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Zaleplon (Starnoc[®])

Introduction

Insomnia has an enormous impact in our society on overall health, productivity and quality of life. Up to 35% of adults experience some form of insomnia. As many as 57% of patients reporting insomnia may have a psychiatric condition or may develop one within one year. Insomnia can be classified into three major categories: transient insomnia, lasting 2 – 3 days, short-term insomnia, persisting for up to 3 weeks, and long-term or chronic insomnia, lasting more than 3 weeks.

In managing insomnia, the patient should be assessed for underlying medical, psychiatric, or environmental factors to rule out these causes. In addition, the importance of behavioral modifications and good sleep hygiene should not be overlooked. Quite often, cases of transient insomnia and short-term insomnia can be managed successfully upon adherence to these non-drug measures.

In cases where non-drug interventions fail to resolve the sleep disorder, pharmacologic treatment can be considered. In choosing the appropriate hypnotic agent, one needs to consider the safety and pharmacokinetic profile of the drug, as well as patient factors such as age, comorbid illness(es), and concomitant medication(s).

With most hypnotic agents, the goal of treatment is to bring forth restorative sleep with minimal impact on daytime functioning. In this regard, one aims to use the lowest effective dose of a sleep medication for a short duration, which is usually 1-4 weeks. If sleep medication is required beyond this treatment period, further investigation into the sleep disorder should be initiated. Prolonged use of sleep medication(s) can lead to adverse effects such as rebound insomnia, residual daytime sedation, tolerance to the effects of the medication(s), and drug dependence. Nonetheless, long-term treatment of insomnia is indicated in certain individuals.

Drugs for treating insomnia include benzodiazepines, sedative antidepressants, chloral hydrate, and zopiclone. Barbiturates and antihistamines are seldom used as hypnotics agents in hospital settings nowadays due to safety and efficacy considerations. Some patients prefer more “natural” products such as valerian and melatonin for sleep induction, but evidence to support their efficacy is conflicting. Recently, a new hypnotic agent, zaleplon, has been approved for treating insomnia and a review of this drug will be presented in the paragraphs to follow.

Pharmacology

Zaleplon is a short-acting hypnotic agent that is structurally unrelated to benzodiazepines, barbiturates or other known hypnotics. Zaleplon acts specifically at the ω -1 benzodiazepine (ω = omega) site on the γ -aminobutyric acid subtype A ($GABA_A$) complex. This drug shows sedative, anxiolytic, muscle relaxant, and anticonvulsive effects. However, as zaleplon preferentially binds to the ω -1 benzodiazepine receptor site, the latter two effects are not likely to be significant at the normal prescribed doses. Zaleplon also does not seem to alter the normal sleep architecture.

Pharmacokinetics

Zaleplon is a lipophilic compound, with a quick onset of action of 15-30 minutes and an elimination half-life of approximately 1 hour. The bioavailability is about 30% due to extensive pre-systemic metabolism. Zaleplon is metabolized primarily by aldehyde oxidase to an inactive metabolite. The remaining portion is metabolized by the cytochrome P450 CYP3A4 isoenzyme.

Food prolongs the absorption of zaleplon and delays the peak concentration by about 3 hours. Therefore, this medication should not be taken with or immediately after food. Clinical data suggest that the

pharmacokinetic profile of zaleplon does not differ significantly between adults and the elderly, nor does it differ between men and women. In addition, this drug's pharmacokinetic profile is not substantially altered in patients with renal insufficiency. Thus, no dosage adjustments are required in these patients.

Drug Interactions

Co-administration with cimetidine increases the plasma concentration of zaleplon, whereas concurrent use with rifampin will significantly decrease the bioavailability of zaleplon. As this drug is partially metabolized by the cytochrome P450 3A4 system, drugs that inhibit or induce this enzyme can alter zaleplon plasma concentrations. Inhibitors of the CYP-450 3A4 enzyme can increase the effect of zaleplon and these include erythromycin, fluoxetine, nefazodone, and grapefruit juice.

Efficacy

Preliminary data suggest that zaleplon improves sleep latency, time to return to sleep from a previously awakened state, and sleep efficiency. As zaleplon has a quick onset of action, it is especially useful in patients whose main difficulty is initiating sleep. In patients who do not fall asleep despite escalating doses of zopiclone or a benzodiazepine, switching to zaleplon may resolve the problem. A quick onset of action also means that zaleplon can be considered for use as PRN medication in situations where an immediate hypnotic effect is desired, such as the case in patients who experience awakenings in the middle of the night.

Zaleplon, with a short duration of action, has shown to have little residual daytime effects. For this reason, this drug may be a useful alternative for those who do not wish to experience any next-day sedation or cognitive impairment.

However, the short half-life of this drug renders it less suitable for patients who have difficulty maintaining their sleep. In these instances, the drug will lose its hypnotic effect, and the patient may be awakened prior to a full night's sleep. Rebound insomnia tends to occur more frequently in hypnotic agents with shorter half-lives. Although preliminary data from zaleplon indicate a low incidence of rebound insomnia, one should be aware that the potential exists for this effect.

Adverse Effects

The most common side effects of zaleplon are headache, dizziness and somnolence. Other adverse effects that have been reported include gastrointestinal complaints, dysmenorrhea, and central nervous system (CNS) symptoms such as depression, nervousness, and anxiety.

Similar to other hypnotic agents, there is a risk for tolerance, cognitive impairment, dependence, and withdrawal effects. Concurrent use with other psychotropic medications can produce additive adverse CNS effects. The safety of zaleplon use during pregnancy has not been established. Small amounts of the drug are excreted in breast milk and so caution is advised in breast-feeding women who use this medication.

Dosing and Administration

Zaleplon is available in 5mg and 10mg capsules. The recommended dose for adults is 10mg, administered immediately before bedtime or after the patient has gone to bed, but has difficulty falling asleep. A dose above 20mg is not recommended. For elderly and debilitated patients, the recommended dose is 5 mg.

Zaleplon should not be taken unless there are four or more hours of sleep remaining before the patient must be active again.

Summary

Zaleplon is the newest approved hypnotic agent. Important beneficial attributes of this drug are:

- Fast onset
- Lack of active metabolites
- Preservation of normal sleep architecture
- Low incidence of daytime impairment or sedation

Some potential drawbacks are:

- Potential for rebound insomnia
- Lack of long-term data on safety and efficacy
- Higher cost
- Potential for drug interactions
- Caution for use in those with hepatic impairment

Zaleplon has two distinguishing features (fast onset and short half-life) that render it a useful agent in the armamentarium of hypnotic agents. However, this drug is presently 4-5 times the cost of zopiclone, and much more higher in cost than most benzodiazepines. In the

treatment of insomnia, zaleplon cannot be considered first-line therapy at present, but can be considered as an alternative hypnotic agent in patients who show poor or no response to existing hypnotic agents. Zaleplon may also have a role in patients where a rapid onset of hypnotic effect is desired.

Zaleplon is presently not a benefit item under the provincial drug plan and is presently not listed in the Riverview Hospital Pharmacy Formulary. A cost comparison of selected hypnotic agents is presented in the following table:

Comparison of Cost:

DRUG	UNIT COST
Zaleplon 10 mg	\$1.23
Zaleplon 5 mg	\$1.00
Zopiclone 7.5 mg	\$0..20
Zopiclone 5 mg (brand name)	\$0.30
Temazepam 30 mg	\$0.11
Temazepam 15 mg	\$0.11
Oxazepam 30 mg	\$0.04
Lorazepam 0.5 mg	\$0.04
Lorazepam 1 mg	\$0.05
Trazodone 50 mg	\$0.12
Trazodone 100 mg	\$0.21
Chloral Hydrate 500 mg	\$0.20

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