Elevation of serum xanthine oxidase activity following halothane anesthesia in man

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Summary. Halothane, but not methoxyflurane, was found to cause specific hepatocellular damage, the hepatotoxicity being prompt but transient. The hepatotoxicity was demonstrated by the elevation in the serum activity of xanthine oxidase, a highly sensitive marker for acute liver damage.

Halothane and methoxyflurane are commonly employed anesthetic agents. Since their introduction, contradictory reports have been published concerning their hepatotoxicity[1-3]. Massive hepatic necrosis rarely occurs following halothane[2-4], and methoxyflurane anesthesia[1,5], but whether these compounds have a more common specific, although mild, hepatotoxic effect is a matter of dispute. To solve this question, various markers for the detection of liver damage have been used. Most investigators studied the activity in serum of hepatocellular enzymes, such as the transaminases, SGOT and SGPT, or other parameters of liver function, such as serum bilirubin and plasma prothrombin time[6-12]. Whereas in some of the studies no hepatotoxicity could be demonstrated following halothane and methoxyflurane anesthesia[12-14], in others evidence of hepatotoxicity was indeed found and was shown to be of similar[8,15,16] or even greater magnitude than that caused by other anesthetic agents[6,7,9-16]. Xanthine oxidase activity in man is confined mainly to the liver tissue[17]. Significant enzyme activity has also been demonstrated in jejunal mucosa and in colostrum[18-20]. However, experimental studies in the cat have demonstrated that ischemia of the small intestine did not increase serum xanthine oxidase (SXO) activity, whereas liver injury resulted in rapid and remarkable rise in SXO activity[21]. Several studies have established that SXO activity originates almost exclusively from the liver[21,22], its release to the serum being highly sensitive to hepatocellular damage[23,24]. Employing SXO as a marker for hepatocellular damage, we could demonstrate in the rat that halothane has a hepatotoxic effect[25] which was not detectable by the more commonly used enzymatic marker SGOT. In the present study, we utilized the specific and

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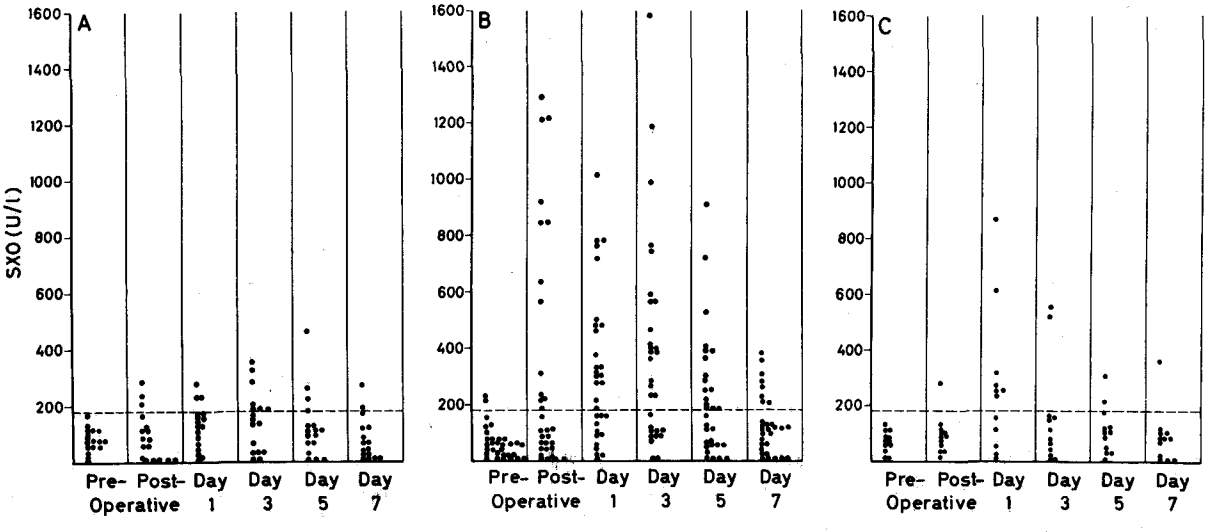

Changes in SXO level following anesthesia (the actual values are given): *A* Control. *B* Halothane. *C* Methoxyflurane. Dotted line represents upper normal limit (mean + 2 SD).

highly sensitive marker SXO to clarify whether halothane or methoxyflurane are hepatotoxic in man. The serum levels of the intracellular enzymes SGOT and LDH were studied for comparison.

Materials and methods. 60 patients, scheduled for elective surgical procedures such as repair of inguinal hernia, hemorrhoidectomy, plastic or minor orthopedic surgery, were chosen for the study. None of them had a history of liver disease.

Venous blood samples were taken before induction of anesthesia, immediately following completion of surgery, and on each of the mornings of the 1st, 3rd, 5th and 7th postoperative days. Blood samples were allowed to clot, centrifuged and the separated sera were assayed for SXO by measuring radiochemically the conversion of C^{14}-labelled hypoxanthine to uric acid[24]. SGOT and LDH were analyzed by Technicon Autoanalyzer SMA 12/60. All patients were premedicated with 2 ml of Thalamonal (dehydrobenzperidol 5 mg and Fentanyl 0.1 mg) and atropin 0.5 mg i.m. 1 h prior to operation. Anesthesia was induced with sodium thiopental 0.4 mg/kg b.wt, followed by succinylcholine chloride 1 mg/kg b.wt, to facilitate endotracheal intubation. All 60 patients were given a mixture of nitrous-oxide (60%) and oxygen (40%) at a total flow rate of 8 l/min, using a semiclosed circle system with carbon dioxide absorption.

The patients were randomly divided into 3 groups: 31 patients received halothane, 12 patients received methoxyflurane and 17 patients served as controls. In the group anesthetized with methoxyflurane, anesthesia was maintained through a Pentec II vaporizer. Methoxyflurane concentration of 1.0% was used for 5 min, then 0.5% for the remainder of the operation. In the halothane group a concentration of 1.0% was delivered through a Fluotek Mark II Vaporizer. The control group received Fentanyl 0.002 mg/kg b.wt and Alloferine 0.2 mg/kg b.wt i.v., and ventilation was controlled with a volume-limited ventilator.

Results. The mean values of SXO, LDH and SGOT in the 3 groups of patients, prior and following anesthesia, are presented in the table. The scattering of SXO activities prior and following anesthesia is depicted in a histogram (figure). In the control group of patients, the mean SXO, LDH and SGOT values following anesthesia were not significantly elevated, in comparison with the preoperative values. In the halothane group, in comparison with the preoperative level, there was significant elevation in SXO activity immediately following completion of anesthesia, the activity increasing to maximum value on the 3rd postoperative day (more than 6fold the preoperative value), then decreasing gradually. The SXO level was still significantly elevated on the 7th postoperative day, the last day it was measured. When, however, the SXO levels on the different days following halothane anesthesia were compared with the respective values obtained in the control group, a significant elevation was found immediately following anesthesia and on the 1st and 3rd postoperative days only. On the other hand, the post-halothane LDH

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Effects of anesthetic agents on serum levels of intracellular enzymes

Anesthetic group	Enzyme activity (U/l) SXO Mean	SD	P_1	P_2	LDH Mean	SD	P_1	P_2	SGOT Mean	SD	P_1	P_2
Control (17)												
Preoperative	78.5	43.9			164.4	23.4			28.7	9.3		
Postoperative												
Immediately	90.7	93.2	n.s.		166.8	35.3	n.s.		27.9	9.1	n.s.	
Day 1	121.3	84.4	n.s.		178.4	37.5	n.s.		30.0	10.3	n.s.	
Day 3	147.8	113.3	n.s.		184.6	28.4	n.s.		32.3	12.4	n.s.	
Day 5	127.5	127.8	n.s.		174.0	29.6	n.s.		28.4	8.6	n.s.	
Day 7	76.9	85.1	n.s.		172.7	18.9	n.s.		32.6	5.7	n.s.	
Halothane (31)												
Preoperative	63.6	62.3			164.8	32.1			26.7	7.01		
Postoperative												
Immediately	313.1	412.8	<0.01	<0.05	164.8	47.8	n.s.	n.s.	25.4	7.2	n.s.	n.s.
Day 1	309.8	272.5	<0.001	<0.01	191.9	39.4	<0.01	n.s.	31.3	10.0	<0.05	n.s.
Day 3	392.4	387.3	<0.001	<0.02	212.5	60.1	<0.001	n.s.	34.2	12.1	<0.01	n.s.
Day 5	206.0	227.3	<0.01	n.s.	197.0	53.0	<0.01	n.s.	30.8	12.7	n.s.	n.s.
Day 7	132.1	127.0	<0.02	n.s.	175.6	38.1	n.s.	n.s.	28.8	11.6	n.s.	n.s.
Methoxyflurane (12)												
Preoperative	71.2	44.4			168.8	57.7			27.7	7.7		
Postoperative												
Immediately	99.0	78.3	n.s.	n.s.	161.9	35.5	n.s.	n.s.	26.6	7.8	n.s.	n.s.
Day 1	267.7	279.1	<0.05	n.s.	189.4	24.9	n.s.	n.s.	27.3	10.3	n.s.	n.s.
Day 3	156.0	206.8	n.s.	n.s.	209.9	36.3	n.s.	n.s.	32.3	11.0	n.s.	n.s.
Day 5	115.5	105.1	n.s.	n.s.	171.5	42.6	n.s.	n.s.	27.8	13.3	n.s.	n.s.
Day 7	95.3	108.3	n.s.	n.s.	168.0	25.7	n.s.	n.s.	26.6	10.8	n.s.	n.s.

Numbers in parentheses indicate numbers of subjects. Values represent mean ± SD, n.s., not significant. P_1, statistical significance (Student's t-test) in comparison to the preoperative values in the same anesthetic group. P_2, statistical significance (Student's t-test) in comparison to the values on the operative day in the control anesthetic group.

and SGOT levels which rose significantly, when compared with their respective preoperative values, the former on the 1st, 3rd and 5th, and the latter on the 1st and 3rd postoperative days, did not differ significantly from the respective values following control anesthesia. In the group of patients anesthetized with methoxyflurane, the mean SXO levels, when compared to the preoperative values, were significantly elevated on the 1st postoperative day only (almost 4fold the preoperative value) but when compared with the respective values following control anesthesia, no significant elevation was found at any time. Methoxyflurane anesthesia did not cause a significant alteration in LDH and SGOT activities when compared to the preoperative value, and to the respective control group.

Discussion. We have reported previously that surgical procedures performed on body parts other than the upper abdomen (biliary tract and gastric surgery) are not associated with an increase in SXO activity[22]. None of the patients chosen for the present study were subjected to intraabdominal operations, thus increased SXO activity in the patients studied should be considered to reflect liver damage due to the anesthetic agents involved and not due to the surgical procedures undertaken.

Since halothane and methoxyflurane were administered in addition to N_2O/O_2 mixture, an increase in serum enzyme activity above that caused by N_2O/O_2 administration exclusively was considered to indicate liver damage. According to the change in SXO level, halothane but not methoxyflurane was found to cause hepatocellular damage. The halothane hepatotoxicity was both prompt and transient. These results are compatible with those of several investigators who reported that halothane has a specific hepatotoxic effect[7,9-11], but is incompatible with studies of others who found the hepatotoxic effect of halothane to be comparable with that caused by other anesthetic agents, such as diethyl ether, and chloroform[8,15,16], or failed to demonstrate any hepatotoxic effect of halothane at all[12,14]. The advantage of SXO as a marker for acute hepatocellular damage was again verified in the present study, in man. Out of the 3 intracellular enzymes, SXO, SGOT and LDH, employed for the detection of hepatocellular damage induced by anesthetic agents, only SXO was found to be significantly increased.

Toxicity of *Parthenium hysterophorus* L. to cattle and buffaloes[1]

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Summary. Parthenium hysterophorus L., when fed to buffalo bull calves and cross bred bull calves resulted in acute toxicity leading to death. The former animals developed severe dermatitis. Autopsy revealed ulceration of alimentary tract. Extensive pathological changes were noticed in liver, kidney and skin.

Parthenium hysterophorus L., a native weed of South and Central America, accidentally introduced into India, is posing a threat to agriculture in southern parts of the country where it has invaded food and fodder crops fields[4]. Although Parthenium has been found to be responsible for allergic contact dermatitis in humans in these parts[4,5], its toxicity to domestic animals has not been investigated. Cattle and buffaloes graze occasionally, while goats graze more freely on the weed in areas where waste lands and pasture fields are heavily infested with Parthenium. Many animals, however, graze grass in between Parthenium in the fields. Even in the latter case, the possibility of some Parthenium being ingested can not be ruled out. We therefore studied the toxicity of the weed to cattle and buffaloes, the results of which are presented in this communication.

9 buffalo bull calves and 7 cross bred calves (each 9–12 months old) weighing about 80–100 kg and free of any external and internal parasites in an apparently healthy state, were selected for the study. Feeding chaff cut aerial parts of Parthenium hysterophorus L., ad libitum initially for 48 h was replaced with equal quantities of Parthenium and hybrid napier grass. Control animals throughout the experiment were fed on hybrid napier grass. All the animals received 300 g of concentrate feed mixture every day.

The animals consumed the weed without much resistance but developed diarrhea within 24 h which subsided in 3 to 4 days. 6 buffalo bull calves and 5 cross bred bull calves died within 8–30 days. The controls remained healthy throughout the experimental period. 24 h prior to death, the experimental animals showed signs of excitability and muscular twitching.

The buffalo bull calves developed itching 7 days after feeding Parthenium, followed by the appearance of papular erythematous eruptions involving the tip and base of ears, all along the neck which gradually extended on either side of the thoracic region, dorsal aspects of the abdomen and the lesions extending to knee, hock joints and the brisket region. A few papulae were noticed on the ventral surface of the abdomen. 3 weeks later, the affected areas became alopetic at neck and shoulder region. Depigmentation in patches was marked in these areas. The surviving animals developed oedema around eyelids and the facial muscles. None of the cross bred bull calves, however, suffered from dermatitis.

There was ulceration on the muzzle, on autopsy ulceration on dental pads, dorsum of the tongue, the upper palate extending down to oesophagus was seen in all animals. Liver, gastrointestinal tract and kidney revealed marked lesions on autopsy. There were areas of necrosis with severe congestion in liver and gastrointestinal tract. Ulceration throughout the abdomen and fundic region

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