

## Is Low-Flow Anesthesia with Sevoflurane Safe? An Interactive Discussion

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### Abstract

Administration of sevoflurane at low-flow rates is a practice that remains contested amongst anesthesiologists. To some, low-flow rates are advocated as safe, environmentally friendly, and cost-effective. Others remain adherent to the practice of higher-flow rates due to the concerns of Compound A and renal injury. In this episode of the Depth of Anesthesia podcast, we explore the claims that low-flow (< 2 L/min) administration of sevoflurane produces Compound A, and that Compound A exposure leads to renal injury. We also investigate the origins of the claims in addition to conflicting recommendations by manufacturers and regulatory agencies. The original podcast soundtrack is available on the Depth of Anesthesia website (<https://depthofanesthesia.com/24-is-low-flow-anesthesia-with-sevoflurane-safe/>) and on all major podcast platforms.

### Keywords

Sevoflurane, Low-flow anesthesia, Renal injury, Compound A

### Introduction

This is an interactive discussion for the Depth of Anesthesia published on April 27<sup>th</sup>, 2021 [1]. Minor edits were made for readability purposes. In the following abbreviation, David is Dr. David Hao, Cas is Dr. Nicholas Woinarski, and Ross is Dr. Ross Kennedy. Research and writing of the episode were led by Dr. Davies Agyekum and Dr. Nicholas Woinarski with assistance from the listed authors.

**David:** Welcome back to Depth of Anesthesia. This is a podcast that critically explores our clinical practices. I'm David Hao and I'm an anesthesia resident at the Massachusetts General Hospital.

Today, I'm joined today by two exciting guests. My first guest is Dr. Cas Woinarski. Dr. Woinarski is a Senior

Anesthetic Registrar based in Melbourne, Australia. Dr. Woinarski, welcome to the show!

**Cas:** Hi Dr. Hao, thanks for the offer. Really glad to be here, big fan of the show.

**David:** We are also joined by Associate Professor Ross Kennedy, who is a New Zealand anesthetist with research interests in pharmacokinetics and pharmacodynamics, especially with respect to inhalational agents and environmental sustainability. Professor Kennedy - welcome to the show!

**Ross:** Thanks very much for the opportunity to be here talking about this, and well done on the initiative, both of you.

**David:** Dr. Woinarski, can you just start us off and tell us a little bit about what got you interested in exploring this topic in the first place?

**Cas:** Thanks for the opportunity to discuss this with you, David. I became interested in this topic after practicing in New Zealand with Ross, where it seemed that almost all sevoflurane anesthesia cases were managed with very low fresh gas flow rates of about 500 ml/min after induction. When I relocated that to Melbourne, I found the practice was much more varied, and fresh gas flow rates were invariably higher.

There was much more discussion and consideration around Compound A formation, with the claim that Compound A leads to kidney injury. Low-flow anesthesia represents a cost-effective opportunity to decrease the environmental footprint by changing our practice [2]. Hospital administrators will also be pleased to know that low-flow anesthesia is a cost saving mechanism.

But patient safety is our first priority and so I'm really glad we're here today to discuss the evidence behind these claims and the evidence of low-flow sevoflurane anesthesia.

**David:** Our case today is that of a healthy 50-year-old man who is presenting for an umbilical hernia repair. General anesthesia is induced with lidocaine, propofol, fentanyl and vecuronium. After confirming correct placement of the endotracheal tube, the resident sets the sevoflurane dial to approximately 1 MAC and then turns the flows down to 0.5 L per minute of oxygen and 0.5 L per minute of air for a total of 1 L per minute of fresh gas flow.

The attending notices the flow rate and asks the resident to turn up the flows to a total of 2 L per minute. When the resident asks for the rationale and the attending comments that the FDA recommendation is for 2 L per minute with sevoflurane and advises the resident to read a bit more about Compound A and renal injury with low-flow rates.

A claim, as our listeners will know, is a practice decision that we either believe is true or is something we default to. Dr. Woinarski, what are some of the claims in this case?

**Cas:** So, I think there are a couple of claims that the consultant is making here: The first would be that low-flow sevoflurane anesthesia produces Compound A; that Compound A exposure leads to kidney injury; high fresh gas flow rates of > 2 L/min prevents the creation of Compound A, and this will decrease the potential for kidney injury.

**David:** So here now are two questions for our listeners to think about.

What is the level of your agreement with the claim that a low-flow sevoflurane anesthetic may lead to kidney injury via Compound A?

And what is the level of evidence for what you believe?

**David:** Back in 1995, the Food and Drug Administration, or FDA, in the United States approved the use of sevoflurane but with a warning that, sevoflurane exposure should not exceed 2 MAC-hours at flow rates of 1 to < 2 L/min. Fresh gas flow rates < 1 L/min were not recommended. They further state that sufficient data had not been presented to establish the safety of Sevoflurane in low-flow states.

Professor Kennedy, can you start us off with what exactly constitutes low-flow anesthesia?

**Ross:** That's a very good question, and I think we suffer from a lack of really good definitions. But low-flow anesthesia is often defined as a fresh gas flow of 1 L/min

or less. Obviously, these rates require use of re-breathing system such as a circle system.

An alternative functional definition is a fresh gas flow rate where the rebreathing fraction is at least 50%. That is, that more than half the exhaled gas volume is retained in the breathing system, obviously after passing through a carbon dioxide absorber. In most machines, that point is around about 1-2 L/min fresh gas flow. Although many modern machines optimize rebreathing so this point may be at the lower end of the range.

And remember that a circle system allows fresh gas flow rates down to around 250 or even 200 ml/min, where really just the oxygen being consumed by the patient is added back into the system. As Cas says, flows well under one liter a minute are common in many places. Modern machines with minimal leaks and the use of standard monitoring of oxygen and agent levels remove most of the historical safety concerns. We're also starting to see a new generation of anesthetic machines that automate the delivery of agents to maintain a preset end-tidal vapor concentration while minimizing flow rates and keeping the oxygen concentrations constant, but I don't think these are available in the US at the moment.

Just to expand on what Cas was saying, I think it's worth stepping back a bit and briefly looking at why we'd want to use low fresh gas flows at all.

Remember that inhalational agents are quite different from drugs given IV. With an IV drug, all of the drug gets into the patient's blood stream. In a typical anesthetic only a tiny proportion of the inhaled agent that leaves the vaporizer actually gets into patient. While a small amount is needed to maintain the partial pressure gradients, most of this excess is pure waste. Reducing this waste by reducing flow rates makes no difference to the amount of agent reaching the patient, given that we've been monitoring agent concentration routinely for more than 25 years. Initially the driver for low flows, and certainly my interest in it, was financial; that was certainly the case when the new, expensive, agent called isoflurane appeared when I was a resident in my department. These days, as Cas mentioned, there's a big focus on the environmental footprints of these agents which can be reduced significantly by reducing the gas flows.

**David:** I think that's all super interesting because I also saw some of the evolution of that in my own practice. I remember back when I was a CA-1, there was even a little sticker on our anesthetic machines that showed how much a vial of sevoflurane versus a vial of isoflurane costs. I don't know where that sticker is now, but the conversation has definitely seemed to shift a little bit more towards the environmental concerns.

When the FDA came out with some of their initial comments, they did share concerns that sevoflurane may cause adverse renal effects at low flows, which Cas alluded to. This was specifically due to a byproduct created through degradation by the strong bases that were present in CO<sub>2</sub> absorbers. This byproduct is known as fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether or Compound A.

What are some of the current stances in this controversy?

**Ross:** Well, for one perspective, Professor Jan Baum, in a booklet he wrote in about 2003 on low-flow anesthesia. The booklet that was written for Drager, a German manufacturer of anesthesia machines. He said that:

“The formation of Compound A had been a matter of concern for several years. The use of sevoflurane with a fresh gas flow rate of at least 1.0 L/min is assumed to be safe even in longer anesthetic procedures by the American FDA. Due to current knowledge no flow restriction at all seems to be justified, as in not a single clinical case renal impairment was found even after long lasting closed system anesthesia.”

Just remember that was written almost 10 years ago. Now, compare that with the Drug Product information from one manufacturer of Sevoflurane (Ultane), which states:

“Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest that there is a potential for renal injury which is presumed due to Compound A. Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC hours and at fresh gas flow rates of < 2 L/min may be associated with proteinuria and glycosuria. During sevoflurane anesthesia the clinician should adjust inspired concentration and fresh gas flow rate to minimize exposure to Compound A. To minimize exposure to Compound A, sevoflurane exposure should not exceed 2 MAC-hours at flow rates of 1 to < 2 L/min. Fresh gas flow rates < 1 L/min are not recommended. Because clinical experience in administering sevoflurane to patients with renal insufficiency is limited, its safety in these patients has not been established.”

Which is all very long-winded... To add to the uncertainty, one company that provides sevoflurane in both Australia and New Zealand has almost identical product information, that runs to 16 or 17 pages. The difference is that in the Australian version there is almost a page that's very close to that previous quote while in the New Zealand version that whole section is missing. It was removed around 15 years ago in line with changes that were made in product information in the EU.

**David:** I appreciate that you pointed out where that information was coming from because obviously, we have high potential for bias here as I would imagine that the anesthesia machine manufacturers, for example, Drager, might be incentivized to promote the ability to operate low-flow anesthesia on their machines, whereas if you think about the sevoflurane manufacturer, they're probably compelled to have clinicians use as much as possible.

**Ross:** I think that's a very reasonable perspective and I think as we move into generic products where the unit price is lower that may be even more of a factor. And while the FDA made a safe decision at the time, the evidence base has grown since their recommendations were made.

**David:** Before we dive into some of the evidence that the FDA ultimately based their decision on, Cas, can you tell us a bit more about Compound A and what the concern is about?

**Cas:** Yes, so Compound A is produced by the interaction between sevoflurane and calcium hydroxide-based carbon dioxide absorbents in the presence of potassium hydroxide and, to a lesser degree, sodium hydroxide. Potassium hydroxide and sodium hydroxide are found in Baralyme and soda lime respectively. Compound A is produced with greatest quantities when the CO<sub>2</sub> absorbent is dry or desiccated.

Compound A is a dose dependent nephrotoxin in rats, with a proposed threshold dose for renal injury of 150 to 314 ppm/hr e.g., 75 ppm breathed for two hours produces 150 ppm/hr. For doses exceeding the threshold, renal necrosis correlates with the ppm/hr of Compound A.

**David:** And Cas, you did mention that the presence of potassium hydroxide or sodium hydroxide is required for Compound A production. Does this imply that carbon dioxide absorbers without those two agents do not produce Compound A?

**Cas:** Yeah, so that does seem to be the case, and this area gets quite complex with the range of CO<sub>2</sub> absorbers that are available now. The CO<sub>2</sub> absorbers that do not contain potassium or sodium hydroxide use calcium or lithium hydroxide, and/or silica. Canisters that contain potassium hydroxide have mostly been pushed out of the market because the manufacturers of sevoflurane recommend against using CO<sub>2</sub> canisters that contain potassium hydroxide.

One study from Keijzer and colleagues published in 2007 looked at this in detail and compared 7 commercially available CO<sub>2</sub> absorbers to determine the level of Compound A production. Carbon monoxide production was also examined, but this was less of a clinical concern.

Compound A production was relatively low for all absorbents under all conditions, with no peak Compound A concentrations above 22 ppm. It was identified that four of the seven tested did not produce any Compound A when the absorbent was appropriately humidified. Two out of seven CO<sub>2</sub> absorbers, which were free of strong bases, sodium and potassium hydroxide, did not produce any Compound A, even when the absorbent was desiccated.

So therefore, it seems that if you choose an appropriate absorbent or CO<sub>2</sub> canister, you can eliminate Compound A from your breathing system, and then eliminate it from the discussion.

**David:** Great. So, we seem to have evidence that not all carbon dioxide absorbers are made equal with respect to generation of Compound A and the study that you mentioned certainly seems to suggest that in absorbers without strong bases, even in desiccated conditions, Compound A is not generated.

Now, given this information and knowing that Compound A has been associated with renal injury in a rat model, Professor Kennedy, what evidence do we now have for renal injury with sevoflurane in human patients?

**Ross:** Well, several studies have examined healthy volunteers exposed to sevoflurane at varying flow rates to look at renal injury. By and large, these studies use the presence of albuminuria or proteinuria as markers of glomerular injury, and/or enzymuria or glycosuria as markers of tubular injury. These markers are used because they are more sensitive to subclinical renal injury than measured by BUN or plasma creatinine.

Most of these studies demonstrate no renal injury, but a concept of an “injury threshold” became prevalent when doses of Compound A > 150 ppm/hr. However, this has not been a consistent finding in later studies that expose a patient to Compound A levels above this threshold.

It is also fair to say that these are a small number of studies in quite a small number of subjects. They were mostly performed in the 1990s and often didn't control for other factors, especially hypotension which we look very closely at today.

**David:** Yeah, so it sounds to me like the evidence suggests that Compound A really has rarely demonstrated an impact at least on BUN or creatinine but might have had some transient effects on other markers of injury, like to the glomerulus or tubules, as you mentioned, especially at higher doses.

Given that studies that did demonstrate an impact on highly sensitive markers of renal injury were conducted mostly in volunteers, has this question been considered in a clinical setting?

**Ross:** Yes, it has, David, and there are a couple papers that are worth looking at address that question.

The first by Kharasch and colleagues from 2001 looked at 55 patients undergoing prolonged orthopedic surgery. 28 subjects were randomized to receive low dose sevoflurane, and 27 patients received low dose isoflurane [3-8]. These patients underwent neck resection for tumor, or spinal reconstruction and were classed ASA 1-3. The average flow rate was 800 ml/min, the absorbent was Baralyme, and the average duration of the case was 9 hours.

This study found no difference in the serum creatinine between the two groups at 24 or 72 hours, and also no difference in the more sensitive markers of proteinuria. The authors were unable to find a correlation between any measure of renal function and Compound A exposure. The longest recorded anesthesia was 17 hours, accumulating 428 ppm/hr of Compound A exposure, and this was not associated with renal injury.

**David:** So, it sounds like postoperative renal function, at least by the measures used in this study, was not different after relatively long sevoflurane and isoflurane anesthetics, in spite of a fair amount of Compound A being generated.

But obviously, as you did mention, we are dealing with relatively low numbers here. Cas, what about the second paper?

**Cas:** So, the second paper to discuss was by Fukuda and colleagues in 2004 and it looked at 25 patients, ASA 1 or 2 status, undergoing major orthopedic surgery and a vascularized free flap transplantation and a surgery duration greater than 10 hours [4]. These patients were allocated to either low-flow sevoflurane, low-flow isoflurane or high-flow sevoflurane.

By designing this study in such a way, they attempted to create a group that was exposed to Compound A in the low-flow sevoflurane group, compared to a group that wasn't within the high-flow sevoflurane group, compared with a control of low-flow isoflurane. The authors investigated for renal and hepatic injury in the postoperative period. Blood pressure was controlled within 80-120% of baseline mean arterial pressure and the absorbent was sodalime.

The baseline characteristics, anesthetic duration, and anesthetic exposure were similar in each group, and the Compound A exposure was higher in the low-flow sevoflurane group, as expected. All groups showed an increase in liver transaminases, and a BUN decrease which normalized by day 7. There was a trend in the low-flow sevoflurane group to have a greater degree of glycosuria on day 1 without statistical significance, and again this returned to baseline by day 7. There was no significant rise in plasma creatinine or creatinine clear-

ance across the 3 groups. In contrast to the previous paper mentioned, no patients developed proteinuria.

**Ross:** So, this would suggest that there's no difference in the renal outcomes between high or low-flow volatile anesthesia, however, these are still small trials, and they may be underpowered to detect renal injury anyway. For comparison, the RELIEF trial looking at fluid administration demonstrated an acute kidney injury rate of 5% in the fluid liberal arm or 8.6% in the fluid restrictive arm, indicating that on average 1-2 patients out of 20 are likely to have an acute kidney injury [9-14].

**David:** And Professor Kennedy, given that you've mentioned now several times that studies examining Compound A production and renal injury are probably underpowered, what kind of evidence or what kind of study would even be needed to demonstrate safety of low-flow sevoflurane?

And perhaps more broadly, can safety even be adequately demonstrated via a clinical trial?

**Ross:** Well David, I'd suggest that formal clinical studies may not be necessary, and probably unable to answer the question anyway. Quoting the late Ted Eger talking about halothane hepatitis, he said that "One cannot disprove the existence of dragons". It's very hard to design a study to disprove the occurrence of harm. Almost 20 years ago, Evan Kharasch wrote that at that time "120 million sevoflurane anesthetics had been administered without any evidence of human nephrotoxicity" [7]. He pointed out that both halothane hepatitis and methoxyflurane nephrotoxicity were recognized within a few years of the introduction of these agents.

We need to remember that in those days post marketing surveillance was much less rigorous than it is now. There are other more recent examples of drugs that were approved by the FDA and other regulators, yet major problems occurred after wide release. In the anesthesia domain a couple of examples include rapacuronium which was withdrawn in 2001, less than two years after gaining approval, and also Vioxx which was approved in 1999 and withdrawn less than five years later.

Sevoflurane has been in use for more than fifteen years now. In Europe and many other parts of the world, including New Zealand, it has almost always been used at low-flow rates and we're still not hearing reports of problems that appear to be clinically significant. So, as you suggest, a formal clinical trial is unlikely to be useful.

**David:** Thanks for your insights Professor, and Cas, could you summarize some of the evidence we've reviewed in this episode?

**Cas:** The evidence behind the claim that low-flow anesthesia results in Compound A which therefore results in kidney injury is not particularly robust and the ma-

ajority of the data suggests that there is no evidence for clinically significant renal injury in cases where low-flow sevoflurane anesthesia is used. Importantly, when used in conjunction with modern CO<sub>2</sub> absorbers, the practice of low-flow anesthesia appears safe, as the amount of Compound A produced is negligible.

**David:** For our listeners and readers, let's now revisit the questions we posed at the top of the show.

What is the level of your agreement with the claim that a low-flow sevoflurane anesthetic may lead to kidney injury via Compound A?

And what is the level of evidence for what you believe?

We hope this episode has encouraged you to think more critically about your own clinical practices and to explore the primary literature to learn more about the evidence.

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