Abstract

Objective: An overview on the most recent study done on chronokinetics, the rhythmic changes on drug kinetics.

Data Source: Search in the internet and IOWA drug information service using the term chronokinetic. All papers are reviewed and summarized in this article.

Conclusion: The future of kinetic studies of important and dangerous drugs as anticancer agents depend on chronokinetic since we are hopeful to find a specific time of day in which these agents are more effective and less toxic.

Introduction

Drug Absorption, distribution, metabolism and elimination are influenced by many different physiological functions of the body which may vary with time of day. Thus, the pharmacokinetic parameters characterizing these different steps, conventionally considered to be constant in time, depend on the moment of drug administration. However, the time of day has to be regarded as an additional variable influencing the kinetics of a drug since many drugs are affected by time of administration and the activity or rest period of the human or animal. Chronokinetic studies have been reported for many drugs in an attempt to explain chronopharmacodynamic phenomena and demonstrate that the time of administration is a possible factor of variation in the kinetics of a drug (3).

Definition

Chronopharmacokinetics deals with the study of the temporal changes in absorption, distribution, metabolism and elimination and thus takes into account the influence of time of administration on these different steps. Temporal changes can be involved at each step of the sequence of pharmacokinetic processes: temporal variations in drug absorption from the gastro-intestinal tract (due to circadian variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow), plasma protein binding and drug distribution, drug metabolism (temporal variations in...
enzyme activity, hepatic blood flow) and in renal drug excretion (due to variation in glomerular filtration, renal blood flow, urinary pH and tubular resorption). Thus, the time of administration of a drug is an important source of variation which must be taken into account in kinetic studies and particular methodological aspects of chronokinetics are needed (5,3).

Aim of chronokinetic studies

The main aim of chronokinetic studies is to control the time of administration which among others, can be responsible for variations of drug kinetics but also may explain chronopharmacological effects observed with certain drugs.

When do we need chronokinetic studies?

There are some instances in which a chronokinetic study is needed: 1) when possible daily variations in pharmacokinetics may be responsible for time dependent variations in drug effects (e.g. some antimicrobial agents are more effective at a specific time of day), (2) when drugs have a narrow therapeutic range, (3) when symptoms of a disease are clearly circadian phase-dependent (e.g. nocturnal asthma, angina pectoris, myocardial infarction, ulcer disease) (4) when drug plasma concentrations are well correlated to the therapeutic effect in case the latter is circadian phase-dependent. (5) when the drug has some serious adverse effects that can be avoided or minimized because they are related to time of administration (e.g. aminoglycosides nephrotoxicity).

Drugs that undergo chronokinetics

Antibiotics: many studies have reported temporal variations in the pharmacokinetics of antimicrobial drugs. Experimental animal models have shown that for Antibiotics such as beta-lactams that have concentration-independent killing effects in vitro, the time that the antibiotic concentration remains greater than the MIC ($T_{>}$ MIC) is the most important factor for determining the in vivo efficacy. Therefore, daily Variations in pharmacokinetics may account for impairment in the chemotherapeutic effects. This is of great importance when bacteria with low susceptibility are involved in the infectious processes.(1) Other important aspect of chronokinetics in antibiotics is that not only the efficacy of the drug may increase but also the toxicity of certain drugs may decrease at different time of day as we will see in aminoglycosides.

The most important results in chronokinetics studies of antibiotics include: 

Aminoglycosides: Peak renal toxicity was observed when aminoglycosides were injected in the
middle of the rest period of the experimental animals, while lower toxicity was found when they were treated in the middle of the activity period. Based on many studies and on the evidence available in the current literature, it is quite clear that the renal toxicity of aminoglycosides can be reduced by giving the drug as a single daily injection when patients are active (at day time or in other words in the activity period). The mechanisms responsible for the temporal variation in renal toxicity of aminoglycosides are still unknown.(2)

Gentamicin: both the effectiveness and the toxicity of gentamicin varied over the 24-h Period and that the efficacy was best at the time when the toxicity of the drug was the lowest. So the administration of gentamicin in the beginning or the middle of the day in humans may reduce renal toxicity and increase the efficacy of these antibiotics. (2)

Tobramycin: Tobramycin was administered at 0200 h (dark period), the CLT was significantly higher and AUC was lower than the values when tobramycin was given at 1400 h (light period).(1)

Amikacin: amikacin in humans showed higher values for kel in the morning than in the evening.(1)

Ceftriaxone: total clearance of ceftriaxone varies rhythmically during the day, with its maximum during the dark (activity) period and its minimum during the light (rest) period in rats.(1)

Ciprofloxacin: In humans, the amount of ciprofloxacin eliminated in urine was greater when the drug was administered at 1000 h than when it was given at 2200 h.(1)

4-Ampicillin: Ampicillin biliary and renal clearances were significantly higher during the active cycle of rats than during the sleep cycle.(1)

Antihypertensive drugs: Nearly all physiological functions as well as pathophysiological events display reproducible rhythmic changes within 24 hours of a day, including the cardiovascular system. Clinical chronopharmacological studies with antihypertensive drugs gave evidence that effects on the rhythms in blood pressure and heart rate are also dependent on the time of day. Chronopharmacokinetic studies with propranolol, oxprenolol, nifedipine, verapamil, etc. also revealed daily variations in the drugs’ kinetics. In general, Cmax was higher and/or tmax shorter after morning than evening dosing of these rather lipophilic drugs. However, independently of whether or not daily variations in the kinetics were found the dose-response relationship was always dependent on the time of day.

Valporic acid: After oral administration, mean total VPA concentrations in plasma were significantly higher in the morning than in the evening during the absorption phase. Cmax tended to be higher, tmax was shorter and absorption rate constant (ka) tended to be larger for VPA in the morning.
than in the evening, although no difference was demonstrated in other pharmacokinetic values between morning and evening trials.

**Sumatriptan:** (sumatriptan is a drug of choice in migraine treatment) migraine is a disorder that exhibits periodicity in its symptoms and so chronotherapy may be beneficial in treating the problem. The mean peak serum concentration following the 0700 h administration was significantly higher than after the 1900 h administration. The mean area under the serum concentration-time curve from time zero to the last time-point (AUC0-t), the area under the serum concentration-time curve from zero to infinity (AUC0-infinity), and the area under the first moment curve (AUMC) were significantly higher following the 0700 and 0100 h administrations than after the 1900 h administration. Following administration at 0700 h, the mean oral clearance and the apparent volume of distribution were significantly lower than after the 1900 h administration. The variations may be due to the time dependent changes in the extent of absorption and/or circadian variations in hepatic blood flow. (7)

**Cyclosporine:** one study done on cyclosporine pharmacokinetics in five recipients of pancreatic allografts. Results from these patients demonstrate a slightly increased area under the concentration-time curve resulting from decreased apparent clearance during the resting (PM) versus activity (AM) period. A significant delay in mean residence time was observed after the PM dose, and the PM area under the moment curve was larger than the AM value. We propose three chronopharmacokinetic dosing methods that alter either the PM dose administration time or redistribute the daily dose to produce equal exposure to cyclosporine during the active and resting periods. These trends and differences suggest that more sophisticated time-dependent cyclosporine dosing methods are needed to balance AM and PM drug exposure and thereby improve immunosuppression. (8)

**Methotroxate:** in a study involving 6 children with leukemia to hom methotroxate doses was administered at 10a.m and 9 p.m. the result was a significant decrease in plasma clearance at night. These differences (among other causes) would be mainly linked to variations in passive tubular reabsorption resulting from the rhythm in urine pH. In another study on animals (4 pigs) a significant circadian rhythm of methotroxate serum concentration was found in two pigs at 1:00 p.m. (9)

**NSAID:** *ketoprofen:* The rate of absorption of Ketoprofen was also found to be higher when it was administered in the morning. (10)
Indomethacin: Markedly higher and earlier peak concentrations were obtained when the drug was given at 07:00 or 11:00 h than at 15:00, 19:00 or 23:00 h. (10)

**what is new?**

New tools, such as new formulation procedures or pumps with constant or programmable delivery rates, now make it possible to deliver a drug at a definite time, or during a definite span of time and at a controlled rate in chronokinetic studies.(4)

**Conclusion**

The future of kinetic studies of important and dangerous drugs as anticancer agents depend on chronokinetic since we are hopeful to find a specific time of day in which these agents are more effective and less toxic.

**References:**

8- Cipolle R J; Canafax D M; Rabatin J; Bowers l d; et al.1988. time-dependent disposition of cyclosporine after pancreas transplantation, and application of chronopharmacokinetics to improve immunosuppression.pharmacotherapy. 8: 47-51