Barry K. Logan,[1,2] *Ph.D. and Fiona J. Couper,*[2] *Ph.D.*

Zolpidem and Driving Impairment

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ABSTRACT: Zolpidem, a non-benzodiazepine hypnotic, was identified in the blood of 29 subjects arrested for impaired driving. Zolpidem concentrations ranged from 0.05 to 1.4 mg/L (mean 0.29 mg/L, median 0.19 mg/L). In the subjects whose cases we reviewed where zolpidem was present with other drugs and/or alcohol, symptoms reported were generally those of CNS depression. Symptoms included slow movements and reactions, slow and slurred speech, poor coordination, lack of balance, flaccid muscle tone, and horizontal and vertical gaze nystagmus. In five separate cases, where zolpidem was the only drug detected (0.08–1.40 mg/L, mean 0.65 mg/L, median 0.47 mg/L), signs of impairment included slow and slurred speech, slow reflexes, disorientation, lack of balance and coordination, and "blacking out." Although no quantitative relationship between blood concentrations and degree of driving impairment is currently possible, it is reasonable to conclude that because of its specific activity as a sleep inducer, blood concentrations consistent with therapeutic doses of zolpidem have the potential to affect driving in a negative way, and that concentrations above the normal therapeutic range would further impair a person's level of consciousness and driving ability.

KEYWORDS: forensic science, zolpidem, driving, impairment

Other workers have previously reported that subjects taking the popular sleep inducer zolpidem (Ambien®) have been arrested for impaired driving (1), and in our own jurisdiction, we have encountered a number of cases with similar fact patterns. This prompted us to review the literature on the pharmacology and performance effects of this drug, and to document the circumstances, indicia of impairment, patterns of combined drug use, and driving behavior in these cases in order to assist with the evaluation of future cases.

Methods

Cases of suspected drug-impaired driving are referred to the Washington State Toxicology Laboratory by law enforcement agencies for drug and alcohol testing. Cases where the alcohol concentration cannot reasonably account for the degree of impairment observed in the subject are tested by EMIT and gas chromatography/mass spectrometry (GC/MS) for drugs with weakly acidic and basic character. The enzyme multiplied immunoassay technique (EMIT) procedure screened for cocaine metabolites (cutoff limit 100 ng/mL), opiates (10 ng/mL), amphetamines (100 ng/mL), cannabinoids (10 ng/mL), methadone (100 ng/mL), phencyclidine (10 ng/mL), propoxyphene (100 ng/mL), barbiturates (100 ng/mL), benzodiazepines (50 ng/mL), and tricyclic antidepressants (100 ng/mL). The GC/MS methods are described elsewhere (2,3). Zolpidem (Fig. 1) is isolated in the basic fraction of the drug screen, and appears in the chromatogram in the same region as quinine and alprazolam. It has the mass spectrum shown in Fig. 2. When identified in a subject's blood, zolpidem was quantitated using a five-point calibration curve (0.00, 0.10, 0.25, 0.50, 1.00 mg/L). Calibration was determined to be linear over the range 0.05 to 2.00 mg/L, and the correlation coefficient was typically better than 0.990. The limit of quantitation (LOQ) was defined as 0.05 mg/L, the lowest concentration at which the assay was determined to be linear. Any peaks with the correct retention time, quantitating at less than 0.05 mg/L, but for which a mass spectrum of zolpidem was obtained, were reported as <0.05 mg/L.

In cases where the drug was identified, the circumstances of the incident, including alcohol or other drugs detected, driving behavior, subjects' appearance, statements, performance in field sobriety tests, etc., were tabulated from the arrest report and are included in Table 1.

Results and Discussion

In total, 29 cases of suspected impaired driving in which zolpidem was identified were encountered between January 1997 and December 1999. Concentrations ranged from <0.05 (LOQ) to 1.4 mg/L (mean 0–29 mg/L, median 0–19 mg/L). Zolpidem was usually present with other drugs including alcohol (9 cases), antidepressants (10 cases), narcotic analgesics (7 cases), muscle relaxants (5 cases), benzodiazepines (3 cases), and valproic acid (2 cases). In five cases, however, zolpidem was the only drug detected. In these cases the concentration range was 0.08 to 1.40 mg/L (mean 0.65 mg/L, median 0.47 mg/L).

Structurally, zolpidem is an imidazopyridine (Fig. 1), and unrelated to the benzodiazepines. It acts as a non-benzodiazepine agonist of $GABA_{A1}$ function, resulting in sedative/hypnotic effects, without significant anxiolysis, anticonvulsant, or muscle relaxation properties. It is prescribed for the short-term treatment of insomnia and other sleep disorders. The drug is normally prescribed in 5 to 20 mg doses, to be taken before going to bed. Its rapid absorption after oral ingestion (peak concentrations are achieved in 1 to 2 h), and short half-life (~1 to 2 h) make it very effective as a sleep inducer, promoting a short-lasting sleep with rapid onset, and limited potential for hangover effects.

Following administration of a single 15 mg oral dose of zolpidem, Mattila et al. (4) reported blood zolpidem concentrations of 0.196 ± 0.045 mg/L at 1.5 h, declining to 0.065 ± 0.013mg/L by 5.5 h. Following 10 and 20 mg doses, peak plasma concentrations (C_{max}) of 0.125 ± 0.015 mg/L and 0.232 ± 0.017 mg/L, respectively, have been reported by Greenblatt et al. (5). Time-to-peak

[1] State toxicologist, Bureau of Forensic Laboratory Services, Washington State Patrol, 2203 Airport Way S., Seattle, WA.

[2] Washington State Toxicology Laboratory, University of Washington, 2203 Airport Way S., Seattle, WA 98134.

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and half-lives for both the 10 and 20 mg doses were 1.7 and 2 to 2.2 h, respectively, and both doses effectively induced sleep. The pharmacokinetics appeared unchanged following 15 consecutive nights of administration of 20 mg (6). A review of other studies shows that C_{max} normally achieved in subjects following a 20 mg oral dose have been reported as between 0.192 and 0.324 mg/L at 0.75 to 2.6 h post-dose, and dose proportionality with respect to AUC and C_{max} have been reported over the dosage range of 2.5 to 40 mg (7). Concentrations of 0.05 mg/L or greater (the LOQ for this study) would likely represent levels present in the blood no more than 6 to 8 h after ingestion of a normal therapeutic dose, and would be on the low end of concentrations associated with a therapeutic effect. No differences in pharmacokinetics have been noted between ethnic groups or gender (7,8). Bianchetti et al. (9) have reported that time-to-peak blood concentrations appear unaffected by the presence of food in the stomach.

Zolpidem is metabolized oxidatively to a series of inactive hydroxylated metabolites (10). Metabolism appears to be directed through CYP450 3A4, 1A2, and 2D6. This raises the possibility of longer half-lives and greater AUC for zolpidem in patients taking medications with significant inhibitory effects on these P450 isozymes. These include the SSRI drugs fluoxetine, paroxetine, venlafaxine, and sertraline, which are substrates for, and inhibitors of, P450 2D6. Of potential significance is the observation that grapefruit juice ingestion appears to increase bioavailability of drugs subject to first-pass metabolism by P450 3A4 (11), and this may increase bioavailability of zolpidem.

Although less than 1% of a dose of zolpidem is reportedly excreted unchanged in the urine, Levine et al. (12) reported measurable zolpidem concentrations in urine of deceased subjects both in overdose and during therapeutic use. In the cases we reviewed, urine was tested in only one case and found to be qualitatively positive for zolpidem.

In the subjects whose cases we reviewed where zolpidem was present with other drugs, symptoms reported were generally those of CNS depression. Nine of these subjects were evaluated by drug recognition (DRE) officers, who expressed the opinion that the subject was under the influence of a CNS depressant. Of these nine cases, five involved erratic driving causing near collisions while the other four involved vehicle collisions. Signs of impairment included horizontal gaze nystagmus (HGN) (7 cases), vertical gaze nystagmus (5 cases), lack of balance and unsteady gait (8 cases), poor or slow coordination (7 cases), poor performance of standardized field sobriety tests (8 cases), slow and/or slurred speech (5 cases), muscle flaccidity (4 cases), and impaired or double vision (3 cases). One driver refused to perform the standardized field sobriety tests. The drivers usually had the general appearance of drowsiness, tiredness, confusion, and disorientation. However, symptoms associated with individual drugs cannot readily be resolved in poly-drug cases. Harvengt et al. (13) have reported some increase of impairment in alertness when zolpidem is given with other drugs with CNS depressant properties, including chlorpromazine, imipramine, and haloperidol.

In five cases zolpidem was the only drug detected. Concentrations ranged from 0.08 to 1.40 mg/L, with a mean of 0.65 mg/L, and a median of 0.47 mg/L. (Note, however, that because of the short half-life, any delay between the driving and the collection of the blood will result in a drop in the concentration.) Signs of impairment included slow and slurred speech, slow reflexes, disorientation and confusion, lack of balance and coordination, loss of short-term memory, and "blacking out." Horizontal gaze nystagmus was present in every case in which it was evaluated. The following histories are from these five DUI cases. All subjects underwent blood alcohol analysis, an EMIT screen for drugs of abuse and several prescription drug classes, and a GC/MS screen for acid,

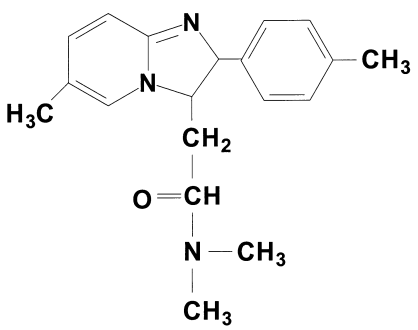

FIG. 1—*Structure of zolpidem.*

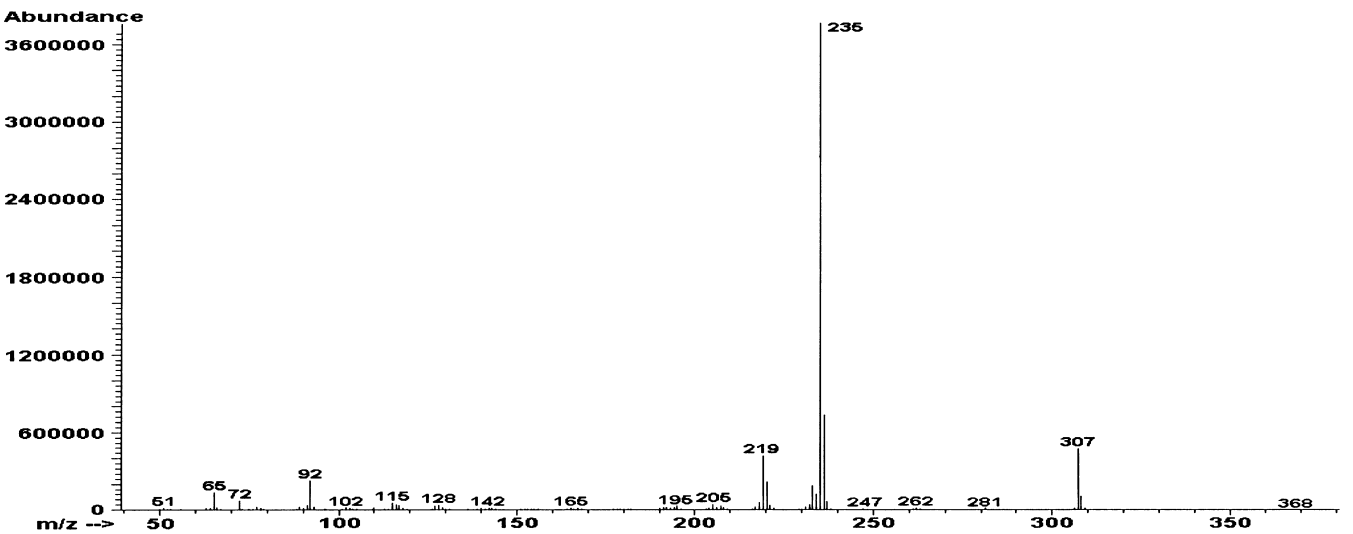

FIG. 2—*Electron impact mass spectrum of zolpidem.*

TABLE 1—*Circumstances and driving behavior in 29 drivers testing positive for zolpidem.*

Case	Age	Sex	Zolpidem (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)	Circumstances/Impairment
					ZOLPIDEM AND OTHER DRUGS		
1	U/K	F	<0.05	neg	ibuprofen	12.50	Involved in collision
					butalbital	<1.00	
2*	34	M	<0.05	0.05	sertraline	<0.05	Collision-causing driver—poor coordination, lack of balance, unsteady gait, HGN, VGN, impaired vision, slurred speech, muscle flaccidity, failed SFSTs
					norsertraline	<0.05	
					oxycodone	<0.05	
					hydroxyzine metabolite	pos	
					trazodone	0.06	
3	46	F	0.06	neg	acetaminophen	7.40	Collision-causing driver—poor SFSTs
					codeine	0.06	
					tramadol	0.12	
					tramadol metabolite	<0.05	
					amitriptyline	0.15	
					nortriptyline	0.09	
4*	41	M	0.07	0.02	meprobamate	16.40	Erratic driving, lack of balance, appeared under the influence of alcohol and drugs, slurred speech, slow movements, refused to perform SFSTs
					carisoprodol	3.00	
					hydrocodone	0.05	
5	50	F	0.10	neg	sertraline	0.11	Single-vehicle accident
					desmethylsertraline	0.60	
6*	32	F	0.10	neg	trazodone	0.73	Near collision—slow and unsteady coordination, lack of balance, slow speech, muscle flaccidity, poor SFSTs, appeared tired and groggy
					paroxetine	0.08	
					diazepam	<0.05	
					nordiazepam	<0.05	
7	40	M	0.13	neg	codeine	<0.05	Drove over curb, struck parked vehicle, appeared "under the influence of alcohol"
8*	44	F	0.15	neg	meprobamate	13.39	Erratic driving—poor coordination, HGN, double vision, lack of convergence, slow and slurred speech, muscle flaccidity, poor SFSTs, appeared confused
9	39	F	0.15	neg	meprobamate	24.60	Single-vehicle accident—lack of balance, slurred speech
					carisoprodol	7.20	
10	48	F	0.17	neg	fluoxetine	0.20	Collision-causing driver—erratic driving, poor coordination, lack of balance, unsteady gait, HGN, VGN, slow speech, poor SFSTs, (no formal DRE performed)
					methadone	0.07	
11	34	M	0.17	0.11	…	…	Single-vehicle accident
12	16	F	0.17	0.12	…	…	Erratic driving—violent and combative, appeared highly intoxicated
13*	52	F	0.19	neg	nordiazepam	0.07	Collision-causing driver—poor coordination, lack of balance, unsteady gait, HGN, VGN, lack of convergence, double vision, poor SFSTs, appeared sleepy
14*	46	M	0.20	neg	valproic acid	48.00	Collision-causing driver—unsteady gait, hand tremors, HGN, VGN, lack of convergence, repetitive speech, muscle flaccidity, appeared drowsy and dazed
					codeine	<0.10	
15	30	F	0.25	neg	desmethylsertraline	<0.05	Involved in accident–appeared disorientated and confused
					venlafaxine	0.72	
					desmethylvenlafaxine	0.11	
					valproic acid	85.40	
16	43	M	0.29	neg	methocarbamol	20.70	Collision-causing driver
					sertraline	<0.10	

continues

TABLE 1—*(continued)*.

Case	Age	Sex	Zolpidem (mg/L)	Alcohol (g/100 mL)	Other Drugs	Conc. (mg/L)	Circumstances/Impairment
17	…	M	0.31	neg	lorazepam	<0.05	Minor multi-car collision—causing driver was staggering around, admitted taking a sleeping pill about an hour before
					fluoxetine	0.57	
					norfluoxetine	0.34	
					chlorpheniramine	<0.05	
					dextromethorphan	<0.05	
18*	34	F	0.31	neg	sertraline	<0.05	Erratic driving—collision-causing driver, lack of balance, HGN, poor coordination, poor SFSTs
					trazodone	<0.05	
19*	30	F	0.33	neg	sertraline	0.10	Erratic driving, near collision–poor coordination, lack of balance, required assistance to walk, HGN, VGN, muscle flaccidity, poor SFSTs, appeared disorientated and confused
					norsertraline	0.13	
					doxepin	<0.05	
					desmethyl doxepin	<0.05	
20	48	M	0.36	0.26	trazodone	0.72	Single-vehicle accident—officer observed signs of impairment
					venlafaxine	0.06	
					desmethyl venlafaxine	0.21	
21	27	M	0.39	0.02	…	…	Collision-causing driver
22*	42	M	0.43	0.05	desalkylflurazepam	0.14	Collision-causing driver—HGN, poor SFSTs
					chlorzoxazone	26.40	
					acetaminophen	9.19	
23	32	F	0.48	neg	hydromorphone	0.01	Collision-causing driver
24	77	M	0.52	0.09	…	…	Collision-causing driver
					ZOLPIDEM ONLY		
25	17	M	0.08	neg	…	…	Erratic driving—lack of balance, slow reflexes, slow and slurred speech, double vision
26	59	M	0.43	neg	…	…	Collision-causing driver—unable to stand or walk, appeared dazed and disoriented
27	37	F	0.47	neg	…	…	Erratic driving—hit parked car and red stop light, slurred speech, lack of balance, fell asleep
28	52	F	0.88	neg	…	…	Erratic driving—HGN, VGN, poor SFSTs, slurred speech, lack of balance, amnesia, confused
29	44	F	1.40	neg	…	…	Single-vehicle accident—drove through red light, blacked out, no recollection

* Cases which underwent drug recognition evaluation expert (DRE)/Standard field sobriety tests (SFSTs) (19).
HGN–Horizontal gaze nystagmus; VGN–Vertical gaze nystagmus.

neutral and basic compounds as indicated above. In each case, all tests were negative for alcohol or for drugs other than zolpidem.

Case 1—A 17-year-old male was stopped by police for erratic lane travel. The subject's speech was slow and slurred, his pupils were dilated, and he was experiencing double vision, lack of balance, and lack of coordination. The subject also performed several field sobriety tests poorly (such as "finger dexterity" and "walk and turn" tests). The subject admitted to taking two white pills half an hour prior to the DUI stop, but did not know what pills they were. Several hours after the arrest, the subject was suffering from amnesia. Blood was drawn an hour and a half after driving, and the zolpidem concentration was 0.08 mg/L.

Case 2—A 59-year-old male was the causing driver in a two-car collision, having hit another vehicle at an intersection. The subject was unable to walk or stand without assistance and appeared dazed, lethargic, and disorientated. He had poor attention and was unable to perform any standardized field sobriety tests since he was unable to stand without support. He could not follow a stimulus for a test of nystagmus; however, his eyes showed a lack of smooth pursuit. The subject had taken two Ambien® tablets 30 min before the collision. Blood was drawn about an hour after driving, and the zolpidem concentration was 0.43 mg/L.

Case 3—A 37-year-old female was stopped by police for erratic driving. The subject had hit a parked car, garbage cans, and a stop sign, and then continued driving. The subject's speech was slow and slurred, her actions were very slow and she was unaware of what had just happened. The subject was extremely disorientated and had a marked upper body sway and lack of balance. She appeared very tired and fell asleep during the evaluation, and was suffering from amnesia. The interval between blood draw and driving was not known, but the blood zolpidem concentration was 0.47 mg/L.

Case 4—A 52-year-old female was stopped by police on the freeway after drifting into the northbound lanes while driving south, where she then continued to drive. The subject was slow to respond to police, and was disoriented, confused, and dazed once stopped. Her speech was slurred and shaky. She was dressed only in her underwear and a shirt, and told the officer she was returning from the store. Several standardized field sobriety tests were performed and the subject showed all six clues of horizontal nystagmus, and displayed vertical nystagmus also. She had extremely poor balance on the "one leg stand" and "walk and turn" tests, and could not touch the tip of her nose. When asked to estimate 30 seconds she stopped at 14. The subject could not remember her address and other details about herself, or her current circumstances. Blood was drawn an hour and forty-five minutes after driving, and the zolpidem concentration was 0.88 mg/L.

Case 5—A 44-year-old female was involved in a single-vehicle traffic accident. The subject had driven through a red traffic light, blacked out, and then driven down an embankment; however, she had no recollection of the event. The subject admitted being prescribed Ambien® and Remeron® (temazepam) for depression. The subject was alert but stated she must have blacked out. The officer did not detect any apparent signs of impairment; however, the subject was in considerable pain and could not perform any field sobriety tests. Blood was drawn an hour and twenty-five minutes after driving, and the zolpidem concentration was 1.40 mg/L.

In each case, in the absence of any other reasonable explanation for the impairment, it was attributed to the ingestion of zolpidem. There was no apparent correlation between the stated time of zolpidem ingestion and the corresponding blood concentration. Two separate subjects stated they had taken a single Ambien® tablet approximately 12 h prior to being arrested. The corresponding zolpidem concentrations were 0.33 mg/L and <0.05 mg/L. In another subject, zolpidem was taken within 1 to 2 h prior to the arrest, and the zolpidem blood concentration was 0.31 mg/L. In a similar case, a subject ingested two Ambien® tablets 30 min prior to the arrest, with the corresponding zolpidem blood concentration being 0.43 mg/L. Four or five 10 mg Ambien® tablets were allegedly ingested by another subject whose blood zolpidem concentration after five hours was <0.05 mg/L. Roger et al. (14) have reported a poor correlation ($r^2 = 0.21$) between dose and blood concentration of zolpidem at ten hours post administration.

During the same period a single case of a fatally injured driver testing positive for zolpidem was identified. This was a 49-year-old male who had multiple sclerosis and a seizure disorder. He was the causing driver in a three-car accident, going through a red light, and striking two other vehicles. He had been observed driving in an erratic manner prior to the accident. This individual had a blood drug concentration identified as follows: zolpidem 0.38 mg/L, carbamazepine 4.13 mg/L, hydroxyzine 0.36 mg/L, and pentazocine 0.18 mg/L. The other drug concentrations are in the normal therapeutic range, while the zolpidem concentration is sufficient to result in sedation and sleepiness, and consistent with concentrations in drivers showing significant impairment (see Table 1).

Other instances of drivers apparently impaired by zolpidem have been reported. Meeker (1) reported six cases of subjects driving under the influence of zolpidem, four of whom were involved in automobile accidents, three of which were single-vehicle crashes. Blood zolpidem concentrations in these cases ranged from 0.10 to 0.73 mg/L (mean 0.31 mg/L, median 0.17 mg/L), and symptoms included slow slurred speech, unsteady gait, confusion, and disorientation. This is consistent with observations in our subjects, including the overlap of the blood concentrations with the therapeutic range for sleep induction.

For many drugs, there is justifiably some reluctance in equating blood concentrations with a specific degree of impairment. We believe in the case of zolpidem, however, that this issue is clearer than for many other drugs, since the specific function of zolpidem is to induce sleep. For many other drugs the sedative effects are merely an inconvenient and often infrequent side effect. Therefore, for the purposes of determining whether the drug would affect a person, we advocate collection and analysis of a blood sample, as opposed to a urine sample. Because of its short half-life (~2 h), a morning urinary void would almost certainly test positive for zolpidem, even though the blood concentrations have fallen below effective levels. This short half-life also means that any delay between the time of driving and the blood draw could result in an appreciable drop in the blood zolpidem concentration, which should be taken into consideration in interpretation.

Rush (15) has reviewed the performance impairing effects of zolpidem and notes that the general consensus of these studies was that zolpidem did cause significant psychomotor impairment, equivalent to clinically effective doses of the sedative hypnotics triazolam, temazepam, or midazolam. Specifically, the studies reviewed found impairment in standard psychological tests such as picture recall, digit entry and recall, digit symbol substitution tasks, circular lights task, balance, time estimation, trails making,

and a variety of other tests of cognitive and psychomotor function. Tolerance to the sleep latency effects of the drug has been documented, making it most effective for treatment periods of less than 28 days. Tolerance to the psychomotor impairing effect has not been documented.

Information from the manufacturer (16) indicates that the drug should not be taken before driving, and in fact, that performance decrements might persist into the next day following use of the drug. Only 1.1% of patients in pre-clinical trials reported daytime drowsiness, however, and given the short half-life of the drug when properly managed hangover or residual effects should be unlikely, but risk of subjective feelings of sedation increases with an increasing dose (17). The *Physicians Desk Reference* (16) notes that patients taking zolpidem may experience effects similar to those associated with alcohol, and recommends that zolpidem not be taken with alcohol, since the effects would be additive.

Vermeeren et al. (18) have reported on the impairment of actual driving performance resulting from use of zopiclone and zaleplon, two other recently introduced hypnotic drugs used in the treatment of insomnia. They found that zopiclone (7.5 mg), with a half-life of 3.5 to 6 h administered within 10 h of the driving test, produced an increase in lateral drift (weaving) equivalent to a blood alcohol concentration of 0.10 g/100 mL. Zaleplon, on the other hand, with a much shorter half-life of 0.9 to 1.1 h, produced less next-day sedation, and no driving impairment when administered as little as 5 h prior to the driving test. Zolpidem, with a half-life of around 2 h, could reasonably be expected to exhibit a potential for hangover effects, intermediate between these two related hypnotic drugs.

Given the specific role of zolpidem as a sleep inducer, its simple pharmacokinetics, and the known relationship between fatigue, sleepiness, and decrements in driver performance and the associated increased accident risk, it appears reasonable to conclude that even normal doses of the drug have the potential to affect driving in a negative way for several hours after use.

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Additional information and reprint requests:
Barry K. Logan, Ph.D., DABFT
Director, Bureau of Forensic Laboratory Services
Washington State Toxicologist
Washington State Patrol
2203 Airport Way S.
Seattle, WA 89134
blogan@wsp.wa.gov