

Effect of sevoflurane and ketorolac on renal function in hypertensive patients undergoing major surgery

Thesis

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Abstract

Background:

Despite mounting clinical evidence that supports its safety, the question of the potential adverse effects of sevoflurane on renal function continues to generate some controversy.

Its potential of causing renal toxicity is still questioned for two reasons: first, because it reacts with carbon dioxide absorbents to produce the vinyl ether (Compound A), and second, because it is biotransformed to inorganic fluoride (F^-).

It is claimed that increased plasma levels of inorganic fluoride are nephrotoxic as they were regularly associated with a vasopressin-resistant polyuric renal failure after methoxyflurane anesthesia.

The NSAID ketorolac nonselectively inhibits the function of cyclooxygenase enzymes and the synthesis of renal vasodilating prostaglandins, and this can impair renal blood flow.

Aim of work:

The purpose of this study is to compare the effects of sevoflurane alone and in combination with ketorolac in normotensive and hypertensive patients undergoing major surgery with new and more sensitive markers for both renal tubular damage and ischemic renal insult.

Methods:

Sixty adult patients of (ASA) physical status I or II undergoing elective major surgery were allocated into four equal groups of 15 patients each ($n=15$). Normotensive patients ($n=30$) receiving either sevoflurane (**G-1**) or sevoflurane and ketorolac (**G-2**) (15 patients each) and hypertensive patients ($n=30$) receiving either sevoflurane (**G-3**) or sevoflurane and ketorolac (**G-4**) (15 patients each).

Blood samples were collected for measurement of serum creatinine, serum cystatin C and serum phosphate concentration before surgery and on the first and second postoperative days. Urine samples were collected before surgery, 2 hours after the start of anesthesia and 12 hours after the end of anesthesia for measurement of urine creatinine and urine phosphate concentration.

Results:

Serum cystatin C did not change during our study period, indicating intact glomerular function.

Urine phosphate levels decreased significantly and serum phosphate remained stable on the first postoperative day in our groups, indicating intact tubular function.

There were no statistically significant differences between the four study groups regarding serum cystatin C, serum creatinine, and serum phosphate.

Also, there were no statistically significant differences between the four study groups regarding urine creatinine, and urine phosphate.

Conclusion:

In conclusion, we found that the administration of ketorolac to patients given high-flow sevoflurane anesthesia (for a moderate duration; MAC-hr $\approx$ 5-6) was not associated with evidence of renal toxicity, and this combination can be considered safe in healthy, well hydrated patients as well as in controlled hypertensive patients.

Key Words

- Sevoflurane
- Compound A
- Serum inorganic fluoride
- Ketorolac
- Hypertensive glomerulosclerosis
- Renal function
- Serum cystatin C

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List of abbreviations

%	Percent
λ b/g	Blood/gas partition coefficient
<	Lesser than
>	Greater than
$\pm$	Plus or minus
$\approx$	Almost equal to
$\leq$	Lesser than or equal to
$\geq$	Greater than or equal to
$^{\circ}\text{C}$	Celsius degree
μg	Microgram
μmol	Micromole
^{51}Cr -EDTA	Chromium-51–ethylenediaminetetraacetic acid
^{99}Tm -DTPA	Technetium-99m–diethylenetriamine pentaacetic acid
AAP	Alanine amino peptidase
ACE	Angiotensin-converting enzyme
ADH	Antidiuretic hormone
AIN	Acute interstitial nephritis
ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
AOAA	Aminooxyacetic acid
APL	Adjustable pressure limiting
AQP2	Aquaporin-2
ASA	American Society of Anesthesiologists
AUC	Area under the curve
AVP	Arginine vasopressin
b/min	Beats per minutes
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CBC	Complete blood count
CBF	Cerebral blood flow
C_{cr}	Creatinine clearance
CKD	Chronic kidney disease
cm	Centimeter
cm H ₂ O	Centimeter of water

cm ³	Cubic centimeter
CNS	Central nervous system
CO ₂	Carbon dioxide
COX	Cyclooxygenase enzyme
cr	Creatinine
creatinine _P	Plasma concentration of creatinine
creatinine _U	Urinary concentration of creatinine
C _{thio}	Sodium thiosulfate clearance
CVP	Central venous pressure
CYP 2E1	Cytochrome P450 2E1 isoform
Cys C	Cystatin C
d	Dalton
dL	Deciliter
e.g.	Exempli Gratia (for example)
ECG	Electrocardiogram
ESF	Erythropoiesis-stimulating factor
ESRD	End-stage renal disease
<i>et al.</i>	Et alii (and others)
F ⁻	Inorganic fluoride
FDA	Food and Drug Administration
FF	Filtration fraction
FGF	Fresh gas flow
FiO ₂	Fraction of inspired oxygen
g	Gram
GFR	Glomerular filtration rate
GS	Glomerulosclerosis
GSH	Glutathione
h	Hour
H ₂ O	Water
Hg	Mercury
hr	Hour
Ht	Height
i.e.	Id Est (that is)
I.M.	Intramuscular
I.V.	Intravascular
IU	International units
IVP	Intravenous pyelography
K ⁺	Potassium
kd	Kilodalton
kg	Kilogram
kPa	Kilopascal

L	Liter
LAP	Leucine amino peptidase
lbs	Librae = 327.45 grams (Pounds)
m ²	Cubic meter
MAC	Minimum alveolar concentration
MAC _{EI}	Minimum alveolar concentration for endotracheal intubation
MAC-hr	One MAC for one hour
MAC _{LMI}	Minimum alveolar concentration for laryngeal mask insertion
MAP	Mean arterial blood pressure
mEq	Milliequivalent
mg	Milligram
min	Minute
ml	Milliliter
mm Hg	Millimeter of mercury
mmol	Millimole
mo	Month
mOsm	Milliosmole
n	Number
N.B.	Nota Bene (note well)
N/C	No change
N ₂ O	Nitrous oxide
NAG	N-acetyl-beta-D-glucosaminidase
NDA	New drug application
NSAID	Nonsteroidal anti-inflammatory drug
O ₂	Oxygen
P value	Probability value
PACU	Post-anesthesia care unit
PAH	Para-aminohippurate
PAH _P	Plasma concentration of PAH
PAH _U	Urinary concentration of PAH
P _{ET} CO ₂	End-tidal Carbon dioxide tension
PG	Prostaglandin
P _{GC}	Glomerular capillary hydrostatic pressure
PGD ₂	Prostaglandin D2 isoform
PGE ₂	Prostaglandin E2 isoform
PGI ₂	Prostaglandin I2 isoform
PH	Hydrogen ion concentration
POD	Postoperative day
ppm	Part per million
prn	Pro re nata (as needed)

P _u O ₂	Urine oxygen tension
RBF	Renal blood flow
R-isoform	Levorotatory isoform
RPF	Renal plasma flow
SD	Standard deviation
SI	Système international (international system)
S-isoform	Dextrorotatory isoform
SpO ₂	Peripheral arterial oxygen saturation
SPSS	Statistical Package for Social Science
TATI	Tumor-associated trypsin inhibitor
TIVA	Total intravenous anesthesia
TR _x	Tubular reabsorption of substance X
TS _x	Tubular secretion of substance X
U	Units
UAE	Urinary albumin excretion
UGT	Uridine 5'-diphosphate glucuronosyltransferase
VIMA	Volatile induction and maintenance of anesthesia
vs.	Versus
W.H.O.	World health organization
Wt	Weight
y	Year
yr	Year
α1M	Alpha1-microglobulin
αGST	Alpha-glutathione-S-transferase
β ₂ M	Beta 2-microglobulin
γGTP	Gamma glutamyl transpeptidase
πGST	Pi-glutathione-S-transferase

Introduction and aim of the work

Rationale and background:

Anesthesiologists have been concerned about the potential renal toxicity of inhaled anesthetic agents since 1966, when Crandell *et al.*⁽¹⁾ described nephrotoxicity associated with methoxyflurane anesthesia. A single observation of vasopressin-resistant polyuric renal insufficiency in a patient after methoxyflurane anesthesia for abdominal surgery was reported. This was followed by an enormous number of similar reports as well of clinical studies documenting that renal failure following methoxyflurane anesthetic, in fact, was not a rare event.⁽²⁾

Sevoflurane, fluoromethyl 2, 2, 2, trifluoro-1-ethyl ether, has become one of the commonly used inhalational agents. It is has no pungent odor, does not irritate airway passages and allows rapid induction as well as emergence from anesthesia. It has minimal effects on the cardiovascular and respiratory systems and minimal effects on cerebral blood flow.⁽³⁾ Nevertheless its effects on renal function are still questionable. Serum inorganic fluoride (F⁻) released during the hepatic metabolism of sevoflurane may increase to levels associated with nephrotoxicity after methoxyflurane anesthesia and renal tubular dysfunction has been reported in some patients anesthetized with sevoflurane.⁽⁴⁾

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly given intraoperatively to control postoperative pain. The non-steroidal anti-inflammatory drug ketorolac nonselectively inhibits the function of cyclooxygenase enzymes and the synthesis of renal prostaglandins E₂ and I₂ which are important renal vasodilators and this can impair renal blood flow. Clinically, the renal vasoconstrictive effect of NSAIDs is reflected in decreased urine output in the postoperative period.^(5, 6)

Furthermore, atherosclerotic vascular damage in essential hypertensive patients has been reported to be associated with renal dysfunction.⁽⁷⁾ This may be another additional independent renal risk factor for morbidity and mortality.

Conventional investigations for renal function as creatinine clearance, serum creatinine, BUN, and urine output have been used in previous studies to assess renal function. However, new markers are being currently investigated.

Serum cystatin C (Cys C) is a recently identified nonglycosylated 13-Kd basic low molecular weight protease inhibitor that has been suggested to be an early sensitive marker of deterioration of glomerular filtration rate (GFR).⁽⁸⁾ It is produced by all nucleated cells and unlike creatinine; it is independent on muscle mass. It has been investigated in pregnant females as a marker, not only for impaired renal function, but also for the degree of glomerular endotheliosis and increase in glomerular volume in pregnancy. In renal transplant patients it has been used as a more sensitive endogenous marker to detect early GFR impairment more than enzymatic measures of creatinine.⁽⁹⁻¹²⁾ Serum cystatin C has been studied as an early prognostic marker of type 2 diabetic nephropathy.^(13, 14)

Increased phosphate excretion into urine is an indicator for tubular reabsorption defect.^(15, 16)

Hypothesis:

The combination of two potential renal toxins sevoflurane and ketorolac could be harmful to the kidneys. This may be augmented in hypertensive patients with subclinical renal dysfunction.

Conventional investigations have been used but yet may not be as indicative as recent sensitive markers. Thus the renal insult by such agents remains incompletely resolved and requires further investigations.

Objective:

The purpose of this study is to compare the effects of sevoflurane alone and in combination with ketorolac in normotensive and hypertensive patients undergoing major surgery with new and more sensitive markers for both renal tubular damage and ischemic renal insult to detect even subclinical renal toxicity. Conventional markers of renal dysfunction will be investigated as well.

Chapter (1)

Pharmacology of sevoflurane

Introduction; Inhalation Anesthetics:

Nitrous oxide, chloroform, and ether were the first universally accepted general anesthetics. Ethyl chloride, ethylene, and cyclopropane were also used; the latter was particularly popular because of the fast induction associated with its use. Recovery from cyclopropane was notable; because of its rapidity of effect and the fact that it did not result in delirium, patients were more clear headed. Toxicity and flammability of these drugs led to their withdrawal from the market.⁽¹⁷⁾

Methoxyflurane and enflurane, two halogenated agents in use for many years, are no longer used because of their toxicity and efficacy. Methoxyflurane was the most potent inhalation agent, but its high solubility and low vapor pressure limited its rate of induction and emergence. Up to 50% of it was metabolized by cytochrome P-450 enzymes to free fluoride (F^-), oxalic acid, and other nephrotoxic compounds. Methoxyflurane was associated with a vasopressin-resistant, high-output, renal failure that was most commonly seen when F^- levels increased to greater than 50 $\mu\text{mol/L}$. Enflurane has a nonpungent odor and is nonflammable at clinical concentrations. It depresses myocardial contractility and sensitizes the myocardium to epinephrine. During deep anesthesia, high-voltage, high-frequency electroencephalographic changes can progress to a spike-and-wave pattern that culminates in tonic-clonic seizures.⁽¹⁸⁾

Although chloroform, ether, methoxyflurane, and enflurane are no longer used (chiefly because of problems with toxicity and flammability), five inhalation agents continue to be used in clinical anesthesiology: nitrous oxide, halothane, isoflurane, desflurane, and sevoflurane (table 1).⁽¹⁹⁾

Inhalation anesthetics are particularly useful in the induction of pediatric patients in whom it may be difficult to start an intravenous line.⁽²⁰⁾ In contrast, adults usually prefer rapid induction with intravenous agents, although the nonpungency and rapid onset of sevoflurane have made inhalation induction practical for adults.