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Project Summary

Study of Chlorine Dioxide and Its Metabolites in Man

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To assess the relative safety of chronically administered chlorine water disinfectants in man, a controlled study was undertaken. The study was conducted in three phases. Phase I, a rising, single dose tolerance investigation examined the effects of chlorine disinfectants in normal healthy adult male volunteers. Phase II considered the effect on normal subjects of daily ingestion of disinfectants at a concentration of 5 mg/L over a 12 week period. In phase III, chlorite, at a concentration of 5 mg/L, was administered daily to a limited number (3) of glucose-6-phosphate dehydrogenase (G-6-PD) deficient subjects. Physiological impact was assessed by evaluation of a large battery of qualitative and quantitative tests.

In general, the study affirmed the relative safety and tolerance of normal healthy adult males and normal healthy adult male G-6-PD deficient individuals to the daily ingestion of 2.5 mg of chlorite for a 12 week period.

This Project Summary was developed by EPA's Health Effects Research Laboratory, Cincinnati, OH, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

Chlorine dioxide (ClO_2) has been identified as a potential water disinfectant alternative to chlorination. A three-phase human investigation was undertaken to assess the safety of ClO_2 and its metabolites.

In Phase I. Rising-Dose Tolerance Study, a controlled double-blind study was initiated to assess the safety of single dose administration of ClO_2 and its metabolites over a broad range of concentrations. Normal healthy adult males were treated with successive increasing doses of chlorine dioxide, chlorite, chlorate, chloramine, chlorine or untreated water (control). The concentration ranges examined were as follows: chlorine dioxide, 0.1 to 24.0 ppm; chlorite, 0.01 to 12.0 ppm; chlorate, 0.01 to 12.0 ppm; chloramine, 0.01 to 24.0 ppm; and chlorine, 0.01 to 24.0 ppm

In Phase II: Chronic Administration to Normal Subjects. Sixty volunteers were divided, at random, into six double-blind treatment groups of 10 subjects each for the administration of ClO_2, ClO_2 metabolites, chlorite (ClO_2^-) and chlorate (ClO_3^-); chloramine (NH_2Cl); chlorine; and control, distilled water. The 20-week protocol involved a 12 week period of daily oral administration of 500 mL of treated water followed by an 8-week observation period. The concentration of water disinfectants was 5 mg/L. Urine and blood samples collected at weekly intervals were subjected to complete routine clinical analysis and to special determinations for methemoglobin, glutathione, G-6-PD and thyroid function. Subjective evaluation of the qualitative clinical tests was coupled with the statistical evaluation of all quantitative chemical parameters.

In Phase III. Chronic Administration to G-6-PD Deficient Subjects. Three

healthy male volunteers found to be deficient in G-6-PD were chosen for the study. All three subjects ingested chlorite; no concurrent control study was performed The study protocol was identical to that of Phase II in temporal design and evaluation procedures. Volunteers received 500 mL daily of sodium chlorite at a concentration of 5 mg/L chlorite.

Materials and Methods

Subject Selection

Normal healthy adult male volunteers selected for inclusion in this study were required to satisfy the following criteria:

1. Subjects were between 21 and 45 years of age and were not confined to an institution.

2. Subjects had no significant abnormal physical findings at the pretreatment physical examination.

3. Subjects had no laboratory values significantly outside the normal range at the pretreatment evaluation.

4. Subjects weighed at the time of the pretreatment evaluation within ± 10% of the normal body weight for their frame and stature based on a standard weight table.

5. All subjects gave written consent to participate in the study.

Subjects were excluded from the study if they.

1. Had symptoms of significant clinical illness in the two weeks preceding the study;

2. received any drugs in the four weeks preceding the initiation of this study;

3. required any concomitant medication;

4. had one or more surgical or medical condition which might interfere with the absorption, metabolism or excretion of substances by the body;

5. had a known hypersensitivity to drugs, food or environmental factors;

6. had a history of cardiac, renal, hepatic, neurologic, hematologic or gastrointestinal disease; and

7. had a history of drug addiction

For Phase III, volunteers were defined as G-6-PD deficient on the basis of a hemoglobin G-6-PD level of less than 5.0 IU/GM hemoglobin in the pre-study screening. Phase III subjects were normal in all other respects

No subject who entered this study was undergoing concurrent drug therapy. However, once on study, a record was kept of the occasional episode of any physician-administered drug therapy that was required because of intercurrent illness. No subject was dropped from the study because of any intercurrent illness that developed during this study.

Discussion

During the course of the three phase study, a massive volume of raw data was acquired. For each of the participants, subjective information was collected at regular intervals concerning general medical well-being. The interpretation of physical examinations, electrocardiograms, Coombs tests, and hemoglobin electrophoresis increased the amount of available information Vital signs (blood pressure, heart rate, body temperature and respiratory rate) for each study subject were determined and compiled. Qualitative examinations of individual blood and urine samples were made. Further, 47 quantitative chemical parameters derived from the extensive battery of blood and urine testing procedures were recorded regularly. The conclusions drawn in this report were drawn from this body of information.

The incidence of minor illnesses, such as "colds" and the "flu" were evenly distributed among treatment groups and control groups. Physical examinations revealed no treatment-related pathology. Coombs test results were consistently normal throughout the study for the treatment groups and the control groups. The incidence of borderline abnormal hemoglobin electrophoresis was greatest during the posttreatment observation period; no relationship between treatment and the presence of abnormal hemoglobin electrophoresis could be established. Examination of individual vital sign parameters and statistical evaluation of those parameters failed to identify any changes in vital signs which could be attributed to treatment with any of the water disinfectants. Abnormalities in the qualitative blood and urine analyses were few and, again, appeared to be randomly distributed.

Conclusion

All three phases of this large controlled and double blinded clinical evaluation of ClO_2 and its potential metabolites in human male volunteer subjects were completed uneventfully, There were no obvious undesirable clinical sequellae noted by any of the participating subjects or the observing medical team. In several cases statistically significant trends in certain biochemical or physiological parameters were associated with treatment; however, none of these trends were judged to have physiological consequence. One cannot rule out the possibility that, over a longer treatment period, these trends might indeed achieve clinical importance. However, within the limits of the study, the relative safety of orgal ingestion of ClO_2 and its metabolites, chlorite and chlorate, was demonstrated.

Recommendations

This study was limited in some respects:

1. Only male volunteers participated.

2. Treatment was limited to 12 weeks

3. The number of G-6-PD deficient subjects was very small.

4 The dose of disinfectants was fairly low.

With this in mind, we make several recommendations. In use of chlorine dioxide as a water disinfectant, the entire population will ingest the disinfectant and its byproducts over a long period of time. The safety of ingestion in women and children must be assessed. The length of study should be increased. Furthermore, on the basis of Phase III, the absence of detrimental effects on potentially susceptible individuals cannot be ascertained with confidence; the sample size was limited and no concurrent control was run. If chlorine dioxide is to be used as a primary disinfectant, human invegtigations at

increased dose levels ought to be conducted.

Supplementary information including computer printouts, tables, figures, vital sign tabulations, subject histories, and clinical/chemical parameters are on file at the Health Effects Research Laboratory, Cincinnati, Ohio.

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***Richard Bull** is the EPA Project Officer (see below).*

The complete report, entitled "Study of Chlorine Dioxide and Its Metabolites in Man," (Order No. PB 82-109 356; Cost: $9.50, subject to change) will be available only from:

National Technical Information Service
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Springfield, VA 22161
Telephone: 703-487-4650

The EPA Project Officer can be contacted at:

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