Title: **RANDOMISED PROSPECTIVE CONTROLLED STUDY OF METABOLISM AND HEPATOTOXICITY OF HALOTHANE IN MAN**

Authors: M.J. Cousins, MD, G.K. Gourlay, Ph.D, K.M. Knights, BSc(Hons), P. de la M. Hall, FRCPA, C.A. Lunam, BSc, and P. O'Brien, FRACS.

Affiliation: Departments of Anaesthesia and Intensive Care, and Histopathology, Flinders Medical Centre, and The Flinders University of South Australia, Adelaide 5042, Australia.

Introduction: Recent clinical studies indicate a high incidence (20-40%) of transient abnormalities in liver function following repeated halothane anesthetics[1]. Because of the low incidence (1 in 10,000) of hepatic necrosis following a single halothane anesthetic, prospective studies have not reported changes in liver function and liver pathology has not been studied prospectively. Reductive halothane metabolites 2-chloro-1,1,1-trifluoroethane (CTF) and 2-chloro-1-1-1-difluoroethylene (CDF) were detected in the breath of patients anesthetised with halothane[2]. Reductive metabolism is associated with free radical formation and hepatotoxicity in an animal model[3]. Therefore, could sensitive indices of liver function and pathology detect transient abnormalities due to a single halothane anesthetic in man? The present study aims to answer this question.

Methods: In a randomised prospective clinical study ** of patients undergoing abdominal surgery, halothane 0.5%, N_2O/O_2 and pancuronium (Group 1, n=8) was compared with N_2O/O_2, pancuronium and pethidine infusion (60 mg load dose, then 25 mg/hour) (Group II, n=8); and with enflurane 0.8%, N_2O/O_2 and pancuronium (Group III, n=8). Twenty-four hours prior to surgery and for 2 days postoperatively, blood and urine were collected for measurement of halothane metabolites and liver function, including serum alanine aminotransferase (ALT). In all groups, antipyrine clearance (C_{AP}) was measured pre-anesthesia and at 48 hours post-anesthesia. Indocyanine green clearance (C_{ICG}), as an indirect index of hepatic blood flow, was determined pre-anesthesia (Stage I), during 'basal anesthesia' with N_2O/O_2 and muscle relaxant (Stage II) and following the introduction of halothane, enflurane or pethidine (Stage III) and immediately before closing the abdomen (Stage IV). During anesthesia direct measurement of radial artery blood pressure was continuously recorded and arterial blood gases were measured at each of Stages I-IV. End tidal halothane or enflurane concentration was monitored with a infrared analyser and end tidal $\%CO_2$ and $\%O_2$ were adjusted to 5% and 70%, respectively, with the aid of mass spectrometry. Volatile reductive metabolites (CDF and CTF) were measured in end tidal breath from all patients in Group I at Stage II, and at 20 minute intervals during halothane anesthesia. Liver biopsy (by needle) was obtained under N_2O/O_2, thiopental, pancuronium, as soon as the abdomen was opened, then either halothane, enflurane or pethidine infusion was commenced and at the end of operation, prior to closure of the abdomen, a further needle biopsy of the liver was obtained. Liver sections were examined by light microscopy by a pathologist who was unaware of treatment group. A computerised technique was used to quantitate liver cell components for subsequent statistical analysis. Blood AP concentration was measured by gas chromatography, and ICG was measured by spectrophotometry. Pharmacokinetic parameters were determined from iterative non-linear least squares regression of blood concentration against time. Pre- and post-anesthesia data for each variable for each group was compared using analysis of variance. Significant differences within and between groups were sought. For C_{ICG} the same analysis was carried out with respect to Stages I-IV.

Results: Mean time of supplementation with halothane, enflurane and pethidine was approximately 2 hours in each group. Hemodynamics and blood gases were not significantly changed from Stage I to Stage IV. CDF and CTF were detectable within 20 minutes of the start of halothane anesthesia and increased until a plateau was reached after approximately 60 minutes. The concentration of CTF was always greater than CDF: cumulative means ± S.D. from 60-120 minute samples were 0.36 ± 0.07 ppm for CTF and 0.11 ± 0.03 ppm for CDF. Serum ALT was not significantly changed in Group I, II or III. C_{ICG} at Stage III compared to Stage I was significantly ($p < 0.05$) decreased (30 to 50%) in all groups. C_{AP} was significantly ($p < 0.05$) reduced in Groups I (halothane) and III (enflurane), but not in Group II (pethidine). The largest reductions in C_{AP} (50 to 70%) were in Group I and these patients tended to have the greatest reductions in C_{ICG} at Stage III. Liver biopsies showed no statistically significant difference ($p > 0.5$) for Groups I, II and III in liver cell size or nuclear to cytoplasmic area ratio when biopsies taken at Stage II were compared to those obtained at Stage IV.

Discussion: The presence of CDF and CTF in the exhaled air of all patients anesthetised with halothane indicated that some free radical may be formed in man. Reductions in C_{AP} could reflect transient hepatic damage. However, recent studies indicate a poor correlation between changes in C_{AP} and hepatic damage[4]. In the present study light microscopy did not show liver injury due to halothane, enflurane or pethidine immediately after 2 hours of exposure to each agent. Since ethical considerations do not permit examination later in the post-operative period, more subtle ultrastructural studies may be required to detect abnormalities in liver structure as early as 2 hours from the start of anesthesia. Significant changes in serum ALT and liver pathology have been observed at the end of a 2 hour halothane anesthetic in the hypoxic rat model[5].

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