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Pilot-Reported Beta-Blockers Identified by Forensic Toxicology Analysis of Postmortem Specimens

Dennis V. Canfield
Kurt M. Dubowski
James E. Whinnery
Estrella M. Forster

Civil Aerospace Medical Institute
Federal Aviation Administration
Oklahoma City, OK 73125

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16. Abstract

Introduction: This study compared beta-blockers reported by pilots with the medications found by postmortem toxicology analysis of specimens received from fatal aviation accidents between 1999 and 2015. Several studies have compared drugs using the standard approach: Compare the drug found by toxicology analysis with the drug reported by the pilot. This study uniquely examined first the pilot-reported medication and then compared it to that detected by toxicology analysis. This study will serve two purposes: (1) determine the capability of a toxicology laboratory to detect reported medications, and (2) identify pilots with medications below detectable limits. Method: All information required for this study was extracted from the Toxicology Data Base system and was searched using ToxFlo or SQL Server Management Studio. The following information was collected and analyzed: pilot-reported trade and/or generic drug, date specimens received, time of accident, type of aviation operations (CFR), state, pilot level, age, class of medical, specimen type, specimen concentration, dose reported, frequency reported associated with the accident, quantity reported, National Transportation Safety Board (NTSB) accident event number, and all NTSB reports. Results: There were 319 pilots that either reported taking a beta-blocker or were found to be taking a beta-blocker by postmortem toxicology analysis. Metoprolol and Atenolol were the most commonly found beta-blockers (81%) in this study. Discussion: Time of death, therapeutic concentration, and specimen type were found to be factors in the ability of the laboratory to detect beta-blockers. Dose did not correlate with the ability of the toxicology laboratory to detect the beta-blocker. Conclusions: Beta-blockers taken by pilots will, in most cases, be found by a competent postmortem forensic toxicology laboratory at therapeutic concentrations. The dose taken by the pilot was not found to be a factor in the ability of the laboratory to identify beta-blockers. Time of dose, route of administration, specimen tested, and therapeutic concentration of the drug were found to be factors in the ability of the laboratory to identify beta-blockers in postmortem specimens taken from pilots that died in aviation accidents.

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Contents

PILOT-REPORTED BETA-BLOCKERS IDENTIFIED BY FORENSIC TOXICOLOGY ANALYSIS OF POSTMORTEM SPECIMENS

PILOT-REPORTED BETA-BLOCKERS IDENTIFIED BY FORENSIC TOXICOLOGY ANALYSIS OF POSTMORTEM SPECIMENS

INTRODUCTION

Several papers have been written over the years about a pilot's failure to report medications found by postmortem toxicology analysis (1, 2), however, no one has published research findings on the ability of a postmortem toxicology laboratory to detect pilot-reported medications. This study looked at some of the factors that might affect the ability of a toxicology laboratory to detect beta-blockers in postmortem specimens.

This research intended to determine the ability of a forensic toxicology laboratory to identify beta-blockers reported in a pilot's medical records and the factors that influence the detection of medications taken by pilots in postmortem specimens. Beta-blockers were selected for this study because they are one of the most commonly prescribed medications and should provide statistically significant numbers for analysis. In addition, the Aerospace Medical Certification Division of the Federal Aviation Administration (FAA) Civil Aerospace Medical Institute (CAMI) approves the use of these medications on a case by case basis, and we would expect to find these medications reported by pilots found by toxicology analysis.

MATERIALS AND METHODS

Postmortem Biological Specimens

By law (3), the autopsied biological samples (blood, urine, liver, kidney, vitreous fluid, and other body specimens) collected from pilot fatalities in civil aircraft accidents are submitted to CAMI for toxicological testing. Not all of the pilots involved in these accidents are necessarily certified by the FAA to fly an aircraft. The specimens submitted for analysis are coordinated through the FAA's Office of Accident Investigation and the National Transportation Safety Board (NTSB) (4). The collected samples are submitted in custom-built FAA evidence containers (TOX-BOX) that provide all necessary instructions and materials for standardized toxicological collection and processing.

Toxicology Analysis

Postmortem specimens from pilots taking a beta-blocker with medical records on file with the FAA between 1999−2015 were included in this study. Biological specimens received for testing are routinely analyzed for the presence of combustion gases (carbon monoxide and hydrogen cyanide), a wide range of illicit, prescription, and nonprescription drugs, along with alcohol/volatiles. Specimens are screened, confirmed, and quantitated for the analytes mentioned above. All specimens are analyzed according to established standard procedures approved for use by the CAMI Laboratory. The methods used included gas chromatography, liquid chromatography, ultraviolet/visible spectrophotometry, immunoassay, gas chromatography/mass spectrometry (GC/MS), and liquid chromatography/mass spectrometry (LC/MS). Ethanol analysis is performed by headspace gas chromatography. Analytical procedures used are dependent upon their sensitivity and specificity, the nature of analytes, and the availability of sample types and amounts. An analyte might not necessarily be detected, or even analyzed in a particular case, because the specimen is unsuitable for analysis.

If urine is available in an aviation accident it is screened for drugs because the urine normally has high concentrations of drug relative to other biological specimens, and it is an easier biological matrix to recover drugs. In those cases where urine is not available, blood is screened for drugs. When there is no urine or blood, liver is screened for the presence of drugs. If all three of these biological matrixes are unavailable one of the other tissues will be selected for analysis based on the condition of the specimen and its availability.

Beta-blockers are screened by GC/MS, LC/MS, and LC/UV/FL. The confirmation of beta-blockers is based on a publication in the Journal of Analytical Toxicology (5). The laboratory can identify beta-blockers

at concentrations below 20 ng/mL. The normal therapeutic concentrations are greater than 10 ng/mL for beta-blockers with the most commonly used beta-blockers above 50 ng/mL.

Data Analysis

All toxicology case results from civil aircraft accident fatalities that occurred between 1990 and the present are stored electronically in a SQL database maintained at CAMI, called the Toxicology Data Base (ToxDB). All trade Drug names, trade drug components, and doses were obtained from Rx Drugs Data (http://rxdrugdata.com/) a subscription web-based service. The ToxDB database was searched for pilots with reported and/or positive beta-blockers to identify the number of pilot fatalities taking beta-blockers during the period from 1999 to 2015 using the ToxFlo (Discoversoft Development, LLC), or Microsoft SQL Server Management Studio software packages. Information gathered from the ToxDB included cases with beta-blockers reported and/or found by toxicology analysis, drug, dose, time of accident, specimen, class of airman certificate, class of medical certificate, age, accident location, associated pathologies, and the type of flight certification of the associated accidents. Statistical analysis of data was performed using Microsoft Excel.

RESULTS

General Findings

The beta-blockers, in order of prevalence, found by postmortem toxicology analysis of specimens from pilot fatalities received by the CAMI toxicology laboratory, are listed in Table 1. A search of the ToxDB identified 319 pilots from fatal aviation accidents with reported or detected beta-blockers. The average age of the pilots taking beta-blockers was 64 (SD=10) years with a minimum age of 24 and a maximum age of 89. Most of the pilots (95%) were flying private aircraft (general aviation). No pilots were flying Part 121 air transport aircraft in this study, and only 2.5% were flying air taxi or commercial aircraft. Fifty-three percent of the pilots were designated as private pilots, 28% were classified as commercial pilots, and 15% were classified as air transport pilots.

Metoprolol and Atenolol were the most common beta-blockers found (81%) by postmortem toxicology. Seventy-six percent of the pilots' medical records reported the pilot was taking Metoprolol or Atenolol, the two most commonly prescribed beta-blockers (4). The majority (63.8%) of the beta-blockers reported in the medical records were identified by postmortem forensic toxicology analysis. More than 50% of the beta-blockers found by postmortem forensic toxicology analysis were not reported in the medical records (Table 1).

Carvedilol was found by postmortem toxicology analysis in 13 fatal aviation accidents, and only 3 of these pilots reported taking the medication. Six pilots reported taking Carvedilol but the toxicology laboratory only confirmed 3 of these pilots as taking carvedilol at the time of the accident.

Nadolol was detected in 3 pilots, and 2 of these were reported in the pilot's medical record (Table 1). Four pilots reported taking the medication, and Nadolol was found in 2 of these pilots (Table 2). One of the pilots reporting Nadolol was actually found by postmortem toxicology analysis to be taking Amlodipine, a different antihypertensive medication.

Timolol was only detected in one pilot reporting the medication. Six pilots reported taking the medication. All 6 of the reported Timolol cases were eye drops used in the treatment of glaucoma.

Sotalol was detected in one pilot who did not report the medication. Three pilots reported taking the medication, but the drug was not found in specimens from the deceased pilots.

Alprenolol was included in this study because it has been detected in a non-aviation accident, and it is considered to be a beta-blocker. It is not approved for use by the FDA and can only be purchased from another country.

Table 1. Beta-blockers Identified by Postmortem Toxicology Analysis

Beta-Blocker	Toxicology Found	Not Reported	% Not Reported
Metoprolol	124	65	52.4
Atenolol	87	45	51.7
Propranolol	18	11	61.1
Carvedilol	13	10	76.9
Bisoprolol	9	6	66.7
Labetalol	4	2	50.0
Nadolol	3	1	33.3
Timolol	1	0	0.0
Sotalol	1	1	100.0
Nebivolol	0	NA	NA
Betaxolol	0	NA	NA
Acebutolol	0	NA	NA
Alprenolol	0	NA	NA
Total	**260**	**141**	**54.2**

Table 2. Reported Beta-blockers Identified in Postmortem Specimens

Beta-Blocker	Reported in Medical	Tox Positive	Tox Negative	% Positive
Metoprolol	81	59	22	72.8
Atenolol	60	42	18	70.0
Propranolol	10	7	3	70.0
Carvedilol	5	3	2	60.0
Bisoprolol	6	2	4	33.3
Labetalol	2	2	0	100.0
Nadolol	4	2	2	50.0
Timolol	6	1	5	16.7
Sotalol	3	0	3	0.0
Nebivolol	5	0	5	0.0
Betaxolol	2	0	2	0.0
Acebutolol	1	0	1	0.0
Alprenolol	0	0	0	0.0
Total	**185**	**118**	**67**	**63.8**

Table 3. Reported Beta-Blockers Found in Postmortem Specimens

Specimen	Positive	Negative	Count	% Positive
Blood	88	32	120	73.3
Urine	69	10	79	87.3
Liver	44	13	57	77.2
Kidney	16	2	18	88.9
Heart	1	0	1	100.0
Lung	6	0	6	100.0
Muscle	8	4	12	66.7
Total	**232**	**61**	**293**	**79.2**

Specimen Type

All lung and heart specimens from cases where a beta-blocker was reported as being taken were found to be positive for the medication. Muscle was the least likely specimen to find reported beta-blockers.

Time of Death Findings

The percentage of reported beta-blockers identified by postmortem toxicology analysis decreased as a function of the time the accident occurred (Figure 1).

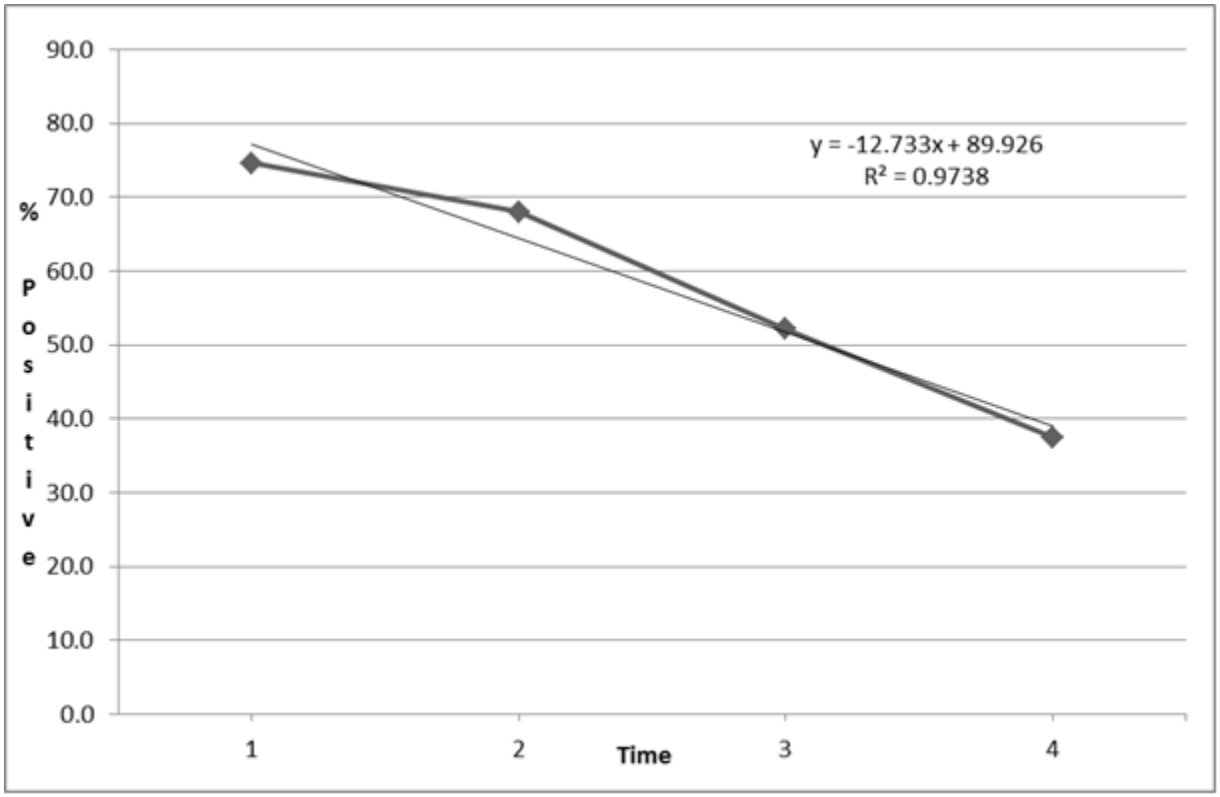

Figure 1. Percentage of Reported Beta-Blockers found by Postmortem Toxicology and time of death
Time (Hours): 1 = (0601-1200), 2 = (1201-1800), 3 = (1801-2400), 4 = (0001-0600)

Dosage Findings

As found in this study, Metoprolol is the most commonly reported beta-blocker detected in postmortem toxicology specimens from fatal aviation accidents as found in this study. Metoprolol was, therefore, selected to determine the impact of dose on toxicology findings. Barely half (54%) of the pilot medical records reported the beta-blocker dose taken by the pilot. The medically reported Metoprolol dosage information was sorted by dose and toxicology results (Table 4).

Table 4. Detection of Metoprolol in Postmortem Toxicology Specimens Relative to Dose

Dosage	Positive	Negative	Count	% Detected
100	4	4	8	50.0
50	18	5	23	78.3
25	8	3	11	72.7
12.5	2	0	2	100.0
Total	**32**	**12**	**44**	

DISCUSSION

Time of Death

The time of death, as might be expected, showed a decrease in the positive toxicology cases for deaths occurring between 1800 and 0600 hours (Figure 1). There was a steady decline in the ability of the CAMI toxicology laboratory to detect beta-blockers in postmortem specimens as a function of the time of death. The laboratory was able to detect 75% of the pilot-reported beta-blockers in pilots that died between 0601 and 1200 and only able to identify 37% of the pilot-reported beta-blocker medications in pilots that died between 0001 and 0600 hours. Most patients take beta-blockers once a day in the morning, so we would expect to find the highest concentrations of the drug in the morning and the lowest concentrations in the evening and very early morning when the concentrations in the body should be at their lowest levels—the data supported this expectation.

Dose

Although one might expect the dose taken by the pilot to be a major factor in detecting the reported beta-blocker, it was not found to be true in postmortem toxicology cases from fatal aviation accidents in this study (Table 4). Pilots taking a 100 mg dose were far less likely (50% positive) than pilots taking 12.5 mg doses (100% positive) to be positive by postmortem toxicology. Considering patients are dosed according to their weight and metabolism to achieve a therapeutic concentration in blood (6), we would not expect to see significant differences in concentration of the drug in blood based on dose, assuming the pilot was dosed (and executed such dose) correctly.

The variability in the volume of distribution (VD) for the individual and the half-life of the drug for the individual taking the medication appear to be the most likely factors in the detection of the medication. The ability of the toxicology laboratory to detect the medication varied widely for some individuals of the same weight and who were taking a different dose of Metoprolol. The VD for Metoprolol, the beta-blocker used to evaluate the effect of dose on the detectability of the drug, varies from 2.5 to 5.6 L/Kg and a half-life that varies from 2.5 to 7.5 Hrs depending on the individual taking the medication.

Therapeutic Concentration

The therapeutic concentrations for beta-blockers vary from a low of 0.007 to a high of 3.0 ug/mL. When one only considers drugs with 5 or more cases and for which the medication was taken orally, there does appear to be a correlation between therapeutic concentration and the ability of the laboratory to detect the medication. Beta-blockers with a mean therapeutic concentration below 0.100 ug/mL were detected less often (33% positive) than beta-blockers having a mean therapeutic concentration above 0.50 ug/mL (70% positive).

Specimen Analyzed

A correlation found between the type of specimen screened and the ability of the toxicology laboratory to detect beta-blockers is shown in Table 3. In many postmortem toxicology laboratories, blood is the specimen of choice for screening drugs, but it may not be the best specimen for detecting trace levels of beta-blockers. It is the job of the CAMI forensic toxicology laboratory to detect drugs at sub-therapeutic concentrations to enable investigators to identify medical conditions that may have contributed to the cause of an accident. In this study, reported beta-blockers were identified 100% of the time when lung and heart were analyzed. The next best specimens for screening beta-blockers were urine and kidney, with an average positive rate of 88% for reported beta-blockers. In some aviation accidents, there are limited specimens available due to high speed impact and significant damage to the body. In some cases, the muscle is the only recoverable specimen. However, there is still a high probability (66.9% positive) that the medication will be detected even in a muscle specimen.

Route of Administration

Medications can be taken by several different routes of administration including oral, sublingual, inhalation, topical, or injection. The route of administration does play a part in the ability of the laboratory to identify the medication. Timolol is an example of how the route of administration affects the ability of the laboratory to detect the medication. All of the reported Timolol cases were topically applied directly to the eye as an eye drop for the treatment of glaucoma. The dose applied to the eye is approximately 0.34 mg and not all of this dose would have actually been absorbed into the eye. This is a very small dose and is unlikely to be detected in most cases. The medication needs to be absorbed from the vitreous fluid into the blood stream prior to metabolism and excretion diluting the dose even more. There were 6 medically reported Timolol cases, and the laboratory only identified one of these cases. Recently, the laboratory did a technical refresh of all laboratory equipment and started using these new highly sensitive instruments in 2014 that allow the laboratory to detect drugs at very low concentrations. One Timolol case was detected and reported in 2015. Timolol started to be reported in the medical records in 2003, but the laboratory did not detect the medication in these older cases. The one Timolol case reported in 2015 had approximately 0.004 ug/mL in blood and 0.010 ug/g in liver. It is highly unlikely that this concentration would have been detected using the older instrumentation.

Missed Doses

One factor that could not be assessed using the data available in this study was missed doses by the pilot. However, studies have shown that approximately 30% of patients miss taking their medications (7-9). The "reasons for nonadherence were provided: 123 (73%) forgetfulness; 18 (11%) side effects; and 17 (10%) the medication was not needed.(9)" These findings could account for the 70% of the reported beta-blockers being found in postmortem toxicology analysis and 30% where the medication was not found.

Conclusion

The majority of the pilots (70%) reporting commonly used beta-blockers were found to be taking the beta-blocker by postmortem forensic toxicology analysis. In those cases where the medication was not found, there does exist the possibility that the pilot missed taking the medication on the day of the accident. In some cases, pilots were found to be taking a different beta-blocker than was reported in their medical records. There are many other reasons why a postmortem forensic toxicology laboratory might not detect a beta-blocker in a postmortem specimen, such as the elapsed time from taking the medication resulting in the concentration of the beta-blocker dropping below therapeutic concentrations and detectable limit.

Metoprolol and Atenolol were the most prevalent medication taken by pilots, which is consistent with the reported top 200 prescription drugs (10). Metoprolol, the most commonly found beta-blocker (48%) in postmortem forensic toxicology analysis of pilots, is ranked as the 16th most prescribed medication and Atenolol (33%) is ranked as the 82nd most prescribed medication.

Although one might assume the dose taken by the pilot would be a factor in the laboratory's ability to detect a beta-blocker, there is no evidence that this is true based on the data considered in this study. If one assumes the pilot is taking a therapeutic dose consistent with weight and metabolism, one would expect the concentration to be in the normal therapeutic range of the medication.

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