

More Data Back Value of Later School Start Times

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FROM THE ARCHIVES OF PEDIATRIC AND ADOLESCENT MEDICINE

Delaying the start of school for as little as 30 minutes not only improved several measures of sleep in adolescents at a boarding school, it also improved depressive symptoms, the motivation and alertness to learn, and even some dietary habits, a study shows.

"The results of this study add to the growing literature supporting the potential benefits of adjusting school schedules to adolescents' sleep needs, circadian rhythm, and developmental stage and of optimizing sleep and alertness in the learning environment," said Dr. Judith A. Owens of Hasbro Children's Hospital, Providence, R.I., and her associates.

They assessed the impact of delaying the school start time from 8:00 a.m. to

8:30 a.m. at a college-prep boarding and day school in southern New England for 357 students in grades 9-12. Participating students anonymously completed the 8-page Sleep Habits Survey before (225 students) and after (201 students) a 2-month trial period in which the daily class schedule was delayed for 30 minutes (Arch. Ped. Adolesc. Med. 2010;164:608-14).

The Sleep Habits Survey covers typical sleep and wake behaviors during the

preceding week, sleep- and wake-behavior problems such as difficulty falling asleep and difficulty awakening, depressed mood, and daytime sleepiness under varying conditions.

After the change in school start time, students showed a significant 45-minute increase in sleep duration on school nights.

This was attributable to both waking later on school mornings and going to bed earlier on school nights.

Anecdotal comments indicated that once the adolescents perceived the benefits of getting more sleep in the mornings, they elected to go to bed earlier as well.

The proportion of students who reported that they rarely or never got enough sleep declined significantly from 69% to 34%, as did the proportion who reported that they "never" got a good night's sleep, which dropped from 29% to 12%.

The percentage of students who got fewer than 7 hours of sleep on school nights decreased markedly, from 34% to 7%. The percentage who got at least 8 hours of sleep on school nights rose substantially, from 16% to 55%.

Similarly, the study subjects' perception of their daytime sleepiness and related impairments showed highly significant improvements. The percentage of students who reported being bothered by feeling "too tired and unmotivated" to do schoolwork, socialize, or participate in sports much of the time decreased significantly.

Data from the school's health center supported the students' perception that they were less fatigued after school start time was delayed. Significantly more students visited the health center for fatigue-related symptoms before the intervention than afterward, while visits for other medical concerns showed no change.

Scores on a measure of depressed mood were significantly negatively correlated with sleep duration on both surveys. After school start time was delayed, the percentage of students who rated themselves as at least somewhat unhappy or depressed decreased significantly from 66% to 45%, as did the percentage who reported feeling irritated or annoyed much of the time (from 84% to 63%).

This benefit in depressive symptoms is particularly noteworthy, "given the recent concerns raised regarding the relationship between insufficient sleep and both depressive symptoms and suicidal ideation in adolescents," Dr. Owens and her colleagues said.

The researchers cautioned that this study was limited in that it did not include a control group and relied on retrospective subjective self-reports rather than on objective measures of sleep variables.

Disclosures: The study was sponsored by Lifespan Hospitals of Rhode Island, a not-for-profit hospital network.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

FANAPT caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m² basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m² basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m² basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

There are no adequate and well-controlled studies in pregnant women. FANAPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of FANAPT on labor and delivery in humans is unknown.

8.3 Nursing Mothers

FANAPT was excreted in milk of rats during lactation. It is not known whether FANAPT or its metabolites are excreted in human milk. It is recommended that women receiving FANAPT should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

8.5 Geriatric Use

Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with FANAPT in pre-marketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia [see *Boxed Warning and Warnings and Precautions (5.1)*]. The safety and efficacy of FANAPT in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with FANAPT, vigilance should be exercised.

8.6 Renal Impairment

Because FANAPT is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of FANAPT. Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations (C_{max}) of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 any of the three analytes measured. AUC_{0-∞} was increased

by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

8.7 Hepatic Impairment

A study in mild and moderate liver impairment has not been conducted. FANAPT is not recommended for patients with hepatic impairment.

8.8 Smoking Status

Based on *in vitro* studies utilizing human liver enzymes, FANAPT is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FANAPT is not a controlled substance.

9.2 Abuse

FANAPT has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, FANAPT, will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of FANAPT misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of FANAPT was documented in eight patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a three-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a four-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms where those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension) of FANAPT.

10.2 Management of Overdose

There is no specific antidote for FANAPT. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

16 STORAGE

Store FANAPT tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect FANAPT tablets from exposure to light and moisture.

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