DOT/FAA/AM-99/29

Office of Aviation Medicine
Washington, D.C. 20591

Prevalence of Chlorpheniramine in Aviation Accident Pilot Fatalities, 1991-1996

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December 1999

Final Report

This document is available to the public through the National Technical Information Service, Springfield, Virginia 22161.

U.S. Department of Transportation

Federal Aviation Administration

NOTICE

Technical Report Documentation Page

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
DOT/FAA/AM-99/29		

4. Title and Subtitle	5. Report Date
Prevalence of Chlorpheniramine in Aviation Accident Pilot Fatalities, 1991-1996	December 1999
	6. Performing Organization Code

7. Author(s)	8. Performing Organization Report No.
Soper, J.W., Chaturvedi, A.K., and Canfield, D.V.	

9. Performing Organization Name and Address	10. Work Unit No. (TRAIS)
FAA Civil Aeromedical Institute P.O. Box 25082 Oklahoma City, Oklahoma 73125	11. Contract or Grant No.

12. Sponsoring Agency name and Address	13. Type of Report and Period Covered
Office of Aviation Medicine Federal Aviation Administration 800 Independence Ave., S.W. Washington, DC 20591	14. Sponsoring Agency Code

15. Supplemental Notes

This work was accomplished under the approved task AM-B-98-TOX-202.

16. Abstract

Chlorpheniramine, a popular nonprescription antihistaminic, is known to cause drowsiness. This side effect has a potential to impair performance and to be a factor in accidents. Therefore, this study was conducted to establish the prevalence of this drug in pilot fatalities of aviation accidents. During fatal aircraft accident investigations, postmortem samples collected from the pilots at autopsy are submitted to the Civil Aeromedical Institute for toxicological evaluation, and the findings are maintained in a database. Those data were examined for the presence of chlorpheniramine in the fatalities, which occurred during a 6-year (1991-1996) period. It was determined that there were 47 (2.2%) accidents involving chlorpheniramine. In 16 of these cases, only chlorpheniramine was found, with the mean concentrations of 109 ng/ml (n = 4) in blood and 1412 ng/g (n = 12) in liver. Other drugs were also present in the remaining 31 cases, wherein the mean chlorpheniramine concentrations were 93 ng/ml (n = 18) in blood and 747 ng/g (n = 12) in liver. Ninety-five percent of all the quantitative blood values were at or above the therapeutic (10 ng/ml) level, giving a 100 ng/ml (n = 21) blood mean level. The drug's mean concentration in the liver of all the cases was 1080 ng/g (n = 24). The average chlorpheniramine blood value was approximately 10 times higher than its therapeutic value. The presence of other drugs did not appear to significantly alter the blood level of chlorpheniramine, but no such correlation could be established with the hepatic value. The approximate 10-fold increase in the liver concentration, as compared with the blood value, was consistent with the general trend of the distribution of drugs in the hepatic compartment. However, the contribution of postmortem redistribution of the drug to alter its concentration cannot be entirely ruled out. The findings from this study suggest that chlorpheniramine was present in some aviation fatalities at levels higher than therapeutic perimortem levels.

17. Key Words	18. Distribution Statement
Chlorpheniramine, Antihistaminics, Sedatives, OTC Medications, Post-mortem Drug Analysis, Abused Drugs, Aircraft Accident Investigation	Document is available to the public through the National Technical Information Service, Springfield, Virginia 22161

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	8	

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Prevalence of Chlorpheniramine in Aviation Accident Pilot Fatalities, 1991-1996

INTRODUCTION

Chlorpheniramine, a popular nonprescription antihistaminic, is known to cause drowsiness (1). Therefore, individuals are advised, not to operate heavy machinery while using this drug (2). This side effect has a potential to impair performance (3) and to be a potentially significant factor in aircraft accidents.

In addition to direct effects of this drug on pilot reaction time, the medical conditions for which this drug is customarily taken may also impair pilot performance. Since chlorpheniramine is one of the most popular antihistamines (4), we conducted this study to establish the prevalence of this drug in pilot fatalities of aviation accidents.

METHODS

During fatal aircraft accident investigations, postmortem samples collected from the pilots at autopsy are submitted to the Civil Aeromedical Institute (CAMI) for toxicological evaluation. Analytical data are collected for the presence of ethanol, over-the-counter drugs (OTCs) including antihistamines (e.g., chlorpheniramine), and sympathomimetic amines (e.g., pseudoephedrine). Samples are also analyzed for abused drugs and for various prescription medications. These drugs are analyzed according to current laboratory procedure manuals, and the analytical findings are maintained in a computer database. Those data were examined for the presence of chlorpheniramine in fatalities that occurred during a six-year (1991-1996) period.

RESULTS AND DISCUSSION

As shown in Table 1, there were 16 cases in which only chlorpheniramine was found. In 6 of these cases blood was received in the toxicological samples submitted for analysis, while in 10 additional cases there was insufficient blood available for submission. There was a total population of 47 chlorpheniramine-related Pilot fatalities that occurred during the six-year period ranging from 1991-1996. The therapeutic level of chlorpheniramine in blood is 10 ng/ml (5), and the detection limit of the assay used was 5 ng/ml. Four of these 16 cases had a total drug level in blood at or above the detection limit of the assay. The mean value of the blood concentration in these cases was 109 ng/ml. The drug was only detected in blood in an additional two cases.

Chlorpheniramine was also quantitated in liver in three cases in which corresponding blood samples were obtained; the liver mean value in these cases was 2423 ng/g. The drug was further quantitated in liver in another nine cases obtained in the absence of

Table 1. Concentrations of Chlorpheniramine in Cases in Which Only This Antihistaminic Was Present

	Chlorpheniramine (Average; ng/ml (or g)			
	Blood	Liver	Lung	Urine*
With Blood (n = 6)**	109 (8-238; n = 4)	2423*** (1075-3674; n = 3)	3260 (n = 1)	Detected (n = 6)
Without Blood (n = 10)	-	1075 (153-4900; n = 9)	1160 (n = 1)	Detected (n = 1)

*Urine samples are routinely analyzed for qualitative analysis only. Therefore, detection simply means that chlorpheniramine was present in the sample.

**In two blood samples, concentrations were below the limit of quantitation of the analytical procedure (< 5 ng/ml).

***The mean value of all liver samples analyzed was 1412 ng/g (n = 12).

additional blood samples. The mean concentration of chlorpheniramine in these cases was 1075 ng/g. The combined mean of all liver samples in the absence of additional drugs was calculated to be 1412 ng/g (n = 12).

Chlorpheniramine was detected in seven urine samples and two lung samples, as indicated in Table 1. A value of 478 ng/ml was found in spinal fluid in one case. The drug was detected in muscle fluid in a separate case.

As depicted in Figure 1, the median level of all blood samples for chlorpheniramine in the absence of other drugs was 94 ng/ml, with a range of 8-238 ng/ml (n =4). It should be noted that the majority of these blood samples fell at or below a concentration of 50 ng/ml. The median level of all liver samples for chlorpheniramine in these cases was 561 ng/g, with a range of 153-4900 ng/g (n = 9). While the majority of liver cases fell at or below 500 ng/g, a significant number were above 2500 ng/g.

As given in Table 2, there were 31 cases (with and without blood) in which chlorpheniramine was detected in cases in which other drugs were also present. Eighteen of these 31 cases had a chlorpheniramine drug level at or above the assay detection limit of 5 ng/ml. The mean blood concentration in these cases was 93 ng/ml. The drug was detected in this tissue in an additional five cases. In one case, unusually high concentrations of this drug were found in various tissues (6100 ng/ml blood; 4970 ng/ml liver fluid; and 47000 ng/g in lung). These values were not used to calculate indicated averages but are included in the total number of cases.

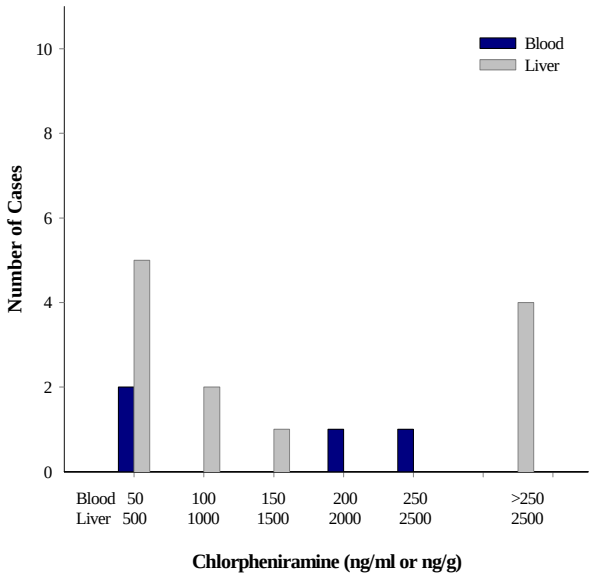

Figure 1. Chlorpheniramine Tissue Distribution in Absence of Other Drugs

Chlorpheniramine was also quantitated in nine liver samples in which corresponding blood samples were obtained; the mean value of chlorpheniramine for these samples was 916 ng/g liver. The drug was further quantitated in liver in another three cases obtained in the absence of additional blood samples. The mean concentration of chlorpheniramine in these cases was 241 ng/g. The combined mean value for all liver samples in the presence of other drugs was calculated to be 747 ng/g (n = 12).

Table 2. Concentrations of Chlorpheniramine in Cases in Which Other Drugs Were Also Present

	Chlorpheniramine (Average; ng/ml (or g))			
	Blood	Liver	Lung	Urine*
With Blood (n = 23)**	93 (10-493; n =18)	916*** (50-6299; n = 9)	6483 (365,12600; n = 2)	Detected (n = 13)
Without Blood (n = 8)	-	241 (24-600; n = 3)	731 (n = 1)	Detected (n = 5)

*Urine samples are routinely analyzed for qualitative analysis only. Therefore, detection simply means that chlorpheniramine was present in the sample.

**In four blood samples, concentrations were below the limit of quantitation of the analytical procedure (< 5 ng/ml). One additional sample in an abnormally high case was also excluded from calculation of average values.

***The mean value of all liver samples analyzed was 747 ng/g (n = 12).

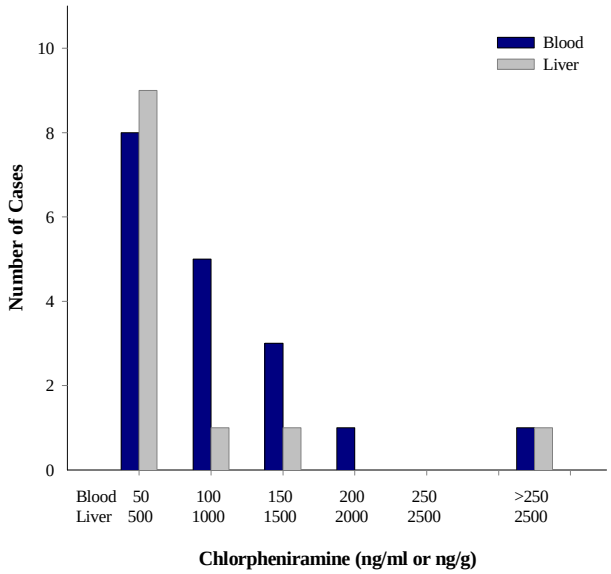

Figure 2. Chlorpheniramine Tissue Distribution in Presence of Other Drugs

Chlorpheniramine was detected in 18 urine samples and three lung samples (Table 2). An average level of 43 ng/ml was obtained in two kidney fluids. A value of 183 ng/ml was obtained in an additional heart fluid sample.

As depicted in Fig. 2, the median level of all blood samples for all cases in which this antihistaminic was present, in addition to other drugs, was 67 ng/ml, with a range of 10-493 ng/ml (n = 18). Figure 2 shows that the greatest number of cases involving blood fell at or below 50 ng/ml, with continually decreasing numbers of cases thereafter. The median level of all liver samples for chlorpheniramine in the presence of other drugs was 126 ng/g, with a range of 24-6299 ng/g (n = 12). As with blood cases, the greatest number of liver samples fell at the lowest concentration range recorded.

Table 3 presents data for the distribution of chlorpheniramine in all cases in which the drug was at or above 10 ng/ml (or g) in blood or liver. This concentration is considered a therapeutic level in blood (5). Thirty-six cases were found to have chlorpheniramine present in blood or in other tissues at a concentration at or above 10 ng/ml (or g). These cases were taken from the total pool of all 47 cases. They included all situations in which chlorpheniramine was found both in the absence and in the presence of additional drugs. Twenty-one of these cases had blood values above the therapeutic level. The average value of these blood cases was 100 ng/ml, with a range of 10-493 ng/ml. Twenty-four of the liver cases had values above 10 ng/g. The average value of these cases was 1080 ng/g, with a range of 24-6299 ng/g. Twelve of the 24 cases with liver values had no corresponding blood samples available.

Table 4 presents data describing the number of cases in which chlorpheniramine was found by itself, as well as with additional compounds. The additional compounds detected include other sedating antihistaminics, over-the-counter (OTC) drugs, and other pharmacologically active agents.

Table 3. Average Concentration of Chlorpheniramine Found in Blood and Liver for All Cases

Tissue Type	Chlorpheniramine (ng/ml (or g))	
	Average Value	Range
Blood (n = 21)*	100	10-493
Liver (n = 24)	1080	24-6299

*All blood and liver concentrations were at or above therapeutic levels of 10 ng/ml (or g).

Table 4. Distribution of Number of Cases in Which Additional Antihistaminics, Over-the-Counter (OTC) Drugs, and Other Agents Were Present in Addition to Chlorpheniramine

Analysis Type	Chlorpheniramine Only	Chlorpheniramine Plus Diphenhydramine /Doxylamine	Chlorpheniramine Plus Diphenhydramine /Doxylamine and other agents*	Chlorpheniramine and Non-sedating OTC drugs
Blood	5	3	2	10
Liver	9	1	1	1
**Other Types	2	1	-	3
Total Cases	16	5	3	14

*Other agents include ethanol, prescription drugs, and controlled substances. Cases involving controlled substances are summarized in Table 5.

**Other analysis types include urine, bile, and kidney.

Chlorpheniramine was found as the only drug present in 16 cases (Table 4). Five cases were found in which chlorpheniramine was present, along with the sedating antihistaminics diphenhydramine and doxylamine. These cases indicate the simple consumption of OTC medications, where the only other sedating drug was another antihistaminic. Three additional cases involving these sedating antihistaminics also involved various combinations of ethanol, prescription drugs, and/or controlled substances. Non-sedating medications such as acetaminophen, salicylates, and other sympathomimetic amines were also found as the only additional compounds in conjunction with chlorpheniramine. Fourteen cases are listed in this category.

As can be seen from Table 4, there were 16 cases involving chlorpheniramine alone, and there were 14 cases involving chlorpheniramine in the presence of only non-sedating OTC agents. Finally, there were five cases in which the only other sedating agents were additional sedating antihistaminics. The summation of these various categories yields 35 cases. In two other cases, carbon monoxide or atropine was also detected in blood. Ethanol was detected in six additional cases out of the total drug population of 47 cases. In one of these cases, the antidepressant fluoxetine and the calcium–channel blocker diltiazem were also found in addition to ethanol.

There were seven cases in which chlorpheniramine was detected in conjunction with controlled substances (Table 5). Narcotic analgesics that were found in three separate cases were hydrocodone, morphine, and norpropoxyphene. Cocaine (benzoylecgonine) was detected in one case, while butalbital was also detected in a blood sample in conjunction with norpropoxyphene. Benzodiazepines were detected in urine, liver, or blood in three separate cases. Five cases involved various combinations of ethanol, scheduled drugs, and sedating antihistamines, while one case involved the simultaneous occurrence of all three classes of compounds.

Table 5. Distribution of Number of Cases in Which Controlled Substances Were Present in Addition to Chlorpheniramine

Analysis Type	Narcotic Analgesics	Cocaine*	Barbiturates	Benzodiazepines
Blood	2	-	1	2
Liver	-	1	-	-
Urine/Bile	1	-	-	1

*Cocaine was detected as its metabolite benzoylecgonine.

CONCLUSIONS

In the time covered by this study, 2172 pilot fatalities were received at CAMI. In 111 of these fatalities, we found evidence for the presence of various antihistamines. Therefore, 5.1% (111) of all pilot fatalities involve antihistamines. Chlorpheniramine was involved in 47 of the 111 antihistamine related pilot deaths and accounts for 42% of all such fatalities. This antihistamine was detected in 2.2% (47) of all pilot casualties. In 16 of these 47 cases, in which only chlorpheniramine was found, its mean concentration in blood was 109 ng/ml and was 1412 ng/g in liver. The median concentrations in these tissues were 94 ng/ml and 561 ng/g, respectively.

For the remaining 31 cases, in which other drugs were also present, the mean chlorpheniramine concentration in blood was 93 ng/ml and was 747 ng/g in liver. The median concentrations in these tissues were 67 ng/ml and 126 ng/g, respectively. Ninety-five percent of all quantitative blood values were at or above the therapeutic (10 ng/ml) level, giving a 100 ng/ml blood mean level. The drug's mean concentration in the liver of all the cases was 1080 ng/g. Thirty-five of the 47 chlorpheniramine-related cases involved only chlorpheniramine or other OTC medications. These medications are commonly used in self-treatment of allergies or upper respiratory infections. Therefore, the total number of simple OTC cases is 35, or 74% of all cases.

The average chlorpheniramine blood value for all observed cases was 100 ng/ml. This value was approximately 10 times higher than the therapeutic value of 10 ng/ml. The mean and median values for blood concentrations in the absence and presence of other drugs did not vary significantly. Therefore, the presence of other drugs did not appear to significantly alter the blood level of chlorpheniramine. No such correlation could be established, however, with the hepatic value. The approximate 10-fold increase in the mean liver concentration, as compared with the blood value, was consistent with the general trend of the distribution of drugs in the hepatic compartment. However, the contribution of postmortem redistribution of the drug to alter its concentration cannot be entirely ruled out. The findings from this study suggest that chlorpheniramine was present in those aviation fatalities at levels higher than therapeutic perimortem levels

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