THE EFFECT OF REPEATED ADMINISTRATION OF HALOTHANE ON THE LIVERS OF HEALTHY MONKEYS

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THE RECENT CONTROVERSY concerning the role of halothane in the production of hepatic necrosis is difficult to resolve by the study of human patients. Rarely if ever can other possible hepatotoxic factors related to disease or treatment be completely excluded, and a controlled experiment in man designed to test the hepatotoxicity of the drug is impossible.

Several observers have suggested that halothane produces a hepatic lesion in man similar to that associated with fulminating viral hepatitis.¹⁻³ It has been pointed out that typically the hepatic necrosis which has been attributed to halothane has not occurred after a single exposure, but after a second or subsequent exposure to the drug following a rest period, suggesting that the injury may be the result of sensitization of the liver cell to halothane.

An experiment was designed to test the effect of repeated exposure to halothane on the livers of healthy Patas monkeys, and to compare any hepatic lesions so produced with those commonly associated with viral hepatitis in the same species.

METHOD

Four healthy Patas monkeys, native to West Africa, were used as subjects. Preliminary liver biopsies were done on each animal before exposure to halothane. Once each week for ten weeks the animals were anaesthetized for one hour with halothane vaporized in oxygen. Several days following each halothane anaesthetic a liver biopsy was done under ether anaesthesia which lasted less than one minute, and blood was taken for transaminase determinations.

The animals were anaesthetized by means of an M.I.E.† Infant Set with a mask and open-end reservoir bag, without an absorber. Halothane and oxygen were delivered from the open circuit of a Boyle's machine with a Fluotec vaporizer in series. A flow of five litres per minute was used throughout the first five sessions. During the last five sessions the five-litre flow was used for the first five minutes and then reduced to four litres per minute for the balance of the hour, since it was evident that these small monkeys did not require a greater flow.

The animals were held by the limbs and the back of the neck during induction with three per cent halothane. Induction time was one minute or less. The animals breathed spontaneously, and the concentration of halothane was reduced if there was evidence of respiratory depression.

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RESULTS

The results in each of the four animals are shown in the protocols. In no instance was a lesion evident in the biopsies of the liver which could be attributed to halothane; neither was there any variation in the blood levels of the serum glutamic-oxalic transaminase or glutamic-pyruvic transaminase which would suggest hepatic destruction.

One of the animals (Patos 517) suffered circulatory arrest on seven occasions during halothane anaesthesia and once during the brief ether anaesthesia required for liver biopsy. On each occasion the animal was resuscitated by artificial respiration and external cardiac compression, and in each instance awakened promptly on termination of the anaesthetic.

Two of the animals (502 and 503) contracted an intercurrent infection with massive diarrhoea to which these animals are subject. They were not given antibiotics because it would then have been impossible to attribute any subsequent hepatic damage to the halothane alone, and both died within the week following the ninth exposure to halothane. Necropsy showed no hepatic necrosis in either case, and in neither case is there any suggestion that halothane contributed to the deaths.

PROTOCOL: PATAS 502 (FEMALE, 2 LBS.)

1 May	SGOT 47	SGPT 23	Liver biopsy—excess cells in sinusoid. Moderate infiltration of portal tracts. Collections of lymph around swollen Kupffers cells. Liver cells healthy.
4 May			Halothane 1 hour.
8 May	SGOT 61	SGPT 25	Liver biopsy—no change.
11 May			Halothane 1 hour.
15 May	SGOT 52	SGPT 33	Liver biopsy—still a little infiltration of portal tract.
18 May			Halothane 1 hour.
22 May	SGOT 52	SGPT 20	Liver biopsy—a normal liver.
25 May			Halothane 1 hour.
29 May	SGOT 76	SGPT 33	Liver biopsy—occasional swollen Kupffer cells and portal change due to needle track.
1 June			Halothane 1 hour.
5 June	SGOT 100	SGPT 61	Liver biopsy—a little infiltration of some triads only.
8 June			Halothane 1 hour.
12 June	SGOT 64	SGPT 23	Liver biopsy—a little portal infiltration.
15 June			Halothane 1 hour.
19 June	SGOT 45	SGPT 26	Liver biopsy—a normal healthy liver.
22 June			Halothane 1 hour.
27 June	SGOT 72	SGPT 31	Liver biopsy—a little portal infiltration only.
29 June			Halothane 1 hour.
3 July	SGOT 36	SGPT 21	Liver biopsy—slight fatty change.
6 July			Halothane 1 hour.
6 July			Dead. Necropsy—no necrosis. Dilation of sinusoids due to post mortem change. Infiltration of triads.

Clinically small animal. Always awakened quite rapidly. Easy to anaesthetize. On last occasion looked very ill and died same day.

PROTOCOL: PATAS 503 (MALE, 2 LBS.)

1 May SGOT 86 SGPT 31
 Liver biopsy—a normal liver.
 4 May Halothane 1 hour.
 8 May SGOT 47 SGPT 16
 Liver biopsy—a normal liver.
 11 May Halothane 1 hour.
 15 May SGOT 76 SGPT 25
 Liver biopsy—a normal liver.
 18 May Halothane 1 hour.
 22 May SGOT 72 SGPT 21
 Liver biopsy—a normal liver.
 25 May Halothane 1 hour.
 29 May SGOT 95 SGPT 51
 Liver biopsy—a normal liver but a little fatty change in sinusoids and portal changes due to needle track.
 1 June Halothane 1 hour.
 5 June SGOT 77 SGPT 48
 Liver biopsy—normal liver.
 8 June Halothane 1 hour.
 12 June SGOT 61 SGPT 22
 Liver biopsy—portal infiltration. Excess cells in sinusoids. One or two areas of centrilobular necrosis.
 15 June Halothane 1 hour.
 19 June SGOT 52 SGPT 23
 Liver biopsy—minor infiltration of triads. No excess necrosis. Swollen Kupffers cells in some areas.
 22 June Halothane 1 hour.
 27 June SGOT 103 SGPT 28
 Liver biopsy—a little periportal fatty change.
 29 June Halothane 1 hour.
 3 July SGOT 49 SGPT 8
 Liver biopsy—no necrosis. Excess cells in sinusoids.
 3 July Dead. Necropsy—no necrosis. Excess cells in sinusoids.

PROTOCOL: PATAS 516 (MALE, 3½ LBS.)

1 May SGOT 44 SGPT 21
 Liver biopsy—a normal liver.
 4 May Halothane 1 hour.
 8 May SGOT 38 SGPT 16
 Liver biopsy—one focus of infiltration.
 11 May Halothane 1 hour.
 15 May SGOT 68 SGPT 18
 Liver biopsy—a normal liver.
 18 May Halothane 1 hour.
 22 May SGOT 50 SGPT 16
 Liver biopsy—a normal liver.
 25 May Halothane 1 hour.
 29 May SGOT 73 SGPT 21
 Liver biopsy—no significant change.
 1 June Halothane 1 hour.
 5 June SGOT 12 SGPT 15
 Liver biopsy—a normal liver.
 8 June Halothane 1 hour.
 12 June SGOT 38 SGPT 10
 Liver biopsy—a normal liver.
 15 June Halothane 1 hour.
 19 June SGOT 39 SGPT 14
 Liver biopsy—degeneration and infiltration of triads due to adjacent needle track.
 22 June Halothane 1 hour.
 27 June SGOT 82 SGPT 16
 Liver biopsy—portal changes due to needle tracks.
 29 June Halothane 1 hour.
 3 July SGOT 44 SGPT 14
 Liver biopsy—no changes.

6 July Halothane 1 hour.
 10 July SGOT 58 SGPT 22
 Liver biopsy—no necrosis but some portal infiltration.

Clinically lively and sometimes hard to catch.

PROTOCOL: PATAS 517 (FEMALE, 3½ LBS.)

1 May SGOT 58 SGPT 25
 Liver biopsy—a normal liver.
 4 May Halothane 1 hour.
 8 May SGOT 64 SGPT 26
 Liver biopsy—a normal liver.
 11 May Halothane 1 hour. Cardiac arrest.
 15 May SGOT 52 SGPT 21
 Liver biopsy—a normal liver.
 18 May Halothane 1 hour. Cardiac arrest.
 22 May SGOT 60 SGPT 19
 Liver biopsy—a normal liver.
 25 May Halothane 1 hour. Cardiac arrest.
 29 May SGOT 56 SGPT 20
 Liver biopsy—a normal liver. Cardiac arrest.
 1 June Halothane 1 hour. Cardiac arrest.
 5 June SGOT 44 SGPT 21
 Liver biopsy—a little degeneration of triads due to previous needle track.
 8 June Halothane 1 hour. Cardiac arrest.
 12 June SGOT 55 SGPT 18
 Liver biopsy—no change.
 15 June Halothane 1 hour. Respiratory arrest 7 mins.
 19 June SGOT 49 SGPT 22
 Liver biopsy—no change.
 22 June Halothane 1 hour.
 27 June SGOT 64 SGPT 23
 Liver biopsy—no change.
 29 June Halothane 1 hour. Cardiac arrest.
 3 July SGOT 44 SGPT 12
 Liver biopsy—most of the tissue is necrotic probably the result of an old needle track.
 6 July Halothane 1 hour.
 10 July SGOT 55 SGPT 25
 Liver biopsy—no abnormality.

Clinically a most difficult animal to manage. Always awakened rapidly. Arrest occurred suddenly with cessation of respiration, and heart beat could not be felt. Inflation with oxygen and pressure over precordium always resuscitated the animal successfully.

DISCUSSION

Since all observers are agreed that the incidence of hepatic failure in any way associated with halothane anaesthesia in man is very small, no general conclusions can be drawn from the results of the present experiment because of the small number of animals involved. It is evident from our results however, that halothane is not a specific hepatotoxin in the monkey.

RÉSUMÉ

Plusieurs observateurs ont émis l'opinion que l'halothane produit chez l'homme une lésion hépatique semblable à celle qui survient à la suite d'une hépatite virale suraigue; de plus, il a été signalé que cette nécrose hépatique typique qui a été attribuée à l'halothane n'est pas survenue à la suite d'une seule administration d'halothane, mais après une deuxième administration de ce médicament précédée d'une période de repos.

Nous avons établi un procédé expérimental pour étudier l'effet de plusieurs administrations d'halothane à des singes Patas et pour comparer toutes les lésions produites à celles observées ordinairement à la suite d'hépatite virale sur la même sorte d'animal.

Durant dix semaines, à toutes les semaines, durant une heure, nous avons pratiqué une anesthésie à l'halothane avec oxygène sur quatre singes en bonne santé. Entre les administrations d'halothane, nous avons fait des biopsies hépatiques sous anesthésie à l'éther; les taux sanguins de SGOT et de SGPT étaient recherchés. Dans aucun cas, nous avons dépisté une lésion hépatique et, à l'autopsie, nous n'avons trouvé de nécrose hépatique, chez deux sujets qui sont morts d'infection intercurrente.

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