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CLINICAL TOXICOLOGIC STUDIES ON FREON ® FE 1301

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Summary

After conducting appropriate animal tests to ascertain safe levels, human subjects were exposed to concentrations of from 1.25% to 16.9% V/V of FE 1301. Assessment of judgement, alertness and neuromuscular skill indicated minimal but discernible effects at the lowest concentration in some individuals. At 10% V/V all subjects were effected. Stage I anesthesia occurred at 15% and Stage II would probably have occurred at 20%. A marked cardiac arrhythmia resulted in one subject exposed to 14%. There was complete recovery in all subjects within 20 minutes after exposure. No liver dysfunction occurred. The critical level for effective fire control is near 6%. This level would be acceptable on clinical toxicologic criteria.

Introduction

This study of the pharmacology and toxicology of the fluorocarbon fire extinguishing agent, Freon ® FE 1301, has special reference to possible myocardial sensitizing properties of the compound, and effects on the central nervous system.

It was conducted for the purpose of evaluating the medical aspects of toxicological hazards inherent in the release of FE 1301 into closed spaces such as aircraft cockpits or cabins. Although no adverse effects have been encountered in the use of portable extinguishers containing FE 1301, it is known that some halogenated hydrocarbons, as well as simple hydrocarbons, can cause abnormalities in cardiac rhythm when inhaled by persons with high blood levels of adrenalin.

The investigation was done in two parts. The first part involved exposure of dogs to various levels of FE 1301 under fright-producing situations in order to ascertain whether endogenously released epinephrine would cause myocardial arrhythmias. The second part was concerned with exposure of human subjects to varying concentrations with measurement of mental alertness and acuity and monitoring of the electrical activity of the myocardium. Extensive animal studies had been conducted by the toxicology group at the du Pont Company, the Hazelton Laboratories and Dr. Back, Wright-Patterson Air Force Base, Dayton, Ohio.

Stoppes of the Haskell Laboratories exposed three volunteers to concentrations up to 10% for 3-1/2 minutes. No other studies had previously been conducted on man. The intent of this study was to obtain data which might help define those levels which could be considered as safe for passengers and operative personnel in those situations where there might be need for exposure to FE 1301.

Experimental Approach

Material

The test material FE 1301 is identified chemically as bromotrifluoromethane (chemical symbol: $CBrF_3$). The material was furnished through the courtesy of Freon Products Division of E. I. du Pont de Nemours and Company. The material was described as typical of commercial production and free from impurities. Fluorocarbon 22B1 ($CHBrF_2$) and fluorocarbon 12B2 (CBr_2F_2) were stated to be present at concentrations of less than 1 ppm though specifications on the product would allow up to 50 ppm of either compound. Free halogen or acids were stated to be absent.

Exposure Facilities

All exposures took place in a cubicle exposure chamber of 8064 liter capacity. The chamber was lighted and equipped with circulating fans. All exposures were made in a static environment. Exposure in man lasted up to 25 minutes.

Determination of FE 1301

An appropriate method was developed for the determination of air concentrations of FE 1301 utilizing an Aerograph 600 gas-liquid chromatograph. For this purpose we used a hydrogen flame ionization detector and a stainless steel tube column, i.d. 4 mm. and 15 cm. in length, packed with 80-100 mesh Polapak "A". A volume of one ml. of gas under these conditions gave a full scale deflection at 16 volumes percent with X4 attenuation.

Production of Desired Concentration

FE 1301 gas was allowed to flow from the cylinder at a metered rate into the chamber to give the desired nominal concentrations. The air and FE 1301 input were adjusted to achieve the desired concentration which was then monitored and maintained at this level (or within 1.4% of this level) for the remainder of the exposure.

Exposure of Human Subjects

Test Subjects

Fifteen test subjects were used in assessment of the effects of FE 1301 on behavior and 10 on myocardial irritability. They were drawn from the population of research personnel, medical and dental students from the professional schools at the University of California at San Francisco. The nature of the test and the risks involved were explained to each subject emphasizing that the clinical pharmacology of the substance had not been fully ascertained and that this was part of the purpose of the experiment.

General Procedure

Subsequent to acceptance into the program we questioned them concerning their previous experience with anesthetics, allergies and sensitivities, and current drug ingestion. A physical examination was performed and their mood and affect appraised. Where high concentrations were to be used an electrocardiogram was taken. Prior to exposure all subjects were trained to acceptable levels of performance on tests measuring mental alertness and neuromuscular coordination. The FE 1301 was administered to four subjects at 1.25%, six subjects at 2.5%, four subjects at 5% and six at 10%. While in the chamber, subjects made observations as to sensory stimulation and carried out tests for mental alertness and neuromuscular coordination. All exposures were for 22 minutes or until the subjects completed the schedule given below:

Time (Minutes)	Test
0	Record Sensory Experience
1	Record Sensory Experience
2	Record Sensory Experience
5	Record Sensory Experience
6	Perform Romberg
7	Perform Finger-to-Finger
8	Perform Maze
10	Record Sensory Experience
11	Perform Pursuit Rotor
15	Record Sensory Experience
16	Perform Simple Reaction
20	Record Sensory Experience
21	Perform Maze
	Leave chamber and narrate description of exposure experience.

Experiments Monitoring Vital Signs

Ten subjects were administered FE 1301 in concentrations of 5-16% by mask. During this time pulse, respirations, blood pressure and electrical activity of the heart were monitored. Carbon dioxide at 5-10% was administered intermittently to six subjects.

Control of Bias

The experiment was carried out on a single blind basis but without placebo control, subjects being unaware of the concentrations that were being administered. Final interpretation of the electrocardiograms was made without the reader's knowledge of the concentration to which the subjects had been exposed.

Results

Characteristics of the Subjects

The age span was 22 to 33 years of age. Only one of the subjects was receiving chronic medication. Seven had a past history of allergies and sensitivities. Two of these were currently clinically active. One subject had a systolic murmur accentuated by exercise and had a history of a congenital heart problem.

Levels of Exposure

The concentrations determined by GLC were close to nominal concentrations in all runs.

Unusual Events

The experiment proceded satisfactorily according to experimental design and it was not necessary to significantly alter any of the procedures during the course of the investigation. No subject asked to terminate his chamber exposure; however, three subjects breathing mask-concentrations of 12% or greater had a feeling of impending unconsciousness. Subject 5 developed an unusual myocardial activity and dissociation of the pace maker after reaching a level of 16.1%, so his exposure was discontinued. Return to normal rhythm occurred within 3 minutes. It was not necessary to use any resuscitative devices at any time. All subjects recovered from their central nervous system depression within 20 minutes after exposure. Two subjects reported headache during or following exposure; one of these persisted for 12 hours.

Mental Alertness and Neuromuscular Coordination

There was a deterioration in performance in one or more tests at all of the four levels of exposure. Test in which the fingers were brought into proximation was the most sensitive and showed decreased performance at the lowest level tested. The maze test was second in sensitivity and decreased performance and was correlated with increasing FE 1301 concentration. The Rombeg test was the least sensitive showing no effect until the 10% level was reached when 3 of 6 subjects failed the test. Scores obtained in the rotor and simple reaction time tests did not correlate with concentration; in a number of instances in both tests there was improvement following exposure. At the 1.25% concentration there was convincing evidence of decrement in the finger-to-finger test and decrement in 4 of the 8 maze tests. At 2.5% finger-to-finger test again was more poorly performed by all subjects and there was a decrease in coordination as measured by the rotor test. There was no significant change at the 5% level of exposure. At

the 10% level there was a marked decrement in performance of the maze test as well as the finger-to-finger coordination test and failure of Romberg test. Improvement in skill test scores when the is exposed to central nervous system depressants is not the expected event but is sometimes observed in tests of the type used here. Two explanations are 1) an increase in the learning curve which continues during the testing session and 2) relaxation of tensions with a decrease in tendency to over-correct. At the 10% level there were 6 tests in which there were improvements, 7 in which there was no change and 23 in which there was a decrement performance.

Descriptive Words

The results of this test indicated a clear pattern of change in self appraisal of mood and mental clarity. There was a decrease in words with positive values such as alert, careful, clear-headed, forceful, industrious, resourceful and increase in words with negative values such as detached, drowsy, dull, elated, groggy, irritable, lackadaisical, lightheaded, sluggish and talkative. Fifty percent of the subjects at the lowest level indicated a feeling of lightheadedness. This generally was noted after 3 to 5 minutes of exposure.

Sensory Appraisal

The majority of subjects did not experience eye irritation, nose irritation or pulmonary discomfort during most of the period of testing. No eye irritation was noted at the two lower levels. Two subjects noted a slight irritation at both the 5 and 10% levels while one responded with moderate irritation at the 10% level. Only slight nasal irritation was noted by any subjects at the three lower levels; however, one subject classified nasal irritation at the 10% level as severe. This was identified as a bromine-like odor. Pulmonary discomfort described as either a feeling of coolness in the respiratory tract or nasal stuffiness was rated as no more than slight at any level. Olefactory recognition was rated as moderate in intensity by one or more subjects at all levels. Generally there was a decreased olefactory cognition with time. Lightheadedness just detected at the lower levels of exposure increased to a moderate disturbance in alertness and mental acuity in one of the four subjects at the 5% level, while three of the six subjects at the 10% level described marked sensation of giddiness and loss of normal alertness. Judging from all factors, it can be concluded that at concentrations at 10% a state of inebriation was beginning to appear.

The narrative descriptions defined varying degrees of central nervous system depression with paresthesias, alteration in auditory perception, euphoria, and silliness occurring at levels of 5%. There was numbness about the lips and beginning inebriation at the 10% level. A feeling of pending unconsciousness was related by three subjects at concentrations of 14.4 to 16.9%. Only one subject who reached 15% did not feel markedly confused.

Electrocardiographic Changes

There were no significant and unexpected findings at the baseline electrocardiograms. No changes occurred in seven of the EKG's during exposure even when concentrations of as high as 16.9% were reached. One subject had lowering of the T-wave 5 minutes after exposure to 8.2% of FE 1301 and 26 minutes later at a concentration of 12.1% when carbon dioxide had been added to the inhalant mixture. A second subject had flattening of the T-waves after 10 minutes of exposure at 12.5% FE 1301 and increased sinus arrhythmia at a later time. The most marked changes were noted in a 24-year old, 165 pound, Caucasian male of athletic build, hypertonic in mood and affect. Five minutes after exposure to 12.8% of FE 1301, he developed a flattening of the T-wave. This was followed in two minutes by premature ventricular contractions and one minute later when the concentration had reached 14% by auricular-ventricular dissociation. Rhythm was restored two minutes after cessation of the exposure.

Discussion

Study of the toxicity and biology of the fluorocarbons indicates that FE 1301 is one of the least toxic members of this class. The majority of overt pharmacologic signs refer to the central nervous system, the principal effect being narcosis, and anesthesia. However, there have been reported tremors and convulsive reactions in dogs exposed at high concentrations. Based on our experiments the only effect on the central nervous system of man which would be expected at concentrations short of those producing unconsciousness would be decreased awareness and alertness and slight confusion. A large number of halogenated hydrocarbons may cause cardiac sensitization to epinephrine; according to the evidence developed in animals and now in man FE 1301 would have to be classified among these compounds. The occurrence of cardiac arrhythmias is dose related, based on extensive experience with the anesthetics cyclopropane and chloroform. Arrhythmias produced by these compounds and presumably FE 1301 include a wandering pacemaker, atrial extrasystoles, atrial fibrillations, sporadic ventricular extrasystoles, mild focal and multifocal ventricular tachycardias and bigeminal rhythm. Given a large enough series of exposed persons at high enough concentrations and under severe conditions of epinephrine release, the probability exists that FE 1301 could produce myocardial sensitization and significant cardiac arrhythmia. The question therefore evolves about the relative degree of risk. The number of subjects in our study in whom the electrical activity was monitored is small, however we observed

no arrhythmias at concentrations below 10%. We did not establish an anesthetic level for our human subjects. However, the majority approached Stage I (analgesia) at concentrations of about 14%. The stage of delerium would probably have been achieved when an additional 2-3% was present. Loss of consciousness would occur, in our opinion, in most people at about 20 volumes %. At concentrations of 10% of FE 1301 or greater all subjects experienced some degree of confusion, misinterpretation of the surroundings or unsteadiness and giddiness. Clearly, one would have difficulty in sustaining complex operations at such concentrations. Tasks requiring precise timing and high degree of coordination would undoubtedly deteriorate. At the 5% level while effected to some degree by lightheadedness and change in mood, skilled tasks could be performed and even balance and locomotion were unimpaired. In the sitting position the sensation was not at all unpleasant nor was there any distress. Inhalation of the FE 1301 produces a sensation which in the inexperienced is slightly disturbing; however, those who previously had received anesthetics or consumed moderate quantities of alcoholic beverages were familiar with the sensation produced and were not disturbed by the exposure at concentrations of 10% or below.

There is no reason, based on our study, to believe that passengers would have any significant degree of confusion or be incapable of leaving their seats were rapid evacuation of the cabin area necessary at a FE 1301 level of 6%.