Toxicologic pathology study of diclofinac in rats by oral intubation


Abstract

Aim of the study: This study aimed to evaluate the toxic effect of the diclofinac since this drug is one of the most common non steroidal anti inflammatory drugs which is widely used as a pain relief for several pathological cases.

Materials and methods: Rats were kept in the animals house for two weeks to get acclimatization then treated with 25 mg/kg/day and 50 mg/kg/day as intermediate and high dose respectively by oral intubation daily for three months to show the toxic effect of the drug.

Results: Heart showed vacoulation of myocardial muscle cells, liver showed degenerative changes and periportal fibrosis.But the more severe toxicological pathological changes were in the kidney as dilated bowman's space with fluid distention in glomeruli, degenerate/ necrotic cortical mineralized tubules and changes in medullary collecting ducts. The above changes were more severe in high dose than in intermediate dose which was considered as dose related changes.

Conclusions: diclofinac has a toxic effect on several organs in the body if it is use for long period even within the normal therapeutic doses.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), which are often used for the relief of non-specific fever, continue to be important for the palliation of pain. They are the most frequently used medications for the treatment of a variety of common chronic and acute inflammatory conditions, and continue to be important for the palliation of pain and in decreasing inflammation and fever (14).Diclofenac is one of the most commonly used non-steroidal anti-inflammatory drug which is used for the treatment of arthritis, soft tissue injuries (15), dysmenorrhoea and menorrhagia (3), but there are clinical reports of severe hepatic reactions associated with their use (6, 12, 10). In addition to this, there are indications that borderline increases in serum transaminases occur in approximately 15% of patients taking the drug regularly, which suggest that diclofenac associated hepatotoxicity might be more common than previously recognized (7). Another researches reported that the drug have a toxic effect on other organs like brain, kidneys, spleen, muscle... etc(7).

Materials and Methods

Eighteen Rattus norvegicus rats were selected for this experiment and housed in normal photoperiod regime in the laboratory for two weeks to give a chance for acclimatization and for anti-bacterial and anti-parasitic drug administration. Animals were divided in to three groups, control group, intermediate dose treated group and high dose treated group, each group consist of six animals. Animals of the control group were given normal physiological saline, the group of intermediate dose treated with diclofinac sodium orally 25 mg/kg daily for three months, while the group of high dose treated with 50 mg/kg diclofinac sodium in the same way. The animals of all groups were killed in the end of the experiment and the organs (liver, kidney and heart) fixed in 10% formalin and sent to laboratory for sectioning.

Results

The liver, kidney and heart of the control group were showed normal histological structure.In the group of intermediate dose the liver showed congestion, minimal fibrosis in the periportal area and degenerative changes in...
the hepatocytes, minimal fibrosis with infiltration of inflammatory cells, the kidney showed degeneration in the renal tubular epithelium in the cortical region and fluid accumulation in the bawmans space which lead to dilation of the bawmans capsule and pressure atrophy of the glomeruli, while in the heart there were moderate vacoulation in the myocardial muscle cells. In the group of high dose the liver revealed vacuolation of hepatocytes with congestion of the portal vein and marked fibrosis in the periportal area and subcapsular region, in the kidney there were degeneration of medulary renal tubular epithelium and marked calcification of the cortical tubules with glomerular necrosis, in the heart there were severe vacoulation in the myocardial muscle fibers. Most of the rats of high dose group died early during the study because of the toxicity of the tested compounded.

Fig (1) showed normal histology of the liver of the control group
H&E 125x
Fig (2) shows normal histology of the kidney  H&E  125x

Fig (3) shows normal histology of the myocardial muscle cells  H&E 125x
Fig (4) liver of intermediate group, shows A) congestion B) Minimal fibrosis with infiltration of inflammatory cells C) vacoulation of hepatocytes. H&E  500x

Fig (5) kidney of intermediate group, A) degeneration of renal tubular epithelium B) Glomerular vacoulation (specially in the mesengial cells). H&E  125x
Fig (6) Kidney of intermediate group, dialation of bawmans capsul, glomerular atrophy, and fluid accumulation. H&E 500x

Fig (7) heart of intermediate group, vaccoulation of myocardial muscle fibers. H&E 500x
Fig (8) liver of high dose group, congestion of the portal vein with fibrosis of periportal area. H&E  500x

Fig (9) liver of high dose group, fibrosis with proliferation of bile duct. H&E  500x
Fig (10) kidney of high dose group, degeneration of renal tubular epithelium in the medullar region. H&E 500x

Fig (11) kidney of high dose group, mineralization of renal cortical tubules. H&E 500x
Discussion

The most histopathological changes which occurs in the liver belong to the hepatotoxic effect of the diclofenac sodium which is due to that the diclofenac like other non-steroidal anti-inflammatory drugs. The clinical use of diclofenac has been associated with a small significant incidence of hepatotoxicity ranging from mild, asymptomatic, reversible increases in liver function test to jaundice and hepatitis, this agreed with (1), which reported that the dilofinac sodium decrease the hepatic ATP content and induces hepatocytes apoptosis, also some investigators showed that the diclofenac cause negative effect on development and differentiation of hepatocytes (2), while others showed that the toxic effect of the
drug belong to the drug-induced mitochondrial impairment, together with a futile consumption of NADPH (1). The degenerative and necrotic changes which noticed in the kidneys also indicate that diclofenac sodium has nephrotoxic effect this agreed with some investigators whom dosed this drug to the birds and showed the nephrotoxicity of the drug (9). Some investigators showed that the mechanism of action of diclofenac in mammalian species is based on the inhibition of cyclooxygenases (COX) and subsequent inhibition of prostaglandin synthesis. Prostaglandins, however, not only play a role in mediating pain, but are involved in the regulation of blood circulation, vascular permeability and especially kidney function, including ion retention (12). Some of the adverse side effects associated with diclofenac therapy, such as nephropathy, are thought to be directly related to inhibition of prostaglandin synthesis (13). However, other effects, including formation of protein adducts and oxidative damage, have also been suggested as causative for the adverse symptoms, e.g. gastrointestinal ulceration, nephropathy and idiosyncratic hepatotoxicity (5). The effect of the drug on the blood circulation vascular permeability and ion retention interpreter the fluid retention and the degenerative changes which occur in the myocardial muscle fibers.

References


دراسة سمية مرضية لتاثير عقار الديكلوفيناك في الجرذان المختبرية بالتجريع

الخلاصة

في دراسة اجريت لتقييم التأثير السمي للمضادات لعلاج الديكلوفيناك في الجرذان المختبرية، حيث عولمت المجموعة الأولى ب 25 ملغ/ كغم كجرعة متوسطة أما المجموعة الثانية فقد عولمت ب 50 ملغ/ كغم كجرعة عالية للعقار يومياً ولعدة ثلاثة اشهر بالتجريع عن طريق الفم. أظهرت تغيرات صورية في القلب والكبد، أظهرت التغييرات في خلايا الرئة وضعاف الشريان الدموي في تكبيز. ولكن التغييرات المرضية الشديدة كانت في الكبد حيث أظهرت تورم في محفظة دم الكبد، فيما كانت تغيرات تكبيزية في كل من الكبد والكبد الكثيف، وعالية في منطقة القلب والكبد. هذا بالإضافة إلى التضخم الذي وجد في منطقة القلب والكبد. هذه التغييرات أظهرت تورم في محفظة دم الكبد، فيما كانت تغيرات تكبيزية في كل من الكبد والكبد، وعالية في منطقة القلب والكبد. لهذه التغيرات الشديدة في المجموعة المختبرية، مما هي عليه في الجرعة المتوسطة حيث كانت التغييرات التنكسية في عضلة القلب والكبد. ودكّر الله تأثيرات التغذية الشديدة بالإضافة إلى التغذية التي ظهرت في المجموعة المختبرية بالجرعة المتوسطة من العقار.