High Fluoride Levels With Isoflurane Critical Care Sedation Does Not Cause Nephrotoxicity

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Introduction/Rationale: Inhalational anesthesia agents such as isoflurane can be used to provide critical care sedation. These agents contain fluoride with early data showing that high serum fluoride levels > 50 umol/L was associated with acute renal dysfunction with use of an older generation agent called methoxyflurane.(1) There is limited data assessing the association of fluoride levels with modern day anesthesia agents. We are conducting a safety and feasibility pilot trial assessing the use of isoflurane for long term critical care sedation. This report assesses fluoride levels and the impact on renal function.

Methods: The 'Use of Volatile Anesthetic Agents of Long-Term critical Care Sedation' (VALTS) Trial is a parallel RCT recruiting patients who require mechanical ventilation > 48h. With consent and institutional board approval, patients are randomized to receive either inhaled isoflurane or intravenous propofol/midazolam using a bedside analgo-sedation protocol. Serum fluoride levels and patients glomerular filtration ratio (GFR) are measured every 48 h until sedation stops.

Data is reported as median (IQR) for continuous variables and analysed using a Mann Whitney U test. Categorical data is expressed as percentage and analysed using a Chi or Fisher's Exact test. The association of serum fluoride levels with renal function (GFR) was examined using a multivariable linear regression analysis with risk adjustment for chronic renal dysfunction (CRD), diabetes, apache score, haemoglobin and admission type. A generalized estimating equation (GEE) was used to adjust for within group data correlation. A second model was used to assess factors that raise serum fluoride levels. All analysis was conducted in SAS v.9.4 (Cary, N.C.).

Results: 27 patients received isoflurane and 6 received propofol/midazolam sedation. Univariate analysis demonstrated median fluoride levels were significantly higher among patients who received isoflurane sedation (15 vs.1.95 umol/L). Levels were also significantly higher among surgical rather than medical and non-operative surgical patients. GEE modelling demonstrated that chronic renal dysfunction was the most significant factor at lowering GFR (-30.18, 95% confidence interval -47.24 to -13.12, $p < 0.0005$). There was no statistically significant relationship between fluoride levels and GFR (-0.13, -0.4 to 0.16, p 0.38).

Variables associated with the fluoride levels were patients who received isoflurane sedation (1.32, 0.66 to.98, $p < 0.0001$) and surgical patients (0.46, 0.35 to1.54, $p = 0.002$).

Conclusion: Isoflurane sedation significantly raises serum fluoride levels. However, elevated fluoride is not associated with reduced renal function.

1. Cousins et al. Anesth 1973; 38: 557

Parameter	Estimate	Standard Error	95% Confidence Limits	Z	Pr > |Z|	
Intercept	89.2861	34.4242	21.8159	156.7563	2.59	0.0095
fluoride	-0.1285	0.1465	-0.4156	0.1585	-0.88	0.3802
Volatile sedation	3.9658	8.3475	-12.3950	20.3267	0.48	0.6347
Surgical group	-10.3181	9.7574	-29.4423	8.8061	-1.06	0.2903
diabetes	-6.9431	8.7080	-24.0104	10.1243	-0.80	0.4253
Chronic renal dysfunction	-30.1829	8.7051	-47.2446	-13.1212	-3.47	0.0005
Apache	-1.4351	0.8589	-3.1185	0.2483	-1.67	0.0948
haemoglobin	0.2933	0.1834	-0.0662	0.6528	1.60	0.1098

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