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Editorial

Renal toxicity of compound A with sevoflurane anesthesia: The benefits of sevoflurane appear to outweigh the risks

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It is generally accepted that sevoflurane reacts with carbon dioxide absorbents in the anesthetic circuit and is decomposed to compound A [1].

Compound A is nephrotoxic in rats at high inhaled concentrations, causing a distinctive proximal tubular lesion characterized biochemically by elevation of blood urea nitrogen, and urine glucose, protein, and ketone bodies, and histologically degeneration and necrosis of tubules, confined to the outer strip of the medulla [2,3].

Morio et al. [2] and Gonsowski et al. [3] have reported that the LC_{50} of compound A is 330–360 ppm in rats subjected to inhalation exposure for 3–12 h. Although compound A, itself, is not nephrotoxic, it is further metabolized to compound A glutathione and cysteine conjugates. These conjugates serve as a substrate for the β-lyase enzyme, with the subsequent formation of reactive thioacyl halide intermediates that could cause nephrotoxicity [4]. As reported by Frink et al. [5] and Bito and Ikeda [6], the concentration of compound A (as a degradation product of sevoflurane) is 10–35 ppm in humans. Two recent studies [7,8] of the nephrotoxicity of compound A in rats have reported conflicting results. Jin et al. [7] in 1995, showed that aminooxyacetic acid (AOAA), a competitive inhibitor of renal cysteine conjugate β-lyase, partially protected against intra-peritoneal compound A (0.1 mmol/kg)-induced diuresis and proteinuria. These findings suggest that glutathione conjugate formation, subsequent processing to cysteine conjugates, and cysteine conjugate metabolism by renal β-lyase may be important factors in the pathogenesis of compound A-mediated nephrotoxicity in rats. However, in 1996, Martin et al. [8] reported that neither AOAA nor AT-125 (both of which compounds block β-lyase), protected against inhaled compound A (150 ppm for 3h)-induced renal injury in rats. The histological studies of Martin et al. [8] suggested that these blockers tended to increase renal injury, indicating that these pathways mediate detoxification rather than medicating toxicity; the cysteine-S-conjugate-β lyase pathway did not appear to be the mechanism of compound A-induced nephrotoxicity. In their later study, Martin et al. [9] confirmed that these blockers increased renal injury in rats that had inhaled higher concentrations of compound A (600 or 800 ppm for 1 h). Martin and colleagues [9] suggested the cause of the discrepancy between their findings in both their studies, compared with the findings

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of Jin et al. [7] was the difference in the route of administration of compound A. However, this explanation is not convincing and the reason for the discrepancy unclear remains.

Renal β-lyase activity in humans is one-tenth that in the rat kidney [4]. Although we cannot extrapolate these results in rats to humans, we can conclude that humans would be expected to be less susceptible to compound A-induced nephrotoxicity than rats.

In regard to the safety of sevoflurane, Roizen [10] has stated that if there have been only few potentially adverse events (these not being clearly attributable to sevoflurane) reported after use at rates of more than 2.5 l/min in more than 2.5 million patients in Japan, one has to agree with comments by the United States Food and Drug Administration (FDA) advisory committee that sevoflurane may indeed be an anesthetic whose benefits substantially outweigh its risks. In this situation, I believe that further clinical investigations are necessary.

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