# An Open-label Comparison of a New Generic Sevoflurane Formulation With Original Sevoflurane in Patients Scheduled for Elective Surgery Under General Anesthesia

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## ABSTRACT

**Purpose:** To compare the stability, effectiveness, and safety profiles of a new generic sevoflurane with those of the original sevoflurane formulation in patients undergoing elective surgery.

**Methods:** An accelerated 3-month storage test was performed to evaluate the compositional changes in generic sevoflurane stored in glass bottles. In addition, 182 patients were randomly allocated to receive generic (n = 89 [54 men and 35 women]; mean [SD] age, 49.9 [11.6] years) or original (n = 93 [61 men and 32 women]; mean [SD] age, 49.6 [11.1] years) sevoflurane at a gas flow of 3 L/min for approximately 3 hours. The mean minimum alveolar concentration (MAC) during sevoflurane anesthesia was evaluated, and gas samples for measuring compound A were collected from the inspiratory limb of the circuit at preset intervals. Blood samples for measuring serum inorganic fluoride were obtained at preset intervals (pharmacokinetic group: generic/original sevoflurane = 45/46). Renal biomarkers, such as *N*-acetyl-β-glucosaminidase, α- and π-glutathione-S-transferase, albumin, urine protein and osmolality, serum creatinine and osmolality, creatinine clearance, and blood urea nitrogen, were measured at preset intervals (renal biomarker group: generic/original sevoflurane = 44/47). Adverse reactions were monitored for 72 hours after discontinuation of sevoflurane use.

**Findings:** Generic sevoflurane contained in glass bottles was stable for 3 months. The mean MAC was similar for generic and original sevoflurane (median [range], 0.93 [0.67–1.29] vs 0.94 [0.63−1.5] vol%). Adverse event rates were similar (90.3% vs 84.3%), as were the $AUC_{last}$ of inorganic fluoride (333.7 [112.7−1264.7] vs 311.9 [81.5−1266.5] hours · μmol/L) and compound A (51.8 [6.3−204.5] vs 55.3 [10.8−270.6] hours · ppm). Biomarkers associated with renal injury were not significantly different between the 2 formulations.

**Implications:** No significant difference was found in the mean MAC between generic and original sevoflurane. ClinicalTrials.gov identifier: NCT01096212. (*Clin Ther*. 2015;37:887–901) 

**Key words:** compound A, effectiveness, generic sevoflurane, inorganic fluoride.

## INTRODUCTION

Sevoflurane, an inhalational agent, has gained popularity worldwide as a general anesthetic since it was first synthesized in the United States.[1,2] Before the introduction of wet-type sevoflurane, a specific lot of original sevoflurane was recalled in the United States because of the pungent odor produced by an impurity in the glass bottle, which had reacted with the

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sevoflurane to generate Lewis acids.[3,4] Since then, sevoflurane has been added to water (wet-type method) and stored in polyethylene naphthalate bottles to prevent sevoflurane degradation interactions with Lewis acids (metal halides and oxides) in glass sevoflurane bottles and anesthesia equipment. The hydrofluoric acid formed from this reaction, even in minute amounts, is highly reactive, corrosive, and toxic and can cause respiratory irritation or pulmonary hemorrhage.[5]

Generic sevoflurane products launched after the patent on original sevoflurane expired in 2006 were produced with low water content (dry-type method) because of valid patents on the wet-type method and the polyethylene naphthalate bottles used for storage.[2] These generic formulations do not contain sufficient water to prevent sevoflurane degradation by Lewis acids and the production of toxic hydrogen fluoride, raising safety concerns. To overcome this problem, a generic sevoflurane* is stored in aluminum bottles lined with an epoxy phenolic resin.

After the recent expiration of the patent on the wet-type method in Europe and Korea, a generic sevoflurane† with a high water content (421 ppm of water) was commercialized and approved for marketing in Korea by the Korea Food & Drug Administration. Since the patent on polyethylene naphthalate bottles has not yet expired, this formulation is bottled in brown glass containers, necessitating safety evaluations. In addition, the interaction of sevoflurane with carbon dioxide absorbents forms fluoromethyl-2 and 2-difluoro-1-(trifluoromethyl) vinyl ether (compound A), and oxidative metabolism of sevoflurane results in the generation of inorganic fluoride ($F^-$). Both substances have been associated with renal injuries in animals and humans that result in the urinary secretion of proximal and distal renal tubular enzymes.[6–9] Biological markers, including the proximal tubular enzymes *N*-acetyl-β-D-glucosaminidase (NAG) and α-glutathione-S-transferase (GST) and the distal tubular enzyme π-GST, can be valuable tools for determining the nature and severity of renal injuries.[9,10] The in vitro productions of $F^-$ and compound A are influenced by the water content of sevoflurane and/or the vaporizer.[5,11] To our knowledge, few clinical studies have assessed the in vivo generation of these compounds when generic sevoflurane is used in patients for general anesthesia.[12]

This study was therefore designed to investigate the in vitro changes in the composition of generic sevoflurane with high water content stored in glass containers for 3 months, to compare the effectiveness and safety profiles in patients receiving original sevoflurane‡ and generic sevoflurane with high water content, and to assess the in vivo production of compound A and $F^-$ by these 2 sevoflurane formulations.

## METHODS

### Changes in Generic Sevoflurane Composition in an Accelerated Storage Test

Four glass bottles of generic sevoflurane were prepared by a laboratory researcher working for the manufacturer (Hana Pharmaceutical, Co., Ltd.). The researcher conducted the analysis at the laboratory of the manufacturer, which is certified by the Korea Food & Drug Administration. Sealed bottles were stored at a mean (SD) of 40°C (2°C) and a mean (SD) relative humidity of 75% (5%) for 0, 1, 2, and 3 months. One sealed bottle was opened at each time point, and $F^-$, compounds A, B, and C, and water content were analyzed. Two milliliters of each sample were withdrawn and analyzed by gas chromatography (model 6890A; Agilent Technologies, Inc., Palo Alto, California) under the following conditions[13]: detector, flame ionization; column, 0.32-mm × 30-m fused-silica capillary column coated with a 3.0-μm film of liquid phase G43; temperature, 40°C for 10 minutes, followed by increases of 10°C/min up to 200°C and then 14 minutes at 200°C; injection port temperature, fixed temperature of approximately 200°C; detector temperature, 225°C; carrier gas, helium; flow rate, 1 mL/min; and injection size, 2 μL.

System suitability was indicated by the relative SD from the peak area ratio of sevoflurane to the internal standard solutions of <3%. Standard solutions were prepared by transferring 2-mL aliquots of ethylene dichloride to screw-capped vials, which were immediately sealed with a cap and septum and placed on a balance. With the use of a microsyringe, approximately 20 μL of sevoflurane reference standards from the US Pharmacopeia were transferred to each vial by inserting the syringe needle through the septum, with

*Trademark: Sevoness® (Baxter, Deerfield, Illinois).

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