What's new in therapeutics?

Modafinil: A gift to portmanteau

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Abstract

This article reviews the use of modafinil in palliative care, and its use in promoting vigilance and wakefulness. Modafinil's therapeutic and chemical class, mechanism of action, pharmacokinetics, indications, dosage, side effects, and drug interactions are also discussed. Modafinil seems to fit the requirements of portmanteau, using one drug to treat multiple symptoms.

Key words: α_1-antagonists, antidepressants, depression, fatigue, modafinil, palliative care, pharmacotherapy, pharmacokinetics, psychopharmacology, psychostimulants, symptom management, vigilance, wakefulness

Introduction

Psychostimulants are used in palliative care for a variety of symptoms including fatigue and depression. When used in terminally ill patients experiencing these symptoms, psychostimulants have proven to be useful where other agents have failed. While there is a fair amount of data regarding the use of methylphenidate and amphetamines in this setting, the same cannot be said for modafinil.

Therapeutic and chemical class

Modafinil is a vigilance and wakefulness-promoting central nervous system (CNS) stimulant. While its effects are similar to that of amphetamines and methylphenidate, modafinil is structurally and pharmacologically unique.[1]

Mechanism of action

The mechanism of action of modafinil is, to this point, unclear. However, a variety of actions have been proposed. Modafinil loses its effect in the presence of α_1-antagonists, such as prazosin, suggesting that it may have direct or indirect α_1-adrenergic agonism.[2] Additionally, while earlier studies suggest modafinil does not possess dopaminergic activity, recently published animal data demonstrate an increase of cerebral dopamine release in genetically modified canines and rats, following the administration of modafinil.[3] It has also been hypothesized that modafinil decreases the release of the inhibitory neurotransmitter γ-aminobutyric acid and increases the release of the excitatory neurotransmitter glutamate in the cortex, hypothalamus, and other areas of the brain.[2] Perhaps of greatest importance is modafinil's site of action, which is thought to be primarily localized to the anterior hypothalamus, whereas methylphenidate and amphetamine generally act throughout the striatum and cortex.[4] This characteristic may explain modafinil's more favorable side effect profile as well as its relatively low abuse potential.

Pharmacokinetics

Following oral administration, absorption of modafinil is rapid, with peak plasma levels occurring at two to four hours.[5] Food may decrease the rate, but not the extent of absorption;

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Table 1. Summary of possible CYP-450 interactions		
CYP-450 isoenzyme	**Nature of interaction**	**Possible implications**
CYP-3A4	Autoinduction at doses > 400 mg/d	Monitor closely when coadministered with drugs known to alter CYP-3A4 (*i.e.*, carbamazepine, phenobarbital, ketoconazole, cyclosporine).
CYP-2C19*	Inhibition	May increase levels of drugs metabolized via that pathway (*i.e.*, diazepam, phenytoin, TCAs).
CYP-2C9	Inhibition	May increase levels of drugs metabolized via that pathway (*i.e.*, warfarin, phenytoin), monitor appropriately when initiating or changing dose of modafinil.
*Clinically relevant only in the presence of CYP-2D6 deficiency.		

therefore, modafinil may be administered without regard to meals. Modafinil is well distributed to the tissues, with a volume of distribution of approximately 0.8 l/kg, and has a half-life of approximately 15 hours.[6] Sixty percent of absorbed drug is protein-bound, primarily to albumin; therefore, drug interactions stemming from competitive protein binding are unlikely.

Indications

Modafinil is indicated by the Food and Drug Administration (FDA) for the treatment of excessive daytime sleepiness associated with narcolepsy. However, its use is not limited to such patients. Modafinil has been used to promote vigilance and wakefulness in patients with cancer-related fatigue, and has been shown to be beneficial when used as an adjunctive antidepressant.[7,8]

Patients with illnesses such as cancer, Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD) commonly experience fatigue that interferes with activities of daily living (ADL), leading to a compromised quality of life.[7,9] While the etiology of fatigue varies, its treatment may not only relieve its symptoms, but also improve patients' overall ability to function. A recently published series of case studies, evaluating the use of modafinil in the treatment of chronic fatigue, demonstrate that the effectiveness of modafinil may be as high as 84 percent when used in patients with fatigue associated with diseases ranging from epilepsy to stroke.[7]

Depression is also a common problem among patients with terminal illness. The prevalence of major depression among patients with a medical illness has been estimated to be as high as 15 percent. Moreover, up to 30 percent of patients experience significant depressive symptoms.[10] Fortunately, approximately 80 percent of patients that receive conventional antidepressant therapy have a favorable response.[11] For patients that do not respond or have only a partial response, augmentation with modafinil may be beneficial. Case studies have demonstrated that modafinil, when administered as an adjunctive agent to patients meeting the *DSM-IV* criteria for major depression, produced a 50 percent decrease in Hamilton Rating Scale for Depression (HAM-D) scores in five of seven patients.[8] Doses used in these studies ranged from 100 mg to 200 mg daily.

Dosage

The recommended dose of modafinil when used to treat excessive daytime sleepiness is 200 mg, given either once daily in the morning, or in divided doses each morning and at noon. Doses up to 400 mg daily have been well tolerated, but it is unclear whether this higher dosage provides additional benefit. However, when used in the elderly, more conservative doses, such as 100 mg daily, may be warranted, owing to the observation that hepatic insufficiency and polypharmacy are more prevalent in this population. In addition, the recommended dose of 200 mg should be reduced by 50 percent when administered to patients with severe hepatic dysfunction.

Side effects

Modafinil is thought to act in areas of the CNS that are associated with the sleep-wake cycle, rather than inducing generalized excitation, such as that seen with methylphenidate and amphetamines.[4] The fact that modafinil

may act more locally within the CNS seems to be responsible, at least in part, for its relatively low incidence of side effects. In clinical trials, the most commonly reported adverse effects included headache, nausea, diarrhea, xerostomia, and nervousness. Most of these adverse effects were mild, and some were transient upon chronic dosing. While modafinil seems to be relatively safe, it may not be appropriate for use in patients with left ventricular hypertrophy or mitral valve prolapse, since, in clinical trials, a few of these patients have experienced exacerbations of symptoms including dyspnea, palpitations, angina, and transient ischemic T-wave changes. In addition, modafinil should be used with caution in individuals with a history of psychosis, as case reports have demonstrated that these patients may be at increased risk for developing symptoms, such as auditory hallucinations, secondary to modafinil use.

Drug interactions

As stated, modafinil is extensively metabolized by the liver via mechanisms that include hydrolytic deamidation and glucuronide conjugation. More importantly, a dose-dependent induction of CYP1A2, CYP2B6, and CYP3A4 has been observed during *in vitro* studies.[8] The induction of these isoenzymes may reduce serum concentrations of co-administered drugs that are dependent on these isoenzymes for their metabolism. Two members of the CYP450 family (CYP2C19, CYP2C9) have been identified as being inhibited by modafinil,[12] The inhibition of CYP2C19 is important in palliative care, since this isoenzyme acts as an ancillary pathway for tricyclic antidepressant (TCA) metabolism; therefore, patients receiving a TCA should be observed for signs of toxicity after initiation of modafinil. CYP2C9 is important in the metabolism of warfarin; therefore, the same caution should be exercised when these drugs are administered concomitantly.

Summary

Portmanteau (a French word meaning purse or wallet) is a term coined by Davis *et al.* to describe the concept of using one drug to treat multiple symptoms.[13] It has been suggested that using these types of drugs can significantly decrease the number of medications a patient is receiving, thereby decreasing the risk of drug interactions, improving outcomes, and increasing health-related quality of life. Modafinil seems to fit this description well. In addition to its ability to improve disease-related fatigue, modafinil seems to be an effective antidepressant. As clinical experience with this medication increases, other benefits may be elucidated.

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