EDITORIAL VIEWS

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Shibboleths and Jigsaw Puzzles

The Fluoride Nephrotoxicity Enigma

One of the intriguing and confounding aspects of medicine is that problems and questions remain remarkably similar over the years, but the answers frequently change. A major difficulty for physicians in any medical discipline, including anesthesiology, is awareness and compliance with new scientific advances so that shibboleths can be discarded to conform with advanced information. A candid example of information deeply ingrained into the clinical folklore of anesthesiology is that of direct cause and effect of fluoride ion plasma concentration derived from hepatic metabolism of halogenated volatile anesthetics and high output nephrotoxicity. For example, a standard textbook of anesthesiology states, "Detectable renal dysfunction is likely when the administered dose of methoxyflurane results in serum F concentrations that exceed 50 μM/L." [1] The data are based on pioneering work by Mazze and Cousins[2] with methoxyflurane but unfortunately have been applied to all halogenated anesthetics that release fluoride ion in an unmodified fashion. This shibboleth, a 50-μM/l threshold for nephrotoxicity was neither challenged nor reevaluated for more than 20 yr after its announcement. However, the rule was applied in *a priori* fashion to all fluorinated anesthetics.

With such extrapolation, difficulties appear that have been glossed over for some time. Corollaries of this dictum imply any anesthetic that produces ≥50 μM/l fluoride ion concentration in plasma in unequivocally nephrotoxic. There have been admonitions that patients with preexisting kidney disease should not be exposed to anesthetics such as enflurane. Despite these warnings, there appeared to be no reduction in renal function in renally impaired patients who received enflurane.[3] Similarly, when sevoflurane, an anesthetic that is biotransformed in a quantitative fashion similar to enflurane, was first investigated, there was concern that renal toxicity would render usefulness of the drug equivocal at best.

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* Callan C, Abbott Laboratories: Personal communication.

However, fluoride-related toxicity was not observed as part of early clinical assessment of sevoflurane in Japan[4] or as part of the experience accumulated during the Abbott Sevoflurane Clinical Program in Europe and North America, despite the fact that 7% of the adult patients/volunteers had plasma fluoride levels greater than 50 μM/l* or in volunteer studies during prolonged anesthesia with sevoflurane (9.5 MAC h) where peak fluoride concentrations of 47 ± 3 μM/l were attained.[5]

Even more curious is the report from the United Kingdom in which patients in intensive care units were sedated continuously with isoflurane for periods of 24 h or longer. Inorganic fluoride ion concentrations were sustained at high levels for prolonged times (>90 μM/l) with no nephrotoxicity observed.[6] The Fischer 344 rat has been the standard model of methoxyflurane (and enflurane) toxicity for years. However, the amount of NaF that must be administered intraperitoneally to produce decrements of urine concentrating ability in this animal is magnitudes greater than the amount of fluoride released during methoxyflurane or enflurane biotransformation (100–200 μmol NaF intraperitoneally/kg).[7] Other rat subspecies are quite resistant to methoxyflurane induced nephrotoxicity. Studies in volunteers given enflurane anesthesia demonstrated a 25% decrement of urinary concentrating ability when the maximal plasma fluoride concentration was only 33 μM/l.[8] Thus, many parts of the jigsaw puzzle of fluoride nephrotoxicity do not fit: the answer is not straightforward.

In this issue of the Journal, Kharasch *et al.*[9] postulate that intrarenal production of fluoride ion may be a more important factor for nephrotoxicity than hepatic metabolism, which causes increased plasma fluoride ion levels. If various rat subspecies have differential rates of intrarenal biotransformation, then this site of metabolism with varying cytochrome P-450 isoforms helps solve the genetic issue. Substantiation of the hypothesis proposed by Kharasch *et al.* would explain why patients can have an increased concentration of plasma fluoride after receiving drugs such as isoflurane and sevoflurane without evidence of nephrotoxicity.

Although fine points of this paper, particularly methodologic activities such as cytochrome P-450 subtype

specificities for antibody testing and inhibitors, can be argued, the major thesis 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. Each day brings us new knowledge from investigations, humble and profound, mundane and exotic, and we must learn to discard old indoctrinated mechanisms when they no longer stand the tests of time.

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