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Nephrotoxicity of Halogenated Inhalational Anaesthetics: Fictions and Facts

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Key Words

Sevoflurane · Compound A · Serum fluoride · Renal function · Nephrotoxicity

Introduction

Anaesthesiologists have been concerned about the potential renal toxicity of inhaled anaesthetic agents since 1966, when Crandell et al. [1] described nephrotoxicity associated with methoxyflurane anaesthesia. A single observation of vasopressin-resistant polyuric renal insufficiency in a patient after methoxyflurane anaesthesia for abdominal surgery was reported. This was followed by an enormous number of anecdotal reports as well of clinical studies documenting that renal failure following methoxyflurane anaesthetics, in fact, was not a rare event.

Developments of animal models and clinical studies established that the condition was dose related and secondary to biotransformation of methoxyflurane to inorganic fluoride. Subsequently, extensive studies were undertaken to further characterise the pathomechanisms responsible for this observation which included a broad range of severity of the abnormalities: from mild cases with only minor and transient increases of markers of reduced renal function such as serum creatinine and blood urea nitrogen up to severe courses of polyuric failure requiring dialysis or even leading to death due to acute renal failure.

Degradation of methoxyflurane by hepatic cytochrome P450 isoenzymes produces considerable amounts of inorganic fluoride ions which can subsequently be detected in the circulating blood. Because evidence of methoxyflurane renal dysfunction was not observed when peak fluoride concentrations were less than 50 μ*M*, this concentration was considered to be the threshold of fluoride nephrotoxicity. The hypothesis of a 50-μ*M* threshold was later extended to all inhaled anaesthetics and clinical approval was only sought for those substances for which liberation of fluoride was not part of their metabolism.

The hypothesis that it were indeed the elevated serum fluoride concentrations which were responsible for postoperative renal damage was based on the following notions: (1) There was a fairly well correlation of postoperative peak serum fluoride concentrations with the degree of renal dysfunction in humans [2]. (2) A similar type of vasopressin-resistant polyuric renal insufficiency was reproduced by intraperitoneal application of fluoride in Fischer 344 rats [3]. (3) Inhibition by fluoride ions of a variety of enzyme systems including those mediating antidiuretic hormone effects [4]. As a consequence, the renal injuries seen in surgical patients following methoxyflurane anaesthesia led to withdrawal of this anaesthetic from clinical use. Since that time every new halogenated inhalational anaesthetic was extensively studied in ani-

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mal models as well as in human studies to identify – if present – its potential for producing changes in renal function and nephrotoxicity.

Sevoflurane is a relatively new inhalational anaesthetic which was introduced into clinical practice in Europe and North America in 1994/95. Its excellent pharmacokinetic profile in combination with its pleasant smell facilitated seek for clinical approval. However, with regard to renal function sevoflurane is still a controversially discussed agent for two reasons: (1) Hepatic metabolism of sevoflurane releases inorganic fluoride. Albeit total metabolism and hence resulting serum fluoride concentrations are less than those observed with methoxyflurane, approximately 7% of surgical patients will postoperatively face serum concentrations above the nephrotoxic threshold of 50 μM. (2) A small portion of sevoflurane is degraded to compound A by the carbon dioxide absorbents integrated into the circle systems of all modern anaesthesia machines. Compound A has been shown to produce nephrotoxicity in rats. The intention of this paper is to review the own investigations in combination with further human and animal studies from other authors with respect to the potential of sevoflurane for producing nephrotoxicity.

Animal Studies

Renal Perfusion

A well investigated factor leading to postoperative renal dysfunction is hypoperfusion during the perioperative period. Many drugs including anaesthetic agents have been shown to induce hypoperfusion and this – alone or in combination with other noxious stimuli – could easily serve as an alternative hypothesis explaining a deterioration of renal function as seen after methoxyflurane. Therefore, maintenance of renal blood flow is a prerequisite for use of all modern anaesthetic agents and also, these agents should not interfere with principles of blood flow regulation, i.e. autoregulation perfusion should be maintained.

To rule out an interference with blood flow regulation, we assessed the effects of sevoflurane on renal perfusion in Sprague-Dawley rats. Animals were anaesthetised with different concentrations of sevoflurane and perfusion was assessed by radioactive microsphere technique. At mean arterial pressures within the autoregulated range perfusion was well maintained with sevoflurane and this was also the case with isoflurane. Constant perfusion was due to a decrease in vascular resistance which compensated the reduced perfusion pressure. When arterial pressure was lowered below the autoregulated range, perfusion started to decrease (fig. 1). Thus, regulation of perfusion did not differ from the awake physiologic state and the obvious conclusion from these experiments was that there was no genuine negative effect on blood flow [5].

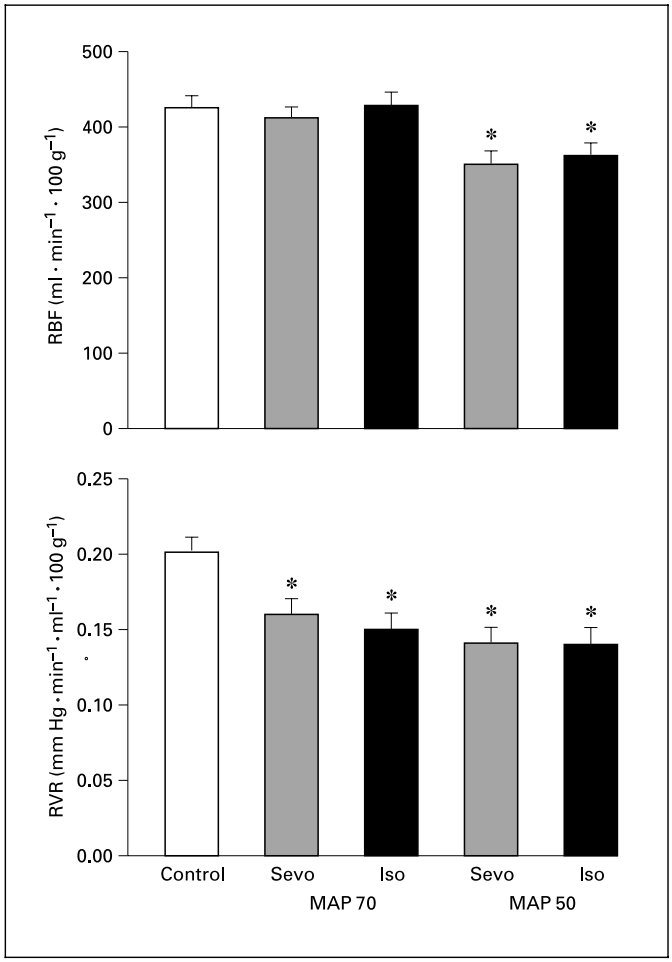

Fig. 1. Changes in renal blood flow (RBF) and renal vascular resistance (RVR) in rats during sevoflurane (Sevo) and isoflurane (Iso) anaesthesia. Control denotes baseline values during infusion of i.v. chloralose. Concentrations of sevoflurane and isoflurane were adjusted to maintain stable haemodynamic parameters, i.e. equal mean arterial pressures. Measurements were done under normotensive (MAP 70) and hypotensive conditions (MAP 50). Values are given as means ± SEM. MAP = mean arterial pressure in mm Hg. * $p < 0.05$ vs. control. Data from [5].

Inorganic Fluoride

Inorganic fluoride serum concentrations in rats during and after sevoflurane anaesthesia were increased over the preoperative control but were only about half the concen-

trations seen after methoxyflurane. In surgical patients serum fluoride levels after methoxyflurane reached from 50–80 μ*M* to over 175 μ*M* after 2.5–3.0 and 7–9 MAC·h, respectively [6]. In contrast, after sevoflurane fluoride levels were reported to be 29.3 ± 1.8 μ*M* after 1.0–7.0 MAC·h [7] and 42.5 ± 4.5 μmol/l after long-term (13.4 ± 0.9 h) anaesthesia [8]. In both studies, peak serum inorganic fluoride levels in excess of 50 μM were obtained in a significant number of patients (5/25, 5/10). Phenobarbital induction of hepatic enzyme activity yielded inorganic fluoride levels after sevoflurane comparable to those after methoxyflurane but without enzyme induction [9]. However, while methoxyflurane produced nephrotoxicity in the Fisher 344 rat, sevoflurane was devoid of such problem [10].

While the rates of sevoflurane and methoxyflurane defluorination by hepatic microsomes were comparable in vitro, the urinary fluoride excretion after sevoflurane amounted to only one third to one fourth of that after methoxyflurane [10]. The conclusion of these diverging observations is that beside hepatic metabolism to inorganic fluoride there must be another additional factor contributing to metabolism of methoxyflurane and another source for liberation of fluoride ions. This additional factor might also explain the diverging consequences for renal function.

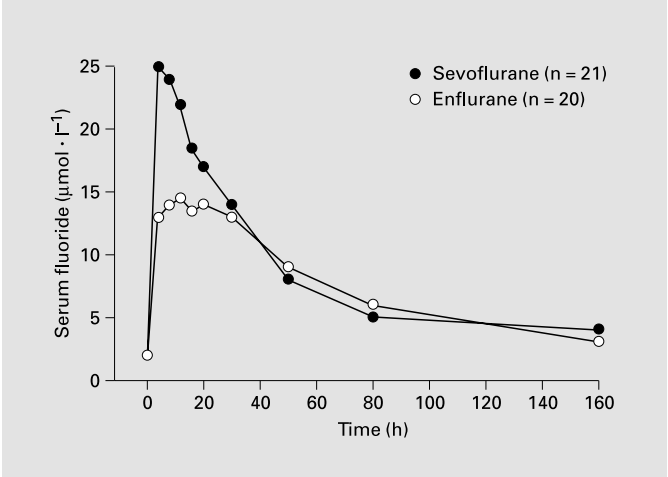

Fig. 2. Mean plasma inorganic fluoride ion concentrations during and after sevoflurane or enflurane anaesthesia. Measurements were obtained in patients with a stable preexisting renal insufficiency. Peak values and concentrations during the first postoperative day were significantly higher in sevoflurane anaesthetised patients. Mean values from all patients are presented. Data from [15].

Patient Studies

Inorganic Fluoride

Sevoflurane metabolism by the human hepatic cytochrome P450 system ranges between 3 and 7% of total uptake. Two major degradation products have been identified, hexafluoroisopropanol and inorganic fluoride. The degree of sevoflurane metabolism is usually estimated from clearance of these products [11]. Since its rate of degradation is higher, sevoflurane metabolism results in higher peak serum fluoride levels as compared to isoflurane, halothane and, enflurane [12]. Nevertheless, due to its low blood gas partition coefficient and hence its rapid elimination at the end of anaesthesia average total exposition to fluoride is lower after sevoflurane than after enflurane. Hexafluoroisopropanol is rapidly eliminated from the body and devoid of toxic problems.

In the clinical setting, it must be expected that about 7% of anaesthetised patients will have peak serum fluoride concentrations in excess of 50 μ*M*, which is the presumed threshold for nephrotoxicity. In one study looking specifically at surgical cases of prolonged duration, five out of ten patients had serum inorganic fluoride concentrations exceeding 50 μ*M* after sevoflurane. This study also reported a positive correlation between serum inorganic fluoride concentration and the applied sevoflurane dose [8]. There was good correlation between the total dose of sevoflurane (MAC·h) and either total fluoride production or peak fluoride concentration. Such a relationship was absent in the isoflurane group (n = 25/25) [13].

Also another study reported serum inorganic fluoride concentrations above 50 μ*M* regularly after prolonged (>7 h) sevoflurane anaesthesia [14]. To date there is an ample number of publications addressing this problem. The most remarkable finding of all of these investigations is that renal problems did not occur more often in patients having fluoride levels above the presumed nephrotoxic threshold as compared to patients remaining below.

Patients with chronically reduced renal function are at an increased risk for suffering a further deterioration of function perioperatively. Therefore, it is a prerequisite for every new drug to be approved for clinical use that its safety in this patient population has been documented. Vice versa, such patients might provide a sensitive model for evaluating the consequences of increased levels of plasma inorganic fluoride on renal function since even small changes in function must be expected to be followed by marked alterations in laboratory tests of renal function.

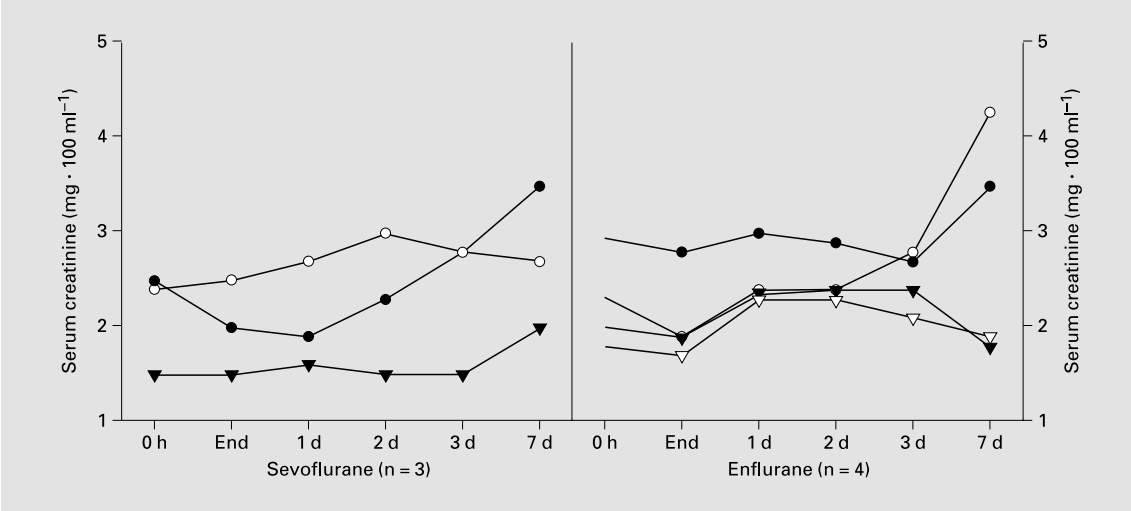

Fig. 3. Serum creatinine measurements in patients with increases above the preoperative control of 20% or more. Measurements were obtained before (0 h), at the end of anaesthesia (End), and in the postoperative course. Only patients with a preexisting stable renal insufficiency were included. Increases in creatinine were more likely to occur in the late postoperative period than at days 1 or 2. Also, the likelihood for an increase was not higher after sevoflurane than after enflurane. These results suggest that the observed increases were independent of the perioperatively elevated fluoride concentrations which had been significantly higher in patients with sevoflurane (see fig. 2). Data from [15].

To address this problem, we recently randomised surgical patients with a chronic impairment of renal function (defined as stable elevation of serum creatinine concentration above 1.5 mg/dl) to receive either enflurane or sevoflurane anaesthesia. Comparisons were based on effects on renal function as measured by changes in urine and serum variables. Despite a significantly higher peak serum inorganic fluoride concentration in the sevoflurane group there was no effect on renal function as shown by standard test in either group (fig. 2) [15]. In fact, renal function remained fairly stable in both groups. Only few patients had increases in their creatinine (fig. 3) or blood urea nitrogen concentrations but there was absolutely no difference in incidence among anaesthetics.

This study of our group provided further evidence against a significant role of circulating inorganic fluoride for producing the type of renal failure which was observed following methoxyflurane. While there was a close relationship of the resulting fluoride concentrations with renal injury after methoxyflurane, this relationship is absent with sevoflurane and enflurane. Cause or coincidence? The results from this and from other clinical trials strengthened the belief that circulating fluoride was not a major pathogenic factor for the well described renal problems after methoxyflurane.

Pathomechanism of Fluoride Nephrotoxicity

Cytochrome P450 isoforms are manifold and vary in their concentrations and activities from organ to organ. Kharasch and co-workers [16] studied defluorination of sevoflurane, enflurane, methoxyflurane, and isoflurane by human liver microsomes in vitro. Cytochrome P 450 2E1 was identified as the predominant human hepatic enzyme responsible for metabolism of sevoflurane. This is in contrast to methoxyflurane which was also metabolised by P450 isoforms 1A2, 2C9/10, and 2D6 [16]. Reduced release of inorganic fluoride from sevoflurane following administration of disulfram, a potent inhibitor of cytochrome P 450 2E1, supports absence of metabolism by other isoforms [17].

Methoxyflurane undergoes extensive renal defluorination in animals, at a rate almost half that occurring in the liver. In contrast, sevoflurane undergoes little renal defluorination. Methoxyflurane is metabolised by several P450 isoforms, whereas sevoflurane is metabolised predominantly by P450 2E1 [11]. Thus, in humans, meaningful renal metabolism may be uniquely associated with methoxyflurane. Therefore, renal (not hepatic) defluorination of methoxyflurane, but not of sevoflurane, underlies the nephrotoxicity of methoxyflurane but not of sevoflurane.

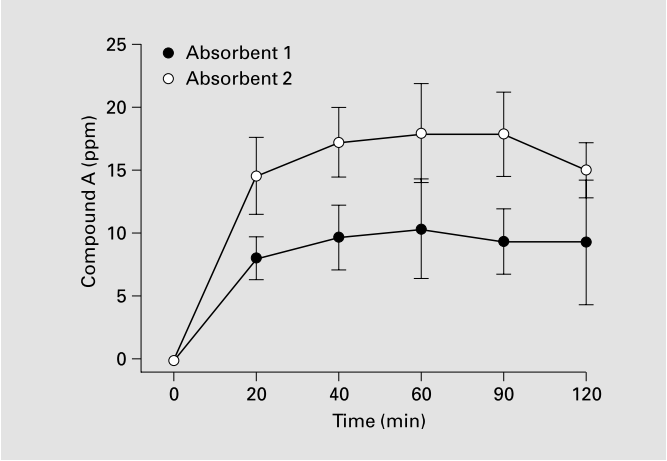

Fig. 4. Inspiratory compound A concentrations during sevoflurane anaesthesia (2 vol %) for laparoscopic cholecystectomy under low-flow conditions. Two different carbon dioxide absorbents were used: Sodasorb® (Absorbent 1) and Soda Lime® (Absorbent 2). Albeit absorbent 1 is free of the strong alkali potassium hydroxide, degradation of sevoflurane is more pronounced and this results in higher compound A levels. Mean values ± SEM are given. Data from [32].

Compound A

Compound A (fluoromethyl 2,2-difluoro-1-(trifluoromethyl)-vinyl-ether) does not originate from hepatic metabolism of sevoflurane but from a chemical reaction with strong alkali components of carbon dioxide absorbents (potassium- and sodiumhydroxide). The formation and accumulation of this olefin, for simplicity called compound A, in rebreathing anaesthesia circuits is especially high with low fresh gas flows. The ubiquitous presence of rebreathing systems and the economic and ecological pressures for using low fresh gas flows mandate absence of any type of toxicity from this source in humans at all potential scenarios.

Animal Studies

Wistar rats exposed to compound A by inhalation of different concentrations ranging from 0 to 400 ppm for a 3-hour exposure showed histological signs of renal injury (necrosis of the outer strip of the outer medulla) at concentrations of 50 ppm and above. The threshold for nephrotoxicity in rats thus reaches the range of values for compound A which is also attained in clinical practice in some patients [18] but not regularly during routine surgery of short to intermediate duration (fig. 4).

Compound A-derived cysteine S-conjugates are substrates for renal beta-lyase in rats [19]. Further enzymatic degradation results in highly reactive acylating agents which covalently bind to a variety of macromolecules within the renal tubular cells [20]. This binding again results in molecular destruction, cellular necrosis and the type of renal damage seen in various rat models (increases of blood urea nitrogen and creatinine, glucosuria, proteinuria).

Alleviation of compound A-induced proteinuria by aminooxyacetic acid, a competitive inhibitor of renal cysteine conjugate β-lyase, suggests that glutathione conjugate formation, subsequent processing to cysteine conjugates, and cysteine conjugate metabolism by renal β-lyase indeed is an important factor in the pathogenesis of compound A-mediated nephrotoxicity [21]. High-dose acetaminophen treatment producing glutathione depletion led to renal cortical injury on exposure to 100 ppm compound A [22]. A study with inhibitors of renal organic anion transport and S-conjugate uptake, of γ-glutamyl transferase, an enzyme that cleaves glutathione conjugates to cysteine conjugates, suggests that renal uptake of compound A-glutathione or compound A-cysteine conjugates and cysteine conjugate metabolism by renal β-lyase mediate at least in part compound A nephrotoxicity in rats [23].

The latter study was conducted with intraperitoneally administered compound A and this was critizised but a study with inhaled compound A showed comparable results [24].

It is important to stress that species differences are very important for compound A nephrotoxicity. While there is ample evidence that compound A is toxic in rats and other rodents, this type of damage was not reproduced in other species including dogs and monkeys. E.g. a study in beagles showed no increase in the excretion of renal tubular enzymes during and after repeated low-flow sevoflurane anaesthesia [25]. It has been shown that tubular cell β-lyase activity in the latter animal species, as well as in man, is much lower than in rodents. This results in a far lower formation of highly reactive compound A conjugates and, as a consequence, in a lower likelihood of renal injury.

Human Studies

As already stated above, compound A is the only degradation product detected in significant amounts in anaesthesia circuits during long-duration, low-flow sevo-

flurane anaesthesia. In an early Japanese study, the individual maximum concentrations of this breakdown product ranged between 13.6 and 35.1 ppm (mean value: 24.3 ± 2.4 ppm) [26]. This study as well as a large number of further studies from countries all over the world failed to document any relevant effect of compound A on renal function. For assessing renal injury these studies either used the standard laboratory parameters for reduced renal function (i.e. creatinine, blood urea nitrogen, excretion of protein or glucose), or the presumed more sensitive markers of renal injury (excretion of tubular intracellular enzymes such as NAG).

Exposure of children to sevoflurane may be higher than in adults because of their higher MAC values and hence the higher sevoflurane concentrations needed intraoperatively. There is certainly also a positive correlation for compound A formation with body surface area in children but the absolute exposition to compound A is not higher than in adults. Correspondingly, there was no evidence of renal dysfunction in children [27].

To date, there is only one study available claiming a potential of compound A for producing renal injury in humans. A relatively small study performed in healthy volunteers reported transient elevations of what the authors called sensitive markers of renal dysfunction. They reported post-anaesthetic albuminuria indicating injury of the glomerulus, glucosuria and increased urinary α-GST as signs of proximal tubular injury, and increased urinary π-GST indicating distal tubular injury. However, serum routine parameters of renal function such as creatinine, blood urea nitrogen or the ability to concentrate urine (vasopressin test) remained unchanged [28].

The authors in addition believe that there is a threshold for compound A nephrotoxicity in man. This is inferred from a follow-up study in which post-anaesthetic albuminuria, increased urinary α-GST and slightly increased serum creatinine occurred after 4 h but not after 2 h of anaesthesia with 1.25 MAC sevoflurane or about 40 ppmh compound A. It was concluded that the threshold for inducing renal damage in humans is between 80 and 160 ppm·h compound A which is similar to the threshold found in rats [29]. However, attempts by other authors to copy the results of these studies failed. Frink et al. [27] while using the same experimental protocol and the same laboratory tests were unable to duplicate the type of injury reported by Eger et al. [28, 29]

There is no good explanation for the puzzling results obtained in one single lab. It must not be forgotten that even prolonged (≥ 10 h) sevoflurane (high or low fresh gas flow) or isoflurane anaesthesia increased urinary excretion of glucose, albumin, protein, and N-acetyl-β-D-glucosaminidase to the same extent. There were no significant differences between the three groups at any time point after anaesthesia. Despite an average compound A uptake of 277 ± 120 ppm·h during low-flow sevoflurane anaesthesia the effect on the kidney was the same as with high-flow sevoflurane and low-flow isoflurane anaesthesia [30]. These observations certainly are a strong argument against the existence of a nephrotoxic threshold as proposed by Eger and coworkers.

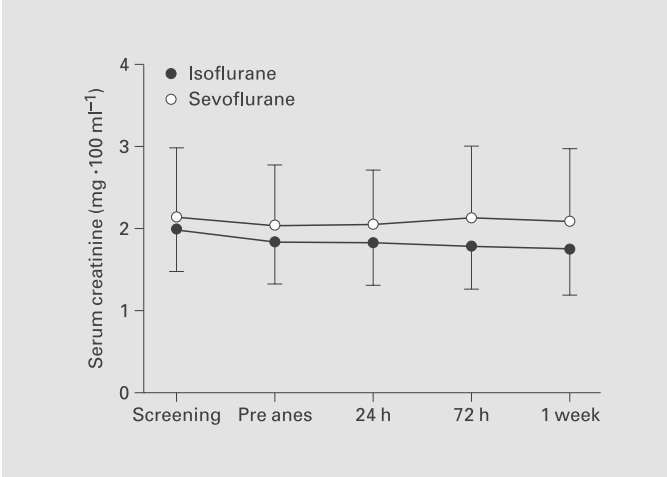

Fig. 5. Serum creatinine concentrations in patients with a stable preoperative renal insufficiency (>1.5 mg/dl). Patients underwent general anaesthesia for surgery with either low-flow sevoflurane or isoflurane. Sevoflurane but not isoflurane patients had been exposed to compound A intraoperatively. Stable creatinine concentrations in the postoperative course indicate that renal function was not affected by compound A. Data submitted for publication by Conzen et al.

A just finished study performed in our department was directed towards patients with chronic renal impairment. For this purpose chronic impairment was again defined as stable preoperative elevation of serum creatinine ≥ 1.5 mg/dl. All patients were randomised to receive low-flow anaesthesia of at least 3 h duration with either sevoflurane or isoflurane. As the results indicate, there were absolutely no differences in routine renal function parameters after low-flow sevoflurane and low-flow isoflurane anaesthesia (fig. 5). We also measured sensitive markers of renal injury as β2-microglobulin, N-acetyl-β-D-glucosaminidase, α-, π-GST in a subgroup of patients. Again there were no differences between groups. Therefore, we can conclude from this study as well as from earlier published data that the sevoflurane breakdown product compound A is not a relevant toxin in humans.

Mechanism for Compound A Toxicity in Rodents

Bioactivation of many haloalkenes, such as compound A, results in localised cytotoxicity in renal proximal tubules. The complex scheme, collectively called β-lyase pathway, has been elucidated for myriads of haloalkenes. Results from recent investigations in rats provide evidence that certain key enzymes of the β-lyase pathway also mediate compound A nephrotoxicity [23].

Mediation of compound A nephrotoxicity by the renal cysteine conjugate β-lyase pathway obviously has important implications regarding interspecies differences in compound A effects. Human renal β-lyase activity and β-lyase metabolism of compound A cysteine conjugates are approximately 8–30 times less than that in rat kidney [31]. It is speculated that far higher concentrations of compound A than those observed in clinical practice would be required to produce a clinically relevant injury in surgical patients. This interspecies difference in enzyme activities could easily explain the obvious differences of compound A toxicity – well documented injury in the rat and in other rodents, while absence of toxicity in humans.

Conclusion

A large variety of inhalation anaesthetics with the potential for use in humans have been synthesised during the past decades. However, only a small portion has reached clinical approval. Many substances were withdrawn already at early stages of approval because of potential toxicity and other risk factors. This also was partly the case with sevoflurane. Two factors delayed its approval: (1) sevoflurane is partly metabolised by hepatic cytochrome P450 to inorganic fluoride. The clinical experience with methoxyflurane suggested that elevated fluoride concentrations may be nephrotoxic. (2) Sevoflurane undergoes dehydrofluorination by carbon dioxide absorbers of anaesthesia machines, producing small quantities of degradation products. Compound A is quantitatively predominant and this product has been shown to be nephrotoxic in rats.

Both factors, inorganic fluoride and compound A have been extensively studied in the years prior to approval for human use. To date, there is no evidence for any type of renal injury associated with this anaesthetic. This implies that application of results concerning toxicity of halogenated anaesthetic agents to another species or to another anaesthetic must be done with great caution. Our clinical studies in patients with stable renal insufficiency have clearly shown that even renal risk patients can be anaesthetised with sevoflurane as safely as with any other modern halogenated anaesthetic.

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