nas)}$ (L/hr)	4.9	1.3	3.2–5.4

[a] Mean pharmacokinetic parameters for the 27 patients, standard deviations of the means, and ranges are given.

The plasma concentration/time curve after nasal instillation of 400 μg fenoterol is shown in Fig. 3. On average, 14 ± 6% of the delivered dose was absorbed, with an absorption half-life of 8.9 (±2.3) min. Patients inhaled fenoterol with a high variability (Fig. 3); the average fraction absorbed was 9% (11 ± 9% for 400 μg, 7 ± 9% for the 200-μg dose). The mean absorption half-life was 29 ± 15 min for the 400-μg dose (no reliable estimate could be obtained from the 200-μg data).

Pharmacodynamics

Airway resistance was reduced after injection, infusion,



Scheme I. PK/PD model for constant infusion (k_0) with one of the two peripheral compartments (X_{p1}) as the effect compartment. K_{12}, k_{21}, k_{13}, k_{31}, and k_{10} are the intercompartmental rate constants. E_{max} and EC_{50} are the pharmacodynamic parameters within the E_{max} relationship.

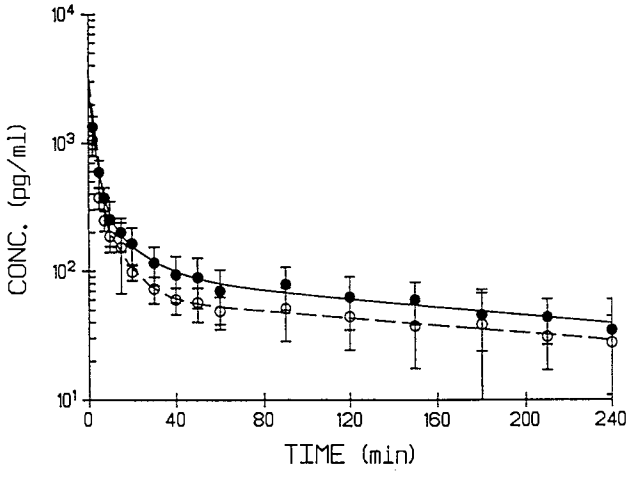


Fig. 1. Plasma concentration–time profiles after intravenous bolus of 12.5 μg (○; group 1) and 25 μg fenoterol (●; group 2).

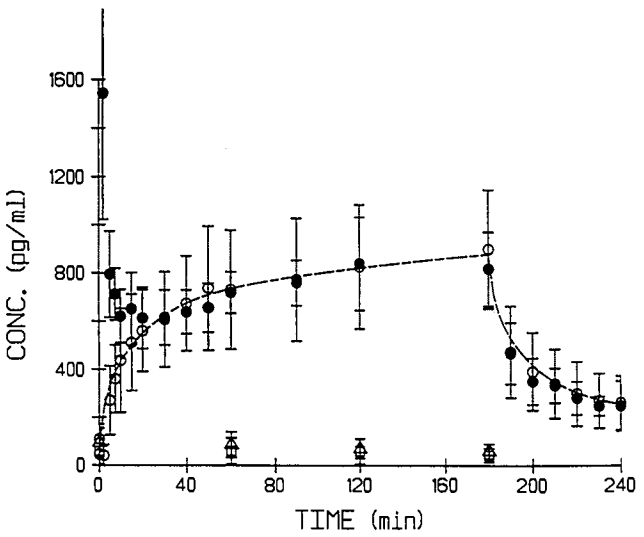


Fig. 2. Plasma concentration–time profiles after intravenous infusion of 200 μg/180 min fenoterol with (●; group 2) and without (○; group 3) 25-μg loading dose. Fenoterol levels for placebo treatment of group 1 (△) and group 2 (□).

nasal administration, and inhalation (Fig. 4) with pronounced intrapatient variability (relative SD for a given time point, 50–70%), which was omitted from the figures for the reason of clarity. When AUCs, as measure of the cumulative effect, were analyzed within the groups over a 4-hr observation period, no significant differences between inhalation and infusion were detected [$P = 0.980$ for group 1 (Gr1), $P = 0.487$ for Gr2, $P = 0.298$ for Gr3; power to detect a 30% difference at α of 0.05, 80%]. Furthermore, the effects after inhalation of 200 and 400 μg fenoterol were statistically not distinguishable ($P = 0.830$).

A significant decrease in the area under the IGV time curve (Fig. 5) was also observed during the 4-hr observation period after inhalation ($P < 0.003$ for Gr1-3) and infusion ($P < 0.002$ for Gr1-3), with no significant differences between administration forms ($P = 0.935$ for Gr1, $P = 0.953$ for Gr2, $P = 0.394$ for Gr3); however, the power of this test was

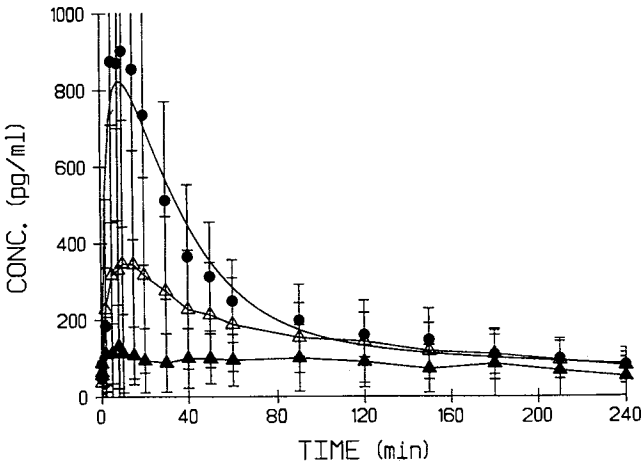


Fig. 3. Plasma levels after nasal administration of 400 μg (●) and after inhalation of 200 μg (▲; group 2) and 400 μg (△; groups 1 + 3) of fenoterol.

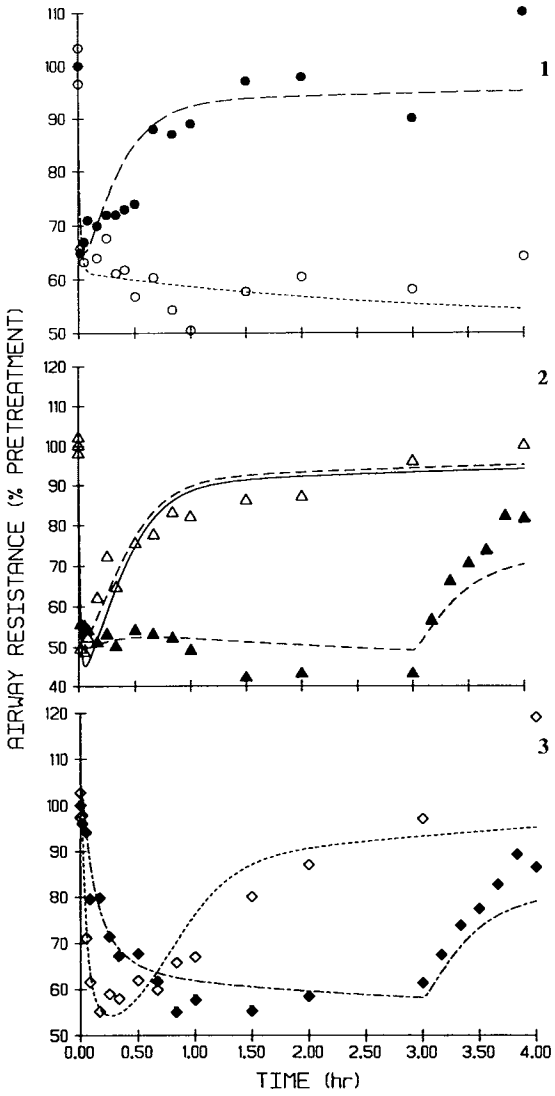


Fig. 4. Mean effects on airway resistance. Group 1: (●) 12.5-μg injection; (○) 12.5-μg bolus + 200-μg/4 hr constant infusion; Group 2: (△) 25-μg injection; (▲) 25-μg bolus + 180-μg/3 hr constant infusion; Group 3: (◇) 400-μg nasal administration; (◆) 180-μg/3 hr constant infusion. Dashed lines represent the model dependent fits. Solid line for group 2: prediction of the effect–time curve for the 25-μg injection.

rather low because of the pronounced variability of the data (power to detect 30% difference at α of 0.05, 47%).

Heart rate, analyzed over a 4-hr period, increased significantly only after infusion (Fig. 6; $P < 0.0001$). For shorter observation periods, significant increases were observed after injection (0–20 min, $P = 0.002$ for Gr1; 0–60 min, $P = 0.004$ for Gr2) and nasal administration (0–60 min, $P = 0.0001$ for Gr3) but not after inhalation (0–60 min, $P = 0.083$ for Gr1 and $P = 0.376$ for Gr2; $P = 0.138$ for Gr3). However, the power of these tests was low (power to detect 30% difference at α of 0.05, 56%).

Pharmacokinetic/Dynamic Correlation

For the airway resistance as a pharmacodynamic parameter, a model with the central compartment as the effect

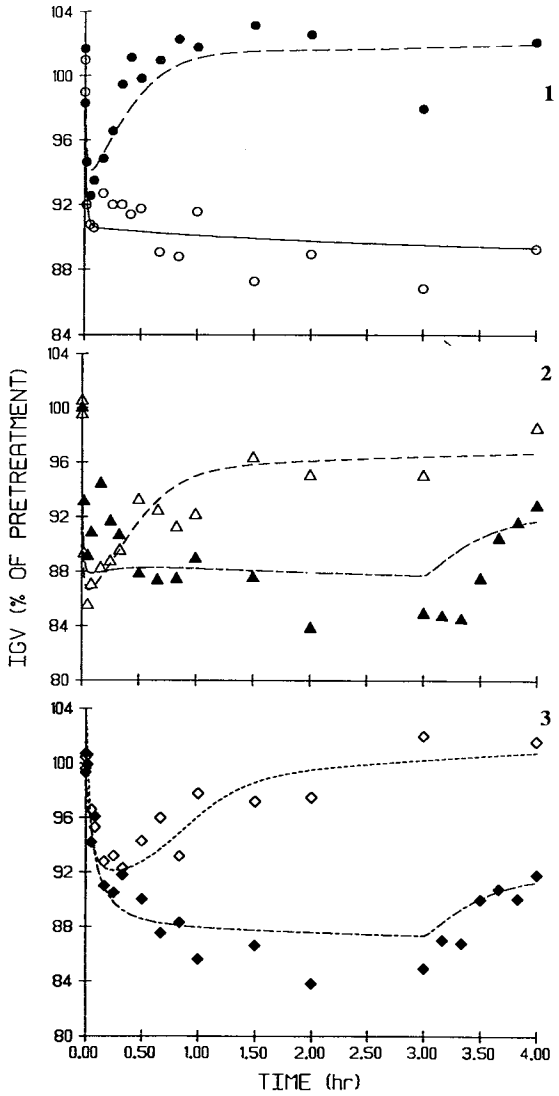


Fig. 5. Mean effects on intrathoracic gas volume. For symbols see the legend to Fig. 4.

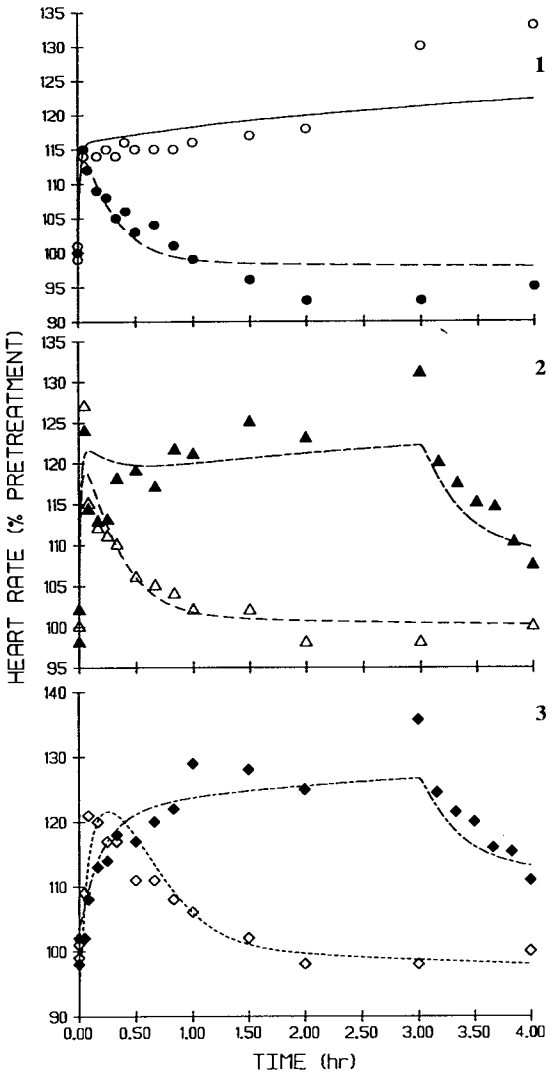


Fig. 6. Mean effects on heart rate. For symbols see the legend to Fig. 4.

compartment described adequately the effect–time profiles observed after injection, infusion, and nasal administration (MSC, 1.48). However, fits improved when the shallower of the two peripheral compartments (MSC, 2.11; Scheme I) but not the deep compartment (MSC, 0.35) was defined as the effect compartment. No further improvement was noticed when predose levels of fenoterol (MSC, 2.06) or the Hill coefficient N (MSC, 2.07) were included in the model. The incorporation of a hypothetical effect compartment, which was linked to the central compartment (8) via a model-dependent rate constant, improved the fit only slightly (MSC, 2.16). The model shown in Scheme I was selected, as it was less complex than the latter model with nearly identical MSC values (2.11/2.16). The same model was also found suitable for correlating heart rate and IGV data. Figures 4–6 show the resulting fits for all pharmacodynamic parameters. The resulting pharmacodynamic parameters are listed in Table II. To demonstrate the prediction power of the correlation, the data set for the airway resistance was reanalyzed without incorporation of the 25-μg injection data. The resulting pharmacodynamic parameters (similar to those shown in Table II) predicted the effect after 25-μg injection (solid line in Fig. 4, group 2).

Airway resistance data were also analyzed for individual patients and administration forms of group 3. Results revealed a distinct interpatient variability (Table III), while the intrapatient variability was less pronounced (Table III).

Attempts to incorporate the inhalation data into the PK/PD-correlation failed for the lung function. Separate data analysis resulted in EC_{50} values 20 times lower than those for noninhalation data. Figure 7 compares the observed effects for airway resistance and heart rate with those predictable with the pharmacodynamic parameters in Table II. Areas under the observed lung function–time curves (400 μg, 10,000 ± 6000 min; 200 μg, 11,000 ± 3500 min) differed clearly from predicted values (400 μg, 4500 min; 200 μg, 2800 min); while changes in heart rate could be predicted.

DISCUSSION

Contrary to previous pharmacokinetic studies in humans (7,9), the availability of a highly sensitive and selective

Table II. Pharmacodynamic Parameter Estimates Based on Noninhalation Data

	EC_{50} (pg/ml)	E_0 (%)[a]	E_{MAX} (%)	Model selection criterion[b]
Airway resistance	380 (±80)	96 (±2)	66 (±7)	2.11 (r = 0.94)[c]
		98 (±2)	72 (±6)	
		103 (±2)	66 (±6)	
IGV	230 (±20)	99 (±1)	14 (±2)	1.71 (r = 0.92)
		98 (±1)	15 (±2)	
		103 (±1)	14 (±2)	
Heart rate	1040 (±460)	97 (±1)	−71 (±14)	1.65 (r = 0.91)
		99 (±2)	−58 (±9)	
		101 (±1)	−65 (±9)	

[a] The three values listed for E_0 and E_{MAX} in every category represent values determined for groups 1–3.
[b] For definition see Materials and Methods.
[c] r = coefficient of correlation for the observed vs the predicted effect.

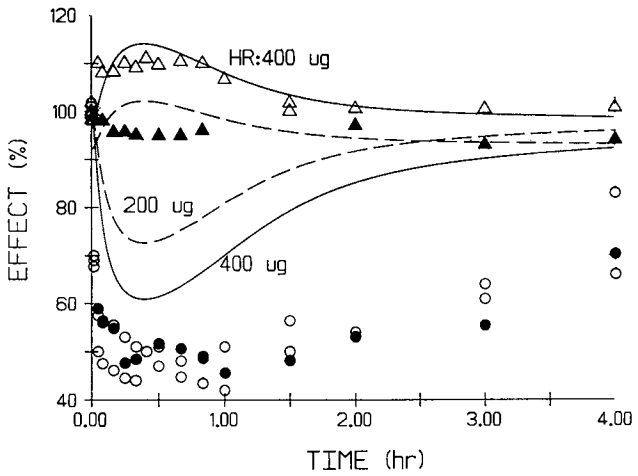


Fig. 7. Airway resistance after inhalation of 200 μg (●, group 2) and 400 μg (○; groups 1 and 3) and model-predicted profiles (dashed and solid lines). Heart rate after inhalation of 200 μg (▲) and 400 μg (△; average of groups 1 and 3) and its predictions are shown.

radioimmunoassay (5) allowed us to evaluate the pharmacokinetics of the intact drug. Although this is a major improvement, the assay was not able to distinguish between the two existing enantiomers. Studies on isolated rat hepatocytes suggested stereoselective glucuronidation of fenoterol enantiomers with a slight (30%) difference in the intrinsic clearances for both enantiomers (10). Although the main metabolite in humans is the sulfate and stereoselective metabolism of fenoterol has not yet been reported in humans, these potential shortcomings should be kept in mind during the pharmacokinetic/dynamic evaluation.

Comparison with other β_2-adrenergic drugs revealed a similar $V_{d_{ss}}$ for fenoterol (140 L), salbutamol [156 L (11)], and terbutaline [83–140 L (12)]. However, fenoterol differs in the total clearance (63 L/hr), which is higher for fenoterol than for salbutamol [29 L/hr (11)] and terbutaline [10–16 L (12)]. After nasal administration, a significant portion of the administered dose (14%) was absorbed, resulting in a pronounced pharmacodynamic effect. Hence, nasal instillation might represent a useful alternative, especially when a comatose patient is not able to use the aerosol.

In contrast, the equipotency of inhalation and constant infusion in improving lung function in conjunction with the significantly smaller cardiac effects after inhalation argues for the proposed benefits of a lung-targeted inhalation approach with a high local efficacy and reduced systemic side effects.

The proposed PK/PD correlation linked satisfactorily the shallow pharmacokinetic compartment to the pharmacodynamic effects. Further, the correlation was able to predict rather well the effect–time course of "unknown" dosage regimens (Fig. 4).

The EC_{50} as one integral pharmacodynamic parameter allows one to probe for the activity of a drug at the site of action. As the EC_{50} values for airway resistance and IGV were rather similar (Table II), with differences within the statistical error, both processes are likely to be mediated via the same receptor subtypes. The EC_{50} of 11.3 nM for terbutaline (4), a drug with nearly identical volumes of distribution (12), suggests a 10- to 15-fold higher activity of fenoterol (EC_{50}, 0.75–1.2 nmol/l) at the site of action. Interestingly, similar activity differences were reported for the effects on cAMP accumulation in intact S49 cells (13).

The heart rate was investigated as an indicator for systemic, predominantly β_1-receptor-mediated cardiovascular side effects. EC_{50} values for this parameter were three to five times higher than those for the β_2-mediated lung function, indicating the potential of the PK/PD correlation to identify effects mediated via different receptor subtypes.

It is known that a great variation toward bronchodilator therapy exists among asthmatic patients. Not surprisingly, the area under the effect–time curves differed considerably among the patients, with standard deviations of the area under the effect–time curves close to 100% for a given treatment schedule (data not shown). It was therefore of interest to apply the PK/PD correlation to the assessment of intra- and interpatient variabilities on the pharmacodynamic level (EC_{50}, E_{max}; Table III). Analysis of nasal and infusion data for individual patients in group 3 resulted in estimates which were within the statistical error of the analysis. This is in agreement with the stable clinical conditions of the patients. In contrast, differences in the pharmacodynamic parameters

Table III. Intra-/Interpatient Variability[a]

	EC_{50} (pg/ml)		E_{MAX} (%)	
Patient	Nasal	Infusion	Nasal	Infusion
AK	88 (±53)	210 (±139)	100 (±16)	100 (±21)
HL	420 (±290)	430 (±260)	44 (±9)	36 (±8)
HK	67 (±27)	350 (±96)	72 (±7.9)	73 (±22)
LL	1100 (±1600)	1200 (±2900)	99 (±81)	100 (±160)
MD	210 (±76)	110 (±100)	58 (±7)	52 (±16)
MH	280 (±220)	140 (±150)	84 (±22)	42 (±11)
PH	860 (±1200)	820 (±430)	100 (±89)	100 (±28)

[a] Data for infusion and nasal administration were analyzed for individual patients using pharmacokinetic parameters of the individual patients.

among different patients were pronounced with standard deviations of about 90%. Hence, the interpatient differences in therapeutic effect can be attributed to both pharmacokinetic and pharmacodynamic factors.

In contrast to the systemic side effects (heart rate), lung function after inhalation (Fig. 7) could not be incorporated into the correlation. Although this outcome was to be expected, our data allow us for the first time to quantify the local component of the inhalation therapy by comparing the observed effects after inhalation with those predictable from fenoterol plasma levels. The two- to fourfold difference between observed and predicted AUCs for the two inhalation dosages demonstrates that inhalation of fenoterol achieves lung-specific drug targeting.

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