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ARTICLE

Toxicity from modafinil ingestion

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Introduction. Modafanil, a non-amphetamine stimulant, is used for narcolepsy, sleep apnea, and shift work sleep disorder. There is little available information on the toxicity of modafinil overdose. *Method.* We performed a retrospective multi-poison center chart review of patients from 11 states who had a single substance ingestion of modafanil with follow up to a known outcome for the years 2000–2007. Data collected included age, gender, dose ingested, clinical effects, length of hospital stay, and medical outcome. *Results*. There were 137 patients, of whom 85 (63%) were female. Ages ranged from 1 to 82 years with a mean and median of 22 years (+18) and 20 years, respectively, with 43 patients (31%) aged <6 years. Most frequently reported clinical effects were tachycardia (n = 38), insomnia (n = 33), agitation (n = 27), dizziness (n = 25), and anxiety (n = 24). Forty-five patients were managed at home and 92 in a health-care setting, with only 23 (17%) requiring a medical admission. Therapies included benzodiazepines (n = 14), diphenhydramine (n = 5), β-blockers (n = 3), haloperidol (n = 2), IV fluid hydration (n = 2), and one each of nitroglycerin, epinephrine, benztropine, and promethazine. *Conclusions.* In this case series, clinical effects of modafinil overdoses were generally mild with predominantly tachycardia and CNS toxicity. However, clinically significant effects warranting specific therapy occurred in a minority of patients.

Keywords Modafinil; Acute poisoning; Stimulant

Introduction

Modafinil is a non-amphetamine stimulant the Food and Drug Administration (FDA) approved in 1998 to improve excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. Additionally, it has been investigated for use in attention deficit hyperactive disorder, treatment of post-anesthetic sedation, cocaine dependence and withdrawal, excessive sleepiness in Parkinsonism, and excessive fatigue in cancer patients.

The mechanism of action of modafinil is complex and not fully understood. Unlike sympathomimetics, it does not appear to depend on monoamine systems (1). There is conflicting evidence as to the extent to which α1-adrenergic agonism plays a role in the wakefulness properties of modafinil (2–4). Modafinil decreases γ-aminobutyric acid (GABA) release and increases glutamate release in the hippocampus and thalamus (5–8). Additionally, stimulation of hypocretin-secreting neurons in the perifornical area may in turn stimulate glutaminergic nerve firing as well as release of histamine in the tuberomammillary nucleus, influencing arousal and sleep–wake cycles (9,10). Modafinil appears to lack the peripheral sympathomimetic effects observed with amphetamines. The usual adult therapeutic dose is 200–400 mg daily in two divided doses. Neither efficacy nor safety has been established in children and adolescents <16 years of age. Common side effects with therapeutic use include headache, nervousness, anxiety, insomnia, dizziness, palpitations, nausea, and stomach ache. Skin rashes (erythema multiforme and Stevens–Johnson syndrome), psychiatric toxicity, and nervous system toxicity have been reported when its use has been studied in pediatric patients.

A search of the published literature up to February 2008 found very limited information on modafinil overdose or toxicity. Two small case series reported in abstract form and a single case of adverse drug reaction affecting a co-ingestant have been reported (11–13). During clinical trials, high doses (1,000–1,600 mg) were administered to 32 subjects, and

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several intentional acute overdoses administered to patients who ingested 4,000 mg and 4,500 mg were also reported (14). Excitation, agitation, insomnia, and tachycardia occurred. There was no life-threatening toxicity.

Limited acute toxicity data present a difficult dilemma in regard to triage and treatment decisions when faced with accidental or intentional overdoses of modafinil. Therefore, we performed a multi-center retrospective chart review of all patients reported to 15 poison centers covering 11 states. The objective was to describe toxic effects and dose information in order to develop triage and treatment guidelines for modafinil overdose.

Methods

A retrospective multi-center study of modafinil exposures was conducted. A search of the electronic database for cases from 2000 to 2007 was conducted at each of the participating centers to locate cases meeting inclusion criteria. The participating poison centers were the Kentucky Regional Poison Center, the Texas Poison Center Network – Central Texas Poison Center, Central Ohio Poison Center, Massachusetts and Rhode Island Poison Center, Florida Poison Center Network – Jacksonville, the Hennepin Regional Poison Center, Maryland Poison Center, and the University of Kansas Hospital Poison Center. Inclusion criteria were single substance exposure (modafinil) and patient followed to known outcome. Exclusion criteria were presence or history of co-ingestants and inadequate follow-up to determine medical outcome.

Once cases were identified, all personal identifiers, except patient age and date of occurrence, were removed. These cases were sent to the primary investigator for input into another database and subsequent analysis. The data collected included age, gender, weight, dose ingested, symptoms, duration of clinical effects, site of exposure, treatment site [home or health-care facility (HCF)], length of hospital stay, treatment, and clinical outcome. Definition for reason for exposure and medical outcome categories were standards used by all US poison centers and have been published in detail elsewhere (15).

Dose ingested was obtained by patient history, which included calculation by pill count of medication missing or by observed amount ingested. In cases where the history of dose ingested was not clearly documented, the dose was considered unknown. Those patients managed at home (outside of a HCF) were followed by telephone periodically throughout the day following the ingestion, with inquiries about the occurrence of symptoms and the condition of the patient. Clinical effects such as tachycardia and hypertension were not assessed in home-managed patients. However, outcome severity (no effect and minor, moderate, and major effect) and obvious clinical effects such as vomiting, hallucinations, hyperactivity, and seizures were assessed.

Statistical analysis was performed using EpiInfo version 3.4.1 (Center for Disease Control and Prevention). The study was either approved or determined to be exempt by the Institutional Review Board at each of the participating poison centers.

Results

One hundred and thirty-seven patients met inclusion criteria, of which 85 (62%) were female. Mean age was 22 years with a range from 1 year to 82 years. Forty-three patients (31%) were <6 years of age and 18 patients (13%) were school age children (617 years).

The majority (67%) of the total study population received direct medical evaluation; however, only a minority required hospital admission (17%). See Table 1 for location of patient management.

Thirty-eight patients experienced tachycardia. Mean maximum recorded heart rate was 120 bpm with a range of 100 to 150 bpm. No conduction disturbances were noted. Of the five patients with reported hypertension, the mean systolic and diastolic pressures were 159 and 93 mmHg, respectively. Clinical effects reported are listed in Table 2.

Dose ingested was known for 108 patients (79%). Mean and median dose ingested was 1,031 and 400 mg, respectively, with a range of 50–7,000 mg. Medical outcome by dose ingested is presented in Table 3.

Therapies included benzodiazepines (n = 14), diphenhydramine (n = 5), β-blockers (n = 3), haloperidol (n = 2), IV fluid hydration (n = 2), and one each of nitroglycerin, epinephrine, benztropine, and promethazine.

The reasons for exposure are listed in Table 4. Eleven of the "Unintentional – general" (18%) category were adults who had taken a significant other's medication by mistake.

The single major effect was a 19-year-old male who gave a history of ingesting 6 g of modafinil. He presented with agitated delirium after having been missing through the night and found naked in the woods the following morning. Vital signs were as follows: heart rate, 140 bpm; blood pressure, 150/93 mmHg; temperature, 98.4°F. A urine drug screen for opiates, cocaine, amphetamines, benzodiazepines, and barbiturates was negative. The patient's initial triage history reported that he had smoked phencyclidine (PCP), but during

Table 1. Location of patient management

Location of patient management	Number of patients (%)
Onsite non-HCF (e.g., home)	45 (33%)
Emergency department and discharge	52 (38%)
Hospital (medical) admission	23 (17%)
Emergency department and psychiatric admission	15 (11%)
MD office	2 (2%)

Table 2. Clinical effects reported from modafinil exposure

Clinical effect	Number of patients	Percentage of total group
Tachycardia	38	28
Insomnia	33	24
Agitation	27	20
Dizziness	25	18
Increased anxiety	24	18
Nausea	11	8
Dry mouth	9	7
Headache	9	7
Dystonia	7	5
Chest pain	6	4
Hypertension	6	4
Tremors	6	4
Vomiting	4	3
Hyperactivity/"giddy"	3	2
Diarrhea	3	2
Numbness	2	1
Elevated CPK	2	1
Seizure	1	1
Delirium	1	1
Hallucinations	1	1
Palpitations	1	1
Blurred vision	1	1

CPK, creatine phosphokinase.

a second history by the emergency department (ED) physician, the patient denied PCP use and admitted to taking a newly filled prescription of 30 tablets of 200 mg modafinil. The drug screen did not test for PCP. Laboratory values were unremarkable except for an elevated creatine phosphokinase (CPK) of 54,158. The patient received benzodiazepines for sedation and required 48 h for his mental status to clear.

The single patient with a seizure was a 45-year-old woman with a history of a seizure disorder, who was non-compliant with her phenytoin use. She had ingested 800 mg of modafinil. She did not experience tachycardia or agitation and was admitted for psychiatric evaluation after her ED evaluation.

Discussion

Overdoses of modafinil only are infrequent, considering that this report involved cases from 15 poison centers from 11 states over a period of 8 years. Among the 137 cases reported here, grave or life-threatening toxicity was rare. This is similar to the findings of two smaller case series, with a total of 56 adult and pediatric patients (12,13). However, clinically significant effects warranting specific therapy developed in a minority of patients in our case series. Agitation, increased anxiety, chest pain, elevated CPK, and dystonias were the clinical effects that most frequently triggered specific therapy.

Modafinil is classified as a Schedule IV drug by the US Drug Enforcement Agency and may cause psychoactive and euphoric effects, with alterations in mood and perception. Intentional abuse was recorded in only seven cases over the 8-year period, suggesting modafinil is not commonly abused. It is unclear if this low number of abuse cases is because of limited availability due to the select group of patients who are prescribed modafinil or is a reflection of reduced abuse potential of modafinil. Other potential findings might be 1) the fact that cases involving co-ingestants were excluded from this study and it is possible that some of these cases involved abuse of modafinil with other substances and 2) patients of modafinil abuse may not have contacted a poison center for consultation.

In this study, we evaluated a subgroup of children <6 years of age. We found no significant toxicity with <400 mg ingestion. An abstract of a smaller case series of pediatric modafinil ingestion reported no moderate or major outcomes. Dosage was not reported (13). Modafinil is available as a 100 and 200 mg tablet. This suggests that ingestion of 200 mg or less may be safely observed outside of the HCF in a small child. However, with only 43 children under 6 years of age, this study was insufficiently powered to pick up negative outcomes. Further study of an appropriate triage dose for small children may be warranted.

Study limitations include the retrospective design and reporting bias introduced by the voluntary nature of reporting to poison centers. Laboratory confirmation that modafinil

Table 3. Medical outcome versus dose ingested by history

	No effect	Minor effect	Moderate effect	Major effect
All patients (n = 137)	63 (46%)	51 (37%)	22 (16%)	1 (1%)
Patients with known dose (n = 108, 79% of total group)	51 (47%)	44 (40%)	13 (12%)	1 (1%)
Mean and median dose	528 mg, 200 mg	1,272 mg, 600 mg	1,808 mg, 1,200 mg	6,000 mg
Range	50–6,000 mg	100–7,000 mg	400–5,000 mg	
All patients <6 years (n = 43)	36 (84%)	6 (14%)	1 (2%)	0
Patients <6 years with known dose (n = 32, 74% of age group)	27 (84%)	4 (13%)	1 (3%)	0
Mean and median dose	125 mg, 100 mg	250 mg, 250 mg	400 mg	
Range	50–400 mg	100–400 mg		

Table 4. Reason for modafinil ingestion

Reason for ingestion	Number of patients (% of total)
Unintentional – general	60 (44)
Suspected suicide attempt	35 (26)
Mis-dosing	21 (15)
Adverse drug reaction	8 (6)
Intentional – abuse	7 (5)
Intentional – misuse	3 (2)
Intentional – unknown	3 (2)

was actually ingested is not possible, because plasma modafinil concentrations are not routinely available.

In summary, we found in this case series that clinical effects of modafinil overdoses were generally mild with predominantly tachycardia and CNS toxicity. However, clinical effects warranting specific therapy occurred in a minority of patients. Ingestion of 200 mg or less in a small child may be safely observed outside of the HCF.

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