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# Hyperbaric Oxygenation Improves Survival in Rats Poisoned with Carbon Tetrachloride

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Troop BR, Majerus T, Bernacchi A, Belzerg H, Myers RAM. Hyperbaric oxygenation improves survival in rats poisoned with carbon tetrachloride. J Hyperbaric Med 1986; 1(3):157–161.— One hundred and sixty-six rats were studied to determine if treatment with hyperbaric oxygenation would improve the survival of carbon tetrachloride-poisoned rats. Group A was treated within 1 h of poisoning, and group B, 4 h after poisoning. Group C was not treated. Group D was given a placebo and then treated with hyperbaric oxygen. There was a statistically significant improvement in survival in the group treated within 1 h. Although survival was better if treatment was begun after 4 h when compared to untreated animals, this was not statistically significant. Rats given a placebo and then treated with hyperbaric oxygen had no mortality. The following conclusions are offered: (a) Hyperbaric oxygenation improves survival from carbon tetrachloride poisoning; (b) the response rate is time related; and (c) improved survival with hyperbaric oxygen is due to decreased hepatotoxicity. The mechanism whereby the liver is protected is not yet explained; however there is sufficient evidence of the benefit of hyperbaric oxygenation on carbon tetrachloride poisoning to recommend its clinical use.

*hepatotoxicity, carbon tetrachloride, hyperbaric oxygen*

## Introduction

Although carbon tetrachloride ($CCl_4$) hepatotoxicity is found less frequently in clinical practice, it still remains difficult to treat. Various chemical compounds have been tried in an attempt to limit the hepatotoxicity, but with limited success (1, 2). Several studies in Europe have suggested that hyperbaric oxygenation helps to limit the liver injury caused by $CCl_4$ (3–7). Unfortunately, these studies are limited in their clinical applicability because of the extreme oxygen exposures given the experimental animals, an intraperitoneal dosing method that is not seen in humans, and nonstandard hepatotoxicity models. None of these studies varied the interval between dosing and treatment, and all of them reported a beneficial effect of hyperbaric oxygenation (HBO) in spite of study design limitations. The protection of hepatocytes specifically by HBO has been demonstrated recently (8). The clinical objective is survival of

the intoxicated patient. Several case reports suggest that HBO is effective for survival, even when given hours after ingestion (9–11).

The usual human route of $CCl_4$ poisoning is intragastric. Obviously, treatment must begin at some time after ingestion. The time between ingestion and treatment should be varied. Ideally, any treatment plan for experimental animals should be nontoxic for humans. In this study, an $LD_{50}$ dose of $CCl_4$ was given intragastrically, and a standard therapeutic table was given for treatment. This study evaluates the use of HBO in a more clinically similar intoxication and treatment scenario.

## Materials and Methods

Adult, female Wistar rats (Charles River) with weights between 140 and 280 g were divided into 4 groups. Three groups were given carbon tetrachloride intragastrically at the dose of 0.5 ml/100 g of body weight, and a fourth group was given a dose containing 0.3 ml olive oil. Immediately after dosing, these rats were randomized into groups A, B, or C. Group A ($n = 42$) was treated with HBO, treatments beginning within 1 h. Hyperbaric oxygenation schedule was at 2.8 ATA (60 fsw) for 90 min on 100% $O_2$, twice daily for a total of 6 treatments. Group B ($n = 59$) was treated like group A except that the first dive began 4 h after $CCl_4$ dosing. Group C rats ($n = 42$) were not given hyperbaric oxygen treatments. Group D ($n = 12$), the fourth group, were given intragastric olive oil and water and treated with hyperbaric oxygen on the same schedule as groups A and B.

The rats were not anesthetized during this portion of the study. Rats which were given improper doses or died during handling were removed from the study.

Survival rates were compared for significance by chi-squared analysis. In this study, rats were allowed free access to food and water except during hyperbaric treatments.

## Results

Animals placed in the hyperbaric oxygen environment after being given olive oil and water were all alive and healthy after 4 wk of observation. Group A rats had a 76% survival rate at 72 h, which was significantly better ($P < 0.05$) than the 41% rate of group B or the 33% rate of group C (Fig. 1). Rats treated after a 4-h delay had a higher survival rate, but this was not statistically significant ($P > 0.05$). None of the groups had additional mortality beyond 72 h, when followed 3 wk later.

Gross morphology and histologic examinations of the livers of representative animals were done, and have been described elsewhere (8). No attempt was made to identify renal or pulmonary toxicity in this model because $CCl_4$ is almost totally cleared by the liver when given in this manner (12).

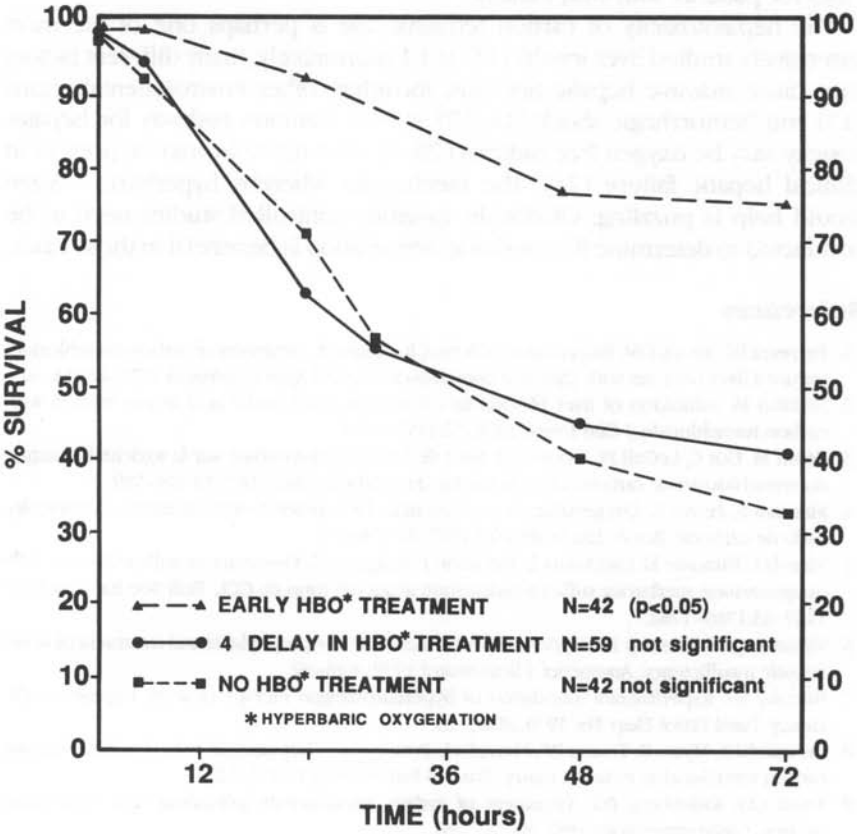


Fig. 1—Survival in rats poisoned with $CCl_4$.

## Discussion

This study demonstrates clearly an improvement in survival in rats treated with HBO, if given in less than an hour after intoxication. Although a trend toward increased survival is noted for treatment begun at 4 h, this is not statistically significant. The few human cases reported suggested beneficial effects if treatment is begun much later than 4 h (9–11). In these cases, other factors may have affected absorption, and the dose taken is not well established.

It is also clear that early treatment is better than delayed treatment. Although the treatment schedule used in this study is easily applicable to humans, we have not established what the optimum dive depth should be, or indeed if only one dive suffices. Sufficient animal data and clinical experience exist to state that HBO for acute $CCl_4$ hepatotoxicity is effective. The treatment by HBO

at doses recommended here is safe for humans. Therefore, we recommend HBO for patients with $CCl_4$ toxicity.

The hepatotoxicity of carbon tetrachloride is perhaps one of the most extensively studied liver insults (13–16). Unfortunately, many different factors may cause massive hepatic necrosis, including other environmental toxins (17) and hemorrhagic shock (18, 19). A final common pathway for hepatotoxicity may be oxygen free radicals (20–23), but tissue hypoxia is present in clinical hepatic failure (24). The mechanism whereby hyperbaric oxygen would help is puzzling. Obviously, carefully controlled studies need to be conducted to determine if hyperbaric oxygenation is beneficial in those cases.

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