CORRESPONDENCE

that there may be no advantage of intrathecal sedation, in particular for the elderly patient with a history of early respiratory depression.

It is interesting that raising intrathecal sedation suggested by Hays and associates (3) to a level that would delay the patient's recovery rate every 15 min for the next 24 h, in the absence of sensory change, may have improved the recovery profile of patients scheduled for single- or multi-dose long-acting regional anesthetic techniques, e.g., for labor analgesic or postoperative analgesic.

C.A., F.F.A.R.C.Sc., F.ACA Critical Care Anesthesia, Critical Care Anesthesia

In Reply.—My editorial (1) was focused only on my thoughts concerning the article by Kharausch et al. (2) in the same issue. The toxicity of compound A, hexafluoroisopropanol, and other aspects of sevoflurane, both clinical and scientific, were not discussed. The editorial was strictly confined to commentaries on the novel concept that local renal production and hence high renal concentrations of fluoride ion may be of greater importance in renal toxicity from fluorinated inhalation anesthetics than is hepatic fluoride production as measured by the plasma fluoride concentration. Contrary to Tinker and Baker's contention, neither my editorial (nor Kharausch et al.'s original paper) (2) discounted the nephrotoxic potential of fluoride ions. The issue was whether renal or hepatic production of fluoride was the more important vector of nephrotoxicity with inhalation anesthetics. The fact remains that several publications have documented plasma fluoride concentrations well in excess of 50 μM, whether from sevoflurane, enfurane, isoflurane, or fluoride ion in toxicity without evidence of renal toxicity. Tinker and Baker refer repeatedly to "heavy biotransformation" of sevoflurane. Let me supply the facts. Eight percent of the enfurane dose and 3-5% of the sevoflurane dose (3) are metabolized. Tinker and Baker are

References


(Accepted for publication April 29, 1995.)

Anesthesiology, V 83, No 1, Jul 1995

In Reply.—My editorial (1) was focused only on my thoughts concerning the article by Kharausch et al. (2) in the same issue. The toxicity of compound A, hexafluoroisopropanol, and other aspects of sevoflurane, both clinical and scientific, were not discussed. The editorial was strictly confined to commentaries on the novel concept that local renal production and hence high renal concentrations of fluoride ion may be of greater importance in renal toxicity from fluorinated inhalation anesthetics than is hepatic fluoride production as measured by the plasma fluoride concentration. Contrary to Tinker and Baker's contention, neither my editorial (nor Kharausch et al.'s original paper) (2) discounted the nephrotoxic potential of fluoride ions. The issue was whether renal or hepatic production of fluoride was the more important vector of nephrotoxicity with inhalation anesthetics. The fact remains that several publications have documented plasma fluoride concentrations well in excess of 50 μM, whether from sevoflurane, enfurane, isoflurane, or fluoride ion in toxicity without evidence of renal toxicity. Tinker and Baker refer repeatedly to "heavy biotransformation" of sevoflurane. Let me supply the facts. Eight percent of the enfurane dose and 3-5% of the sevoflurane dose (3) are metabolized. Tinker and Baker are...
correct that some anesthetic toxicity is due to biotransformation. I am not aware of their contrapositive argument that all biotransformation results in toxicity. No clinical pharmacologist believes this either. It is unfortunate that Tinker and Baker are prepared to pontificate with the statement that sevoflurane is a step backward: a statement obviously made without access to the facts established with the clinical development of sevoflurane.

I again propose that the major hypothesis that nephrotoxicity is agent-specific, occurs primarily because of intrarenal fluoride ion production, and is not primarily dependent on fluoride ion plasma concentration is impressive. It underscores the rule that medicine can never rest on its laurels; minds should remain open, vigilance should be maintained, and new data should be continually sought.

Burnell R. Brown, Jr., M.D., Ph.D., F.R.C.A.
Professor Emeritus
Department of Anesthesiology
University of Arizona
College of Medicine
Tucson, Arizona 85724

Anesthesiology
© 1995 American Society of Anesthesiologists, Inc.
Lippincott–Raven Publishers

In Reply—Tinker and Baker disagree with our analysis that “neither peak systemic fluoride concentrations nor duration of fluoride increase alone can be applied nonspecifically to all anesthetics to explain or predict nephrotoxicity.” We believe the data support our statement: Enfuran anesthesia in isoniazid-treated humans resulted in peak plasma fluoride concentrations exceeding 50 µM (as great as 130 µM), but there was no evidence of renal dysfunction. Prolonged isoflurane anesthesia resulted in peak plasma fluoride concentrations exceeding 50 µM for 2–5 days but had no deleterious effect on any measure of renal function. Prolonged isoflurane sedation resulted in peak plasma fluoride concentrations exceeding 50 µM (as great as 93 µM) but no adverse effects on renal function. During prolonged isoflurane sedation, in which fluoride concentrations remained increased for as long as 52 days, there were no significant changes in renal function. Sevoflurane anesthesia resulted in peak plasma fluoride concentrations exceeding 50 µM, but no adverse effects on renal function have been observed to date. In contrast, enfuran anesthesia can result in significantly diminished urine concentrating ability at plasma fluoride concentrations less than 50 µM. Thus, the enfuran experience does not appear to apply equally to all anesthetics.

Tinker and Baker attribute to us the notion that serum fluoride is no longer important in nephrotoxicity. We have made no such asserion.

Tinker and Baker claim that we “suggest, without proposing any mechanism, that the small amount of fluoride produced in the kidney is irrelevant to nephrotoxicity, whereas the large amount of serum fluoride that passes through the kidney for excretion is irrelevant.” There is no such statement in our paper, and furthermore, there are no data on which to argue the point. Renal parenchymal fluoride concentrations in vitro resulting from either renal anesthetic metabolism or tubular fluoride reabsorption have never been measured with enfuran or any other volatile agent. Tinker and Baker are correct in that we proposed no mechanisms of nephrotoxicity. We did not propose any mechanisms of nephrotoxicity because we did not study nephrotoxicity—we studied metabolism.

Tinker and Baker reject the potential that a metabolite or metabolic consequence of sevoflurane biotransformation other than plasma fluoride may contribute to nephrotoxicity because, “after many years of methoxyflurane study, none has been found.” However, there has been scant study of methoxyflurane nephrotoxicity in the last two decades. The absence of proof is not the proof of absence. Indeed, in only one of two papers published since 1980 which remotely address this issue, the use of analytical methodologies not available during the methoxyflurane era led to a reevaluation of methoxyflurane hepatic metabolism.

Methoxyflurane nephrotoxicity is intimately and unquestionably related to biotransformation. Methoxyflurane is biotransformed to a number of metabolites. Identification of fluoride as the nephrotoxic metabolite was based on associations between serum fluoride concentration and toxicity in humans: on correlations between changes in metabolism, serum fluoride concentrations, and nephrotoxicity in rats, and on the ability of fluoride (at unknown serum concentrations) to cause toxicity in animals. However, data in humans establishing a causal link between increased serum fluoride concentrations and nephrotoxicity of methoxyflurane or any other anesthetic has never been published. The clinical observations about enfuran, isoflurane, and sevoflurane cited above are pertinent. They call into question the appropriateness of applying a fluoride hypothesis developed to explain methoxyflurane nephrotoxicity nonselectively to.

References

( Accepted for publication April 29, 1995 )