Concentration-effect relations of anti-asthma medications. Studies on inflammation markers

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The contribution of pharmacokinetic-pharmacodynamic modelling to the study of anti-inflammatory agents

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INTRODUCTION

The study of the in vivo relationship between anti-inflammatory drugs and their effects on inflammation is not without any difficulties. For example: it is often not easy to find objective measures of anti-inflammatory drug action and the relation between drug concentration and effect may be unknown. The clinical relevance of a drug response to anti-inflammatory action may not be well defined and in the case of chronic disease, the relations to clinically important endpoints of disease may be unknown or may be measurable only after years. Furthermore, spontaneous fluctuations in time of the expression of the severity of inflammatory diseases can make it difficult to estimate drug effects over an extended period of time. If the disease is not systemic or not very severe, it can be hard to obtain easily accessible and measurable endpoints that change proportionate to the severity of the inflammation. Efficacy may differ in various tissue, the inflammatory process may itself influence the efficacy of a drug or influence the measures of its effects and PK/PD relations defined from single-dose studies cannot automatically be extrapolated to multiple doses and findings of animal studies cannot simply be extrapolated to man. And finally, it has to be stressed that inflammatory diseases are often treated with multiple drugs, acting jointly on the same parameters. These obstacles to studying the action of anti-inflammatory drugs apply not only to PK/PD modelling, but nevertheless set the challenge to do such studies. PK/PD modelling can shed more light on the rationale of otherwise empirical regimens of treatment. The basis of PK/PD modelling and its various applications has been well documented. Here we shall focus on studies that have investigated concentration-effect time-relations of glucocorticosteroids and non-steroidal anti-inflammatory agents (NSAIDs). We shall evaluate the contribution that PK/PD modelling has made in accruing knowledge that can help in the development of rational treatment of inflammation. One can argue that some examples are
immunosuppressive in nature rather than anti-inflammatory, but this distinction cannot always be well delineated.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS

Inhibition of the inducible enzyme cyclo-oxygenase-2 (COX-2) is regarded to be the drug action that results in the therapeutic anti-inflammatory action of NSAIDs, whereas inhibition of the constitutive enzyme cyclo-oxygenase-1 (COX-1) has been related to adverse effects (6). With the exception of aspirin, NSAIDs bind reversibly both to the COX-1 and COX-2 enzymes, although other mechanisms of binding have been suggested (7-9). For a long time it was believed that there was no dose-effect relations for NSAIDs (10-17). A few single-concentration - response relationships could be established though, such as for indomethacin and Prostaglandin E (18), nambutone and thromboxane (19), and for fenclofenac and grip strength reduction (20). In the early studies on concentration-effect relations basic clinical pharmacological principles were often neglected, as the following examples illustrate: measurement of total instead of free drug concentration, while e.g. free synovial drug concentrations at steady state were higher than the measured plasma concentrations (21-23), not taking into account stereoisomerism with interconversion and differences in distribution, elimination or activity of the enantiomers (9,24-27) and disregarding baseline effects such as spontaneous leakage of the measured parameter of inflammation out of the synovial space (17).

CONCENTRATION-EFFECT RELATIONSHIP IN VITRO

Efficacy and safety of NSAIDs have been expressed traditionally by the
ratio of the IC$_{50}$ values for the two COX enzymes. Recently, it has been appreciated that in vitro IC$_{50}$ values are highly dependent on the system used: models that use human whole blood give the best results (28). Selectivity of enzyme inhibition is an important factor for the risk/benefit ratio of NSAIDs (29). Since the concentration-inhibition relation is non-linear, being a hyperbola with a slope that differs for the two enzymes, the risk/benefit ratio changes with concentration (28). Thus, the ratio of the IC$_{50}$s of the COX-2 and COX-1 isoenzymes in whole blood as a relative safety index, is only of relevance for steady state concentrations that are actually achieved in clinical situations. However, when the complete concentration-effect relation curve is described with PK/PD modelling by linking the ex vivo results of single dose studies to a sigmoid Emax formula, the benefit/risk ratio of NSAIDs can be predicted for any steady state concentrations. Time dependency of enzyme inhibition due to pharmacokinetics can then also be described (19,30). Furthermore, possible influences that pharmacokinetics may have on the safety profile can then be accounted for (19).

CONCENTRATION - EFFECT RELATIONSHIP IN MAN

Direct markers of inflammation
A relation was found for synovial tolmetin concentration and synovial PGE levels in rheumatoid arthritis. The observed PGE time course suggests that some concentration-effect relation continued to exist even after seven days of treatment (31). Clinical efficacy of the active enantiomer of naproxen in rheumatoid arthritis, as measured by subjective parameters, correlated with the unbound drug concentration in synovial fluid (22, 32). Concentration-effect relations for both the active S enantiomer of naproxen in serum and total naproxen concentration in synovial fluid were described (33, 34), and for racemic ketoprofen concentration in synovial fluid (35). PK/PD modelling,
using a sigmoid Imax model, was employed to study the inhibition by zileuton of leukotriene B4 biosynthesis after stimulation of the blood ex vivo \(^{36}\).

**Analgesic effect**

The pharmacokinetic-pharmacodynamic relations for analgesics and the contribution of PK/PD modelling in identifying relations between drug concentration and effect has been reviewed recently \(^{37}\). In man, central and peripheral effects of NSAIDs on pain can be separated, and peripheral pain-related signals can directly be recorded non-invasively \(^{38}\). The peripheral analgesic effects of NSAIDs are mostly due to inhibition of cyclooxygenase \(^{39-43}\).

There was a correlation between contemporaneous serum concentrations of ibuprofen and pain intensity difference after third molar extraction, especially in the first two hours after dosing \(^{44}\). No enantiomers were measured separately, nor was possible hysteresis of the concentration and effect time-relation taken into account, which would have caused the correlation only to have occurred during the first two hours. An inflammatory model of nociception showed that diclofenac with respect to blood concentrations causes delayed and prolonged anti-nociception in arthropathy via an effect-compartment \(^{45}\). Studies in man had found anti-nociceptive or anti-inflammatory effects of diclofenac that had no direct relationship with the actual plasma concentration \(^{46,47}\). However, the effect data were well fitted by a sigmoid Emax model, the data suggesting slow equilibrium kinetics between the concentration of diclofenac in blood and at its site of action, leading to a delayed onset of the anti-nociceptive effect as well as a longer duration of the response, resulting from drug accumulation in synovial fluid.

A pain model in rats has been used to describe the analgesic effect of naproxen \(^{48}\). No effect-compartment was needed to relate the effect to a sigmoid Emax model, but only mean kinetic data could be used. The effect
of co-administration of caffeine on the action of naproxen has also been investigated. The interaction was not described, but as the authors stated that caffeine had no influence on naproxen kinetics, the effect, although seemingly delayed, was greatly increased. Proper dynamic/kinetic modelling that includes an interaction model could give a clearer insight into the analgesic effect of caffeine as an adjuvant (5, 49).

The relation between pharmacodynamic effects and plasma concentrations of the analgesic bromfenac has been assessed using semiparametric PK/PD modelling (50). Using an Emax model, an EC$_{50}$ was calculated that was identical to the value found for the analgesic effect of bromfenac in mice. With the results predictions could be made on the duration of effect after a single dose, which were in reasonable agreement with clinical observations.

**Antipyretic effect**

Pharmacokinetic-pharmacodynamic modelling using a hypothetical effect compartment and a linear effect model was applied to the effects of ibuprofen and acetaminophen on body temperature of febrile children (51). From the slow equilibrium rate constant for effect compartment concentrations, it was concluded that regular dosing was preferable to as-needed dosing if sustained temperature reduction was desired. Garg suggested that since the temperature reduction is related to physiological processes, an indirect pharmacodynamic response model should be used (51). The temperature reduction is probably mediated by reduced prostaglandin production in the brain (52). The exact relation between anti-inflammatory effects, such as reduced prostaglandin concentrations, and the antipyretic effect of NSAIDs are still to be established (53).

**CONCENTRATION - EFFECT RELATIONSHIP IN ANIMALS**

Most of the studies of NSAIDs that have investigated the relation between
the direct anti-inflammatory effect and the concentration-time course with PK/PD modelling have been performed in animals. Unlike the study of glucocorticosteroids, where cortisol and lymphocytes are readily available as surrogate markers for studying \textit{in vivo} effects, active inflammation has been artificially induced in most PK/PD studies on NSAIDs for obtaining markers of inflammation \cite{54}. Therefore, these same models are not applicable to studies in humans. Still, the studies give insight in pharmacokinetics and the related drug action and provide clues of how concentration-effect relationship studies in humans might be designed. Many of the animal studies have made use of a so-called tissue cage inflammation model: a surgical implantation of a subcutaneous tissue cage, into which carrageenan is injected. From this site, various inflammation parameters are collected and measured. Besides the application of artificially induced inflammation, PK/PD modelling has also been done in healthy animals without artificially induced inflammation, using naturally occurring markers of inflammation \cite{55}.

With PK/PD modelling the effects of the separate ketoprofen enantiomers have been studied with a tissue cage model of inflammation in the horse. The concentration-effect time relation of the S(+) -ketoprofen was described with a sigmoid Emax equation. The inhibition of synthesis of serum thromboxane B2 and exudate prostaglandin E2 served as markers for COX-1 and COX-2 inhibition respectively. Furthermore, there was partial inhibition of beta-glucuronidase release into inflammatory exudate and also of bradykinin-induced skin oedema \cite{56}.

Using the same model of inflammation, the pharmacokinetics and pharmacodynamics of ketoprofen, flunixin, and tolfenamic acid have been studied in calves \cite{57-60}. Similar effect-profiles were observed. There was no inhibition by ketoprofen of 5-lipoxygenase and leukotriene B4, nor any effect on concentrations of IL-1 and IL-6.

PK/PD modelling of the effect of the thromboxane synthetase inhibitors DP-1904 and ozagrel on serum TXB2 has been studied in rabbits, based on
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an indirect response model (60, 61).

PK/PD modelling has been used to make comparisons of the anti-inflammatory actions of two NSAIDs in horses (62, 63). No differences were found in the inflammatory markers that were influenced by the two drugs, but there were potency differences for most of the parameters. There were also differences in equilibration half-life for effect compartment drug concentrations. The effects of phenylbutazone and flunixin meglumine were compared to each other (64) with an artificially induced arthritis of the carpal joint.

The EC$_{50}$ value for local skin temperature was similar to that obtained for more 'functional' effect parameters, namely rest angle flexion and stride length.

Although concentration-effect relations for effects of NSAIDs have been found, much remains unclear about the variability of their responses (65).

GLUCOCORTICOSTEROIDS

The actions of glucocorticosteroids can be divided into genomic and non-genomic mechanisms. Both the indirect or DNA-mediated and the Non-DNA-mediated or direct effects are thought to be mediated through the glucocorticoid receptor, although the latter can also occur via other ways (66, 67). The rapid and long-lasting decrease of glucocorticoid receptor number that was observed after a single dose of a glucocorticosteroid, which is an indirect effect, can influence both direct and indirect effects (68). Moreover, two types of human glucocorticoid receptors (hGR) must be distinguished (69). The hGR-alpha type mediates the glucocorticoid action, while the hGR-beta type does not bind glucocorticoids and could be an inhibitor of glucocorticoid action. The differential expression of these two receptors
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could have a role in corticosteroid sensitivity in various tissues. Also the enzyme 11-beta-hydroxysteroid dehydrogenase, which converts active glucocorticoids to inactive metabolites, and has a greater activity in peripheral than in mucosal lymphoid organs, maybe of importance (70). The interconversion of the 11 beta-OH into the corresponding 11-keto group and vice versa is concentration dependent and tissue specific (71). Ultimately, the concentration-effect relations of corticosteroids and their time courses will be further understood when molecular response dynamics on mRNA production and their translations can be measured, as has been done for example for tyrosine amino transferase induction or glucocorticoid receptor mediated glutamine synthetase production (68, 72).

PK/PD MODELLING OF GLUCOCORTICOIDS

Pharmacokinetic/pharmacodynamic modelling has been used to describe the relations between a dose of a glucocorticosteroid and the extent and time course of its effects. Two types of models have often been applied for describing the effects of glucocorticoids: the direct and the indirect (or so called physiological) models. The direct models have the advantage that the meaning of the parameters can be easily understood intuitively, and since it uses integrated equations, an outcome is readily calculated for each concentration level (73). On the other hand, the indirect models can take into account physiological events and parameter value estimations are dose independent. However, the parameters are more difficult to interpret, because the effect of drug concentration on rate constants is estimated, instead of the direct effect on the response. Furthermore, differential equations are used, which are easy to make but can slow down the computer modelling process. However, recently integrated models have been described which will make the use of physiological models more valuable, because now the area between baseline and effect curve can be explicitly
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solved \(^{(74,75)}\).

The physiological models assume that the drug influences the response variable indirectly, by inhibiting or stimulating the production or loss of the response variable \(^{(76-78)}\). Four basic models using differential equations have been applied for characterising indirect pharmacodynamic responses. Partially integrated solutions have been sought which allow a better understanding of the roles of model parameters and pharmacokinetic functions in affecting the time course of drug effects \(^{(75)}\).

Physiological models have not been used as much as the direct models, although they definitely have some favourable traits not shared by modelling with direct models \(^{(79)}\). Parameters appeared to be dose-independent when calculated with the physiological models, in contrast to direct models using a hypothetical effect compartment \(^{(76,77)}\). Using computer simulations with physiological models, the time of the maximum inhibitory or stimulative response was nearly proportional to log dose, while the maximum response was non-linear \(^{(78)}\).

SURROGATE MARKERS

Clinical efficacy of steroids was originally measured by the vasoconstrictor test, the mitotic index suppression method, and the atrophogenic potential assay for topically applied steroids \(^{(80)}\). When PK/PD modelling of glucocorticoids was introduced, cortisol suppression was often used as the effect parameter. This parameter can also reflect the systemic availability of corticosteroids \(^{(81)}\). Cortisol suppression can also be regarded as a parameter for both the immunomodulatory and anti-inflammatory effects of glucocorticosteroids \(^{(82,83)}\). Lymphocytopenia and lymphocyte proliferation tests have also often been used to serve as anti-inflammatory parameters. Ideally, one would like to differentiate drug action on different sub-populations of T-lymphocytes, since there may be differential efficacy
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on different cells in, for example, chronic or acute inflammation \(^{70, 73}\).

**GENOMIC RESPONSES**

Genomic drug effects are supposed to result from the receptor-corticosteroid complex causing a cascade effect altering DNA transcription, RNA, mRNA and proteins or enzymes \(^{84}\). PK/PD models for these effects in the rat have been made, describing hepatic tyrosine aminotransferase (TAT) enzyme induction and the down-regulation of receptors or their recycling between cytosol and nucleus \(^{68, 85-89}\).

Autoregulation of glucocorticoid receptor (GR) concentration was assessed and compared with regulation of tyrosine aminotransferase (TAT) expression in liver tissue taken from rats treated with methylprednisolone \(^{90}\). Receptor occupancy occurred rapidly and cytosolic receptors reappeared over 2-12 h. TAT activity rose between 2 and 6 h and then dissipated. Reduction in mRNA levels occurred very rapidly, being detectable by 30 min after steroid administration and reached a steady-state after 2 hours which was maintained for over 18 h. In contrast, TAT induction occurred with a sharp peak, maximal induction occurring 5-6 h with a return to baseline at 8-10 h after induction. Unlike TAT induction, glucocorticoid receptor message down-regulation in vivo does not require the continual presence of hormone.

**SYSTEMIC RESPONSES**

**Endogenous hydrocortisone**

Exogenous corticosteroids influence the production rate of cortisol, but they are also agonists that compete with cortisol for the same receptor. A threshold-Emax model used by Oosterhuis, that takes hydrocortisone concentration into account as a time-averaged parameter, showed that
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hydrocortisone and prednisolone are about equipotent with respect to the lymphocytopenic effect, and that the concentration threshold for effect represents prednisolone replacing lost hydrocortisone (91-93). Another model, in which hydrocortisone production was described as a continuous intravenous infusion that stops and starts instantaneously, described the influence of the time of day of dexamethasone administration on the suppression of plasma hydrocortisone Morning dosage of dexamethasone gave a larger hydrocortisone suppression than the evening dosage (94). With a similar approach the kinetics of both dexamethasone and hydrocortisone were integrated with an equation for competitive agonism to describe lymphocytopenic effects (95). An indirect model has described the circadian-episodic influx of cortisol into plasma in normal children (96). Besides the effect on hydrocortisone hormone the suppression on osteocalcin has been studied (97).

Lymphocyte proliferation and Lymphocytopenia

The time courses of prednisolone concentration and lymphocytopenia or the proliferative response of peripheral blood lymphocytes in whole blood were related by a PK/PD model, with a sigmoidal Emax formula with the incorporation of a threshold concentration parameter (91,93,98). The prednisolone-induced lymphocytopenia was concluded not to be related to mRNA transcription and protein synthesis. Prednisolone and hydrocortisone seemed to be equipotent in man with respect to the studied effect. The delay in effect was explained on the basis of pharmacokinetics rather than cell kinetics. Smaller doses of prednisolone were relatively more effective, which was explained by saturation of the effect and increasing depletion of endogenous hydrocortisone by higher doses. It was suggested that total lymphocyte counts could be used as a measure for monitoring the indirect immunosuppressive effect of prednisolone. Indirect models have been used to study the inhibition of normal trafficking of lymphocytes and granulocytes by corticosteroids (99-101). It was suggested
that corticosteroids cause a decrease in the recirculation of these cells from peripheral compartments (102). Trafficking of T cells in response to various single doses of methylprednisolone in man have been described, with simulations demonstrating the log-linear role of steroid dose on the total effect (103). However, the rat proved to be an unsuitable model for characterizing such cell trafficking (104). A physiological pharmacodynamic model has been used to describe changes in circulating lymphocytes as a function of both endogenous cortisol and methylprednisolone concentrations (105).

GLUCOCORTICOID RECEPTOR AFFINITY

A relation between glucocorticoid receptor affinity and its in vivo effect has been demonstrated with the help of PK/PD modelling. With knowledge of glucocorticoid receptor affinity and of pharmacokinetics of the unbound fraction, it was proven to be possible to predict systemic effects of various glucocorticoids reliably, as well as the effect of the time of dosing on cortisol suppression (106, 107). Systemic steroid activity on cortisol suppression (108, 109), lymphocytopenia and increase in granulocytes (109-111) and glucose (111) was so evaluated for cloprednol (110), fluocortolone (108), triamcinolone (109), methylprednisolone (107, 111, 112), for dexamethasone and triamcinolone acetonide (107), and for deflazacort and prednisolone (112).

DOSE DEPENDENCE OF CORTICOSTEROID RESPONSES

Pharmacodynamic modelling has been used to predict and quantitate "dose-sparing" effects that are achieved by prolonging methylprednisolone or prednisolone plasma concentrations (113-116). Appropriately timed doses of a steroid can be used in an optimally efficacious manner by first occupying
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all receptor sites and then interrupting steroid administration. Receptors are expected to recycle from nuclear/DNA binding sites as the steroid is eliminated. The effect of fluocortolone on cortisol suppression has been characterised with a model that incorporated the physiological circadian secretion of cortisol under normal and treatment conditions, together with pharmacokinetic data from different single doses of fluocortolone. This approach showed how pharmacodynamic modelling can characterise dose-proportionality data and provide an in vivo measure of drug potency.

MODELS OF ADMINISTRATION

Inhalation

Anti-inflammatory drugs for the treatment of asthma are mostly administered by inhalation. Potency values of inhaled corticosteroids are largely based on blanching tests. Dose-response relations after the inhalation of corticosteroids have recently been studied with urinary cortisol excretion as an effect parameter. Providing that the usually low plasma concentrations are measurable, the relationships between both systemic and lung effects with concentrations can be analysed by PK/PD modelling. This may help in understanding differences between different inhaled drugs in terms of their systemic bioactivity profiles. The kinetics of inhaled formoterol, a long-acting beta-2-agonist, and its effects on the size of the early cutaneous reaction to intradermal injection of an allergen and eosinopenia as anti-inflammatory parameters were assessed by PK/PD modelling. A fractional systemic absorption, enantiospecific kinetics, and an apparent diurnal variation of the wheal skin reaction could be assumed and described by the model. The pharmacokinetics and pharmacodynamics of inhaled flunisolide were studied after the non-pulmonary drug absorption was blocked with oral charcoal, and compared with a situation without charcoal. The flunisolide plasma concentrations
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were linked with the effects on lymphocytes, granulocytes, and cortisol with PK/PD modelling. There was no statistical difference between treatments in the presence or absence of orally administered charcoal. The PK/PD simulations resulted in a smaller degree of cortisol suppression for the drug administered at 10 PM. The cumulative change from baseline was slightly smaller for the effects on granulocytes and lymphocytes than those on cortisol.

**Liposomal formulation**
A liposomal formulation of methylprednisolone targeted to the spleen gave a prolonged local immunosuppression, as measured by lymphocyte proliferation in spleen cells. The cortisol suppression did not differ from the suppression observed with a regular formulation \(^{(123)}\). There was a non-linear relation between suppression of splenocyte proliferation and the concentration of bound glucocorticoid receptors in the spleen.

**Intra-articular injection**
After an intra-articular steroid injection, children had transient suppression of endogenous cortisol production lasting 10-30 days. During this period the circadian rhythm of cortisol production and the hypothalamic pituitary-adrenal axis were abnormal \(^{(124)}\).

**EFFECT OF EXTRANEOUS FACTORS**

**Use in renal Failure**
Methylprednisolone pharmacokinetics and its directly suppressive effects on cortisol secretion and cell trafficking have been compared in patients and healthy controls with physiological pharmacodynamic models \(^{(125)}\). Pharmacokinetics and pharmacodynamics of methylprednisolone were not changed in renal failure, in contrast to altered pharmacokinetics of other
corticosteroids. Although lower total AUCs of prednisolone were found in nephrotic patients, an increase in drug effect was seen, attributable to lowered EC₅₀ values \(^{(126)}\).

**Effect of obesity**

Intrinsic pharmacodynamic differences in sensitivity for methylprednisolone were not found in obese subjects. However, dosing should be based on lean body mass, and the dosing interval should be lengthened in obesity, because of decreased clearance and changed absolute distribution \(^{(127)}\). The steady-state volume of distribution, corrected for body weight, of total prednisolone was 20% smaller in obese subjects than in healthy subjects, which could be related to limited prednisolone uptake by fat \(^{(128)}\). Free prednisolone clearance correlated with the degree of obesity. However, in the obese, endogenous cortisol concentrations were initially higher before exogenous steroid dosing, were suppressed at an identical rate, and returned to baseline more slowly than in healthy subjects. Thus, increased clearance of prednisolone in obesity is counterbalanced by increased inhibition of cortisol production by prednisolone, arguing for prednisolone against body-weight adjusted dosing based on lean body weight. PK/PD modelling showed a 80% decreased efficiency for prednisolone induced TAT induction in obese rats, due to doubled base-line receptor levels and an increase of both prednisolone plasma clearance and volume of distribution \(^{(129)}\).

**Sex and age**

Although women are more sensitive to methylprednisolone, as measured by cortisol suppression, they eliminate the drug more quickly, generally giving a similar net response \(^{(130)}\). Men had a greater 24-hour net suppression in blood basophil numbers, but there was no difference in net cortisol and T-helper lymphocyte suppression. In the elderly, compared with young healthy men, methylprednisolone clearance was reduced, resulting in
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Increased cortisol suppression\(^{(131)}\).

**Effects of depression**
The effects of depressive disease on exogenous and endogenous corticosteroid characteristics have been described in several studies with the use of PK/PD modelling. The reduction in metapyrone response was related to the severity of the disease, and reduced suppression of hydrocortisone production loss was found, which was ascribed to both kinetic and dynamic causes\(^{(132-134)}\).

**Effect of inflammatory diseases on plasma concentration**
Prednisolone shows a higher free concentration in inflammatory diseases in rats\(^{(135)}\). Both acute and chronic inflammation reduced considerably the in vitro plasma protein binding of prednisolone, the reduction being much greater after chronic inflammation. The mean values of half-life and apparent volume of distribution at steady-state in each group were similar.

**Drug interactions**
Glucocorticoids were shown to interact with oral contraceptives, producing an increase of basophil suppression, a raise of cortisol base-line levels, and an increase of prednisolone concentrations with a raised EC\(_{50}\) for the inhibition of mixed lymphocytes cultures\(^{(126, 136)}\). Although dehydroepiandrosterone is relatively little potent, a synergistic dynamic interaction with prednisolone in rat was found\(^{(137)}\). NSAIDS can interact with glucocorticoids. A reduction of the clinically unimportant renal clearance of prednisolone by 50% by tenidap in men has been found\(^{(138, 139)}\). An increased induction of hepatic TAT by indomethacin in rat was seen\(^{(129, 130)}\). Methylprednisolone clearance is substantially increased during concomitant therapy with ketoconazole and gives an extended cortisol suppression in healthy subjects\(^{(140, 141)}\).
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CONCLUSIONS

Held against the large number of studies on anti-inflammatory drugs, it may be surprising to see the limited number that involves PK/PD modelling techniques. The complex dynamic processes that take place during inflammation, and which are not all homogeneous, make it difficult to choose relevant effect parameters. These parameters should also be obtainable and measurable easily, cheaply, repetitively, sensitively, and reliably. Furthermore, inflammatory diseases such as asthma or rheumatoid arthritis, are often treated with multiple drugs, influencing common endpoints. Although it would be advantageous if an effect parameter was uniquely influenced by a single drug, this probably will be rare. Methods like population modelling or artificial intelligence can possibly be valuable tools to overcome these particular problems. Population modelling uses population kinetics to estimate and to predict PK/PD parameters. The advantage of population modelling compared to individual curve fitting is that few data points per single individual can be counterbalanced by the larger number of curves. Additionally, the relation between parameters and covariates like concomitant medication or disease, severity of the disease, age, sex, etc. can be included in the analysis. For example, concentration-effect relations of anti-inflammatory actions for NSAIDs have been studied with this technique.

In PK/PD studies, cortisol depletion has often been used as effect parameter for the relative systemic action of corticosteroids and cortisol has mostly been chosen as a safety index rather than markers of efficacy. Reduction of adverse effects or comparison of adverse effects of different drugs should be studied in relation to their efficacy. More (surrogate) markers of inflammation should be tested for their usefulness, and biological models of inflammation in healthy subjects must be sought.

PK/PD relations can potentially be used to optimise treatment for inflammatory diseases, for example in asthma, where bronchoalveolar
lavage fluid and endobronchial and transbronchial biopsies suggest that inflammation persists in severely symptomatic asthmatics, despite treatment with high doses of glucocorticoids\(^{144}\). PK/PD modelling will then also provide more insight in the mode of action of anti-inflammatory drugs and give a better understanding of the dose-effect relations and the temporal course of the responses of these drugs.

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