Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

SPECIAL ARTICLE
Bilingual edition English/Spanish

Topical sevoflurane: a galenic experience

Sevoflurano tópico: una experiencia galena

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Received 27 May 2021;
Accepted 5 June 2021.
Early Access date (07/21/2021).
DOI: 10.7399/fh.11735

How to cite this paper
Fernández-Ginés FD, Gerónimo-Pardo M, Cortiñas-Sáenz M. Topical sevoflurane: a galenic experience. Farm Hosp. 2021;45(5):277-81.

Abstract

Sevoflurane is a volatile liquid from the family of ether-derived halogenated hydrocarbons that is approved for the induction and maintenance of inhalational general anesthesia in the hospital setting. This review describes the pioneering experience of a Spanish Pain Unit in the home treatment of complicated painful wounds using topical sevoflurane instillations according to a protocol approved for off-label use. Aspects of safety and efficacy, both analgesic, antimicrobial and pro-healing are addressed, and some future lines of research are discussed in terms of new formulations for topical use. After more than seven years of use of the protocol, an experience of over 70,000 applications of topical sevoflurane has been gained. In general terms, the analgesic effect appears quickly, is highly intense and persists for several hours. As a result, patients can reduce their consumption of systemic analgesics and benefit from an improvement in their quality of life. In addition, there are signs that suggest sevoflurane also possesses antimicrobial and pro-healing properties. Regarding safety, pruritus at the level of the periulcerous skin is the most frequently reported adverse effect, although it is usually transient and well-tolerated, and no systemic toxicity has been reported. Overall, the risk-benefit balance of the drug has so far been very favorable. To avoid manipulation of this volatile liquid, we have developed a new formulation of sevoflurane in gel form, which has made it possible to successfully apply sevoflurane in the context of painful pathologies where the skin remains intact. Furthermore, these types of new formulations, including sevoflurane microspheres, which we have also developed, could improve the efficacy and safety of topical sevoflurane while reducing the occupational exposure of healthcare staff. This means that the development of new formulations is a field with a very promising future.

KEYWORDS
Anesthetic drugs; Topical drugs; Sevoflurane; Skin ulcer; Wound healing; Pain management.

Resumen

El sevoflurano es un líquido volátil de la familia de los hidrocarburos halogenados derivados del éter que está aprobado para realizar la inducción y el mantenimiento de la anestesia general inhalatoria en ambiente exclusivamente hospitalario. En esta revisión se expone la experiencia pionera de nuestra Unidad del Dolor en el tratamiento domiciliario de heridas dolorosas complejas mediante irrigaciones de sevoflurano tópico según un protocolo aprobado para su uso fuera de ficha técnica. Se abordan aspectos de seguridad y eficacia, tanto analgésica como antimicrobiana y procicatrizante, y se comentan algunas líneas de futuro en cuanto a nuevas formulaciones para uso tópico.

Tras más de 7 años de vigencia del referido protocolo, contamos con una experiencia acumulada de más de 70.000 aplicaciones de sevoflurano tópico. En líneas generales, el efecto analgésico aparece rápidamente en cuestión de minutos, es de gran intensidad, y de duración prolongada por espacio de varias horas; gracias a ello los pacientes pueden reducir el consumo de analgésicos sistémicos y, en general, su calidad de vida mejora. Además, existen indicios que sugieren que también ejerce acción antimicrobiana y procicatrizante. En cuanto a seguridad, el prurito a nivel de la piel periulcerosa es el efecto adverso más frecuentemente comunicado, aunque suele ser transitorio y bien tolerado, y no hay signos sugerentes de toxicidad sistémica. Globalmente, el balance beneficio-riesgo es muy favorable para los pacientes hasta el momento.

Para evitar la manipulación de la presentación líquida y volátil hemos desarrollado una nueva formulación de sevoflurano en tipo gel, lo cual ha permitido tratar satisfactoriamente patologías dolorosas que cursan con piel íntegra; además, este tipo de nuevas formulaciones, incluyendo las microesferas de sevoflurano que también desarrollamos, podrían mejorar la eficacia y la seguridad del fármaco tópico a la vez que se reduce la exposición ocupacional del personal sanitario, por lo que el desarrollo de nuevas formulaciones es un campo con un futuro muy prometedor.

PALABRAS CLAVE
Fármacos anestésicos; Fármacos tópicos; Sevoflurano; Úlcera cutánea; Cicatrización úlcera; Manejo del dolor.

Introduction

Sevoflurane, i.e. fluoromethyl-1,1,1,3,3,3-hexafluoro-2-propyl ether, is a fluoridated derivative of methyl isopropyl ether. A common characteristic of this family of drugs is that they are volatile liquids that vaporize rapidly at room temperature[1]. This feature allows them to be administered by inhalation to induce or maintain general anesthesia, which is the indication for which sevoflurane is currently approved. The drug is insufflated through an endotracheal tube to the pulmonary alveoli, from where it is carried to the bloodstream and to different target sites in the central nervous system so that hypnosis can be induced. The precise pharmacological targets of sevoflurane, however, remain unidentified although over 170 years have elapsed since the first documented use of ether[2].

Sevoflurane is currently approved for the induction and maintenance of general anesthesia given its hypnotic effect on the central nervous system[3]. This class of drugs was for a long time considered to have no effect on the peripheral nervous system[2]. Nonetheless, in 2011, Pardo *et al.* reported on the first satisfactory clinical results following direct clinical instillation of sevoflurane into a painful vascular ulcer (VU) as an analgesic. This was the first indication that sevoflurane can have an effect on the peripheral nervous system[4]. The idea of using a sevoflurane solution as a topical analgesic came about when a drop of the drug accidentally fell on the above-mentioned author's lip and immediately anesthetized it.

After this paper, the off-label use of topical sevoflurane as an analgesic for the treatment of painful chronic wounds has expanded. However, the main limitation reported by several systematic reviews[5,6] is the lack of confirmatory clinical trials. The only evidence currently available has been based on case reports and case series.

Since 2011 case reports on a total of 466 patients have been published reporting on the use of topical sevoflurane, with a total of 3,055 aggregate treatment days[4,7-33].

Use of topical sevoflurane in the outpatient setting

In 2013 a multidisciplinary working group was created at the Pain Management Unit of the Torrecárdenas University Hospital (Spain). The main goal behind the creation of the group was to administer topical sevoflurane treatment to patients presenting with skin ulcers (SUs) not amenable to surgical revascularization with por pain control and where systemic analgesic treatment had failed or had triggered adverse reactions and/or where invasive analgesic therapies were contraindicated. Another purpose behind the setting up of the working group was to apply topical sevoflurane to patients with painful Sus either at home or in their health center.

To achieve both goals, the group filed a request for off-label use of sevoflurane under the provisions of Royal Decree 1015/2009, which regulates the use of drugs in special situations and allows the use of drugs in conditions different from those contemplated in their label. The group subsequently submitted the cases of three patients with painful VUs for whom there were no available therapeutic alternatives to the Off-label and Rare Diseases Subcommittee of the Torrecárdenas University Hospital, requesting authorization to treat them with topical sevoflurane. Once the Subcommittee granted its approval, and once the clinical efficacy and safety of sevoflurane was ascertained in these patients, a clinical protocol was drawn up for the treatment in the Torrecárdenas Hospital of patients with SUs with poor pain control who were refractory to other systemic and/or invasive analgesic therapies. The protocol was approved first by the hospital's Research Ethics Committee (approval code: CCF-SEV-2014-01, 24/09/13) and then by the Biomedical Research Ethics Committee of Andalusia (CEIBA).

Protocol for preparing and dispensing preloaded syringes

Application of a sevoflurane solution to SUs was not always technically straightforward. Before approval of the above-mentioned protocol, the three patients were treated by extracting the sevoflurane from a 250 mL bottle directly with a syringe. Subsequently, sevoflurane-preloaded syringes were developed to facilitate application to the ulcer site. A handbook was prepared with instructions for patients and their caregivers on how to apply the drug correctly in the outpatient setting. The hospital's Pharmacy Department drew up a series of norms about the safety and sterility conditions that syringes had to meet to be delivered to patients. The protocol was as follows:

Preparation procedure

1. Preparation should be conducted in a vertical laminar flow hood. The facility was not audited by the occupational health authorities.
2. The hood must be cleaned with alcohol 96º and sterile gauze. A sterile surgical drape should be placed at the bottom of the hood.
3. Insert the empty (previously sterilized) BD 10 mL oral opaque propylene syringes into the hood together with the white "tip caps".
4. Introduce 250 mL sevoflurane bottles, which should have been cleaned previously with alcohol 96% and sterile gauze, plus 1 glass of 500 mL precipitates and a glass stir rod. All the materials should have been previously sterilized.
5. Pour the sevoflurane (Sevorane®) into the flask containing the 500 mL precipitates with the help of the stir rod, pressing the valve of the sevoflurane bottle. Flasks from different manufactures can be used on condition that they are provided with a safety cap.
6. Load the 10 mL syringes with sevoflurane by drawing 10 mL from the precipitate flask. Once the syringe has been loaded, place the cap on the syringe.
7. Place the syringes into sterilized plastic bags, entering the number of syringes in each bag on the labels provided and sticking each label on the outer surface of its corresponding bag.
8. Keep in the refrigerator.

Previously, a study on the physicochemical stability of sevoflurane (preloaded into polypropylene syringes) was carried out to find out how long these preloaded syringes could be stored for[34] as there were no studies on the subject and the idea was to provide patients with a enough number of syringes to tide them over for a month, which is when they would have their next visit to the Pain Unit. The physicochemical study was carried out using two analytical imaging techniques (magnetic resonance imaging and gas chromatography with flame ionization detection) recommended by the European and US Pharmacopoeias and by the International Conference for Harmonization Good Clinical Practice Guidelines to study the chemical stability of drugs[35-37].

The study confirmed the structural integrity of the sevoflurane molecule as conserved in propylene syringes at a wide range of temperatures (–10 °C, 4 °C and 25 °C) for 45 days[34]. Subsequently, another study was conducted under the same conditions as the previous one but over a total of 365 days at temperatures ranging from 4 °C to 25 °C. Once again, this study found a lack of sevoflurane as packed in polypropylene syringes.

Efficacy evaluation

Analgesic effect

The protocol above has now been in operation for 7 years, which provides for an accumulated experience of over 70,000 applications of topical sevoflurane. The analgesic effect observed in our patients following application of a dose of approximately 1 mL/cm^2 is characterized by a rapid onset of action (a few minutes), a highly intense analgesic effect [with reductions on the visual analog scale (VAS) of up to 7-8 points], and a long duration (it usually persists for several hours, up to 48 on some occasions)[15]. These characteristics have been described by all the authors who have applied topical sevoflurane to SUs[4,11-33].

Sevoflurane's quick onset of action and short latency set it far apart from EMLA® cream, the only drug currently approved for debriding venous ulcers, which must be applied between 30 and 45 minutes before debridement of cleaning of the ulcer. Even in the absence of comparative studies, sevoflurane appears to be a more effective alternative for high-temperature working environments.

As regards the intensity and duration of the analgesic effect, the fact that the pain can often be controlled almost fully and for a period of 10-12 hours, is associated with the added advantage that patients will lower their consumption of other analgesics[16-19,30], which is particularly useful in the case of opioids. Furthermore, none of the tolerance and/or dependence issues typically related to opioid consumption have so far been reported, which constitutes a significant advantage for topical sevoflurane.

Topical application of sevoflurane has shown itself to be effective not only with regard to somatic pain but also vis-à-vis neuropathic pain[7,10,25,32]. It has also demonstrated its effectiveness in extreme clinical situations where common analgesic procedures had failed, helping in some cases avoid amputations[25] and notably improving the patients' quality of life[7,10,25,32].

Quality-of-life improvements were formally documented in a series of patients with painful venous ulcers[18], especially in the setting of palliative care. These were frail patients where administration of systemic analgesics, especially opioids, would have probably resulted in adverse events and in an impairment of their quality of life. In our experience, topical sevoflurane can also be useful in cancer patients to relieve the refractory pain caused not only by vascular ulcers[10,33], but also by neoplastic ones[23]. In these cases, sevoflurane made it possible to reduce the administration of opioids and, allowing a progressive disappearance of adverse clinical events and improving the patients' quality of life until their death. These published experiences could serve as a proof of concept of the usefulness of sevoflurane in the setting of palliative care.

A negative aspect regarding the duration of the effect of sevoflurane that could be considered a limitation to its use is that on occasion the analgesic effect obtained is insufficient to cover the whole period between dressings, making it necessary to provide patients with additional systemic analgesia to relieve their pain.

Healing effect

It has been observed that ulcers tend to heal gradually but fully following application of sevoflurane. This unexpected finding should be considered within the context of our clinical protocol, which included patients with ulcers not amenable to revascularization who presented with associated comorbidities such as diabetes, which often compromised wound healing. Moreover, these patients usually have their ulcers treated at home, which means that they are treated in a much less controlled environment than the hospital setting[14,30].

Other authors also reported on sevoflurane's highly favorable healing profile either with similar data to ours, or even higher healing rates[4,9,16].

There are two aspects worth mentioning about our findings, based on a series of 67 patients with VUs treated with sevoflurane. Firstly, ulcers were often seen to recur in patients with poorly controlled underlying conditions. In these situations, sevoflurane's analgesic performance was similar to the performance exhibited at the first application. Secondly, when ulcers treated with sevoflurane did not decrease in size or even worsened, a biopsy was considered mandatory to rule out potentially infrequent conditions not related to vascular disease. Such biopsies led to identification of tuberculous ulcer and two Marjolin ulcers.

Antimicrobial effect

The antimicrobial effect of sevoflurane was observed in vitro vis-à-vis clinical and ATCC (American Type Culture Collection) strains of de *Staphylococcus* spp, *Pseudomonas* spp and *Escherichia coli*[38]. Imbernon *et al.* also described the drug's antimicrobial effect *in vivo* in a patient with a CU superinfected by a strain of multiresistant *Pseudomonas aeruginosa*[11], with other authors subsequently reporting on its potential antimicrobial effect *in vivo*[9,12,31,32]. Although sevoflurane's bactericidal mode of action remains to be elucidated, some authors have suggested that both ether and its halogenated derivatives act as solvents at the level of the cell membrane[11,12,39,40].

Our experience in the antimicrobial field does not indisputably demonstrate that infections caused by pathogens present in the ulcer site may be controlled only by sevoflurane instillations. For example, presence of a bacterial infection was a common complication in our series of critical patients with pressure ulcers (PUs). Specifically, 70% of patients treated with sevoflurane presented with an infection, caused mainly my organisms such as *Staphylococcus*, *Enterobacter*, *Pseudomonas*, and *Enterococcus*[30]. In the present study, debridement, cleaning, dressing change and intraoperative intravenous antibiotic administration may account for the significant bacterial load reduction observed in the two patient groups. Nonetheless, we did not find the decrease in bacterial load found in the ulcers of patients treated with topical sevoflurane to be significantly greater that the decrease observed in the group not treated with the drug.

Safety

Staff safety

Patients on ambulatory treatment with sevoflurane were followed up at the Pain Unit in the course of specific consultations which could last up to 5 hours. Considering that these patients were administered sevoflurane at the wound dressing room that same day, it was a foregone conclusion that the healthcare providers seeing to the patient were exposed to the drug. This exposure could, on some occasions, result in a mild headache.

For that reason, an environmental measurement study was undertaken to evaluate the safety of the room where sevoflurane is instilled[41].

The US National Institute for Occupational Safety and Health (NIOSH) is working on a specific environmental exposure threshold for sevoflurane[42], with most European countries, including Spain, still lacking a specific regulation on the subject[43,44]. It should also be mentioned that the few countries that do possess a regulation, among them the Nordic countries, have not so far established uniform threshold levels of sevoflurane[43,45]. Threshold levels for sevoflurane range between 5 parts per million (ppm) in Denmark[46] and 20 ppm in Norway[47]. Finland and Sweden have established two threshold levels: one for long-term exposure (along an 8-hour working day), which is 10 ppm, and another for short-term exposure (up to 15 minutes), which is 20 ppm[48,49]. In Spain, the National Health and Safety Institute's Best Practice Guidelines mention that mild short-term sequelae have been reported (confusion, vertigo, nausea and drowsiness) associated with acute exposure to isoflurane, sevoflurane y desflurane at the concentrations required for anesthesia (1,000 to 10,000 ppm, depending on the gas used)[44].

In our experience[41], the conditions under which topical sevoflurane is applied seem to be environmentally safe for healthcare providers as exposure levels are within the ranges accepted in several European countries for anesthetic procedures[47,48]. As a result, we consider it important to recommend that sevoflurane be applied in well-ventilated spaces or ensuring that the air is exchanged at least three times an hour. These were the conditions under which our environmental study was conducted[41].

Patient safety

The local adverse events most commonly associated with the treatment were heat, pruritus and erythema around the ulcer, which were often transient and did not result in discontinuation[14,30]. As regards sevoflurane's safety with respect to systemic absorption, none of our patients exhibited symptoms attributable to a systemic effect of sevoflurane.

Future outlook

Application of a sevoflurane solution is technically complex. First of all, because of the need to protect healthcare workers from excessive exposure. Moreover, the drug cannot be used to treat conditions where the skin remains intact, as the latter as a diffusion barrier. These problems were resolved by preparation of a new sevoflurane 0.5% formulation where the drug was encapsulated in micelles converted to a gel-like structure, facilitating its application to the intact skin. This made it possible for sevoflurane to be successfully used as a topical analgesic in a patient with plantar fasciitis[50]. The strong and lasting analgesic effect obtained in these patients can be attributed to the fact that, under this new formulation, sevoflurane is encapsulated in a microemulsion, which reduces volatilization allows the drug to remain on the skin for longer and diffuse to the internal tissues. This patient never experienced pruritus or erythema, two of the most common adverse events following the use of topical sevofflurane[14]. The absence of local adverse events associated with sevoflurane in this patient could be due to the use of a highly diluted microemulsion as compared with the standard liquid formulation and to the fact that the micelles that encapsulate the drug protect the healthy skin from direct contact. This first successful clinical experience could be conceived as a new research area, opening up the possibility that this new sevoflurane formulation might be used to treat other painful conditions where the skin remains intact.

As far as the ulcers are concerned, a problem observed in some of the patients treated with the liquid formulation was that the analgesic effect lasted only a few hours, with patients reporting pain between one dressing and the next. This problem could be addressed by preparing yet another

new formulation whereby sevoflurane would be encapsulated into microspheres. This system, which would allow for gradual elution of the drug over time, could be used also for other ether-based halogenated anesthetics[51]. The main advantage of this new formulation would lie in being able to control the amount of drug being released into the ulcer site over time. In addition, encapsulation would reduce volatility and therefore the potential exposure of the healthcare staff to the drug. Finally, as the microspheres are endowed with bioadhesive properties, they would bind only to the ulcer site, sparing the skin around the wound and preventing the appearance of the adverse events commonly observed in that area.

These new formulations could be useful for the treatment of painful conditions that do not damage the skin such as the already mentioned plantar fasciitis as well some rheumatologic conditions such as trapeziometacarpal osteoarthritis or some skin disorders such as atopic dermatitis, etc.

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