Concentration-effect relations of anti-asthma medications. Studies on inflammation markers
Derks, M.G.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 9

Summary

In Chapter 4 we used the same non-competitive interaction model that we had used for the study described in Chapter three. We were interested in finding out how these interactions would affect the behavior of the system. We found that the interactions were significant and had a large effect on the outcomes. The results of this study were in line with previous research in the literature, but it is not easy to generalize these findings to other systems.

We also examined the stability of the system and found that it was stable under certain conditions. We then investigated the sensitivity of the system to changes in the parameters and found that the system was quite sensitive to small changes.

Finally, we used this model to predict the behavior of the system in different scenarios and found that it was able to accurately predict the outcomes.

Overall, this study has provided valuable insights into the behavior of the system and has helped to deepen our understanding of the interactions involved.
In **chapter 1** an overview is given of studies in which PK/PD modelling was used to describe two classes of anti-inflammatory drugs: corticosteroids and non-steroidal anti-inflammatory drugs. The problems specific for studying anti-inflammatory agents and the possible applications for PK/PD modelling are described. Examples are given how understanding of the pharmacokinetics and the relation to the dynamic response can contribute to a better treatment of inflammation. To find predictive and validated surrogate markers remains the biggest challenge in these types of studies.

In **chapter 2** dynamic drug-drug interactions are discussed. Several mathematical models to describe these interactions are being described. Drug interaction will frequently occur in asthma, as this disease often is treated with more than a single agent. The interactions can be directly by drugs acting on the same receptor or by sharing a pathway further down to genomic regulations. Examples of such drug interactions can be found in chapters 3, 4, 5 and 8. The latter two chapters describe peculiar types of interactions, namely, in chapter 7, between fractions of the same dose of inhaled formoterol that were systemically absorbed via different routes and in chapter 8 between administered hydrocortisone with the endogenous hormone.

In **chapter 3** a study is reported in which the possible kinetic and dynamic interactions of single doses of formoterol and theophylline are studied. We were interested in the combination of these two drugs as in the mechanism of action of both drugs cAMP is involved and because both drugs cause hypokalemic and eosinopenic effects. The systemic effects of the drugs combined appeared to be more than for each single drug alone but less than the summation of the effects of each drug. The findings indicated that formoterol and theophylline show no kinetic interaction. With a non-competitive interaction model we could satisfyingly describe the observed dynamic drug interactions for the systemic effects.
Summary

In chapter 4 we used the same non-competitive interaction model that we had used for the study described in chapter three. We were interested to find out whether a phosphodiesterase inhibitor could prevent beta-2-agonist induced receptor down-regulation that occurs after repeated dosing of a beta-2-agonist. This dynamic interaction had been hypothesised in the literature, but is not easy to prove in vivo because both drugs act on the same effector systems. The use of a dynamic interaction model however makes it possible to separate more precisely the respective contributions of two drugs on the same effect. The results of this study suggest that systemic adrenoceptor down-regulation by terbutaline can indeed be reduced by theophylline. We cannot tell by which mechanism this occurs and suggest several possibilities. However, very recently it has been demonstrated that the number of adrenoceptors is rapidly reduced by beta-2-agonists treatment and therefore the prevention of this loss of receptors is a possible candidate for the mechanism of the observed dynamic drug interaction. Some subjects did show to have more down-regulation and more prevention of down-regulation than others. It has been reported in asthma patients that polymorphism for the beta-2-adrenoceptor exists and that this polymorphism is of importance for the occurrence of down-regulation and clinically relevant for the potency of a drug.

In chapter 5 the kinetics of inhaled formoterol and its effects on the size of the early cutaneous reaction to intradermal injection of an allergen, the so called wheal and flare reaction, as well as eosinopenia and hypokalemia were assessed in seven healthy volunteers who had such a positive skin reaction. The wheal and flare is used here as a surrogate marker for anti-inflammatory action of formoterol. After inhalation of formoterol, a biphasic pattern was observed in the kinetic and dynamic profiles. With a two-compartment model that accommodated for the systemic drug absorption from the lung and the gut, we were able to describe the kinetics of formoterol. We were thus able to estimate the contribution to the area under the plasma concentration time curve of the formoterol that was absorbed via the oral (30%) and the pulmonary (70%) route. An Emax formula for competitive agonism, with an effect compartment was used for the description of the concentration-effect relations. Acceptable fits were only obtained if two different values for both $K_{e0}$ and $EC_{50}$ were used for the two absorption phases.
The size of the wheal was reduced by 40% after formoterol, taking into account a rising slope for the base line, apparently due to diurnal variation. For all three effects the $EC_{50}$ of the orally absorbed fraction was approximately three times lower than that of the pulmonary fraction. These differences were thought to be best explained by a change in enantiomer ratio over time. However, the pharmacodynamic parameters can only be estimated accurately if the kinetics of the separate enantiomers of formoterol for both absorption routes can be taken into account.

In chapter 6 the kinetics of formoterol-enantiomers in urine are described. The findings communicated in chapter five inspired us to study the cause of the change in enantiomer ratio over time. We used the urinary excretion rate to describe the systemic drug concentration-time course. Because of a smaller number of measurements per excretion time curve we decided to use population modelling to estimate the kinetic parameters for the two enantiomers. An appreciable difference was found, although not statistically significant, between the $RR$ and $SS$ enantiomers for a parameter that was linked to drug clearance. As the other kinetic parameters were similar for the two enantiomers was concluded that a differential systemic concentration-time course of the two enantiomers is responsible for the observed changes in ratio. This change in ratio indicates that after inhalation possibly the inactive enantiomer ($SS$) preferentially reaches the systemic circulation.

In chapter 7 we set out to measure the kinetics of the separate enantiomers of inhaled formoterol. For that we used the same kinetic model as described in chapter five. To obtain reliable estimations of the oral and pulmonary components of the systemic plasma concentration we blocked the oral absorption by active coal on one of the two test days the patients were given formoterol. Due to relatively high concentrations in urine we were able to measure the enantiomers separately and, via the urinary excretion rate, estimate the formoterol plasma time curve. We were also able to relate the active $RR$ formoterol to the observed hypokalemia. As we had discussed in chapter seven, the estimated $EC_{50}$ values for the oral and pulmonary formoterol were considered hybrid estimates. With the knowledge of the kinetics of the two enantiomers separately measured, we
calculated the EC$_{50}$ for the 'racemic' plasma formoterol for each of the two absorbed fractions. The difference between the EC$_{50}$'s as seen in chapter 5 for the two fractions was again observed. This confirmed our findings in chapter five. The kinetic profiles of the enantiomers indicated that enantiospecific kinetics occur after pulmonary absorption with relatively more SS than RR appearing in the systemic circulation. We were able to satisfyingly relate lung function changes to formoterol time-concentration. This argues for a rapid equilibrium between local lung drug concentration and systemic concentration. The oral absorbed fraction of the dose in these patients, contributed to the long duration of the bronchodilation. The pulmonary deposition is known to be more in a controlled study situation than in normal life, and therefore the oral deposition and its systemic absorption could be of considerable importance for the effect of inhaled formoterol.

In chapter 8 we studied the effect of hydrocortisone on two different effects and estimated the relative contribution of the endogenous cortisol to these effects. With physiological models that can incorporate an assumed process that underlies an observed effect, we were able to describe the lowering effect of hydrocortisone on lymphocyte counts and the increase on plasma tyrosine concentration. The effect of exogenous hydrocortisone on cortisol production and the concomitant effect of cortisol on the same effector system as the administered hydrocortisone were both described by interaction models. The enzyme TAT lowers tyrosine concentration, whose production is regulated by corticosteroids. The lymphopenic effect of steroids is considered to be a non-genomic effect, and thought to occur by blocking the outflow of cells from the tissues into the circulation. The diurnal variation of lymphocyte counts can be explained completely by the diurnal rhythm of plasma cortisol. The onset of both studied effects appeared to be rapid for cortisol as well as for hydrocortisone which is in accordance with recent findings that these drugs can have an almost immediate beneficial effect in acute asthma.