J Anesth (1997) 11:316–317; ©JSA 1997

RE: Yuge O: Renal toxicity of compound A with sevoflurane anesthesia: the benefits of sevoflurane appear to outweigh the risks (editorial). *J Anesth* 11:1–2

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To the editor: In his editorial [1], Professor Yuge suggests that: (1) the benefits of sevoflurane appear to outweigh its risks; (2) compound A (a product of sevoflurane degradation by carbon dioxide absorbents [2–6]), itself, is not nephrotoxic; and (3) compound A produces renal injury in rats by its degradation via the β-lyase pathway. He concludes that the data for rats do not apply to patients because humans have much less β-lyase activity than rats. In contrast, and benefiting from information not available to Professor Yuge, we suggest that (1) compound A, itself, is nephrotoxic; (2) the β-lyase pathway does not explain the toxicity of compound A; and (3) the use of intraperitoneal injections of compound A invalidates studies purporting to document the importance of the β-lyase pathway to the nephrotoxicity of compound A.

We are unaware of evidence that compound A, per se, is not toxic, instead finding indirect evidence that it is. Blood proteins degrade and probably bind to compound A [7]. Compound A also is genotoxic [8] at concentrations found clinically [9]. Genotoxicity does not require metabolic conversion of compound A to a reactive intermediate [8]; the intrinsic reactivity of compound A is sufficient. Finally, administration of dl-buthionine-*S*,*R*-sulfoximine (BSO) increases the nephrotoxicity of compound A [10,11]. BSO depletes glutathione stores [12]. Glutathione interacts directly or enzymatically with compound A [13], and glutathione depletion leaves more compound A free to cause injury directly. These considerations suggest that compound A, itself, may be nephrotoxic.

Several observations bring into question the relevance of the β-lyase pathway to the nephrotoxicity of compound A [14]. We found that neither aminooxyacetic acid (AOAA) nor acivicin protects rats from nephrotoxicity produced by *inhalation* of compound A [10,11]. AOAA and acivicin block the β-lyase pathway and should decrease injury if the β-lyase pathway leads to compound A-induced nephrotoxicity. These observations contrast with those of Jin et al. [15] and Kharasch et al. [13], who reported that AOAA partially protects against the nephrotoxicity caused by *intraperitoneal* injection of compound A. We suggested that the intraperitoneal route compromised interpretation of their findings [10], but Professor Yuge remained unconvinced, probably because we did not indicate our reasoning. We do so next.

The major problem with intraperitoneal delivery is that it produces glutathione conjugates but cannot reveal the independent expression of compound A toxicity. Intraperitoneal injection delivers compound A to the portal system, and thus to the liver, before passage to the lungs (Fig. 1). After first-pass hepatic conjugation of some compound A with glutathione [16], residual (unconjugated) compound A passes to the lungs, where ventilation clears most of the remaining, poorly soluble [5], compound A. The per cent clearance equals $100/[1 + \lambda(Q/V_A)]$ where λ is the blood/gas partition coefficient for compound A, Q is the cardiac output, and V_A is the alveolar minute ventilation [17]. Known values for the oil/gas and saline/gas partition coefficients [7] allow an estimate of 0.31 for λ. Q/V_A equals approximately 1.25 (e.g., a cardiac output of 5 $l \cdot min^{-1}$ and an alveolar ventilation of 4 $l \cdot min^{-1}$). By this reasoning, ventilation removes 72% of compound A that survives transit of the liver, leaving only 28% of an already depleted supply of compound A to circulate to the kidney and other organs. Thus, intraperitoneal injection of compound A delivers glutathione conjugates but not much compound A, itself, to the kidney. If glutathione conjugates and compound A are each independently nephrotoxic, intraperitoneal injection primarily tests the toxicity of the conjugates alone, but

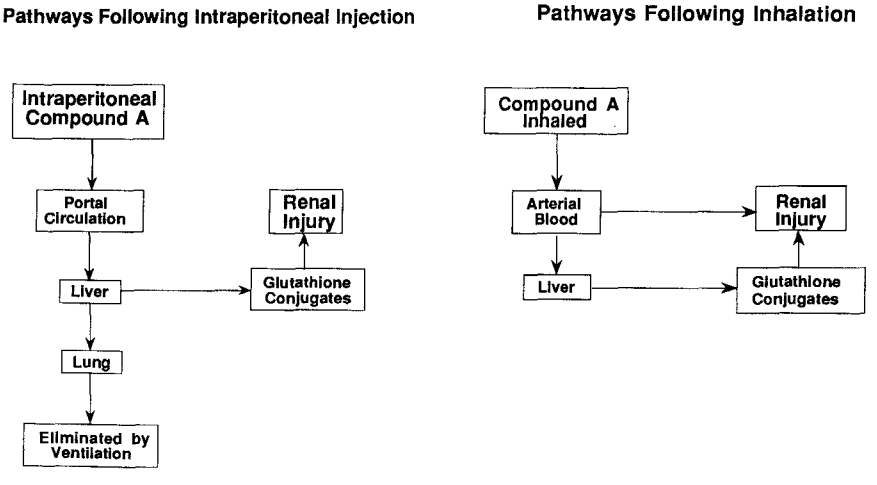

Fig. 1. Intraperitoneal injection of compound A delivers glutathione conjugates but not compound A to the kidney. In contrast, inhaled compound A delivers both compound A and glutathione conjugates to the kidney. The latter approach reflects clinical practice. When compound A is delivered by inhalation, blockade of the β-lyase pathway (i.e., blockade of the degradation of the glutathione conjugates to a putatively noxious reactive thiol) does not change or increases renal injury [10,11], proving that the β-lyase pathway is not important to the injury produced by compound A

not the independent toxicity of compound A. In contrast, inhalation of compound A (Fig. 1) delivers an identical compound A partial pressure to the liver and kidney, a condition that reflects the clinical situation and allows the independent manifestation of the toxicities of compound A and the formed conjugates.

Professor Yuge correctly observes that since human renal β-lyase activity is one-tenth that in the rat [18], if the β-lyase pathway explains compound A toxicity, humans should be far less vulnerable to injury. However, we find that humans are not less vulnerable [19]. We gave 1.25 MAC (3%) sevoflurane to volunteers for 8 h, producing an average concentration of 40 ppm of compound A, for a total "dose" of 320 ppm·h^{-1}. This dose produced renal injury (albuminuria, glucosuria, and urinary excretion of α-glutathione-*S*-transferase), whereas 1.25 MAC (9%) desflurane given for 8 h did not produce injury. A dose of compound A of 320 ppm·h lies within the range of concentration times hour that produce threshold injury in rats [2,3,5,6].

We conclude that the β-lyase pathway is not relevant to the toxicity of compound A. Whether the benefits of sevoflurane anesthesia outweigh its risks should, as Professor Yuge suggests, be the subject of further investigations.

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(Received for publication on March 6, 1997; accepted on May 28, 1997)