Short Communication

Annals of Clinical Trials and Vaccines Research

Diethyl nitrosamine-Initiated and Phenobarbital-Promoted Mice Tumor Model Liver Carcinogenesis is Prevented by Bicyclol, a Novel Antihepatitis Drug

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Received: 01-Feb-2023, Manuscript No. ACTVR-23-88008; **Editor assigned:** 04-Feb-2023, PreQC No. ACTVR-23-88008(PQ); **Reviewed:** 18-Feb-2023, QC No. ACTVR-23-88008; **Revised:** 25-Feb-2023, Manuscript No. ACTVR-23-88008(R); **Published:** 28-Feb-2023; DOI: 10.37532/ACTVR.2023.13(1).11-13

Abstract

Bicyclol, an anti-hepatitis drug, has been shown by Chinese researchers to prevent the malignant transformation of WB-F344 rat liver epithelial cells caused by 3-methylcholanthrene and 12-O-tetradecanoylphorbol-13-acetate. This work provides further evidence of its efficacy as a chemo preventive agent in experimental mice with liver cancer that was induced by diethylnitrosamine (DEN) and accelerated by phenobarbital (PB). The liver tissue and serum were gathered. In the two-stage mouse model of hepatocarcinogenesis, bicyclol oral treatment (100, 200 mg/kg) before DEN injection greatly reduced the formation of hepatocellular foci, nodules, or cancer. Hepatocellular carcinoma (HCC) and hepatoma were not seen in the mice pre-treated with bicyclol (200 mg/kg) at week 20, however the mice pre-treated with DEN/PB developed 33.3% HCC and 55.6% hematoma. Additionally, bicyclol slowed the loss of body weight and lowered the expression of AFP and proliferating cell nuclear antigen in the liver tissue. The control and bicyclol-treated animals (200 mg/kg) revealed no HCC and hepatoma formation at the time of termination, whereas DEN/PB-induced mice had 100% hepatoma and 50% HCC, according to the findings of this study. These findings further demonstrate the chemo preventive potential of bicyclol for carcinogen-induced liver carcinogenesis.

Keywords: Novel drug • Anti-hepatitis • Hepatocellular carcinoma • Liver tissue • Cancer

Introduction

More than 500,000 new cases of hepatocellular carcinoma (HCC), which accounts for 90% of all human liver tumours, are recorded each year. Previously mostly diagnosed in Asia, this cancer is now increasingly being detected in both Europe and North America. Environmental variables are causally linked to the development of HCC, including chemical carcinogen exposure and hepatitis virus infections. The cause of about 80% of human HCC cases is infection. HCC is 100-400 times more likely to develop in chronic hepatitis B virus (HBV) carriers than in nanocarriers. Following HBV, Hepatitis C virus (HCV) is the second most frequent cause of HCC. At the moment, HCC accounts for more than 4% of all cancer cases worldwide and results in at least 315,000 fatalities annually. Although early HCC can be treated with surgical resection, most HCC patients do not receive a timely diagnosis since many HCC cases are asymptomatic [1].

Chemoprevention, which is anticipated to obstruct the start, promotes, or progression of carcinogenesis, is a successful method of cancer control. In general, both chronic HBV and HCV require long-term therapy. In addition to improving abnormal liver function and inhibiting the reproduction of the hepatitis virus, an Antihepatitis medicine might be deemed to be of substantial clinical value if it prevents or suppresses the growth of hepatocarcinogenesis.

A novel anti-hepatitis medicine called bicyclol (4,4′-dimethoxy-2,3,2′,3′-dimethylene-dioxy-

6-hydroxymethyl-6′-carbonyl-biphenyl) was created by Chinese researchers. Bicyclol has been shown in clinical trials to be beneficial in treating chronic hepatitis B patients' impaired liver function and in preventing HBV replication. Pharmacologically, bicyclol demonstrates anti-fibrotic effects on CCl4-induced liver fibrosis in rats and mice, a protective action against liver damage caused by hepatotoxins in mice and rats, and anti-hepatitis. Additionally, bicyclol increased the detoxifying metabolism of AFB1 in the rat liver, which reduced AFB1 hepatotoxicity in rats and caused differentiation of human hepatocarcinoma cells (HepG2 and Bel-7402 cells). Bicyclol significantly inhibited the malignant transformation of WB-F344 rat liver epithelial cells caused by 3-methylcholanthrene (3MC) and 12-O-tetradecanoylphorbol-13-acetate (TPA), according to the most recent study. These findings raise the potential that bicyclol inhibits liver carcinogenesis through chemoprevention [2].

Materials and Method

The Beijing Union Pharmaceutical Plant graciously donated 99% pure white crystalline bicyclol, which was suspended in 0.5% sodium carboxymethylcellulose (Na CMC) for in vivo application. From Sigma Chemical Co., we obtained DEN, PB, dithiothreitol (DTT), phenylmethanesulfonyl fluoride (PMSF), aprotinin, leupeptin, N, N-methylene-bis-acrylamide, and acrylamide (St. Louis, MO, USA). Beihuakangtai Chemical Reagent Co., Ltd. provided the kits for measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) (Beijing, China). Shanghai Shenxiong Biotech Company provided the ELISA kit for measuring -fetal protein (AFP) (Shanghai, China). The Beijing Chemical Agents Company provided all additional chemicals, which were of analytical quality (Beijing, China) [3].

Inflammation is significantly linked to the development of cancer, according to a number of earlier researches. Tumor formation is influenced by inflammation, which is self-regulatory. Reactive oxygen species (ROS) and reactive nitrogen intermediates (RNIs), two inflammatory inducers that in turn promote mutations, are released as a result of it. The release of cytokines including tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin 1 beta (IL-1 beta) from white blood cells is thought to be activated by inflammation. These cytokines encourage premalignant and tumour cells to proliferate, invade, and develop blood vessels [4].

Four groups of 15 mice each, housed five to a cage, were formed from the experimental mice at random. A single intraperitoneal injection of DEN at a dose of 100 mg/kg body weight in normal saline resulted in the development of liver tumours in all groups with the exception of the control group. The mice were maintained on 0.05% PB-containing water after a one-week treatment-free break, while the control group was maintained on PB-free water for 19 weeks. The animals were pretreated with bicyclol (100, 200 mg/kg) given orally two days prior to DEN injection in order to assess the prophylactic effects of the drug. Following DEN injection, bicyclol was given for 20 weeks once daily throughout six days of the week [5].

Discussion

In order to ascertain whether bicyclol has a chemo preventive impact on hepatocarcinogenesis in vivo, we adopted the DEN/PB two-stage procedure in this investigation. Only male mice were employed and examined in our investigations because female mice are known to be resistant to hepatocarcinogenesis in experimental mouse models, including those utilising chemical carcinogenesis. In this investigation, we discovered that oral bicyclol pre-treatment (100, 200 mg/kg) significantly reduced the number of liver tumour nodules per liver [6]. The model control group at week 20 developed 33.3% HCC and 55.6% hematoma, per the histological diagnosis. However, the mice who had previously received 200 mg/kg of bicyclol did not develop hematomas or HCC in their livers. There was still no tumour formation in the 200 mg/kg bicyclol group ten weeks after the promoter and bicyclol were stopped being administered, whereas there was 100% hematoma and 50% HCC in the DEN/PB model group. These findings further demonstrated that bicyclol had a lasting preventative impact on hepatocarcinogenesis brought on by carcinogens [7].

The deterioration or breakdown of the cell membrane, which results in the release of transaminases and ALP from the liver tissue, might cause liver damage brought on by DEN and PB. Transaminases and ALP levels in the serum are markers of liver function, and their elevated levels signify liver impairment. The study of these marker enzymes is important for cancer chemoprevention and treatment. Hepatocellular injury is frequently blamed for the elevation of ALT levels, which are typically accompanied by an increase in AST levels. ALP level growth reflects a pathogenic change in biliary flow [8]. Pre-treatment with bicyclol in the current study reduced the elevated ALT and ALP activities brought on by DEN/PB, but only bicyclol-treated mice (100 mg/kg) demonstrated statistically significant results when compared to the DEN/PB group. Serum AST levels in the model and bicyclol-treated groups did not change. It has been demonstrated that bicyclol promotes liver parenchymal cell regeneration, preserves membrane integrity, and reduces enzyme leakage (results in). The findings presented in this research further imply that the primary mechanism by which bicyclol exerts its chemo preventive effects is not its protective effect on cell membranes [9].

The current study showed that chronic PB application, which was previously reported to only induce HCAs but not HCCs, caused the progression of hepatocellular adenomas into carcinomas in homozygous Ogg1; PB is a non genotoxic carcinogen that is not mutagenic according to the Ames test. Furthermore, it has been proposed that PB has a dual role in the development of liver tumours by encouraging the growth of HCA while suppressing the growth of HCC. As a result, the Ogg1 gene's mutation and inactivation were linked to the acceleration of mouse hepatocarcinogenesis. Ogg1 and other DNA repair genes have previously been linked to inactivating mutations in human malignancies of the liver, ovary, kidney, breast, and colon [10].

Conclusion

In conclusion, the results of the current in vivo investigation support the findings of our in vitro experiments, which showed that bicyclol inhibits the malignant transformation of WB-F344 cells brought on by 3MC and TPA. When taken as a whole, bicyclol has the ability to potentially inhibit the liver carcinogenesis brought on by carcinogens. This is an intriguing finding, and more research is required to see whether bicyclol can stop the liver cancer development brought on by chronic viral hepatitis. To assert bicyclol as a viable chemo preventive medication against liver cancer brought on by carcinogens, further research is required to identify further molecular pathways behind its chemo preventive activity.

Conflict of Interest

None

Acknowledgement

None

References

1. Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. *Journal of Herpetology* 41,864-880 (2004).
2. Mineno J, Okamoto S, Ando T *et al*. The expression profile of microRNAs in mouse embryos. *Nucleic Acids Research*. 34, 1765-1771 (2006).
3. Yamagata K, Fujiyama S, Ito S *et al*. Maturation of microRNA is hormonally regulated by a nuclear receptor. *Molecular Cell.* 36,340-347 (2009).
4. Liu WH, Yeh SH, Chen PJ *et al.* Role of microRNAs in hepatitis B virus replication and pathogenesis. *Biochim Biophys Acta*. 1809, 678-685 (2011).
5. Hu H, Wang CJ, Gong L *et al.* (2007) Expression and significance of apoptosis inhibitor living in hepatocellular carcinoma. *Chinese Journal of Hepatobiliary Surgery*. 13,348 (2007).
6. Sarma DS, Rao PM, Rajalakshmi S *et al*. Liver tumour promotion by chemicals: models and mechanisms. Cancer Surveys. 5, 781-798 (1986).
7. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib: a syndrome. *N Engl J Med*. 262, 908-12 (1960).
8. White JC. Multiple benign cystic epitheliomas. *J Cutan Genitourin Dis*. 12, 477-84 (1894).
9. Silverman MK, Kopf AW, Grin CM *et al.* Recurrence rates of treated basal cell carcinomas. *J Dermatol Surg Oncol*. 18, 549-54 (1992).
10. Thissen MR, Neumann HA, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. *Arch Dermatol*. 135, 1177-83 (1999).