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Evaluation of a New Equation for Calculating the Maximum Wait Time for Pilots That Have Used an Impairing Medication

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16. Abstract <p>Pilots that use an impairing medication to treat a medical condition are required to wait an appropriate amount of time after completing the treatment before returning to duty. However, toxicology findings for pilots involved in fatal aviation accidents have proven that not all pilots wait a sufficient period of time before returning to duty.</p> <p>Those pilots were found to have impairing concentrations of the drug in the blood at the time of the accident. In the past, somewhat arbitrary wait times were used based on medication half-lives, dosage intervals, class of drug, and other subjective methods to estimate a return-to-duty time. These methods do not take into consideration the time required for the drug to decrease from therapeutic concentrations to a safe sub-therapeutic concentration.</p> <p>An equation was developed based on the therapeutic range and the maximum expected half-life of the medication to objectively calculate a safe return-to-duty time for pilots. The equation developed assumes the treating physician will not dose the patient beyond the upper therapeutic range of the medication and the person taking the medication has the maximum half-life reported in the literature. The equation $n = \ln(0.5 * C_{min} / C_{max}) / \ln(0.5)$ was developed to determine the number of half-lives (n) required to reach one half of C_{min}, where C_{min} = lower therapeutic concentration, and C_{max} = upper therapeutic concentration. This equation was evaluated for use in determining a safe return-to-duty time for pilots.</p> <p>Anonymous subjects were recruited according to an approved IRB protocol. All subjects had a preexisting medical condition treated with some type of medication. Blood and plasma were collected at approximately C_{max} (2-3hrs) and again after waiting approximately 5 more hours. Subjects were asked to provide information on the drug name, dose, dosing interval, age, height, weight, and gender.</p> <p>Toxicological analysis was performed on the specimens collected to determine the concentration of the medication at the first and the second collection times. The new equation was evaluated to determine if the wait times calculated by the equation and other methods were sufficient to eliminate the medication to a concentration below the lower therapeutic concentration of the medication.</p>					
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EVALUATION OF A NEW EQUATION FOR CALCULATING THE MAXIMUM WAIT TIME FOR PILOTS THAT HAVE USED AN IMPAIRING MEDICATION

INTRODUCTION

The Federal Aviation Administration (FAA), Office of Aerospace Medicine (OAM) is tasked with monitoring pilot medical status and issuing medical certificates to pilots that are considered medically qualified to safely operate an aircraft. To achieve this task, OAM develops medical standards to determine a pilot's fitness to fly. These standards help protect the pilot and the public from injury or death due to a medication or medical impairment. Research was requested by OAM to assist in the identification of the best method for calculating a safe return-to-duty time for pilots after using an impairing medication. This study evaluated a new equation developed at the Civil Aerospace Medical Institute (CAMI) for calculating return-to-duty times.

The medical profession has used several different methods to determine the length of time required to reduce the concentration of a medication from therapeutic concentrations to sub-therapeutic concentrations, including: number of hours (1,2) for a class of drug, three half-lives, five half-lives (3), two times the dosing interval (4), and five times the dosing interval (5). These all represent subjective methods and do not take into consideration the therapeutic range of the medication. Some of the current methods being utilized may not allow sufficient time, while others require excessive time for adequate drug clearance. Consequently the several referenced methods currently employed yielded diverse results for return-to-duty times, indicating the need for a more objective approach to solving the problem. There has been limited or no research conducted for determining safe return-to-duty times and therefore few definitive guidelines published (6,7).

MATERIALS AND METHODS

Equation

An equation was developed by the principal investigator based on the maximum and minimum therapeutic concentrations and the maximum expected half-life. The equation assumes the treating physician does not dose the patient beyond the upper therapeutic range, and the patient has the maximum half-life reported for the medication in the literature. The equation calculates the time required for the upper therapeutic blood concentration (C_{max}) to decrease to one-half of the minimum therapeutic concentration ($\frac{1}{2}C_{min}$), thereby providing a margin of safety for the pilot. Minimum and maximum therapeutic concentrations for the equation were obtained from published literature references. Most minimum and maximum concentrations for medications are available on the CAMI Drug Information website: <http://www.faa.gov/go/toxlab>.

The equation calculates the number of half-lives required to reach $\frac{1}{2}C_{min}$ concentration. Therefore, $\frac{1}{2}C_{min} = C_{max} \times (\frac{1}{2})^n$ where n equals the number of half-lives needed to reach one half the minimum therapeutic concentration (C_{min}). Solving the equation for the number of half-lives required to reach $\frac{1}{2}C_{min}$ provides the derived equation $n = \ln(0.5 \times C_{min}/C_{max})/\ln(0.5)$. This equation is effective in determining a safe return-to-duty time for pilots. The number of half-lives (n) determined from the above equation was multiplied by the upper half-life limit of the medication, rounded up to the nearest hour. This equation was evaluated experimentally to determine if the wait times calculated were sufficient to eliminate the medication to a concentration below minimum therapeutic concentration (C_{min}).

Human Subject Study

IRB approval #09001 for this research was granted on May 1, 2009, by the Civil Aerospace Medical Institute's Institutional Review Board (IRB, IRB00006891). Volunteers, 21–70 years old (excluding pregnant females), were treating pre-existing medical conditions using over-the-counter (OTC) medications (Aspirin™, Tylenol™, antihistamines, etc.), provided blood specimens. No privacy data were collected by the researchers involved in this study regarding the subjects.

Specimen Collection

Volunteers provided approximately 40 mL of blood during the course of this study. The primary medication taken by the subjects was diphenhydramine, an impairing OTC medication. Nine subjects taking diphenhydramine, seven male and two female, provided blood specimens on 12 separate occasions. These subjects were taking 25 to 50 mg of diphenhydramine once a day in the morning. They weighed between 145 and 325 lbs. Blood specimens were collected from January 15 to June 24, 2010, and subjects were restricted to participate on two separate occasions. The volunteers provided 20 mLs of blood 2 to 3 hours after taking the medication for the last time and did not take the medication again until the final specimen was collected approximately 7 to 8 hours after taking the last dose. One 10 mL tube containing an anticoagulant and preservative (gray top tube) was filled with blood. Specimens were collected in the CAMI Clinic, using standard venipuncture procedures. The medication being used, dose, dosing interval, date and time medication was last taken, date and time of specimen collection, gender, age, height, and weight were collected on each subject by the CAMI Clinic and supplied to the researchers along with a clinic ID number.

Specimen Analysis

Analysis was performed at the CAMI Bioaeronautical Sciences Research Laboratory (AAM-610) toxicology laboratory on whole blood specimens collected to determine the diphenhydramine concentration: a.) 2 to 3 hrs after taking the medication and b.) after waiting an additional 4 to 5 hours. Specimens were analyzed according to established procedures used by the CAMI Forensic Toxicology Laboratory. Specimens were analyzed to determine elimination rates and estimated times to reach half the impairing concentration of diphenhydramine. The time required for the concentration of diphenhydramine to reach half the impairing concentration was calculated using the elimination rate determined from the two specimens collected and analyzed for each subject. A comparison of all of the times calculated to reach half the impairing concentration were compared to the three different methods used to determine a safe return-to-duty time.

RESULTS

The variation in the number of half-lives (n) needed to reach ½ the minimum therapeutic concentration calculated with the CAMI equation for 18 different medications resulted in an average mean of four half-lives, SD 0.8, and a CV of 0.2, with a low of 2.6 half-lives to a high of 5.6 half-lives (Table 1). Using twice the dosing interval, the number of half-lives required ranged from 0.2 up to 10.7, with a mean of 1.3, SD of 2.5, and a CV of 1.9 for the medications in Table 1. Using the subjective wait times reported in Reference 1 of Table 1, the number of half-lives ranged from a low of 0.6 to a high of 6.0, mean of 2.0, SD 1.7, and a 0.9 CV.

Table 1. Comparison of return-to-duty time for new equation and established recommended times.

Medication	Half-life Max Hrs	Military Hrs	Time (1) Half-lives	2 x Dose (2) Interv Hrs	Half-lives	CAMI (3) Eq Hrs	Half-lives
Codeine	4.0	24	6.0	8.0	2.0	15	3.6
Morphine	7.0	24	3.4	8.0	1.1	31	4.3
Oxycodone	5.0	24	4.8	12.0	2.4	20	3.9
Butalbital	40.0	72	1.8	8.0	0.2	172	4.3
Cyclobenzaprine	37.0	24	0.6	12.0	0.3	148	4.0
Temazepam	13.0	12	0.9	48.0	3.7	52	4.0
Zolipidem	4.5	12	2.7	48.0	10.7	22	4.7
Diphenhydramine	14.0	24	1.7	8.0	0.6	49	3.5
Chlorpheniramine	43.0	24	0.6	8.0	0.2	129	3.0
Brompheniramine	35.0	24	0.7	8.0	0.2	110	3.1
Doxylamine	12.0	24	2.0	8.0	0.7	32	2.6
Sertraline	36.0	72	2.0	48.0	1.3	191	5.3
Bupropion	24.0	72	3.0	48.0	2.0	117	4.8
Acetaminophen	3.0	NA	NA	8.0	2.7	13	4.3
Fluoxetine	72.0	72	1.0	48.0	0.7	227	3.2
Citalopram	36.0	72	2.0	48.0	1.3	166	4.6
Dextromethorphan	4.0	24	6.0	8.0	2.0	23	5.6
Cetirizine	10.0	24	2.4	48.0	4.8	40	4.0
SD			1.7		2.5		0.8
Median			2.0		1.3		4.0
CV			0.9		1.9		0.2

1. Coast Guard Aviation Medicine Manual. In: Guard USC, ed. Washington, DC, 2003 (2).
2. Safety Recommendation I-00-1 through – 4, Washington, DC: NTSB; 2000:13-14 (4).

Subjects took a single dose of 25 to 50 mg of diphenhydramine prior to the initial blood collection. Concentrations of diphenhydramine in blood collected 2-3 hours after taking diphenhydramine ranged from 7 to 89 ng/mL for the nine subjects and 12 blood specimens collected from these subjects. The concentration of diphenhydramine after approximately 8 hours from dosage ranged from 0.0 to 33 ng/mL. Calculated return-to-duty times for the subjects, based on measured elimination rates, ranged from 1 to 12 hours, using a return-to-duty time of half the lower therapeutic concentration (C_{min}). The measured elimination rates ranged from 0.3 to 11 ng/hr. Within-subject differences for the four subjects that participated on two separate occasions exhibited, in some cases, significant changes in elimination rates (1.8 and 0.6 ng/hr), maximum concentrations after 2 to 3 hours (88.6 and 16.9 ng/mL), and calculated wait times (9.71 and 1.91 hours).

DISCUSSION

Existing methods for establishing return-to-duty times, compared to the proposed equation for calculating return-to-duty times, do not always agree on a safe return-to-duty time (Table 1). The current human subject study was conducted with subjects dosed with diphenhydramine because it is the most commonly found impairing medication in pilot fatalities involved in aviation accidents (6%) (8). This study identified some individuals with concentrations substantially above impairing concentrations even after waiting 8 hours (2 x dosing interval), and the subject would have taken approximately 12 hours (3 x dosing interval) to reach half the impairing concentration of the medication. The CAMI equation calculated a wait time of 49 hours for diphenhydramine. This would allow adequate time for all pilots to reach a safe return-to-duty time, even for individuals on the extreme metabolic margins of the general population.

The variation in $t_{1/2}$ (calculated by the CAMI equation) for different medications are more consistent than other methods with an average mean of 4 half-lives, SD 0.8, and a CV of 0.2 for a safe return-to-duty time. However, the CAMI method did vary from a low of 2.6 half-lives to a high 5.6 half-lives and was dependent on the medication used. Considering $t_{1/2}$ alone could overestimate the wait times for some medications and under-estimate for other medications.

Two times the dosing interval resulted in $t_{1/2}$ ranging from 0.2 to 10.7 half-lives for different medications. This relatively large variability suggests the method would, in some cases, allow pilots to return to duty at impairing concentrations and in others require the pilot to wait an excessive amount of time before returning to duty. In the case of the medication with a calculated 2 times the dosing interval, short $t_{1/2}$ of 0.2, the pilot would only

be required to wait 8 hours, whereas the CAMI equation would require the pilot to wait 4.3 half-lives, or 172 hours for the same medication. The medication with the excessive 10.7 half-lives or 48 hours wait time for pilots using 2 times the dosing interval required the pilot to wait only 4.7 half-lives, or 22 hours, using the CAMI equation. The 2 times the dosing interval method of calculating wait times would make the pilot wait more than 2 times longer than is actually necessary.

The subjective wait times reported in reference 1 of Table 1 would, in some cases, result in a $t_{1/2}$ that is exceptionally short for some impairing medications and would most likely result in pilots not waiting long enough time before returning to duty.

It is interesting to note that within-subject changes in elimination rates, maximum concentration, and calculated return-to-duty times varied significantly and cannot necessarily be attributed to genetic differences between subjects alone. Most variables were held relatively constant, including collection times, height, weight, age, dose, and gender. Diet and fluid intake were not controlled and could have been a factor in the changes noted in this study.

It is possible to modify the CAMI equation to include the dose and weight of the pilot to calculate the necessary wait time for pilots. The CAMI equation assumes that the pilot has the maximum reported therapeutic concentration in their blood when calculating wait times. However, we know the maximum therapeutic concentration is dose- and weight-dependent. The CAMI equation can be adapted to use the minimum volume of distribution (V_d) to calculate the maximum expected concentration in the blood for a given dose and weight. For example, a 124-lb person taking a 25-mg dose of diphenhydramine would have a maximum wait time of 49 hours, the same as the CAMI equation using the maximum reported therapeutic concentration. However, the wait time would decrease to 45 hours for a 150-lb person taking the same dose; a 300-lb individual taking a 25-mg dose would only need to wait 31 hours.

If the 300-lb person mentioned above had taken a 50-mg dose, the wait time would have been 45 hours, which is approximately the same as the 49 hours using the standard CAMI equation without considering weight or dose. The standard CAMI equation assumes the patient is taking the maximum therapeutic dose, whereas the dose weight adaptation of the CAMI equation would result in relatively the same wait time if the pilot is using the appropriate dose for their weight. The reason the wait times are approximately the same, using the standard CAMI calculation and the weight dose CAMI calculation, is the 300-lb pilot would normally need to take a 50-mg dose instead of the 25 mg taken by the 150-lb person to obtain the same therapeutic concentration.

CONCLUSIONS

The new equation provides an objective way of calculating a safe return-to-duty time and could be used to standardize the process of determining return-to-duty wait times for pilots that have taken an impairing medication. The CAMI equation for determining a safe return-to-duty time was used to successfully predict a safe wait time for pilots taking diphenhydramine in an actual human study. This equation gave relatively similar half-lives for different medications, as would be expected.

Some of the referenced methods used did not always result in a safe return-to-duty time and had an unexpectedly large variation in half-lives from medication to medication. The need to err on the side of safety should be adhered to and yet balanced with the reality of preventing encumbrance of the requirements of the pilot population. The CAMI equation has considered both requirements with additional research aimed at meeting this balance.

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