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Failure to Detect Toxicity with the Concomitant Use of Cyclophosphamide and Halothane in Humans

JEFFRY T. LEE, M.D.,* PETER H. ERBGUTH, M.D.,† AND WENDELL C. STEVENS, M.D.‡

Concomitant administration of cyclophosphamide (CTX) and halothane is lethal in laboratory animals.^{1,2} Bruce recommended that CTX should be discontinued at least 12 h prior to administering a general anesthetic to patients.² However, no data are available to verify whether a toxic halothane-CTX interaction occurs in man. A prospective evaluation cannot be done. Before we became aware of the previously mentioned animal data in early 1985, 23 patients with intracranial neoplasms received CTX during halothane anesthesia at our institution.³ Anesthesia was administered to accomplish blood-brain-barrier (BBB) disruption⁴ with mannitol and concurrent administration of CTX as part of cancer chemotherapy. These patients provided an opportunity for a retrospective search for possible adverse effects of the concomitant use of halothane and CTX. Since 1985, we have discontinued the use of halothane for this procedure.

METHOD

During the period of July 1982 to February 1985, 23 patients (ages 14-66 yr, mean 43 ± 13 yr) with tissue-confirmed diagnosis of intracranial glioblastoma underwent a total of 44 BBB disruption procedures under halothane and N₂O anesthesia. Transient, reversible BBB disruption is an experimental procedure in which delivery of chemotherapeutic drugs to neoplastic tissue is enhanced by administering the drug into the internal carotid or vertebral artery after osmotically disrupting the BBB. The disruption is accomplished with 250 to 320 ml of 25% mannitol solution injected over 25 to 30 s through the internal carotid or vertebral artery. The chemotherapeutic agents given consisted of cyclophosphamide, 10-30 mg/kg, injected iv immediately prior to disruption and methotrexate 0.75-1.0 gm given *via* the internal carotid or vertebral artery immediately after disruption.

All of the patients were ASA Class I or II except for the presence of intracranial tumor and seizure. Dexa-

methasone plus phenobarbital or dilantin were the maintenance medications. All of the 44 disruptions were performed under general endotracheal anesthesia. Following thiopental induction of anesthesia and with 60-70% nitrous oxide, halothane in an amount sufficient to keep patients from moving or coughing was administered (0.5-1.0% inspired concentration). Inspired oxygen concentration was monitored and maintained at 30% or greater.

Hyperventilation was instituted without the use of muscle relaxants, although end-tidal or PaCO₂ was not measured routinely. After the 1- to 2-h procedure, patients were transferred to the intensive care unit for 24 h of observation.

RESULTS

The average exposure to halothane was estimated to be 0.725 MAC hours based on anesthesia record review. Each patient received an average of 22 mg/kg of CTX. There were no complications encountered during anesthesia in any patient. Laboratory analysis (complete blood count, platelet count, blood urea nitrogen, creatinine, urea nitrogen, uric acid, electrolytes, total protein, albumin, cholesterol, total and direct bilirubin, alkaline phosphatase, lactic dehydrogenase and serum glutamic oxaloacetic transaminase) were performed pre- and 24 h post-BBB disruption procedure. There were no significant differences between the two sets of results. Six patients had transient decreases in the numbers of platelets (*i.e.*, decreased by 50,000 cells/mm²), which returned to control in 2-3 days. Long-term follow-up (2-3 months) showed no abnormality attributable to the combined use of CTX and halothane.

DISCUSSION

CTX is the most commonly used alkylating agent for antineoplastic chemotherapy and has a wide spectrum of efficacy. Many patients with cancer or immune diseases who undergo surgery are receiving CTX either acutely or on a more chronic basis. Animal studies demonstrated enhancement of CTX toxicity by volatile anesthetics, and the combination of halothane and CTX was found to be lethal in both mice and rabbits.^{1,2} Necropsies and histologic examination in some of the animals failed to provide any explanation for their death. The toxicity appeared to be CTX dose-dependent^{1,2} and halothane exposure-

* Resident in Anesthesiology.

† Assistant Professor of Anesthesiology.

‡ Professor & Chairman, Department of Anesthesiology.

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Address reprint request to Dr. Erbguth.

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time-dependent.² Survival time varied greatly between rabbits (3–8 h) and mice (15–30 days), the rabbits exhibiting acute toxicity and the mice a more delayed form of toxicity. Interestingly, CTX plasma concentrations were consistently higher in halothane-pretreated mice than in untreated mice.¹ CTX has been shown in pentobarbital-anesthetized rhesus monkeys to induce immediate dose-dependent hypotension and bradycardia.⁷ Histamine levels in blood were found to be elevated. In an isolated and blood perfused dog heart preparation CTX caused a dose-dependent decrease in the force of contraction and the heart rate.⁷ These experiments suggest that CTX causes a nonspecific, direct cardiac depression and possible histamine release. Based on these animal studies, a putative danger is ascribed to the combined use of CTX and halothane in humans. Therefore, anesthesiologists are cautioned to discontinue CTX at least 12 h prior to general anesthesia.² Large, single doses of CTX (144 mg/kg and higher) given to unanesthetized patients prior to bone marrow transplant can cause acute myopericarditis and death from refractory myocardial failure.⁶ On autopsy hemorrhagic myocardial necrosis was found secondary to endothelial damage, allowing extravasation of blood containing high drug concentrations. Early signs of CTX cardiomyopathy include loss of R waves and ST-T wave changes, the incidence of which appears to be about 20% with single iv doses of 120 mg/kg. Our patients received only one-quarter to one-half of the single doses associated with cardiomyopathy. With these doses of CTX in the presence of halothane, we did not observe any evidence of cardiotoxicity as monitored by arterial blood pressure and electrocardiogram.

Our patients showed no ill effects that we could attribute to the combination of CTX and halothane. An average CTX dose of 22 mg/kg (10–30 mg/kg) was given iv over a 10-min period during halothane anesthesia. All patients tolerated the combination of CTX and halothane well as evidenced both by stable cardiovascular variables and electrocardiogram during the course of anesthesia and 24 h of observation in the intensive care unit and by 24 h follow-up laboratory test results. Most patients returned for repeat BBB disruption over several months. We could not find any evidence of delayed toxicity on readmission electrocardiogram, arterial blood pressure, or laboratory tests. There was not any evidence of cardiovascular, hepatic, or renal problems at discharge from the hospital or between admissions. In studies performed with mice,^{1,2} a single CTX dose of 600 mg/M² was given intraperitoneally. This is comparable on a weight basis to the 22 mg/kg iv dose used in our protocol. The exposure of halothane was somewhat greater in mice (0.35–0.5% for 2–20 h) than in our patients. However, even with exposures as small as 2 h of 0.5% halothane, median survival of CTX-treated mice was decreased to less than 25% of the control population.

The apparent benign outcome in humans following the co-administration of CTX and halothane contrasts greatly with the lethality seen in mice and rabbits. There appears to be a species difference to account for the benign outcome when CTX and halothane are used concomitantly in humans.

CTX requires activation by the hepatic microsomal mixed-function oxidase (cytochrome P-450) system. It undergoes a series of complex metabolic transformations, yielding products such as phosphoramidate mustard and acrolein, both of which are cytotoxic.⁵ Halothane is also metabolized by hepatic microsomal enzymes and it affects the activity of the cytochrome P-450 system and other hepatic enzymes. Given the extensive heterogeneity of cytochrome P-450 systems in humans, perhaps differing patterns of drug metabolism account for the lack of toxicity we saw. Interestingly, all of our patients received medications known to induce microsomal enzymes. Theoretically, toxicity from metabolites of CTX and halothane should be increased with induction of the cytochrome P-450 system. In addition, our patients received halothane before the administration of CTX, which should result in higher plasma concentrations of CTX than without halothane pretreatment, as Van Dyke and Powis¹ found in mice, accentuating any toxic interaction. Perhaps a hepatic basis for the interaction is not a key factor since hepatic necrosis was not a prominent feature of toxicity in animals. Perhaps overall circulatory adequacy and delivery of oxygen to tissues was preserved better in our patients than in the laboratory animals.

In conclusion, in this retrospective study, the co-administration of CTX and halothane was without apparent complications in humans. Our findings contrast greatly with the lethal effects of the combined use of these drugs found in mice and rabbits.

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