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J Pharm Pharm Sci. Author manuscript; available in PMC 2015 February 18.

Published in final edited form as:
J Pharm Pharm Sci. 2014 ; 17(1): 34–91.

Understanding the Hysteresis Loop Conundrum in Pharmacokinetic / Pharmacodynamic Relationships

Christopher Louizos[1], **Jaime A. Yáñez**[2], **Laird Forrest**[3], and **Neal M. Davies**[1]

[1]Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada

[2]Ocular Pharmacokinetics and Disposition. Alcon Research, Ltd., a Novartis Company, Fort Worth, TX, USA

[3]School of Pharmacy, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, USA

Abstract

Hysteresis loops are phenomena that sometimes are encountered in the analysis of pharmacokinetic and pharmacodynamic relationships spanning from pre-clinical to clinical studies. When hysteresis occurs it provides insight into the complexity of drug action and disposition that can be encountered. Hysteresis loops suggest that the relationship between drug concentration and the effect being measured is not a simple direct relationship, but may have an inherent time delay and disequilibrium, which may be the result of metabolites, the consequence of changes in pharmacodynamics or the use of a non-specific assay or may involve an indirect relationship. Counter-clockwise hysteresis has been generally defined as the process in which effect can increase with time for a given drug concentration, while in the case of clockwise hysteresis the measured effect decreases with time for a given drug concentration. Hysteresis loops can occur as a consequence of a number of different pharmacokinetic and pharmacodynamic mechanisms including tolerance, distributional delay, feedback regulation, input and output rate changes, agonistic or antagonistic active metabolites, uptake into active site, slow receptor kinetics, delayed or modified activity, time-dependent protein binding and the use of racemic drugs among other factors. In this review, each of these various causes of hysteresis loops are discussed, with incorporation of relevant examples of drugs demonstrating these relationships for illustrative purposes. Furthermore, the effect that pharmaceutical formulation has on the occurrence and potential change in direction of the hysteresis loop, and the major pharmacokinetic / pharmacodynamic modeling approaches utilized to collapse and model hysteresis are detailed.

INTRODUCTION

A central tenet of clinical pharmacotherapeutics is that there often exists a relationship between drug concentration and pharmacological and toxicological effects for drugs. The most common pharmacokinetic-pharmacodynamic (PK-PD) models assume that plasma

Corresponding Author: Dr. Neal M. Davies, Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada. neal_davies@umanitoba.ca.

concentration is in equilibrium and proportional with the effect site (biophase) concentration. In its simplest form a plasma drug concentration versus effect graph demonstrates a direct linear relationship between the two variables where effect is directly proportional to drug concentrations at the active site and this relationship is independent of time [1] (Figure 1a).Where equation 1 is:

$$E=S*C \quad (1)$$

E is the effect, C is the drug concentration and S is the slope parameter. This linear function model does not predict a maximum pharmacological effect (E_{max}). The relationship between drug concentration and pharmacological effect more often follows a sigmoidal E_{max} model (Hill equation) (Figure 1b). This simple mathematical relationship is based on receptor theory that defines the drug concentration effect relationship with two parameters E_{max} and EC_{50} (the concentration producing 50% of the maximum effect). It allows for differences in the shape of this relationship, where *n* is the number of molecules combining with each receptor molecule that affects the shape of the curve. The relationship between drug concentration at the receptor and the response is defined using equation 2.

$$E=\frac{(E_{\max})*(C^n)}{{EC_{50}}^n+C^n} \quad (2)$$

E is the observed effect, E_{max} is the theoretical maximal effect that can be attained, *C* is the concentration, EC_{50} is the *C* value that produces an effect equivalent to 50% of the theoretical maximal effect and *n* is a slope factor parameter that determines the steepness of the curve. The time courses of drug effect and concentrations may not be completely superimposable. Time-dependent concentration-effect relationships exist with a time lag present between measurable effect and measurable concentration. In these cases, when pharmacodynamics and drug concentration data are connected in time series at a later point compared with a previous time point there is a discordance in the plasma concentration versus effect relationship with respect to time. Hence, the magnitude of pharmacological effect either increases or decreases at any given plasma drug concentration. The term “hysteresis” has been utilized to describe this time lag. The term “hysteresis” is derived from the Greek *husterēsis* or *husteros* meaning ‘shortcoming, to come late or to come behind’. Hysteresis is the dependence of a system on both its current and past environments. Figure 1c and d present the graphical evidence of a temporal relationship of dependence between the pharmacological effect and the drug plasma concentration. As the data modeling field in pharmaceutical science examining the concentration versus effect relationships and simulations has grown, there has been some debate regarding the terminology used to describe these phenomena when encountered. It has been suggested that instead of using the term clockwise hysteresis, the moniker “proteresis” should be employed. “Proteresis” is a term also derived from the Greek language with *proteros* meaning ‘former, before or to mark an earlier event’. Similarly, instead of stating that a “counter-clockwise” or “anti-clockwise” hysteresis is present it was proposed to simply state the vernacular of ‘hysteresis’ to avoid redundancy [2]. However, the term ‘proteresis’ has not become the conventional lexicon and most studies in the literature still utilize the appellatives ‘clockwise’ or ‘counter-clockwise' hysteresis. For consistency and clarity in this review clockwise hysteresis will be used instead of proteresis, and counter-clockwise hysteresis instead of simply hysteresis or anti-clockwise hysteresis.

In the counter-clockwise scenario (Figure 1 c) there is often non-instantaneous distribution of a drug to the effect site (biophase), as the drug appearance is delayed into the pharmacodynamic (PD) effect site at a slower rate than that in which it appears in plasma, this temporal delay in delivery results in a mismatch between declining concentrations and the response [3, 4]. When the biophase is not in the central compartment, it exhibits a counter-clockwise hysteresis loop when followed over time (Figure 1c). In this instance, there is a small effect at a given drug concentration; however, after some time has passed the same drug concentration gives rise to a greater measured effect than expected. Thus, the same drug concentration produces two different magnitudes of pharmacological effects depending on the temporal sequence in which the effect is measured. Counter-clockwise hysteresis has been generally defined as the process in which effect increases with time for a given drug concentration [5]. These phenomena can be caused by uptake into an active site, cascade activity, active metabolites or sensitization (Table 1) [5].

In the opposite scenario a hysteresis loop may also occur where a clockwise hysteresis loop is evident, for example if tolerance is developed to a drug such as an opioid (Figure 1d). Here it can be seen that the same plasma concentration has a greater effect early on in temporal sequence and that after some time the effect diminishes at the same plasma concentration. In the case of clockwise hysteresis the measured effect decreases with time. These phenomena can be mechanistically induced by active antagonistic metabolites, tolerance, learning effects, or feed-back regulation etc. (Table 1) [5].

An analysis of the pharmaceutical literature using PubMed, EMBASE and Google Scholar searches indicates that there are many plausible mechanistic proposed reasons for explaining the findings of hysteresis loops in drug concentration versus effect plots (Tables 1–3). Situations that may lead to a clockwise hysteresis are the development of tolerance to a drug, antagonistic metabolites that are formed as the drug is metabolized, down-regulation of receptors and feedback regulation [6]. Some potential causes for counter-clockwise-hysteresis include distribution delay between the plasma and effect site, response delay, sensitization of receptors, the formation and subsequent accumulation of active metabolites through drug metabolism as well as up regulation of receptors after ongoing exposure [6, 7]. Once this type of hysteresis loop relationship has been discovered further mathematical modeling, such as the effect compartmental modeling, or one of its many modifications such as indirect modeling, can be applied to the data to take into account lag times, formation of active metabolites or multiple receptor sites in order to mechanistically define and simplify the concentration-effect relationship [1].

As hysteresis loops become readily evident during attempts to correlate the pharmacokinetic (PK) measurement [concentration (C)] of a drug with its measured PD measurement [effect (E)], an accurate determination of the PD measurement is critical.[8] In general, most of the clinical pharmacology study designs include *in vivo* PK and *in vivo* PD endpoint measurements; however, in the case of antibiotics or immunosuppressants it is common to have *in vivo* non-steady state dosing of drug, and the sampled matrix is used to determine *in vitro* PD effect, which can make the interpretation of hysteresis more straightforward. However, in early stages of drug discovery/development analytical assays are sometimes incapable of differentiating parent drug from its metabolite(s) and therefore would not be able to account for the presence/degree of *in vivo* pharmacological active metabolite(s) [8]. From the pharmacological and mechanistic point of view, counter-clockwise and clockwise hysteresis loops are a phenomenon that occurs under specific conditions, and the amount, activity and potency of parent and metabolite ratio is a key concept in the development and direction of a determined hysteresis.

Counter-clockwise hysteresis loops in PK-PD relationships could be explained and defined [319] as a consequence of a number of factors illustrated below in Figure 2.

Counter-clockwise Hysteresis

1. Disequilibrium caused by a temporal displacement can occur because of rate limiting steps:

   Step A: Instantaneous equilibrium between C and effect site concentrations (C_e) is not attained, which results in a temporal displacement (between C and C_e), where $C_{(t)}$ in plasma and C_e in the effect site are not identical and $C_{(t)} > C_e$.[8]

   Step B: The rate of change of C_e is much greater than the rates of pharmacological receptor activation/deactivation (R*). For instance the number of activated receptors (R*) is not reflective of C_e at time (t), resulting in a temporal displacement (between C_e > and R*).[8]

   Step C: The overall rate of conversion of signal transduction induced by R* to measured E is much less than the rate of change of R* so that $E_{(t)}$ is not equal to $R^*_{(t)}$, resulting in temporal displacement between R* >and E. The concentration (C) of drug binding with a receptor (R) forms a transient (CR) drug-receptor complex and this altered complex is affected by the receptor association and dissociation on and off the receptor. K_d is the receptor dissociation rate constant and is equal to the ratio of K_{off}/K_{on}.

2. Transformation of a drug or prodrug into a metabolite(s) with agonist actions (MPC_A / MPPCA or MPNCA) are formed from the parent drug (D or E) and are included in the contribution of the combined measurement of E.

   Step D: Common Receptor-Common Transduction Mechanism MPCA or MPPCA is a competitive agonist or competitive partial agonist with lower intrinsic activity, for which it occupies the same receptor (R*) as the parent drug concentration [E_{max}MPCA or E_{max} MPPCa is less than $E_{max(C)}$]

   Step E: Separate Receptor-Common Transduction Mechanism. Metabolite with non-competitive agonist actions (MNCA) occupies a different receptor but the same effect is achieved through a similar mechanism.

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Step J: Separate Receptor Separate Transduction Mechanism MNCA is a non-competitive agonist, for which a different pharmacological receptor (R2) is occupied but the same E achieved through a different mechanism.

3. Step K: Changes in PD over time. PD has a distinct temporal component. For instance, up regulation of receptor response (R*) (Step K) (sensitization) when the EC_{50} might reduce over time.

4. Indirect physiological mechanism of drug action with changes in PD over time. A biosensor process leads to a positive modulation in production K_{in} or a negative change in degradation K_{out} of the biosignal may occur and be transduced (Step L) into an E.

5. The measurement of $C_{(t)}$ is not specific and analysis should seek to measure the active component.

    A. Total (unbound and bound) drug analyzed is being measured over time rather than unbound concentration of drug being measured over time and time-dependent protein binding due to protein binding changes over time are occurring such that unbound pharmacologically active concentration reduces with time.[9]

    B. Total achiral (all enantiomers) drug concentration is being measured over time rather than enantiospecific concentration of a racemic drug through the use of non-stereospecific assays [10]. Stereospecific pharmacokinetics and pharmacodynamics are occurring leading to 1. Stereospecific disequilibirum 2. Stereospecific metabolism and/or 3. Stereospecific changes in PD occurring.

        a. Common Receptor-Common Transduction Mechanism Stereospecific Competitive Agonist/Partial Agonism.

        b. Separate Receptors-Common Transduction Mechanisms. One enantiomer with non-competitive agonist actions occupies a different receptor but the same effect is achieved through a similar mechanism.

        c. Separate Receptor Separate Transduction Mechanism. One enantiomer is a non-competitive agonist, for which a different pharmacological receptor (R2) is occupied but the same E achieved through a different mechanism.

    C. Total (parent drug + metabolites) concentration together are being measured by a non-specific analytical assay (i.e. radioimmunoassay, radioactive assay, or high performance liquid chromatographic assay, etc.), which is non-specific for the parent drug such that an assumed E vs. C plot is in actuality an E vs. C+MPCA or E vs. C+MPPCA plot.

        5) A specific analytical assay has been developed to measure C, however, an unknown or unidentified agonist metabolite is adding to the E.

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Clockwise hysteresis

Clockwise hysteresis loops in PK-PD relationships could be explained and defined as a consequence of a number of factors illustrated below in Figure 3.

1. Disequilibrium caused by a temporal displacement that occurs because of a major rate limiting step: Step A: Disequilibrium occurs when C_e temporally precedes $C_{(t)}$. For instance, the rate of equilibration between arterial plasma concentrations (compartment delivering drug to effect site) and venous plasma concentrations (sampling compartment for drug concentration analysis) is significantly less between arterial concentrations and C_e such that $C_{(t)}$ is not equal to $Ce_{(t)}$, resulting in temporal displacement (between $C_{(t)}$ and C_e.)

2. Metabolite(s) with antagonistic actions (MpCAn) are formed. Step D: Common Receptor-Common Mechanism. MpCAn is a competitive antagonist with no intrinsic activity, for which the same receptor (R*) is occupied as the administered drug concentration but it lacks pharmacological activity [$E_{max(MANTCA)\sim0}$ <<<< $E_{max(C)}$] so that receptor blockade occurs.[8]

   Step G: Common Receptor-Common Transduction Mechanism. MPPA is a partial competitive agonist with low intrinsic activity, for which it occupies the same receptor (R*) as the parent drug concentration [$E_{max(MPOa)}$ is less than $E_{max(C)}$]

   Step J: Separate Receptor-Separate Mechanism. MpCA is a non-competitive antagonist (reverse agonist), for which it interacts with a different receptor (R1) than the drug concentration administered and has opposing effects over the measured $E_{(t)}$.

   Step N. Changes in PD over time. PD has a measurable temporal component. For instance, with tolerance down regulation of receptors leads to EC_{50} to increase and/or the E_{max} would decrease overtime.

3. Indirect mechanism of drug action with changes in PD over time. A biosensor process leads to a negative modulation of production K_{in} or a positive increase in degradation in K_{out} of the biosignal may occur and be transduced (Step O) into E.

4. Counter regulatory feedback regulation (Step P).

5. The measurement of $C_{(t)}$ is not-specific.

   A. Total (unbound and bound) drug measured is being measured over time rather than unbound free concentration of drug being measured over time and time-dependent protein binding such as the protein binding changes over time are occurring such that unbound pharmacologically active concentration decreases with time [9].

   B. Total achiral (all enantiomers) drug concentration is being measured over time rather than enantiospecific concentration of a racemic drug through the use of non-stereospecific assays [10].

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Stereospecific pharmacokinetics and pharmacodynamics are occurring leading to 1. Stereospecific Disequilibrium, 2. Stereospecific Metabolism and/or 3. Stereospecific Changes in PD occurring. A. Common Receptor-Common Mechanism Competitive Antagonism, where one enantiomer is active and the other has affinity but no activity.

B. Total (parent drug + metabolites) concentration together are being measured by a non-specific analytical assay is being utilized (i.e. radioimmunoassay, radioactive assay, or high performance liquid chromatographic assay, etc.) that is non-specific for the parent drug such that an assumed E vs. C plot is in actuality an E vs. C+MpCAN or E vs. C+MpCA plot.

A specific analytical assay has been developed to measure parent compound concentration, however, an unknown or unidentified antagonist metabolite is adding to the E.

The following overview of hysteresis loops aims to provide a comprehensive rather than exhaustive appraisal of the available pharmaceutical and biomedical literature in which hysteresis in either direction has been observed or studied. The goal of this article is to provide the reader with a more comprehensive understanding of the mechanistic reasons underlying why these phenomena can occur, provide examples of which drugs and group of drugs have been reported to exhibit these characteristics (Table 2 and 3), the effect that pharmaceutical formulation may have on the occurrence and change in direction of a hysteresis loop, and the main pharmacokinetic-pharmacodynamic modeling approaches utilized to further understand hysteresis relationships.

COUNTER-CLOCKWISE HYSTERESIS

A counter-clockwise hysteresis loop may signify an increasing pharmacological effect compared with earlier temporal pharmacological effects obtained with the same plasma concentration of drug. There are a variety of examples in the literature that suggest this type of pharmacokinetic / pharmacodynamic relationship as demonstrated in Table 2 [11–79, 298–312, 318, and 327–329]. A counter-clockwise hysteresis may mechanistically manifest due to a variety of underlying mechanisms as discussed below.

Distribution Delay into Site of Effect

Counter-clockwise hysteresis loops can occur because of a distribution delay between the systemic drug concentration and the time to reach the effect site. This is the most commonly encountered underlying mechanism responsible for the finding of a counter-clockwise hysteresis loop. Effect-concentration is time-dependent and an indirect link is made between the two variables.

For example, a delay for a drug to be transported from the systemic circulation to its site of action to elicit a response has been reported for Δ-9-tetrahydrocannabinol (THC) after intravenous, oral or smoking administration, and after various intravenous doses [107]. It was observed that counter-clockwise hysteresis was evident after intravenous and smoking administration because THC takes a finite time in order to equilibrate with one of its sites of action (brain). However, it was also observed that after oral administration no hysteresis loop was evident because more time was allowed for penetration into the brain [107]. In the case of intravenous and smoking administration, the time necessary to reach equilibrium was approximately 15 minutes (Figure 4a). Furthermore, it can be observed that the counter-clockwise hysteresis loop was evident after all the intravenous doses (Figure 4b), indicating that this phenomenon is both dose and route-independent [107]. It can be observed that the location and the protective barriers surrounding the active site, in this case the brain, plays a critical role in the occurrence of hysteresis. As the brain possesses multiple protective barriers such as the blood-brain barrier (BBB) it could be expected that a delay in reaching the site of action would occur. This type of hysteresis was also observed for morphine after subcutaneous administration (14 μmol/kg) to rats with renal failure in which counter-clockwise hysteresis was developed between anti-nociceptive activity and morphine plasma concentrations, which correlated with an equilibrium delay as the consequence of the ability of morphine to cross the BBB [58].

The organic nitrate isosorbide dinitrate (ISDN) exhibited counter-clockwise hysteresis after intravenous infusion (0.133 mg/min for 15 min) or sublingual (5 mg) administration (Figure 5) [44]. It was observed that the changes in standing systolic pressure were greater during the declining phase than in the ascending phase after IV and sublingual administration [44], this correlated with previous studies after oral administration [108].

The proposed mechanism for this hysteresis was a delay in distribution to the active site in tissue, a delay in saturation at the receptor level because it is a non-instantaneous event, or contribution of vasoactive metabolites [109, 110] which are less active than parent drug [44]. However, the main factor responsible appears to be the delay in equilibrium between the plasma and the site of action [44].

Slow Receptor Kinetics

Drug receptor theory states that as drug concentration increases the occupancy of the receptor will increase rapidly at first but then it will progressively decrease as the receptors become occupied, and that the drug concentrations necessary to achieve maximal effect (E_{max}) can be many fold higher than that necessary to produce a 50% response. [5]. However, not all drug receptor interactions can be described by an E_{max} model since there are limitations in the type of binding, regulation, type of receptors, and the use of surrogate sample-feasible biological matrices (i.e. blood) instead of the actual receptor binding site [5]. However, besides the limited access of drugs to the site of action the presence of slow receptor kinetics are recognized as one of the main causes of counter-clockwise hysteresis [111]. It has been reported that in the case of anti-psychotic drugs they need to traverse not only the BBB but also the transporters that reside in this barrier [12]. The rate at which drugs bind to the receptor (k_{on}) and the rate at which it dissociates from a receptor (k_{off}) determine the kinetics of a drug such as in the case of anti-psychotic drugs and their relationship with the dopamine D_2 receptor [12]. For these types of drugs the k_{on} values show low variability for various drugs, but the k_{off} can vary within a 1000-fold range [112]. This switching movement has been evaluated by positron emission tomography (PET) studies in dopamine receptor occupancy after single oral administration of aripiprazole (2, 5, 10 or 30 mg) to healthy subjects, which reported that a high receptor occupancy was present after administration (lower arm of hysteresis), but low receptor occupancy was observed at later time points post-drug administration (upper arm of hysteresis) [12].

In the case of telmisartan, an angiotensin receptor antagonist, counter-clockwise hysteresis was observed between plasma concentration and angiotensin II response after oral administration (20, 40 or 80 mg) following an angiotensin II challenge [74]. It was determined that the hysteresis could be explained because of the tight binding and subsequent slow dissociation of telmisartan from the receptor (AT_1) on the vascular smooth muscle cells [74], which was based on the ^{3}H-telmisartan binding to rat lung AT_1 receptors and slow dissociation ($t_{1/2}$ = 5.9 h) from the binding sites [113]. Furthermore, the slow dissociation from the AT1 receptor can also contribute to the antagonism of telmisartan [74, 114]. Similarly, candesartan cilexetil and losartan after oral dosing exhibited counter-clockwise hysteresis after angiotensin II challenge in healthy subjects, and it was reported that candesartan exhibited a slower off-rate from the AT1 receptor than losartan [22]. However, the extent of insurmountable antagonistic activity [115–117] or differences in distributional phenomena could also occur. The slow onset of the inhibitory effect on blood pressure for candesartan [23,118–119] could result in a longer than expected PD effect based on the plasma concentrations [22]. On the contrary, in the case of irbesartan the pharmacological effects in the renin-angiotensin system (RAS) are related to the blockade of AT_1 receptors by increasing the plasma angiotensin II and plasma renin activity for which an actual clockwise hysteresis was reported [92]. It was reported that the duration of the antagonism of AT1 receptor for irbesartan would be longer than predicted using plasma concentrations [92] as demonstrated after single 150 mg PO for which the antagonism lasted for 2 days, which was much longer than valsartan and losartan [120].

Delayed or Modified Activity

The pharmacological response of a drug is not only bound by the rate of binding to a specific receptor, but can also be related to a progressive series of stochastic events that could cause a modification or delay in pharmacological activity. [63]. For both regular and neutral protamine Hagedorn (NPH) insulin after a single subcutaneous injection of 10 U or 25 U, the time to reach maximum infusion rate of glucose infusion (R_{max}), namely TR_{max}, occurs at a later time than t_{max} indicating a delay between maximum serum concentrations and the maximum PD effect. This delay was more obvious for regular insulin, and when the serum concentrations were correlated with glucose infusion rate (GIR) values, a counter-clockwise hysteresis loop was observed for both types of insulin. As the difference in delay between regular and NHP insulin is appreciable, the hysteresis loop was greater for regular insulin than NPH insulin [63].

In the case of molsidomine [a prodrug for the formation of nitric oxide (NO)] it first requires biotransformation (rapid hydrolysis) to its active metabolite SIN-1, which downstream will release NO [56]. It is because of this metabolic delay in the formation of NO from SIN-1 that counter-clockwise hysteresis has been reported in the change of diastolic diameter after a single oral dose (4 mg) of molsidomine to coronary artery disease (CAD) patients [121]. These findings correlated with a separate study in which finger pulse curve as a PD effect exhibited counter-clockwise hysteresis after administration of molsidomine (8 mg) to healthy subjects [122].

Active Agonist Metabolite

As the existence of first pass metabolism occurs predominantly in the liver, the route of administration may play a critical role in the appearance of a hysteresis loop. Hysteresis is possible because a drug can be converted to an active metabolite that has a C_{max} and a combined peak activity at a later time point compared to the parent drug [5]. For instance, midazolam exhibited a slower reaction time when administered orally compared to intravenous administration, and when the concentrations were combined (both oral and intravenous routes) a counter-clockwise hysteresis loop was evident. However, when the active metabolite α-hydroxy midazolam was analyzed, their combined concentrations gave similar reaction times regardless of the route of administration [123].

Itraconazole (ITZ) is a chiral oral active triazole anti-fungal agent that has non-linear PK in rats and humans and dose-dependent first pass metabolism [124–127], and it is also metabolized by CYP3A to the major chiral metabolite hydroxyitraconazole (OH-ITZ) that has similar anti-fungal activity compared to ITZ [125, 128]. Counter-clockwise hysteresis was observed between the ITZ and OH-ITZ concentrations entering the liver (expressed as an average of portal venous and aortic concentrations, assuming that the liver receives 25% of total blood flow via the hepatic artery and 75% via the portal vein) after duodenal infusion of ITZ (5 or 40 mg/kg) to chronically catheterized rats [46]. Once the change in hepatic availability (F_H) versus ITZ concentrations were plotted over time, a counter-clockwise hysteresis loop was observed indicating an equilibration delay between ITZ and effect (F_H) or another factor that would control FH such as the production of an active metabolite. The importance of metabolism was evident because of the lack of hysteresis and only a direct hyperbolic relationship between F_H and OH-ITZ. This lack of hysteresis indicates that this metabolite or some other factor with a similar time course would be the key regulator of CYP3A inhibition and the hepatic availability (F_H) of ITZ. Similar relationships were obtained at the 40 mg/kg dose [46]. However, although analytical assays were capable of measuring the parent compound and its metabolite, no stereospecific analysis was undertaken to delineate the importance of chirality of this racemic drug and the influence of stereoselective metabolism, which should be considered in the interpretation of the mechanism underlying the hysteresis loop.

The cholinesterase inhibitor eptastigmine was administered to healthy volunteers as a single oral dose (10, 20 or 30 mg), and counter-clockwise hysteresis was observed between plasma eptastigmine concentrations and both red blood cell acetyl-cholinesterase inhibition and plasma butyrylcholinesterase inhibition [32]. It was evident that eptastigmine is more effective and provides a longer duration in inhibition of cholinesterase in RBC (acetyl-cholinesterase) than in plasma (butyryl-cholinesterase), which is similar to previous reports in young [129,130] and elderly subjects [131]. However, these previous findings do not correlate with *in vitro* studies in which it has been reported that eptastigmine is more active on butyryl-cholinesterase compared to acetyl-cholinesterase [132], which could be attributed to the formation of active metabolites such as 3'- and 5'-carboxylic acid derivatives and 3'-

carboxylic acid-1-demethyl derivative [133]. Thus, the therapeutic drug monitoring should not be performed using the unchanged eptastigmine concentrations [32]. Furthermore, the observed counter-clockwise hysteresis in RBCs indicates that eptastigmine does not develop acute tolerance, which could be explained by the formation of active metabolites but also because eptastigmine slowly dissociates from acetyl-cholinesterase in RBCs [134]. The observed invertible character of the hysteresis loop in plasma butyryl-cholinesterase inhibition s suggests that eptastigmine reaches immediate equilibrium with the enzyme [32].

Furthermore, as presented by Gupta *et al.* [8] the potency of parent compound and the agonistic metabolite (MA) was estimated using generated plasma concentration-time and plasma concentration-effect curves. The degree of counter-clockwise hysteresis increases as the agonistic metabolite accumulates [as elimination rate of the metabolite (k_{mo}) decreases and is not formation rate limited]. Furthermore, the degree of hysteresis is also reflective of the potency of the parent compound and agonist metabolite M_A since as the ratio of potency parent compound/agonist metabolite decreases in magnitude (potency of agonist metabolite increases), the degree of hysteresis will increase.

Indirect Physiological Response

Often drugs act via an indirect mechanism of action and the pharmacologic effect takes considerable time to become evident as concentrations of drug are decreasing. Response is governed by the stimulation or inhibition of factors which can modulate the response [320]. There are two indirect situations following drug administration where the response measured when related to drug concentrations will produce a counter-clockwise hysteresis. Counter-clockwise hysteresis occurs when input is stimulated (i.e. stimulating the release of an endogenous physiological factor) or the output is inhibited (inhibiting or degrading the release of an endogenous physiological factor). For example stimulation of insulin or prolactin leads to a counter-clockwise hysteresis and the inhibition of anticholinesterase or diuresis leads to a counter-clockwise hysteresis [321–330] Terbutaline is a bronchodilator that increases cyclic AMP this in turn leads to bronchial smooth muscle dilation. Pyridostigmine and other agents inhibit cholinesterase preserving acetylcholine leading to an increase in muscular activity leading to a gain in muscular response. An indirect response can result in counter-clockwise hysteresis [321–323].

CLOCKWISE HYSTERESIS

A clockwise hysteresis loop may signify a decreasing pharmacological effect compared with earlier temporal pharmacological effects obtained with the same drug concentration. There are a variety of examples in the literature that suggest this type of pharmacokinetic/pharmacodynamic relationship as reported in Table 3 [80–102, 313–317, and 330]. A clockwise hysteresis may mechanistically manifest due to a variety of underlying mechanisms as discussed below.

Venous vs Arterial Blood Concentrations

Drug concentration is often measured in venous blood sampling sites and the site of effect equilibrates with arterial concentrations at different rates. When the effect site (i.e. the brain or heart, etc.) concentration at the receptor site (leading to drug effect) equilibrates faster with arterial concentration than forearm venous blood concentration, clockwise hysteresis may occur.

In the case of the opioid remifentanil after IV infusion (3 μg/kg/min for 10 min), it was observed that as opioid concentration increases the spectral edge decreases in the form of counter-clockwise hysteresis as a result of an equilibrium delay between arterial remifentanil concentration and the site of action (brain) (Figure 6a) [69]. However, a significant difference in arteriovenous concentrations in healthy subjects was reported and the direction of the hysteresis loop was reversed in venous drug concentrations (Figure 6b) and it was determined that the venous concentration lag behind the drug effect (clockwise hysteresis) [69]. It was suggested that the arterial drug concentration and effect site reach equilibration faster than the equilibration between arterial and venous concentration [69,103–106].

Tolerance (Down Regulation of Receptors)

Tolerance is a time-dependent loss of intrinsic activity that can occur within the time course of a single dose, and is called acute tolerance or tachyphylaxis. In the case of pharmacodynamic tolerance intrinsic responsivity of the receptor diminishes over time. Many drugs present clockwise hysteresis due to tolerance because they present a reduced pharmacological effect at the same concentration than earlier leading to an increased effect [140–145]. After oral administration of the benzodiazepine diazepam (0.28 mg/kg) clockwise hysteresis was observed between tracking or digit-symbol substitution impairment and unbound diazepam concentrations relative to receptor occupancy [85]. Acute tolerance to the psychomotor effects of other benzodiazepines like alprazolam [146,147], midazolam [148], and triazolam [149] has been reported. However, it needs to be acknowledged that the actual mechanism of tolerance development to benzodiazepines is poorly understood [81]. There is no consensus delineating the actual mechanism but there are reports that consider that a decrease in binding potential and/or decrease in receptor functionality could explain the appearance of tolerance [150]. However, other mechanisms such as desensitization associated with receptor phosphorylation, uncoupling, and protein internalization or degradation have been proposed [151].

In the case of temazepam (30 mg oral dose), clockwise hysteresis was observed between plasma concentration and sedation score with or without the co-administration of aluminum hydroxide gel (30 mL) in end-stage renal patients (Figure 7) [101]. The hysteresis loops were very similar with or without the co-administration of aluminum hydroxide gel, but the main difference was the presence of the lag time of 1 h when temazepam was administered alone, but it was concluded that aluminum hydroxide gel had no effect on the absorption of temazepam [101]. The clockwise hysteresis was attributed to tolerance [152], which could be a consequence because of a discrepancy between its effective $t_{1/2}$ and receptor binding affinity [153]; however, psychological adaptation [154] and functional disturbance [155] can also play a role since sedation has some subjectivity in scoring, as a patient can force themselves to stay awake after an entire morning of sleep or the opposite may occur [101].

Interestingly, when temazepam is administered as a racemate a clockwise hysteresis is evident in its sedation. It is likely that stereospecific pharmacokinetics and pharmacodynamics contribute to this relationship [9–10]. Use of a non-stereospecific assay for a chiral drug could lead to an apparent clockwise hysteresis loop where this relationship might not be apparent if the stereospecific concentrations were measured.

In the case of morphine after intragastric administration as a single dose (15 mg/kg) to rats, it was observed that clockwise hysteresis was evident between unconjugated and conjugated morphine concentrations and anti-thermal pain effect. It was proposed that the fast and short-lasting anti-thermal pain effect of unconjugated and conjugated morphine was due to tolerance [59]. Morphine administered as an IV bolus to rats caused less tolerance than IV infusions at two different rates, with tolerance stronger for the higher infusion rate [156]. Similarly when morphine was administered SC (14 μmol/kg) to rats tolerance (clockwise hysteresis) developed between antinociceptive activity and morphine brain concentrations in renal failure-induced rats, which has been suggested to most likely involve a post-opioid receptor transduction mechanism [58, 157].

In the case of diltiazem after a single oral dose (120 mg) to healthy subjects, clockwise hysteresis was observed in 4 out of 6 subjects (Figure 8) [86]. Significant effects on arteriovascular (AV) conduction were observed as expressed by the prolongation of PR interval, and because of the inverse relationship between PR interval and heart rate [158] diltiazem would decrease the heart rate in order to increase the PR interval [86]. Furthermore, acute tolerance has been reported for diltiazem after a single oral dose (180 mg) of sustained-release formulations to healthy subjects based on the observed clockwise hysteresis for PQ and PR interval prolongation [87]. However, previous reports indicated counter-clockwise hysteresis after a single IV administration of diltiazem [159–162], which could occur because a delay before equilibrium is reached between systemic and site of action concentrations, or the contribution of active metabolites [163]. But also because tolerance [164], arteriovenous differences during sampling [69, 165, 166], or the presence of inhibitory metabolites with increasing metabolite-to-parent concentration ratio [164]. The arteriovenous equilibrium differences would result in time-dependence over short time intervals, but hysteresis occurred over an extended interval of many hours [86]. The metabolites N-desmethyldiltiazem and desacetyldiltiazem [167–169] are produced and have been reported to have equal or lower hemodynamic effects than parent drug [170, 171]; however, it is unknown how active the unbound metabolites compete/react with the receptor active sites in contrast with diltiazem [86]. The proposed tolerance of diltiazem is not caused by compensating physiological mechanisms because a decrease in blood pressure would indirectly increase the heart rate; however, this does not appear to be evident [86].

Feedback Regulation

Mammalian physiology has multiple feedback mechanisms to control various pathophysiological processes such as biochemical, nerve and enzymatic functions [5]. In the case of clockwise hysteresis these negative feedback mechanisms decrease the activity for the same concentration. For instance, when almitrine bismesylate (a respiratory stimulant) was infused (0.5 mg/kg) over 30 minutes to phase II chronic obstructive lung disease (COLD) patients, it was observed that almitrine concentrations increased to a plateau around 500 ng/mL at 30 minutes but rapidly decreased after the infusion was over. Furthermore, oxygen levels (PaO_2) reached a maximum around 15 minutes and rapidly declined exhibiting a clockwise hysteresis loop [172]. It has also been reported that in the case of almitrine, the production of a feedback mechanism would be present at higher concentrations than 500 ng/mL [173]. Furthermore, the formation of almitrine inhibitory metabolites has also been proposed as a mechanism, but these have been isolated and synthesized and reported to have poor uptake by the carotid body and have little activity in rats [174]. However, studies in cats have reported that almitrine stimulates the carotid body under the feedback mechanism of the automatic sympathetic ganglioglomerular nerve (GGN) and on a lesser intensity by the contralateral carotid nerve (CCN) [175].

Active Antagonistic Metabolite

The occurrence of antagonistic metabolites is rare in the pharmacokinetic-pharmacodynamic literature. Typically metabolite concentrations are lower than parent drug in humans, and generally metabolites are more polar and less active than parent and may go unnoticed. However, if an antagonistic metabolite is present and with sufficient potency, the parent drug would appear to be less effective and could have a shorter activity [5]. This has been reported for oxyphenylbutazone affecting the elimination of phenylbutazone [176], 5-hydroxypentobarbital and pentobarbital [177], and hydroxydiphenylhydantoin and hydantoin [178]. Clearly, the greater the potency of the antagonistic metabolite relative to the parent compound, and the slower the elimination rate constant relative to the parent drug, the larger the hysteresis loop [8].

Indirect Physiological Response

Often drugs act in an indirect mechanism of action and the pharmacologic effect takes considerable time to become evident and response is governed by the stimulation or inhibition of factors that modulate the response [320]. There are two situations following drug administration where the response measured when related to drug concentrations will produce a clockwise hysteresis. Clockwise hysteresis occurs when input is inhibited or the output is stimulated. For example, acid secretion is inhibited by H_2-receptor antagonists, and the formation of angiotensin II is inhibited by angiotensin converting enzyme inhibitors and certain anticoagulants such as warfarin that inhibit prothrombin complex activity, methylprednisone and other corticoids that inhibit cortisol. Similarly, diuretics such as furosemide may stimulate secretion of electrolytes into urine, and warfarin inhibits coagulation through prothrombin complex activity. In these situations we would readily expect the appearance of clockwise hysteresis if an effect versus concentration relationship is plotted [321–323].

INPUT RATE: PHARMACEUTICAL FORMULATION EFFECTS AND THE DIRECTION OF HYSTERESIS LOOPS

As various formulation efforts are designed to provide a desired therapeutic profile, variations in pharmacokinetics and pharmacodynamics are common. Thus, by altering the formulation in which a drug is prepared and thereby altering its input rate may also affect the direction of the hysteresis loop at various steps in the process (Figures 2 and 3). For instance, the loop diuretic bumetanide (1 mg) was administered orally to healthy subjects as tablets and as retarded capsules (containing sustained release granules) [20]. In the case of the tablet formulation a counter-clockwise hysteresis was present and it was determined that this was caused due to the time lag between plasma concentration and diuretic effect because bumetanide acts directly in the renal tubule or because of variations in absorption rate from the GI tract [20]. However, in the case of the bumetanide retarded capsules a clockwise hysteresis was evident in the relationship between urinary excretion rate and urine flow rate. In this case the urine flow rate maximum was achieved before the plasma C_{max} or maximum of urinary excretion in the case of bumetanide [20]. Similar results were obtained with furosemide (another loop diuretic) for which minimal counter-clockwise hysteresis was observed for plain tablets (Furix®) while controlled release formulations (Furix Retard® and Lasix Retard®) exhibited clear clockwise hysteresis when the diuretic effect versus furosemide excretion rate were correlated [38]. The occurrence of the counter-clockwise hysteresis indicated that after the administration of the plain tablet there was a minimal delay of the effect related to furosemide excretion rate. However, in the case of the clockwise hysteresis of the two controlled release formulations, tolerance and upregulation of the biosignal of the Na-Cl-K transporter protein may be the main mechanism of action responsible for the effect [38]. These results were parallel to the ones observed in a similar study where a regular tablet and a retarded furosemide capsules were administered to healthy subjects [39]. Therefore, the higher diuretic effect (related to the amount of excreted furosemide) could have been the result of the slower output of drug from the controlled release formulations compared to the plain tablet, indicating that the diuretic response is independent of intrinsic activity and maximum response [135].

Another relevant example includes lisdexamphetamine mesylate (prodrug that gets metabolized to D-amphetamine and L-lysine) and immediate-release (IR) D-amphetamine when it was administered intraperitoneally (IP) to rats at equivalent doses (1.5 mg/kg D-amphetamine base) [28]. Counter-clockwise hysteresis between D-amphetamine (from lisdexamfetamine and IR D-amphetamine) plasma concentrations and striatal dopamine efflux was evident [28]. The counter-clockwise hysteresis was evident because the magnitude of the increase in extracellular dopamine was greater when the concentrations of D-amphetamine were decreasing instead of increasing. When the D-amphetamine plasma concentrations were related with the locomotor activity, it was observed that lisdexamfetamine (1.5 or 5.0 mg/kg IP) presented counter-clockwise hysteresis, whereas there was no hysteresis for IR D-amphetamine, demonstrating the important effect of formulation in the PK-PD relationship. Hysteresis was also analyzed between the striatal extraneuronal dopamine concentration and locomotor activity [28]. In this case counter-clockwise hysteresis was evident for lisdexamphetamine; however, in the case of IR D-amphetamine clockwise hysteresis was observed because there was a greater locomotor response during the ascending portion of the dopamine concentration profile [28].

The observed differences in pharmacokinetics and hysteresis between lisdexamphetamine and IR D-amphetamine could be explained because the prodrug lisdexamphetamine is hydrolyzed by red blood cells and by a rate-limited enzymatic reaction to D-amphetamine [136]. This would cause a more sustained gradual release of D-amphetamine compared to the IR formulation causing a more prolonged and sustained efficacy [137–139]. The counter-clockwise hysteresis observed was linked with the requirement of D-amphetamine to cross the blood-brain barrier in order to enter the striatal nerve terminals before releasing dopamine to produce locomotor activity (functional outcome) [28]. Therefore, lisdexamphetamine would be a lesser stimulant than an equivalent dose of IR D-amphetamine. However, lisdexamphetamine offers a later, more gradual and more sustained increase of striatal dopamine compared to a rapid achieving but rapidly declining effect for IR D-amphetamine [28].

The calcium sensitizer levosimendan when administered as a single dose via different routes: IV infusion (2 mg for 5 min), slow-release tablet (SR, 2 mg), conventional tablet (CT, 2 mg) or conventional capsule (CC, 2 mg) to healthy humans exhibited counter-clockwise hysteresis in all the formulations for the electromechanical systole corrected for heart rate (QS2i) (Figure 9) [49]. It was observed that the SR formulation resulted in lower concentrations and generally weaker effects compared to the other formulations. The observed hysteresis was proposed to occur because of an equilibration delay that reflects the time that the drug is required to distribute from the plasma to its site of action (heart) and the difference between formulations may be due to the physiological barriers and physicochemical properties of the actual formulations that would render different absorption and distribution profiles [49]. Furthermore, counter-clockwise hysteresis in QS2i has also been reported in severe congestive heart failure patients after IV infusion (0.2 μg/kg/min for 6 hours) or oral dose (2 mg), for which also the fact that levosimendan has inotropic and vasodilatory effects could contribute to development of hysteresis [48]. It is evident that in all cases the later effect is higher at 0 ng/mL than before the study commenced. These is exactly what would be predicted if you have a specific assay for the parent drug and have an active metabolite that is not detected or accounted for. More recent literature has demonstrated that levosimendan has two active metabolites OR-1896 and OR-1855 that have mean elimination half-lives of 72.6 and 81.3 hours, respectively, compared to the elimination half-life of parent drug that ranges between 1.1 to 1.4 hours [324].

Theoretical and Practical Considerations: Clockwise and Counter-clockwise Hysteresis and the Importance of Specific Measurement of Concentration

Total (drug concentration + metabolites) together can be measured by a non-specific analytical assay method.

This would most often occur with the use of a radioimmunoassay, or by measuring radiolabelled drug in early pharmaceutical development. Using non-specific methods of analysis, drug concentration and concentration of metabolite would be measured simultaneously and could be plotted together versus effect. As presented in simulations by Gupta *et al.* [8] the potency of the parent compound and the generated agonistic metabolite (MA) were estimated using generated plasma concentration-time and plasma concentration-effect curves. Different derived equations were used to describe parent and MA PK, and plasma concentration-effect profiles using PD models in which the effect was considered a linear function of parent and MA (equation 3) [8].

$$E=P_{PAR}*C+P_{MA}*C_{MA} \quad (3)$$

where, P_{PAR} is the pharmacological potency of the parent compound and P_{MA} is the pharmacological potency of the metabolite. A competitive agonist E_{max} model was developed using equation 4 [8]

$$E = E_{\max}\left(\frac{C}{EC_{50}}\frac{C_{MA}}{EC_{50MA}}\right)/\left(1+\left(\frac{C}{EC_{50}}+\frac{C_{MA}}{EC_{50MA}}\right)\right) \quad (4)$$

E vs. C plot is in actuality an E vs. C+CMA in these instances (Figure 10). When the parent compound and metabolite are equipotent no hysteresis was observed (PPAR/PMA ratio = 1 or EC_{50}/EC_{50}MA) (Figure 10a) Clockwise hysteresis was present when C > MA in potency (Figure 10 b) and counter-clockwise hysteresis was reflective of MA > C in potency (Figure 10c). Similar findings were demonstrated and applicable using Equation 3. Therefore, the potency of the metabolite relative to parent compound is the key to the hysteresis and its direction, and it needs to be considered that nonspecific analytical assays such as RIA or achiral analytical methods in PK-PD studies could cause interpretational problems but also warrants the need to identify all of the active metabolites or stereoisomeric forms.

What is apparent is that if using a non-specific method of analysis (Figure 11b), a direct linear relationship could be interpreted between concentration and effect (Figure 1a, Figure 11b), however employing a specific method of analysis (Figure 11a) demonstrates the existence of a counter-clockwise hysteresis loop. Likewise, a clockwise hysteresis loop could be incorrectly assigned to a situation where a counter-clockwise hysteresis is occurring (Figure 10a and Figure 11a). Finally, a larger counter-clockwise hysteresis may be evident (Figure 10c) than if a specific method of concentration analysis utilized (Figure 11a).

Time-Dependent Protein Binding

In a simulation study the time-dependent protein binding can occur as a consequence of a time dependent decrease in protein concentration in serum, by displacement of a metabolite. When pharmacological effect was plotted versus total drug concentration in serum counter-clockwise hysteresis was evident; however, when concentration of free drug in serum, which was correlated with pharmacological effect, was plotted no hysteresis was evident [9]. Time-dependent protein binding that can occur as a consequence of an increase in protein concentration in serum can lead to a decrease in free fraction of drug. When pharmacological effect was plotted versus total drug concentration in serum (i.e. free and bound drug) clockwise hysteresis was evident; however, when concentration of free drug in serum was correlated with pharmacological effect no hysteresis was evident [9]. Despite these theoretical simulations and modeling no examples of studies in the literature demonstrating this phenomenon are apparent to date.

Racemic Drug and Chirality

The utility of using non-stereoselective assay methodology for measuring concentration of a racemic drug can lead to interpretation errors in the concentration versus pharmacological effects correlation and the assignment of a hysteresis loop [10, 179]. Indeed as stated by Ariens 30 years ago [297] an analytical assay that does not measure the enantiomers of a racemic drug and attempts to relate total concentrations to effect without stereochemical knowledge is “highly sophisticated scientific nonsense”. However, many examples from studies in both Tables 2 and 3 continue to produce this achiral scientific gibberish. After oral administration when enantiomers differ substantially in total body clearance and when an active enantiomer has lower clearance, counter-clockwise hysteresis was evident between plasma concentration of total drug and its pharmacological effect. The active enantiomer would constitute a greater proportion of the total concentration as time progresses. In addition, when the V_d of an active enantiomer is larger than the inactive enantiomer and a different half-life of the enantiomers ensues, the proportion of the active enantiomer in the total concentration would be higher over time. In the case of zero-order absorption, which could be possible when enantiomers are orally absorbed and transported via carriers, and when the K_a of the active enantiomer is less than that of the inactive enantiomer hysteresis was evident. The implications of chirality on pharmacodynamics modeling were also simulated when enantiomers acted as competitive agonists, partial agonists, competitive agonists, enantiomers may also have affinity and activity and intrinsic activity at separate receptors, separate transduction mechanisms or affinity and intrinsic activity at separate receptors but with a common transduction mechanism. When the more active enantiomer had higher clearance or a smaller volume of distribution plots of pharmacological effect versus non-stereospecific plasma concentration produced anti-clockwise hysteresis loops [179].

When a racemic drug’s active enantiomer has a higher total body clearance a clockwise hysteresis describes the relationship between total concentration and pharmacological effect as the active enantiomer would be a lower proportion of the total concentration over time. In addition, when the volume of distribution of active enantiomer is smaller than the inactive enantiomer and a different half-life of the enantiomers ensues, the proportion of the active enantiomer in the total concentration would be lower over time. In the case of zero-order absorption which could be possible when enantiomers are orally absorbed and transported via carriers and when the K_a of the active enantiomer is greater than that of the inactive enantiomer hysteresis was evident.

Many studies identifying hysteresis using racemic drugs (i.e. Tables 2 and 3) and that have utilized non-stereospecific assays may therefore require further evaluation of their underlying mechanisms. The implications of chirality on pharmacodynamics modeling extended the importance of pharmacodynamics to the hysteresis relationship [179]. There are a variety of possible pharmacological interactions between enantiomers that were evaluated through the use of simulation of the pharmacological effect-time profile and ultimately clockwise hysteresis was also evident. Enantiomers may act as competitive agonists, partial agonists or competitive antagonists. Enantiomers may also have affinity and activity and intrinsic activity at separate receptors, separate transduction mechanisms or affinity and intrinsic activity at separate receptors but with a common transduction mechanism. In cases where the more active enantiomer had higher clearance and a smaller volume of distribution, plots of pharmacological effect versus non-stereospecific plasma concentration produced clockwise hysteresis loops. The plots outlined in Figures 10 and 11 are also applicable to achiral analysis of total enantiomers of a racemate [8,10, 179]. Depending on both the pharmacokinetic and pharmacodynamic behaviours of the enantiomers, the less active enantiomer may significantly affect the observed effect and therefore the reliability of any hysteresis loop obtained with the use of suspected achiral concentration data. All of the eight different clockwise hysteresis examples that use racemic drugs in Table 3 may be similar to Figure 10b but could in fact produce counter-clockwise hysteresis if stereospecificity was considered in the analysis.

PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) MODELING

The general assumption is that drug in the surrogate biological matrix, such as plasma, and the drug at the biophase are at equilibrium [5]. However, this assumption may not be correct because the drug concentrations change as a result of the innate pharmacokinetics of the drug, and the pharmacodynamics could also change independently or in an opposite direction to the drug concentration. Various approaches for simultaneous PK-PD modeling have been explored [180], including compartmental models [181], system dynamics models [182], distributed log analysis [183], or numerical deconvolution [184]. All of these approaches have advantages and disadvantages due to the complexity of the inherited mathematical equations utilized.[185, 325–326].

Effect Compartment Model

The most commonly used PK-PD model is the effect compartment model (Figure 12), which assumes that the active site compartment receives a negligible amount of drug and has a negligible volume [4, 164, 186–189].

This approach has now been implemented in various modeling software with the so called non-parametric or parametric link model [190].The use of an effect compartment model has been widely used to collapse the hysteresis loop, which is generally performed by linking it to the PK model as it was originally proposed by Segre [191] and by Galeassi *et al.* [192], and later elaborated and described by Holford and Sheiner [164] and by Sheiner *et al.* [3]. The effect compartment model has been described by equation 5.

$$Ce=\frac{KAD}{\frac{Vd}{F}}\left(\frac{(K21-KA)e^{-KAt}}{(\alpha-KA)(\beta-KA)(KeO-KA)}+\frac{(K21-\alpha)e^{-\alpha t}}{(KA-\alpha)(\beta-\alpha)(KeO-\alpha)}+\frac{(K21-\beta)e^{-\beta t}}{(KA-\beta)(\alpha-\beta)(KeO-\beta)}+\frac{(K21-KeO)e^{-KeOt}}{(KA-KeO)(\alpha-keO)(\beta-KeO)}\right) \quad (5)$$

where, C_e is the effect compartment concentration, *KA* is the absorption rate constant, *K* is the elimination rate constant, K_{21} is the transference rate constant from the peripheral to the central compartment, V_d/F is the volume of distribution corrected by the bioavailability of the oral dose *D*, α and β are the hybrid rate constants corresponding to the initial and terminal slope factors, respectively, and K_{e0} is the constant of the disappearance of the effect [29, 164].

The main assumption necessary to make the hysteresis loop collapse is that the effect depends on the drug concentration in an effect compartment rather than in the systemic compartment. Furthermore, the effect is correlated to C_e by the sigmoidal E_{max} PD model using equation 6 [29].

$$E=\frac{(E_{\max})*(Ce^{h})}{EC_{50}{}^{h}+Ce^{h}} \quad (6)$$

where, E is the observed effect, E_{max} is the theoretical maximal effect that can be attained, C_e is the effect-compartment concentration, EC_{50} is the C_e value that produces an effect equivalent to 50% of the theoretical maximal effect and h is a parameter that determines the steepness of the curve.

The fitting procedures then can be performed using a PK/PD modeling software. The effect compartment model has been applied to the observed counter-clockwise hysteresis between diclofenac blood concentrations and functional index (FI) recovery after oral diclofenac administration to male Wistar rats (Figure 13a) [29]. This hysteresis loop has been previously reported to be due to the formation of active metabolites; however, diclofenac metabolites do not exhibit anti-nociceptive activity [193, 194] and local administration of diclofenac causes an anti-inflammatory effect [195]. Another proposed mechanism of action was a cascade of physiological events [196] because the anti-nociceptive effect of diclofenac is an indirect response from the inhibition of prostaglandin synthesis [197]; however, it has been reported that diclofenac has a rapid pharmacodynamic effect when administered locally [195] indicating that once it reaches the site of action it has a rapid pharmacological response without delay. Therefore, the lag in anti-nociceptive effect onset occurs because there is a slow equilibrium kinetics between blood concentration in the central and effect compartment [29]. The use of the effect compartment model results in the collapse of the hysteresis loop (Figure 13b), because the derived effect data exhibited good fit as a function of the estimated C_e [29].

Tolerance Model: Incorporation of the Hypothetical Non-Competitive Antagonist

A tolerance model was developed by Prochet *et al.* [199] in which a hypothetical non-competitive antagonist is included to represent the factor driving tolerance (Figure 14), and this has been applied to diltiazem [86], clonidine [25], ephedrine [200], and morphine [41]. This model can describe tolerance based on competitive or non-competitive inhibition of response by down-regulation of receptors or by a metabolite [86].

where, E is the measured PR interval, E_0 is the baseline PR interval, C is the drug plasma concentration, S is the slope of the linear relationship between effect and concentration in the absence of antagonist, C_{ant} is the concentration of the hypothetical antagonist, and C_{ant50} is the concentration of hypothetical antagonist resulting in 50% inhibition of effect. Hypothetical antagonist concentration units are those of steady-state drug concentrations [86].

In the case diltiazem after a single oral dose (120 mg) to healthy subjects, the same model was not only applied to parent drug but also to the metabolites N-desmethyldiltiazem and desacetyldiltiazem. The best fit of the various options tested was obtained with the incorporation of the hypothetical non-competitive antagonist rather than the use of any of the metabolite concentration (Figure 15) [86]. Panel B is the best fit. The 400– 800 min times demonstrate a lack of weighting.

Indirect Physiological Response Turnover Model

As the pharmaceutical industry has diversified from small molecules into administration of proteins and peptides we have seen effects that are more discordant in time and production or degradation of a mediator that is often responsible for drug action. [321–330] As the mechanism of action of many drugs involves protein synthesis, a drug may affect the net response measured by altering either then K_{in} or K_{out} that will evoke the response measured (Figure 16). Indirect models allow for a later T_{max} with larger doses of drug. Of course partial inhibition or synergism can be adapted, circadian variation accounted and cascade models could be developed and transduction effects incorporated into these models. As many xenobiotics act indirectly through physiological and biochemical mediators and enzymes there is broad applicability of this approach. Jusko has pioneered the work in turnover model systems by pointing out that four main mechanisms are involved in stimulating or inhibiting production of the biosignal that is measured as the effect, or inhibiting or stimulating its removal [321–323].These models can be further extended by adding more transit compartments which are similar to steps in the transduction of the progression of the measured effect.

DISCUSSION

The appearance of hysteresis loops in PK-PD analysis indicates that the relationship between drug concentration and the effect being measured is not direct but has an inherent time delay and disequilibrium. As hysteresis depends on both pharmacokinetics and pharmacodynamics including all the innate factors affecting either of them this has a critical role in the appearance, direction, magnitude and collapse of a hysteresis loop. Some of these factors include the equilibrium / disequilibrium between sampled PK concentration and effect site concentration, rate of pharmacological receptor activation/deactivation, rate of signal transduction at the receptor level, presence of agonist or antagonist active metabolites, upregulation/downregulation of pharmacological response, rate of equilibration between arterial plasma concentrations (compartment delivering drug to effect site) and venous plasma concentrations (sampling compartment for concentration analysis), among others.

In addition, the study design can play a major role since the availability of a specific analytical method plays a critical role in the ability to detect the pharmacologically relevant analyte (parent vs. metabolite, or racemate vs. enantiomer). Also, it is critical to understand the nature of the activity of a metabolite (namely agonist or antagonist) because generally an agonist metabolite would aid in the development of a counter-clockwise hysteresis, while an antagonist metabolite would do the same for clockwise hysteresis loops.

It can be observed that hysteresis loops are present for a wide range of drugs and the mechanism of action (MOA) sometimes overlap between each other. In the case of clockwise hysteresis the most common MOA is tolerance, which is a constant concern in the therapeutic use of benzodiazepines, opioids and CNS drugs. However, tolerance has also been reported for loop diuretics and nitrates. Feedback mechanisms can also play a critical role in hysteresis because they control various physiological processes and it has been reported that they can also decrease the pharmacological effect for the same drug concentrations, which could cause inhibition and/or depletion at the terminal/receptor level [93, 201, 202]. Another factor to consider is drug and effect location and the protective barriers surrounding the active site such as the brain. As the brain possesses a protective blood-brain barrier (BBB) it would be expected that a delay in reaching the site of action would occur. Another factor that may be neglected in PK-PD interpretation is the potential differences in arteriovenous concentrations of a drug, because arterial blood delivers the drug to the effect site and venous blood is typically the sampled matrix. This for instance has been observed for thiopental in which concentrations were higher in the arterial samples during infusion but became comparable to venous samples after the infusion, and at the time of adding the pharmacodynamics component (EEG frequency reduction by spectral edge analysis), it was observed that the hysteresis loop was evident for arterial but not for venous blood [165].

The current ability to measure receptor binding using positron emission tomography (PET) or an equivalent technology can help us understand better the rate at which drugs bind to the receptor (k_{on}) and the rate at which it dissociates from a receptor (k_{off}) to determine the kinetics of drugs such as antipsychotics, in which the k_{on} values show low variability, but the k_{off} can vary within a 1000-fold range [112]. This interplay is critical because with the help of PET the dopamine receptor occupancy after single oral administration of aripiprazole was evaluated. It was observed that high receptor occupancy was present after the administration (lower arm of hysteresis) but low receptor occupancy was observed at later time points post drug administration (upper arm of hysteresis) [12].

The relevance of using different pharmaceutical formulations and routes of administrations has been presented to illustrate the need to be considered in order to achieve the desired therapeutic profile. For instance, bumetanide as a tablet exhibited counter-clockwise hysteresis because a time lag between plasma concentration and diuretic effect is evident since the drug acts directly in the renal tubule or because of variations in absorption rate from the GI tract. However, in the case of the retarded capsules a clockwise hysteresis was present because the maximum urine flow rate was achieved before the plasma C_{max} or before the maximum of urinary excretion [20]. Thus, it can be clearly observed that the pharmaceutical formulation may change the pharmacodynamics of a drug. However, the change from one formulation to another does not follow a constant pattern in the direction of occurrence of a hysteresis loop as this is dependent on the drug itself and the actual effect site. Other drug delivery formulation approaches have centered on the modification of the lipophilicity of a drug and having a closer delivery to the site of action in order to try to circumvent biological barriers. For instance, morphine and fentanyl were formulated into a pressurized olfactory delivery (POD) device. Clockwise hysteresis was observed after POD administration of both morphine and fentanyl, but counter-clockwise hysteresis was observed after nasal drops and IP administration of morphine, while no clear hysteresis after nasal drops and IP administration of fentanyl [57]. These observed differences could be attributed to significant differences in hydrophobicity and ability to penetrate the BBB, which not only affected the systemic plasma concentrations but also the delivery to the nasal olfactory epithelium.

With the relevance that hysteresis loops have, various modeling approached have been proposed to collapse hysteresis and allow for adequate PK and PD estimates, and the most commonly used model remains the effect compartment model, which assumes that the active site compartment receives a negligible amount of drug and has negligible volume [4, 164, 186–189]. However, variation of this model such as the tolerance model has also been implemented [102] where a tolerance (use of a linear PD model) and pseudo-tolerance (use of an effect compartment model) PK-PD model were evaluated for different drugs [104, 105, 203]. Also as proposed by Gupta *et al.* [8], the potency of the metabolite relative to parent compound is the key to the hysteresis and its direction, and it needs to be considered that non-specific analytical assays such as RIA or achiral analytical methods in PK-PD studies could cause interpretational problems but also warrants the need to identify all of the active metabolites and enantiomers.

Ultimately it can be seen that the presence of a hysteresis loop provides guidance on how to model pharmacokinetic-pharmacodynamic relationship of a particular drug, it allows the pharmaceutical scientist to design studies more appropriately when arteriovenous drug versus venous concentration differences are large and to provide a more rational basis for dosage individualization. A very clear example is the case of piritramide, for which it is recommended that it should be initially administered as an intravenous bolus of at least 5 mg to circumvent its pronounced hysteresis [96].

CONCLUSIONS

The linking of pharmacokinetics and pharmacodynamics is taking on greater relevance because of the necessity to understand the concentration-time profiles of drugs and the need for the ability to determine dosing regimens that will achieve the necessary concentrations for optimal efficacy. These complex relationships have allowed us to be able to detect hysteresis loops and to begin to understand the various mechanisms of action, metabolic and rate limiting steps that cause them. It can be observed that there are various modeling alternatives to collapsing hysteresis loops when determining PK and PD estimates. Special attention needs to be placed on the study design with the various caveats that could arise from the selection of PD estimates as well as the selection of formulation and route of administration. Inter-disciplinary approaches are warranted to aid in the further understanding of hysteresis loops to help us develop drugs with a clearer understanding of their complicated pharmacokinetic-pharmacodynamic interactions and behaviours.

ACKNOWLEDGMENTS

The authors would like to acknowledge the assistance of Nicole R. Messinbird BSc(Pharm) for initial collation of some references utilized for this paper and Dr. Matthew R. Wright for his seminal discussions and insights on this topic in the early 1990’s.

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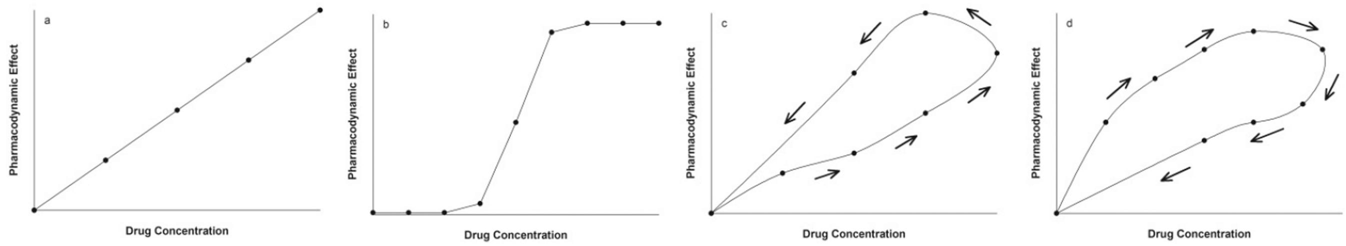

Figure 1.

(a) Representation of a linear relationship between plasma concentration of a drug and measured pharmacological effect **(b)** Representation of a Sigmoidal Emax model relationship between plasma concentration of a drug and measured pharmacological effect **(c)** Representation of counter-clockwise hysteresis between plasma concentration and measured pharmacological effect **(d)** Representation of clockwise hysteresis between plasma concentration and measured pharmacological effect.

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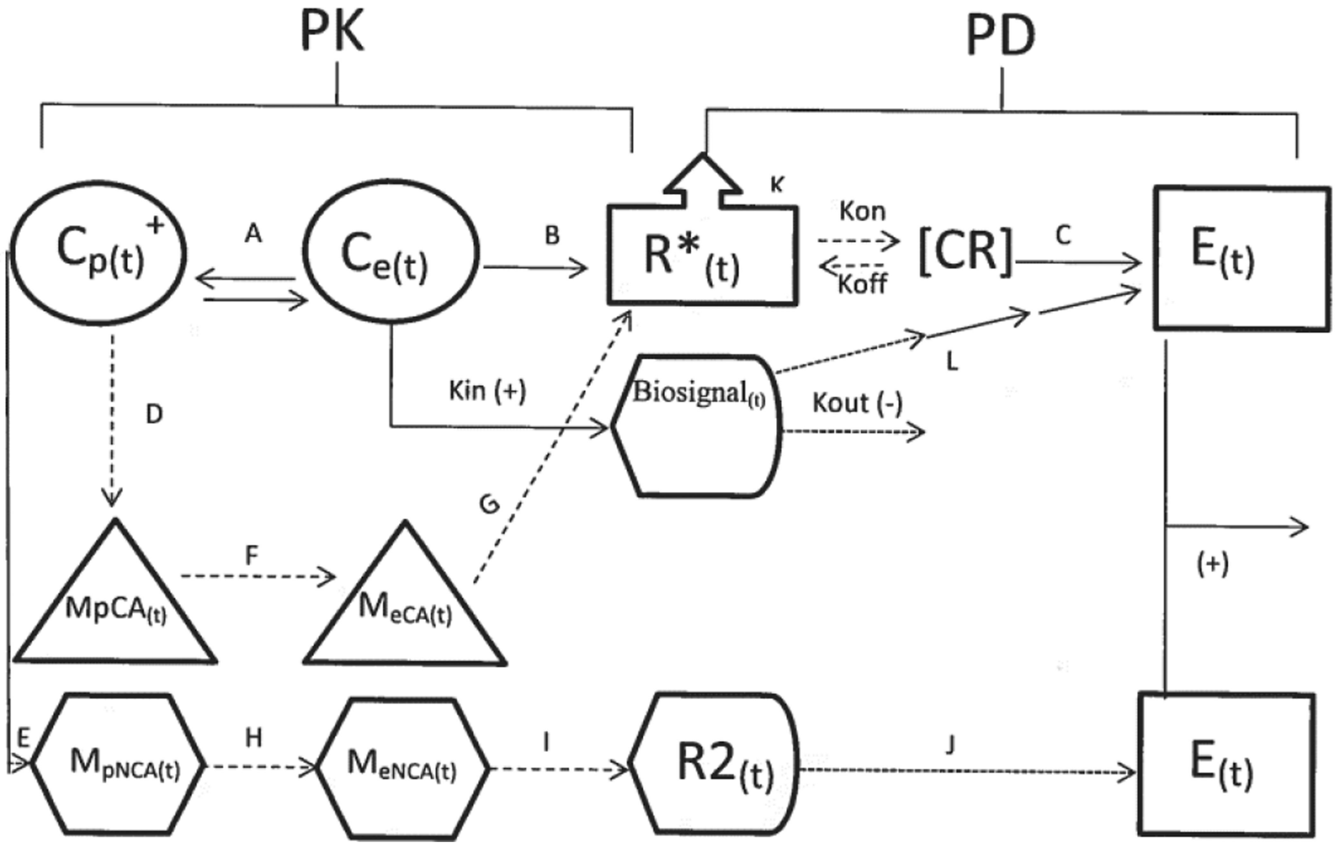

Figure 2.

Factors Influencing Counter-clockwise Hysteresis $C_{p(t)}$ = Plasma parent drug concentration, $C_{e(t)}$ = “Effect site” concentration, $R*_{(t)}$ = Receptor site, $E_{(t)}$ = Effect, MPCA(t) = Metabolite(s) in plasma which are competitive agonists, MeCA(t) = Metabolite(s) in “Effect site” which are competitive agonists, MPNCA(t) = Metabolite(s) in plasma which are competitive agonists /(MPPCA) partial agonists which have noncompetitive agonist action acting on a different receptor BUT same Effect, MeNCA(t) = Metabolite(s) in “Effect site” which are competitive agonists which have non-competitive agonist action acting on a different receptor BUT same Effect, R2 = Alternate receptor site (with same Effect).

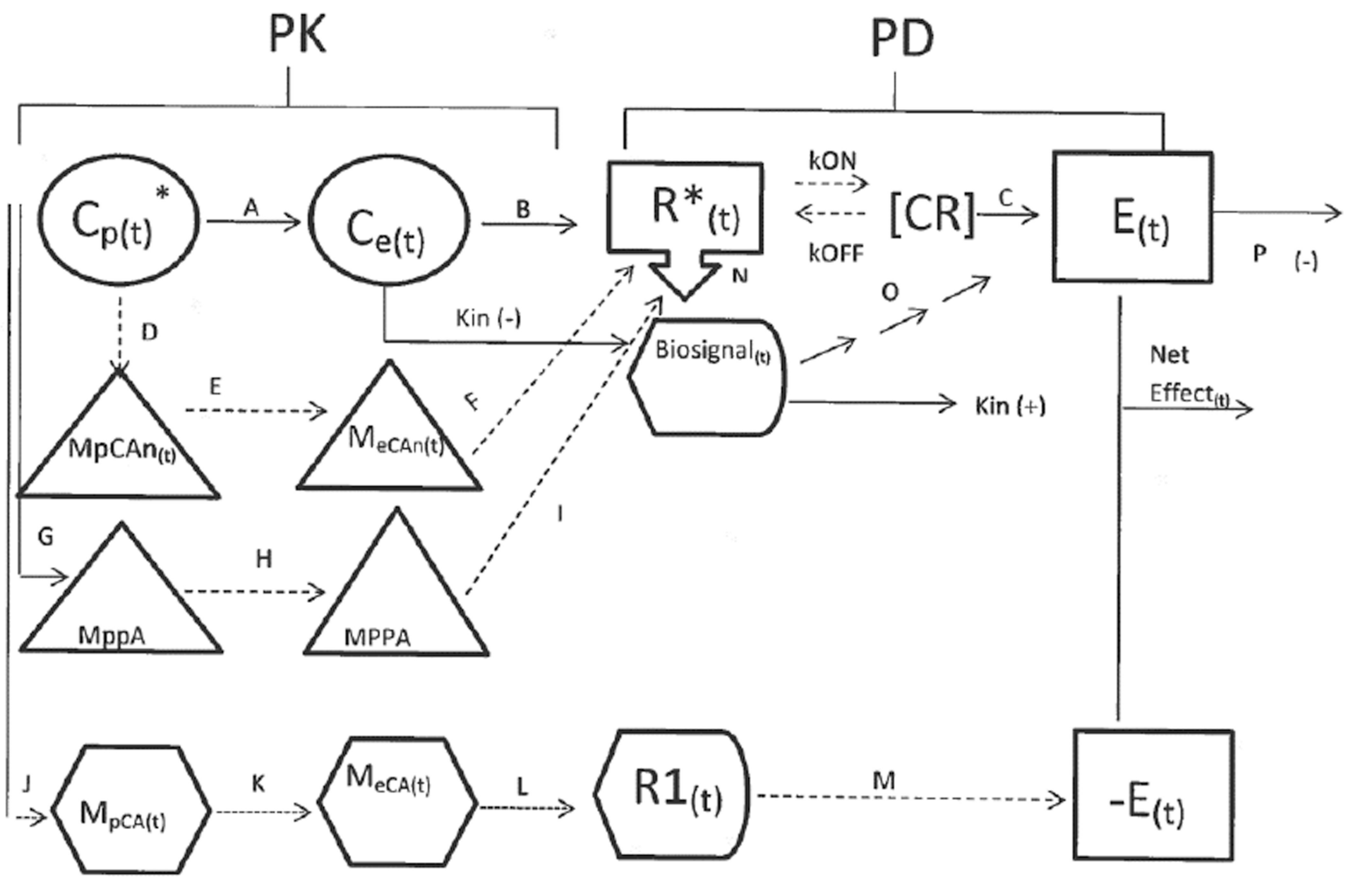

Figure 3.

Factors Influencing Clockwise Hysteresis $C_{p(t)}$ = Plasma parent drug concentration, Ce(t) = "Effect site" concentration, R*(t) = Receptor site, E(t) = Effect, MpCAn(t) = Metabolite(s) in plasma which are competitive antagonists, MeCAn(t) = Metabolite(s) in "Effect site" which are competitive antagonists, MpCA(t) = Metabolite(s) in plasma which are competitive antagonists which have competitive agonist action acting on a different receptor BUT same Effect, MeCA(t) = Metabolite(s) in "Effect site" which are competitive antagonists which have competitive agonist action acting on a different receptor BUT same Effect, R1 = Alternate receptor site (with same but opposite Effect).

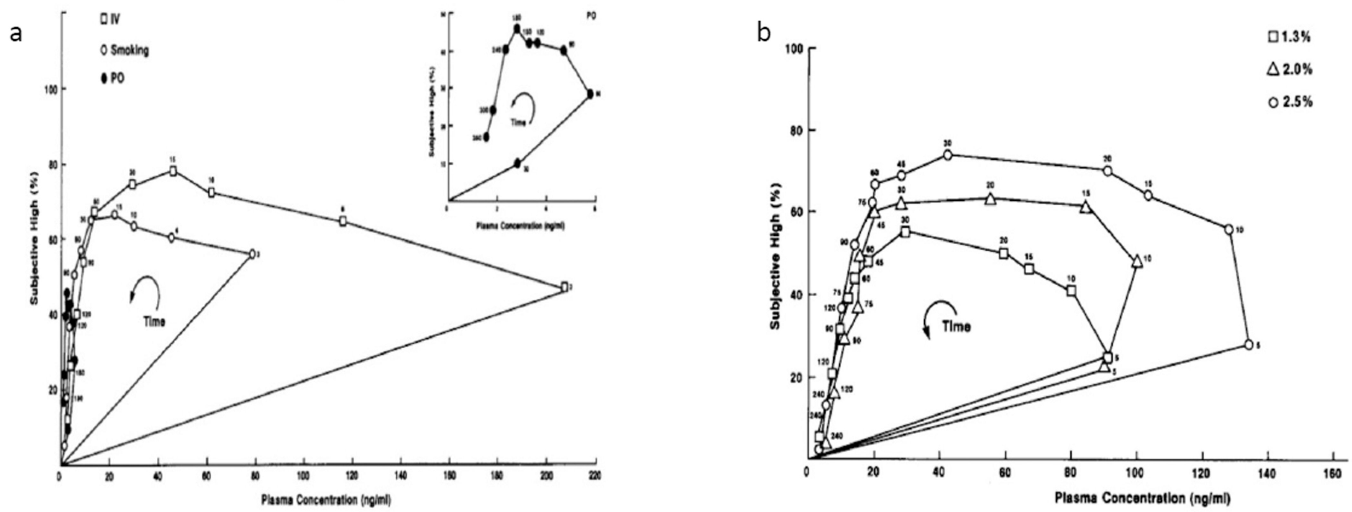

Figure 4.

Counter-clockwise hysteresis of Δ-9-tetrahydrocannabinol (THC) plasma concentrations versus self-reported subjective "High" effect (**a**) different routes of administration and (**b**) different dosages. Reprinted by permission from Macmillan Publishers Ltd: Clinical pharmacology and therapeutics, [107], copyright 1984.

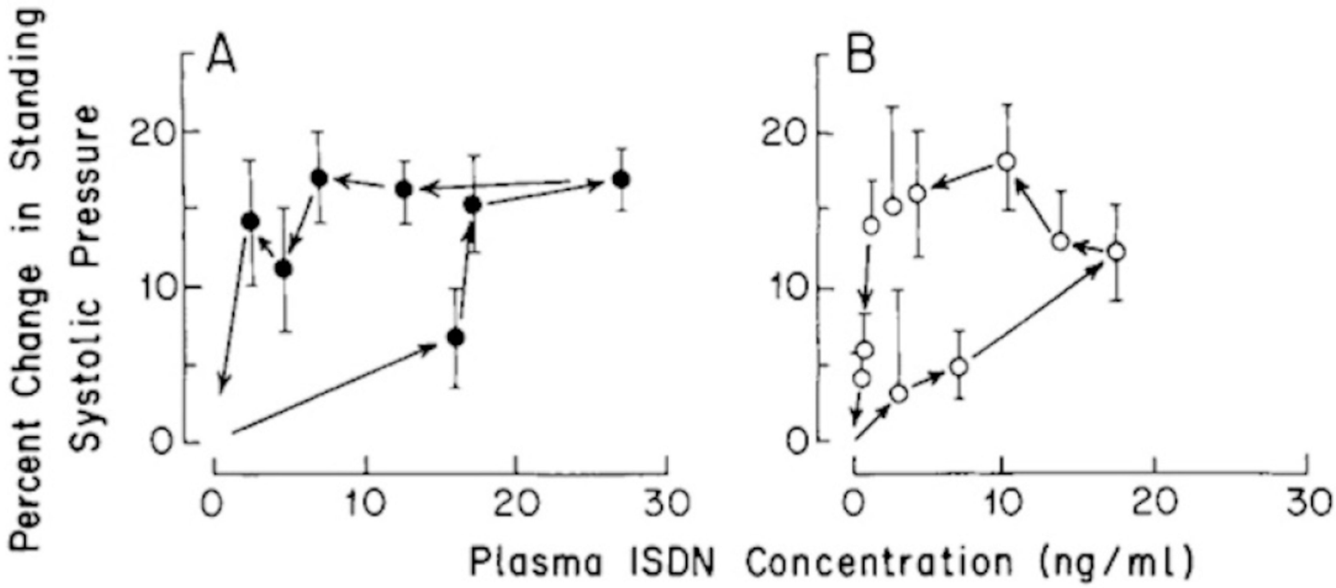

Figure 5.

Relationship between plasma ISDN concentration and response after intravenous (●) and sublingual (○) dosing. Reprinted by permission from Macmillan Publishers Ltd: Clinical pharmacology and therapeutics, [44], copyright 1983.

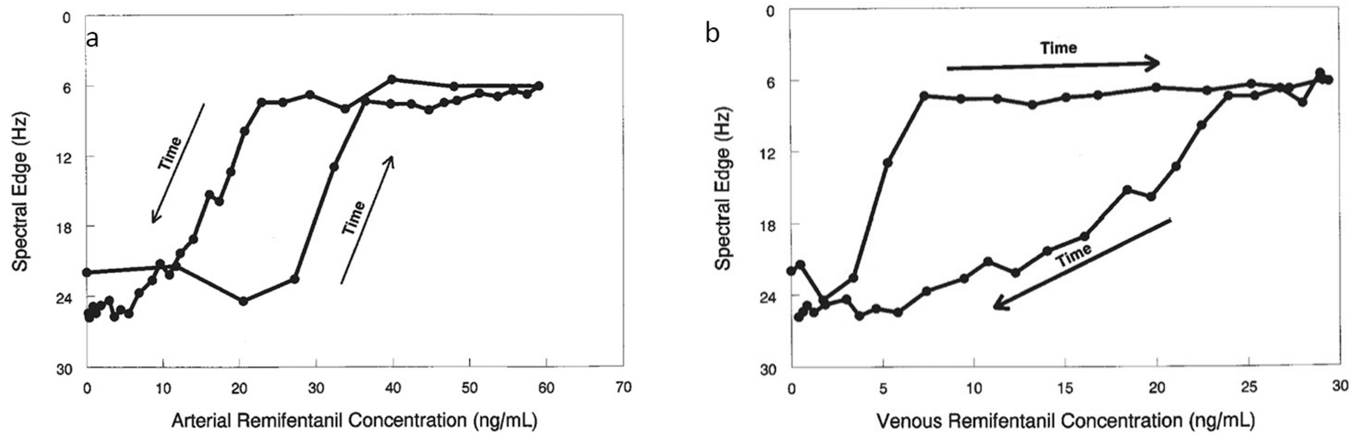

Figure 6.

(a) Opioid effect plotted against arterial remifentanil concentration from a representative subject (subject 12). Note the counter-clockwise direction of the hysteresis loop. **(b)** Opioid effect plotted against venous remifentanil concentration from a representative subject (subject 12). Note the clockwise direction of the hysteresis loop. Reprinted by permission from Macmillan Publishers Ltd: Clinical pharmacology and therapeutics, [69], copyright 1999.

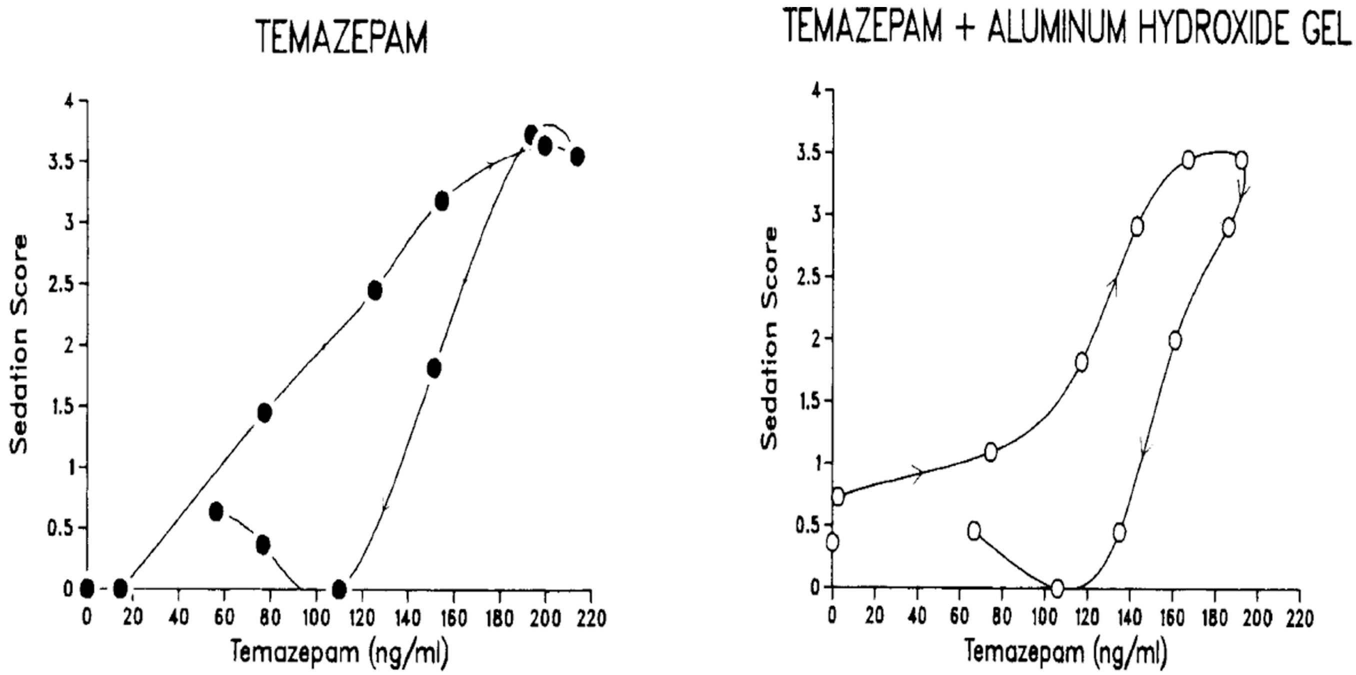

Figure 7.

Relationship between mean plasma temazepam concentrations and the NRSS after TM (●) and TM + AHG (○). Reprinted by permission from Macmillan Publishers Ltd: Clinical pharmacology and therapeutics, [101], copyright 1985.

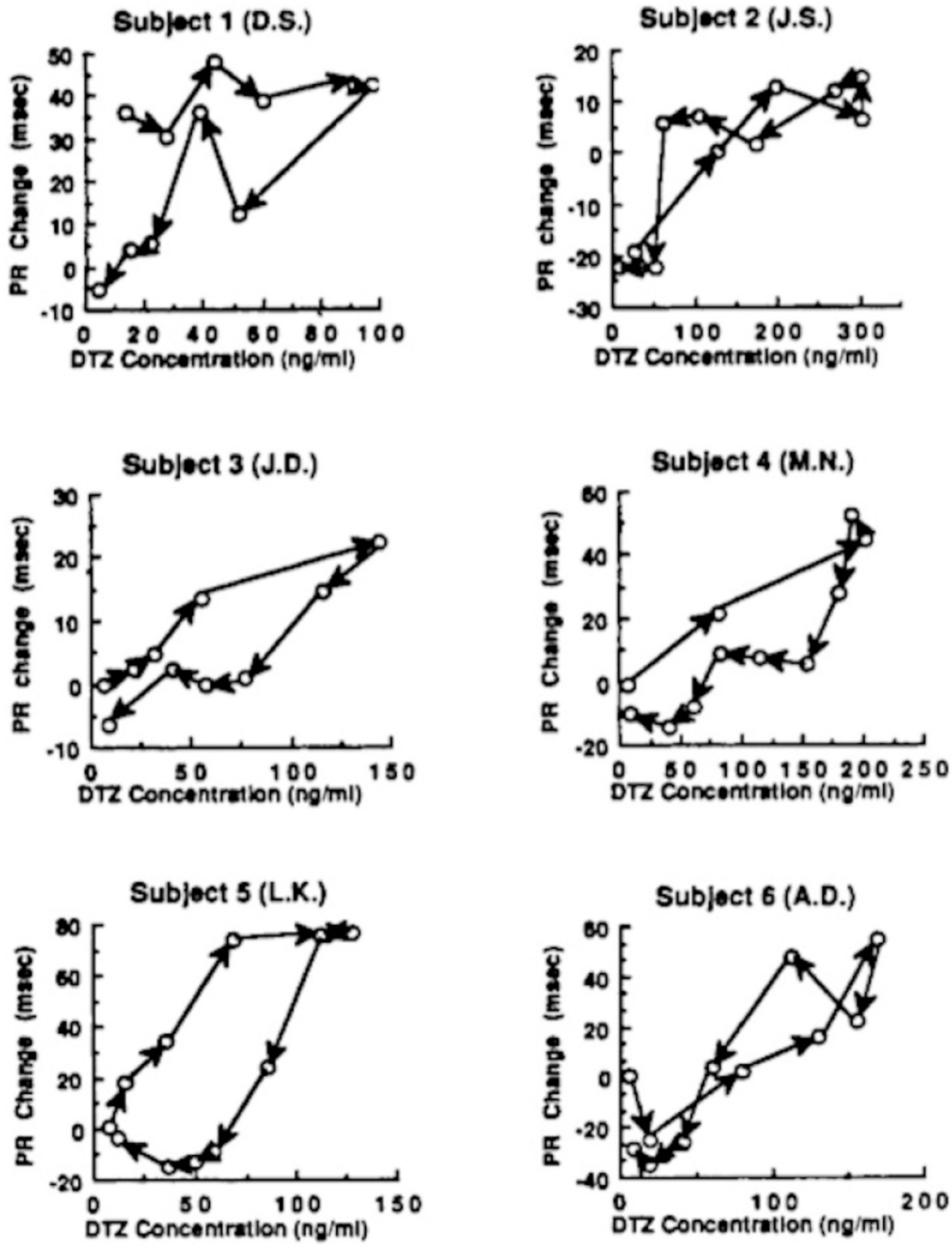

Figure 8.

Plots of change in PR interval versus concentration of diltiazem for each of the six subjects over 24 hours. The direction of the arrows indicates the chronologic order of the concentrations. Reprinted by permission from Macmillan Publishers Ltd: Clinical pharmacology and therapeutics, [86], copyright 1989.

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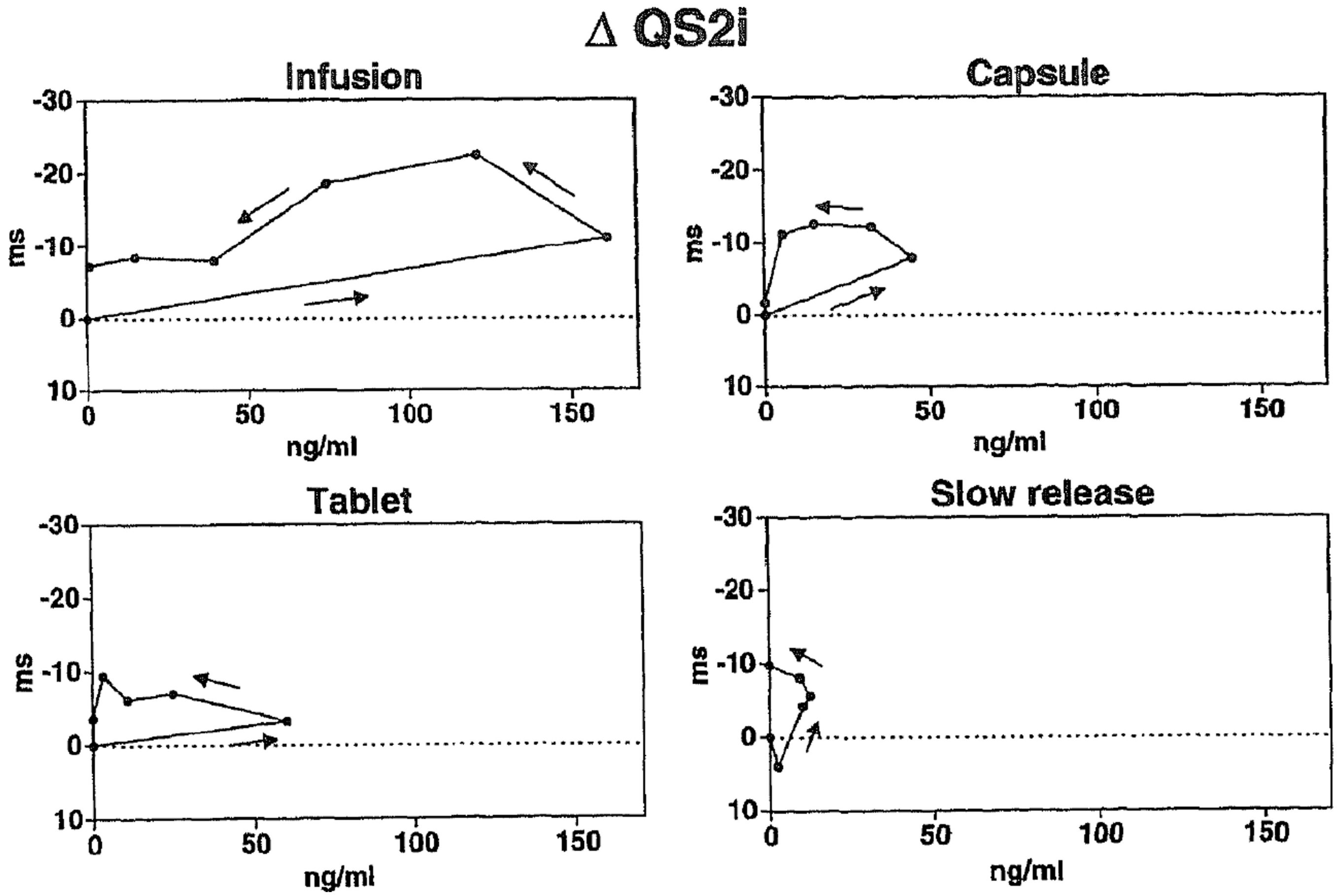

Figure 9.
The concentration-effect loops for QS2i after single doses of 2 mg of levosimendan as an intravenous (n = 10) and three different oral formulations (n = 8) in healthy subjects. The levosimendan concentrations and corresponding QS2i values are plotted in the graph and the points are connected in time order. Reprinted by permission from Dustri-Verlag: International Journal of Clinical Pharmacology and Therapeutics, [49], copyright 1998.

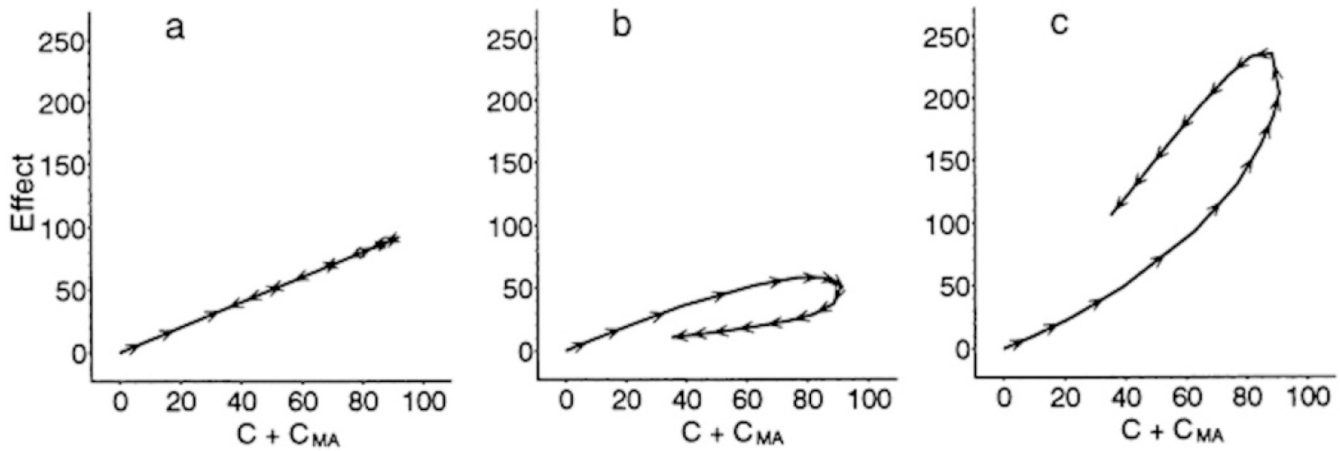

Figure 10.
Plot of observed effect (E) vs. unbound plasma concentration ($C + C_{MA}$) for parent compound and agonistic metabolite (M_A). The pharmacodynamics of parent compound and M_A are described by a linear model (Equation 3), and where, for M_A pharmacokinetics, $k_{mo} = 0.05$ and $P_{PAR} = 1$: collapsed hysteresis with $P_{MA} = 1$ (a), clockwise hysteresis with $P_{MA} = 0.33$ (b) and counter-clockwise hysteresis with $P_{MA} = 3$ (c). Reprinted by permission from Springer Science and Business Media: Pharmaceutical Research, [8], copyright 1993.

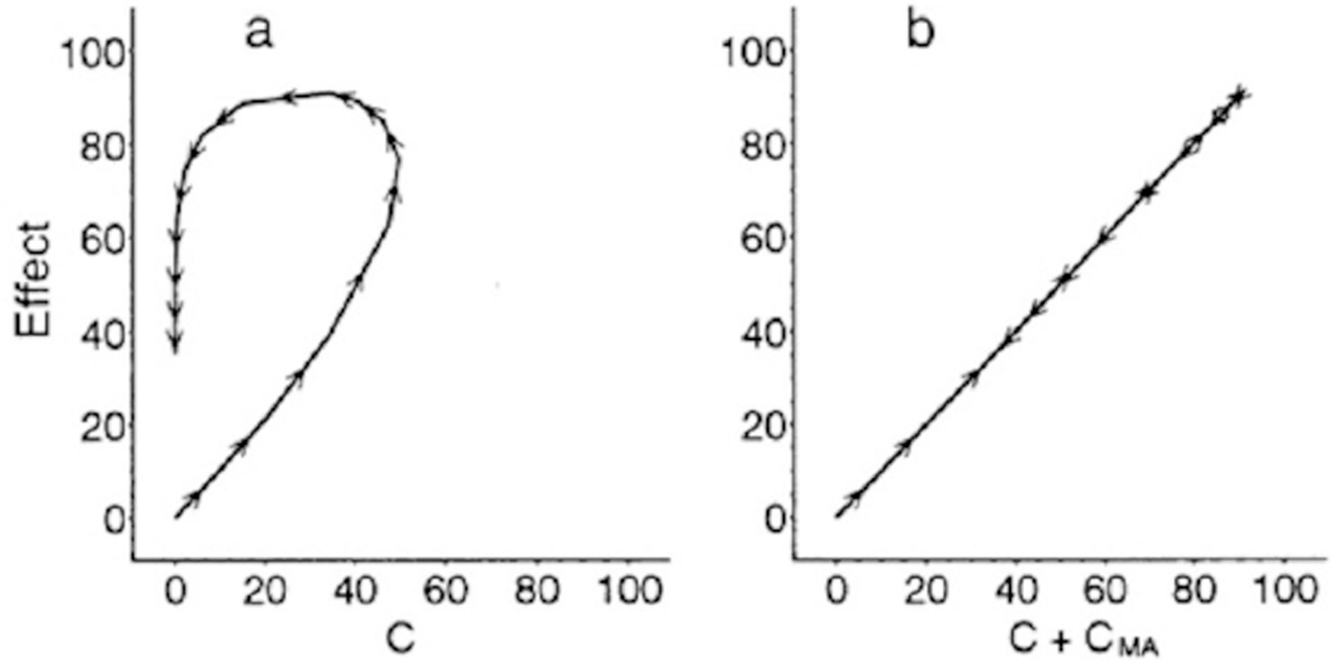

Figure 11.

(a) Plot of observed effect (E) vs. unbound plasma concentration for parent compound (C) showing counter-clockwise hysteresis. The pharmacodynamics of parent compound and agonist metabolite (M_A) are described by a linear model, with $P_{PAR} = P_{MA} = 1$ and k_{mo} = 0.05. (b) Plot of observed effect (E) vs. unbound plasma concentration ($C + C_{MA}$) for parent compound and MA showing collapsed hysteresis, where the pharmacokinetic-pharmacodynamic model is as in a. Reprinted by permission from Springer Science and Business Media: Pharmaceutical Research, [8], copyright 1993.

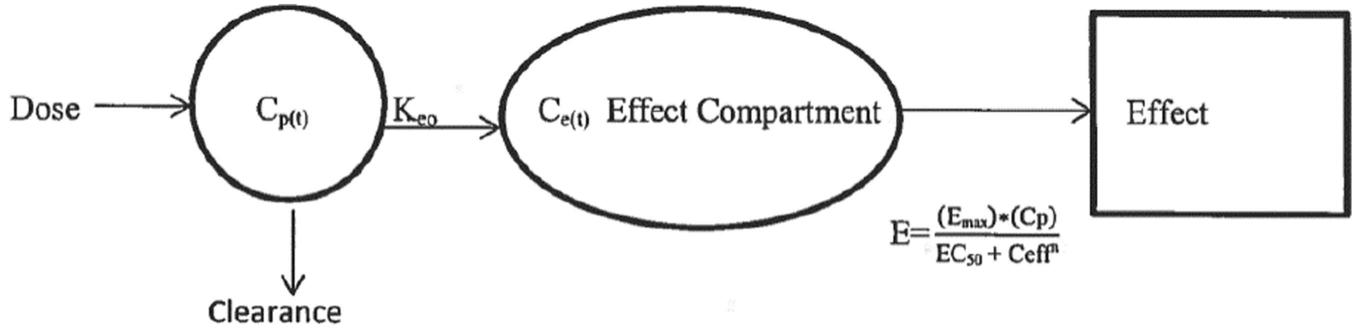

Figure 12.
Effect Compartment Model

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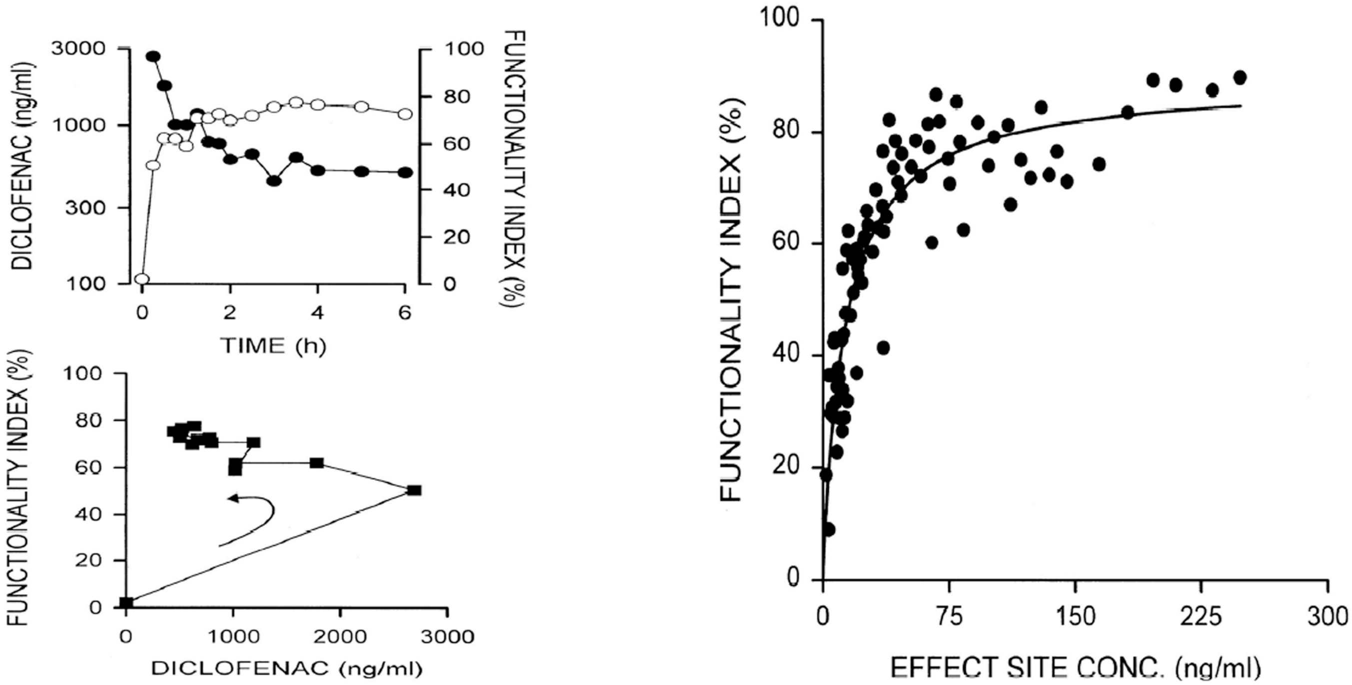

Figure 13.

(a) Relationship between the measured blood concentration of diclofenac and the observed anti-nociceptive effect expressed as FI recovery after oral administration of a 10 mg/kg sodium diclofenac dose to rats that were injected with uric acid in the right hind knee. **(b)** Relationship between the observed anti-nociceptive effect, measured as FI recovery, and calculated effect-compartment Diclofenac concentrations corresponding to PO administration of 0.56, 1, 1.8, 3.2, 5.6 and 10 mg/kg of sodium diclofenac. Reprinted by permission from American Society for Pharmacology and Experimental Therapeutics: The Journal of pharmacology and experimental therapeutics, [29], copyright 1997.

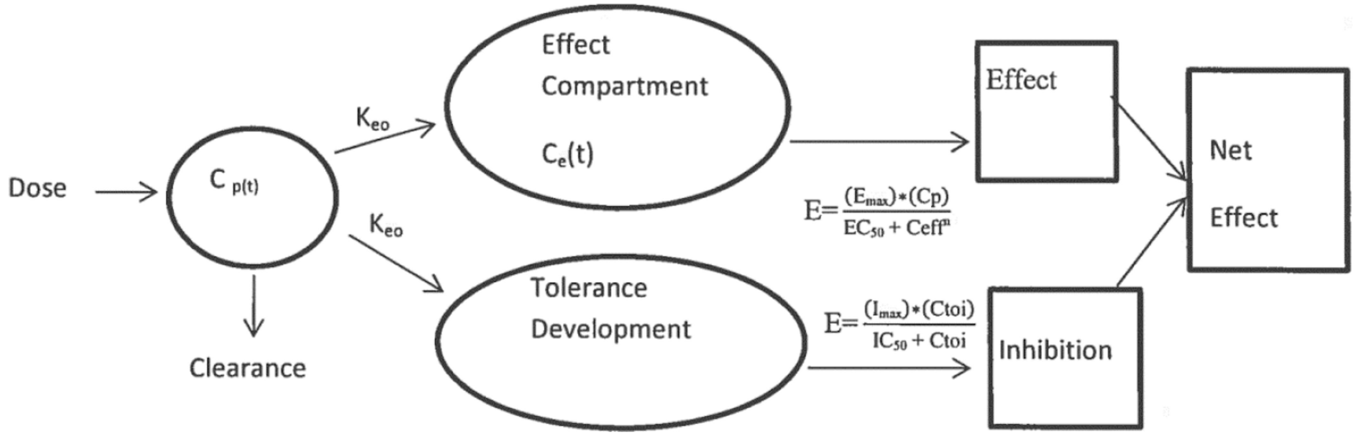

Figure 14.
Tolerance Model

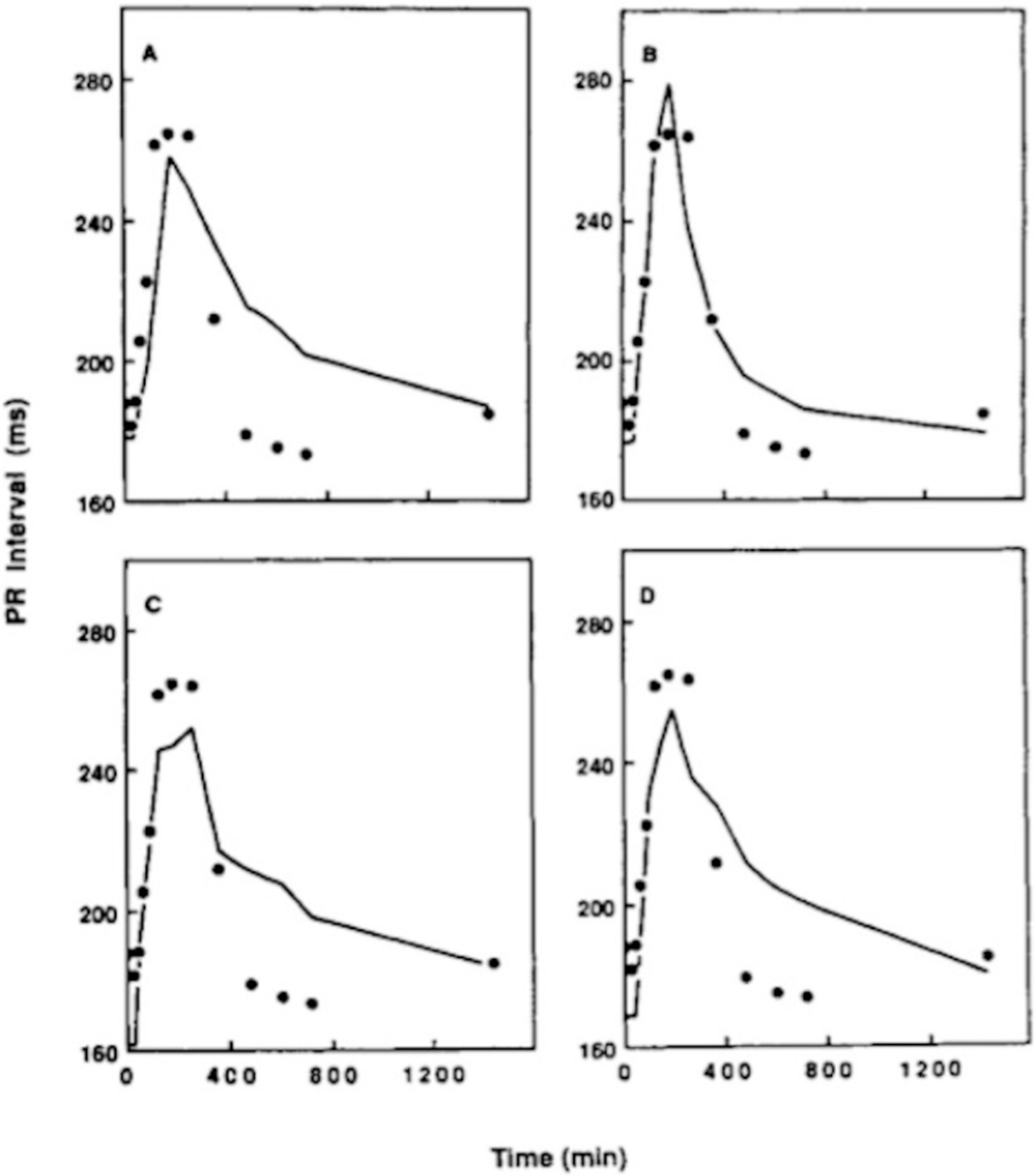

Figure 15.

Plots of PR interval versus time for subject 5 showing the results of pharmacodynamic fitting procedures. A, Fit to linear pharmacodynamic model assuming no tolerance. B, Fit to model of acute tolerance that incorporates the effect of a hypothetical antagonist. C, Fit to model of acute tolerance, assuming N-desmethyldiltiazem is an antagonist. D. Fit to model of acute tolerance, assuming desacetyldiltiazem is an antagonist. Reprinted by permission from Macmillan Publishers Ltd: Clinical pharmacology and therapeutics, [86], copyright 1989.

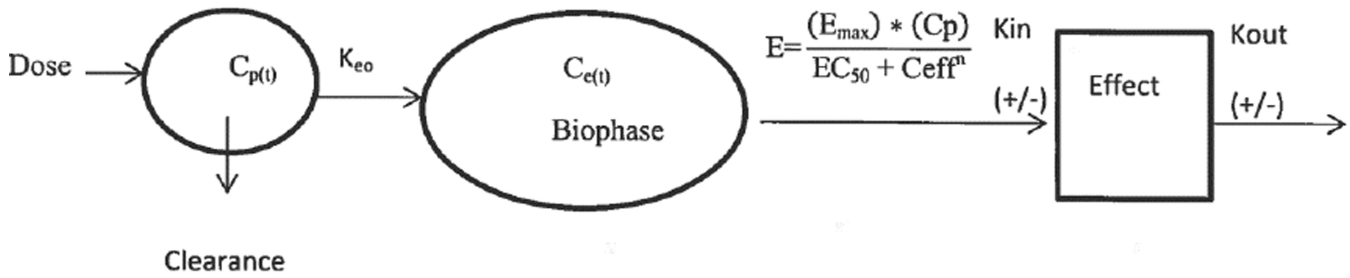

Figure 16.
Indirect Response Turnover Model

Table 1

Mechanistic Explanations for Hysteresis

Counter-clockwise Hysteresis	**Clockwise Hysteresis**
Sensitization (up regulation of receptors)	Tolerance (down regulation “desensitation” of receptors)
Input rate	Input rate
Distribution delay into the site of Effect	Disequilibrium between arterial and venous concentrations
Active agonist metabolite	Active antagonistic metabolite
Indirect effect(positive input or negative output)	Indirect effect (negative input or positive output)
Slow receptor kinetics	Feedback regulation
Time dependent protein binding	Time dependent protein binding
Racemic drugs and non-stereospecific assays	Racemic drugs and non-stereospecific assays

Table 2

Counter-clockwise Hysteresis

Drug name	Drug /Class (Indication)	Population / species studied (comorbidities)	Route of Administration	Proposed mechanism	Effect(s) measured	Site of drug concentration measure	Reference
Alpha-human atrial natriuretic peptide	Peptide drug	Rats	6–12 μg/kg iv infusion over 60 min	Site of action, for diuretic effect, must be in a tissue or site other than the blood vessels.	Diuretic effect (%)	Plasma concentration (ng/mL) α-hANP	[11]
Aripiprazole	Atypical antipsychotic	18 humans (healthy)	2, 5, 10, 30mg single po doses	Limited access to the site of action due to the brain-blood barrier and transporters molecules on the barrier	Dopamine receptor occupancy (%)	Plasma concentration (ng/mL) of aripiprazole	[12]
Astragaloside IV	Anti-inflammatory and immunoregulatory (Traditional Chinese Medicine)	Rats	20 mg/kg Astragaloside IV, Atractylenolide I 2.165 mg/kg and 116.9 mg/kg Prim-O-glucosylcimifugin via intragastric lavage	Disequilibrium between effect site and central compartment	Spleen cell growth rate	Plasma concentration (ng/mL)	[13]
(+/−) Atenolol	Beta-1 Selective Beta-Blocker	10 rats	Immediate release pellets 16 mg/kg po single dose	Disequilibrium between effect site and central compartment	Change in Systolic blood pressure (mmHg)	Atenolol concentration (μg/mL)	[14]*
Atracurium	Neuromuscular blocking agent	10 humans (critically ill with acute respiratory distress)	1 mg/kg iv bolus followed by 1mg/kg/hr for 72 hrs	Lag time between concentration and effect, effect may not begin until 80% of receptors are occupied	Train of four count as index of therapeutic effect	Plasma atracurium concentration (μg/mL)	[15]
Azithromycin	Macrolide antibiotic	Rats	40, 100 mg/kg/h iv over 90 min	Delayed distribution in the effect site, potassium channels on ventricular myocytes	Change in QT interval (msec)	Plasma concentration of azithromycin (μg/mL)	[16]
(+/−) Baclofen	Skeletal muscle relaxant	Mice	1–3 mg/kg intraperitoneally	2- compartment open model of effect	Antinociceptive effect (% MPE)	Baclofen blood concentration (μg/mL)	[17]
Befloxatone	Reversible and selective MAO inhibitor	12 humans (healthy)	5 mg po twice daily or 10 mg po once daily	Compartment effect or an indirect response	% of DHPG decrease from baseline	Plasma concentration of befloxatone (ng/ml)	[298]
Benidipine	Dihydropyridine calcium channel blocker	Rats	1 mg/kg po	Effect-compartment model	Change in blood pressure (%)	Plasma concentration of benidipine (ng/mL)	[18]
Bromocriptine	Dopamine agonist	Rats	2.5, 10 mg/kg ip	Equilibration delay between concentrations in the brain and concentration in plasma	Number of rotations (/15min)	Plasma bromocriptine concentration (ng/mL)	[19]
Bumetanide	Loop Diuretic	3 humans (healthy)	1 mg IR tablet po	Absorption rate	Urine flow rate (ml/h)	Plasma concentration of bumetanide (ng/ml)	[20]*
Bunazosin	Alpha-1 blocker	9 humans (renal insufficiency) 11 humans (healthy)	3 mg po (single dose)	Delay in the equilibration between the plasma concentration and concentration at the effect site	ΔSBP (mmHg) ΔDBP (mmHg) ΔHR (bpm)	Plasma bunazosin concentration (ng/mL)	[21]
(+/−) Buprenorphine	Opioid analgesic	4 Rats	8 μg/kg iv over 20 seconds	Kinetics of target site distribution and receptor association/dissociation kinetics	Change in latency in cerebellum, the rest of brain, and specific binding site (sec)	Concentration of buprenorphine (ng/mL)	[22]
(+/−) Candesartan	Angiotensin II receptor blocker	12 humans (healthy)	8 mg po	Distributional delay between the concentrations in plasma and effect site	Pharmacodynamics (areas under the effect time profile: DR-1)	Pharmacokinetics (concentration equivalents: nKi)	[22]
(+/−) Candesartan	Angiotensin II receptor blocker	12 humans (healthy)	4, 8, 16 mg po (single doses)	Slow off-rate of candesartan from the receptor site	Diastolic BP	Plasma concentration of candesartan (ng/mL)	[23]
Cibenzoline	Class I antiarrhythmic agent	6 humans (healthy)	100 mg iv over 20 minutes	Lag between drug concentration and effect	QRS prolongation (% increase from baseline)	Cibenzoline plasma concentration (ng/mL)	[24]
Clarithromycin	Macrolide antibiotic	Rats	6.6, 21.6, 43.2 mg/kg/h iv over 90 min	Delayed distribution in the effect site, potassium channels on ventricular myocytes	Change in QT interval (msec)	Plasma concentration of clarithromycin (μg/mL)	[16]
Clonidine	Alpha2- adrenergic agonist	10 humans (healthy)	200 μg po	Delay between drug receptor binding and observed effects	Rm threshold (mA) MAP (mmHg)	Clonidine concentration (ng/mL)	[25]
Cocaine	Drug of abuse	7 humans	Smoked doses (10, 20, and 40 mg)	Lag between blood concentration and effect due to drug being transported through tissues in the effect compartment	Heart rate mean change (BPM) and pupil diameter mean changr (mm)	Plasma cocaine concentration (ng/ml)	[299]*

Drug name	Drug /Class (Indication)	Population / species studied (comorbidities)	Route of Administration	Proposed mechanism	Effect(s) measured	Site of drug concentration measure	Reference
Cocaine	Drug of abuse	9 humans (healthy)	Smoked dose (12.5, 25, and 50 mg) and i.v. doses (8, 16, 32 mg)	Rapid distribution of drug to the brain	Mean change in systolic and diastolic pressure (BPM) and ratings of stimulated, high or drug liking	Arterial plasma cocaine concentration (ng/ml)	[300]*
Cyclosporin A	Calcineurin Inhibitor Immunosuppressant	Rats	Sandimmune single injection 1 and 10mg/mL	Delay in distribution of the drug to effect site	Calcineurin inhibition (%)	Cyclosporin A concentration (ng/mL)	[26]
Cysteamine	Cysteine depleting agent	11 humans (nephropathic cystinosis)	Varied for each person, QID	Lag time between drug concentration and effect	White blood cell cysteine concentration (nmol ½ cysteine per mg protein)	Mean cysteamine concentration (μM)	[27]
D-amphetamine	Stimulant	22 rats	1.5 mg/kg D-amfetamine base IR	Delay of drug crossing the BBB and entering the striatal nerve terminals before releassing dopamine to produce the functional outcome	Striatal dopamine concentration (% of baseline) and Locomotor activity	Plasma amphetamine (ng/mL)	[28]*
[D-Penicillamine^{2,5}] en kephalin (DPDPE)	Opioid pentapeptide	Mice [FVB and mdr1a(2/2)]	10 mg/kg i.v.	The site of action in both strains was pharmacologically distinct from the central compartment	Antinociception (% MPR)	Dose normalized blood concentration (ng/ml per mg/kg)	[329]
Diazepam	Benzodiazepine	12 humans (healthy)	0.1 mg/kg and 0.2 mg/kg iv infusion (four separate occasions)	None described	Digital Symbol Substitution Test Score (number correct)	Plasma concentration of Diazepam (ng/ml)	[301]*
Diazepam	Benzodiazepine	3 humans (healthy)	15, 30, and 50 mg iv infusion at 10 mg/min	Disequilibrium between plasma and effect compartment	EEG drug effect (uV)	Plasma concentration of Diazepam (ng/ml)	[302]*
Diclofenac	Non-steroidal anti-inflammatory agent	30 rats	0.56, 1, 1.8, 3.2, 5.6, 10 mg/kg po	Slow equilibrium kinetics between diclofenac concentration in the central and effect compartments	Functionality index (%) (observed antinociceptive effect)	Blood concentration of diclofenac (ng/mL)	[29]
Diclofenac	Non-steroidal anti-inflammatory agent	20 humans (healthy)	50 mg and 100 mg Diclofenac-Na effervescent po	Time delay between the plasma concentrations of diclofenac and the effect versus time profiles	Analgesic effects using an experimental human pain model	Blood concentration of diclofenac (ng/mL)	[30]
Dofetilide	Antiarrhythmic agent	10 humans (healthy)	0.5 mg iv infusion over 30 min	Delay of drug penetration to the active site	QTc (ms)	Plasma concentration of dofetilide (ng/mL)	[31]
Eptastigmine	Acetyl-cholinesterase inhibitor	8 humans (healthy)	10, 20, 30mg po single dose	Formation of active metabolites and/or a slow association to and dissociation from the enzyme in red blood cells	Average plasma cholinesterase inhibition (%) Average RBC cholinesterase inhibition (%)	Average eptastigmine plasma level (ng/mL)	[32]
Escitalopram	Selective serotonin reuptake inhibitor	Mice	1 mg/kg single sub cut injection	Slow permeation over the blood-brain barrier	5-HTP Score	Escitalopram serum concentration (ng/mL)	[33]
Fantofarone	Calcium antagonist	6 humans (healthy)	100 mg and 300 mg po single dose	Effect compartment	PR Interval duration (ms) and Brachial Artery Flow (%)	Fantofarone SR 33671 Concentration (ng/ml)	[303]
(+/−) Felodipine	Calcium channel blocker	18 humans (4 healthy and 14 with impared renal function)	10 mg felodipine orally as steady state	Slow equilibrium between drug and receptor	Effect of Diastolic Blood Pressure (% reduction)	Plasma Concentration (nmol/l)	[34]
Fenretinide	Synthetic retinoid	50 children with neuroblastoma	100–4000 mg/m^2 po daily for 28 days	Presence of an effect compartment (possibly the liver)	Percentage reduction in retinol levels	Fenretinide (μM)	[35]
(+/−) Fexofenadine	H_1-antagonist	6 humans (healthy)	60 mg po tablet	Equilibration delay between the plasma concentration and effect site compartment	QTc interval in milliseconds	Fexofenadine concentration (ng/mL)	[36]
(+/−) Flurbiprofen	Non-steroidal anti-inflammatory agent	8 rats	10 mg/kg gastric intubation sustained release granules	Intestinal permeability changes by the sustained release formulation is not only due to systemic availability of the NSAID since it may be also resulted from continuous exposure of the intestinal tract to the drug	Change in intestinal permeability	S-Flurbiprofen concentration (μg/mL)	[37]
Furosemide	Loop diuretic	26 humans (healthy)	60 mg tablet po	Delay of effect	Diuresis (mL/min)	Furosemide excretion rate (μg/min)	[38]*
Furosemide	Loop diuretic	4 humans (healthy)	40 mg IR tablet po	Inhibition of the reabsorption of sodium and chloride at Loop of Henle was delayed due to fast absorption resulting in rapid excretion	Diuretic rate (ml/h)	Excretion rate of furosemide (mg/h)	[39]*

Drug name	Drug /Class (Indication)	Population / species studied (comorbidities)	Route of Administration	Proposed mechanism	Effect(s) measured	Site of drug concentration measure	Reference
Furosemide	Loop diuretic	11 humans, Middle Eastern Arabs (healthy) 12 humans, Asian (healthy)	40 mg tab po single dose	Delay in drug action/delay in equilibrium	Furosemide excretion rate	Plasma concentration of furosemide	[40]*
Furosemide	Loop diuretic	8 humans (healthy)	10 mg iv infusion over 10 minutes	Delay between excretion rate and the diuretic effect	Diuresis (mL/min) and Natiuresis (mmol/min)	Furosemide excretion rate (μg/min)	[41]*
Indomethacin	Non-steroidal anti-inflammatory agent	6 rats	10 and 20 mg/kg po doses	Effect-compartment model	Mean urinary ^{51}Cr-EDTA excretion	Indomethacin plasma concentration (mg/L)	[42]
Insulin (Regular and NPH)	Peptide hormone	16 humans (healthy)	10 Units regular insulin given subcutaneously or 25 Units NPH given subcutaneously as single dose	Delay between serum insulin concentrations and effect	Glucose Infusion Rate (mmol/min)	Insulin serum concentration (pmol/L)	[304]
(+/−) Irbesartan	Angiotensin II Receptor Blocker	36 humans	150 or 300 mg tablet po single dose	Vasodilatory effect of irbesartan on the AT1 receptor (effect compartment model)	DBP (mmHg) SBP (mmHg)	Plasma drug concentration of irbesartan (μg/mL)	[43]
(+/−) Irbesartan	Angiotensin II Receptor Blocker	10 dogs	2 mg/kg or 5 mg/kg po dose (2 treatments 3 weeks apart)	Time needed for the drug distribution from the central compartment to AT1 receptors	Inhibitory effect on SBP (mmHg)	Plasma drug concentration of irbesartan (ng/mL)	[305]*
Isosorbide dinitrate	Antianginal agent	11 humans (coronary artery disease)	2 mg iv over 15 min, 5 mg sublingual tablet	Changes in blood pressure response lag behind changes in plasma Isosorbide dinitrate concentration	Percent change in standing systolic pressure	Plasma isosorbide dinitrate concentration (ng/mL)	[44]
(+/−) Isradipine	Dihydropyridine Calcium channel blocker	10 humans (healthy)	1 mg iv infusion 5 mg po solution 5 mg tablet 10 mg slow release formulation	Possible active metabolite	DBP fall (mmHg)	Concentration of isradipine (ng/mL)	[45]
(+/−) Itraconazole	Antifungal agent	Rats	5 & 40 mg/kg 5 min infusion	Factors other than itraconazole determine the time course for the inhibition of CYP3A	Hepatic availability	Itraconazole concentration (μM)	[46]
Lafutidine	H_2-receptor antagonist	5 humans (healthy)	10 mg po tablet	Equilibration delay between the plasma concentration and effect site	Δ pH after postprandial dose	Lafutidine plasma concentration (ng/mL)	[47]
Levosimendan	Calcium sensitizer	29 humans (congestive heart failure)	0.2 μg/kg/min 6 hr continuous infusion or 2 mg single po dose	Delay of drug distribution to its cardiac site of action	QS2i mean change (ms) sBP mean change (mmHg) dBP mean change (mmHg) HR mean changes (bpm)	Levosimendan (ng/mL)	[48]
Levosimendan	Calcium sensitizer	10 humans (healthy)	2 mg iv, tablet, capsule, SR tablet (single doses)	Takes time for the drug to distribute from plasma to its cardiac site of action	Δ QS2i (ms)	Plasma concentrations of levosimendan	[49]
Lignocaine (Lidocaine)	Anesthetic	5 sheep	50 mg, 75 mg and 100mg iv bolus	Lack of pseudo equilibrium between the drug concentrations in the blood and at the receptor sites responsible for drug action in the myocardium	Percentage decreases of myocardial contractility	Atrial lignocaine concentrations (μg/mL) in arterial blood and coronary sinus blood	[50]
Lisdexamfetamine	Stimulant	22 rats	1.5 mg/kg ip D-amphetamine base 5 mg/kg ip D-amphetamine base	None described	Striatal dopamine concentration (% of baseline) and locomotor activity	Plasma amphetamine (ng/mL) Dopamine concentration in the striatum (% of baseline)	[28]*
(+/−) Lorazepam	Benzodiazepine	6 humans (healthy)	0.057 mg/kg solution single oral dose	The site of action of lorazepam is kinetically distinguishable from the plasma compartment and there is a distinct time lag between changes in plasma concentration and changes in CNS effects	Subcritical tracking, sway open and digit symbol substitution	Plasma lorazepam concentration (ng/mL)	[51]
(+/−) Lorazepam	Benzodiazepine	9 humans (healthy)	2 mg bolus iv loading dose followed by a 2 μg/kg/hr infusion for 4 hrs	Delay in equilibration of lorazepam between plasma and the site of pharmacodynamics action in the brain	Percent beta EEG amplitude (change over baseline)	Plasma lorazepam concentration (ng/mL)	[52]
Losartan	Angiotensin II receptor blocker	12 humans (healthy)	50 mg po	Distributional delay between the concentrations in plasma and effect site	Pharmacodynamics (areas under the effect time profile: DR-1)	Pharmacokinetics (concentration equivalents: nKi)	[22]
(+/−) Meperidine	Opioid analgesic	Sheep	100 mg iv dose over 1 second	None described	Contractility (% reduction)	Concentrations of meperidine in myocardium and coronary sinus blood (mg/L)	[53]*
Metformin	Biguanide anti-hyperglycemic	22 humans (healthy)	500 mg po	Time delay between the change in plasma concentration and the drug effects	Change % for baseline in plasma glucose concentration	Plasma concentration of metformin (μg/mL)	[54]

Drug name	Drug /Class (Indication)	Population / species studied (comorbidities)	Route of Administration	Proposed mechanism	Effect(s) measured	Site of drug concentration measure	Reference
Metocurine	Neuromuscular blocking agent	15 dogs 5 pigs	Brief, constant rate infusion	Equilibration delay between drug concentration in the plasma and drug concentration at the site of effect	% NM blockade	Plasma metocurine (μg/mL)	[55]
Midazolam	Benzodiazepine	8 humans (healthy)	0.1 mg/kg constant rate iv infusion for 1 min	Equilibration effect-site delay	Change in %SB	Plasma midazolam concentration	[52]
Midazolam	Benzodiazepine	12 humans (healthy)	0.03 mg/kg and 0.07 mg/kg iv infusion (four separate occasions)	Lag time to onset of peak effect	Digital Symbol Substitution Test Score (number correct)	Plasma concentration of Midazolam (ng/ml)	[301]
Midazolam	Benzodiazepine	3 humans (healthy)	7.5, 15, and 25 mg iv infusion at 5 mg/min	Disequilibrium between plasma and effect compartment	EEG drug effect (uV)	Plasma concentration of Midazolam (ng/ml)	[302]
Molsidomine	Vasodialator	11 humans (CAD)	4 mg po (single dose)	Active metabolite	Decrease in end-diastolic diameter	Plasma concentration of molsidomine (μg/mL)	[56]
(+/−) Morphine	Opioid analgesic	Rats	2.5 mg/kg Intraperitoneal 2.5 mg/kg Nose drops	Direct nose-to-CNS drug transport mechanisim	Analgesic effect (%MPE)	Morphine (ng/ml)	[57]*
(+/−) Morphine	Opioid analgesic	Rats	14.0 mmol/kg morphine	Delay of polar morphine crossing the BBB	% Anti-nociceptive response (using tail flick method)	Plasma morphine (μmol/L) and Brain morphine (nmol/g),	[58]*
(+/−) Morphine	Opioid analgesic	Rats	15 mg/kg morphine through intragastric administration (single dose)	Disequilibrium between biophase and plasma compartments	%MPE on MPR (mechanical pain response)	Concentration of blood morphine (μg/L), concentration of CSF morphine (μg/L), both conjugated and unconjugated	[59]*
Morphine	Opioid analgesic	Rats	10 minute i.v. infusion at 4 mg/kg	Effect compartment	EEG amplitude 0.5–4.5 Hz (μV)	Morphine blood concentration (ng/ml)	[328]*
Naproxen	Non-steroidal anti-inflammatory agent	Rats (induced hepatitis)	6 mg/kg po (single dose)	Slow transport of naproxen from circulation to its site of action	Protection (%)	Plasma concentration of naproxen (μg/mL)	[60]
Nitroglycerin	Vasodilator	6 humans (healthy)	10, 20, 40 μg/min iv infusions	End product inhibition or saturable binding of nitroglycerin to blood vessels	Nitroglycerin Css (ng/mL)	Infusion rate (μg/min)	[61]
Nitroglycerin	Vasodilator	4 dogs	10, 20, 50, 70 μg/min iv infusion	Active metabolites	Systolic blood pressure decreases (mmHg)	Nitroglycerin concentration (ng/mL)	[62]
NPH insulin	Intermediate acting insulin	6 humans (healthy)	25 U single subcutaneous dose	Delay between serum insulin concentrations and effect	Glucose infusion rate (mmol/min)	Measured serum concentration (pmol/L)	[63]
Pancuronium	Neuromuscular blocking agent	11 humans (undergoing elective surgery)	2 or 4 μg/kg/min by i.v. infusion	Effect compartment	Degree of neuromuscular paralysis (%)	Plasma concentration (μg/mL)	[307]*
Paroxetine	Selective serotonin reuptake inhibitor	Mice	0.27 mg/kg single sub cut injection	Slow permeation over the blood-brain barrier	5-HTP Score	Paroxetine serum concentration (ng/mL)	[33]
(+/−) Penbutolol	Beta-blocker	7 humans (healthy)	40 mg po film-coated tablets	Active metabolite formation	Standardized antagonist concentration in plasma (I_{AN}/K_{IAN})	Standardized penbutolol concentration in plasma (C_{pen}/K_{ip})	[64]
Perindoprilat	Perindopril (ACEI) active metabolite	10 humans (CHF)	4 mg po (single dose)	Effect compartment	Plasma converting enzyme activity (PCEA) and brachial vascular resistance (BVR)	Plasma concentrations of perindoprilat (ng/ml)	[310]
Pimobendan	Vasodilator	8 humans (healthy)	7.5 mg po 5 mg iv	Effect-compartment model	% of maximal decrease in LVESD	Pimobendan in plasma (ng/mL)	[65]
Pinacidil	Vasodilator	12 humans (healthy)	25 mg tablet or capsule po once daily for 1 week	Time lag to equilibrium	Mean HR (beats/min) Mean ΔHR (beats/min) Mean DBP (mm Hg) Mean ΔDBO (mm Hg)	Mean extrapolated CP (ng/mL)	[66]
Pregabalin	Analgesic/anticonvulsant	Rats	6mg/kg po	Not active metabolite	% protection MES	Pregabalin ECF concentration (ng/mL)	[67]
Propofol	General anesthetic	Sheep	100 mg iv infusion over 2 min	Disequilibrium due to organ drug uptake following rapid drug administration.	Depth of anesthesia (% baseline) CBF (mL/min)	Arterial concentrations (μg/mL) Sagittal sinus concentrations (μg/mL) Arterial concentrations (μg/mL)	[68]*
(+/−) Propranolol	Beta-blocker	6 humans	3 × 20 mg PL po tablet or 60 mg LA po tablet	Two distinct beta-adrenoceptor binding sites on the surface membrane which differ in lipophilic characteristics	Beta-blocking activity (%R)	Plasma propranolol concentration (μg/mL)	[304]*

Drug name	Drug /Class (Indication)	Population / species studied (comorbidities)	Route of Administration	Proposed mechanism	Effect(s) measured	Site of drug concentration measure	Reference
(+/−) Quinine	Antimalarial	6 humans (healthy)	15 mg/kg po dose and 15 mg/kg iv infusion administered over 6 hours	None described	Hearing threshold shift (dB)	Quinine plasma concentration (μmol/L)	[309]
(R)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-pyridin-2-ylamine (PF02341066)	ATP-competitive small molecule inhibitor of cMet receptor tyrosine kinase	Mice (GTL16 gastric carcinoma or U87MG glioblastoma xenografts)	Oral administration of 8.5, 17, and 34 mg/kg; 3.13, 6.25, 12.5, 25, and 50 mg/kg; and 3.13, 6.25, 12.5, 25, and 50 mg/kg	Slow distribution to tumors	cMet phosphorylation response	Plasma concentration of PF02341066 (ng/ml)	[327]
Ranitidine	H_2-receptor antagonist	41 humans (renal impairment)	Single 50 mg and 25 mg iv doses	Effect compartment	Gastric pH	Serum ranitidine concentration (ng/ml)	[310]
Regular insulin	Peptide hormone	10 humans (healthy)	10 U single subcutaneous dose	Delay between serum insulin concentrations and effect	Glucose infusion rate (mmol/min)	Measured serum concentration (pmol/L)	[63]
Remifentanil	Opioid analgesic	10 humans (healthy)	3 μg/kg/min for 10 minutes	Equilibrium delay between arterial opioid concentration and concentration at the site of drug effect (brain)	Spectral Edge (Hz) (opioid effect)	Arterial remifentanil concentration (ng/mL)	[69]*
Risperidone	Antipsychotic agent	9 humans (healthy)	1 mg po (single dose)	Drug moves from the plasma to the effect compartment after time delay	EEG effect	Plasma concentration of risperidone (ng/mL)	[70]
Roxithromycin	Macrolide antibiotic	Rats	20, 40 mg/kg/h iv over 90 min	Delayed distribution in the effect site, potassium channels on ventricular myocytes	Change in QT interval (msec)	Plasma concentration of roxithromycin (μg/mL)	[16]
Sertraline	Selective serotonin reuptake inhibitor	Mice	2.2 mg/kg single sub cut injection	Slow permeation over the blood-brain barrier	5-HTP Score	Sertraline serum concentration (ng/mL)	[33]
Sevoflurane	General anesthetic	21 Humans (healthy)	Inhalation initially at 1% then increased by 1% to a max of 8%. Then decrease to 1%	Delay of drug concentration at the effect site	QTc interval (m sec)	End-tidal sevoflurane concentration (%)	[71]
Sinemet	Anti-parkinson’s agent	11 humans (Parkinson’s)	Carbidopa 25mg/L-DOPA 100mg po	Takes time for L-DOPA to distribute to the central nervous system	Taps per 60 seconds	Levodopa (μg/mL)	[72]
Tacrolimus	Calcineurin Inhibitor	Rats	Prograf single injection 0.1 and 5mg/mL	Delay in distribution of the drug to effect site	Calcineurin inhibition (%)	Tacrolimus concentration (ng/mL)	[26]
Tacrolimus	Calcineurin inhibitor	5 guinea pigs	0.01 or 0.1 mg/hr/kg iv infusion	The delay in distribution from blood to the ventricle	Change in QTc (msec)	Plasma tacrolimus concentration (ng/mL) Whole blood tacrolimus (ng/mL)	[73]
Telmisartan	Angiotensin II receptor blocker	48 humans (healthy)	20, 40, 80mg po	Delay and longer persistence of effect than expected, slow dissociation from the receptor	Inhibition (%)	Plasma concentration of telmisartan (mg/L)	[74]
Terfentanil	Opioid analgesic (investigational)	14 humans (healthy)	4 μg /kg/min for a maximum of 30 minutes or until maximum EEG changes occurred (adjusted by investigators)	Effect compartment	Spectral edge (95%) Hz	Plasma terfentanil concentration (ng/ml)	[318]
Tesofensine active metabolite (M1)	serotonin–noradrenaline–dopamine reuptake inhibitor	228 mice	0.3 to 20 mg/kg iv and po	Distribution of the molecules between the plasma and the central nervous system	Inhibition (%)	Tesofinsine plasma concentration (ng/mL)	[75]
(+/−) Thiopental	General anesthetic Barbiturate	4 sheep	750 mg iv over 2 min	Presence of effect compartment	Maximum rate of change of left ventricular pressure (% reduction from baseline)	Thiopental concentrations of arterial (μg/mL) and coronary sinus (μg/mL)	[76]
Tinzaparin	Low molecular weight heparin	6 dogs	4 mg/kg sC	Delay in systemic availability	Anti-factor Xa activity (IU/mL) (biological effect)	Plasma concentration of heparin material	[77]
Triazolam	Benzodiazepine	10 humans (healthy)	1 mg solution po (single dose)	The site of action of triazolam is kinetically distinguishable from the plasma compartment and contains a distinct time lag between changes in the plasma concentration and changes in CNS effect	Subcritical tracking, body sway and digit symbol substitution	Plasma triazolam (ng/mL)	[78]
Trimoprostil	Prostaglandin E_2 analog	dogs	250μg po capsule 500μg po capsule 250μg po solution	Delay in equilibrium between plasma concentrations and concentrations at the site of action	Mean % inhibition of gastric acid secretion	Mean trimoprostil plasma concentrations (ng/mL)	[79]

Drug name	Drug /Class (Indication)	Population / species studied (comorbidities)	Route of Administration	Proposed mechanism	Effect(s) measured	Site of drug concentration measure	Reference
(+/−) Verapamil	Calcium channel blocker	22 humans (healthy)	Single dose i.v. infusion (0.15 – 0.22 mg/kg)	Time lag between plasma verapamil concentrations and maximal drug effect on AV conduction	Change in PR interval (ms)	Plasma verapamil concentration (ng/ml)	[311]
Zabiciprilat	Zabicipril (ACEI) active metabolite	6 humans (healthy)	0.5 and 2.5 mg po zabicipril	Effect compartment	Plasma converting enzyme activity (PCEA) and brachial/femoral artery flow (BAF, FAF ml/min)	Zabiciprilat plasma concentration (ng/ml)	[312]

+/− Indicates Racemic Drug with Enantiomers

* Indicates Drug listed in both Table 2 and 3

Table 3

Clockwise Hysteresis

Drug name	Drug Class (Indication)	Population / species studied (Comorbidities)	Route of Administration	Proposed mechanism(s)	Effect(s) measured	Site of drug concentration measure	Reference
Alprazolam	Benzodiazepine	21 humans (healthy)	10 mg SR po	Tolerance	Mean percentage of decrement in Digit-symbol substitution test scores (sedation scores)	Venous blood samples from antecubital vein Mean alprazolam concentration	[80]
Alprazolam	Benzodiazepine	24 humans (healthy)	2 mg po (two single doses 15 days apart)	Tolerance	Relative B-1 activity (%), relative alpha activity (%), total number of responses, correct number of responses, activity (mm), drowsiness (mm)	Alprazolam plasma concentration (ng/ml)	[81]
Amitriptyline	Tricyclic anti-depressant	24 humans (healthy)	75 mg po controlled drug delivery or IR tablets	Tolerance and distributional characteristics	Change in dry mouth from baseline (VAS), change in drowsiness from baseline (VAS)	Amitriptyline plasma concentration (ng/mL)	[82]
(+/−) Apomorphine	Non-selective Dopamine Agonist	10 humans (advanced Parkinson's disease with end of dose fluctuations)	0.5,1,2,4 mg subcut	Tolerance Redistribution from effect site	CURS (Columbia University Rating Scale)	Apomorphine (pMol/ml)	[83]
(+/−) Atenolol	Beta-1 Selective Beta-Blocker	10 rats	Sustained release pellets 16mg/kg po single dose	Tolerance induced by desensitization or production of regulatory substances	Change in Systolic blood pressure (mmHg)	Atenolol concentration (μg/mL)	[14]*
Befloxatone	Selective monoamine oxidase A inhibitor	12 humans (healthy)	5 mg capsules bid po or 10 mg capsules once daily po	Compartment effect or an indirect response	% of DHPG decrease from baseline	Befloxatone concentration (ng/ml)	[84]
Bumetanide	Loop Diuretic	3 humans (healthy)	1mg SR capsules po	Tolerance	Urine flow rate (ml/hr)	Plasma concentration of bumetanide (ng/ml), urinary excretion rate of bumetanide (μg/h)	[20]*
Bumetanide	Loop Diuretic	3 humans (healthy)	1 mg IR tablet po	Tolerance	Urine flow rate (ml/h)	Urinary excretion rate of bumetanide (μg/h)	[20]*
Cocaine	Anesthetic/Drug of abuse	7 humans	Smoked doses (10, 20, and 40 mg)	Tolerance (acute)	Mean change in systolic and diastolic pressure (mmHg)	Plasma cocaine concentration (ng/ml)	[299]*
Cocaine	Drug of abuse	9 humans (healthy)	Smoked dose (12.5, 25, and 50 mg) and i.v. doses (8, 16, 32 mg)	Rapid distribution of drug to the brain	Mean change in systolic and diastolic pressure (BPM) and ratings of stimulated, high or drug liking	Venous plasma cocaine concentration (ng/ml)	[300]*
Cyclohexylamine	Sympathomimetic amine	Rats	30 or 60 mg/kg iv infused over 20 min or 30, 60, or 120 mg/kg infused over 40 min	Tolerance (acute)	Mean Arterial Blood Pressure (mmHg)	Plasma Cyclohexylamine (μg/ml)	[323]
Cyclohexylamine	Sympathomimetic amine	Humans	5 mg/kg po single dose	Tolerance	Mean Arterial Blood Pressure (mmHg)	Plasma Cyclohexylamine (μg/ml)	[324]
D-amphetamine	Stimulant	22 rats	1.5 mg/kg D-amfetamine base IR	None described	Locomotor activity (min/15 min interval)	Dopamine concentration in the striatum (% of baseline)	[28]*
Diazepam	Benzodiazepine	17 humans (healthy)	0.28 mg/kg	Tolerance	Adjusted subcritical tracking (rms-cm) Adjusted digit symbol substitution (sec)	Diazepam plasma level × free fraction (ng/mL)	[85]*
Diltiazem	Non-dihydropyridine calcium channel blocker	6 humans (healthy)	120 mg po single dose (2×60 mg tablets)	Tolerance	PR change (msec)	Diltiazem concentration (ng/ml)	[86]
Diltiazem	Non-dihydropyridine calcium channel blocker	20 humans (healthy)	180 mg SR capsule with wax matrix 180 mg SR tablet	Tolerance	Changes in PQ interval (% of baseline)	Diltiazem plasma concentration (ng/ml)	[87]
Distigmine Bromide	Long acting acetyl-cholinesterase inhibitor	Rats	0.3, 1, 3 mg/kg po (single dose)	Time lag between arrival of distigmine at the site and the onset of its inhibitory effect.	AChE activity (%)	Plasma Concentration of distigmine (ng/ml)	[88]
Fentanyl	Opioid analgesic	Rats	15 μg/kg Nasal (pressurized olfactory delivery device)	Tolerance	Analgesic effect (%MPE)	Fentanyl (ng/ml)	[57]*
Furosemide	Loop diuretic	26 humans (healthy)	60 mg CR po (two different formulations)	Tolerance	Diuresis (mL/min)	Furosemide excretion rate (μg/min)	[38]*

Drug name	Drug Class (Indication)	Population / species studied (Comorbidities)	Route of Administration	Proposed mechanism(s)	Effect(s) measured	Site of drug concentration measure	Reference
Furosemide	Loop diuretic	8 humans (healthy)	10 mg iv infusion over 30, 100 and 300 minutes	Tolerance	Diuresis (mL/min) and Natiuresis (mmol/min)	Furosemide excretion rate (μg/min)	[41]*
Furosemide	Loop diuretic	4 humans (healthy)	40 mg SR tablet po	Tolerance	Diuretic rate (ml/h)	Excretion rate of furosemide (mg/h)	[39]*
Furosemide	Loop diuretic	11 humans, Middle Eastern Arabs (healthy) 12 humans, Asian (healthy)	40 mg tab po single dose	Tolerance	Chloride, sodium, calcium, magnesium and potassium excretion rates	Furosemide excretion rate (μg/hr)	[40]*
Furosemide	Loop diuretic	8 humans (healthy)	40 mg iv after breakfast 40 mg tablet po after breakfast	Tolerance	Urine flow rate (mL/min)	Furosemide excretion rate (μg/min)	[89]
Glutamate-oxaloacetate transaminase (GOT) Glutamate-pyruvate transaminase (GPT) enzymes	Enzymes that metabolize glutamate	46 rats	Single IV bolus injections of 0.03 or 0.06 mg/kg GOT 0.6 or 1.2 mg/kg GPT	None described	Blood glutamate (μM)	Serum GOT or GPT (mg/L)	[90]
Heparin	Anticoagulant	9 humans (healthy)	2000 IU continuous infusion over 40 min	Tolerance - may be caused by depletion of endothelial TFPI sources	Plasma concentration of TFPI (free and total) (ng ml^{-1}) TFPI production rate (μg min^{-1})	Anti-IIa activity (U ml^{-1}), a measure of heparin concentration	[91]
(+/−) Irbesartan	Angiotensin II receptor blocker	24 humans (mild to moderate hypertension)	300 mg po once daily for 4 weeks	Central-effect compartment Receptor antagonism	Seated diastolic blood pressure	Mean irbesartan concentration (ng/ml)	[92]*
(+/−) Meperidine	Opioid analgesic	Sheep	100 mg iv dose over 1 second	Tolerance	Contractility (% reduction)	Concentrations of meperidine in myocardium and coronary sinus blood (mg/L)	[53]*
(+/−) Methylphenidate	Central Nervous System Stimulant	4 rats	2, 5, 10 mg/kg iv (three doses)	Tolerance or Desensitization	Dopamine ratio to basal	Methylphenidate concentration in dialysate (ng/ml)	[93]
Metolazone	Thiazide-related diuretic	5 humans (renal transplant patients) 5 humans (creatinine clearance	5 mg	Tolerance to diuretic effect	Sodium Excretion rate (meq/min)	Urinary metolazone excretion rate (ng/min)	[94]
(+/−) Morphine	Opioid analgesic	Rats	2.5 mg/kg Nasal (pressurized olfactory delivery device)	Tolerance	Analgesic effect (%MPE)	Morphine (ng/ml)	[57]*
(+/−) Morphine	Opioid analgesic	280 rats	15 mg/kg through intragastric administration (single dose)	Tolerance due to drug induced desensitization of receptors or counter regulatory substances	% MPE on TPR (thermal pain response)	Concentration of blood morphine (μg/L), and concentration of CSF morphine (μg/L), both conjugated and unconjugated	[59]*
Nefopam	Non-opioid analgesic	24 humans (healthy)	20 mg po and iv (single doses)	None described	Visual analog scale drowsy (mm)	Nefopam plasma concentration (nM), desmethyl-nefopam plasma concentration (nM)	[95]
(+/−) Nicotine	Stimulant	8 humans (healthy)	2.5 μg/kg/min iv for 30 min, 120 min, and 210 min	Tolerance	Heart rate (BPM)	Blood nicotine concentration (ng/ml)	[315]
Pancuronium	Neuromuscular blocking agent	5 humans (healthy)	4 mg iv	Effect compartment	% twitch depression	Pancuronium concentration (nmol/L)	[316]*
Piritramide	Synthetic opioid analgesic	24 humans (post-abdominal surgery)	7 μg kg^{-1} min^{-1} up to maximum 0.2 mg/kg	Equilibration delay of piritramide between plasma concentration and effect site	Pain intensity VAS measured (0–100) Pain intensity VAS predicted (0–100)	Piritramide concentration measured (μg/L) Piritramide concentration measured (μg/L)	[96]
Propofol	General Anesthetic	18 rats	150 mg/kg·h	Delay of equilibrium of blood and effect site	Electroenceph alographic amplitude	Propofol blood concentration	[97]*
Propofol	General Anesthetic	Rats	30 mg/kg in 5 min iv bolus infusion and 150 mg/kg iv continuous infusion (5 hrs) -both doses tested as 1% in Intralipid® 10%, 1% in Lipofundin® and 6% in Lipofundin® emulsions	Hypothetical multiple compartments	EEG effects	Propofol blood concentration (μg/ml)	[98]*
(+/−) Propranolol	Beta-blocker	8 humans (detoxified alcoholics)	80 mg po	Acute tolerance	Degree of beta-blockade, changes in heart rate (%)	Propranolol plasma concentration (ng/ml)	[317]*

Drug name	Drug Class (Indication)	Population / species studied (Comorbidities)	Route of Administration	Proposed mechanism(s)	Effect(s) measured	Site of drug concentration measure	Reference
Remifentanil	Synthetic opioid analgesic	10 humans (healthy)	3 μg/kg/min for 10 minutes	Equilibration between arterial drug concentration and the effect site occurs more rapidly than equilibrium between arterial drug concentration and venous drug concentration	Spectral edge (Hz) (opioid effect)	Venous remifentanil concentration (ng/mL)	[69]*
Scopolamine	Anticholinergic	90 humans (healthy)	0.5 mg iv infusion over 15 min.	Delayed distribution to effect compartment	Saccadic peak velocity (°s^{-1}) VAS alertness (mm)	Plasma scopolamine concentration (pg ml^{-1})	[99]
Sodium dichloroacetate	Acetic acid analogue	37 humans (healthy)	30 mg/kg, 60 mg/kg or 100 mg/kg iv infusions over 30 min	1) Inhibition of PDH-kinase could be reversible at low concentrations of DCA, becoming irreversible at high concentration 2) PDH-kinase binding of DCA may be more rapid than dissociation 3) There may be Substantial redundancy in the amounts of DCA bound compared with that needed for maximal effect, or 4) A combination of these fairly common pharmacological phenomena	Serum lactate concentration (mM)	Serum Sodium dichloroacetate concentration (μg/mL)	[100]
Spiraprilat	Active metabolite of spirapril (ACEI)	8 humans (CHF)	6 mg po of spirapril	None described	Pulmonary capillary wedge pressure (mmHg)	Spiraprilat plasma concentration (ng/ml)	[330]
(+/−) Temazepam	Benzodiazepine	11 humans (end-stage renal disease)	30 mg capsule po (two single doses)	Tolerance- discrepancy between plasma t1/2 and binding affinity	Sedation score NRSS Nurse rated sedation score (range 0- wide awake to 4-sleeping soundly, not awakened by blood sampling)	Temazepam concentration (ng/ml)	[101]
(+/−) Zopiclone	Short-acting hypnotic	10 humans (healthy)	7.5 mg po single dose	Tolerance or pseudo-tolerance	Saccadic peak velocity and Digital symbol substitution test (sedation scores)	Blood sample from forearm vein zopiclone (ng/ml)	[102]

+/− Indicates Racemic Drug with Enantiomers

* Indicates Drug listed in both Table 2 and 3