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Dosing time matters:

Circadian precision medicine may supplement genetic precision to improve drug action

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Physicians diagnose and administer treatment as needed; time of day is rarely considered. Yet, accumulating evidence shows that our molecular clocks orchestrate 24-hour circadian rhythms in vital cardio-metabolic, endocrine, immunologic, and behavioral functions. Time, therefore, adds a potentially important dimension to medicine. Circadian medicine aims to incorporate knowledge of 24-hour biological rhythms to enhance diagnosis and treatment. How is research and technology shaping this endeavor?

There are two broad strategies in circadian medicine: target the molecular clock or exploit its rhythmic outputs. In the former, the therapeutic target is the molecular oscillator itself. Light therapy for sleep disorders is the hallmark example of this approach, but feeding, exercise, and drugs can also modulate the clock to potentially influence health. Interest in the latter approach, exploiting clock output, goes back at least six decades. But the path to the clinic has been marked by starts, stops, and ambiguity. A series of recent insights, however, has renewed clinical interest.

STARTS, STOPS, AND SCOPE

Fifty years ago, the expression of a rate-limiting enzyme in cholesterol synthesis was shown to oscillate with a 24-hour period in rat liver (1). Twenty years later, simvastatin-a short-

SUPPLEMENTARY MATERIALS

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acting inhibitor of this enzyme—was approved for treating hyperlipidemia, prescribed to be taken “once a day in the evening.” This marked the first translation from knowledge of a circadian mechanism to a widely used medication.

In retrospect, simvastatin might have foreshadowed a wave of circadian drug development. It did not. Although studies in the mid-1990s showed that rhythmically delivered chemotherapy could reduce toxicity in colorectal cancer (2), they did not lead to changes in labeling by the U.S. Food and Drug Administration (FDA), treatment guidelines, or standards of practice. Trials in other therapeutic areas also supported time-dependent dosing (3, 4), with similarly limited influence. In fact, there are few examples of mechanism-based circadian medicine. Only four of the 50 currently most prescribed drugs have FDA-labeled time-of-day dosing recommendation. The 20th World Health Organization’s Model List of Essential Medicines makes no mention of dosing time.

RENEWED CLINICAL INTEREST

Circadian regulation at genomic and physiologic levels is far more extensive than previously understood. The central clock in the hypothalamus coordinates rhythmic behavior. However, local clocks exist in virtually every peripheral tissue in mammals (5). In a high-resolution time-series study of 12 mouse organs, nearly half of protein-coding genes were expressed with a 24-hour rhythm in at least one organ (6). Clock-driven rhythms in gene expression generate rhythms in hormone secretion, lipid and glucose metabolism, lung and cardiovascular physiology, and many other tissue-specific functions. Remote sensors and wearable technology have revolutionized data collection from humans “in the wild.” Using multiple devices, a small feasibility study uncovered daily variation in 62% of physiologic and behavioral measures from six healthy individuals (7).

Expression of many disease phenotypes is also time dependent. The incidence of heart attacks and symptoms in asthma, allergic rhinitis, cancer, arthritis, depression and suicidal intent, peptic ulcers, and pain all show time-of-day variation. Thousands of rhythmically expressed genes metabolize, transport, or are the targets of drugs (6). For drugs with rapid pharmacokinetics (the absorption, distribution, metabolism, and excretion of drugs), circadian time could influence efficacy and/ or toxicity and thus their therapeutic index.

HARMONIZING THERAPY AND RHYTHMS

Animal experiments are defining different ways to leverage circadian time for therapeutic benefit. Timing the administration of a drug to coincide with peak expression of its physiologic target was effective in models of atherosclerosis and obesity, to name a few. Alternatively, drug delivery can be timed to coincide with low expression of an undesired target, as successfully executed in a mouse model of pancreatic cancer (8). Another approach is to harmonize the administration of a drug with rhythms in its absorption, distribution, metabolism, or excretion. For example, a 24-hour rhythm in blood-brain barrier permeability influenced efficacy of an antiepileptic drug in a fruit fly model of seizure (9).

All of this has generated renewed enthusiasm for circadian time as a parameter in medicine; in 2018 alone, 15 reviews were published with “chronotherapy” in the title or abstract. But how do we move the field forward to influence clinical practice?

SUCCESSFUL STRATEGIES

To gain insight into successful strategies, one can consider the results of 106 clinical trials (conducted over the past 50 years) that evaluated time-of-day administration of drugs [see supplementary materials (SM)]. These published studies directly compared at least two different time-of-day treatment schedules and measured efficacy or toxicity. Altogether, these studies comprised 70 distinct drugs or combinations or medical procedures across 15 different therapeutic areas. Among these studies, 75% found that treatment efficacy or toxicity depended on dosing time across a number of conditions, including hypertension, cancer, asthma, and arthritis—diseases with extraordinarily high prevalence and unmet medical need. The number and size of trials in these areas has increased over the past several decades, reflecting well-known 24-hour patterns in their phenotypic severity.

Nevertheless, there are dozens of other indications (many with circadian components) and thousands of other approved drugs for which the impact of time of day is unexplored.

PHARMACOKINETICS MATTER

Pharmacokinetics suggest that only drugs with half-lives of ~6 hours or less would show time-of-day dosing dependencies. Yet among the clinical trials described above, the majority of drugs with half-lives as long as 8 to 15 hours were influenced by dosing time. This suggests that many commonly used drugs have narrow therapeutic windows and are influenced by dosing time.

The influence of drug half-life helps to reconcile seemingly inconsistent trial results, even for drugs of the same class (see SM). For example, whereas short-acting simvastatin (half-life of 3 hours) was consistently more effective when taken in the evening, neither long-acting atorvastatin (half-life of 25 hours) nor extended-release simvastatin have morning-evening differences in the majority of trials. Long-acting formulations likely obscured circadian effects in other areas as well. Amlodipine, a long-acting $Ca2^{+}$ channel blocker (half-life of 40 hours), did not decrease blood pressure in a time-dependent manner. However, when it was combined with a short-acting angiotensin receptor blocker (valsartan or olmesartan) or a diuretic, evening dosing was more effective than morning dosing.

Overall, 85% trials with drug half-lives of less than 15 hours showed dosing time dependence compared with just 39% for longer-acting drugs. This knowledge could be the difference in an FDA approval.

SMALL TRIALS WITH FEW TIME POINTS

There are still numerous discrepancies that cannot be explained by differences in drug kinetics. Limitations in study design may contribute to this. Many of the 106 clinical trials that evaluated time-of-day administration of drugs were small. For example, median

enrollment in the hypertension studies was 62 subjects; only one study included more than 500 patients. By comparison, the most recently FDA-approved antihypertensive (Byvalson) was based on a pivotal trial of 4161 hypertensives. One of Byvalson's components, valsartan, has a short half-life and established time-dependent efficacy. That trial did not test for time-dependency.

Further, these studies were underpowered to detect periodic effects. Approximately 90% compared only two time points, almost always morning versus evening, which might miss circadian effects at other times of day. And most studies did not account for possible interindividual variability in internal circadian phase, arising from differences in lifestyle, work schedule, or chronotype. Eight a.m. on the wall clock is not "morning" for everyone.

Despite these limitations, there is growing evidence that supports circadian medicine. Yet, a major barrier to clinical translation has been the lack of understanding of how the circadian clock governs human physiology and pathophysiology. Even for medicines with demonstrable dosing time–dependent effects, the mechanisms are not well defined.

MECHANISM-DRIVEN CIRCADIAN MEDICINE

Human time-series gene expression data have not been possible at the spatial and temporal resolution of animal models. Although longitudinal studies detected rhythmic gene expression from human samples, taking multiple biopsies from a patient over a 24-hour period is difficult to execute, costly, and limited to the most easily accessible tissues. Alternatively, population-scale rhythms can be detected from single samples taken from many donors (10); however, time of sample collection is often not recorded. An algorithm called CYCLOPS was developed to reconstruct sample order in the absence of sample collection times (8).

CYCLOPS was used to build the first population-scale human atlas of circadian gene expression (11) and showed that regardless of a person's sex, age, or ethnicity, the body's internal clock regulates half of the protein-coding genome. This work connected thousands of different drugs—both investigational and approved—to thousands of cycling genes that encode drug targets, transporters, or metabolizing enzymes. This identified many specific mechanisms by which time of day might influence drug activity.

In addition to mapping dynamic drug targets, the timing of therapies should be examined. Researchers and drug developers can make predictions about the influence of timed dosing of many routinely prescribed short-acting medications, such as those for hypertension, with knowledge of the relative abundance of a drug's target.

Current knowledge might also help mitigate drug-related toxicity. Cardiotoxicity is the leading cause of drug discontinuation at all stages. Many drug classes, although not necessarily indicated for cardiovascular disease, actively target the heart and peripheral vasculature. For example, the-ophyllines—bronchodilators administered for pulmonary disease—function by inhibiting genes that are also critical to normal heart function (12). Several of these "off targets" are rhythmically expressed in the human heart and vasculature (11).

Can dosage time for these and other compounds be leveraged to reduce cardiotoxicity? Time matters for several nondrug interventions as well. At least eight trials have shown that radiation therapy is less toxic when administered at a particular time (see SM), which is thought to be when nontumor cells are less susceptible to radiation damage. Circadian-dependent vulnerability to injury also exists in the context of cardiovascular procedures (13). Even with this understanding, practical limitations make implementation of timed therapy difficult. Despite studies that support timed administration of chemotherapy, this is not standard practice because of multiple barriers (scheduling infusions at specific times with limited infrastructure).

FUTURE DRUG DEVELOPMENT

There are approximately 2000 approved drugs in the United States. Those whose targets oscillate in humans are a good place to start. Still, the best targets and times for treatment in the context of disease need to be determined empirically. The most effective medicines may well incorporate knowledge of 24-hour dynamics in both health and disease. Genome-scale maps of 24-hour rhythms are providing volumes of data for hypothesis-driven circadian medicine.

In addition to focusing on circadian mechanisms, attention could turn to developing shorter-acting agents. Among the clinical studies that evaluated time-of-day administration of drugs, the majority of support for circadian medicine comes from trials of drugs with half-lives of <15 hours (see SM). Although some very long-acting agents showed administration time–dependent effect, the mechanisms are unclear. Trials should strive to delineate drug pharmacokinetics, ideally at more than one dosage time.

The industry trend toward sustained-release formulations, although good for patient adherence, can be problematic from the vantage of circadian biology. Drug exposure is constant over 24 hours, but its target(s) may not be. Flattening a process that is normally rhythmic may be maladaptive. For example, in people with high blood pressure, short-acting antihypertensives were more effective than long-acting forms at restoring the normal nighttime drop in blood pressure, which may improve cardiovascular outcomes (14).

The simplest comparison between morning and evening dosing can only confirm or rule out a difference between these two times. Although medications are typically taken at these times for convenience, other times may be more effective or safe. For drugs with short half-lives, two–time point sampling is likely insufficient. Although the gold standard of hourly sampling for genome-scale circadian analysis may be impractical for human trials, clinical researchers should nevertheless weigh the upstream cost of additional time points against the downstream cost of missing out on an advantage.

Trials in circadian medicine must control for interpersonal differences in phase. At a minimum, a subject’s rest-activity rhythms provide a reasonable estimate of internal circadian phase. Recent studies reported algorithms capable of inferring circadian phase from skin or blood samples. These pave the way for developing biomarkers that help to optimize the delivery time of treatment for patients in whom determining circadian phase may be difficult (such as patients in an intensive care unit).

Another challenge is the setting of clinical trials that evaluate time-of-day administration of drugs. Subjects in inpatient care-often detached from natural environmental fluctuations for extended periods of time-are at risk for circadian disruption. Simply recreating changes in natural light over 24 hours improved recovery in experimental and hospital-based clinical studies. Besides light, noise levels and frequent awakenings are also sources of circadian disruption. This becomes a critical consideration for time-of-day effects and is leading many to rethink hospital layouts from the vantage of circadian biology.

CIRCADIAN PRECISION

The most commonly prescribed drugs help only a minority of patients who take them (15). Although the common refrain to this is a call for better genetic precision, circadian effect sizes can be just as large. Circadian precision medicine aims to deliver treatment in harmony with target physiology and has shown that it can improve efficacy and safety in many feasibility-sized trials in hypertension, arthritis, asthma, and cancer, among others. Recent technological advances in circadian biology have the potential to exert broad influence on medical practice.

Ultimately, trials in circadian medicine will need to demonstrate an unambiguous health benefit over standard-of-care. There is presently one registered clinical trial in the United States with time-of-day end points: *Temozolomide Chronotherapy for High Grade Glioma*. Will circadian biology factor into the future of medical treatment? Time will tell.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES AND NOTES

1. Hamprecht B, Nüssler C, Lynen F, FEBS Lett 4, 117 (1969). [PubMed: 11947160]
2. Lévi FA et al., J. Natl. Cancer Inst 86, 1608 (1994). [PubMed: 7932825]
3. D'Alonzo GE et al., Chest 107, 406 (1995). [PubMed: 7842769]
4. Hendel J, Hendel L, Aggestrup S, Aliment. Pharmacol. Ther 9, 693 (1995). [PubMed: 8824658]
5. Takahashi JS, Nat. Rev. Genet 18, 164 (2017). [PubMed: 27990019]
6. Zhang R et al., Proc. Natl. Acad. Sci. U.S.A 111, 16219 (2014). [PubMed: 25349387]
7. Skarke C et al., Sci. Rep 7, 17141 (2017). [PubMed: 29215023]
8. Anafi RC, Francey LJ, Hogenesch JB, Kim J, Proc. Natl. Acad. Sci. U.S.A 114, 5312 (2017). [PubMed: 28439010]
9. Zhang SL et al., Cell 173, 130 (2018). [PubMed: 29526461]
10. Chen C-Y et al., Proc. Natl. Acad. Sci. U.S.A 113, 206 (2016). [PubMed: 26699485]
11. Ruben MD et al., Sci.Transl. Med 10, eaat8806 (2018). [PubMed: 30209245]
12. Bobin P et al., Arch. Cardiovasc. Dis 109, 431 (2016). [PubMed: 27184830]
13. Montaigne D et al., Lancet 391, 59 (2017). [PubMed: 29107324]
14. Fagard RH et al., Hypertension 51, 55 (2008). [PubMed: 18039980]
15. Schork NJ, Nature 520, 609 (2015). [PubMed: 25925459]