PHARMACODYNAMIC ASPECTS OF MODES OF DRUG ADMINISTRATION FOR OPTIMIZATION OF DRUG THERAPY

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**Abstract:**

Due to various pharmacodynamic properties such as the nonlinearity of the concentration-effect relationship, activation of feedback homeostatic mechanisms, induction of pharmacodynamic tolerance etc. administration of the same dose of drug by different modes is expected to produce different outcomes. This review clarifies the theoretical and practical aspects of the impact of different modes of drug administration on the magnitude of response, and hence on therapy outcomes. It discusses how the interrelationship between the pharmacodynamic properties and the drug input function affect the magnitude of response. To demonstrate this special dimension of drug therapy, relevant pharmacodynamic data was obtained for drugs with different therapeutic applications, including antibiotics, analgesics, diuretics, anti-cancer, anti-ulcer, anti-inflammatory, anti-hypertensive, lipid-lowering anti-parkinsonian, and immunosuppressive drugs. These examples provide guidelines for implementing the role of the mode of drug administration (including rate, schedule and route of drug treatment) during drug development or optimization of drug therapy.

**Keywords:** pharmacodynamics, pharmacokinetics, mode of drug administration, delayed action preparations, tolerance.
1. Introduction

The technological, physicochemical and engineering knowledge for the development of drug delivery systems has now reached the stage where it provides a very wide selection of routes, sites, modes and rates of administration of a drug. To use these capabilities rationally, it is necessary to determine the optimum input pattern of the drug (in terms of efficacy, safety, convenience and economics) for a particular indication and target population.

By now, it has been established that the development of a drug delivery system (DDS) should comply with pharmacokinetic considerations, including aspects of absorption, presystemic biotransformation, distribution, systemic elimination and metabolic fate. In general, the development of DDS was based on a simplified assumption of a direct relationship between drug concentration in the blood and magnitude of response. Accordingly, the basic philosophy behind the development of sustained release (SR) formulations is to reduce fluctuation in drug response by minimizing fluctuations in systemic drug concentrations. However, in most cases, the concentration-effect relationship (i.e. pharmacodynamics) is non-linear. Thus, similar magnitude of fluctuations in drug concentration at different concentration ranges are likely to cause dissimilar fluctuations in the magnitude of response. Consequently, the input function may affect profoundly the magnitude of drug effect(s) and has to be taken into consideration for optimization of drug treatment.

2. The pharmacodynamic profile

2.1 Relationship between fluctuation in drug concentrations and magnitude of response

The mathematical correlation between drug concentration \( C \) and the intensity of effect \( E \) is most commonly described by sigmoid Emax model (see Figure 1):

\[
E = E_0 + \frac{E_{\text{max}} \cdot C^n}{EC_{50}^n + C^n}
\]

where \( E_0 \) is the baseline effect, \( E_{\text{max}} \), the maximal effect, \( EC_{50} \), the drug concentration that elicits 50% of the maximal effect (i.e., the measure of drug potency), and \( n \), shape factor which determines the slope of the curve. The value of \( n \) has no clear physiological meaning, but it is thought to evolve from the heterogeneity of concentration-effect properties of the
individual effector units (such as individual effector cells or channels).³

Different concentration ranges along the pharmacodynamic profile are shown in Figure 1. It can be seen that a certain degree of fluctuation in drug concentration ($\Delta C$) at different zones elicit different degrees of change in magnitude of drug effect ($\Delta E$).² Alterations in drug concentration within $E_0$ zone or $Emax$ zone do not affect the magnitude of drug effect. Within $EC_{50}$ zone, $\Delta E$ is directly proportional to $\Delta C$ (or more specifically to $ln\Delta C$). In contrast, fluctuations in drug concentration in Low $E$ zone and High $E$ zone produce non-proportional change in $\Delta E$. For instance, for $n=1$ a two-fold increase in drug concentration produces an 80% increase of drug effect at low $E$ zone, a 46% increase at the $EC_{50}$ zone, and only a 10% increase at high $E$ zone.

The sigmoidicity of the pharmacodynamic profile has a profound influence on the magnitude of $\Delta E/\Delta C$ and on the width of a specific concentration zone. Generally, when $n < 1$, a shallow pharmacodynamic profile is observed resulting in moderate attenuation in magnitude of effect even for large degrees of $\Delta C$. Consequently, a high increase in drug concentrations is needed in order to proceed from the minimal to maximal extent of drug effects. For such a pharmacodynamic profile, SR formulations that minimize fluctuations in drug concentration are less important. On the other hand, for $n > 1$, the resulting pharmacodynamic curve is steep and is characterized by high affectability of response intensity to a change in drug concentration. For $n > 5$ all-or-none response is observed and small increment in drug concentrations near the $EC_{50}$ region produces rise from $E_0$ to $Emax$. For these drugs the range between $EC_{50}$ and the minimal concentration required to elicit $Emax$ ($EC_{max}$) is very narrow and it is extremely important to maintain drug concentration above $EC_{max}$ (e.g., levodopa – see specific section).

### 2.2 The impact of the rate of administration on the magnitude of drug effect

The fact that pharmacokinetic processes are usually linear but in most cases the concentration-effect relationship is nonlinear leads to profound impact of the drug input function on the extent of the pharmacologic response. To illustrate this issue, a simulation of pharmacokinetic and pharmacodynamic behavior of the drug following administration of the same total dose at different rates was performed (Figure 2). The concentration vs. time profiles were based on a one compartment model by applying bolus mode of drug administration or constant infusion of the same total dose over 2, 4, 8 or 12 hours. The effect vs. time data was produced by linking the concentration-time data to a sigmoidal $Emax$ model.
(\(E_{\text{max}} = 100\%\) and \(EC_{50} = 0.05 \text{ mg/L}\)) with different shapes (\(n = 0.5, 1,\) or 4). The impact of different parameters on the magnitude of drug action may be estimated by comparing AUEC values (area under effect curve) or by using an efficiency factor (\(\text{EF} = \frac{\text{AUEC}}{\text{AUC}}\)).

The simulations show that the magnitude of effect is highly influenced by the rate of drug administration. Prolongation of the administration time increases AUEC values by several-fold. The magnitude of effect depends also on \(n\) value, particularly for lower rates of drug administration. It can be seen that an increase in value of \(n\) from 1 to 4 increases the effect (i.e., AUEC) by approximately 20% for the 4-h and the 8-h infusion regimens. The opposite tendency occurs by prolongation of the infusion time to 12-h because \(C_{ss}\) values drop below \(EC_{50}\) level.

Generally, the overall efficiency value of a certain mode of administration is a function of the time that drug concentrations are maintained at the different concentration zones along the pharmacodynamic curve. For the sigmoidal Emax model, maximum efficiency is produced if the drug concentrations are continuously kept in the high E zone. Thus, for bolus mode of administration relatively large AUC values can be associated with low AUEC value, particularly if the peak drug concentrations happens to be several-fold higher than E\(C_{\text{max}}\). In this case, a sustained drug administration that prolongs the time spent over E\(C_{\text{max}}\) will produce higher EF values (e.g., see section on beta-lactam antibiotics). On the other hand, if \(C_{ss}\) value produced by continuous administration within the \(E_0\) zone, the overall efficiency would be negligible in comparison to a bolus administration of the same dose.

It can be concluded that in most cases the magnitude of drug effect is dependent on the mode of drug administration. The overall drug efficiency is dependent on the interrelationship between several pharmacokinetic and pharmacodynamic parameters, including the dose and rate of administration and the pharmacodynamic profile of the specific response. Simulations showing the relationship between the drug dose and magnitude of drug effects in the sigmoid Emax model were presented recently.

### 3. Time-dependency of pharmacodynamic effects

It should be taken in account that temporal alterations in concentration-effect relationship may occur, influencing the efficiency factor following drug administration. Apparent time-dependency of the drugs pharmacodynamic parameters may result from a delay between the pharmacokinetic and activity time course, or because of intrinsic alterations of pharmacodynamic parameters.
3.1 Hysteresis in the concentration-effect profile

In some cases, the pharmacologic response is delayed in relation to the kinetics of the appearance of the drug in the blood and a counter-clockwise hysteresis is present in the concentration-effect relationship. In certain cases, the reason for this outcome is a slow equilibration between drug concentration in the systemic circulation and peripheral site(s) of action. Consequently, a non-steady state effect-concentration relationship is produced, leading to time-dependent changes in pharmacodynamic parameters. In order to elicit a certain magnitude of effect, higher plasma concentrations are required at the beginning of drug administration, and lower concentrations are needed once the drug is distributed to the biophase. The magnitude of hysteresis is minimized by a slower rate of drug administration, that reduces Cmax concentrations in the systemic circulation. Delayed response may also result from the production of active metabolites, indirect pharmacodynamics due to time-consuming signal transduction (accounting for delay between receptor binding and measured effect), etc.

Several mathematical methods have been developed to overcome temporal discrepancy in concentration-effect relationship and to estimate the intrinsic pharmacodynamic parameters. Collapsing the hysteresis in the concentration-effect curve is a practical approach that utilizes the indirect link model developed by Holford and Sheiner.

3.2 Direct and indirect response

Discrepancy between the time courses of concentration and effect may be related to indirect mechanism of drug action. This is true, for instance, when the observed drug response is secondary to a previous, time consuming synthesis or degradation of endogenous bioactive substance. Four basic pharmacodynamic models of indirect effects were developed by Jusko et al, and were applied for numerous drugs, including hormones, diuretics, etc. Effect of the drug input profile on the overall efficiency of drug effect in these indirect models have been discussed thoroughly in recent review. In this work the concentration vs. time profiles of low, medium and high drug doses were simulated for a one compartment model applying bolus mode of drug administration or constant infusion over 6, 12, 24 or 72 hours. The pharmacodynamic response was generated using four basic models of indirect effects (I-inhibition of synthesis of endogenous substance, II-inhibition of degradation, III-stimulation of synthesis, and IV-stimulation of degradation). The effect of the rate of administration and
drug dose on magnitude of pharmacologic effect is presented in Figure 3.4.

It may be seen that slower rates of drug delivery improve the efficiency of the same total dose. A maximal influence of the rate of drug delivery on the pharmacological response was observed after the high dose. The influence of the infusion rate was the greatest for Model II. While models I, III, and IV produced in a maximum of about 4-fold increase in efficiency factor for continuous infusion compared to bolus mode of administration, model II resulted in a 7-fold increase.

The results of the present simulation indicate that the pharmacodynamic efficiency is dependent on the relationship between the target drug concentrations and IC₅₀ values. For relatively high drug doses, slower rates of drug delivery produce higher AUEC values and comparable maximal effects (E_{max}). Further reduction in the rate of input lowers the maximal effect, while higher AUEC values are attained. If additional attenuation in drug release produces target concentrations that are below IC₅₀, both maximal effect and pharmacodynamic efficiency are reduced.

3.3 Tolerance phenomenon

The concentration-effect relationship of certain drugs is affected by continuous exposure to the drug. Thus, due to changes that occur at the cellular level (such as gradual reduction in the receptor density (down-regulation)), larger concentrations may be required to maintain the same magnitude of effect over time, producing a tolerance phenomenon. Evolvement of tolerance was observed for several drugs, including anticonvulsants, anti-inflammatory drugs, amphetamines, barbiturates, benzodiazepines, caffeine, cocaine and other CNS stimulating drugs, digitalis (heart failure), dopamine agonists, ethanol, indirectly acting sympathomimetics, nicotine, organic nitrates, opiates, vasodilating drugs (heart failure). It should be noted that if the pharmacologic responses of the drug are due to interaction with different types of receptors, tolerance may develop for some, but not necessarily for all drug effects. Magnitude of tolerance is related to the drug input function (i.e., is time- and exposure-dependent) and is enhanced following slow drug input. In general, the influence of the mode of administration is more substantial in the case of acute tolerance development, such as in the case of organic nitrates (see specific section) which indicates that SR mode of administration should be limited, and is less notable in those cases where tolerance development is slow (e.g., levodopa - see specific section).
3.4 Pharmacodynamic alterations due to activation of homeostatic responses

Activity of many of the biochemical and physiological processes in the living body is maintained within a certain limited range by means of feedback loop systems. In such a way the body protects itself from drastic changes that would jeopardize the homeostasis. If the homeostasis is altered due to pharmacological intervention, powerful feedback mechanisms are activated, decreasing the magnitude of drug effect. The extent of activation of feedback mechanisms is highly dependent on the rate of drug administration. While a bolus administration may provoke counter activity, slow drug input may affect the body without acute triggering of homeostatic responses.12

The ‘off response’ should also be taken into account for drugs that affect the body homeostasis. Abrupt termination of drug input in such case may result in potentially dangerous increase in drug effects (rebound activity). This phenomenon is specifically known for antihypertensive drugs.13

4. Therapeutic and toxic effects

Almost all drugs possess multiple pharmacologic activities that are regarded as therapeutic or side effects. It is important to understand that each of the pharmacologic effects of the drug has its own pharmacodynamic profile. In order to optimize drug treatment the pharmacodynamic profiles of both therapeutic and adverse drug effects should be taken into account. As was discussed previously, for a particular pharmacodynamic profile, extent of drug effect is profoundly dependent on the drug input function. Thus, optimization of drug treatment must be applied to the differences in the pharmacodynamic profiles for different drug effects, based on the knowledge of the drug’s pharmacodynamics, applying dosing schedules with a higher ratio of resulting therapeutic/toxic effects.

In the case that different types of drug receptors are responsible for therapeutic and side effects, selective activation/inhibition of receptors may be achieved by applying SR formulations of the drug and producing a relatively narrow range of target drug concentrations. General considerations concerning impact of mode of administration and dose on selectivity of pharmacologic response were discussed recently by Hochhaus and Derendorf.5
5. Measurement of pharmacologic effect: The use of surrogate endpoints as indices of therapeutic outcomes

In some cases, such as anti-cancer and immunosuppressive treatment (see specific chapters), the magnitude of therapeutic effects and clinical outcome following the drug treatment are not readily accessible. In this case, surrogate endpoints may be applied to measure the biological activity and to adjust the treatment schedules. The optimal surrogate endpoint should have the potential to yield unambiguous information about differential treatment effects on the true endpoint. The relationship between surrogate marker and the clinical outcome should be well established, both qualitatively and quantitatively, through relevant epidemiological studies in order to estimate the expected clinical benefit. However, the convenience of relying on biological markers on one hand and the substantial difficulties in quantifying clinical end points and outcomes that are delayed in connection with changes in the disease process, have led researchers to utilize surrogate markers, sometimes without validation of their appropriateness. As noted recently by Colburn, although surrogate markers can expedite the delivery of new therapeutic drugs to the market, if the marker is applied inappropriately, it can prolong the development process and discourage their use.14 For example, use of CD4 counts as surrogate markers for prolonged survival of patients with human immunodeficiency virus (HIV), or reduction in premature ventricular contractions to predict prolonged life expectancy have proven to be invalid.15,16

The issue of surrogate markers is raised here because in many cases they are being used as a graded measure of pharmacological effect, which enables one to produce a reasonably good pharmacokinetic/pharmacodynamic model of the kinetics of drug action. The important issue is to clearly distinguish between those surrogate markers which are validated from those that are associated with drug activity but do not provide sound indication about the real clinical outcome.

6. From theory to practical examples: Pharmacodynamic considerations in treatment of specific diseases

Controlled release (CR) dosage forms of medications have become relatively prevalent in medicine today because of their ability to improve compliance and, perhaps, to increase efficacy.17 CR formulations were developed according to the concept that ‘flatter is better’, and formulation design tended to minimize fluctuations in drug blood concentrations.
As discussed above, this concept has many exceptions that evolve from the pharmacodynamic characteristics of the drug and the mode of administration. The available information about these factors is rather limited, and is only recently gaining momentum. In certain fields the pharmacodynamic considerations have been thoroughly studied and have led to practical modifications in mode of drug administration. For example, this has been seen in SR nifedipine and other anti-hypertensive preparations, and hormonal therapy with gonadotropin releasing hormone (GnRH). For other drugs, the available information about the impact of mode of administration on magnitude of response (of both desired and adverse effects), and hence, on therapy outcome, is scarce. In many cases, pharmacodynamic information that is relevant for understanding the impact of the input function-response relationship is reported indirectly or provides only partial or inconclusive knowledge. The goal of this review is to use the available information in order to draw the picture of the influence of the mode of administration on drug effect(s) in several clinical fields. Selected examples provide guidelines for implementing this dimension of mode of drug administration (including rate, schedule and route of drug treatment) during drug development or for optimization of drug therapy.

7. Pharmacodynamics of antibacterial drugs

The major parameters used to quantify the effect of antimicrobial drugs are the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC). Although these parameters are good predictors of the potency of the drug-microorganism interaction, they do not provide any information on the kinetics of action of the drug. For instance, the MBC value does not provide information on the rate of bactericidal activity and whether this rate can be enhanced by increasing antimicrobial concentrations. Similarly, MIC does not provide any information about the persistent activity of the antimicrobial agent that remains following exposure to the drug. These persistent effects include the postantibiotic effect (PAE), postantibiotic sub-MIC effect (PAE_SME) and the postantibiotic leukocyte enhancement (PALE). The degree of PAE and PAE_SME, that are very different for each class of antimicrobial drugs (and for each specific drug-bacteria interaction), provide a better understanding of the kinetics of drug action, thus furnishing a rational basis for determining optimal dosage regimens for various human infections.

Antibiotics can be divided into three categories based on their pharmacodynamic properties, including both their bactericidal activity and their persistent effects. The first group of drugs (Category I) exhibits minimal concentration-dependent killing and produces
short term or no persistent effect with most bacteria. The killing rate of these antibiotics saturates at concentrations of around four to five times the MBC. Thus, high concentrations will not kill bacteria faster than lower concentrations. Furthermore, bacterial regrowth starts very soon after serum and tissue concentrations fall below MIC. Penicillins, cephalosporins and aztreonam exhibit this time course of antimicrobial activity. The second group (Category II) is characterized by concentration-dependent killing over a wide range of concentrations, and by prolonged persistent effects. The higher the drug concentration, the greater the rate and extent of bacterial killing. This category includes aminoglycosides, fluoroquinolones and metronidazole. Category III contains drugs such as vancomycin, clindamycin and macrolides that demonstrate minimal concentration-dependent killing; however, they have prolonged persisting effects.

7.1 Beta-lactam antibiotics (Category I)

7.1.1 Pharmacodynamic rationale for continuous administration of beta-lactam antibiotics

*In vitro* studies of the pharmacodynamics of beta-lactam antibiotics have shown that killing of bacteria, in particular Gram-negative aerobic rods, is slow, time dependent, and maximal at relative low concentrations. Further elevation of the dose is not associated with increased bactericidal potency. It had been also suggested that at concentrations much greater than the MIC a paradoxical pattern may occur, i.e., a decrease in bacterial kill potency. These findings have led to the hypothesis that continuously maintained concentrations above a certain level, related to the MIC for the specific pathogen, would be more efficacious than the high peak and trough concentrations obtained with an intermittent dosing regimen. Efficacy studies in laboratory animals are in agreement with these *in vitro* findings. It was found that in order to obtain the same efficacy the daily doses have to be eight-fold higher during intermittent infusion regimens than with continuous infusion. Other studies have shown that the percentage of survival of the animals increased linearly with the frequency of dosing and time over the MIC but not with other pharmacodynamic parameters. In addition to the preclinical findings, several clinical efficacy studies corroborate this concept; however, these are still scarce. Schentag *et al* have shown a significant relationship between time to eradication of Gram-negative pneumonia and time over MIC. Weinstein *et al* examined the relationship between beta-lactam concentrations at trough and the success of therapy in patients with acute and chronic osteomyelitis. It was found that maximum efficacy with beta-lactam antibiotics in humans appeared to be
dependent on maintaining levels above the MIC of the infecting organism for the majority of
the dosage interval. The few randomized trials that have compared the efficacy of the beta-
lactams given by continuous infusion vs. intermittent administrations also support this
conclusion.

Exposures of staphylococci, streptococci or enterococci to different beta-lactams are
consistently followed by PAEs of several hours duration. This persistent suppression of
gram-positive cocci growth enabled the development of intermittent dosing regimens for
these drugs. Traditionally, intermittent intravenous infusions or intramuscular injections have
been considered to be the optimal dosing regimens that worked reasonably well in clinical
practice. However, due to the increasing number of immunocompromised patients, the rising
incidence of gram-negative infections, and the availability of improved intravenous drug
delivery systems, new strategies have been introduced for improving antimicrobial therapy
with beta-lactams. These strategies apply continuous infusions of these drugs to provide
improved patient outcome with reduced doses of drug.

In summary, the goal of the dosage regimen of beta-lactam drugs should be to prevent
the drug-free interval between doses from being long enough for the bacterial pathogen to
resume growth.

7.1.2 Potential disadvantages associated with continuous administration of beta-
lactams

It is conceivable that if the infection is located at a site from which the antibiotic is
eliminated by a rate-limiting active transport, intermittent dosing would result in higher
concentrations at the site of infection than would continuous administration (e.g., infections in
the eye or cerebrospinal fluid). However, such a scenario is limited to a particular range of
antibiotic concentrations and then would apply only for those beta-lactams that are handled by
such mechanisms.

Another situation is in a case where the antibiotic drug is eliminated from the site of
infection due to beta-lactamases, again with a rate-limiting step. For example, while an
antibiotic was diffusing to the center of an abscess, degradation by beta-lactamase-producing
bacteria could degrade it, thus producing antibiotic concentrations near zero during
continuous administration.

It was found that not all beta-lactam-bacteria interactions follow the rule of non-
concentration-killing efficacy dependency. For instance, Onyeji et al have showed that
cefaclor exhibited a marked inoculum effect against four pathogens studied, and that there
was concentration dependent killing at a large inoculum.\textsuperscript{27}

With continuous infusion, a delay in drug equilibration to tissues occurs because of the lag time required to reach effective steady state concentrations in serum. However, administration of a loading dose prior to continuous administration would ensure the rapid onset of antibacterial activity.

Another pharmacodynamic concern is a situation where continuous exposure to antimicrobial concentrations is only slightly over the reported MIC. Thus, specific sub-populations of resistant organisms that are typically not detected by MIC testing could grow. Nevertheless, the development of resistance has not been found in any of the clinical trials reported until now, probably because of the contributing activity of the immune system.

\subsection*{7.1.3 The target therapeutic concentration}

Several investigators have proposed, based on \textit{in-vitro} experiments, that a maximum effect is reached at 4x MIC for the target bacterium.\textsuperscript{24} Preclinical investigation clarified that the target ‘therapeutic concentration’ depends on the status of the immune system. For example, serum ceftazidime concentration needed during continuous infusion to obtain 50\% efficacy in normal rats was between one-sixth and one-third the MIC, for the infecting \textit{K. pneumoniae}, depending on the severity of the infection. However, the concentration needed to obtain 100\% efficacy (ED\textsubscript{100}) was dependent not only on the severity of infection but also whether the animals were leukopenic or not.\textsuperscript{24}

\subsection*{7.1.4 The required time over MIC (T>MIC)}

Craig has summarized all the available data from the literature that use mortality as an endpoint and in which animals infected with \textit{S. pneumoniae} were treated with penicillins or cephalosporins.\textsuperscript{28} The duration of time that the serum level needs to be above the MIC to ensure efficacy is shown in Figure 4. It can be seen that the mortality was virtually 100\% if serum levels were above MIC for 20\% or less of the dosing interval. In contrast, as soon as T>MIC was 40\% - 50\% of the dosing intervals or higher, bacteriologic efficacy was 90 to 100\%. Similar results were found in clinical studies that assessed bacteriologic cure in otitis media.\textsuperscript{29} The findings indicates that if serum levels are above the MIC for 40\% to 50\% of the dosing interval, a bacteriologic cure of over 90\% is obtained.

\subsection*{7.1.5 Parenteral versus oral therapy with beta-lactam antibiotics}
The decision to use parenteral or oral therapy to treat an infectious disease has traditionally depended primarily on the severity of the infection. It is often assumed that if the patient with an infection is sick enough to be hospitalized, the patient is also sick enough to receive parenteral antibiotics. The enhanced understanding of the concentration-activity of the antibacterial efficacy has clarified that proper therapy can be achieved with oral administration of antibiotic drugs. According to the rationale discussed above, the preferred parenteral dosing strategy for therapy with beta-lactam antibiotics is continuous infusion. However, this approach has certain limitations, of which the most problematic issues are the patient inconvenience due to decreased mobility, increased risk of bacteremia due to intravenous line infection, increased costs due to necessity for hospitalization and the need for trained medical personnel for parenteral antibiotic administration. Oral therapy can replace part of the parenteral antibiotic therapy. The major trend in oral beta-lactams has been to find new drugs that have increased potency against gram-negative pathogens and longer half-lives. However, several pharmaceutical approaches can also be used to prolong T > MIC. The most obvious approach would be administration of larger doses that produces a longer duration of T > MIC (as illustrated in Figure 5). This approach can be used for a beta-lactam with elimination half life of 1 hr, such as penicillin V-K, that is an inexpensive drug, and whose elevated concentrations are not associated with severe adverse reactions. However, a considerably larger total daily dose is needed to achieve the same magnitude of T > MIC in comparison to continuous administration.

Another approach to prolong T > MIC for beta-lactams is to develop an oral controlled release formulation, which provide continuous administration of the drug from the gut to the systemic blood circulation. Due to flip-flop pharmacokinetics of the sustained release formulation, the apparent elimination half-life of the drug is extended. We have demonstrated this approach with a hydrophilic matrix formulation of amoxicillin. This beta-lactam antibiotic had pharmacokinetic properties that are similar to other drugs from this category, including short elimination half life, and active absorption that is limited to the upper parts of the gastrointestinal (GI) tract. Prolongation of T > MIC for these drugs following oral administration (in vivo) is limited by the narrow absorption window. To overcome this pharmacokinetic limitation the controlled release matrix tablet was designed to release 50% of its content within 3 h, followed by a constant release rate for about 8 h. The rapid onset of drug release was designed to provide an initial ‘loading dose’ and to maximize the absorption phase in those parts of the intestine in which amoxicillin is actively absorbed by a carrier-mediated process. The in vivo evaluation of the new formulation revealed that the extent of absorption of the new formulation is not much different than that of a regular soft gelatin
capsule formulation. Furthermore, the time required to obtain therapeutic concentration (‘onset time’) was found to be identical for the two formulations. However, T > MIC as well as T > 4MIC of the drug against susceptible pathogens was found to be maintained for a significantly longer period.

### 7.2 Pharmacodynamic rationale for pulse dosing of antibiotics with concentration-dependent bacterial killing properties (Category II)

The drugs in this category are characterized by concentration-dependent killing over a wide range of concentrations and by prolonged persistent effects. The goal of a dosage regimen for these drugs is to maximize concentration. The magnitude of the peak level and the AUC in relationship to MIC would be the important determinants of efficacy for these drugs. Wide dosing intervals are also possible because these drugs induce prolonged PAE. Sub-MIC concentrations and the presence of leukocytes can further prolong the PAE. These preferred dosing strategy were found in-vitro and in preclinical studies and were partially confirmed in clinical studies.

#### 7.2.1 Pharmacodynamics of fluoroquinolones

The 24-hr AUC/MIC ratio is the parameter that best correlates with the efficacy of fluoroquinolones as shown in Fig. 6.\(^{18,37}\) When tested for ciprofloxacin, this parameter was better than the peak drug concentration and considerably better than T > MIC, which needed to exceed the MIC for about 20% of the time interval to obtain any bacterial killing. In animal infection models, the magnitude of the 24-hr AUC/MIC required to produce a bacteriostatic effect is ~ 35.\(^{37}\) This value implies that the AUC averages ~ 1.5 times the MIC over 24 hr period (i.e., 1.5 x 24 =36). This value is independent of the dosing interval, the fluoroquinolones used, and the site of infection.\(^{18,38}\) It was found in experimental animal infections and in clinical trails that the fluoroquinolones concentration in serum need on average about 4 times the MIC in order to ensure bactericidal activity and patient cure. \textit{In vivo} preclinical studies confirmed the PAE of these drugs.

The development of the fluoroquinolones is considered to be the major advance over the past decade in oral antimicrobial therapy due to their enhanced activity against gram-negative bacilli. Twice a day dosing, by either oral dosing or intravenous administration produce 24-hr AUC/MIC values that are considerably higher than 125 for various bacterial species.
7.2.2 Once a day aminoglycoside administration

There appears to be a general consensus that pulse dosing of aminoglycosides offers the following advantages: i) relatively easy, straightforward initial dosing; ii) enhanced efficacy due to higher peak levels; iii) enhanced safety due to shorter effective exposure time; iv) convenience for both patients and nurses; v) likely on-time administration; vi) a much reduced need for serum aminoglycoside levels monitoring (reduced cost); vii) facilitation of drug administration through home care services (reduced cost).

While in preclinical investigations the 24-hr AUC/MIC ratio better correlated with therapeutic efficacy than peak/MIC ratio, the opposite was found in the major clinical trials. To achieve a clinical response of >90% the peak concentration should exceed the MIC by 8–10 fold. The once a day regimen that produces such elevated peak concentrations can also reduce the rate of emergence of aminoglycoside-resistant mutants during therapy. This is because the initial exposure of the microorganisms to aminoglycosides down-regulates subsequent uptake of drug, thus higher MICs are exhibited for several hours. Therefore, the larger time intervals that result from once-daily dosing regimen of the aminoglycosides enable this effect to dissipate until next dosing. This, in addition to the prolonged PAE (2–8 hr) of these drugs (which provide continued suppression of bacterial growth despite the decline of the antimicrobial concentration to zero), augments the rationale for increased intervals between doses (i.e. once daily vs. multiple daily dosage regimens).

The pharmacodynamics of aminoglycoside toxicity also corroborates once daily dosing of these drugs. The mechanism of aminoglycoside nephrotoxicity involves an absorptive influx at the proximal convoluted tubule cells that is mediated by a low affinity, high capacity mechanism that can be saturable. Thus the uptake into the kidney is more efficient with low sustained concentrations than with high intermittent concentrations. Several studies have showed that the onset of nephrotoxicity is delayed for several days when the drug is administered once daily. Animal studies that have examined ototoxicity show that the degree of the cochlear damage is more related to the total daily dose of the aminoglycoside rather than the frequency of administration. Hence, saturation of cochlear cells may play a role in determining ototoxicity.

Multiple meta-analysis studies that assessed the impact of mode of aminoglycoside administration on therapeutic outcomes suggest a small, non significant trend towards better efficacy and lower toxicity with once-daily regimen. However, it should be noted that not in all situations once daily dosing would be a better choice than traditional intermittent dosing regimens.
7.3 Optimal dosing regimens of Category III antibiotics

The main pharmacodynamic parameter for drugs in this category is also the duration of exposure. However, the relatively long elimination half-life together with persistent effects allows drug levels to fall below the MIC for considerable portion of the dosage interval. Thus, due to their unique pharmacokinetics and pharmacodynamics, the therapeutic outcomes following therapy with these drugs is not affected by the mode of administration. For instance, the optimal dosing method for vancomycin may be the one that achieves the lowest AUC while concentrations are maintained above the MBC.45

7.4 Targeted antibiotic treatment by SR drug delivery systems: the case of periodontitis

The clinical manifestation of periodontitis is the formation of a deeper space between the teeth root surface and the opposing periodontal tissue. This crevice is termed a periodontal pocket and its depth usually exceeds 5 mm. The anatomic configuration of the periodontal pocket is an ideal habitat for microflora that is mainly composed of gram-negative bacteria (mostly anaerobic). Collagenase and other enzymes that originate from the bacteria can destroy the connective tissue of ligaments, while exotoxins evoke an inflammatory reaction. When mechanically cleaning methods to improve oral hygiene fail, a chemotherapeutic approach may be applied. Systemic administration has been useful in treating periodontal pockets, but repeated, long term use of systemic antibiotics is fraught with potential danger including resistant strains and superimposed infections. Therefore, the periodontal pocket is an excellent example for localized infection site for which local administration of a drug by SR delivery system provides an extremely useful solution. The important factor in the success of this treatment is the ability to control and the release of the drug, thereby maintaining high intra-pocket drug concentrations with very low plasma concentrations.

Intra-pocket delivery systems were found to be very effective clinically. The selection of the antibiotic agent for these SR periodontal delivery systems has to be guided according to the following principles. Since the amount of drug that can be placed in the periodontal pocket is limited, the drug has to be highly specific against the periopathogenic bacteria. It should not cause the development of resistant bacterial strains, and should not affect the soft tissue of the pocket. So far, antiseptic agents, including chlorhexidine, cetylpyridinium chloride and parabens on one hand, and antibiotics such as tetracycline, minocycline, doxycycline, and metronidazole, on the other hand, have provided very effective control of the periodontal microflora and significant reduction of the pocket depth (see Steinberg and Friedman for a recent review46).
The same principles of local SR delivery of antibiotics that were noted above for the treatment of periodontitis can be applied for other localized infections particularly for low-perfused sites.

8. **Anticancer drugs**

Anticancer drugs are characterized by a low therapeutic index and a high extent of intra- and inter-patient variability in pharmacokinetics and drug effects. Pharmacokinetic studies indicate highly variable absorption, tissue distribution and elimination for most anticancer drugs. Several–fold differences in drug clearances within a homogeneous patient population have been observed for major anticancer drugs, including methotrexate, etoposide, doxorubicin, cylophosphamide, etc. The extent of drug effects is also variable and depends on mode of drug administration, tumor- and host-related factors. For certain tumors, the chemosensitivity to certain agents is related to immunophenotype, tumor localization, proliferative potential, and may be a subject to circadian variability. Figure 7 illustrates variability in doxorubicin effect on human bladder tumors applying *ex-vivo* testing of drug activity. In this study, a 35-fold variability in superficial bladder tumor chemosensitivity to doxorubicin was observed, as opposed by only 4-fold variability in tissue pharmacokinetics. Thus, to optimize clinical outcome, the patient status should be assessed frequently and drug dosing should be appropriately adjusted.

Choice of treatment regimens with anticancer drugs in most cases is based on pharmacokinetic principles and clinical empiricism. This is mainly because the desired effect (i.e., a reduction in tumor size or amount of tumor cells) is not readily detected and is not applicable as a measure of clinical outcome. Generally, several types of pharmacokinetic or pharmacodynamic markers can be applied for monitoring cancer patients. In certain cases, the extent of main adverse effects (myelosuppression and gastrointestinal toxicity) appears to be related to the systemic drug exposure, and monitoring of adverse effects may be applied for adjustment of treatment protocols in the specific patient. It should be mentioned that a temporal discrepancy exists between exposure time to the drug and the measured drug effects and clinical outcome.

Anticancer drugs are seldom used as single therapy due to variability of tumor response and elevated risk of emergence of resistance. When combination chemotherapy is applied, pharmacodynamic relationships for individual anticancer drugs can’t be readily resolved. Common use of support medications (i.e., antiemetic drugs, growth factors, protective agents, etc.) and multiple courses of drug treatment further complicate the comparison between
different clinical settings and study of the drugs’ pharmacodynamic profile.

Due to the outlined reasons, little is known about the pharmacokinetic/pharmacodynamic relationships of therapeutic or toxic responses of anticancer drugs. Most pharmacokinetic/pharmacodynamic studies have focused on finding correlations between the drug exposure and the extent of response following certain schedules and modes of administration of the anticancer drug. Theoretical analysis suggests that the pharmacodynamic profile of therapeutic response is related to the mechanism of action of a specific drug, i.e. different profiles are expected for cell-cycle-specific or cell cycle-non-specific anticancer drugs. If a drug’s cytotoxic activity is independent of cell growth cycle (cell cycle-non-specific agents), a direct relationship is expected between the drug exposure (i.e., AUC over a certain threshold concentration) and the response and the sigmoidal Emax model may be used to describe the pharmacodynamic profile. In this case, the total cytotoxic effect of a given dose of drug is independent of the schedule of administration. This is not true for cell-cycle-specific agents whose mode of action is related to the formation of active metabolites or accumulation of intracellular drug complexes. For such drugs, the administration schedule may profoundly affect the extent of response. That is because the response is mostly related to the duration of exposure above a threshold concentration than to peak drug concentrations.

The goal of anticancer therapy is to produce the maximal therapeutic response while producing acceptable toxicity. For a particular drug this may be accomplished by using the difference between the pharmacodynamics of the therapeutic and toxic effects. The focus of this review is mainly on optimization strategies of mono-therapy with selected anticancer drugs, and on the impact of the mode of administration (dosing schedule, dose, and route of administration) on the clinical outcomes.

8.1 Cell cycle-non-specific agents

8.1.1 Doxorubicin

The anthracycline doxorubicin is widely used in the treatment of both hematologic malignancies and solid tumors. Doxorubicin is a cell cycle-non-specific agent, and the extent of therapeutic response for a given dose should not be dependent on the schedule of doxorubicin administration. However, doxorubicin cardiotoxicity appears to be administration rate-dependent. A 24-hr infusion resulted in significantly higher cardiotoxic effect in comparison to a 48- or 96-h infusion, whereas the incidence of myelosuppression and mucositis were not affected. A once-weekly IV bolus administration schedule of doxorubicin significantly reduces cardiotoxicity as compared with a once every 3 week
schedule but still does not affect the magnitude of the cytotoxic effect.\textsuperscript{54} Thus, the extent of cardiotoxicity is related to the peak plasma concentrations, and more prolonged modes of administration are needed to optimize the clinical outcome.

\textbf{8.1.2 Platinum compounds}

Cisplatin and carboplatin are cell cycle-non-specific agents widely used for treatment of a variety of solid tumors. The major adverse effects of cisplatin are renal, neurologic and ototoxic. A recent pharmacodynamic study by Nagai and Ogata showed that AUC values highly correlate with cisplatin induced nephrotoxicity in rats.\textsuperscript{55} The maximum blood urea nitrogen (BUN) level served as a marker of nephrotoxicity. The main results of the study are presented in Figure 8. It may be concluded that an infusion mode of administration produced 2-3-fold less nephrotoxicity, compared to the effect of the same dose administered as bolus. In addition, duration of exposure above a threshold concentration (AUC > C\textsubscript{min}) was shown to be linked to the extent of nephrotoxic effect, irrespectively of dose and schedule (see Figure 9). Clinical studies in patients with various types of cancer showed that extent of nephrotoxicity is mainly correlated with peak concentrations of cisplatin (C\textsubscript{max}),\textsuperscript{56} and that slower administration rate results in lower incidence of gastrointestinal toxicity (emesis).\textsuperscript{57,58} Thus, for cisplatin, the extent of therapeutic activity is largely independent of mode of drug administration, but continuous dosing schedule should be applied to reduce the incidence of adverse effects.

The same considerations should apply for other platinum compounds, despite somewhat different clinical profile. The toxicological properties of carboplatin differ from that of cisplatin, and its primary dose-limiting toxicity is thrombocytopenia. A significant relationship was found between area under the curve (AUC) and tumor response, thrombocytopenia, and leukopenia in patients with advanced ovarian cancer.\textsuperscript{59} Circadian-modulated treatment schedule of carboplatin showed no clinical advantage over flat infusion in patients with advanced cancer.\textsuperscript{60} In contrast, a clinical study with another platinum compound, oxaliplatin, showed lower incidence of neutropenia and vomiting in a circadian-modulated mode of administration to carcinoma patients.

\textbf{8.2 Cell-cycle-specific agents}

\textbf{8.2.1 Etoposide}

Etoposide is cell-cycle-specific drug (late S and early G\textsubscript{2} phases) which is highly active in small-cell lung cancer and lymphoma. The schedule of etoposide administration profoundly
influences the extent of drug effects both in vitro and in vivo. Continuous exposure to low levels of the drug was shown to produce enhanced therapeutic response in comparison to bolus dosing. For instance, five consecutive daily 2-hr infusions produced partial remission in 89% of patients in comparison to a 10% response in a single 24-hour infusion of etoposide in patients with small-cell lung cancer.61 The patient survival curve in this study is presented in Figure 10. The AUC values were identical in the two arms of this study, but the duration of exposure to low concentrations of drug (> 1 mg/L) was doubled in the 5-day arm.

Several clinical studies showed that the hematological toxicity of etoposide is correlated to the systemic drug exposure. For instance, in low-dose etoposide administered orally to children with solid tumors, the time of exposure above a threshold concentration was found to be more strongly correlated with neutropenia than other pharmacokinetic parameters, including dosage and AUC.62 Antitumor activity is generally associated with the maintenance of lower levels of etoposide than hematologic toxicity. Clark et al found that duration of exposure to plasma etoposide > 3 mg/L is predictive of a nadir neutrophil count and > 2 mg/L is predictive of a nadir WBC count.63 Then the same dose of etoposide was administered as 8 daily 75-minute infusions or 5 daily 2-hour infusions to patients with small-cell lung cancer, higher hematologic toxicity was found for 5-day arm of the study due to prolonged periods of time of higher exposure to etoposide.

In addition to schedule dependency of drug effects, clinical treatment with etoposide is complicated by a high degree of inter-patient pharmacokinetic variability. Several clinical conditions associated with elevated risk of adverse effects were identified, including patients with impaired renal function, low serum albumin concentrations, or highly elevated liver enzyme values.64 Thus, monitoring of drug concentrations as well as hematologic toxicity should be applied for adjustment of etoposide doses in individual cancer patients as a means to optimize the clinical outcome, in addition to applying a prolonged mode of etoposide administration.

8.2.2 Fluorouracil (5-FU)

Fluorouracil is the agent of choice for treatment of colorectal cancer. Despite numerous trials, the issue of schedule-dependency of 5-FU treatment remains controversial.65 Bolus injection of 5-FU was shown to produce higher response rates and the same extent of toxic effects in comparison to the same dose administered as short-term infusion (over 10-20 min).66,67 On the other hand, since 5-FU is a cell-cycle-specific antimetabolite agent, prolonged exposure to this drug should result in 5-FU uptake by more tumor cells. Indeed, 48-
hr continuous infusion of 5-FU provided superior antimetabolic effect compared with bolus administration in patients with gastric cancer as evidenced by higher extent of thymidylate synthase (TS) inhibition in cancer cells. Although prolonged continuous infusion regimens of 5-FU (over 24 hrs or more) were found to increase the response rate in comparison to bolus injections, it did not improve the overall survival rate. This clinical outcome may be related to difference in toxicity pattern produced by the different administration regimens.

In some patients tumor resistance evolves following bolus administration of 5-FU. In this case continuous infusion of 5-FU may be applied to overcome the drug resistance. Administration of bolus injections and continuous infusion concomitantly or in alternating order may serve as alternative strategy to improve the patient response.

8.3 Optimization of anticancer treatment

Current treatment protocols of anticancer drugs do not provide optimal clinical outcome in the terms of the response and the patient survival. In order to optimize the clinical outcome, additional preclinical and clinical studies are needed to clarify the relationship between the pharmacokinetic parameters and the therapeutic and toxic effects for individual anticancer drugs. From the currently available data it seems that for cell cycle-non-specific agents the magnitude of therapeutic drug effects is not related to the drug input rate. However, the magnitude of adverse effects for such drugs may be significantly reduced by applying prolonged modes of administration. For cell cycle-specific agents, prolonged mode of drug administration should be applied to keep the drug concentrations within a certain concentration range. This is because decrease in therapeutic effect occurs at lower concentrations, while higher concentrations are associated with elevated magnitude of toxic drug effects.

In addition to optimization of administration mode, profound pharmacokinetic and pharmacodynamic variability of anticancer drugs requires application of individualized treatment regimens for different cancer patients. Monitoring of plasma drug concentrations may be applied to overcome the pharmacokinetic variability and to reach the target drug exposure. However, this approach does not ensure that desired magnitude of drug effects is attained. Monitoring of specific pharmacodynamic markers of tumor response or of toxic effects has therefore a greater potential for reduction of inter-patient variability and for optimization of dosing of anticancer agents.

9. Hormones: Pulsatile vs. continuous mode of administration
The input function of hormonal drugs is known to have a major impact on the magnitude of therapeutic response. This phenomenon is related to physiological processes of secretion and regulation of hormone levels in the body. Many hormones are secreted in pulses, including insulin, somatostatin, C-peptide, growth hormone (GH), PTH and luteinizing hormone (LH). When the delivery system mimics the natural secretory pattern of the hormone, it provides optimal hormone replacement therapy. On the other hand, the continuous administration of large doses may suppress natural hormone secretion by activating the feedback mechanisms in the body. Mazar has clearly described the effect of the input function on the outcome of somatostatin derivative and for gonadotropin-releasing hormone (GnRH). For somatostatin derivatives, optimal suppression of GH secretion in the treatment of acromegaly, was obtained following a constant input rate. Similarly, if GnRH is given continuously, gonadotropin secretion is suppressed through the mechanism of down-regulation, which is used clinically in the treatment of prostate, endometrial and breast cancer. On the other hand, pulsatile delivery of GnRH provides optimal response in stimulating pituitary gonadotropin secretion. This particular response occurs because the wave contour is a specific factor in the pharmacodynamic effects of GnRH on pituitary gonadotropin and the steepness of the rising edge of the GnRH wave contour is a specific determinant of pituitary LH secretion. In a like manner, continuous administration of insulin down-regulates the numbers of insulin receptors, a phenomenon that can be minimized by pulsatile insulin secretion.

10. Anti-ulcer drugs

Current anti-ulcer treatment involves eradication the *H. pylori* infection by applying antibiotic drugs, and concomitant suppression of acid secretion with H2-receptor antagonists, or proton pump inhibitors (PPI). Since pharmacodynamic properties of the antibiotic drugs were already discussed in the previous parts of this review, this chapter will concentrate on the pharmacodynamic aspects of the antisecretory treatment.

The pathogenesis of acid peptic disorders, including gastric ulcers, duodenal ulcers, and gastroesophageal reflux disease, involves an imbalance between acid secretion and gastric mucosal defenses. The patterns of basal acid secretion in ulcer patients are similar to healthy individuals (with the exception that ulcer patients secrete about 30% more acid) and follow a circadian rhythm, with maximum acid secretion occurring during the early evening hours. The acid secretion activity is subject to high inter- and intra-patient variability; day-to-day
variation in the same individual can vary by more than 50%, obscuring the patient response to anti-ulcer agent and distorting the relationship between plasma concentrations and pharmacological response.80

It was generally accepted that ulcer healing is directly correlated to the degree of acid suppression, and that a sustained reduction of gastrointestinal acidity (pH above 3) should be achieved for optimal treatment results.81 Thus, the main pharmacologic approach of ulcer healing involves decreasing of acid secretion by parietal cells using either histamine H₂-receptor antagonists, or proton pump inhibitors (PPI).

10.1 H₂-receptor antagonists

H₂-receptor antagonists were the most commonly prescribed agents for treatment of peptic ulcer treatment, the main agents being cimetidine, ranitidine, and famotidine. These drugs inhibit histamine-mediated gastric acid secretion and, thereby, produce incomplete inhibition of acid secretion in response to meals because acid-secreting parietal cells continue to receive stimulation via cholinergic and gastrin-mediated pathways.82 H₂-receptor antagonists may be administered via oral or intravenous routes. The duration of individual drugs antisecretory action ranges from 6 to 12 hours.83

Repetitive dosing of H₂-receptor antagonists results in rapid development of tolerance (within several hours or days), reducing the drugs acid inhibitory effect.84 The apparent loss of ranitidine efficacy was shown to occur within 12 hours in patients with gastric or duodenal ulcers (see Figure 11).85 This phenomenon is thought to be mediated by the feedback mechanisms elevating acid secretion by gastrin-mediated or alternate pathways, up-regulation of H₂-receptors, or decrease in proton pump turnover.86,87 Adverse effects are uncommon with the H₂-receptor antagonists and are generally mild.

10.1.1 Continuous vs. intermittent administration

Continuous infusions of H₂-receptor antagonists were shown to maintain elevated gastric pH for a significantly longer period of time than bolus regimens in ulcer patients, critically ill patients, and in healthy volunteers.88-90 The gastric pH control could be achieved at equal or lower total doses with continuous infusion.91 This apparent dose-sparing effect of continuous mode of administration may be explained by relatively low ECmax (i.e., the concentrations of H₂-receptor antagonists that are needed to attain the maximal antisecretory effect). Serum concentrations following bolus drug administration exceed this concentration for a shorter period of the dosing interval than following continuous mode of administration.2
Additional explanation relates to the different degree of activation of tolerance-related feedback mechanisms by bolus as opposed to continuous mode of administration. Continuous exposure to lower doses of H$_2$-receptor antagonists may provoke less feedback activation and improved control of gastric acid secretion.

10.1.2 Circadian dependency

The dosing schedules of H$_2$-receptor antagonists were considerably changed over time. Long-term acid suppression was considered obligatory for ulcer healing, and the initial approach applied multiple doses of H$_2$-antagonists to reduce acid secretion for most periods of the circadian cycle. Following this, a single daily night regimen of H$_2$-receptor antagonists was shown to produce better control of gastric pH compared to once-a-day morning administration.\textsuperscript{92,93} This is because the intragastric contents are buffered by food during the day, leading to lower apparent antisecretory effect following morning drug administration. Inhibition of nocturnal acid secretion was considered of primary importance for ulcer healing, and single bedtime dose had become the preferred regimen worldwide.

However, results of several clinical trials produced equivalent clinical outcome in terms of ulcer healing of morning and bedtime doses of H$_2$-antagonists, despite different control of nocturnal acidity.\textsuperscript{94,95} Thus, nocturnal gastric acidity suppression is important but not essential to promote duodenal ulcer healing. Currently, peaks of increased acidity are considered the main factor hampering ulcer healing process, with no particular relevance to which time of the circadian cycle during such peaks occur. Thus, efficient ulcer treatment should prevent appearance of such peaks by implying sustained inhibition of parietal cell activity.\textsuperscript{96}

10.2 Acid (proton) pump inhibitors

The proton pump inhibitors (PPI) that were used in clinical settings include omeprazole, lansoprazole and pantoprazole. Under strongly acidic conditions that exist in the secretory canaliculi in the parietal cell, these drugs are converted to the active species (sulphenamides) that irreversibly bind to the gastric proton pump (H$^+$/K$^-$-ATPase), inactivating the proton transport. Thus, despite the short plasma half-life of 0.7-1.3 hours, this covalent binding causes a prolonged duration of antisecretory effect, enabling a relatively infrequent administration schedule.

Both oral and intravenous routes of administration of PPI were used in clinical practice. The antisecretory effect is related to amount of the drug in the systemic circulation, and is
independent of the route of administration. Adverse effects occurred infrequently with PPI agents and most commonly comprised transient gastrointestinal symptoms.

10.2.1 Administration schedule

Exposure to the relatively high doses of the drug may produce sufficient amounts of active metabolite, which can inhibit acid secretion of actively functioning parietal cells. However, the brief serum half-life of active metabolite may not last enough to affect other populations of parietal cells that may be inactive at the time of administration. As a result, populations of parietal cells that were not actively secreting acid during the time that the active metabolite was in the serum become active afterwards and produce boots of low gastric pH. Thus, the larger bolus dose provides small additional effect, and the degree of acid inhibition increases gradually during the first days of once daily dosing because of an increase in the number of H⁺/K⁺-ATPase enzymes inhibited (see Figure 12).

In contrast to H₂-receptor antagonists, continuous administration of PPI drugs does not result in development of tolerance to the antisecretory effect (see Figure 11). Based on in vitro studies, it was expected that continuous delivery of PPI drugs would inhibit more populations of parietal cells and produce enhanced control of intragastric pH in comparison to bolus doses. Intravenous administration of lansoprazole as bolus injection or infusion to healthy volunteers was reported, however, to produce the same extent of antisecretory action. Nevertheless, these trials applied short-term (24-hour) intragastric pH monitoring and did not necessarily represent the clinical outcomes in prolonged treatment of ulcer patients.

The higher efficiency of fractional administration of PPI drugs was confirmed in a recent experiment when divided dosing of omeprazole provided superior gastric acid suppression compared to once daily regimen in healthy volunteers. Additional studies compared effectiveness of daily omeprazole administration with every other day or twice a week schedules, with slightly improved clinical outcomes following once daily administration.

10.2.2 Circadian dependency

PPI drugs produce lower effects during the night than in daytime, independently of administration time. Possible explanation to this phenomenon is that more proton pumps in the parietal cells are activated by the repeated meal stimuli during the daytime, and become prone to covalent binding of active metabolites, making the same dose of PPI drugs more effective. Another contributing factor may be circadian dependency of the oral
bioavailability of the drug that yield higher plasma concentrations following morning dosing.105,106

10.3 Optimization of anti-ulcer treatment

The concepts concerning role of overall amount of acid and relative importance of acidity during different time intervals in ulcer pathogenesis have overcome major changes in recent years. Currently, strong and continuous acid inhibition is not considered obligatory for beneficial clinical outcome. Instead, short periods of elevated acidity in response to meals or at night seem to be important pathophysiological events, whose control is sufficient to permit quick ulcer healing.96 It seems that a small peak-preventing reduction of gastric acidity can ensure the same therapeutic benefit as a strong and continuous acid inhibition, producing new insights to optimized treatment regimen with antisecretory drugs.

Major pharmacokinetic and pharmacodynamic differences exist between the two groups of antisecretory drugs, profoundly influencing the antisecretory treatment schedule. For instance, the considerably shorter duration of action of H₂-receptor antagonists in comparison to proton pump inhibitors necessitates shorter administration intervals or prolonged modes of administration.82 Pharmacodynamically, the antisecretory activity of H₂-receptor antagonists is weaker than that of PPI drugs (lower Emax), and decreases following continuous exposure to the drug due to tolerance development that further reduces the drug efficacy.84,107

As a consequence, the difference in ulcer healing rates between proton pump inhibitors and H₂-receptor antagonists103,108,109 may be attributed to different control of peaks of elevated gastric acidity by clinically applied regimens of these drugs. Continuous modes of administration of antisecretory drugs may provide better control of gastric acidity and optimize clinical outcomes. For instance, continuous administration of H₂-receptor antagonists provides sustained reduction of gastric acidity and possibly prevents activation of feedback mechanisms of acid secretion. As for proton pump inhibitors, continuous administration may elevate treatment efficacy by increasing the number of inhibited H⁺/K⁺-ATPase enzymes.

11. Controlled release systems in analgesia

Controlled release opioids have become well established in the management of pain, particularly chronic cancer related pain, but also to alleviate non-cancer painful conditions such as severe burns, surgery-induced pain, sickle-cell crisis and arthritis. While oral CR
morphine has predominated in this regard, other oral CR preparations have been developed more recently, including codeine, dihydrocodeine, oxycodone and hydromorphone. In addition, other dosage forms such as rectal morphine and transdermal fentanyl and buprenorphine preparations have been developed for the same indications.

According to the World Health Organization recommendations, pharmacologic treatment with morphine is considered the standard in alleviating moderate to severe pain associated with neoplastic diseases. The drug can be administered via different modes and routes, such as rapid input via multiple i.v. (or oral) bolus administrations, or in a sustained manner by CR tablets or continuous infusion. Tolerance, manifested clinically as an increase in the dose required over time to maintain a pain-free state, develops to the analgesic effect of morphine. Despite the prevalence of this phenomenon, there is very limited quantitative information on the rate and extent of tolerance development in humans. In particular, clinical information is lacking about the relationship between mode of administration and the kinetics of tolerance development. Preclinical studies in rats revealed that tolerance to morphine antinociception developed rapidly within 8 to 12 hr during continuous i.v. infusion. A longer period (7-10 days) is required for tolerance development during morphine administration as multiple s.c. or i.p. bolus doses. Using a pharmacokinetic-pharmacodynamic model that describes the development of tolerance in rats, Ouellet and Pollack found that about the same degree of tolerance is achieved whether morphine is administered as a continuous infusion or as intermittent i.v. boluses. This is because the half-life for tolerance onset and offset is too long to allow significant sensitization between intermittent doses. In their experimental model they showed that increasing the interval between doses to one day does not reduce the magnitude of tolerance development during 13 days of morphine administration. This finding is in contrast to a previous report by Ekblom et al, which used a similar modeling analysis to the continuous vs. bolus modes of morphine administration. They concluded that when administering a bolus dose of morphine, the antinociceptive effect is less influenced by the slow tolerance development than during constant rate infusions. They observed rebound effects after cessation of the infusion but not after the bolus dose. The half life of the tolerance development estimated in both studies was long, between one to 3 days, that shows that tolerance develops slowly over several days. Thus, it is not very clear if intermittent dosing reduces the degree of tolerance development, and further pharmacokinetic/pharmacodynamic investigations are needed.

While the rationale for pursuing opioid pharmacokinetic/pharmacodynamic studies is compelling, the complicating factors that hinder these investigations, especially in the clinical setting, should be appreciated. These include: potential biases within analgesic studies,
that require double blind design; incorporation of the pharmacodynamics of the placebo effect, that is known to be an inherent factor in the response to active treatments; opioid receptors are located outside of the plasma compartment (the site of sampling), and different opioid effects are likely to be mediated by receptors in different pharmacokinetic compartments; metabolite activity may be of clinical importance; different concentration-effect relationship for various pain intensity and pain characters; no stationary disease state; development of acute and chronic tolerance; subjective methods of quantitative measurements of pharmacodynamic effects.

11.1 Opioid analgesics

11.1.1 Controlled release formulations of morphine

The oral route is the preferred mode of morphine administration in cancer pain and the majority of patients can be safely and effectively maintained by this route. The duration of action after oral administration is short; therefore, if permanent relief of pain is required, the drug has to be administered every 4 hr. For this reason, a sustained release formulation of morphine could be very useful allowing a delay in the interval between the administrations, from 6 times a day to twice a day, and even once daily. The efficacy of the marketed formulation of CR morphine (MS-Contin\textsuperscript{R}) has been demonstrated.\textsuperscript{120} The analgesic efficacy of the CR formulations is not significantly different from that observed with reference morphine syrup administered every 4 hr.

In addition to oral CR morphine formulations, many patients require an alternative route of administration at some point in the course of their terminal illness. Common reasons for the use of alternate route of morphine administration include severe nausea or vomiting, dysphagia, bowel obstruction and severe confusion. Presently, the subcutaneous and rectal routes represent the most widely used alternatives. The continuous subcutaneous infusion is an effective procedure, but has certain disadvantages, including restriction of mobility and the required frequent visits to the clinic for dosage adjustments and medication replenishment. An improved approach is the CR morphine suppository formulations that demonstrates equivalent pharmacokinetic and pharmacodynamic properties to the oral CR formulations.\textsuperscript{121}

11.1.2 Other opioids CR formulations

Despite the extensive use of morphine, the occurrence of adverse effects necessitates discontinuation in some patients. Clinicians treating cancer pain report significant variability among patients in efficacy and side effects with available opioid analgesics. Patients who
have poor analgesic efficacy or safety outcomes with one opioid will frequently tolerate another. This finding has led to the growing acceptance and clinical practice of opioid rotation. The recent availability of opioid CR formulations such as oxycodone and hydromorphone provides clinicians therapeutic options for cancer pain management. Maddocks et al have shown that in patients with morphine-induced delirium, the substitution of morphine with oxycodone results in significant improvement in the mental status, nausea and vomiting. Recent evidence suggests that in addition to μ receptor-mediated analgesia, oxycodone possesses intrinsic activity at the κ receptor, providing further rationale for its use in treating patients unable to obtain an optimal analgesic or side effect profile with morphine or hydromorphone.

Oxycodone has been recently formulated into a 12 hr CR tablet which retains an onset of analgesia as prompt as with conventional immediate-release oxycodone with majority of patients reporting pain relief within 1 hr of administration and pain control throughout a 12-hr period. The prompt onset of action results from the dual-release mechanism of the CR delivery system. The rationale for this formulation is to avoid the need for concurrent administration of an immediate release formulation that provide analgesia at the initial phase after administration, until the CR formulation will constitute therapeutic concentration. Another rationale that has been proposed for the biphasic opioid absorption profile is to produce a peak-to-trough fluctuation comparable to conventional immediate release opioid. This rationale is based on the suggestion, mentioned above, that very steady plasma opioid concentrations may lead to tolerance development. The rapid onset of analgesic action is also in accordance with the concept that have been proposed by Levy, that the rate of decline of clinical analgesia after administration of various narcotic and non-narcotic analgesics, and even placebos, is essentially the same, and the maximum degree of analgesia and the duration of action is a function of Cmax. Thus, a rapid mode of administration that provides larger Cmax values (that are not associated with significant adverse effects) could provide a longer duration of pain relief than those obtained after a slower-absorbed dosage form.

Pharmacodynamic evaluation of oxycodone revealed that minimal hysteresis occurred between peak plasma oxycodone concentrations and peak pharmacodynamic effects, indicating little or no delay in pharmacologic effect once oxycodone reached the systemic circulation. In addition, it was found that a doubling of the dosage provided a doubling of plasma oxycodone concentrations. These Cmax concentrations produced dose-related differences in drug effect (measured with a 100 mm visual analog scale (VAS)), 40% and 60% respectively and remained sustained beyond 12 hr. The 20 mm difference in VAS drug
effect test is in the range reported with pain relief scales in relatively sensitive analgesic studies with a doubling of opioid dosage, i.e., well beyond the linear portion of the log concentration-response curve, where measurable changes in effect require dramatic changes in opioid concentration at the receptor.118

A hydromorphone CR formulation that exhibited comparable analgesic efficacy to oxycodone CR was associated with certain degree of hallucinations. There is extensive clinical experience with the use of hydromorphone as an alternative to morphine. The availability of CR formulations enables one to expand the use of this semi-synthetic congener of morphine.

### 11.2 Nonopioid Analgesics

A key issue that should be taken into considerations in the pharmacodynamic rationale to develop SR dosage forms for nonopioid analgesic drugs is the hypothesis (mentioned above) that the analgesic effect depends on the peak blood concentration.129-131 Accordingly, the preferred mode of administration for these drugs would be by bolus (or pulsatile) administration rather than a constant input at a slow rate. In many cases the data support this theory. For instance, when the intensity of analgesic response to acetaminophen was compared in mice following intravenous and subcutaneous injections, the analgesic effect was greater after intravenous administration even at times when the blood levels after the subcutaneous administration were higher.132 In addition, despite similar acetaminophen plasma concentrations after short intravenous or continuous infusion, no significant analgesia was detected after continuous infusion.133 Nielsen et al compared the efficacy of immediate and slow release preparations of acetaminophen. Following administration of the SR tablets the analgesic effect was lower and pain thresholds that were elevated 1 hr post-dose remained relatively constant over the dosing interval.134 In another work, the same group found that the acetaminophen SR preparation failed to produce any detectable analgesia.131 The hypothesis is also supported by the data comparing the magnitude of analgesia induced by naproxen versus naproxen sodium.135 The sodium salt that produced rapid absorption was associated with more pronounced analgesic effect. In addition, it was found that the analgesic effect produced by ibuprofen is stronger following soluble ibuprofen formulation that was associated with faster absorption.136

It should be noted that beside this corroborating evidence that supports the hypothesis of a link between the rate of decay of the analgesic effect and the peak concentration of the analgesic compound, additional contradicting evidence exists. For instance, in a study designed to compare the efficacy of intermittent with continuous administration of ketorolac
during the first 48 h after upper abdominal surgery, it was found that patients who received
the same rate of dosing of ketorolac as a continuous infusion instead of intermittent doses
showed a significant morphine sparing effect.\textsuperscript{137} Thus, more work is needed to further assess
the above mentioned hypothesis, which is a cornerstone for rationale development of analgesic dosage for.

Another pharmacodynamic parameter that is relevant to optimizing drug formulation is
the ceiling effect detected for some of the nonopioid drugs. For instance, despite the linear
kinetics in serum drug concentrations following administration of ibuprofen 400 mg versus
800 mg, there were no differences in drug efficacy.

\textbf{11.2.1 The anti-inflammatory activity of NSAIDs}

\textit{11.2.1.1 Pharmacodynamic Rationale for Sustained Release formulations of NSAID anti-
inflammatory drugs}

In contrast to the pharmacodynamic characteristics of the analgesic effect of NSAIDs,superior suppression of platelet aggregation was attained following administration of a SR
preparation than following a single dose of rapid-release product.\textsuperscript{138} Similarly, it has been
shown that low concentrations of ibuprofen are required to maintain antiaggregatory activity,
which provide the rationale for a SR preparation of NSAIDs for this therapeutic goal.

\textit{11.2.1.2 Regional delivery to the site of anti-inflammatory action}

The pharmacodynamic aspects of regional delivery of NSAIDs were assessed by
Martin \textit{et al} in a preclinical investigation.\textsuperscript{139} They showed that direct administration of S-(+)
ibuprofen into the site of inflammation (air pouch) produced the same concentration (at the
site of inflammation) effect relationship as intravenous administration of the drug. On the
other hand, an advantage following systemic rather than regional administration was revealed
for piroxicam, based on concentration-response analysis, indicating a major systemic anti-
inflammatory component for piroxicam but not for S-(+) ibuprofen. These outcomes also
suggest that continuous administration of S-(+) ibuprofen given either intravenously or via
the air-pouch, provided improved dose-response relationship in comparison to bolus
administration. This is probably because the initial exposure to high concentrations following
the bolus administration is less important than continuous exposure of the inflamed site to the
drug.

\textit{11.2.1.3 Differentiating between the effect of NSAIDs on cyclooxygenase isoforms}
Cyclooxygenase (COX)-1 inhibition by NSAIDs is associated with gastrointestinal and renal toxicity, while COX-2 inhibition has beneficial anti-inflammatory, analgesic and antipyretic effects. The degree of selectivity of a given NSAID on the two distinct isoforms COX-1 and COX-2 provide a convincing rationale for differentiating NSAIDs according to their benefit/risk ratio. The concentration-response relationships established for the inhibition of human COX-1 and COX-2 for meloxicam and naproxen was described recently by Fenner. It was found that meloxicam inhibits COX-2 in human whole blood at concentrations that are at least 10 times lower than those required to inhibit COX-1. In contrast, the concentration-response curves for the inhibition of COX isoforms by naproxen are close, suggesting approximately equipotent inhibition of COX-1 and COX-2. It is expected that reduced fluctuations in blood concentrations due to utilization of SR formulation for these drugs will produce higher degree of selectivity and less adverse effects that result from the inhibition of COX-1. It could be important in view of the large inter-subject variability in both pharmacokinetics and pharmacodynamics. Selective inhibition of COX-2 may be achieved also applying selective COX-2 inhibitors (celecoxib and rofecoxib) that have been marketed recently.

12. Direct administration of antiarrhythmia drugs to the heart

Conventional antiarrhythmia therapy with oral or intravenous administration is often ineffective or results in toxic drug effects because of narrow therapeutic indices of most of these agents. Due to the regional nature of cardiac disease it has been suggested to administer antiarrhythmia drugs directly to the heart by localized cardiac delivery systems, based on drug-polymer implants. This mode of administration may have several advantages, including enhanced drug effects and reduced systemic drug toxicity. Since direct application of the drug to the heart reduce the pharmacokinetic variability associated with absorption and systemic disposition following conventional modes of administration, the efficacy and toxicity would be more predictable.

The customary pharmacokinetic modeling approach cannot be used in this case, since the heart cannot be grouped in the central compartment as drug delivered epicardially accumulate into the heart muscle and produces a ‘depot’, from which the drug will equilibrate slowly with various body compartments.

CR epicardial administration was tested preclinically with several drugs including lidocaine, procainamide, verapamil and d-sotalol and proved to be safe and effective. For instance, it was shown that when sotalol (a non-selective beta-blocker used for the treatment
of supraventricular and ventricular arrhythmias) was given by epicardial implants, comparable myocardial concentrations of the drug were found in comparison to intravenous administration but the total intravenous dose had to be considerably larger.142 Similarly, the CR epicardial sotalol preparations produced electrophysiologic effects comparable to those noted with intravenous administration at a significantly lower dose. This CR epicardial drug delivery approach enables simple and direct ‘targeting’ of the drug to its site of action. Thereby, it widens the therapeutic window of the drug by considerably increasing the margins between therapeutic concentrations ‘seen’ by the target tissue and the systemic concentrations that are associated with toxicity.

13. The antihypertensive effect of calcium antagonist drugs

13.1 The impact of rate of nifedipine administration on magnitude of effect.

Nifedipine can be regarded as a classic example that illustrates the role of input rate on the magnitude of effect. This calcium channel blocker has been used for several years in the treatment of angina pectoris and hypertension. The drug was originally marketed in an immediate release (IR) capsule formulation and later on in a sustained release tablet formulation that had comparable bioavailability (50%). However, while the capsule produces rapid and relatively high peak concentrations, the SR tablet gives a flat plasma concentration profile. It was found that the increase in heart rate (side effect) was far less with the SR tablets than with the IR capsules, whereas with both preparations a slight blood pressure lowering effect was achieved in the normotensive subjects that were examined.143 This finding led to the realization that the rate-of-increase in nifedipine plasma concentration (rather than the absolute concentration) is a determining factor for the drug’s hemodynamic effects. Clear evidence for this explanation was obtained in a study in which nifedipine was given by two i.v. regimens designed to produce the same steady state concentration by a rapid vs. gradual infusion rate. No increase in heart rate occurred with the slow regimen, whereas a substantial and long lasting increase was seen with the rapid regimen.144 On the other hand, a gradual decrease in blood pressure was observed following the slow input while blood pressure was minimally affected. This outcome clarifies that the concentration-effect relationship of the blood pressure lowering effect of nifedipine is shifted to the left and is steeper following a slow input than with a rapid input rate as obtained following the administration of an IR formulation. It has been proposed that following slow input, the activation of the compensatory responses produced by high levels of endogenous agents such as
catecholamines is limited. Therefore, the tolerability of a SR formulation is likely to be enhanced. There is evidence that the rate of input of nisoldipine plays a major role in its hemodynamic activity profile, and it seems likely to be true for some other calcium antagonists as well. These findings should not be regarded as surprising and should rather be expected for vasodilator drugs.

With a rapid decrease in peripheral vascular resistance, baroreflex activation, central sympathetic activation and parasympathetic withdrawal serve to maintain blood pressure and perfusion of vital organs. Heart rate and cardiac contractility increase, resulting in increased cardiac output, and increased circulating catecholamines augment vascular resistance, that blunts the direct drug effect. In contrast, slow drug input and gradual decrease in vascular resistance limit this reflex activation and the direct drug effect can be more reliably observed.

13.2 Sustained release formulations as second generation of calcium antagonists.

In order to minimize the disadvantages associated with rapid administration, and to produce a constant plasma concentration for longer time intervals SR, extended release (ER) and gastrointestinal therapeutic system (GITS) formulations were developed for various early calcium antagonist medications including: nifedipine SR/GITS, nicardipine SR, verapamil SR, and diltiazem SR, which forms the first subclass of the second generation of calcium antagonists. The other subclasses comprises new dihydropyridines such as nisoldipine, nitrenidipine, manidipine and others which posses improved pharmacodynamic and/or pharmacokinetic properties including increased vascular selectivity.

A specific formulation developed to allow once-daily dosing of these drugs is a core coated product, which claims equivalent efficacy to other SR formulations such as the GITS, although the Food and Drug Administration does not consider the products to be bioequivalent. The coat-core (CC) tablet consists of an external coat of slow release nifedipine (or nisoldipine) and an internal core of rapid-release drug. The hemodynamic effects of the long acting CC nisoldipine formulation appear to be similar to those of the immediate release formulation, although differently timed.

The availability of two different SR formulations of verapamil allowed some interesting but inconclusive observations about the pharmacodynamics of the drug. Drug pellets or beads have a much greater surface area than either tablets or caplet, which results in faster drug release from the pellet formulation yielding a higher and earlier peak blood level, with up to 40% increase in total bioavailability. However, no strong correlation exists between blood levels and blood pressure response, at therapeutic concentrations. The data
suggests that once a ‘threshold level’ is reached with, verapamil higher doses and presumably higher concentrations do not necessarily result in greater therapeutic response. This has promoted the introduction of a 180-mg caplet that may represent such a ‘threshold’ dose since its antihypertensive efficacy is similar to that of 240-mg verapamil.

13.3 The third generation calcium antagonists

The development of new molecules, including amlodipine and lacidipine, that can be termed third generation calcium antagonists, has overcome most of the problems encountered with the first and second generation products. Their unique characteristics are their interaction with specific high affinity binding sites in the calcium channel complex and by the inherently long duration of action. The lack of a clinically relevant increase in cardiac or peripheral sympathetic activity, induced by an abrupt blood pressure reduction, is now recognized as perhaps the most important feature of a drug of this class. However, it should be underlined that this lack of autonomic activation does not abolish the minor vasodilator adverse events such as flushing, headache and ankle edema that are still observed with these agents. The inherently long half life (40 – 50 hr for amlodipine), and the high degree of lipophilicity, allow their penetration deep into the lipid layer of the vascular cell membrane where the drug is stored and slowly diffuses into a reservoir in the lipid bilayer where calcium channels are situated. Therefore, it can be concluded that for these drugs no special SR formulations are required.

14. Diuretics

14.1 General pharmacodynamic features

Diuretic drugs are commonly used for the treatment of heart failure or in hepatic, renal or pulmonary disease when salt or water retention has resulted in edema or ascites. Several groups of diuretic drugs are used clinically. Loop diuretics, especially furosemide, are the most frequently prescribed and their clinical pharmacology is better understood.

The main therapeutic effects of diuretic drugs are water excretion (diuresis) and natriuresis that are strongly interrelated. An apparent delay exists between the time of drug administration and onset of diuretic effect. This delay may be partially attributed to penetration of the drug to the site of action in the nephron in order to exert its therapeutic activity. As a result, the magnitude of response is much better correlated to urine concentration of diuretic drugs and not to the blood concentration and the pharmacodynamic profile of diuretic drugs may be described applying a sigmoidal relationship between the...
concentration of the diuretic in the urine and the extent of response.\textsuperscript{155,156} Since diuretic drugs are characterized by indirect mechanism of action, their pharmacodynamics should be more appropriately described applying indirect-response models. Recently such physiologic indirect-response model was successfully applied to describe furosemide pharmacodynamics, including development of tolerance to the diuretic effect following multiple dosing of the drug.\textsuperscript{157}

It was observed that the efficiency of the diuretic drug (i.e. ratio of diuretic effect/systemic exposure) is not constant and varies profoundly with drug concentration and time. Slow administration significantly increases the total diuretic effect per amount of drug recovered in urine, and the cumulative diuretic effect may be highly influenced by the drug’s administration profile.\textsuperscript{158} The extent of diuretic action is also subject to gender and age-related inter-patient variability that may be attributed to alterations in drug metabolism, disposition, or intrinsic diuretic responsiveness at the site of action.\textsuperscript{159,160} Diuretic efficiency depends on additional, intra-patient factors, including development of tolerance and resistance to drug effects. Thus, the extent of diuretic effect in specific patient is influenced by the mode of drug administration.

14.2 Tolerance and resistance

There are two forms of diuretic tolerance: short-term and long-term. Short-term tolerance refers to a decrease in the response to a diuretic drug following repetitive administration. The exact mechanism by which short-term tolerance occurs is possibly related to the activation of rapid homeostatic responses. Time course of tolerance development is influenced by drug input rate, with slow continuous input producing less activation of homeostatic mechanisms and elevating the overall diuretic and natriuretic effects.\textsuperscript{161} Fluid and electrolyte replacement may prevent development of acute tolerance,\textsuperscript{162} and the results of clinical trials applying different experimental protocols can’t be readily compared.\textsuperscript{163,164}

The long-term administration of a loop diuretic leads to hypertrophy of distal nephron segments due to unknown mechanisms. Consequently, sodium that is accumulated in the urine in the proximal parts of nephron is reabsorbed at distal sites, leading to reduced drug effects.\textsuperscript{165} This long-term tolerance to the loop diuretic may be partially prevented and ameliorated by thiazide diuretic action on the distal parts of nephron. Thus, the combination of a thiazide and a loop diuretic produces synergistic response and enhances the overall diuretic efficiency.\textsuperscript{166}

Certain clinical conditions may decrease the concentrations of the drug at the site of action or sensitivity to the drug, producing so-called diuretic resistance. For instance, renal
insufficiency may decrease the delivery of the drug to the nephron and produce a pharmacokinetic-related resistance to diuretics.\textsuperscript{167} Hepatic cirrhosis, on the other hand, diminishes the diuretic response due to unknown pharmacodynamic mechanism, with no effect on the amounts of diuretic drug that reach the site of action. Several other clinical conditions (e.g., congestive heart failure and nephrotic syndrome) produce diuretic resistance due to both pharmacokinetic and pharmacodynamic alterations.\textsuperscript{168}

Several therapeutic strategies may be applied to overcome the tolerance and/or resistance to the diuretic effect in specific clinical conditions. For loop diuretic drugs the main strategies include changing the mode of administration or coadministration with thiazides.\textsuperscript{169}

\subsection*{14.3 Loop diuretics}

The clinically important pharmacokinetic features of loop diuretics are bioavailability and half-life. On average, oral bioavailability of furosemide is 50 percent, but it ranges from 10 to 100 percent due to high inter- and intra-patient variability in drug absorption.\textsuperscript{170} This wide range makes it difficult to predict how much furosemide will be absorbed in an individual patient, and dose escalation must be applied before the drug is considered to be ineffective. In contrast, absorption of bumetanide and torsemide is nearly complete, ranging from 80 to 100 percent.

Loop diuretics are characterized by relatively short plasma half-lives ranging from one hour for bumetanide to 3-4 hours for torsemide demanding frequent administration. When short-acting diuretic preparations are applied (i.e., IV bolus or immediate release oral dosage forms), a rapid and vigorous diuretic effect is produced for a period of up to several hours. This rapid and excessive diuresis may cause side effects related to fluctuations in intravascular volume and electrolyte imbalance. In addition, if the administration interval is relatively large, the effect of a loop diuretic dissipates before the next dose is given. During this time, the nephron can reabsorb sodium, resulting in so-called rebound sodium retention, which may be sufficient to significantly diminish the prior natriuresis.\textsuperscript{157,171} Thus, continuous exposure of nephron to the diuretic drug may attain higher diuretic effect with lower risk of adverse effects.

\subsection*{14.3.1 Continuous intravenous infusion}

In order to overcome the pharmacokinetic limitations and to prevent the development of tolerance and resistance, a continuous intravenous infusion of loop diuretics can be applied. Figure 13 shows that a 4 h infusion of azosemide produced higher diuretic effects in
comparison to IV bolus mode of administration of the same dose in rabbits.\textsuperscript{172}

The superiority and better tolerability of IV infusion was confirmed in clinical studies in patients with congestive heart failure and chronic renal insufficiency. Rudy \textit{et al} gave the same dose of bumetanide as two bolus doses separated by 6 hours or as 12-hour continuous infusion to the patients with chronic renal insufficiency.\textsuperscript{173} The continuous infusion resulted in significantly greater natriuretic effect (infusion, 236 ± 77 mmol, bolus, 188 ± 50 mmol, \(p = 0.01\)). The efficiency of diuretic effect for bolus and infusion modes of administration were 0.25 and 0.33 mmol/\(\mu\)g, respectively.

Additional advantage of continuous infusion of loop diuretics is the possibility of gradual increase of infusion rate and accurate titration of the diuretic effect. Currently, continuous IV infusion is widely used in clinical settings in severely ill patients, or in patients refractory to conventional doses of loop diuretics.\textsuperscript{174} However, this mode of administration can’t be applied in outpatient settings.

\textit{14.3.2 Sustained release formulations}

The pharmacodynamic rationale of sustained input of the loop diuretics was applied for development of sustained release (SR) dosage forms. Despite the lower bioavailability of SR dosage forms due to limited absorption of furosemide in the distal parts of the gastrointestinal tract, comparable diuretic effect was produced for the immediate release and SR dosage forms of furosemide in healthy volunteers.\textsuperscript{175,176} This outcome is due to greater diuretic efficiency for lower furosemide concentrations at the site of action (and consequently for lower drug excretion rates), as shown in Figure 14. Thus, SR dosage forms produce prolonged exposure of nephron to low furosemide concentrations that are associated with enhanced diuretic efficacy.

The maximal extent of furosemide absorption is obtained in the stomach and upper small intestine. Therefore, it was suggested that gastroretentive dosage forms of furosemide are needed in order overcome the pharmacokinetic limitations of the drug absorption from SR formulations.\textsuperscript{177} Several approaches to produce gastroretentive formulations of furosemide were tested in animals\textsuperscript{178} and in human subjects\textsuperscript{179} producing encouraging results in terms of enhanced efficiency, and reduced inter- and intra-patient variability of drug absorption. However, despite the established pharmacokinetic and pharmacodynamic rationale, gastroretentive dosage forms of diuretic drugs currently are not available in clinical settings.
14.4 Pharmacodynamic advantage of prolonged administration of diuretic drugs

The pharmacodynamic profile of loop diuretics was extensively studied in animals and in human patients. It was shown that prolonged continuous exposure to low drug concentrations produces enhanced diuretic effects and is associated with reduced incidence of adverse reactions.

Generally, prolonged kinetics of diuretic action may be achieved by several means. One possibility is to use the drugs with relatively long pharmacokinetic half-life. However, such drugs are not available clinically, and with currently used loop diuretics prolonged effects may be achieved using continuous modes of administration. Continuous intravenous infusion is commonly applied in intensive care settings, and sustained release dosage forms may be used for peroral administration in outpatient settings.

Additional diuretic drugs may be preferably given by continuous modes of administration. An example would be urodilatin, a polypeptide that is synthesized by the kidney. Prolonged infusion of urodilatin lowers preload and increases diuresis and natriuresis without neurohumoral activation or adverse side effects, and may be used as a powerful diuretic agent in patients with congestive heart failure.180,181

15. Anti-hyperlipidemic drugs

Hypercholesterolemia plays a crucial role in the development of atherosclerotic diseases in general and coronary heart disease in particular. The risk of progression of the atherosclerotic process to coronary heart disease increases progressively with increasing levels of total serum cholesterol or low-density lipoprotein (LDL) cholesterol at both the individual and the population level. On the other hand, high plasma concentrations of high-density lipoproteins (HDL) are associated with a reduced risk of coronary heart disease.

Drug therapy for hyperlipoproteinemia is initiated when other means including diet, weight control, exercise and physical fitness program fail to achieve adequate results. The drugs that are clinically used for the treatment of hyperlipoproteinemia can be divided into two groups: compounds that lower triglyceride and cholesterol blood levels (i.e., nicotinic acid (niacin), fibric acid derivatives), and compounds that mainly lower cholesterol levels (anion exchange resins and hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors).

15.1 Niacin

Niacin is one of the oldest hypolipidemic drugs available, and has been in clinical use
for over 40 years. It is used to reduce cholesterol and triglyceride levels and, in particular, to elevate HDL cholesterol levels. Although the drug can be regarded as relatively safe, niacin therapy may be associated with certain adverse, some of which are directly related to the mode of administration. Significant number of patients refrain from using this inexpensive medication due to an intense cutaneous flush and pruritus that involve the face and the upper part of the body. This flushing phenomenon is associated with the rapid onset of peak drug concentration in the systemic blood circulation following oral administration of the immediate release preparation. Continuous administration of the drug by means of SR formulations produces a much slower rise in blood concentration and thereby reduces the flushing phenomenon. On the other hand, SR formulations are far from being a simple solution since this mode of administration produces constant exposure of the liver to relatively high concentrations of the drug which have been reported to cause hepatotoxicity. However, this severe adverse effect tends to be dose-dependent.

The effect of mode of administration of low dose niacin on the magnitude of its hypolipidemic effect was recently investigated in experimentally-induced hyperlipidemic rats. It was found that continuous duodenal infusion, as well as SR tablets produced a significantly larger magnitude of lipid lowering activity (reduction of both total cholesterol and triglyceride levels) than bolus administration of the same doses. In addition, comparison between the magnitude of lipid-lowering activity of continuous administration of the drug to the gastrointestinal tract with equal intravenous infusion of the drug (same rate and dose) indicated that there was no direct correlation between amounts of drug in the systemic circulation and the magnitude of hypolipidemic response. Furthermore, no apparent effect was detected after intravenous administration of the drug whereas continuous duodenal administration significantly affected all three lipid components measured (cholesterol, triglycerides and HDL serum levels). Another important finding of that investigation was that there were no differences between the lipid lowering effects of niacin at 40 or 200 mg/kg. This indicates that there is no apparent dose-response relationship, and no clear advantage of higher dose of niacin. This finding is in agreement with clinical data showing that low dose niacin (500 mg per day) produced effective lipid reduction in hyperlipidemic patients. The outcomes suggest that administration of low dose niacin by an oral SR formulation will enable safe and effective niacin therapy.

15.2 Bezafibrate

Bezafibrate is a fibric acid derivative that is used clinically to reduce blood lipoprotein levels, especially triglycerides (TG), and elevate HDL cholesterol levels. On the basis of
pharmacokinetic rationale, specifically the relatively short biologic half life of the drug (1.5 to 2 hours), SR formulations of bezafibrate were designed and have been in clinical use during the last decade. However, only recently, the pharmacodynamic aspects of this mode of bezafibrate administration have been investigated. In that study, we assessed the role of different routes and modes of administration of the drug on its hypolipidemic activity in three models of experimentally-induced hyperlipidemia in rats. The work examined the hypothesis that the major sites of bezafibrate action are located pre-systemically. Thus, continuous administration of the drug to the GI tract is expected to augment its efficacy and provides a pharmacodynamic rationale for an oral sustained release preparation of the drug. Indeed, the results confirmed that equivalent doses of the drug produced significantly elevated hypolipidemic activity when given at a slow rate directly to the GI tract compared to a PO bolus and even to a slow IV infusion. In addition, administration of bezafibrate in a slow release matrix tablet to the hyperlipidemic rats produced the same magnitude of effect as a continuous duodenal infusion of the drug, thus proving the pharmacodynamic rationale for this mode of administration for this drug. These preclinical experiments revealed lack of a direct correlation between the systemic drug concentration and magnitude of effect. Lower systemic drug concentrations, attained following ‘targeting’ of the drug from the gut to the liver in a sustained manner, produced larger hypolipidemic responses in comparison to higher systemic blood concentrations, and their respective effect, that were found following direct administration of the drug to the systemic circulation.

It was discovered that bezafibrate undergoes a reabsorption process according to the enterohepatic cycle. This enterohepatic cycle enhances the availability of the drug to the presystemic sites of action (even following direct administration into the systemic blood circulation), and is an important feature in the case of a drug like bezafibrate, and other anti-lipid drugs, with a hepatic first pass dynamic response.

### 15.3 HMG-CoA reductase inhibitors

The statins are reversible inhibitors of the microsomal enzyme HMG-CoA reductase, which converts HMG-CoA to mevalonate. The liver is the target organ for the statins, since it is the major site of cholesterol biosynthesis, lipoprotein production and LDL catabolism. However, cholesterol biosynthesis in extrahepatic tissues is necessary for normal cell function, and adverse effects of these drugs may be minimized by reduced systemic exposure to drug and the active metabolite(s), especially during long term treatment. This can be achieved either by specific degree of liver versus tissue selectivity of the drug and/or by targeting the drug to their hepatic sites of action by oral SR formulation that presents the drug to the liver via the portal veins in a sustained manner. An ideal dosing scheme would produce therapeutic levels
of the inhibitor to the liver at a rate that results in a hepatic extraction ratio that approaches unity, thereby minimizing the systemic HMG-CoA reductase inhibitor levels.

McClelland et al. investigated the cholesterol-lowering efficacy of an oral SR dosage form of a potent HMG-CoA reductase inhibitor (water-soluble tromethamine salt of the 3-hydroxyacid form of simvastatin) in comparison to bolus dosing of the drug. In that study, dogs received the drug for 28 days once daily by oral bolus administrations (dry-filled capsules) or by daily administration of an oral SR formulation (a controlled-porosity osmotic pump). The observed mean AUC and Cmax after osmotic pump dosing were 67% and 16% that of the bolus, respectively, while the maximum percentage decrease in serum cholesterol was 34±8% for the SR formulation vs. 17±6% for the bolus. Combining the twofold improvement in efficacy with the lowered systemic drug burden leads to 3- to 12-fold ‘therapeutic’ advantage from the controlled release dosage form.

The increased anti-lipid activity, taken together with the improved safety due to reduced systemic exposure, indicate that SR formulations for these drugs may be advantageous.

16. Levodopa therapy in Parkinson’s disease

Levodopa is the most effective treatment for Parkinson’s disease, but its efficacy is hampered as the disease advances by clinical response modifications, namely motor fluctuation and dyskinesias. As a result of its rapid intestinal absorption and metabolic elimination, plasma levodopa concentration fluctuates widely in relation to each administered dose from IR formulations. Early in the course of illness, no clear-cut relationship between plasma levodopa profile and antiparkinson effect can be appreciated. With the progression of the disease a correlation between levodopa plasma concentration and clinical effect emerges, and in the more advanced stages the pattern of response mirrors the rapid rise and fall in plasma levodopa concentrations after each dose (the ‘wearing-off’ phenomenon). At this stage, the magnitude of drug effect is very sensitive even to small changes in drug concentrations. Studies on the concentration-effect relationship of levodopa at this stage of the disease demonstrated an immediate onset of the motor response when the plasma concentration was exceeded and the appearance of off-reactions when plasma concentration declined below this level. Controlled release preparations of the drug should provide prolonged plasma concentrations above the ‘therapeutic’ threshold. However, fluctuations were reported also with CR-preparations even when elevated plasma concentrations were maintained. Harder et al. investigated whether the concentration-effect relationship of
levodopa is influenced by the rate of drug absorption by comparing an IR and a CR formulation. They found that both preparations produced the same maximal effect; however, the estimated EC\(_{50}\) of levodopa were two fold higher for the CR formulation in comparison to IR. The duration of action was approximately 1.5 longer for the CR formulation. The gain in the duration of the motor response, which might be provided by sustained plasma concentrations of levodopa following CR-preparation, was offset partially by the apparent doubling of the threshold level (EC\(_{50}\)).

The concept that rapidly changing plasma concentrations of levodopa are responsible for the adverse effects of long-term levodopa therapy, have led to initiation of a 5-year multicenter study that compared the efficacy and toxicity of SR vs. IR preparations of low dose carbidopa-levodopa. It was found that the incidence of motor fluctuations was lower than expected for both groups, probably due to the low dose used in this trial. In addition, patients receiving SR preparations fared better on the activities of daily living portion of the Unified Parkinson’s Disease Rating Scale and on portions of the Nottingham Health Profile. Other clinical trials also exhibited somewhat better global evaluation for the levodopa CR formulation in comparison to IR preparation.

It should be noted that the oral absorption of levodopa is limited to a narrow absorption window at the upper part of the GI tract, where absorption via active transport mechanism takes place. Therefore, SR formulation that do not release most of its content during the first 6-8 hr after ingestion will release the drug in the colon where it will not be absorbed. The preferred mode of administration of this drug is by gastroretentive dosage form that will release the drug from the stomach into the duodenum in a sustained manner. Nonetheless, such dosage form is not clinically available. In theory the best practical method to enable constant plasma concentration of the drug would be by continuous intravenous infusion. However, this mode of administration is not very feasible for long term use and it frequently causes phlebitis. In addition, due to limited water solubility of the drug, large volumes have to be infused over a day. For these reasons a new dosage form of levodopa in water dispersion (DuodopaR) has been developed allowing the daily dose to be infused intraduodenally by a portable pump. This route and form of administration have now been in use for several years, with promising results. Paalzow and Sjaland-Brynne have assessed the outcome of this mode of administration in individual patients. It was found that the plasma concentration required to obtain satisfactory mobility decreased with time which indicate that the sensitivity to the drug was elevated with time as indicated by reduced EC\(_{50}\) values. Since all the patients were already on levodopa treatment for 6 to 20 years, it seems that the improved efficacy found should be attributed to the individual titration of drug concentrations.
for each patient together with the fact that following duodenal infusion they were not exposed to high drug concentration (from absorption peaks). Furthermore, the fact that the infusions were turned off during the night gave the body time to regain sensitivity, and reduce the impact of tolerance development to the drug.

17. Antidiabetic drugs

It is well established that chronic hyperglycemia is associated with onset and progression of diabetic complications, namely: microvascular complications, diabetic ketoacidosis, and hyperosmolar coma. On the other hand, excessive glucose-lowering drug regimens may produce life-threatening hypoglycemic episodes. Therefore, optimized diabetes treatment will preserve the plasma glucose levels within the normal range throughout a 24-h period applying appropriate mode of drug administration. In order to achieve this, physiologic metabolic factors should be taken into account, including postprandial elevation of blood glucose, in addition to the pharmacokinetic and pharmacodynamic properties of the specific anti-diabetic drug. Several groups of drugs are used for diabetes treatment, including insulin and its analogs, sulphonylurea drugs, metformin, and others.

17.1 Insulin

Insulin and its analogs have been used for several decades for treatment of diabetes mellitus. Generally, a higher dose of insulin is associated with higher glucose-lowering effect, and the sigmoid Emax model may be applied to describe the dose-response relationship. As seen in Figure 15, a temporal delay exists between the insulin blood concentrations and glucose-lowering effect (resulting in counter-clockwise hysteresis) due to indirect mechanism of insulin action and sustained penetration to the peripheral sites of action. The extent of insulin effect is subject to inter- and intra-subject variability, and depends on administration route, glucose blood level, liver function, and factors related to insulin resistance. Thus, in order to reach appropriate glucose control in the individual patient, treatment regimen should apply insulin analogs or formulations with different duration of action, and glucose blood testing should be performed for dose adjustment in the initiation and throughout the treatment.

17.1.1 Physiology of insulin secretion

Insulin secretion from the pancreatic β-cells is pulsatile in nature and is regulated by several feedback mechanisms related to glucose and insulin blood levels. Two types of
oscillations are recognized, with rapid pulses of approximately 10 min periodicity\textsuperscript{198} being superimposed on much slower waves (every 50-100 min).\textsuperscript{199}

It is not clear if mimicking of pulsatile pattern of insulin secretion is beneficial for clinical outcome. In some trials, pulsatile intravenous administration of insulin to diabetes patients was found to be more efficient than continuous delivery in reducing blood glucose, lowering glucosuria, increasing insulin sensitivity and inhibiting lipolysis.\textsuperscript{200-202} However, a number of clinical trials produced similar metabolic effects for pulsatile and continuous modes of insulin administration.\textsuperscript{203-205} Variable degree of mimicking of insulin secretion pattern in the individual studies (i.e., differences in pulse intervals and amplitude) may explain the difference in metabolic outcomes. So far, pulsatile insulin delivery is rarely applied in clinical practice and is mainly reserved for patients who are unable to attain the tight glucose control through conventional means.\textsuperscript{206}

17.1.2 Route of administration

The most common route of insulin administration remains subcutaneous injection. Intraperitoneal insulin administration has been claimed to offer better glycemic control and insulin sensitivity than subcutaneous insulin by producing a more ‘physiologic’ ratio between portal and peripheral insulin concentrations. However, it was associated with enhanced liver inactivation of insulin, reducing the peripheral effects and producing disadvantageous effect on serum lipids.\textsuperscript{207,208}

Despite considerable efforts, oral administration of insulin is not available clinically due to rapid destruction of insulin in the gastrointestinal tract and limited absorption to the systemic circulation. The benefits and limitations of alternative non-invasive routes of insulin administration, including intranasal, inhaled, etc., are thoroughly discussed in recent reviews.\textsuperscript{197,209-211}

17.1.3 The administration schedule

The so-called ‘conventional’ treatment regimens have been used for most diabetic patients. Their main advantages are simplicity, safety and ease of compliance for the patients, but they can’t achieve perfect control of blood glucose. For more strict control of the blood glucose levels, ‘intensive’ regimens were developed, requiring multiple injections of insulin during the day to mimic the physiologic demands of insulin that are increased following meals.

Continuous insulin infusion may provide improved glycemic control in patients that
still can produce their own insulin in response to postprandial hyperglycemia. Continuous infusion produced improved metabolic effects compared to conventional insulin therapy in diabetes patients, and in patients with diabetic ketoacidosis.

Nighttime glucose control is difficult to achieve because of circadian variations in the pharmacodynamics of insulin. The early morning requirement for insulin is twice as much as the daytime demand and is related to alterations in cortisol and growth hormone secretion. Therefore, the bedtime dose of either intermediate or long-acting insulin or continuous insulin infusion may be applied to improve nocturnal glycemic control.

17.1.4 Optimization of insulin treatment

The insulin requirement and sensitivity throughout the day depends on the metabolic condition of the diabetes patient, and the pharmacokinetic and pharmacodynamic features of the drug formulation. Current treatment protocols apply multiple daily glucose self-tests to adjust the insulin doses and to prevent periods of excessive or insufficient hypoglycemic activity. Various strategies applying novel insulin analogs, changing the dose, timing and the route of the administration, were shown to improve, but not completely optimize glycemic control in diabetic patients.

Further optimization of insulin treatment may be achieved using glucose-controlled feedback (closed-loop) systems. Such a system consists of glucose sensor, insulin pump, and pump control system and may simulate the physiologic release of insulin in order to reach the target blood glucose concentrations. Currently, closed-loop systems may provide satisfactory control of diabetes for over a year, with the major complication being obstruction of the infusion catheter. In the future, the ultimate goal of diabetes treatment may be achieved by restoring the feedback regulation of glucose homeostasis on the cellular level by implantation of genetically-engineered β-cells with controlled insulin-releasing activity.

17.2 Sulphonylurea drugs

Sulphonylurea derivatives are hypoglycemic drugs frequently used in the treatment of type 2 diabetes mellitus (NIDDM). The mechanism of action of sulphonylurea drugs involves receptor-mediated blockade of ATP-sensitive potassium channels (K\text{ATP}), that stimulate insulin release by the pancreatic β cells and the contraction of vascular smooth muscle cells. The later effect leads to impairment of the myocardial contractile function and exacerbation of the myocardial ischemia, but the extent of its clinical relevance is still not clear. Different sulphonylurea derivatives may differ in their selectivity to
Additional adverse effects of sulphonylurea drugs are related to excessive blood glucose reduction, leading to life-threatening hypoglycemic episodes, especially in elderly patients. Short acting sulphonylurea drugs are clinically safer due to lower risk and duration of such episodes. Continuous exposure of pancreatic β-cells to high concentrations of sulphonylurea drugs induces down-regulation of β-cell sensitivity and development of tolerance (i.e., reducing the extent of insulin-releasing effect).

The dose-response relationship of sulphonylurea drugs is characterized by pronounced interindividual variability. A recent study by Rydberg et al investigated concentration-effect relationships for both glibenclamide and its metabolites after oral and intravenous administration to healthy volunteers. Profound counterclockwise hysteresis was observed following administration of the parent drug or the metabolites as a result of indirect mechanism of hypoglycemic action of sulphonylurea drugs. The results of the study imply that the major metabolites of glibenclamide possess a higher hypoglycemic activity at low concentrations than the parent drug, contributing to prolonged duration of action following glibenclamide administration.

The pharmacokinetic characteristics of specific sulphonylurea analogues or drug formulations may be clinically relevant, determining the time to onset of action, magnitude and duration of the glucose-lowering effect, and timing of drug administration in relation to food intake. Immediate release preparations of short-acting sulphonylurea drugs may totally abolish the meal-related elevation in plasma glucose when correct timing is achieved between the mealtimes and the drug administration. On the other hand, sustained-release formulations and longer-acting analogs provide prolonged hypoglycemic activity, but only partially diminish the meal-related elevation in plasma glucose. In this case rapid-acting insulin preparations are added to the treatment schedule to further reduce the fluctuations in blood glucose levels.

Sulphonylurea therapy should always be initiated and maintained at the lowest possible dose. This is because the use of high doses that are associated with elevated incidence of cardiovascular and hypoglycemic adverse effects leads to diminished efficiency of anti-diabetic treatment. On the other hand, prolonged exposure of the β-cells to high doses of sulphonylurea drugs may reduce the extent of desired effects due to development of pharmacodynamic tolerance.

### 17.3 Metformin

Metformin is a biguanide antihyperglycemic agent widely used in the management of
type 2 diabetes mellitus (NIDDM). Metformin lacks a direct insulin-releasing effect. In the diabetic state its main actions include antihyperglycemic, weight-stabilizing, lipid lowering, and insulin-sensitizing effects. Unlike sulphonylurea drugs, metformin does not lower the blood glucose below the normal levels in diabetics and, therefore, is safer in clinical use. The mechanism of action of metformin is combined from several distinct effects in various organs and tissues, including inhibition of gluconeogenesis in the liver, reduction of glucose absorption, elevation of glucose metabolism in the intestine, and indirect inhibition of lipolysis in adipose tissue.227

It seems that the multifactorial mechanism of action of metformin obscures the dose-response relationship of the metabolic effects in individual organs and tissues and complicates the optimization of metformin treatment. Generally, low metformin concentrations seem to improve peripheral insulin resistance, and at higher concentrations a direct glycemia-lowering effect occurs (mainly via inhibition of hepatic gluconeogenesis) leading to further reduction of hyperglycemia.228

The overall metabolic effects of metformin seem to be concentration related. Metformin concentrations were shown to be inversely correlated with serum triglycerides and directly correlated with high density cholesterol (HDL), but not with metformin dose or fasting plasma glucose.229 However, the same group of researchers found later that an inverse correlation exists between metformin concentrations and plasma glucose levels. In addition, a significant correlation was observed between mean plasma metformin concentrations and mean plasma lactate levels.230

The overall extent of drug effects depends on the physiological and metabolic state of the patient and the local tissue concentrations of the drug. However, the relative significance of central and peripheral sites of metformin action to produce metabolic effects remains unknown and seems to vary in different experimental conditions.227

We have shown that bolus administration of metformin to the small intestine provides enhanced glucose-lowering effects in comparison to IV bolus administration of the equivalent dose to streptozotocin-induced diabetic rats.231 This outcome is due to pharmacokinetic differences between the two modes of administration. Following IV bolus, metformin is extensively eliminated from the blood and concentrations rapidly drop below the therapeutic window. Following oral or intra-intestinal administration, metformin accumulates in the intestinal mucosa cells and is absorbed slowly to the systemic circulation.232 As a result, flip-flop pharmacokinetic behavior is observed and therapeutic drug concentrations are kept for prolonged period of time.

Accumulation of metformin in the intestinal mucosa produces a ‘natural’ sustained
release system. Due to this, similar magnitude of glucose-lowering effect is attained when metformin is given intra-intestinally as bolus dose or continuous infusion.\textsuperscript{231} Thus, sustained release of metformin in the gastrointestinal tract does not offer pharmacodynamic advantage over immediate release formulations with respect to the hypoglycemic effect. However, metformin accumulation in the intestinal mucosa apparently leads to gastrointestinal intolerance, a very common adverse effect seen in up to 20\% of patients.\textsuperscript{233} Gradual release of metformin from CR formulations reduces the extent of accumulation and decreases the incidence of gastrointestinal adverse effects. Results from clinical trials confirm the better tolerability profile of CR formulations of metformin in comparison to regular dosage forms.

18. Optimal mode of organic nitrate administration

Organic nitrates are direct-acting vasodilators. They are metabolized by vascular smooth muscle cells to form nitric oxide (NO). The NO then interacts with endogenous thiols to form S-nitrothiol. Both NO and S-nitrothiol activates guanylate cyclase to produce cyclic guanosine monophosphate which causes smooth muscle relaxation. The dilation of the venous system results in a reduction of left ventricular end-systolic pressure and volume and ultimately of oxygen consumption. Due to these activities, the organic nitrates were proved to be effective agents in the management of acute episodes of angina pectoris and are particularly useful in angina prophylaxis.

While the organic nitrates are extremely effective in prophylaxis, in acute therapy it was found that continuous administration of these drugs by either oral or transdermal therapy cause substantial attenuation of the antianginal effects. Thus, during acute therapy the organic nitrates improve exercise tolerance for many hours, but during sustained therapy designed to provide constant effective nitrate concentration throughout a 24-hr period there is significant attenuation of the beneficial effects due to development of tolerance (for review see Abrams\textsuperscript{234} and Elkayam\textsuperscript{235}). Thus, steady-state nitrate levels are undesirable during sustained therapy and therapeutic regimens must be developed to provide a low-nitrate period during a significant portion of the 24 hr period.

These findings demonstrate clearly the necessity to consider the pharmacodynamic properties of the drug during the development stages. Moreover, they emphasize the important role of the mode of administration on the magnitude of response and the need to assess the concentration-effect relationship characteristics over time. The initial development of nitroglycerine (as well as other nitrates) SR formulations was based solely on a pharmacokinetic approach. This approach concentrated on overcoming the short biological
half-life of the drug (several minutes for nitroglycerine), and maintaining steady state drug concentrations over prolonged periods, that could be produced with various transdermal formulations. This pharmacokinetic approach was based on the simplistic assumption that constant blood concentration guarantees constant magnitude of response. The pharmacodynamic information about the acute tolerance was found only after these products were already on the market. These pharmacodynamic findings clarified the need for a drug-free period for the vasculature to regain its reactivity toward organic nitrates. The drug free period was found to be independent of drug formulation.

In conclusion, the ideal nitrate and formulation that can produce around-the-clock protection against effort-induced angina is not yet available. When nitrates are used for prophylaxis, differences in the pharmacokinetic properties of the different organic nitrates are largely obviated by the SR pharmaceutical formulations, and there is no major pharmacological reason to choose one nitrate over another. Several SR formulations, including oral and transdermal products can provide objective anti-ischemic protection for about 12 hr out of a day. The use of a drug free interval of 8-12 hr appears useful in avoiding the development of pharmacological tolerance in some patients.236

19. Conclusions

The review furnishes insights into the important dimension of the input function of drug administration. It draws a picture of the present available information in this area by concentrating on relevant pharmacodynamic data that has been reported on drugs from selected pharmacologic and therapeutic categories.

This review highlights the important role of the mode of drug administration in affecting the magnitude of response and thereby modifying the outcome of drug therapy. It clarified the fact that in many cases the same dose of drug can produce very different therapeutic outcome when administered by different modes of administration. It is important to acknowledge this fact when comparing different pharmacotherapy protocols, especially nowadays, when ‘evidence-based medicine’ (EBM) is becoming the rule in determining the proper therapeutic protocol. This is because EBM, that is based on finding previous reports to answer a specific clinical question, is mainly focused on the type of the drug and the dose while paying not enough attention to the mode of drug administration. Moreover, this issue should be emphasized for those scientists associated with performing meta-analysis of randomized controlled clinical studies in order to determine optimized therapeutic guidelines.

In the last few years, there has been an increasing awareness of this subject and more investigations that compare pulse dosing to sustained delivery of the drug have been reported.
In addition, further pharmacodynamic end points or surrogate markers that enable graded measurement of effect are becoming available. Thus, it is foreseen that in the future, pharmacodynamic aspects of drug delivery (that have been relatively ignored in the past) will be incorporated together with the extensive knowledge that has been gained on the physical aspects of drug delivery systems and the pharmacokinetic properties of drugs in order to establish a sound rationale for optimized temporal patterns of drug therapy.

**Acknowledgments:**

Dr. Amnon Hoffman is affiliated with the David R. Bloom Center for Pharmacy.
Legends:

Figure 1: Illustration of distinct zones of concentration ranges along the sigmoid Emax pharmacodynamic profile (from Hoffman,2 with permission).

Figure 2: Simulation of pharmacokinetic and pharmacodynamic behavior of the drug following administration of the same total dose as IV bolus or constant infusion over 2, 4, 8 or 12 hours. The concentration vs. time profiles were based on a one compartment model, and the effect vs. time data was produced applying sigmoid pharmacokinetic/pharmacodynamic curves of different shape (n = 0.5, 1, or 4).

Figure 3: Simulation of area under the effect curve (AUEC) after administration of low (●), medium (■), and high (▲) dose of the drug by bolus or continuous infusion modes of administration for Models I, II, III, and IV of indirect drug response (from Gobburu and Jusko,4 with permission).

Figure 4: Relationship between the time above the MIC and bacteriologic cure for various beta-lactams against S. pneumoniae (O) and H. influenzae (Δ) in patients with otitis media. The solid and open symbols represent data obtained with penicillins and cephalosporins, respectively (from Craig,28 with permission).

Figure 5: Effect of increasing the dose or changing the dosing regimen of a hypothetical drug on peak/MIC ratio, AUC/MIC ratio, and duration of time that serum levels exceed the MIC (from Craig and Andes, 38 with permission).

Figure 6: Relationship between the 24-hour AUC/MIC ratio of fluoroquinolones and survival among animal models infected with a variety of gram-positive and gram-negative pathogens. The solid and open circles represent data obtained in the thigh-infection model and in other models, respectively (from Leggett et al, 37 with permission).

Figure 7: Inhibition of DNA precursor incorporation by doxorubicin. Human bladder tumor histocultures were treated with doxorubicin for 2 h. Drug effect was measured as an inhibition of the incorporation of BrdUrd. ●, average of all tumors; O, the most sensitive tumor; □, the most resistant tumor (from Gan et al,50 with permission).
Figure 8: Maximum BUN levels versus Cmax and AUC after single bolus injections (●) and 3-h infusions (♦) of unchanged cisplatin (from Nagai and Ogata,55 with permission).

Figure 9: Relationship between AUC estimated by plasma concentration of unchanged cisplatin greater than 0.9 µgPt/ml and maximum BUN level. O, Bolus injections; Δ, 3-h infusion; I, 2-h infusion; V, intermittent bolus injections (from Nagai and Ogata,55 with permission).

Figure 10: Survival curve for patients treated with 24-hour continuous infusion and five-daily infusions of etoposide (from Slevin et al,61 with permission).

Figure 11: Median percentage of time spent above pH thresholds of 4, 5.4, 6, and 6.8 during the 2nd to 12th hour and the 13th to 24th hour with ranitidine or omeprazole in patients with bleeding from either duodenal or gastric ulcer (* p < 0.003) (from Labenz et al,85 with permission).

Figure 12: Median intragastric pH profile before and after the first and fifth daily morning dose of omeprazole, 20 mg PO, 10 mg IV, and 40 mg IV (from Cederberg et al,80 with permission).

Figure 13: Cumulative urine output and mean cumulative urinary excretion of sodium as function of time following 1 min (●) and 4 h (O) infusion of azosomide, 1 mg/kg, to rabbits (from Park et al,172 with permission).

Figure 14: Diuretic efficiency (urine volume adjusted for basal diuresis per amount excreted furosemide) vs. furosemide excretion rate following three 60 mg oral dosage forms during the first 4 hr after dose (● plain tablets, ■ Furix retard®, □ Lasix retard®) and from 4 to 24 h (---). Arrows indicate direction of hysteresis (from Alvan et al,176 with permission).

Figure 15: Relationship of measured serum concentrations to the glucose infusion rate for both regular and NPH insulin. Arrows indicate direction of hysteresis (from Woodworth et al,196 with permission).
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