Influence of Pharmacokinetic Profiles on Safety and Efficacy of Hypnotic Medications

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Occasional trouble sleeping is part of the human condition, but persistent insomnia is not. Pharmacotherapy is the most common treatment for insomnia. Benzodiazepines, nonbenzodiazepine hypnotics, and melatonin receptor agonists are among the most studied compounds for the treatment of insomnia. These compounds differ in their sites of action in the brain, their half-lives, and their durations of action. These differences allow clinicians to make therapeutic choices based on the specific sleep needs of individual patients. For example, medications with a rapid onset of action and a short half-life are likely to be effective for sleep initiation but unlikely to improve sleep maintenance. A compound with a longer half-life would be expected to sustain sleep on a more extended basis but could lead to residual sedation. A (theoretically) ideal compound for promoting and sustaining sleep over a desired period of time would be one with an immediate onset of action, a sustained effect for the desired duration of effect, and rapid reduction in effect after this period of time. The benzodiazepines tend to have longer half-lives than the nonbenzodiazepines but carry a greater risk for residual sedation. The melatonin receptor agonist ramelteon has a short half-life and is not indicated for sleep maintenance.
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One way to affect the duration of action of medications for insomnia is by choosing a medication with a short or long half-life. The half-life of a medication is the length of time required for the plasma level of drug to fall to half of a certain measured level.[1] Figure 1 is an example of a compound with a 1-hour half-life. The concentration of the medication peaks and then falls as it is metabolized. Figure 1 also illustrates the concept of minimum effective concentration, that is, a concentration below which a medication is unlikely to have continued therapeutic effect. For example, the theoretical hypnotic agent represented in Figure 1 would be expected to be of benefit for sleep initiation but would be unlikely to have any continued hypnotic effect after about 3.5 hours. This could be of benefit for a patient with exclusively sleep initiation complaints but no sleep maintenance problems. Alternatively, a patient without sleep initiation complaints but with only sleep maintenance problems could take a medication with this kind of action in the middle of the night, with the expectation it would promote the ability to return to sleep quickly but would be cleared by morning, avoiding risks of residual morning sedation.

A drug with a longer half-life would be expected to have a longer duration of action. Figure 2 illustrates a compound with the same maximum concentration (C_{max}) as the medication in Figure 1, but with a half-life of 2 to 3 hours. Because of this longer half-life, it would be expected to promote sleep for a longer period of time. This medication might have a hypnotic duration of 6 to 7 hours, which could make it a rational choice for patients who hoped to be able to sleep for that period of time. However, for patients with a desired sleep duration of 8 hours, this medication might not last long enough. The longer half-life medication (Figure 2) would also generate a greater risk of residual sedation than the 1-hour half-life medication, a consideration for patients who do not have 6 to 7 hours to sleep at night or who metabolize medication more slowly.

An ideal compound for promoting sleep over a desired period of time would be an agent with an immediate onset of action, a sustained effect for the desired period of time, and rapid offset after the period of time has elapsed. Figure 3 defines the pharmacokinetic profile of such a medication. Unlike the other medications shown in Figures 1 and 2, the pharmacokinetic profile of this idealized agent would resemble a square wave, with a rapid rise to effective level, a stable concentration for the desired period of action, and equally rapid decline prior to awakening. Modified-release formulations come closest to this ideal; however, one formulation of medication would not be a

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Figure 1. Pharmacokinetic Profile of a Hypothetical Medication With a Half-Life of 1 Hour

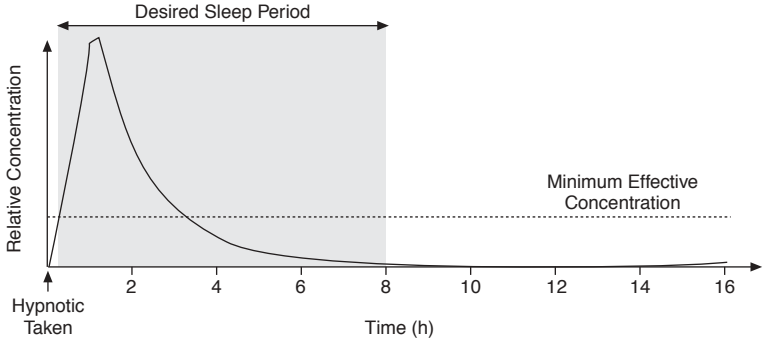


Figure 2. Pharmacokinetic Profile of a Hypothetical Medication With a Half-Life of 2 to 3 Hours

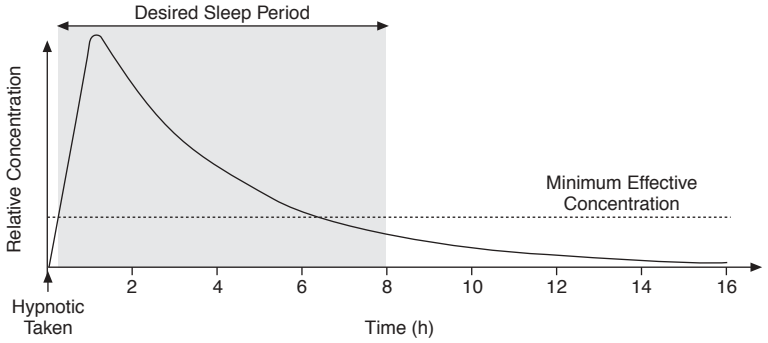
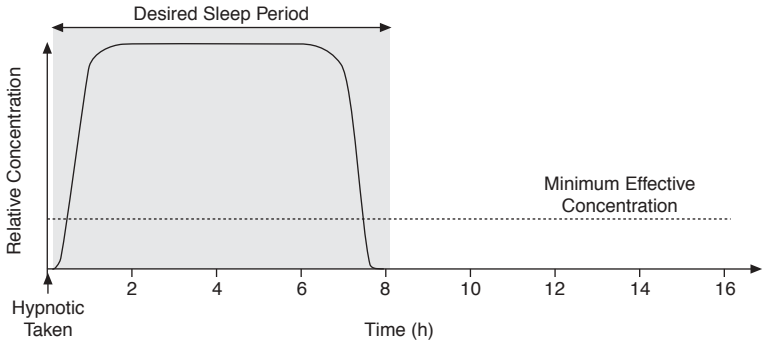


Figure 3. Pharmacokinetic Profile of an Ideal Medication for Sleep



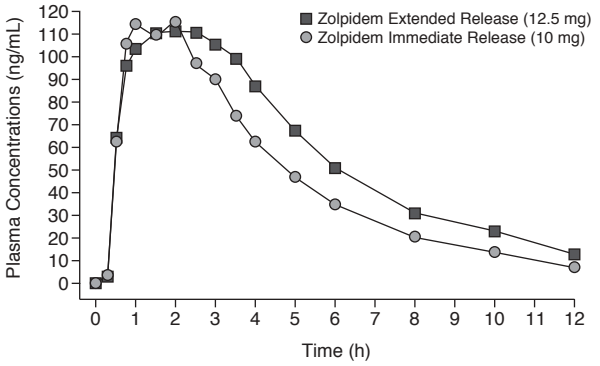
perfect fit for every patient. A patient who desires to sleep for 6 hours, for example, would require a different medication or formulation from one who hopes to sleep for 8 hours.

Dose also has an effect on duration of action. As the dose of the medication increases, so does the level of concentration. At higher doses the medication will have a longer duration of action, but also a higher peak level. As a consequence, the probability of side effects will increase as well.

PHARMACOKINETIC PROFILES OF HYPNOTIC MEDICATIONS

The medications that are available for the treatment of insomnia, which include the benzodiazepines, the nonben-

Figure 4. Pharmacokinetic Profile of Extended-Release Zolpidem[a]



[a]Reprinted with permission from Weinling.[14]

zodiazepine hypnotics, and the melatonin receptor agonist, have a broad range of half-lives. This range gives physicians the opportunity to choose medications that best match the sleep needs of their patients.

Benzodiazepines

Most of the benzodiazepines approved for the treatment of insomnia have longer half-lives and longer durations of action than the approved nonbenzodiazepines. This longer duration of action is likely to become a problem when the therapeutic effect of a sleep-promoting agent extends into the period when patients want to be awake, i.e., when continued sedation becomes a side effect. Flurazepam, for example, has a half-life that ranges from 47 to 100 hours.[2] Obviously, such medications do not promote continuous sleep lasting for several days. However, these compounds with long half-lives promote a longer sleep duration, and therefore, a greater risk of residual sedation.

Other benzodiazepines have shorter half-lives than flurazepam, but most still have longer half-lives than the nonbenzodiazepine hypnotics. These include quazepam (27 to 43 hours),[3] estazolam (10 to 24 hours),[4] and temazepam (3.5 to 18.4 hours).[5] Triazolam has a half-life similar to that of the nonbenzodiazepines, 1.5 to 5.5 hours.[6]

Nonbenzodiazepine Hypnotics

The nonbenzodiazepine hypnotics provide effective and safe treatment for insomnia.[7] The approved nonbenzodiazepine hypnotics currently available for the treatment of insomnia include zaleplon, zolpidem, zolpidem extended-release, and eszopiclone. The half-life and the duration of action of each of these nonbenzodiazepines are short compared with most of the benzodiazepines. These hypnotics have a low probability of residual sedation. They also do not appear to be associated with induction of tolerance.[8–10]

Zaleplon has a half-life of about 1 hour,[11] which is short compared with other hypnotic medications. The rapid onset of action of zaleplon provides effective sleep promotion, but because of its short half-life, it is not effective for sleep maintenance. Zaleplon is approved for the short-term treatment of insomnia.

The original formulation of zolpidem has a relatively short half-life of 2.6 hours[12]; the extended-release formulation of this medication has demonstrated a slightly longer half-life of 2.8 hours.[13] A comparison of zolpidem plasma concentration–time profiles after a single oral dose compared with an immediate-release formulation showed that the mean plasma concentration–time profiles were similar (Figure 4)[14] but that the slow release proportion of medication in the extended-release version of the medication shifts the C_{max} so that higher blood levels are present for a longer period of time, promoting extended sleep maintenance.[14] While the original formulation of zolpidem is approved for the short-term treatment of insomnia, zolpidem extended-release is not restricted to short-term use.

Eszopiclone has a somewhat longer half-life (approximately 6 hours) and a longer duration of action than zolpidem and zaleplon.[15] Eszopiclone has been shown to improve sleep maintenance,[16] but its longer half-life would be expected to produce greater risk for residual sedation than would other nonbenzodiazepines. Eszopiclone is not restricted to short-term use.[15]

Melatonin Receptor Agonist

Ramelteon (8 mg/day) is the only melatonin receptor agonist currently approved for the treatment of insomnia. Because ramelteon has a high selectivity and potency at melatonin receptor sites thought to regulate sleep and circadian rhythm, its mechanism of action is unlike any other sleep medication. It has a half-life of 1 to 2.6 hours and is only indicated for sleep initiation.[17] Ramelteon is not restricted to short-term use.

CONCLUSION

Physicians and patients must work together to establish a treatment plan that is safe and effective and tailored to the sleep needs of the individual patient. Not all patients with insomnia have the same needs, nor do they respond to medication in exactly the same way. Physicians must be educated about the difference between medications and need to recognize that the range of sleep patterns and sleep needs of their patients require individualized selection of medications that will be safe and effective for each patient.

Drug names: estazolam (ProSom and others), eszopiclone (Lunesta), flurazepam (Dalmane and others), quazepam (Doral), ramelteon (Rozerem), temazepam (Restoril and others), triazolam (Halcion and others), zaleplon (Sonata), zolpidem (Ambien), zolpidem extended-release (Ambien CR).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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