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Chapter 3

Pharmacokinetic/pharmacodynamic modelling of the eosinopenic and hypokalemic effects of formoterol and theophylline combination in man

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PK/PD interactions of formoterol and theophylline were evaluated. Oral doses of 144 \( \mu \)g of formoterol and 375 mg of theophylline were given separately or combined to healthy subjects. As effect parameters, eosinophil and potassium concentrations in blood were used. Kinetic interactions between formoterol and theophylline were not found. Observed effects were described using an effect compartment model in combination with a sigmoid \( E_{\text{max}} \) model. The \( E_{\text{max}} \) values ± SD for the hypokalemic effects were 2.29 ± 0.78 mmol/l for formoterol and 1.64 ± 1.16 mmol/l for theophylline (p > 0.05). The \( E_{\text{max}} \) values for the eosinopenic effects were fixed at zero. The EC\(_{50}\) values of the eosinopenic and hypokalemic effects were respectively 91.4 ± 38.2 pg/ml and 128.4 ± 52.9 pg/ml for formoterol, and 11.9 ± 4.6 \( \mu \)g/ml and 15.5 ± 4.8 \( \mu \)g/ml for theophylline. Effects of both drugs combined were described with a non-competitive interaction model. \( E_m \), the maximal achievable effect of the effector system is introduced in this model. The \( E_m \) value for the hypokalemic effects was 0.74 ± 1.02 mmol/l, and zero for the eosinopenic effects. The correlation coefficients of the fits of the eosinopenic and hypokalemic effects were respectively 0.9520 ± 0.0311 and 0.9371 ± 0.0227, supporting our hypothesis of non-competitive interaction.

INTRODUCTION

Formoterol is a long-acting \( \beta_2 \)-adrenoceptor agonist that is used for bronchodilation in asthmatic patients, especially in those who need a prolonged bronchodilation, as in nocturnal asthma. As inhalation medication it has proven to be an effective bronchodilator with a rapid onset of action and a long duration of bronchodilatory effect, lasting more than 12 hours \(^4\). Theophylline induces a modest short lasting effect in large airways \(^5\)-\(^7\) and a more pronounced effect in peripheral airways \(^8\)-\(^9\).

Both the use of \( \beta_2 \)-adrenoceptor agonists and theophylline in the treatment of mild to moderate asthmatic patients has been under much debate lately \(^10\),\(^11\). As for \( \beta_2 \)-adrenoceptor agonists, the concern about a rise in asthma mortality \(^12\),\(^13\) and the
PK/PD modelling of combined formoterol and theophylline

observed tachyphylaxis on the one hand and either possible pro-inflammatory or advantageous anti-inflammatory properties on the other hand, have lead to much discussion. Concerning theophylline, questions have been raised about its usefulness, toxicity and mode of action with also possibly anti-inflammatory effects, especially in low doses. The above indicates the need for more detailed pharmacokinetic/pharmacodynamic research with these drugs. Furthermore, the knowledge of possible kinetic and/or dynamic interactions will be important for optimising the prescription of both drugs simultaneously. The development of a sensitive and selective assay for formoterol after oral administration in healthy subjects was described. The formoterol-induced eosinopenia most likely represents a redistribution of peripheral eosinophils and could hypothetically serve as a surrogate marker for anti-inflammatory activity. Plasma potassium can possibly be used as an alternative parameter for $\beta_2$-adrenoceptor induced FEV$_1$ variations. Theophylline has also shown to decrease eosinophils and potassium in humans.

As formoterol and theophylline increase cyclic AMP most probably via different mechanisms, we set out to test the hypothesis that the effects of both drugs, if given in combination, could be described with a non-competitive interaction model. For this purpose, the pharmacokinetic and pharmacodynamic aspects of formoterol and theophylline were studied after separate and combined administrations to healthy subjects.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of the Academic Medical Center in Amsterdam. Eight healthy, male, non-smoking subjects with a mean age of 22.5 years (range: 19-29) and a mean weight of 75 kg (range: 67-84) were selected, after informed consent had been obtained. Health problems, drug or alcohol abuse and abnormalities in laboratory screening were exclusion-criteria. The subjects received either formoterol or theophylline or both drugs combined, on three different days, each separated by one week. Because of the set-up of the study, the groups were not randomised.
The subjects arrived at the hospital at 8.00 am. An indwelling cannula was inserted in a forearm vein and remained in situ during the entire day, enabling frequent blood collection. The system was kept patent with heparinized saline solution.

During the examination days, any physical strain was to be avoided. A light breakfast was allowed after the study medication had been administered. Caffeinated drinks were not allowed and a standardised lunch was provided.

On each experimental day, before drug administration, blood samples were taken for base line potassium and eosinophil measurements and to exclude the presence of substances that could interfere with the drug determinations. At $t=0$, the subjects were given a single oral dose of 144 $\mu$g formoterol, 375 mg theophylline or both. Drugs were administered in capsulated form. At 15, 30, 45, 60, 90, 120, 180, 240, 330 and 450 minutes after drug administration, blood samples were taken for measurements of formoterol and/or theophylline plasma concentrations, as well as plasma potassium levels and peripheral eosinophil counts. Blood samples were centrifuged for 10 minutes at 4000 rpm immediately after collection. Plasma samples for formoterol or theophylline concentration analysis were stored at -20 °C. The plasma samples for potassium measurements were analysed immediately in the laboratory of the Dept. of Clinical Pharmacology and those for the eosinophil counts were transported as soon as possible to the Laboratory of Clinical Chemistry of the hospital.

Formoterol assay
Plasma levels of formoterol were analysed using an HPLC method with electrochemical detection as described previously. Bromo-formoterol was used as an internal standard. Reversed-phase extraction was carried out, using 1ml PRS-columns. A C8 analytical column was employed in the chromatographic system. The level of quantitation of the assay was 20 pg formoterol per ml plasma. However, due to variation of the sensitivity of the electrochemical detector, the limit of detection, with a signal to noise ratio of 3 to 1, could be as low as 10 pg/ml. In order to improve precision of the concentration measurements, each measurement was performed in duplicate. Daily a calibration curve was made.
Theophylline assay
Plasma levels of theophylline were analysed using an HPLC method with UV detection as described by Cooper et al.\textsuperscript{43}. In order to improve precision of the concentration measurements, each measurement was performed in duplicate. Daily, a new calibration curve was made.

Measurements
For potassium measurements a conventional flame photometer (model 143, Instrumentation Laboratory Inc.) was used. Total blood eosinophil counts were determined with a Technicon H6000 automated differential leukocyte counter using peroxidase enzyme detection.

Data analysis
All pharmacokinetic data were fitted to the appropriate equations using a nonlinear regression computer program\textsuperscript{44}. A tri-exponential equation describing a two-compartment open model with first order absorption was employed to describe formoterol and theophylline pharmacokinetics\textsuperscript{45}.

\[
C_t = A \times e^{-\alpha \cdot (t-t_{lag})} + B \times e^{-\beta \cdot (t-t_{lag})} - (A + B) \times e^{-k_a \cdot (t-t_{lag})}
\]

Estimates were thus obtained for \( C_t \), the concentration calculated for formoterol (pg/ml) or theophylline (\( \mu \)g/ml) at time \( t \), \( k_a \), the absorption rate constant, \( \alpha \) and \( \beta \), the rate constants of the first, rapid and the second, slower distribution, and \( A \) and \( B \), their respective intercepts; \( t_{lag} \) is the time from dosing to the start of the absorption. From these parameters the AUC was calculated.

As the bioavailability after oral administration in these experiments remains unknown, especially for formoterol, the V\textsubscript{area} is expressed as V\textsubscript{d}/F and used as such in further calculations. This does not influence the AUC values because the V is not involved in AUC calculations.

To relate the effects of the formoterol or the theophylline plasma concentrations on plasma potassium concentrations and peripheral eosinophil counts, a sigmoid baseline \( E_{max} \) function as previously described\textsuperscript{46} was applied:
In this equation, $E_0$ is the baseline potassium or eosinophil level; $EC_{50}$ is the $C_e$ that corresponds with 50% of the maximum achievable effect ($E_0 - E_{max}$) and $n$ is the factor expressing the steepness of the concentration-effect relationship. To account for the delay between formoterol or theophylline peak plasma concentration ($t_{maxC}$) and the hypokalemic or eosinopenic nadir, an effect compartment as described by Holford and Sheiner was included in the model. The time course of drug concentrations in the hypothetical effect compartment ($C_e$) for two-compartment kinetics is described by the following equation $^{47}$:

$$C_e = \frac{dose \cdot k_{a} \cdot k_{e0}}{V_c} \cdot \left[ \frac{(k_{21} - \alpha)e^{-\alpha(t-tlag)}}{(\beta - \alpha)(k_{21} - \alpha)(k_{e0} - \alpha)} + \frac{(k_{21} - k_e) e^{-k_e(t-tlag)}}{(\alpha - k_e)(\beta - k_e)(k_{e0} - k_e)} + \frac{(k_{21} - k_e) e^{-k_e(t-tlag)}}{(\alpha - k_e)(\beta - k_e)(k_{e0} - k_e)} \right]$$

In this equation, $V_c$ is the volume of the central compartment, $k_{e0}$ is the rate constant for the elimination of formoterol or theophylline from the effect compartment, $k_{21}$ is the rate constant for transfer of the drug from the peripheral to the central compartment. The only new parameter in this formula is the $k_{e0}$, because the $k_{21}$ and the $V_c$ can be calculated from the previously estimated PK parameters.
The effect data were fitted to an integrated model, consisting of the $E_{\text{max}}$ equation and the $C_e$ equation, using the previously estimated pharmacokinetic parameters of formoterol and theophylline as constants. The sigmoid factor $n$ was estimated by PCNONLIN between predefined integer values of 0 and 5. The upper limit of $k_{e0}$ was fixed at 4.

For the eosinopenic effect induced by formoterol or theophylline, $E_{\text{max}}$-values were fixed to zero, as in all subjects a tendency of the values towards zero was observed when $E_{\text{max}}$ was introduced as a free parameter.

To describe the observed effects after the combined administrations of formoterol together with theophylline, the following equation for non-competitive interaction as given by Ariens and Simonis was used:

$$E_{A+B} = \frac{E_A}{E_m} + \frac{E_B}{E_m} - \frac{E_A + E_B}{E_m^2}$$

In this equation $E_{A+B}$ is the combined effect of both drugs, $E_A$ and $E_B$ are the single drug effects and $E_m$ is the maximum achievable effect of the receptor-effector system. In order to describe effects characterised by a decline from baseline and to incorporate effect compartment concentrations for both drugs we adapted the above formula as follows:

$$E_{\text{comb}} - E_{0 \text{comb}} = \left( \frac{(E_{0 \text{comb}} - E_{\text{max} A}) \cdot C_{e A}^n + (E_{0 \text{comb}} - E_{\text{max} B}) \cdot C_{e B}^n}{EC50_A^n + C_{e A}^n} \right)$$

$$- \left( \frac{(E_{0 \text{comb}} - E_{\text{max} A}) \cdot C_{e A}^n + (E_{0 \text{comb}} - E_{\text{max} B}) \cdot C_{e B}^n}{EC50_B^n + C_{e B}^n} \right)$$

In this equation $E_{\text{comb}}$ is the effect of the combined formoterol and theophylline administration, $E_{0 \text{comb}}$ is the baseline of the combined effect. $E_m$ again is the
hypothetical maximum achievable effect of the receptor effector system. For the description of the effects on plasma potassium, $E_m$, $E_0$comb, $E_{maxA}$ and $E_{maxB}$ were estimated as parameters. However, similar to the modelling procedure of eosinopenic effects after single drug administrations $E_{maxA}$, $E_{maxB}$ and consequently the maximum achievable effect of the system $E_m$ were fixed at zero. For the remaining parameters, values as obtained for the concentration effect relationships after single drug administrations were used.

**Statistics**

For each single drug, pair-wise comparisons of the pharmacodynamic parameters for the effects on potassium and eosinophils were made with the Wilcoxon signed-ranks test for matched pairs. For comparisons of unpaired data the two-sample t-test was used.

**RESULTS**

On the three experimental days (formoterol, theophylline and the two drugs combined), the mean ± SD baseline levels of plasma potassium were respectively 4.06 ± 0.16 mmol/l, 4.11 ± 0.10 mmol/l and 3.94 ± 0.12 mmol/l. Baseline levels of blood eosinophil counts on the three days were respectively 190.2 ± 157.8 x 10^6/l, 195.5 ± 173.9 x 10^6/l and 250.5 ± 202.0 x 10^6/l. The mean potassium baseline values on the day that the drugs were given together, was statistically different from those on the formoterol and theophylline days (p=0.0234 and p=0.0391). There were no statistically significant differences for baseline levels of blood eosinophil counts.

All plasma concentration levels of formoterol and theophylline were within detectable range. Mean peak concentrations ± SD of formoterol and theophylline after the single drug administrations were observed at respectively 1.0 ± 0.62 and 0.37 ± 0.32 hours with values of respectively 137 ± 40 pg/ml and 13.1 ± 7.2 μg/ml. For both formoterol and theophylline the individual concentration-time curves were best described with a two-compartment open model with first order absorption. Mean ± SD pharmacokinetic parameters estimated after single and combined administrations of formoterol and theophylline are shown in table 1.
Unreliable estimates of the pharmacokinetic parameters were obtained for one of the eight formoterol series and of two of the eight theophylline series, judged by the poor fits of the concentration data or intercurrent peaks in the chromatograms. These parameters were not used for the calculation of means. Neither the kinetic parameters for formoterol nor those for theophylline showed statistically significant differences between the days of single and those of combined drug administration.

After administration of a single dose of formoterol, a lowering effect on potassium concentration and on peripheral eosinophils was observed in all subjects. The hypokalemic effect data were described with a mean ± SD correlation coefficient of 0.949 ± 0.024. For the eosinopenic effect, mean ± SD correlation coefficient 0.933 ± 0.027. The mean ± SD estimated nadir of the potassium and eosinophil lowering effects of formoterol occurred at respectively 2.0 ± 0.87 and 3.0 ± 1.16 hour. Mean ± SD estimated nadir values, expressed as change from baseline were 20% (± 4.5%) for potassium and 51% (± 12.3%) for eosinophils. Time courses of formoterol concentrations and of the formoterol induced effects on potassium and eosinophils as determined for a representative subject are shown in fig. 1.

After administration of a single dose of 375 mg theophylline, a potassium lowering effect was observed in all subjects. The models described the effects with a mean ± SD correlation coefficient of 0.849 ± 0.095. The estimated nadir mean ± SD expressed as change from baseline was 10% ± 3.9% and occurred 0.5 ± 0.27 h after dosing. In 2 subjects (no. 3 and 7) no consistent theophylline induced eosinopenic effect was detectable. The mean ± SD correlation coefficient of the fits obtained for the other 6 subjects was 0.757 ± 0.184. The estimated nadir occurred at 3.0 ± 0.79 h and the magnitude expressed as change from baseline was 16 ± 32.5%. Time courses of theophylline concentrations and of the theophylline induced effects on potassium and eosinophils as measured in a representative subject are shown in figure 2.

After administration of a combination of 144 µg formoterol and 375 mg theophylline, the observed effects were more pronounced than after single drug administrations, but less than could have been expected from a summation of the single drug effects. Mean effect-time curves, expressed as change from baseline, for potassium and eosinophils after formoterol, theophylline and their
combination are shown in figure 3. When the observed hypokalemic effects of both drugs combined were described with the non-competitive interaction model, a mean correlation coefficient $\pm$ SD (n=8) of 0.9371 $\pm$ 0.0227 was obtained. For 3 subjects, 2 of which had not shown consistent theophylline induced eosinopenic effect, the scatter of eosinophil counts after the combined drug administration was too large for reliable analysis. For the remaining five subjects, effect-time curves for eosinopenic effects could be described with the non-competitive interaction model.

The nadir mean $\pm$ SD of the potassium and eosinophil lowering effects were now observed at respectively 1.5 $\pm$ 0.80 h and 4.0 $\pm$ 1.27 h. Mean $\pm$ SD nadir values, expressed as change from baseline, were 24 $\pm$ 6.4% for potassium and 58 $\pm$ 12.3% for eosinophils.

The results with individual parameters for the effects on plasma potassium and blood eosinophil counts after the combined administration of formoterol and theophylline are shown in table 3. The observed effect-time courses in a representative subject, together with the calculated effect-time courses for the three days, are shown in figure 4a and figure 4b.

Table 1. Mean kinetic parameters after administration of 144 $\mu$g of formoterol (FOR), 375 mg of theophylline (THEO) or combined (FOR+T and THEO +F).

<table>
<thead>
<tr>
<th></th>
<th>$K_a$</th>
<th>A</th>
<th>$\alpha$</th>
<th>B</th>
<th>$\beta$</th>
<th>$V_d/F$</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(h$^{-1}$)</td>
<td>(pg(\mu g). ml$^{-1}$)</td>
<td>(h$^{-1}$)</td>
<td>(pg(\mu g). ml$^{-1}$)</td>
<td>(h$^{-1}$)</td>
<td>(L)</td>
<td>(pg(\mu g). h.ml$^{-1}$)</td>
</tr>
<tr>
<td>FOR (n=7)</td>
<td>4</td>
<td>284</td>
<td>2.2</td>
<td>133</td>
<td>0.17</td>
<td>1123</td>
<td>1277</td>
</tr>
<tr>
<td>SD</td>
<td>2.9</td>
<td>97</td>
<td>1.8</td>
<td>62</td>
<td>0.11</td>
<td>607</td>
<td>697</td>
</tr>
<tr>
<td>FOR+T (n=8)</td>
<td>3.7</td>
<td>225</td>
<td>2.1</td>
<td>111</td>
<td>0.17</td>
<td>1273</td>
<td>931</td>
</tr>
<tr>
<td>SD</td>
<td>2.3</td>
<td>89</td>
<td>1.6</td>
<td>55</td>
<td>0.1</td>
<td>509</td>
<td>660</td>
</tr>
<tr>
<td>THEO (n=6)</td>
<td>9.6</td>
<td>24.9</td>
<td>4.5</td>
<td>8.9</td>
<td>0.1</td>
<td>41.5</td>
<td>98</td>
</tr>
<tr>
<td>SD</td>
<td>1.7</td>
<td>12.7</td>
<td>2</td>
<td>11.7</td>
<td>0</td>
<td>8.5</td>
<td>30</td>
</tr>
<tr>
<td>THEO+F (n=8)</td>
<td>9.7</td>
<td>47.4</td>
<td>5.6</td>
<td>8</td>
<td>0.1</td>
<td>48</td>
<td>101</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
<td>57</td>
<td>2.8</td>
<td>2</td>
<td>0</td>
<td>12.4</td>
<td>30</td>
</tr>
</tbody>
</table>

58
PK/PD modelling of combined formoterol and theophylline

Fig. 1. Formoterol plasma concentration effect relation.

a: Observed plasma concentrations (●), plasma potassium (□), the concentration in the hypothetical effect compartment (dotted line) and the calculated concentration and effect curves (solid lines).

b: Observed plasma concentrations (●), plasma eosinophils (□), the concentration in the hypothetical effect compartment (dotted line) and the calculated concentration and effect curves (solid lines).
Fig. 2. Theophylline plasma concentration effect relation.

a: Observed plasma concentrations (●), plasma potassium (□), the concentration in the hypothetical effect compartment (dotted line) and the calculated concentration and effect curves (solid lines).

b: Observed plasma concentrations (●), plasma eosinophils (□), the concentration in the hypothetical effect compartment (dotted line) and the calculated concentration and effect curves (solid lines).
PK/PD modelling of combined formoterol and theophylline

Table 2. Pharmacodynamic parameters after single drug administration of 144 μg formoterol or 375 mg theophylline.

<table>
<thead>
<tr>
<th>Formoterol</th>
<th>Potassium</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>EC₅₀ (pg.ml⁻¹)</td>
<td>n</td>
</tr>
<tr>
<td>1.</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>2.</td>
<td>160</td>
<td>3</td>
</tr>
<tr>
<td>3.</td>
<td>180</td>
<td>2</td>
</tr>
<tr>
<td>4.</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>5.</td>
<td>200</td>
<td>2</td>
</tr>
<tr>
<td>6.</td>
<td>142</td>
<td>2</td>
</tr>
<tr>
<td>7.</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>8.</td>
<td>132</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>128.4</td>
<td>2</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Theophylline</th>
<th>Potassium</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>EC₅₀ (μg.ml⁻¹)</td>
<td>n</td>
</tr>
<tr>
<td>1.</td>
<td>24.8</td>
<td>2</td>
</tr>
<tr>
<td>2.</td>
<td>19.3</td>
<td>4</td>
</tr>
<tr>
<td>3.</td>
<td>16.3</td>
<td>4</td>
</tr>
<tr>
<td>4.</td>
<td>13.9</td>
<td>2</td>
</tr>
<tr>
<td>5.</td>
<td>9.4</td>
<td>4</td>
</tr>
<tr>
<td>6.</td>
<td>13.8</td>
<td>4</td>
</tr>
<tr>
<td>7.</td>
<td>11.8</td>
<td>4</td>
</tr>
<tr>
<td>8.</td>
<td>14.5</td>
<td>2</td>
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<tr>
<td>Mean</td>
<td>15.5</td>
<td>3.2</td>
</tr>
<tr>
<td>SD</td>
<td>4.8</td>
<td>1.0</td>
</tr>
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</table>
In table 2, values are shown of the individual dynamic parameters of the effects of formoterol or theophylline on eosinophils and potassium after single drug administrations. When unreliable kinetic parameters made it impossible to estimate dynamic parameters, the kinetic parameters obtained for the corresponding subjects on the day of combined drug administration were used. The mean ± SD $E_{\text{max}}$ values for the hypokalemic effects were $2.29 \pm 0.78$ mmol/l (n=8) for formoterol and $1.64 \pm 1.16$ mmol/l (n=8) for theophylline ($p > 0.05$). The mean ± SD $EC_{50}$ values of the hypokalemic and eosinopenic effects were respectively $128.4 \pm 52.9$ pg/ml (n=8) and $91.4 \pm 38.2$ pg/ml (n=8) for formoterol, and $15.5 \pm 4.8$ µg/ml (n=8) and $11.9 \pm 4.6$ µg/ml (n=6) for theophylline. The estimates for $EC_{50}$ and for the sigmoid factor for the two effects, did not show statistically significant differences. However, differences were found for the $k_{e0}$ values ($p=0.0086$), the one for the eosinopenic effects being approximately half the size of the $k_{e0}$ for the hypokalemic effects.

Table 3. Individual pharmacodynamic parameters describing a hypokalemic and an eosinopenic effect after administration of a combination of 144 µg formoterol and 375 mg theophylline, using a model for non-competitive agonism.

<table>
<thead>
<tr>
<th>Subject corr.</th>
<th>$E_0$ (mmol.L$^{-1}$)</th>
<th>$E_{\text{max}}$F (mmol.L$^{-1}$)</th>
<th>$E_{\text{max}}$T (mmol.L$^{-1}$)</th>
<th>$E_m$ (mmol.L$^{-1}$)</th>
<th>corr.</th>
<th>$E_0$ (10$^6$.L$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94</td>
<td>4</td>
<td>0.5</td>
<td>2.47</td>
<td></td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>3.98</td>
<td>1.26</td>
<td>1.16</td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
<td>3.80</td>
<td>0.30</td>
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<tr>
<td>4</td>
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<td>7</td>
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<td>1.45</td>
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<td></td>
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<td>8</td>
<td>95</td>
<td>3.94</td>
<td>2.27</td>
<td>3.26</td>
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<td>95</td>
</tr>
<tr>
<td>Mean SD</td>
<td>94</td>
<td>3.94</td>
<td>1.83</td>
<td>2.25</td>
<td>0.74</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12</td>
<td>111</td>
<td>113</td>
<td>102</td>
<td>3</td>
</tr>
</tbody>
</table>

Potassium      | Eosinophils

E$_{\text{max}}$F=0

E$_{\text{max}}$T=0

$E_{\text{m}}=0$

Mean

SD

62
DISCUSSION

The use of drug combinations is far from exceptional in asthma therapy and possibilities for drug interactions are a reality. Such interactions can be either unwanted or can have advantageous outcomes. PK/PD modelling can be suitable to study combined drug use and differentiate between kinetic or dynamic mechanisms for drug interactions \(^{46}\).

The difficulties one can encounter with PK/PD modelling as applied to bronchial asthma have been discussed \(^{49}\). Asthma medications are mainly administered via inhalation. This often precludes concentration ('kinetic') analysis because of very low systemic concentrations. This difficulty can be overcome by using less conventional routes of administration, e.g. intra-muscular \(^{23,50}\) or oral as in the present study. To ensure plasma concentrations of formoterol within a detectable range, a relatively high oral dose of 6 times the advised daily inhalation dose was used in the present study. A recent kinetic study of formoterol RR and SS enantiomers in urine after 4 different doses did not give indication for the existence of dose dependent kinetics \(^{51}\). Concentration-effect curves of formoterol and theophylline could be described nicely using a tri-exponential equation describing a two-compartment model. Kinetic interaction between formoterol and theophylline was not found, as the kinetic parameters did not differ significantly between single and combined administration.

Although in the present study somewhat higher EC_{50} values were estimated for the effects on plasma potassium and peripheral eosinophils than in a previous study \(^{35}\), it is remarkable that in both studies the ratio of the potassium EC_{50} / eosinophil EC_{50} was identical, being 1.4. The effects of formoterol or theophylline alone on plasma potassium and peripheral eosinophils, could be described satisfyingly using an effect compartment with an integrated E_{max} formula. The observed eosinopenic effect possibly reflects anti-inflammatory action \(^{36-39}\). Redistribution of eosinophils out of the systemic circulation most likely plays an important role. Whether or not this redistribution is beneficial to asthma patients is not clear.

By using a dynamic model, based on theory of non-competitive agonism, we were able to describe effects on potassium and eosinophils induced by formoterol, theophylline and their combination. Both effects were more profound after administration of the combination than after single drug administrations.
Fig. 3. Observed effects, expressed as % change from baseline value after administration of formoterol (dotted line), theophylline (hair line) or their combination (fat line). a: Effect on potassium. b: Effect on eosinophils.
Fig. 4. Representative curves of observed and calculated effects on plasma potassium (a) and on eosinophils (b), after combined administration of formoterol and theophylline, applying a model for non-competitive agonism. Effect induced by formoterol (dotted line), by theophylline (hairline) or their combination (fat line).
Previously, we have used models for competitive agonism\textsuperscript{52} and for competitive antagonism\textsuperscript{53,54} to get more insight in the pharmacology of asthma medications in human subjects. However, to our knowledge a model for non-competitive agonism has not been used before for the in-vivo study of drug action of pulmonary medication in man. The $E_{\text{max}}$ value for eosinopenic effect was fixed at zero, as in all subjects this value reached zero when initial values were estimated within a broad range of freedom. The observed eosinopenic effect is far more profound after administration of formoterol than after theophylline. As has been suggested before, plasma potassium can be used as surrogate marker for FEV\textsubscript{1} values and possibly can give an indication of effects in the lung\textsuperscript{40,49}. Taking into consideration that the observed hypokalemic effect hypothetically reflects effect on lung function, administration of formoterol and theophylline combined could have a more favourable effect on bronchodilation than single drug administrations alone.

We conclude that administration of a combination of formoterol and theophylline shows no kinetic interaction. Administration of formoterol or theophylline induces an hypokalemic and an eosinopenic effect. The observed hypokalemic and eosinopenic effects caused by the combination of formoterol and theophylline are more pronounced as compared to single drug administrations. The observed effects can be described using a model, based on formulas for non-competitive agonism.

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PK/PD modelling of combined formoterol and theophylline


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PK/PD modelling of combined formoterol and theophylline


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