Date

Title: IN VITRO ANESTHETIC DEFLUORINATION AND IN VIVO LIVER FUNCTION IN FISCHER 344 RATS WITH CHRONIC RENAL FAILURE

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Introduction. It has been reported that serum inorganic fluoride (F^-) levels the day after enflurane anesthesia are no higher in patients[1] and Fischer 344 rats[2] with chronic renal failure than in similar groups with normal kidney function. This is surprising since 40-50% of F^- is excreted by the kidney. A possible explanation for the lack of increased serum F^- levels is decreased anesthetic metabolism secondary to chronic renal failure. Impaired drug metabolism, altered liver to body weight ratios and differences in microsomal enzyme activity are known to occur in the presence of severe renal disease. To better define the problem, in vivo and in vitro hepatic function was measured in Fischer 344 rats with chronic severe renal impairment.

Methods. Eleven month old, male rats were prepared surgically as reported by Sievenpiper:[2] group 1 (control; n=7) had bilateral capsule strippings; group 2 (n=5) had a capsule stripping of the left kidney followed by a right nephrectomy; group 3 (n=8) and group 4 (n=7) had excision of the upper and lower poles of the left kidney followed by a right nephrectomy. After 3½ months, rats were killed. Blood was obtained for renal function tests and for a liver profile including SGOT, SGPT, alkaline phosphatase (Alk Phos), total protein, uric acid, cholesterol, inorganic phosphate, globulin, ionized calcium and total bilirubin (Bili). At sacrifice, livers were immediately removed, rinsed in 0.9 NaCl, blotted dry and weighed. Liver slices were fixed in Bouin's solution for light microscopy. The remaining liver was perfused with cold 1.15% KCl. Microsomes were prepared, protein and cytochrome P-450 contents were determined and the rates of microsomal defluorination of methoxyflurane (MOF), enflurane, isoflurane (ISO), and sevoflurane (SEVO) were measured with an ion-specific electrode. Data was assessed by one-way analysis of variance and differences among groups identified with Neuman-Kuels post hoc test. $P<0.05$ was considered significant.

Results. At the time of sacrifice, groups 3 and 4 rats had terminal renal failure. Serum creatinine values were: group 1, 0.41 ± .04; group 2, 0.43 ± .00; group 3, 2.73 ±.63; group 4, 2.98 ± .40 mg/100 ml. There was, however, no evidence of liver dysfunction in any of the groups; representative values are shown in Table 1. Light microscopic examination of liver tissue showed no morphological differences among the groups. Liver weights were not significantly different, ranging from 10.9 ± 0.9 (group 4) to 12.9 ± 0.5 (group 1). However, body weights were significantly decreased in groups 3 and 4 (320 ± 16 and 294 ± 18) compared to groups 1 and 2 (395 ± 10 and 382 ± 9). This resulted in a significant increase in liver to body weight ratio in group 4 rats. Anesthetic defluorination rates were not significantly different among groups (Table 2). Hepatic microsomal cytochrome P-450 content was significantly decreased in group 4 (0.55 ± 0.06 nmoles/mg protein) compared to group 1 (0.83 ± 0.08).

Discussion. It has been postulated, that in subjects with severe renal impairment administered enflurane, decreased F^- excretion secondary to reduced glomerular filtration rate would result in persistently high serum F^- levels. Failure to find high F^- levels in the studies of Carter[1] and Sievenpiper[2], however, have made it necessary to look for other explanations. One possibility is that there is decreased metabolism of enflurane secondary to hepatorenal disease; alternatively, there may be increased F^- clearance via an extra-renal mechanism, probably sequestration into bone. The present study shows that in the presence of renal failure in Fischer 344 rats, in vivo liver function is normal as is in vitro defluorination of the fluorinated anesthetics. Decreased cytochrome P-450 levels are compensated for by the increased liver to body weight ratio. Thus, normal serum F^- levels in the face of impaired renal function must be due to enhanced extrarenal F^- clearance.

TABLE 1. Serum Values, Mean ± SE

G	SGOT u/L	SGPT u/L	Alk Phos u/L	Protein gm%	Bili mg%
1	279 ±12	142 ±22	244 ±13	6.8 ±.1	.2 ±.0
2	261 ±19	111 ±12	253 ±27	6.4 ±.2	.2 ±.0
3	174 ±27	47 ± 6*	179 ±11	5.8 ±.1*	.2 ±.0
4	227 ±36	60 ±14	213 ±34	5.6 ±.2*	.2 ±.0

*P<0.05 vs Group 1

TABLE 2. nmoles F^-/5 mg protein/15 min

G	MOF	ENF	ISO	SEVO
1	17.3 ±1.2	7.3 ±1.0	2.1 ±0.3	9.1 ±1.2
2	17.0 ±1.4	6.4 ±3.3	3.3 ±0.9	7.1 ±0.5
3	18.8 ±1.4	9.5 ±1.2	4.6 ±0.6	10.5 ±1.2
4	18.1 ±3.5	7.6 ±1.0	3.4 ±1.0	7.1 ±1.8

References.

1. Carter, R., Heerdt, M. and Acchiardo, S.: Fluoride kinetics after enflurane anesthesia in healthy and anephric patients and in patients with poor renal function. Clin Pharmacol Ther 20:565-570, 1976.
2. Sievenpiper, T.S., Rice, S.A., et al: Renal effects of enflurane anesthesia in F344 rats with pre-existing renal insufficiency. J Pharmacol Exp Ther 211:36-41, 1979.