Title: ISOFLURANE METABOLISM IN OBESE RATS WITH CHRONIC RENAL INSUFFICIENCY

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Introduction. Metabolism of the volatile fluorinated ether anesthetics results in the release of a potentially nephrotoxic metabolite, inorganic fluoride (F^-). Exposure of the kidney to F^- can result in high output, vasopressin-resistant, renal failure. The extent of injury appears to depend upon both the peak serum F^- to which the kidney is exposed and the time for which the plasma level is maintained. The plasma F^- level is in turn determined by the balance between production via hepatic anesthetic metabolism and elimination by renal excretion and absorption into bone. In obesity, prolonged release of anesthetic from fat depots and subsequent continued metabolism leads to increased levels of serum F^-. It is possible that the combination of obesity and chronic renal insufficiency (CRI) may enhance nephrotoxicity of the fluorinated anesthetic agents. This animal study was designed to investigate the potential for enhanced isoflurane nephrotoxicity in a Fischer 344 rat model of obesity and mild CRI.

Methods. 40 male, Fischer 344 rats were ranked and paired according to weight. One rat of each pair was randomly assigned to a high fat diet (Potters), while the other was maintained on standard rat chow (Wayne Lab Blox). After 20 weeks, renal insufficiency was surgically produced in half of the rats in each dietary grouping by a two stage procedure. Initially, the upper pole of the left kidney was excised; one week later, a right nephrectomy was performed. After eight weeks, rats were placed in metabolic cages for two consecutive 24-hr collections of urine. Blood was obtained from the tail for measurement of serum fluoride (F^-), creatinine and urea nitrogen. All rats were exposed simultaneously to 1.2% isoflurane for 3 hr. Following anesthesia, 24-hr urine collections were made until termination at 168 hr and blood was collected at 4, 8, 24, 96 and 168 hr. Data were analyzed by ANOVA with sample time as the repeated measure.

Results. Following nephrectomy, CRI rats had higher serum creatinines (0.9 vs 0.6 mg/dl) and blood urea nitrogens (33 vs 18 mg/dl). ANOVA of serum F^- (Table 1) with repeated measures revealed significant differences between obese and non-obese rats, and between nephrectomized and non-nephrectomized rats. The highest level (21.1 ± 3.4 uM) seen was in the nephrectomized obese rats 8 hr after isoflurane anesthesia. ANOVA of 24-hr urine volumes (Table 2) with days as the repeated measure revealed significant differences between obese and non-obese rats and between nephrectomized and non-nephrectomized rats. After anesthesia, there was a 25-30% increase in urine volume in obese rats, and a 6-20% decline in non-obese rats.

Discussion. Although the levels of serum F^- observed in this study were below those known to cause polyuric renal failure, there were clear-cut differences between the animals that suggest the possibility for an increased risk in the obese and CRI groups studied. The significant elevations in serum F^- in obese rats compared to non-obese rats confirm that obesity may significantly affect the total amount of isoflurane that is metabolized. The degree of CRI produced in this study was purposely mild. The time and depth of anesthesia were also kept low. However, there were clear indications that even with this mild degree of CRI, peak serum F^- levels were significantly higher in CRI rats. There is also evidence that the obese animals had an increased urine output after anesthesia, and that this was marginally greater in the obese CRI rats.

The combination of mild CRI and obesity is not an unusual clinical scenario, particularly in the elderly. If this animal study can be extrapolated to humans, it would appear possible that there is the potential for nephrotoxicity following exposure to fluorinated anesthetics in obese patients with CRI.

Table 1. Serum F^- (uM) Pre and Post Isoflurane

		Pre	Post 8 hr	Post 24 hr
Normal	Non-Obese	3.1 ± 0.7	11.9 ± 2.5	6.3 ± 2.2
	Obese	2.8 ± 0.6	12.7 ± 4.9	18.9 ± 2.0
CRI	Non-Obese	4.0 ± 1.0	13.9 ± 3.4	6.1 ± 1.3
	Obese	3.1 ± 1.2	21.1 ± 3.4	15.8 ± 7.7

Table 2. Urine Volumes (ml) Pre and Post Isoflurane

		Pre	Post 24 hr	Post 48 hr
Normal	Non-Obese	8.6 ± 1.6	6.9 ± 1.4	8.2 ± 2.2
	Obese	4.2 ± 0.7	5.2 ± 1.6	3.7 ± 0.7
CRI	Non-Obese	19.1 ± 4.3	17.9 ± 3.0	19.9 ± 3.7
	Obese	6.3 ± 2.0	8.1 ± 3.1	6.7 ± 1.9

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