Analysis of the composition of ‘original’ and generic sevoflurane in routine use†

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Background. Original sevoflurane (Sevofrane) contains a small amount of water, which can inhibit the production of hydrofluoric acid. Hydrofluoric acid is highly pungent, and sevoflurane that contains a high concentration of hydrofluoric acid is not suitable for volatile induction of anaesthesia. Recently, generic sevoflurane (Sevoness) has become available in some countries. The generic product is produced by a different method and kept in a different kind of bottle. We questioned whether the original and generic sevoflurane differed in their composition and thus might differ in their resistance to degradation.

Methods. Sevoflurane from groups of three bottles of Sevofrane and three bottles of Sevoness was kept in the bottle at 24–37°C for 2 weeks or in two kinds of vaporizer for 3 days, and the resulting contents measured by gas chromatography.

Results. Both products contained sevoflurane concentrations exceeding 99.998%. Fluoride ion concentration did not differ between the products (0.043 ppm). The original sevoflurane contained more (0.07% w/v) water than the generic anaesthetic (0.003% w/v). Original sevoflurane contained 5 ppm compound A, 10 ppm sevomethylether, and 5 ppm of unknown materials. Generic sevoflurane contained 32 ppm hexafluoroisopropanol and 12 ppm of unknown materials. While stored in a vaporizer for 3 days, the water content in the original sevoflurane decreased by two-thirds but the water in the generic sevoflurane increased by a factor of three-fold.

Conclusions. Generic sevoflurane contains high-quality sevoflurane and only a small amount of fluoride ions, making it comparable with the original sevoflurane product.


Keywords: anaesthetics volatile, sevoflurane; measurement techniques, chromatography

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Sevoflurane was first synthesized in the USA1 and then developed for approval in Japan in 1990.2 Despite its anticipated usefulness due to its adequate anaesthetic potency, low blood/gas partition coefficient, and absence of pungency, sevoflurane faced limited use in some countries and regions, primarily due to the controversy3 4 that emerged after its launch, over nephrotoxicity of compound A [fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether], which is produced as a result of a reaction between the drug and soda lime, a carbon dioxide absorbent. However, sevoflurane is currently being used in more than 100 countries worldwide with an estimated 100 million operations having been performed using sevoflurane as a general anaesthetic.

Examples of original sevoflurane include Ultane® (Abbott Laboratories, Abbott Park, IL, USA) and Sevofrane® (Maruishi Pharmaceutical Co., Ltd, Osaka, Japan). After the recent expiry of the patent on sevoflurane as a pharmaceutical drug, a generic product (Sevoness®; Baxter, Deerfield, IL, USA) has been launched. This generic product has been approved for sale by the Food and Drug Administration (FDA) of the USA based on the results of an equivalence study, and is currently being launched in China and other countries.

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However, because the patents on the wet-type method (addition of water to the product) and polyethylene naphthalate (PEN) bottles, which were developed as modifications to original sevoflurane to prevent the production of the highly pungent hydrofluoric acid, have not expired, generic products are dry-type products that are kept in aluminium bottles. Therefore, depending on conditions of storage and use, hydrofluoric acid production may be of concern for the generic product, as it initially was for original sevoflurane.

On the basis of this background, we conducted a component analysis of original and generic sevoflurane under different conditions of clinical use. The present study was conducted independently of the companies manufacturing and selling the products.

Methods

The following reagents and materials were used: two kinds of commercially available sevoflurane products, original sevoflurane (Sevofrane®; Maruishi Pharmaceutical Co., Ltd) and generic sevoflurane (Sevoness®; Baxter). The original product Sevofrane® is identical to Ultane® (Abbott Laboratories), which is available in Europe and the USA.

Nine bottles of original (Sevofrane®) and nine bottles of generic (Sevoness®) sevoflurane were prepared, and three kinds of routine use were tested in this study. The first group (n=3 each) was treated under conditions simulating transport of the bottles being used. Specifically, each bottle was opened, closed, stored at a random temperature between room temperature (24°C) and body temperature (37°C), and carried and allowed to shake in the pockets of the surgical gowns of anaesthesiologists during the daytime for 2 weeks. Although this technique seems strange, we had checked by the use of indigocarmine that the technique could shake the bottles better than some popular shaking apparatus. The other two groups (n=3 each) were treated under conditions simulating the use of the drug one weekend after its injection into a vaporizer. Specifically, two different types of vaporizer were completely emptied, and the inside of the vaporizer was purged with oxygen for 6 h at a rate of 6 litre min⁻¹. Subsequently, each sevoflurane product was injected into the vaporizers until they were approximately half full (100–150 ml), and kept in the vaporizers for 3 days (72 h). The vaporizers used were two types of sevoflurane-specific, variable bypass, flow-over, temperature-compensated, and out-of-circuit vaporizers (Sevotec 5; GE Healthcare Co., Fairfield, CT, USA and Vapor 19.3; Dräger, Lübeck, Germany). Each liquid sevoflurane product was carefully sampled and transported at room temperature (22–24°C), and component analysis was performed on the day of sampling. For sampling and transport, all impurities were removed, and glass bottles with an inner coating were used. The bottles were completely sealed with plastic lids.

The following properties were measured: colour tone, fluidity, miscibility and solubility in other solvents, inflammability and volatility, and refractive index. For component tests, sevoflurane and its related substances were measured. Samples (2 µl) were analysed using gas chromatography under the following conditions.

Test conditions:
- detector: hydrogen flame ionization detector;
- column: carloblack B (80/120 mesh) containing 5% RT-1000 was packed into a tube (internal diameter, 2 mm; length, 4 m);
- column temperature: 80°C for 20 min, followed by increases of 8°C min⁻¹ up to 180°C, and then maintained at 180°C for 17 min;
- injection port temperature: fixed temperature around 175°C;
- detector temperature: fixed temperature around 200°C;
- carrier gas: nitrogen;
- flow rate: adjusted such that the retention time of compound A was approximately 8.5 min;
- time period of measurement: approximately three times the retention time of sevoflurane (50 min).

System reproducibility was indicated by a relative standard deviation of <5% per 2 µl of standard solution for peak areas of each known related substance for six replicate assays under the above conditions.

Water content was measured using coulometric titration (15 g). Cerium ion was used to maintain the efficacy of system, and the system compatibility was determined by performing three tests for 1 ml of each standard sample (1 g ml⁻¹), and indicated by water content values (mg g⁻¹) within ±2% of the corrected values of standard samples when obtaining the water content of standard samples.

For quantification, component contents were determined by calculating percentages based on the ratios of all peak areas obtained after removing solvent peaks to the peak area of sevoflurane in accordance with the operation of purity tests for related substances.

Data were expressed in terms of measured values and mean (±SD). Unpaired t-tests were performed for comparisons of measured values, using a significance level of 0.05.

Results

All samples of both products were clear and colourless liquids and extremely soluble in 95% ethanol but equally insoluble in water. All samples were volatile, non-inflammable, and did not ignite when lit in the presence of vaporized and heated sevoflurane. Refraction indices (20°C, D line) were within the range from 1.2745 to 1.2760. These properties all indicated the physical properties of sevoflurane itself. The pH values were constant across all groups, with values of 6.04 (± 0.11) for the original product and 6.03 (± 0.10) for the generic product; no
significant differences between the products were observed ($P=0.91$).

The ingredients of original and generic sevoflurane in this study are shown in Figure 1. Inorganic fluoride content, which reflects hydrofluoric acid levels, was also constant across all groups, with extremely low contents of 0.042 (0.003) ppm for the original product and 0.044 (0.007) ppm for the generic product; no significant differences between the products were observed ($P=0.45$). Samples of the wet-type original product that were opened, sealed, and stored for 2 weeks maintained a constant water content of 0.072 (0.001)% w/v, whereas the dry-type generic product had a significantly lower ($P<0.001$) water content of 0.003 (0.001)% w/v. Although the water content of the original product (wet-type) significantly decreased [0.025 (0.003)% w/v; $P<0.001$] when injected into a vaporizer and left to stand for 3 days, no differences between the two types of vaporizer were observed ($P=0.48$). In contrast, when the generic product (dry-type) was injected into a vaporizer and left to stand, its water content slightly yet significantly increased [0.008 (0.002)% w/v; $P<0.01$], but remained significantly lower than that of the original product ($P<0.001$). No differences between the vaporizers were observed ($P=0.65$). As for sevoflurane content, high purity was observed in both the original and the generic products [99.9985 (0.0002)% and 99.9982 (0.0013)%, respectively], with no differences between the products ($P=0.54$) and low variation (range, 99.9982–99.9987 and 99.9966–99.9993, respectively).

Related substances not mentioned above are shown in Figure 2. Original sevoflurane contained compound A [mean, 4.6 (1.5) ppm; range, 3–8 ppm], sevomethylether [SME; mean, 10.4 (1.1) ppm; range, 9–12 ppm], and other related substances [mean, 4.6 (1.0) ppm; range, 4–7 ppm]. Each of these substances had a low concentration and small variation. No differences in concentrations between the storage methods investigated were observed. Although the generic sevoflurane did not contain compound A or SME, it contained hexafluoroisopropanol (HFIP) [mean, 32.0 (25.9) ppm; range, 12–67 ppm] and other related substances [mean, 12.2 (8.0) ppm; range, 5–22 ppm]. Although a large variation in content of HFIP and other related substances in the generic product was observed between different samples (indicating a large sd), no differences were observed between different groups (conditions). Total content of related substances was significantly higher ($P<0.05$) in the generic product than in the original product. The properties of other related substances contained in either product were not determined in the present study. Each other related substance, however, had a different retention time, indicating a difference in the structure of these substances between original and generic sevoflurane products.

In a preliminary study, we had measured the ingredients of original and generic sevoflurane products in freshly delivered bottles ($n=3$ each), and found no differences in the contents between them and those that had been opened, sealed, and stored for 2 weeks in this study (data not shown).

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**Fig 1** Composition of original and generic sevoflurane products. Data are expressed as mean (sd). *$P<0.05$ vs water content in original sevoflurane product after 2 weeks in a bottle. †$P<0.05$ vs water content in generic sevoflurane product after 2 weeks in a bottle. (A) Inorganic fluoride content was constant across all groups for the generic product; no significant differences between the products were observed, $n=9$ each. (B) In contrast to the samples of the wet-type original product that were opened, sealed, and stored for 2 weeks, the dry-type generic product had an extremely low water content, $n=3$ each. The water content of the original product (wet-type) significantly decreased when injected into a vaporizer and left to stand for 3 days. (C) As for sevoflurane content, high purity was observed in both the original and the generic products, with no differences between the products and low variation, $n=9$ each.
Discussion

Generic products are drugs that become available for clinical use after approval (verification) of their quality by government agencies (e.g., FDA in the USA, the Ministry of Health, Labour, and Welfare in Japan) after the expiry of patents for the original products. Because generic products achieve the same effects as original products at a lower cost, their use is favourable in terms of medical economics. However, due to differences in effects and side-effects in certain cases,5–7 generic products must be verified by tests such as component analysis and clinical comparison for use.8 9 Because sevoflurane is a potent volatile anaesthetic and can thus induce rapid and deep anaesthesia, it may be significantly affected by small amounts of impurities. In addition, considering that sevoflurane is not associated with pungency and is thus currently the only volatile anaesthetic suitable for volatile induction of anaesthesia,10 11 contamination by or generation of highly pungent impurities is an issue of concern.

From 1996 to 1997, a specified lot of original sevoflurane was recalled in the USA due to the presence of a pungent odour. Evaluation revealed that an impurity in the glass bottle had reacted with sevoflurane to produce Lewis acids, which promoted the degradation of sevoflurane and generated hydrofluoric acid producing the pungent odour. Lewis acids such as AlCl₃ and FeCl₃ in the glass bottle of sevoflurane can accept a pair of electrons to form a coordinate covalent bond. Because hydrofluoric acid is not only an irritant to the mucosa of the eyes, nose, throat, and other tissues,12 but can also cause lung damage at high concentrations,13 14 its presence as an impurity could be harmful. In 2001, Abbott Laboratories and CENTRAL GLASS Co., Ltd (Tokyo, Japan) obtained patents for the prevention of degradation of sevoflurane by Lewis acids by adding a small amount of water to sevoflurane. In addition, in 2004, Abbott Laboratories developed and obtained a patent for a special container for inhibiting the production of Lewis acids (PEN). Although generic sevoflurane can be produced based on the original product itself, the patents described above cannot be infringed. Therefore, generic products use sevoflurane containing no water and are stored in coated aluminium bottles. Given this background, it is crucial to determine whether the generic product achieves an inhibition of impurity production in routine use.

Despite a relatively short duration, the present study showed that the properties of both the original and the generic products matched those of sevoflurane for all three kinds of routine use investigated. This finding was suggested by the fact that both the original and the generic products had a high purity of sevoflurane (mean content of 99.9985% and 99.9982%, respectively), with low variation. Inorganic fluoride content, which reflects hydrofluoric acid levels, was also found to be similar between the original and the generic products, and was extremely low (<0.005 ppm) in all samples.

The water content found in the bottles of fresh original and generic sevoflurane differed greatly, being 24 times greater for original [0.072 (0.001)% w/v] vs generic [0.003 (0.001)% w/v] sevoflurane. However, this difference reduced to only three-fold greater [0.025 (0.003)% w/v vs 0.008 (0.002)% w/v] when the sevoflurane was allowed to stand in vaporizers over the weekend. Convergence of values may have resulted from limited exposure to air with evaporation of water from original sevoflurane and absorption of water by the relatively desiccated generic sevoflurane. Regardless of the cause, this finding would suggest that the protective effect of the added water may be largely lost from original sevoflurane, and conversely, that any vulnerability of generic sevoflurane would decrease a relatively short time after placement of the sevoflurane in a vaporizer.

In addition, characteristic differences were observed for the types and levels of related substances. The original product contained small amounts of compound A, which is produced when sevoflurane reacts with soda lime, a carbon dioxide absorbent found in anaesthetic circuits, in addition to SME. These substances, which may have originated from the production process of the original product, are known substances and do not cause problems when present at very low levels.15 Although the generic product contained no traces of these substances, it contained approximately 32 ppm of HFIP. HFIP, which is primarily produced by

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Fig 2 Types and concentrations of related substances present in the original and the generic products. Data are expressed as mean (sn), n=9. SME, sevomethyl ether; HFIP, hexafluoroisopropanol. Original sevoflurane contained compound A, SME, and other related substances. Although the generic sevoflurane did not contain compound A or SME, it contained HFIP and other related substances. Although a large variation in content of HFIP and other related substances in the generic product was observed between different samples, no differences were observed between different groups (conditions). Total content of related substances was significantly higher (P<0.05) in the generic product than in the original product.
metabolism of sevoflurane in the liver,\textsuperscript{16} differs from trifluoroacetic acid that was associated with problems such as halothane hepatitis\textsuperscript{17} and the formation of haptenas, which have cross-reactivity with isoflurane\textsuperscript{18} and enfurane.\textsuperscript{19} Therefore, there was thought to be no risk of hepatitis, which may occur with multiple inductions of anaesthesia.

Finally, although the generic product had a relatively higher concentration of related substances and a greater variation in their concentrations, the clinical implications of these differences are unknown. Although the present study was short in duration, and regardless of the method of use involving contact with the metal part of the vaporizer and changes and differences in water content, both products were thought to be safe for clinical use based on the consistency of inorganic fluoride concentration, sevoflurane purity, and the composition and concentrations of impurities. These findings support those of our clinical study that investigated the characteristics of volatile induction of anaesthesia by sevoflurane in a rather small number of patients (n=30 each, data not shown).

In conclusion, we investigated the ingredients of original and generic sevoflurane. Fluoride ion concentration did not differ between the products (0.038–0.050 ppm). The original sevoflurane contained 0.072% w/v water, the generic anaesthetic had little water (0.003% w/v). Both original and generic sevoflurane products had a high quality of sevoflurane \textit{per se} (more than 99.998%). The remaining materials in original sevoflurane (approximately 20 ppm) were 23% compound A, 53% SME, and 24% unknown materials, whereas generic sevoflurane contained 72% HFIP and 28% unknown materials (total, approximately 45 ppm). Generic sevoflurane product contains high-quality sevoflurane and only a small amount of fluoride ions, making it comparable with the original sevoflurane product.

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**References**