

Hepatic and Renal Effects of Methoxyflurane in Dogs

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SINCE the introduction of methoxyflurane (Penthrane), 1,1-dichloro-2,2-difluoro-2-ethyl methyl ether, in 1959, many of its anesthetic and other properties have been studied. This report presents an extensive investigation of the histological changes in the kidney and liver of dogs following gross overdosage of methoxyflurane.

Sixty-six mongrel dogs weighing between 22 and 70 pounds were studied. Each animal, without premedication, was anesthetized for a period of five hours. Anesthesia was induced with pentobarbital, 12 mg. per pound of body weight, and atropine, 0.4 mg. administered intravenously. The trachea was intubated. A femoral artery was cannulated and systolic blood pressure was monitored with a mercury manometer. A continuous ECG (lead 1) and EEG (bitemporal) were recorded from each animal. Anesthesia was maintained with methoxyflurane and oxygen administered from a closed circle carbon dioxide absorption rebreathing system. The methoxyflurane vaporizer used was the standard Heidbrink ether jar with a wick. Levels of anesthesia considered to be in excess of acceptable clinical concentrations were maintained. For the first thirty minutes to two hours of anesthesia the vaporizer setting was at 10. After this period it was reduced to provide a concentration which allowed spontaneous respiration. Spontaneous respirations were defined for these experiments as a rate of 3 to 4 times a minute without reference to tidal volume. (This represents studies in overdosage situations for which arterial P_{O_2} and P_{CO_2} values are not reported.)

The main factors in determining depth of anesthesia were blood pressure and the EEG tracings. When the systolic blood pressure fell below 60 mm. of mercury and/or if the EEG tracing flattened, the concentration of the inhaled methoxyflurane was reduced until the systolic pressure rose above 60 mm. of mercury. For the most part, however, the

EEG tracing continued to show a pattern of deep anesthesia. The clinical impression of overdosage of anesthesia was confirmed by the greatly reduced respiratory rate. Respirations were neither assisted nor controlled.

Three groups of animals were studied simultaneously. Twenty animals in group 1 were subjected to only five hours of methoxyflurane anesthesia by the technique described. In group 2, 23 animals were likewise maintained in deep methoxyflurane anesthesia for five hours. In addition, during the second hour of anesthesia these animals were bled 10 per cent of their estimated blood volume over a 40-minute period. This blood loss was replaced rapidly with an equivalent volume of lactated Ringer's solution.

The 23 group 3 animals were subjected to deep methoxyflurane anesthesia plus intermittent hypoxia. The latter was achieved by flowing 15 per cent O_2 (1 liter) and 85 per cent nitrous oxide (6 liters) via a semiclosed absorption technique for fifteen minutes of each hour of anesthesia. Hypoxia was verified by ear oximetric readings remaining consistently below 75 per cent hemoglobin oxygen saturation and electroencephalographic evidence of cerebral hypoxia. In the other two groups ear oximetric readings remained at 98 per cent hemoglobin oxygen saturation or better.

At the termination of each experiment the animals' tracheas remained intubated until there was evidence of awakening by "bucking" on the endotracheal tube and active movements of all extremities. Then they were returned to cages and watched closely for several hours to detect respiratory obstruction or vomiting. In addition, according to the hepatic and renal biopsy schedule, each animal was examined on subsequent days for untoward signs of delayed recovery (sluggishness, anorexia, urinary retention).

At times varying from twenty-four hours to twelve days following the anesthetic administration (table 1), the animals were returned to the laboratory, and after pentobarbital administration (12 mg. per pound

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body weight) the peritoneum was opened. A 3 cm. x 2 cm. section was removed from the right lobe of the liver next to its diaphragmatic surface, and a 3 cm. x 2 cm. wedge specimen was obtained from the middle third of the kidney. These specimens were sent to the Department of Pathology and were identified only by the dog's chart number. Each specimen was studied by the same pathologist who was unaware of which series the biopsied specimens represented.

Results

The following excerpts are from the reports submitted by the consultant pathologist:

"Careful examination microscopically, first under unknown and later with known circumstances, failed to demonstrate any significant differences between the three groups in the pathologic findings. Segregating the animals into those thought clinically to be toxic, those clinically tolerating the agent, and those with hypoxia and/or elevated carbon dioxide still failed to produce a pathologic pattern which was singular.

"The liver presented rather consistent changes, and although the abnormalities were found in practically every specimen the changes varied in degree. There was no obvious variable which apparently was responsible for these. In general the changes were more marked about the central lobular portion of the liver where there occurred a fine, diffuse watery vacuolization of the hepatic parenchymal cells. Special stains demonstrated the lack of fat within these vacuoles. Usually, in the regions of such watery vacuolization, the sinusoids were dilated. These changes were among the usual findings seen in 'normal' control dogs. In general it is considered that watery vacuoles in dogs represent an easily reversible process, is quite nonspecific, and is seen in a variety of conditions.

"The kidney specimens show a nonspecific proximal tubular degeneration which varied in intensity but in general was minimal. The glomeruli and the remainder of the collecting system failed to show any changes. Some of the animals had a pre-existent pyelonephritis, both acute and chronic, but these were readily separable as pre-existent changes."

TABLE 1. Postanesthetic Time of Liver and Kidney Biopsies of Dogs Given Gross Overdosage of Methoxyflurane

Group 1 (20 Dogs)		Group 2 (23 Dogs)		Group 3 (23 Dogs)	
Number of Dogs	Time after Anesthesia	Number of Dogs	Time after Anesthesia	Number of Dogs	Time after Anesthesia
8	24 Hours	1	5 Hours	1	Died on table
1	48 Hours	6	24 Hours	1	30 Minutes
2	3 Days	2	3 Days	1	90 Minutes
1	5 Days	1	5 Days	2	4 Hours
3	6 Days	4	6 Days	2	24 Hours
1	8 Days	2	7 Days	2	3 Days
1	9 Days	2	8 Days	2	5 Days
1	10 Days	2	9 Days	3	6 Days
		1	10 Days	1	7 Days
		2	12 Days	1	8 Days
				1	9 Days
				1	10 Days

In addition to five hours of methoxyflurane anesthesia (group 1), 10 per cent of the estimated blood volume was removed from each animal in group 2, and group 3 animals were subjected to five periods of anoxia.

Discussion

This study was undertaken to determine whether methoxyflurane, a halogenated hydrocarbon, would produce significant histologic hepatic or renal changes when administered in a clinically gross overdosage technique under a variety of circumstances. Significant changes in clinical liver function tests have not been noted in patients anesthetized with methoxyflurane.

Clinical liver and kidney function studies were not done in this investigation, since interest was focused upon possible pathological changes in the liver and kidney in circumstances of gross overdosage of the anesthetic agent. This protocol was chosen with the realization that anesthetic agents will periodically be administered in excessive concentrations either by mistaken indication or through inexperience of the one administering the anesthetic.

Stephen¹ has pointed out that coexisting factors may be active in the experimental animal or in the patient which may be misleading in a true interpretation of hepatic and/or renal toxicity of an anesthetic agent. Two of the factors which he mentioned are anoxia and the nutritional status of the subject. Krantz and Carr² have referred to the hepatotoxic effects of chloroform in the anoxic state and have made reference to the effects of other anesthetic agents on liver glycogen and

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the possibilities of liver damage in hypoglycemic states. The plan of experiments in this report included an anoxic or hypoxic series and another series setting the stage for hypoglycemia.

In this study three animals were anesthetized simultaneously. One was maintained for five hours in a clinical state of gross overdosage of methoxyflurane anesthesia, as determined by respiratory rate (four times per minute or less), systolic blood pressure, and flattening of the EEG tracing. The second animal in each experiment was similarly overdosed with anesthetic for five hours but in addition was bled 10 per cent of his estimated blood volume. This was replaced with a lactated Ringer's solution without glucose. The third animal was maintained in a similar plane of anesthesia but was subjected to a fifteen-minute period of hypoxia each of the five hours of anesthesia. The plan of studying one animal in each series simultaneously was chosen to prevent bias perhaps due to different seasons of the year, changes in kennel diet during the course of the investigation, or subtle variations of attitude in those carrying out the investigation.

In attempting to carry out this study with the experimental subjects anesthetized with a gross overdosage of agent we recognize that many other factors could have compounded the action of the drug *per se* upon hepatic or renal processes. Inherent in the techniques used were hypoventilation, hypotension, hypoxia or anoxia, hemorrhage, and perhaps an increased work of breathing. In addition, the subjects were average kennel dogs taken recently from the pound and in less than optimal nutritional status. Even under these circumstances the only consistent change shown in hepatic histology was that of watery vacuolization of cord cells, a change that not only is thought to be an easily reversible process but is also nonspecific and is seen in a variety of conditions.

It can well be appreciated from the description of the technique utilized that there was no attempt to correlate this investigation with an accepted clinical practice of anesthesia. To expose an animal to overdosage on a closed circle absorption system for five hours without any assistance or control of respirations is, in itself, a great challenge to any anesthetic

agent. Conversely, any drug which, under these circumstances, does not produce recognized hepatic or renal pathology can be used clinically with an increased sense of safety in these regards.

As an incidental finding in this investigation during the entire study no electrocardiographic evidence of altered rhythm was noted. This is impressive in view of the planned circumstances under which the drug was administered.

Summary

The effects of methoxyflurane, a halogenated hydrocarbon anesthetic agent, upon the liver and kidney of mongrel dogs were studied. Each animal was anesthetized for five hours with a gross overdosage of methoxyflurane and evaluated by an unassisted respiratory rate of four per minute or less, a systolic blood pressure of 60-80 mm. of mercury, and a flattened EEG tracing.

Twenty dogs were subjected to overdosage of the anesthetic agent alone. Twenty-three animals experienced an additional removal of 10 per cent of the estimated blood volume and replacement with a balanced salt solution without glucose. Twenty-three animals were exposed to a fifteen-minute period of hypoxia during each of the five hours of methoxyflurane anesthesia.

Biopsy specimens of the liver and the kidney removed at various postanesthetic periods were studied by a consultant pathologist. A rather consistent change was watery vacuolization of the cord cells of the liver, thought to be a reversible and nonspecific process. Renal histological changes were not significant. There was no evidence of fatty infiltration or necrosis.

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