CHAPTER 3

CHRONOPHARMACOKINETICS

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“An inch of time is an inch of gold. But an inch of gold can’t buy an inch of

time.... With time and patience the mulberry leaf becomes a silk gown.”

— Chinese Proverb

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3.1 INTRODUCTION

Novel drug delivery systems have recently been developed in order to better
deriver drugs. These procedures involve and depend on pharmacokinetics
principles. Compared to “classical” drug delivery, they allow one to “delay”
the moment of administration of the drug. According to the existence of
biological rhythms and data from chronopharmacology, it is of particular
importance to take into account the hour of administration [1–3]. This
naturally leads to chronopharmacokinetics or chronokinetics, which studies
the influence of the time of administration of a drug on its pharmacokinetics (e.g., absorption, distribution, metabolism, and elimination) [4–11]. Thus knowledge of chronobiology may be used in order to optimize efficacy and safety of novel drug delivery systems, which constitutes chronopharmaceutics [12].

For several years, chronokinetic studies have been reported for many drugs both to partly explain chronopharmacodynamic phenomena and to demonstrate that the time of administration of a drug is a possible factor of variation of its kinetics. Many chronokinetic studies have been reviewed elsewhere [1–11], describing kinetic changes according to several periodicities, for example, time of day (circadian) as well as day of the month (infradian, menstrual): the present chapter only focuses on circadian time-dependent changes in kinetics.

More than simply describing chronokinetics, the aim of this chapter is to define and present principles, methods, and applications of chronopharmacokinetics in order to better understand the influence of biological rhythms on drug delivery systems and to evaluate how chronopharmacokinetics knowledge can contribute to the rational design and evaluation of chronopharmaceutical drug delivery systems [12].

### 3.2 PRINCIPLES OF CHRONOPHARMACOKINETICS

“To produce its characteristic effects, a drug must be present in appropriate concentration at its sites of action” [13]. Thus after introduction into the organism, a drug is absorbed, distributed (most frequently by protein binding) in order to diffuse into tissues and act on specific receptors to produce its pharmacological effects, and then is metabolized and eliminated. This “classical” scheme may be modified according to the existence of biological rhythms: it is now well established that the fate of the drug in the organism depends on its moment of administration: this constitutes chronopharmacokinetics (or chronokinetics), which postulates that the different steps in pharmacokinetics (e.g., absorption, distribution, metabolism, and elimination) are influenced by different physiological functions of the body which may vary with time of day (Figure 3.1). Thus pharmacokinetic parameters characterizing bioavailability, distribution, and elimination, which are conventionally considered to be constant in time, are circadian time dependent [10]. Chronokinetic studies have been reported for many drugs in order to partly explain chronopharmacodynamic phenomena and to demonstrate that the time of administration of a drug is a possible factor of variation of its kinetics. Many chronokinetic studies have been reviewed elsewhere [1–8].

As an illustrative example, chronopharmacokinetics of local anesthetics have been reported [14–18]: the different studies have shown that local anesthetic agents, such as lidocaine and bupivacaine, showed a two times higher peak drug concentration ($C_{\text{max}}$) and shorter time to peak concentration ($T_{\text{max}}$) after dosing at 2200h in rodents (middle of the active period) compared
Figure 3.2 illustrates the chronopharmacokinetics of bupivacaine in mice according to the hour of administration (1000, 1600, 2200 or 0400h). In humans chronokinetic differences were also demonstrated, with higher plasma levels documented after dosing in the afternoon (middle of the active period), which agree well with the opposite synchronization between humans and rodents [18].

Table 3.1 represents a list of drugs that show chronokinetic changes. As representative examples of chronokinetic studies, Table 3.2 summarizes the main chronokinetic changes of nonsteroidal anti-inflammatory drugs in humans [19–33].

From these studies it appears that, in humans, (1) bioavailability of many drugs taken orally is higher when the drug is taken in the morning (e.g., theophylline, salicylates, benzodiazepines, digoxin, nonsteroidal anti-inflammatory drugs); (2) temporal variations are more often observed and marked for liposoluble compounds; (3) sustained released forms decrease chronokinetics; and (4) the route of administration may be involved in a chronokinetic change.

3.2.1 Biological Rhythms Involvement in Kinetics of Drugs

Many biological factors are involved in drug kinetics: for example, gastric emptying, gastric pH, gastrointestinal motility, cutaneous permeability, posture, blood flow, tissue perfusion, plasma protein binding, metabolizing enzyme
activity, renal perfusion, glomerular filtration, and urinary pH (Figure 3.3). As previously mentioned, many of these factors may be circadian time dependent (as well as ultradian or infradian) and thus may be involved in the different steps of the fate of the drug in the organism, leading to chronopharmacokinetics.

### 3.2.2 Mechanisms Involved in Chronokinetics

Possible mechanisms involved in such chronopharmacokinetic variations may be illustrated at different steps, that is, resorption, distribution, metabolism, and elimination of the drug.

**Temporal Variations in Drug Absorption** The oral route is the most often used route of drug administration. Among the different mechanisms by which a drug may be absorbed (e.g., passive or facilitated diffusion, active transport), passive diffusion is the most important process. Many factors may have pronounced effects on drug absorption and the variability of absorption processes: the physicochemical properties of the drug (lipophilicity...
### Table 3.1. Some of the Drugs that Show Chronokinetics in Humans

<table>
<thead>
<tr>
<th>Analgesic and Anti-inflammatory</th>
<th>Antibiotic and Antiinfectious</th>
<th>Anticancer</th>
<th>Cardiovascular</th>
<th>Nervous System</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Amikacin</td>
<td>Busulfan</td>
<td>Atenolol</td>
<td>Amitriptyline</td>
<td>Bezafibrate</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Cefodizime</td>
<td>Carboplatin</td>
<td>Digoxin</td>
<td>Carbamazepine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>Ciprofloxacin</td>
<td>Cisplatin</td>
<td>Diltiazem</td>
<td>Diazepam</td>
<td>Ferrous sulfate</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Gentamycin</td>
<td>Doxorubicin</td>
<td>Enalapril</td>
<td>Lithium</td>
<td>Mequitazine</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Isepicin</td>
<td>5-Fluorouracil</td>
<td>Isosorbide dinitrate</td>
<td>Lorazepam</td>
<td>5-Methoxyxpsoralen</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Nelfinavir</td>
<td>Folinic acid</td>
<td>Dipyridamole</td>
<td>Midazolam</td>
<td>Nicotin</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Netilmicin</td>
<td>Irinotecan</td>
<td>Methylxigoxin</td>
<td>Nortryptiline</td>
<td>Nizatidin</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Rifampicin</td>
<td>Methotrexate</td>
<td>Nifedipine</td>
<td>Oxcarbazepine</td>
<td>Phenylpropanolamine</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Sulfamethoxazole</td>
<td>Oxaliplatin</td>
<td>Nitrendipine</td>
<td>Sertraline</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Sulfanilamide</td>
<td>Vindesine</td>
<td>Pentoxifyline</td>
<td>Sumatriptan</td>
<td>Terbutaline</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Sulfasymazine</td>
<td></td>
<td>Propanolol</td>
<td>Trazodone</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>Vancomycin</td>
<td></td>
<td>Verapamil</td>
<td>Triazolam</td>
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<tr>
<td>Morphine</td>
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<tr>
<td>Methamphetamine</td>
<td></td>
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<tr>
<td>Pranoprofen</td>
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<tr>
<td>Prednisolone</td>
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<tr>
<td>Sodium salicylate</td>
<td></td>
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</tbody>
</table>
Table 3.2. Chronopharmacokinetic Changes of Nonsteroidal Anti-inflammatory Drugs in Humans

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number and Types of Subjects</th>
<th>Administration/Dosing/Hours</th>
<th>Major Significant Findings ( (p &lt; 0.05) )</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Aminosalicylic acid</td>
<td>( n = 12 ), young healthy males</td>
<td>1.5 g x 3 PO every 7 hours Enteric-coated tablets Immediately after meal or 1 h after meal</td>
<td>Diurnal effect: rise of 5-ASA concentrations in early morning</td>
<td>[19]</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>( n = 10 ), healthy</td>
<td>Single oral dose 50 mg at 0700, 1900h</td>
<td>Highest peak at 0700h (32% change); highest AUC (23% change); no significant difference in ( T_{\text{max}} ) and ( T_{1/2} )</td>
<td>[20]</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>( n = 5 ), healthy</td>
<td>Morning versus evening Single oral 300-mg dose Immediate or sustained released forms, food influence</td>
<td>No significant difference for immediate release form; longest ( T_{\text{max}} ) (50% change) and lower bioavailability after morning intake; major influence of food</td>
<td>[21]</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>( n = 9 ), healthy</td>
<td>Single oral dose 100 mg at 0700, 1100, 1500, 1900, 2300h</td>
<td>Highest peak at 0700h and 1100h (52% change); ( T_{1/2} ) highest at 1900h</td>
<td>[22]</td>
</tr>
<tr>
<td>Indomethacin slow release</td>
<td>( n = 16 ), Patients (osteoarthritis)</td>
<td>Single oral dose 75 mg at 0800, 1200, 2000h</td>
<td>Highest ( C_{\text{max}} ) at 1200h (25% change); highest AUC and highest ( T_{1/2} ) at 2000h (10% change)</td>
<td>[23, 24]</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Administration</th>
<th>Peak Levels and Half-Lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin slow</td>
<td>Single oral dose 75 mg at 0900, 1200, 2100h</td>
<td>$T_{\text{max}}$ highest at 2100h (38% change)</td>
</tr>
<tr>
<td>release</td>
<td>n = 10, elderly volunteers</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Single oral dose 100 mg at 0700, 1300, 1900, 0100h</td>
<td>Highest $C_{\text{max}}$ (50% change) and AUC at 0700h (58% change); highest $T_{1/2 \beta}$ at 01.00 (60% change)</td>
</tr>
<tr>
<td>n = 8, healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen slow</td>
<td>Single oral dose 200 mg at 0700, 1900h</td>
<td>Shortest $T_{\text{max}}$ at 0700h (24% change)</td>
</tr>
<tr>
<td>release</td>
<td>n = 10, healthy</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen constant</td>
<td>Constant IV infusion 5 mg/kg/day during 24 hours, sampling every 2 hours</td>
<td>Circadian variations of plasma levels with a peak at 2100h (48% change)</td>
</tr>
<tr>
<td>infusion</td>
<td>n = 8, patients (sciatica)</td>
<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Single oral dose 30 mg at 0700, 1300, 1900, 0100h</td>
<td>AUC higher and Cl lower at 1900 and 0100h, respectively (10% change)</td>
</tr>
<tr>
<td>n = 12, healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pranoprofen</td>
<td>Single oral dose 75 mg at 1000, 2200h</td>
<td>$T_{\text{max}}$ shorter at 1000h; no significant difference of AUC, $T_{1/2 \beta}$, Cl.</td>
</tr>
<tr>
<td>n = 7, healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Single oral dose 1 g, at 0600, 1000, 1800, 2200h</td>
<td>Highest $C_{\text{max}}$ (20% change), AUC (17% change), and $T_{1/2 \beta}$ (20% change) at 0600h</td>
</tr>
<tr>
<td>n = 6, healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Single oral dose 1 g at 0700, 1100, 1500, 1900, 2300h</td>
<td>Urinary elimination longest at 0700h (22% change)</td>
</tr>
<tr>
<td>n = 6, healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td>400 mg/ 8 days at 0800, 2000h</td>
<td>After morning dosing, highest 24-h urinary amount (76% change)</td>
</tr>
<tr>
<td>n = 10, healthy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References:
1. [25]
2. [26]
3. [27]
4. [28]
5. [29]
6. [30]
7. [31]
8. [32]
9. [33]
or hydrophilicity), the structure of the biomembrane, gastric emptying time, pH, motility, gastrointestinal blood flow [8], the drug formulation, and the posture and feeding conditions (e.g., possible influence of food). Most of these factors, such as gastric acid secretion and pH, motility, gastric emptying time and gastrointestinal blood flow, vary along the 24-hour scale, and it is not surprising that many studies have reported temporal variations of drug absorption [1–8]. Such variations may be predicted by physicochemical properties of a drug since most of the lipophilic drugs seem to be absorbed faster when the drug is taken in the morning as compared to evening dosing. At the opposite end, the absorption processes of highly water-soluble drugs were not demonstrated to change according to time of day. The underlying mechanisms of the chronokinetic pattern of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning [34]. Shiga et al. [35] documented differences of chronopharmacokinetic profiles between propranolol, a lipophylic beta-blocker and atenolol, a hydrophylic beta-blocker, in patients with hypertension, showing that propranolol, but not atenolol, is absorbed more rapidly after morning administration compared to evening administration.

Elsewhere, physiological factors such as posture may play a role in temporal variations in drug absorption by influencing, for instance, gastric emptying time. Variations of posture related to usual life conditions may partly explain why gastric emptying time of solids is faster in the morning than during the evening in humans.
The qualitative and quantitative influence of food must not be neglected in chronokinetics studies involving ingestion by the oral route. We reported several years ago on circadian variations in carbamazepine kinetics when the drug was given orally to rats [36]. A circadian time-dependent variation in drug absorption, as estimated by the $C_{\text{max}}/T_{\text{max}}$ ratio, was demonstrated in non-fasting animals. Under fasting conditions, the same experiment confirmed and amplified this variation, demonstrating that food influence is not the only factor involved in the circadian change in drug absorption (Figure 3.4). Ohdo et al. [37] reported for valproic acid that meal composition may influence circadian variations: significant differences in the kinetics of valproate were demonstrated, depending on morning or evening dosing under usual life conditions (light meal as breakfast and heavy meal as dinner). When the same conditions (e.g. same size and content of breakfast and dinner) were applied, no significant circadian changes were detected between morning and evening. This points out the necessity to control and take into account in chronokinetic studies the feeding habits of the patients enrolled in the trials. As an illustrative example, the influence of food and time of administration were documented for sertraline, a serotonin reuptake inhibitor [38]: the kinetics of sertraline were not influenced by the time of administration with or without food. This does not eliminate, obviously, a chronokinetic influence but means that under fasting or nonfasting conditions, kinetics of sertraline are similar after morning and evening dosing. This point will be further underlined as far as methodological aspects of a chronokinetic study are concerned. The above

![Figure 3.4. Temporal variations in carbamazepine absorption in rats: circadian time-dependent changes in $C_{\text{max}}/T_{\text{max}}$ ratio in rats receiving carbamazepine orally according to fasting conditions.](image-url)
chronopharmacological reported data involving the oral route of drug administration must be kept in mind when novel drug delivery devices are to be used.

Drug formulation is also an important factor that may introduce a supplementary variability in drug absorption. As far as chronokinetics are concerned, it is of particular interest to control the drug galenic presentation since it may determine whether or not chronokinetics are present.

Drug resorption by other routes of administration may also be influenced by biological rhythms [39]. For instance, skin penetration of a eutectic mixture of lidocaine and prilocaine was reported to depend on the time of administration: lidocaine plasma levels were higher after evening application as compared to morning in children, while the opposite was demonstrated in rats [40]. Circadian dosing time dependency in the skin penetration of hydrophylic methyl nicotinate and lipophylic hexylnicotinate was also demonstrated [41]. Elsewhere, circadian variations were demonstrated in the ocular absorption of topically applied timolol [42].

Thus to conclude whether or not chronokinetics of a drug are present can only be documented when all factors, including route of administration, feeding conditions, posture, and galenic formulation, are controlled and taken into account.

**Temporal Variations in Drug Distribution** Drug distribution changes may be implicated in kinetic variability. Daily variations for drug protein binding have been reported both in animals and in humans [43, 44]. As reviewed elsewhere [7, 8], the free plasma levels of many drugs were documented for drugs such as bupivacaine [17], carbamazepine [47], cisplatin [48], diazepam [49, 50], etidocaine [17], mepivacaine [17], phenytoin [51], and valproic acid [52, 53] (Table 3.3).

Drug protein binding may depend on the amount of plasma proteins, which are known to be circadian time dependent [43–46], more than on the temporal changes in the affinity of the proteins. As an illustrative example, a chronokinetic study in rats has documented circadian time-dependent kinetics of carbamazepine, an antiepileptic drug [36]. Among the possible mechanisms involved, plasma protein binding was demonstrated, with higher values occurring in the middle of the dark active phase compared to the lowest values occurring at the beginning of the light resting period. A parallel variation of albumin, the main plasma protein involved in carbamazepine binding, was also observed, with highest values observed at the same hour.

These changes may also depend on many factors, such as temperature, pH, and physicochemical properties of the particular drug, which may possibly be subject to temporal variations.

More recently, Ando et al. [54] reported on the diurnal variations of P-glycoprotein (Pgp), a multidrug transporter that contributes to renal, biliary, and intestinal elimination of drugs: these authors have documented daily variations of Pgp expression levels.
It is well established that clinically significant consequences of temporal changes in drug binding are relevant only for drugs that are highly bound (more than 80%). Thus temporal variations in plasma drug binding may have clinical implications only for drugs characterized by a high protein binding and a small volume of distribution. Nevertheless, to our knowledge, clinical consequences due to circadian variations in plasma proteins have not yet been demonstrated.

Some drugs may also bind to red blood cells. We have reported circadian time-dependent changes in the passage of drugs such as local anesthetics (lidocaine, bupivacaine, etidocaine, and mepivacaine), indomethacin, and theophylline into red blood cells [6–8].

Finally, temporal variations in drug distribution may also proceed from circadian time-dependent changes in blood flow and in tissue blood flow as documented in animals as well as in humans [56].

**Temporal Variations in Drug Metabolism** Drug metabolism is generally assumed to depend on enzyme activity and/or blood flow, which were both shown to be circadian time dependent as far as the liver is concerned. Circadian variations in enzyme activity also documented in many other animal tissues, such as liver, kidney, and brain [57–59] can explain some time-dependent changes in the kinetics of drugs [59, 60]. The hepatic metabolism of hexobarbital as well as the hypnotic effect has been shown to be circadian time dependent depending on the circadian rhythm of hexobarbital oxidase in rats. This study was the first work documenting a temporal correlation between the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Species</th>
<th>Main Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>Mouse</td>
<td>Maximum protein binding at 1600 h</td>
<td>[17]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Rat</td>
<td>Minimum free fraction at 0400 h when albumin is highest</td>
<td>[36]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Human</td>
<td>Higher free fraction at 1700h</td>
<td>[47]</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Human</td>
<td>Maximum protein binding at 1600h</td>
<td>[48]</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Human</td>
<td>Higher bound fraction at 0900h</td>
<td>[49]</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Human</td>
<td>Higher bound fraction at 0930h</td>
<td>[50]</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>Mouse</td>
<td>Maximum protein binding at 1000h and 2200h</td>
<td>[17]</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Rat</td>
<td>Maximum free fraction at 1600h</td>
<td>[15]</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Mouse</td>
<td>Maximum protein binding at 0400h</td>
<td>[17]</td>
</tr>
<tr>
<td>Phenytoin (epileptics)</td>
<td>Human</td>
<td>Maximum free fraction during daytime when VPA associated</td>
<td>[51]</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Human</td>
<td>Maximum free fraction between 0200h and 0800h</td>
<td>[52]</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Human</td>
<td>Free fraction clearance higher in the morning</td>
<td>[53]</td>
</tr>
</tbody>
</table>
metabolism and the effect of a drug. Temporal variations have been detected in various oxidative reactions catalyzed by the microsomal monoxygenase systems for compounds such as aniline, benzphetamine, and benzo[a]pyrene in rodents. Time-dependent changes in nonoxidative pathways of drug metabolism (reduction, hydrolysis, and conjugation) were also documented in animals.

In humans, indirect evidence of circadian changes in enzymatic activity was documented. Several clinical chronopharmacological studies have indirectly investigated temporal variations in hepatic drug metabolism capacity by demonstrating chronokinetics of drugs and their metabolites. Thus conjugation, hydrolysis, and oxidation were shown to be circadian time dependent [2–8]. More recently, circadian variations in cytochrome P450 3A activity, mainly involved in drug metabolism, were assessed by establishing daily variations of the urinary 6ß-hydrocortisol to cortisol ratio, a noninvasive index of human CYP3A activity, in humans [61].

Concerning metabolic phenotype determination, Shaw et al. [62] have shown the effect of diurnal variation on debrisoquine metabolic phenotyping, with the slowest metabolism during daytime.

In recent years, research on the molecular mechanisms of circadian oscillation and rhythmic transcription of clock output regulators such as an enzyme of the cytochrome P450 superfamily in liver has progressed. Recently, Tada et al. [63] reported in renal transplant patients that, despite a lack of statistical difference in pharmacokinetics of tacrolimus between 0900h and 2100h, lower nighttime AUC corresponded to the occurrence of clinical acute rejection of transplants.

The hepatic blood flow is of particular importance for drugs with a high hepatic extraction ratio \((E > 0.7)\). Temporal variations in the clearance of these drugs are explained by changes in liver perfusion, dependent on circadian variations in hepatic blood flow. A circadian rhythm in hepatic blood flow estimated by indocyanine green clearance was reported in healthy subjects with higher values at 0800h [56]; this provides strong arguments for circadian time-dependent metabolism of drugs with a high hepatic extraction ratio.

**Temporal Variations in Drug Elimination** Most drugs (particularly hydrophilic ones) are eliminated by the kidneys. As illustrated in Figure 3.1, many physiological factors involved in renal elimination of drugs (e.g., glomerular filtration, renal blood flow, urinary pH, tubular resorption) have been shown to be circadian time dependent, with higher values during daytime in humans [64]. Thus the urinary excretion of many drugs depends on these rhythmic variations [8]. The physicochemical properties of the drug are of particular importance in this field; renal elimination of hydrophilic drugs (mainly excreted unchanged by the kidneys) has been shown to be circadian time dependent (related to the above mentioned circadian rhythms in renal functions). Elsewhere, the ionization of drugs is of particular importance in the renal elimination of drugs: thus temporal changes in urinary pH may modify ionization and explain why acidic
drugs are excreted faster after an evening than a morning administration, as described for sodium salicylate [32] and sulfasymazine [65], for instance. As an illustrative example, time-dependent variations in the duration of excretion of sodium salicylate in healthy subjects were documented [32], salicylate excretion being quicker when urine pH was more alkaline and vice versa. More recently, the influence of food on chronokinetics of antibiotics was documented, showing that feeding restriction may modify the chronokinetic pattern of antimicrobial agents [66].

Recently, the chronokinetics of norfloxacin [67] and ceftriaxone [68], two antimicrobial agents, were documented in rats showing a higher elimination during the activity period (e.g., during the nighttime). As far as ciprofloxacin is concerned, these results are in good agreement with data obtained in humans. These results are of particular importance for determination of the in vivo efficacy: daily variations in kinetics may account for impairment in the chemotherapeutic effects as demonstrated for ciprofloxacin [69].

3.3 METHODOLOGICAL ASPECTS OF A CHRONOKINETIC STUDY

3.3.1 When and Why a Chronokinetic Study May Be Indicated?

As previously mentioned, the aim of such a study may be realized (1) for a theoretical aspect in order to document possible chronokinetic changes, (2) for a registration study of a new drug, or (3) simply as a complementary study seeking to identify the possible involvement of time of administration in the observed variability.

As mentioned previously, the moment of administration of a drug is one possible factor inducing chronokinetic changes, but many other factors may interfere with the kinetics of a drug and thus must be controlled and/or taken into account before starting a chronokinetic study. These factors depend on drug and patient characteristics.

3.3.2 Drug Delivery Conditions

As previously mentioned, different formulation procedures developed elsewhere in this book make it possible to deliver the drug at a definite time, which is the goal of chronotherapy, in order to ameliorate the efficacy and tolerance of the treatment. Thus novel drug delivery systems provide very useful tools for chronotherapy, allowing doctors to choose the best time of administration according to chronopharmacological findings. This point will be developed further, but we want to emphasize here the importance of considering the drug formulation procedure: as previously noticed, chronokinetic differences demonstrated for a standard form may not be observed for the same drug when presented as a sustained released form. This was demonstrated for isosorbide-5-mononitrate [70] and nifedipine [34].
Chronotherapy may involve asymmetric delivery of drugs on the 24-hour scale: as mentioned in other chapters, external or surgically implantable pumps allow delivery of drugs according to programmable rates [71], taking into account possible chronokinetic characteristics of the drugs.

### 3.3.3 Sampling Conditions

A chronokinetic study may be realized according to different goals, inducing differences in the protocol. Such a study may be done under daily practice conditions if the drug must be administrated two times daily: the aim of this chronokinetic study may be to search for a possible kinetic difference between morning or evening intake. On the other hand, in order to conduct a real chronokinetic study (i.e., the search for a circadian time-dependent change), several time points (dosing times) are needed [7]. For ethical (number of samples), financial, galenic (once-a-day formulation), or practical reasons (daily life conditions), many chronokinetic clinical studies are often done by determining only two time points. This must also be interpreted, since the timing of drug administration with respect to meals is a usual fact in drug prescription, while not scientifically justified. Such a protocol may miss a circadian variation while in fact it exists but would detect the variation if two more time points are included in the study. A preliminary experiment is necessary, if only two time points are possible, in order to justify and choose these points according to the peak or trough time of a biological marker, for instance.

New specific sampling methods have been developed recently. Among them, microdialysis is a bioanalytical sampling technique allowing continuous monitoring of chemical events that are occurring at the tissue level [72]. This procedure allows one to monitor endogenous or exogenous compounds (e.g., drugs, neurotransmitters, amino acids) in several tissues, including blood, of the same animal and thus are of particular interest in pharmacological and pharmacokinetics studies. However, surprisingly, very few chronobiological studies were conducted using this technique [73, 74] until now. This technique is also available for clinical use and would be of great interest as a “continuous sampling” tool in chronokinetic studies.

### 3.3.4 Characteristics of the Patients

Chronokinetics may vary according to many physiopathological factors, such as fasting or feeding habits, posture, gender, pathology, mode of synchronization, type of meal, meal timing, working habits, sleeping times, or age. As previously mentioned [7] these factors of variability must be strictly controlled in setting up a study design. Since they all participate to the intrasubject variability, it is of particular importance to control and standardize them in a chronokinetic study. Most of these factors are often not taken into account in
inclusion/noninclusion criteria of clinical studies, which may introduce a bias or at least an increased variability.

3.3.5 Specific Data Analysis in Chronokinetics

The description of the fate of a drug in the organism and its characterization proceed from either noncompartmental analysis or compartmental analysis. Noncompartmental pharmacokinetics involves physiological models with usually determined kinetic parameters summarizing bioavailability (e.g., \( C_{\text{max}} \), \( T_{\text{max}} \), AUC, MRT), distribution (e.g., volume of distribution), drug protein binding characteristics, and elimination (e.g., clearance and elimination half-life). Compartmental analysis implies the use of models with compartments that model the fate of the drug in the organism. The influence of time of administration of a drug on its kinetics may be assumed as a covariable among other factors of variability, which is rarely done [75]. In other words, for a given drug and a given subject, the influence of the time of administration may imply a different kinetic pattern, leading to a different kinetic model related to time of administration [76]. Specific methods may be used for modeling of the chronopharmacokinetic pattern: this has been attempted by Hecquet [76] and Gries et al. [77]. As an illustrative example, Aranson et al. [78] developed a chronokinetic model involving cosine wave time-variant parameters [78] in order to reanalyse some previously reported chronokinetic studies related to nonsteroidal anti-inflammatory drugs.

In order to simulate the drug concentration at its site of action and thus to better characterize its concentration–effects relationships, there is a growing interest in specific analysis methods allowing pharmacokinetic/pharmacodynamic (PK/PD) modeling [75]. As far as chronokinetics are concerned, very few chronopharmacological studies have been conducted using such models [79–81]. However, use of PK/PD modeling in chronokinetic studies may not be useful when chronokinetic changes are not the main mechanism responsible for the chronopharmacological changes observed. For example, the chronokinetics of cardiovascular drugs, while significantly detected, do not represent the main mechanism implicated in their circadian time-dependent effects [82], as demonstrated, for instance, with propranolol [34].

Another analytic approach for characterizing changes in drug clearance throughout the day was proposed by Gries et al. [77] for nicotine. For studying the possible influence of meals and circadian rhythms on nicotine clearance, they described a modeling technique by use of nonparametric incorporation of discrete events; the use of a spline function seems to represent a more realistic model than the parametric one. Once again, this study illustrates the intricate implications of food and circadian variations in kinetics.

Finally, methods used for population pharmacokinetics may be applied to chronokinetic studies in order to reduce the number of samples in a defined subject. Chronokinetic changes may be analyzed with such methods by...
considering time of administration as a covariable component of the intrasubject variability.

3.4 APPLICATIONS: CHRONOPHARMACOKINETICS, A BASIS FOR CHRONOPHARMACEUTICS

We mentioned in introduction that “to produce its characteristic effects, a drug must be present in appropriate concentration at its sites of action.” We may now add to this assertion that this must be done also “at the right moment” related to chronopharmacological effects. Thus chronopharmacology and chronokinetics may be considered as a basis for chronotherapy by justifying the choice of the best moment of administration of the drug. Obviously, choosing the moment of administration of a drug sometimes may seem to be incompatible with usual daily habits and usual drug formulation: for instance, taking a pill in the middle of the night when the patient is sleeping may be problematic! Thus specific tools designed for a timed and delayed delivery are necessary.

Most of the different available novel devices releasing the drug at the chosen site at the chosen time are detailed in this book. We only underline the interest in some of them in relation to chronokinetics findings.

The main novel delivery systems involved are:

- Electronically controlled systems permitting a chronomodulated delivery pattern (i.e., the delivery of a precise dose of drug at precise time—pulse or sinusoidal delivery)
- Diffusion-controlled systems where the controlled diffusion and the lag time are governed mainly by the rate of water penetration into the system
- Chemically activated systems based on changes in the property of the matrix
- Compartmental systems allowing drug release at a predetermined time from different compartments

All of these novel drug delivery systems allow a timed administration: they permit delivery at a fixed, determined clock hour according to a time-dependent delivery. Thus chronopharmaceutics allows using intelligently novel drug delivery systems.

Nevertheless, most of the systems using the oral route introduce an additional chronobiological factor. The system itself may depend on chronobiological factors: the delivery lag time may change according to pathological and physicochemical rhythmic changes. For instance, as far as diffusion-controlled systems are concerned, the time-dependent delivery may vary according to the hour of application: related to circadian variations of gastric pH, gastrointestinal tract mobility, and other possible factors (e.g., osmotic
process may not be similar according to time of application). Thus drug release (lag time and duration) from timed delivery systems must take into account the hour of administration along the 24-hour scale. Specific studies are needed to better characterize chronobiological release from drug delivery systems.

Nevertheless, chronopharmaceutics provide useful and powerful tools for chronopharmacology and thus chronotherapy. The sinusoidal delivery pattern of anticancer drugs has optimized their efficacy and safety in cancer patients: this is achieved by internal or external programmable infusion pumps that deliver the drug intravenously or subcutaneously. To our knowledge, new delivery drug devices do not permit such delivery patterns for the oral route: this is needed for future chronotherapeutic studies. Data from chronokinetics contribute to a better understanding of the fate of a drug in an organism according to biological rhythms and thus provide a basis for chronopharmaceutics.

Future experimental and clinical studies will take advantage of the convergence of pharmaceutics and chronobiology, permitting an optimization of medical practices.

REFERENCES

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