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Antiemetics With Concomitant Sedative Use in Civil Aviation Pilot Fatalities: From 2000 to 2006

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16. Abstract

Many drugs commonly used for the treatment of various ailments can be dangerous when used in combination. Antiemetics and sedatives are two drug classes that contain compounds that may have harmful side effects when mixed. A drug such as chlorpheniramine with antiemetic properties can dramatically increase the negative side effects of numerous drugs in the sedative class. This phenomenon is especially dangerous for pilots. Although many of these compounds are considered disqualifying and are not allowed by the FAA, their use does occur in the pilot community. Pilots that use these drugs may be unaware of the danger that can arise when compounds from these two drug classes are taken together. Our laboratory was interested in evaluating the circumstances surrounding accidents in which the pilot was found positive for drugs from each of these two classes. Epidemiological, toxicological, and aeromedical findings from pilots involved in such accidents were collected for a 7-year period, 2000 - 2006. Case histories, accident information, and the probable cause of the aviation accidents were obtained from the National Transportation Safety Board (NTSB). Toxicological information was obtained from the Civil Aerospace Medical Institute's (CAMI's) Forensic Toxicology Research Laboratory. There were 2,184 fatal aviation accidents over this time period. Of these accidents, 26 were found positive for compounds from both the antiemetic and the sedative drug classes. All 26 aircraft were operated under 14 CFR Part 91 as general aviation. All pilots involved in these accidents were male; 21 tested positive for a disqualifying substance that may have affected their ability to control the aircraft.

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INTRODUCTION

Taking antiemetic medications with concomitant sedative use can potentially lead to adverse drug interactions and negatively affect a pilot's ability to control his/her aircraft. These drug-drug interactions may have numerous effects on the body, including but not limited to, a reduction in the effectiveness of one or both of the drugs, unexpected and dangerous side effects, and/or an increase in the action of one or both of the drugs. Undesirable pharmacokinetic drug interactions may occur when certain compounds are either substrates, inducers, or inhibitors of the same pathway of metabolism as a co-administered compound(s).[1] Undesirable side effects can range from a simple reduction in therapeutic efficacy to severe toxicity and can result in death.[1] This study will examine the prevalence of pilot fatalities that, after toxicological analysis, were found positive for the potentially dangerous combination of antiemetics, sedatives and compounds with properties from these two classes of drugs. These accidents all occurred within the 7-year period, 2000 to 2006.

Antiemetics are compounds that are effective against vomiting and nausea. These drugs are prescribed to treat motion sickness as well as the adverse side effects of opioid analgesics, general anesthetics, and chemotherapy directed against cancer. This drug class includes 5HT3 receptor antagonists, dopamine antagonists, antihistamines (H_1 histamine receptor antagonists), steroids, benzodiazepines, and cannabinoids. Antihistamines are readily available and commonly used, but the undesirable effect of sedation can occur at even low doses.[2] For this reason, many over-the-counter (OTC) sleep preparations contain an antihistamine such as diphenhydramine.[3]

Sedatives are used to depress the central nervous system (CNS). These compounds can evoke calmness, relaxation, reduction of anxiety, drowsiness, slowed breathing, slurred speech, staggered gait, poor judgment, and slow reflexes. Some sedatives, such as ethanol, are addictive and may be abused to produce an overly-calming effect. At high doses, these drugs can cause unconsciousness and death. The most common types of sedatives and compounds with sedative properties seen in pilot fatalities include some antidepressants, barbiturates, benzodiazepines, typical/atypical antipsychotics, sedating antihistamines, sedative hypnotics, and ethanol.

Antiemetics and drugs with antiemetic properties such as metoclopramide, diphenhydramine (a sedating antihistamine), meclizine, midazolam, chlorpheniramine (a sedating antihistamine), and cannabinoids were all detected in pilot fatalities during routine toxicological examination. The following sedatives and compounds with sedative properties were also detected: ethanol, trazodone (Desyrel® a triazolopyridine antidepressant drug that is often co-prescribed with other antidepressants as a sleep-inducing agent because of its sedative effects),[1] pentobarbital, diazepam, oxazepam, temazepam, olanzapine, doxylamine, butalbital, meprobamate, fluoxetine, sertraline, and zolpidem. In 26 pilot fatalities, drugs from these 2 classes were taken simultaneously. This combination can have dangerous side effects that may affect the ability to control their aircraft. The toxicological results from these cases are described in detail below. Also presented is the National Transportation Safety Board's (NTSB's) probable cause for these accidents when available and whether the compounds present in the pilot's system were either a cause or a factor in the tragic event.

METHODS

All information pertaining to case history, accident information, and the probable cause of aviation accidents is available through the NTSB. The NTSB's database can be accessed online at www.ntsb.gov/ntsb/query.asp. Other information related to the incident and the airmen's medical certification was obtained from the Civil Aerospace Medical Institute's (CAMI's) Decision Support System (DSS) and Aeromedical Certification System, including the Document Information Workflow System (DIWS), which records medical information and flight experience reported by the pilot (on FAA Form 8500-8) to the Aviation Medical Examiner (AME) at the time of his/her medical examination and as part of his/her certification process.[4] CAMI's Forensic Toxicology Research Laboratory analyzes postmortem specimens collected from pilots involved in civil aviation accidents.[5,6] Toxicological information for cases in which pilots were found to have used both sedative(s) and antiemetic(s) was obtained from CAMI's ToxFlo™ (DiscoverSoft Development, LLC) toxicology database.

Case Histories

The following are brief descriptions of the 26 pilot fatalities that tested positive for both antiemetics and sedatives between 2000 and 2006. The compounds found in these cases, as well as the concentrations determined, if available, are presented. A summary of this information is presented in Table 1.

Case 1

A 46-year-old male died when his Cessna 150G collided with power lines. Following toxicological evaluation, the sedative nordiazepam, an active metabolite of diazepam (Valium®), was found in his blood and urine. This sedative compound was consumed in conjunction with the victim smoking marijuana, as 0.013 µg/mL of tetrahydrocannabinol (THC, the active compound in marijuana) was detected in his blood. Tetrahydrocannabinol carboxylic acid (THCA, an inactive metabolite of tetrahydrocannabinol) was present in the blood as well, and 0.028 µg/mL THCA was found in the urine. Additionally, tramadol was detected in blood and liver. Amphetamine and methamphetamine were each detected in his blood and urine.

Case 2

A 52-year-old male died after his plane struck the ground shortly after takeoff. The pilot was found positive for trazodone, an antidepressant with sedative side effects, at a concentration of 0.130 µg/mL in the blood. He had also taken chlorpheniramine, an OTC sedating antihistamine, which was found at a concentration of 0.079 µg/mL in his blood. Both of these compounds were also detected in the urine. Both ephedrine and pseudoephedrine were also detected in the pilot.

Case 3

A 40-year-old male was fatally injured in a helicopter accident. Doxylamine, an antihistamine with sedating effects, was found in his liver and kidney at concentrations of 0.292 µg/g and 0.089 µg/g, respectively, and was also detected in the urine. Diphenhydramine, a sedating antihistamine antiemetic, was found at levels of 2.28 µg/g in his liver, 0.753 µg/g in his kidney, and was also detected in the urine. Additionally, dextromethorphan, dextrorphan**,** pseudoephedrine, phenylpropanolamine (PPA), and acetaminophen were all detected in the urine. Medications containing doxylamine, a sedating OTC antihistamine, and diphenhydramine, an OTC antihistamine with sedative effects, are required to "carry warnings that indicate the possibility of drowsiness with their use and can call for caution while driving or operating machinery."[7]

Case 4

A 55-year-old male was fatally injured when his plane struck a bluff. The pilot had consumed both ethanol and butalbital, which are sedatives, and chlorpheniramine, an antiemetic antihistamine. Ethanol was found at a concentration of 61 mg/dL in the blood. Butalbital was found at a concentration of 2.506 µg/mL in the blood, and a therapeutic level of chlorpheniramine, 0.018 µg/mL, was also found. The pilot was also found positive for PPA, quinine, and acetaminophen.

Case 5

A 72-year-old male died when his aircraft struck a power line. The pilot was found to have taken the combination of doxylamine and chlorpheniramine; both antihistaminic medications may cause drowsiness when taken alone. Also found in his system were dextromethorphan and pseudoephedrine.

Case 6

A 38-year-old male died while maneuvering his homebuilt aircraft. This pilot was found with a disqualifying combination of drugs in his system. These included 126 mg/dL ethanol and 0.022 µg/mL diphenhydramine in his blood; diphenhydramine was also detected in the urine and liver. Additionally, cocaine, benzoylecgonine (a cocaine metabolite), and cocaethylene were detected in his urine.

Case 7

A 37-year-old male died when his aircraft struck a power line. Large amounts of the sedative ethanol were found in the pilot, including 124 mg/dL in blood, 74 mg/hg in brain, 214 mg/dL in urine, and 125 mg/hg in skeletal muscle. The antiemetic THC was also found in this pilot's blood, as well as 0.006 µg/mL THCA in his blood and 0.040 µg/mL THCA in his urine. The NTSB determined the probable cause of the accident to be "impairment by alcohol."

Case 8

A 70-year-old male died while operating an unregistered homebuilt aircraft. Following toxicological examination, these sedative compounds were detected: temazepam at 0.303 µg/mL, oxazepam at 0.46 µg/mL, and nordiazepam (not quantitated) in the urine. Nordiazepam was detected at 0.14 µg/mL in blood. The antiemetic compound diphenhydramine was found at 0.146 µg/mL in blood, and it was also detected in urine. Additionally, atenolol and ranitidine were detected in urine; atenolol was also detected in blood. The pilot had reported taking pravachol, atenolol, hydrochlorothiazide, and ranitidine.

Case 9

A 68-year-old male was fatally injured after his Piper PA-22-108 crashed. Pentobarbital was found at concentration of 0.067 µg/mL in blood, and it was also detected in liver. Diphenhydramine, lidocaine, and atropine were detected in blood, liver, and lung. Morphine and acetaminophen were both detected in blood, and morphine was also detected in liver.

Case 10

A 37-year-old male pilot impacted terrain while attempting to land and died during the accident. Both sedatives and antiemetics were found in the pilot. Oxazepam, a benzodiazepine sedative, was found at 0.101 µg/mL in his urine, and nordiazepam was detected in the blood. Diphenhydramine was detected in the pilot's urine. The NTSB report for this case stated that "diphenhydramine is not recommended for use while performing safety-sensitive activities due to its sedating effects."

Case 11

A 48-year-old male died when his aircraft collided with another aircraft on a taxiway. Following toxicological evaluation, the pilot was found with the relatively common sedative/antiemetic combination of diphenhydramine and chlorpheniramine. Both of these compounds were found in the pilot's urine and liver. Butalbital, a sedative barbiturate, was also detected. Butalbital, at a concentration of 0.609 µg/mL, was found in the pilot's blood. Therapeutic concentrations of metoprolol were also detected in the pilot's urine and liver.

Case 12

A 49-year-old male was found dead after his aircraft collided with trees. A combination of doxylamine and diphenhydramine was found. Doxylamine was found at a concentration of 0.042 µg/mL in the blood and was detected in urine. Diphenhydramine was found at a concentration of 0.107 µg/mL in the blood and was detected in urine. Pentobarbital, a sedative barbiturate, was also detected. Pentobarbital, at a concentration of 0.067 µg/mL, was found in the pilot's blood. Other compounds found in the pilot were ranitidine and acetaminophen. According to the AME, the victim occasionally used Benadryl® (diphenhydramine) "but does not take it within 24 hours of flying." Doxylamine is a sedating over-the-counter antihistamine and is often used in sleep aids and in nighttime multi-symptom cold relievers. The NTSB attributed the effects of diphenhydramine, and possibly, the effects of doxylamine as a contributing factor in the accident.

Case 13

A 55-year-old male crashed his home-built aircraft and did not survive. This pilot had consumed a combination of ethanol and diphenhydramine prior to his flight. Ethanol was found at a concentration 96 mg/dL, and diphenhydramine was detected at a concentration of 0.177 µg/mL in the pilot's blood. Additionally, PPA was also detected in his blood. The NTSB determined that a contributing factor to the accident included the use of an over-the-counter antihistamine.

Case 14

A 65-year-old male was fatally injured when his aircraft collided with trees. Following toxicological evaluation of this case, it was determined that this pilot had taken numerous medications with dangerous side effects. Drugs from both the antiemetic and sedative classes were found in the pilot's blood, including doxylamine at a concentration of 0.165 µg/mL, diphenhydramine at a concentration of 0.410 µg/mL, and chlorpheniramine at a concentration of 0.112 µg/mL. Each of these compounds was also present in the pilot's urine. Additionally, PPA, dextrorphan, dextromethorphan, acetaminophen, pseudoephedrine, and ephedrine were detected. The NTSB noted that the toxicological findings were consistent with the ingestion of at least 3 different OTC medications that contained sedating antihistamines. The pilot's wife stated that the victim was "fighting a bad cold for about a week" prior to the accident and that the victim was taking NyQuil® to "get through the night." She also stated that it was possible he had taken Benadryl® as well. The NTSB determined the cause of the accident was the pilot's impairment due to the over-the-counter medications, which resulted in a loss of aircraft control while maneuvering.

Case 15

A 36-year-old male was found dead after losing control of his aircraft. This pilot had taken a sedating antihistamine and had recently smoked marijuana. Doxylamine was detected in the victim's blood and liver. Both THC and THCA were found in the pilot's blood at concentrations of 0.003 µg/mL and 0.017 µg/mL, respectively. The NTSB report stated that investigators found in the wreckage a plastic bag containing drug paraphernalia including a green leaf-type substance, which local law enforcement officials determined to be consistent with marijuana. The NTSB determined that the pilot's impairment by marijuana was a factor in the accident.

Table 1. Toxicological findings, pilot information, and NTSB findings for the 26 cases examined.

Case	Sedatives Found (concentration, specimen type)	Antiemetics Found (concentration, specimen type)	Other Substances Found	Drugs Reported to AME	Medical Certificate Category	Flying Certificate Category	NTSB findings (Cause/Factor)
1	Nordiazepam (detected, blood)	THC (0.013 µg/mL, blood) THCA (detected, blood)	Amphetamine Methamphetamine Tramadol	None	Third Class	Student	Ran out of gas
2	Trazodone (0.130 µg/mL, blood)	Chlorpheniramine (0.079 µg/mL, blood)	Ephedrine Pseudoephedrine	None	Third Class	Private	Failure to maintain control of aircraft
3	Doxylamine (0.089 µg/g, kidney; 0.292 µg/g, liver)	Diphenhydramine (0.753 µg/g, kidney; 2.280 µg/g, liver)	Phenylpropanolamine Acetaminophen Pseudoephedrine Dextrorphan Dextromethorphan	None	Second Class	Commercial	Collision with trees due to fog. Use of cold medication noted
4	Butalbital (2.506 µg/mL, blood) Ethanol (61 mg/dL, blood)	Chlorpheniramine (0.018 µg/mL, blood)	Acetaminophen Quinine Phenylpropanolamine	None	Second Class	Commercial	Cause: Impairment due to ethanol and drµgs
5	Doxylamine (detected, urine)	Chlorpheniramine (detected, blood)	Pseudoephedrine Ephedrine Phenylpropanolamine Dextromethorphan Dextrorphan	Sular	Third Class	Private	Cause: Spatial Disorientation, lack of instrument flight experience
6	Ethanol (126 mg/dL, blood)	Diphenhydramine (0.022 µg/mL, blood)	Benzoylecgonine Cocaine Cocaethylene	None	Third Class	Private	Factor: Impairment due to ethanol
7	Ethanol (124 mg/dL, blood)	THC (detected, blood) THCA (0.006 µg/mL, blood)	None	None	Third Class	Private	Cause: Impairment due to ethanol
8	Temazepam (0.303 µg/mL, urine Nordiazepam (0.142 µg/mL, blood) Oxazepam (0.460 µg/mL, urine)	Diphenhydramine (0.146 µg/mL, blood)	Atenolol Ranitidine	Pravachol, Atenolol, HCTZ, Zantac	Third Class	Private	None
9	Pentobarbital (0.067 µg/mL, blood)	Diphenhydramine (0.011 µg/mL, blood)	Lidocaine Acetaminophen Morphine Atropine	Coumadin Synthroid	Third Class	Student	Lack of experience
10	Oxazepam (0.101 µg/mL, urine) Nordiazepam (detected, blood)	Diphenhydramine (detected, urine)	None	None	Third Class	Student	Aircraft stalled by the student pilot
11	Butalbital (0.609 µg/mL, blood)	Chlorpheniramine (detected, urine) Diphenhydramine (detected, urine)	Metoprolol	None	Third Class	Private	Inadequate visual lookout of both pilots
12	Doxylamine (0.042 µg/mL, blood)	Diphenhydramine (0.107 µg/mL, blood)	Ranitidine Acetaminophen	Atenolol, HCTZ, Zestril, Lipitor, Lopid, Ranitidine	Third Class	Private	Factor: judgment impaired due to diphenhydramine and doxylamine
13	Ethanol (96 mg/dL, blood)	Diphenhydramine (0.177 µg/mL, blood)	Phenylpropanolamine	None	Third Class	Private	Factor: Use of diphenhydramine

Table 1. Toxicological findings, pilot information, and NTSB findings for the 26 cases examined (continued).

Case	Sedatives Found (concentration, specimen type)	Antiemetics Found (concentration, specimen type)	Other Substances Found	Drugs Reported to AME	Medical Certificate Category	Flying Certificate Category	NTSB findings (Cause/Factor)
14	Doxylamine (0.165 µg/mL, blood)	Chlorpheniramine (0.112 µg/mL blood) Diphenhydramine (0.410 µg/mL, blood)	Dextromethorphan Ephedrine Phenylpropanolamine Acetaminophen Pseudoephedrine	Advil, Lipitor	Second Class	Commercial	Cause: Impairment due to OTC Meds
15	Doxylamine (detected, blood)	THC (0.003 µg/mL, blood) THCA (0.017 µg/mL, blood)	None	None	Third Class	Private	Factor: Use of marijuana
16	Oxazepam (0.203 µg/mL, blood) Ethanol (190 mg/dL, blood)	THC (detected, blood) THCA (0.003 µg/mL, blood)	None	Prozac	Second Class	Commercial	Cause: Impairment due to ethanol
17	Sertraline (0.218 µg/mL, blood) Desmethylsertraline (0.734 µg/mL, blood)	THC (0.005 µg/mL, blood) THCA (0.018 µg/mL, blood) Diphenhydramine (0.398 µg/mL, blood) Chlorpheniramine (0.141 µg/mL, blood)	Phenylpropanolamine Pseudoephedrine	N/A	None Listed	Student	N/A
18	Fluoxetine (0.772 µg/mL, blood) Norfluoxetine (0.552 µg/mL, blood) Trazodone (0.293 µg/mL, blood)	Diphenhydramine (0.065 µg/mL, blood)	None	N/A	None Listed	None Listed	Hypoglycemia
19	Doxylamine (0.052 µg/mL, blood)	Chlorpheniramine (0.015 µg/mL, blood).	Acetaminophen Pseudoephedrine	None	Third Class	Private	Ice/Mechanical
20	Fluoxetine (1.226 µg/mL, blood) Norfluoxetine (0.462 µg/mL, blood) Zolpidem (detected, liver) Olanzapine (detected, liver)	Diphenhydramine (detected, blood)	Topiramate Lamotrigine Quinine	Topamax Lamictal Zyprexa Prozac	Third Class	Private	High terrain
21	Fluoxetine (2.022 µg/mL, blood) Norfluoxetine (3.048 µg/mL, blood) Olanzapine (detected, blood)	THC (0.037 µg/mL, blood) THCA (0.092 µg/mL, blood)	Naproxen	None	Third Class	Private	Factor: Marijuana use
22	Diazepam (1.454 µg/g, liver) Nordiazepam (3.315 µg/g, liver) Doxylamine (detected, liver)	Diphenhydramine (detected, liver)	Dextromethorphan Dextrorphan Pseudoephedrine	Naproxen, Zocor, Allegra, Lisinopril	Third Class	Private	fog
23	Ethanol (89 mg/hg, muscle)	Chlorpheniramine (detected, liver)	None	Flomax, Tamsulosin, Proscar, Zocor	Second Class	Commercial	N/A
24	Ethanol (290 mg/dL, blood)	Diphenhydramine (0.019 µg/mL, blood)	None	None	First Class	Commercial	Factor: Ethanol/Suicide
25	Ethanol (140 mg/dL, blood)	THC (0.002 µg/mL, blood) THCA (0.008 µg/mL, blood)	None	None	Second Class	Commercial	N/A
26	Meprobamate (2.08 µg/mL, blood).	Chlorpheniramine (detected, urine)	Carisoprodol	None	First Class	Airline Transport	N/A

Case 16

A 51-year-old male was found dead after his plane collided with power lines. This pilot had combined and consumed 2 powerful sedatives and an antiemetic before the fatal accident. Oxazepam, at a concentration of 0.203 µg/mL, was detected in the pilot's blood and was also found in his urine. High concentrations of ethanol were found, including 190 mg/dL in blood, 472 mg/dL in urine, 239 mg/dL in vitreous, and 164 mg/hg in brain. THC was detected in the pilot's blood, and THCA was quantified in the blood and found at a concentration of 0.004 µg/mL. The victim had reported taking Prozac® (fluoxetine) but none was found during the toxicological review. The NTSB determined the cause of the accident to be the pilot's failure to maintain clearance from an object while maneuvering and alcohol impairment; additionally they determined a factor in the accident to be the pilot's drug impairment.

Case 17

A 58-year-old male was found dead after his aircraft collided with terrain. This pilot had taken four compounds with potentially dangerous side effects prior to his flight. THC was found in the pilot's blood at a concentration of 0.005 µg/mL. THCA was found in the blood at a concentration of 0.018 µg/mL. Diphenhydramine was detected in the pilot's blood and urine. Chlorpheniramine was found at a concentration of 0.141 µg/mL in his blood. Therapeutic concentrations of sertraline (0.218 µg/mL) and its active metabolite norsertraline (0.734 µg/mL) were found in the victim's blood. Additionally, pseudoephedrine and PPA were also found.

Case 18

A 56-year-old male pilot was found dead after his aircraft collided with power lines. Sedatives found in this pilot included 0.293 µg/mL of trazadone in his blood, 0.772 µg/mL fluoxetine in the blood, and norfluoxetine (an active metabolite of fluoxetine) was found at 0.552 µg/mL in the blood. These compounds were also each detected in the pilot's liver. The pilot had also taken diphenhydramine, which was found at a concentration of 0.065 µg/mL in the blood and was detected in the liver. The pilot possessed neither a valid pilot's certificate nor a valid airman's medical certificate. The pilot had a history of coronary heart disease and was an insulin-dependent diabetic.

Case 19

A 49-year-old male, operating an Iniziative Industrali Sky Arrow, was fatally injured just after takeoff. The sedative, doxylamine, was detected at 0.052 µg/mL in the pilot's blood and was also detected in his urine. The antiemetic, chlorpheniramine, was detected in his liver and at 0.015 µg/mL in blood. Toxicological findings also revealed acetaminophen in his blood and pseudoephedrine in the liver.

Case 20

A 51-year-old male was fatally injured in an aviation accident. Two powerful sedatives were found in the pilot's system. Zolpidem (Ambien®) and olanzapine were both detected in the pilot's liver. Also, high levels of fluoxetine were found in the pilot's blood. The concentration of fluoxetine was determined to be 1.23 µg/mL. Fluoxetine was also present in the liver, and norfluoxetine was present in the blood and liver. This pilot had also taken diphenhydramine, which was detected in both his liver and blood. Additional compounds found were topiramate, lamotrigine, and quinine. The NTSB reported that the victim had a history of depression and was denied his airman medical certificate in October 1997. The NTSB report stated only that the blood levels of the prescription antidepressants found were much higher than expected.

Case 21

A 42-year-old male glider pilot, fatally injured during a crash, was determined to have taken two different sedatives and one antiemetic prior to his flight. Olanzapine was detected in the pilot's blood and urine. Fluoxetine was found at a concentration of 2.022 µg/mL in his blood, and a norfluoxetine blood concentration of 0.305 µg/mL was determined. Both of these compounds were also positive in the victim's urine. THC and THCA were detected in the pilot's blood at concentrations of 0.004 µg/mL and 0.002 µg/mL, respectively, and both were found at concentrations of 0.024 µg/g and 0.031 µg/g in his liver. Naproxen was also found in this case. The NTSB report stated that "toxicology evaluation detected tetrahydrocannabinol (the primary active substance in marijuana) and its metabolite at levels consistent with very recent use, likely during or just prior to the flight." The NTSB determined the use of marijuana and his unreported mental condition were contributing factors in the accident.

Case 22

A 67-year-old male lost control of his aircraft and was fatally injured. A mixture of several impairing drugs was found, including diazepam, nordiazepam, doxylamine, and diphenhydramine. Diazepam was found at a concentration of 1.454 µg/g and 0.318 µg/g in his liver and kidney, respectively. Nordiazepam, 0.690 µg/g, was found in the liver as well. Doxylamine and diphenhydramine were each detected in both the liver and the kidney.

Additionally, dextrorphan, dextromethorphan, and pseudoephedrine were detected in the liver and kidney. The use of diazepam (Valium®) precludes a pilot from obtaining a medical certificate.

Case 23

A 59-year-old male was found dead after his Augusta 109E helicopter impacted trees and terrain. Following toxicological evaluation, chlorpheniramine, an OTC sedating antihistamine and antiemetic, was detected in his blood. In addition, ethanol was found in concentrations of 89 mg/hg in the muscle and 34 mg/hg in the liver.

Case 24

A 21-year-old male was determined to have intentionally crashed his plane, resulting in his death. The pilot was found to have consumed large quantities of alcohol, as 290 mg/dL ethanol was found in his blood, 192 mg/dL in the vitreous, 175 mg/hg in the muscle, and 230 mg/hg in the brain. Also, diphenhydramine was detected in his blood at a concentration of 0.019 µg/mL. The NTSB report stated the pilot made a phone call in-flight, indicating that he was going to commit suicide. Law enforcement personnel who searched the pilot's apartment located a three-page note, "which revealed his intention to commit suicide." The NTSB attributed the cause of the accident to be the pilot's "intentional suicide" and one of the factors to be the pilot's impairment by alcohol.

Case 25

A 59-year-old male died after his Ercoupe 415C crashed while landing. Ethanol was detected at concentrations of 140 mg/dL in blood, 170 mg/dL in urine, 107 mg/hg in skeletal muscle, and 134 mg/hg in brain. This sedative compound was taken while the victim was smoking marijuana, as 0.002 µg/mL of THC was detected in his blood and 0.219 µg/g in the lung, THCA was found at 0.008 µg/mL in the blood, 0.008 µg/mL in urine, and 0.010 µg/g THCA was found in the lung.

Case 26

A 41-year-old male was fatally injured when he crashed his Cessna 560. Meprobamate, an anti-anxiety medication with sedating effect, was detected at 2.08 µg/mL in his blood and was also detected in a urine specimen. In addition to Meprobamate, the antiemetic compound chlorpheniramine was detected in his liver and urine. Carisoprodol, a muscle relaxant, was also detected in the blood, urine, and liver examined from this case.

RESULTS AND DISCUSSION

Epidemiological and Toxicological Aspects

The NTSB is the primary federal agency responsible for investigating civil aviation accidents and for determining the probable cause(s) of such accidents. The NTSB determines whether the use of an impairing substance(s) was the probable cause or a factor in an aviation accident only when the toxicological evidence supports those findings. Over the 7-year period, 2000-2006, there were 2,184 fatal aviation accidents, of which 26 pilots were found with concurrent use of antiemetic(s) with a sedative(s). The prevalence of concomitant drug use in general aviation pilot fatalities is low and accounted for only approximately 1.2% (26 of 2,184) of all fatal general aviation accidents. Although infrequent in occurrence, combining drugs from these two classes can lead to dangerous consequences.

All 26 fatal aviation accidents examined were operated as general aviation, Title 14 of the Code of Federal Regulations (CFR) Part 91. The aircraft used in these accidents were predominantly single engine (19 of 26) and fixed landing gear (23 of 26) aircraft. One of the accidents involved an ultralight aircraft and one involved a glider. All pilots included in this study were male, with a median age of 51 years (range 21-72). Of the 26 airmen, 1 did not hold an airman medical certificate at any point in his flying career and two did not hold valid certificates. The uncertificated pilot was operating an experimental aircraft and did not hold either an airman's medical or pilot certificate. One pilot was operating an ultralight aircraft and had held a student pilot certificate that was issued in 1975. One pilot had been denied his airman medical certificate at his last examination, which took place 6 months prior to his accident. One pilot's airman medical certificate had expired. Of the 22 pilots who held airman medical certificates, 10 were granted "clear" (unrestricted) certifications on their last airman exam date. Twelve had "limited" certifications that were due to the requirement of corrective lenses. In addition to corrective lenses restrictions, Cases 9 and 14 had "miscellaneous" restriction and time restriction on validity of certificate, respectively, which were likely due to their various medical issues. Case 2 held a "limited" certification, but the limitation was not noted on the certificate.

Fifteen of the 26 airmen had not reported the use of any eligible or disqualifying substances during their medical certification process or thereafter. Eight airmen had reported the use of some type of prescription or OTC medication such as pravastatin, atenolol,

hydrochlorothiazide, warfarin, levothyroxine, gemfibrozil, ranitidine, ibuprofen, fluoxetine, naproxen, simvastatin, fexofenadine, nisoldipine, tamsulosin, finasteride, and lisinopril.

Toxicological findings revealed diphenhydramine in 14 of the 26 pilots concomitantly used with a sedative or substance with sedating effects, including benzodiazepines, antihistamines, ethanol, barbiturates, serotonin modulators, and/or sedative-hypnotics. Antihistamines such as diphenhydramine are commonly used. The undesirable effect of sedation can occur at low doses, and, as previously stated, many OTC sleep preparations contain an antihistamine, such as diphenhydramine.[3] In a study of insomnia management, Folkse found that "Although diphenhydramine (and other antihistamines) may improve insomnia, they are associated with impairment of daytime functioning even at low doses."[8] Folkse also found that the use of diphenhydramine in older individuals, concomitantly with other medications that act on the CNS, has a potential for causing delirium.[8] THC, the active compound in marihuana, and its inactive metabolite THCA, were detected in 7 pilots, of which benzodiazepines, doxylamine, diphenhydramine, and/or ethanol were also present (Cases 1, 7, 15, 16, 17, 21, 25).

Ethanol was detected in eight of the pilots, of which 3 had also taken diphenhydramine (Cases 6, 13, 24), marijuana was detected in 3 airmen (Cases 7, 16, 25), and chlorpheniramine was detected in 2 (Cases 4, 23). All of the eight ethanol-positive values were above the FAA cutoff of 40 mg/dL, and 6 of the pilots tested positive for ethanol above 100 mg/dL, indicating significant impairment (Cases 4, 6, 7, 16, 24, 25). H_1-receptor antagonists such as diphenhydramine interact with alcohol, enhancing its effects.[9] In a study evaluating the effects of diphenhydramine alone and in combination with ethanol, it was found that of the areas tested (reaction time, tracking performance, tracking variability, body sway, subjective effects, smooth pursuit velocity, saccade reaction time, saccade duration, and peak saccade velocity) the combination produced greater effects in all areas in as little as 1 hour after administration than use of either of the two compounds alone.[9]

Five of the cases tested positive for diazepam or one of its active metabolites (nordiazepam, temazepam, oxazepam; Cases 1, 8, 10, 16, 22), two also tested positive for marijuana (Cases 1, 16), and three also tested positive for diphenhydramine (Cases 8, 10, 22). Diazepam is prescribed mainly as an anti-anxiety agent and a muscle relaxant, and some of its side effects include drowsiness, tiredness, dizziness, and weakness. The concomitant use of diazepam and diphenhydramine has shown to depress psychomotor performance.[10] Additionally, diphenhydramine significantly enhances the previously mentioned effects of diazepam.[10] Benzodiazepines can cause pharmacodynamic interactions such as increased sedation, confusion, and respiratory depression when given with other CNS depressants such as alcohol.[11] Therefore, the presence of diazepam and its metabolites, in addition to marijuana and diphenhydramine, suggests possible cognitive impairment.

Trazodone was detected in two cases (Case 2, 18), along with chlorpheniramine and diphenhydramine, respectively. Trazodone is a triazolopyridine antidepressant drug and is often co-prescribed with other antidepressants as a sleep-inducing agent because of its sedative effects.[1] The active metabolite is m-chlorophenylpiperazine (mCPP), which has been suggested may contribute to the antidepressant efficacy of trazodone and a drug interaction that alters the production of mCPP, could have clinically significant effects.[1] Fluoxetine and its metabolite norfluoxetine were also detected in one of the pilots (Case 18). In a study on trazodone and mCPP, Rotzinger et al. found "Clinical interactions between trazadone and fluoxetine have been reported in the form of adverse side effects such as headaches, dizziness, and excessive sedation as well as increased levels of trazadone and mCPP."[1] The victim did not hold an airman medical or pilot certificate, so his use of these substances was not reported or monitored by an Aviation Medical Examiner.

Doxylamine was detected in 6 airmen (Cases 3, 5, 12, 14, 15, 19) along with diphenhydramine (Cases 3, 12, 14). Doxylamine, an antihistamine, causes drowsiness as a side effect and is used in the short-term treatment of insomnia. It is also used in combination with decongestants to relieve cough and cold symptoms. Chlorpheniramine was detected with doxylamine in 3 pilots (Cases 5, 14, 19). In Case 15, THC and THCA were also detected. Barbiturates (butalbital and pentobarbital) were detected in 3 airmen (Cases 4, 9, 11) along with chlorpheniramine and diphenhydramine. Two airmen tested positive for olanzapine (Cases 20, 21). One airman tested positive for zolpidem, a sedative hypnotic used to treat insomnia, along with diphenhydramine (Case 20). The other airman tested positive for marijuana (Case 21). Olanzapine is used to treat the symptoms of schizophrenia, episodes of mania, or mixed episodes (symptoms of mania and depression that occur together) in patients with bipolar I disorder. Its side effects include drowsiness, dizziness, restlessness, and unusual behavior. Atypical antipsychotics such as olanzapine are occasionally used at low doses for their sedative and calming effects.[11] Each of the compounds found in these aviation accident victims has the potential to cause impairment by affecting both judgment and physical abilities. These substances may have played a role in the events that led to these fatal accidents.

Certification Aspects

Norwood states that the FAA's regulatory medicine, which considers public safety as paramount, is different from private practice medicine, where the physician-patient relationship takes precedence.[12] It remains that both have the health of the patient as a common factor and both rely on what the individual reveals in his medical self-report and what is found during the medical examination. Of the eight airmen who had reported using some type of drug or compound, none had reported the use of any sedatives or antiemetics (including compounds with these properties) to their Aviation Medical Examiner at the time of their exam. In all 26 cases, toxicological findings revealed at least two compounds in each victim. In the most extreme case, findings revealed eight different compounds (Case 14). As with the non-flying public, additional education may be needed for pilots on the safety of taking multiple substances and operating an aircraft.

CONCLUSION

Various drugs may be dangerous when taken in combination. Compounds from two such drug classes, antiemetics and sedatives, can produce particularly harmful side effects when mixed. We have investigated the occurrence of aviation accidents over a seven-year period in which the pilot tested positive for compounds from both drug classes. Although the percentage of accidents in which the pilot tests positive for a compound from each class is relatively small, it is important for all pilots to understand the dangerous consequences that may arise from self- medicating and concomitant use of such substances. Furthermore, many of the drugs in these two classes are commonly used and readily available. This only increases the potential danger for pilots. Since the under-reporting of medications by pilots during their certification process may occur, education is the key to preventing inadvertent drug-drug interactions.

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