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BRIEF REPORT

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Inorganic fluoride concentration after long-term sedation with isoflurane

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Abstract We report on five patients in whom long-term sedation with isoflurane for up to 7 days was used successfully. Serum inorganic fluoride concentrations were measured daily. The concentrations ranged from 12 mmol l^{-1} to 29 mmol l^{-1}. These were well below the described renal toxic level of 50 mmol l^{-1}. There was no deterioration in renal function attributable to the use of isoflurane.

Key words Isoflurane · Inorganic fluoride · Sedation · Intensive care

Introduction

The choice of a sedative agent for a critically ill patient can be difficult. Pharmacokinetic and pharmacodynamic changes which occur in this patient population can predispose to drug and metabolite accumulation and tachyphylaxis. Isoflurane has been suggested as an alternative. It possesses many of the properties of the ideal agent. Its rapidity of onset and offset, and minimal cumulation or metabolism within the body, give ease of control sedation. Its major disadvantages are its cost and potential for environmental pollution.

Kong et al. [1] demonstrated its safety up to 24 h in critically ill patients, and there have been several other reports [2, 3] of its clinical efficacy and safety in this patient population for up to 72 h.

However, some fear has been expressed regarding the accumulation of fluoride after prolonged use [4, 5]. Such accumulation is suspected of producing impairment of renal function, as was reported following the use of methoxyflurane [6].

Few reports relating to the use of isoflurane in intensive care have mentioned the measurement of serum fluoride concentrations. We report on the effect on the serum fluoride concentration after prolonged use of isoflurane for sedation in five critically ill patients (Table 1). The analysis was performed using an ion-specific electrode for fluoride (EDT London, UK).

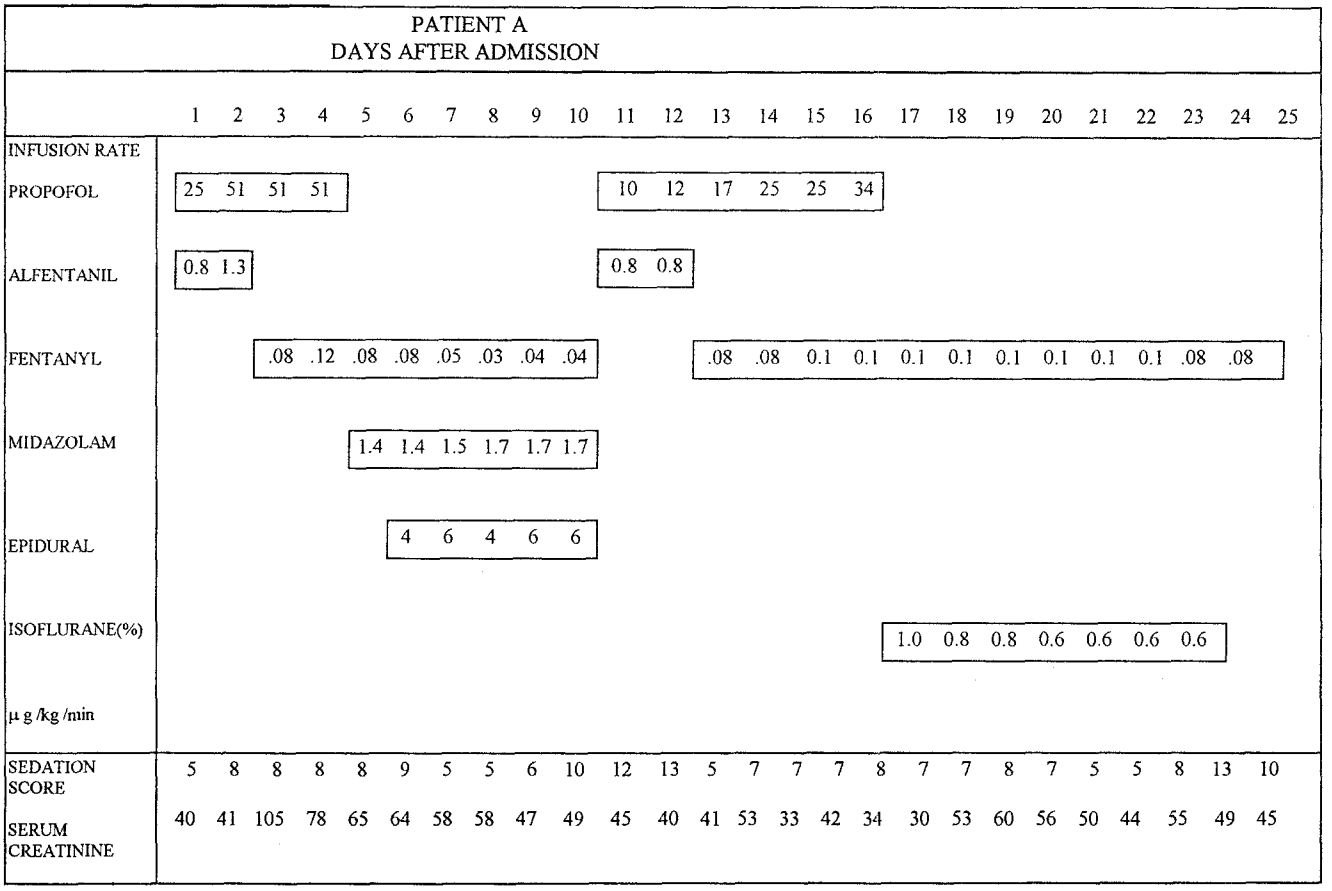
Patient A

This 52-year-old obese man was admitted to the intensive care unit (ICU) with severe necrotizing pancreatitis. The serum amylase was >15000 IU l^{-1}. He required mechanical ventilation of the lungs, and ultimately his clinical course was complicated by the develop-

Table 1 Serum fluoride concentration (μmol l^{-1}). Day 1 = start of sedation with isoflurane. Coefficient of variation of resutls <5%

Day	Patients				
	1	2	3	4	5
Pre-isoflurane			2.1	2.4	
2			11.8		
3	11.8		23.0		
4	13.4	10.9	27.9		
5	12.5	13.4			8.4
6	15.6				
7	13.0	20.7		23.3	12.3
8[a]	10.2				

[a] 24 h after discontinuation of isoflurane



ment of the systemic inflammatory response syndrome (SIRS) [7] and the acute respiratory distress syndrome (ARDS) [8].

Initially, satisfactory sedation, as measured by a sedation score (Appendix) [9], was achieved using infusion of propofol and fentanyl (Fig. 1). Ideal sedation corresponded to a score of 8. Tolerance to both agents developed over four days. Midazolam was then substituted for propofol. This proved unsatisfactory within 24 h and an epidural was added for 5 days. The sedation was then changed to propofol and tolerance again developed over 6 days. In view of the previous problems with midazolam, isoflurane was substituted. Isoflurane was administered using the Ohmeda Isotec 5 vaporizer for 7 days.

The inspired concentrations of isoflurane required to achieve a sedation score of 8 was constant (0.5 to 1%).

Throughout the period of sedation with isoflurane, cardiovascular, renal and hepatic function were within normal limits, except for the serum γ-glutamyl transpeptidase, which was consistently in the range of 250 to 370 IU l^{-1}.

Serial serum fluoride estimations were performed (Table 1).

On termination of the infusion, the patient was able to obey commands within 10 min. He was subsequently weaned from mechanical ventilation and returned to the ward 9 days later. He has now been discharged home.

Patient B

A 39-year-old male was admitted for intensive care after initial surgery for severe necrotizing pancreatitis. He required mechanical ventilation of the lungs.

Fig. 1 Patient A. The drugs given for sedation on a daily basis with the day after admission displayed across the top. All drug doses are in μg/kg per min except isoflurane, which is shown as a percentage, and epidural, which is in ml/h of 0.125% bupivacaine with 2 μg/ml fentanyl. Serum creatinine is in μmol/l

Sedation was achieved initially with a combination of infusion of fentanyl and midazolam (Fig. 2). Adequate sedation (score of 8) was not obtainable within the first 48 h. Consequently, midazolam was discontinued and isoflurane started. Analgesia was produced with an infusion of fentanyl. The inspired concentrations of isoflurane required to achieve a sedation score of 8 were constant.

Serial serum fluoride estimations were performed (Table 1). Renal and cardiovascular parameters remained within normal limits.

Isoflurane was discontinued after 6 days. Sedation was then achieved using midazolam and morphine infusions. Weaning from mechanical ventilation began 21 days later and he was transferred to the ward 14 days later.

Patient C

A 29-year-old man was admitted to another hospital 7 days previously with severe alcohol-induced necrotizing pancreatitis. He was transferred to our care and underwent pancreatic necrosectomy, following which he developed SIRS and required mechanical ventilations of his lungs.

Sedation was difficult to achieve with infusion of midazolam and morphine (Fig. 3). In view of this, the sedation regimen was

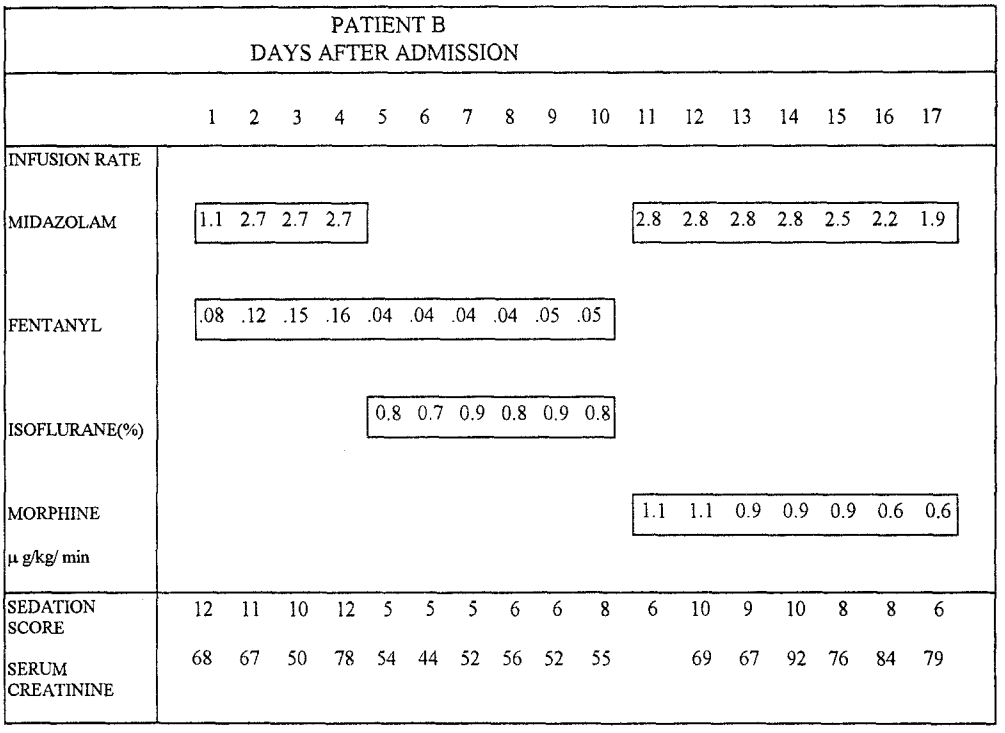


Fig. 2 Patient B. The drugs given for sedation on a daily basis with the day after admission displayed across the top. All drug doses are in μg/kg per min except isoflurane, which is shown as a percentage. Serum creatinine is in μmol/l

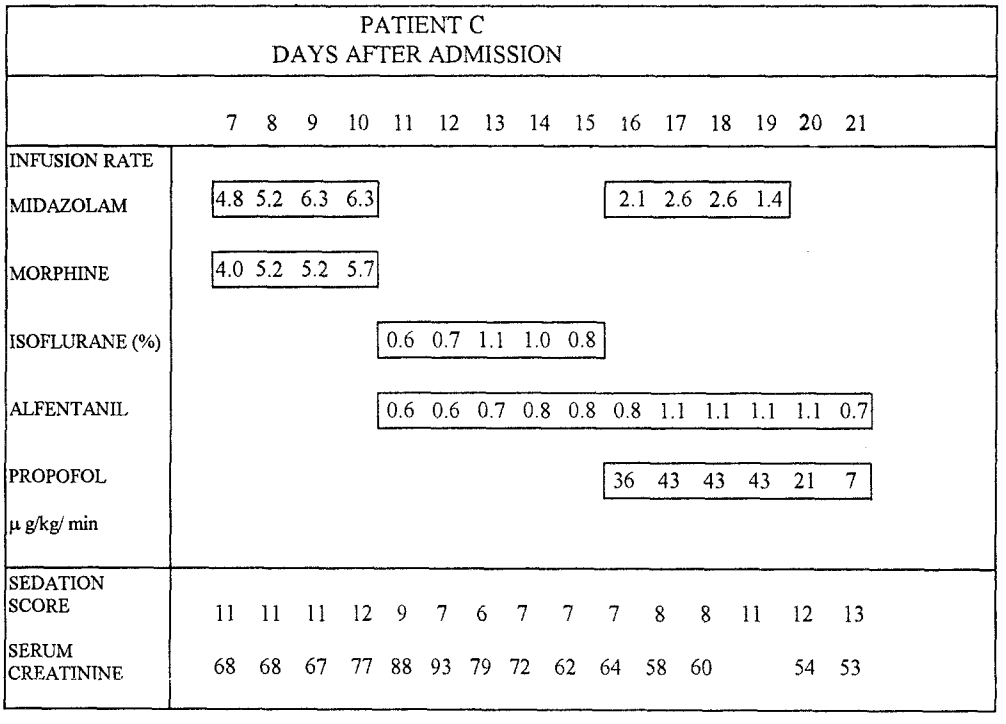


Fig. 3 Patient C. The drugs given for sedation on a daily basis with the day after admission displayed across the top. All drug doses are in μg/kg per min except isoflurane, which is shown as a percentage. Serum creatinine is in μmol/l

changed to inhalational isoflurane and an alfentanil infusion for analgesia. This regimen was used for 5 days. The inspired concentrations of isoflurane required to achieve a sedation score of 8 were constant (0.8 to 1.0%).

Serial serum fluoride estimations were performed (Table 1). No deterioration in cardiovascular or renal parameters was observed during the use of isoflurane.

After discontinuing isoflurane, sedation was achieved using infusions of midazolam, propofol and alfentanil. Weaning from mechanical ventilation began 11 days later. He was finally discharged to a ward after 11 days.

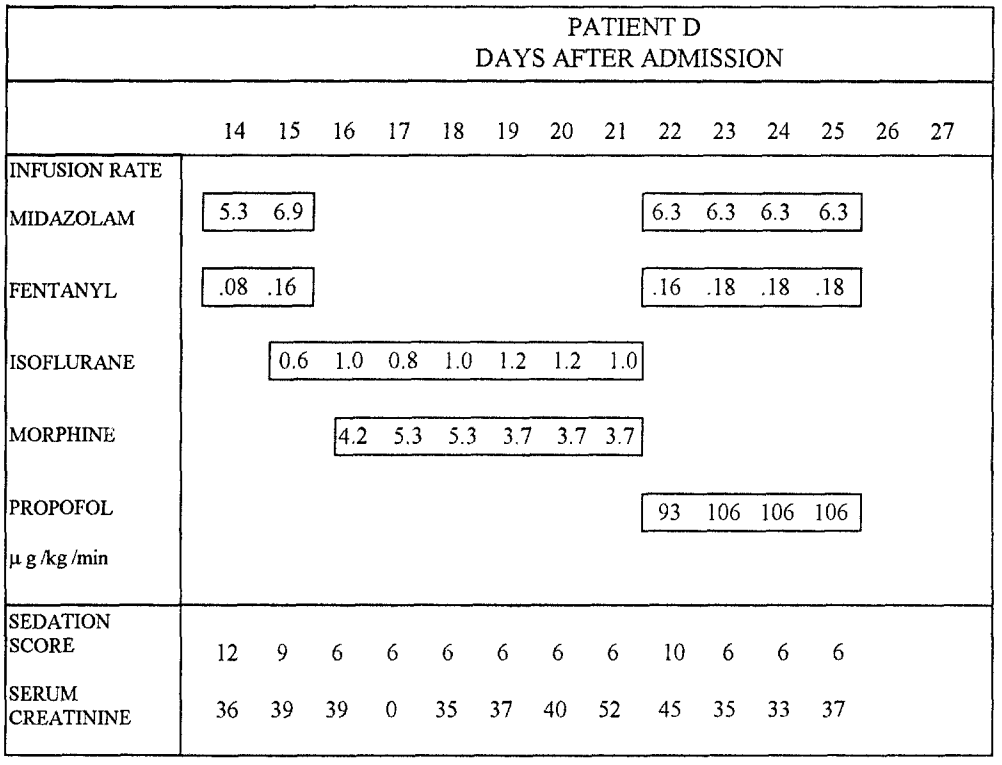


Fig. 4 Patient D. The drugs given for sedation on a daily basis with the day after admission displayed across the top. All drug doses are in μg/kg per min except isoflurane, which is shown as a percentage. Serum creatinine is in μmol/l

Patient D

A 26-year-old woman was admitted to the ICU following a caesarean section, laparotomy and small bowel resection for volvulus. She required mechanical ventilation of the lungs. Sedation was poorly controlled (score of 12) using a combination of infusions of midazolam and fentanyl (Fig. 4). Inhalational isoflurane (0.8 to 1%) replaced the use of midazolam. A morphine infusion was chosen to replace the fentanyl and was administered for 7 days. Throughout its use, the sedation score was constant.

Serial serum fluoride estimations were performed (Table 1).

Patient E

A 54-year-old obese (140 kg) woman was admitted to the ICU with multiple organ failure, following revision of a vertical banding gastroplasty. She required mechanical ventilation of the lungs.

Sedation and analgesia were initially satisfactorily achieved using infusions of propofol and fentanyl (Fig. 5). This produced a sedation score of 9. Isoflurane was introduced after 5 days and the fentanyl infusion continued. Adequate sedation was obtained with an inspired isoflurane concentration of 1% (sedation score 7).

Serial serum fluoride estimations were performed (Table 1). During the period of use there was no deterioration in creatinine clearance. She died 11 days after admission due to overwhelming sepsis.

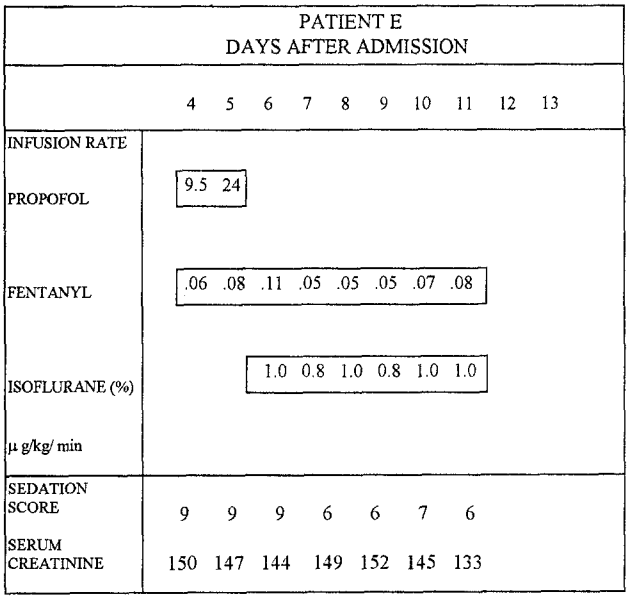


Fig. 5 Patient E. The drugs given for sedation on a daily basis with the day after admission displayed across the top. All drug doses are in μg/kg per min except isoflurane, which is shown as a percentage. Serum creatinine is in μmol/l

Discussion

Sedation of the critically ill patient is often a problem, for which there is no currently available ideal agent. Isoflurane (a fluorinated ether) possesses many of the properties of the ideal agent. It has been used to provide safe and reliable sedation with minimal side-effects [1, 3, 10].

In our patients it provided good, reliable sedation with predictable inspired concentrations. Awaking, when ap-

propriate, was rapid – in less than 15 min. There was no evidence of acute tolerance to the sedative effects, even after 8 days' use.

The use of an inhalational anaesthetic for long-term sedation in the critically ill patient has a long history. Previous examples (e.g. nitrous oxide) have led us to expect problems to arise with long-term use. The main potential for toxicity with isoflurane relates to the production of fluoride ions during the metabolism of the agent. In previous work on the nephrotoxicity of methoxyflurane [6], a serum fluoride concentration of 50 $\mu mol\,l^{-1}$ was reported to be the threshold associated with subclinical laboratory evidence of renal toxicity as evidenced by beginning signs of hypernatraemia, serum hyperosmolality and an increase in urea and urine volume [6].

It also identified plasma concentrations of 100 $\mu mol\,l^{-1}$ to be associated with evidence of renal impairment on routine biochemical testing [6]. Clinical renal impairment developed if the plasma concentration exceeded 120 $\mu mol\,l^{-1}$ [6].

The fluoride levels in our patients should also be considered in relation to other reference ranges. The normal serum fluoride level is $<50\ \mu g\,l^{-1}$ or $<2.6\ \mu mol\,l^{-1}$ [11]. This is compatible with our two pre-isoflurane fluoride concentrations.

The therapeutic range recommended for fluoride treatment of osteoporosis is $5.3-13.2\ \mu mol\,l^{-1}$, although some people have tried levels up to 30 $\mu mol\,l^{-1}$.

Wide variability has been noticed in the individual fluoride levels after equivalent methoxyflurane exposure. This was attributed to genetic variability and enzyme induction [6].

The fluoride levels obtained in our patients were all below the threshold level of 50 $\mu mol\,l^{-1}$, and we were unable to demonstrate any new renal dysfunction which could be attributed to isoflurane, even after 8 days' use.

From the limited results available, there is a wide variation in the fluoride levels. It has been postulated that variation in production of inorganic fluoride ions is a reflection of such factors as degree of hepatic enzyme induction and age [6].

It is of interest that the patients (B, C and D) with the highest serum fluoride concentration also had significantly elevated γ-glutamyl transpeptidase concentrations. Patient C had a tenfold increase in the serum fluoride concentration over the 4 days.

Other concerns about the use of isoflurane stem from its high cost, particularly if a low flow circuit is not employed, and the difficulties associated with the scavenging of spent gases. In order to minimise both of these, we used the Ohmeda Modulus II Plus Anaesthesia System, with a low fresh gas flow and the circle system. Ventilation and monitoring was by the integral Ohmeda 7810 Ventilator and Ohmeda 5250 Respiratory Gas Monitor (BOC Healthcare). Using such a system, the difference in cost compared to conventional intravenous agents is minimal.

In conclusion, isoflurane produced satisfactory and reliable sedation in five critically ill patients, with inspired concentrations of $<1\%$ for up to 7 days. A deterioration in renal function, either biochemically or clinically, could not be attributed to the use of isoflurane in any patient. The direct association between the serum inorganic fluoride concentration and renal dysfunction in the critically ill patient has still to be defined.

In view of the rapid rate of the rise of the fluoride ion concentration in one patient, we recommend regular measurement of the serum inorganic fluoride ion concentration if isoflurane is used for more than 4 days.

Appendix

Sedation score: four point scoring system. A composite score is made from the parameters below. Aim for a score of 8

A Eyes open
- 4 Spontaneously
- 3 To speech
- 2 To pain
- 1 None

B Response to nursing procedures
- 4 Obeys commands
- 3 Purposeful movement
- 2 Non-purposeful movement
- 1 None

C Cough
- 4 Spontaneous and strong
- 3 Spontaneous and weak
- 2 On suction only
- 1 None

D Respirations
- 5 Spontaneous extubated
- 4 Spontaneous intubated
- 3 SIMV triggering
- 2 Weak or occasional respiratory action bearing no relationship to ventilation
- 1 No respiratory efforts

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