Optical microscopic analysis of liver of sildenafil citrate treated albino rats

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Abstract
Background: Sildenafil citrate, an oral therapy for Erectile dysfunction (ED), is a selective inhibitor of cGMP - specific phosphodiesterase type 5 (PDE5). Our aim was to study the drug induced histological changes in the liver of Albino rats treated with Sildenafil citrate.

Materials and methods: 48 healthy male Wistar Albino rats were chosen and divided into eight groups, each consisting of six animals in it. Group S_1 served as the control and was treated with conductivity water (@ 1µg /g body wt.). Groups S_2, S_3, S_4 and S_5 served as the experimental groups, being treated with a single dosage of the experimental drug (i.e.) Sildenafil citrate (@ 1µg /g body weight) and were sacrificed after 1hr, 2½ hrs, 4 hrs, and 24 hrs. Groups S_6, S_7 and S_8 were treated with a single dosage of the drug for 15, 30 and 45 days and were sacrificed after 4hours of the last dosage. A vertical ventral midline incision was made in the abdominal wall to collect the liver samples.

Result: Liver damaging effects were observed, more in the case of animals with prolonged exposure to Sildenafil citrate.

Conclusion: Sildenafil citrate, if administered to Albino rats on long- term basis, will have adverse effects on the structure and vital metabolic functions of the Liver.

Introduction:
Erectile dysfunction (ED) is a common and multifactorial disease that strongly impairs the quality of life in many. It provides a paradoxical situation to both the patients and physicians. Approximately about 52% of the surveyed men aged between 40 and 70 years suffer from some degree of ED. Though Sildenafil citrate, a selective inhibitor of cGMP- Specific Phosphodiesterase type 5 (PDE5), has been reported to induce some mild side effects, is an effective oral therapy for ED. The mode of action of the drug has been elaborately studied by various researchers. Since Sildenafil citrate has been the drug of choice even among common man, it is worth studying the detrimental impacts on the structure and functions of Liver of Albino rats.

Materials and methods:
Sildenafil citrate (CAVERTA from India) purchased from the market has been used as the drug to carry out the present investigation. The experimental animals were administered with the above drug at the rate of 1µg/ g body wt. of the animal, using conductivity water as the solvent. 48 healthy male Wistar Albino rats, weighing about 250-300 gm, were obtained from Animal House, Raja Muthiah Medical College, Annamalai University, Tamil Nadu. The experimental protocol was approved by the Institutional Animal Ethical Committee following the guidelines of CPCSEA (Committee for the purpose of Control and
Supervision of Experiments on Animals for Laboratory Animal Facility).

The animals were acclimatized for a period of seven days before starting the study. Standard environmental conditions such as temperature (24±2°C), humidity (60-70%) and 12 hours of light/dark cycle was monitored. Food and water were allowed ad libitum under strict hygienic conditions. For the present study, the chosen animals have been divided into eight groups, each consisting of six animals in it. Here S_1 served as the control while the rest of the seven groups, namely S_2, S_3, S_4, S_5, S_6, S_7 and S_8 served as the experimental ones. The control animals were treated with a single dosage of conductivity water while the experimental groups S_2, S_3, S_4 and S_5 were treated with a single dosage of the drug and sacrificed after 1 hr, 2 ½ hrs, 4 hrs and 24 hrs of the last dosage. The experimental animals belonging to the groups S_6, S_7 and S_8 were treated with a single dosage of the drug daily for 15, 30 and 45 days respectively and sacrificed after 4 hours of the last dosage.

Chloroform anaesthesia was used and a vertical ventral midline incision was made in the abdominal wall to collect the liver samples. The organs were preserved in 10% formalin, processed and stained with Eosin and Hematoxylin stain.

**Result:**

The outcome of the present investigation clearly points out the following observations:

The section of Liver of Control (S_1) animals indicates the normal architecture of Liver of Albino rats [Figure 1]. However, in the case of S_2 (1 hr), S_3 (2 ½ hrs) and S_4 (4 hrs) groups; there occurred a mild congestion of the central vein and dilation of the hepatic artery in the portal triad. The section of Liver of S_4 (4 hrs) group of animals, shows clearly the increased dilation of hepatic artery accompanied by the increased congestion of the central vein. As the animals tried to regain the normal conditions, the Liver samples of S_5 (24 hrs) group, indicate the normal pattern of Hepatic lobule and central vein.

The Liver samples of S_6 (15 days) and S_7 (30 days) group of animals quite obviously exhibits marked dilation of the sinusoidal spaces and congestion of central vein besides the occurrence of crenated nucleus and vacuolated cells [Figure 2 and Figure 3].

In the case of S_8 (45 days) sample the histo-architecture of the hepatic lobule has been found to be disturbed prominently. Besides the congestion of the central vein and the disappearance of the Hepatic cells, there occurred an increased number of vacuolated cells as well as necrotic cells [Figure 4].

**Discussion:**

Long-term Caverta treatment of Albino rats leads to well marked changes in Liver such as distorted histo-architecture of the Hepatic lobule, most prominent central vein congestion, widened sinusoidal spaces, disappearance of Hepatic cells towards the central vein, increased number of vacuolated cells and necrotic cells. Similar symptoms were observed in the case of Chickens fed with Giberellic acid, Albino rats treated with Gibberellin A₃, Albino mice administered with chemicals such as Zineb and Maenab and mouse treated with brodifacum.

Occurrence of vacuolated cells is one of the important primary responses to all forms of cell injury. Increase in the number of vacuolated cells due to the long-term drug exposure, may be attributed to the increases permeability of cell membrane leading to an increase of intracellular water ultimately resulting in cytoplasmic vacuolization. As Liver is responsible for detoxification and excretion of xenobiotics, it is the first organ to be exposed to drug hazards via portal circulation. Therefore, the cell infiltration and the
increased number of necrotic cells in the Liver may cause a decrease in the detoxification capacity of Liver. 

**Conclusion:**

It is quite obvious, from the present study that Sildenafil citrate (CAVERTA), if administered for a long-term, will produce adverse effect on the structure and vital functions of Liver of Albino rats.

**Figure 1:** Section of Liver of Albino rats [0 hr] showing (1) Hepatocytes, (2) Normal Sinusoidal space and (3) Portal triad

**Figure 2:** Section of Liver of drug-treated Albino rats [15 days] showing (1) Marked dilation and congestion of Sinusoidal Space, (2) Normal Hepatocytes and (3) Vacuolated Hepatocytes

**Figure 3:** Section of Liver of drug-treated Albino rats [30 days] showing (1) Vacuolated cells and (2) prominent dilation and congestion of sinusoidal space

**Figure 4:** Section of Liver of drug-treated Albino rats [45 days] showing (1) Vacuolated cells and (2) Necrotic cells

**References:**


