Comparative toxicity study of meloxicam and etodolac (cox-2slective Inhibitors)

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SummarySummaryNon steroidal anti-inflammatory drugs are used extensively in clinical medicine as analgesic, antipyretic, and anti-inflammatory drugs and account for nearly 5% of all prescribed medications. In spite of their therapeutic utility, however, these drugs have significant adverse effects, a circumstance that may limit their use. Nephrotoxicity and hepatotoxicity are the only major adverse drug reactions associated with NSAIDs.These drugs act substantially by inhibiting both COX-1 and COX-2 isoenzymes, which are responsible for PG synthesis. Recently, the introduction of the selective COX-2 inhibitors, have been associated with a decreased incidence of GI side effects and increased GI tolerability compared to the traditional NSAIDs. Many substances with an anti-inflammatory action influence DNA metabolism and can thus give rise to later damage in the genetic material. Since NSAIDs are usually administered over a long periods, appraisal of mutagenic risk of these drugs would appear to be especially important. The majority of NSAIDs causes apoptosis. Apoptosis is likely to play an extremely important role in the pathogenesis of NSAIDs-induced GI ulceration and is also likely to be involved in regression of cancer colon and other neoplasms, which is one of the most important therapeutic uses of these drugs nowadays.This study was carried out to evaluate and compare the possible toxic effects of selective COX-2 inhibitors; meloxicam and etodolac as regards their genotoxic effects on the bone marrow cells, biochemical, histopathological and apoptotic changes in liver and kidneys, in normal adult albino rats. The reversibility of these effects is one objective of the study. The study was carried out on 150 Albino rats of the female sex, their body weight ranging from 120 — 150gm.199SummaryAcute toxicity studyThe study was carried out on 60 albino rats of the female sex and were divided into 3 groups; Group I (Control group), Group II (Etodolac group), and Group Ill (Meloxicam group).Short—term chronic toxicity studyThe study was carried out on 90 albino rats of the female sex and were divided into 3 groups; Group I (Control group), Group 11 (Etodolac group), and Group III (Meloxicam group). Each group consisted of 30 rats. These were examined after 2, 4 weeks of the administration of daily oral doses of the tenth of LD50 of the tested drugs and 4 weeks after stopping drug administration (follow up).The results of the present study can be summarized in the following:1-Chromosomal StudyAcute toxicity studyResults of acute toxicity study revealed that both etodolac and meloxicam produced very highly significant increase in the percentage of total number of structural anomalies (TSA) as regard (total with gap &total without gap

structural abnormalities) and in the percentage of fragments and deletions while produced a non significant increase in the percentage of other tested parameters when compared with those of control group.Chronic toxicity studyAt the end of the 2nd week, etodolac produced a very highly significant increase in the percentage of CF, total with gap as well as total without gap structural anomalies, a highly significant increase in the percentage of CD and a significant increase in the percentage of PP; while produced a non significant increase in the percentage of other tested parameters when compared with those of control group. Meloxicam200Summaryproduced a very highly significant increase in the percentage of CF, total with gap as well as total without gap structural anomalies, and a highly significant increase in the percentage of CD while produced a non significant increase in the percentage of other tested parameters when compared with those of control group.At the end of the 4’h week, etodolac induced a very highly significant increase in the percentage of CF, total with gap and total without gap, a significant increase in the percentage of CD and CS and a non significant increase in the percentage of other tested parameters when compared with those of control group. Meloxicam induced a very highly significant increase in the percentage of CF, total with gap and total without gap, a significant increase in the percentage of CD and non significant increase increase in the percentage of other tested parameters when compared with those of control group. •At the end of the follow up period, statistical analysis of these chromosomal anomalies showed that both etodolac and meloxicam induced a highly significant increase in the percentage of total number of structural anomalies as regard total with gap and total without gap, meloxicam induced a significant increase in the percentage of CS; while both drugs induced a non significant increase in all other tested parameters as compared with those in control rats indicating that these effects were more or less reversible.2-HepatotoxicityAcute toxicity studyAt the end of acute toxicity study etodolac treated rats showed a very highly significant increase in serum AST, and ALP, a significant increase in ALT, and BIL when compared with those in control rats, while meloxicam treated rats showed a very highly significant increase in serum ALT, AST, and ALP and a highly significant increase in BIL when compared with those in control rats.201SummaryHistopathological examination of all treated rats’ livers after theacute toxicity study showed various pathological changes, which nearly confirmed the previously mentioned biochemical changes in LFTs. The lesions were in the form of dilatation and congestion of the central vein and sinusoids, dilatation of portal venules and lymphocytic infiltration of portal tract, hyDROPic degeneration of hepatocytes with obliteration of some sinusoids, and fatty changes appearing as intracytoplasmic microvesicles. Hepatic focal necrosis and bile ductular proliferation were also shown.Chronic toxicity studyAt the end of the 2nd week, etodolac and meloxicam treated rats experienced a very highly significant increase in almost all tested parameters of LFTs when compared with those in control rats. The previously mentioned changes in LFTs became less pronounced at the end of the 4th week of each drug administration.Histopathological examination of all treated rats’ livers after the short—term chronic toxicity study showed various pathological changes, which nearly confirmed the previously mentioned biochemical changes in LFTs. The

lesions were in the form of dilatation and congestion of the central vein and sinusoids, dilatation of portal venules and lymphocytic infiltration of portal tract, hyDROPic degeneration of hepatocytes with obliteration of some sinusoids, and fatty changes appearing as intracytoplasmic microvesicles. Hepatic focal necrosis and bile ductular proliferation.Comparative studies showed that meloxicam was more hepatotoxic than etodolac.3-NephrotoxicityAcute toxicity studyAt the end of the acute toxicity study etodolac treated rats showed a significant increase in BUN, but a non significant increase in plasma Cre202ISummary when compared to control group while meloxicam treated rats showed a very highly significant increase in BUN, but a non significant increase in plasma Cre when compared tc control group.Histopathological examination of all treated rats' kidneys after the acute toxicity study showed different pathological changes, which nearly confirmed the previously mentioned biochemical changes in KFTs. The lesions were int the form of dilatation and congestion of intertubular vessels, interstitial hemorrhage, mild cellular oedema, chronic lymphoplasma infiltration, glomerular hemorrhage, inflammatory cellular infiltration mostly perivascular, cloudy swelling, hyDROPic changes, and focal hyaline cast formation.Chronic toxicity studyAt the end of the 2nd week, etodolac treated rats showed a very highly significant increase in KFTs when compared with those of control rats. Meloxicam treated rats showed a very highly significant increase in plasma Cre but a non significant increase in BUN when compared with those in control rt.ts. The previously mentioned changes in KFTs became less pronounced at the end of the 4th week of each drug administration.Histopathological examination of all treated rats' kidneys after the short—term chronic toxicity study showed different pathological changes, which nearly confirmed the previously mentioned biochemical changes in KFTs. The lesions were in the form of dilatation and congestion of intertubular vessels, interstitial hemorrhage, mild cellular oedema, chronic lymphoplasma infiltration, glomerular hemorrhage, inflammatory cellular infiltration mostly perivascular, cloudy swelling, hyDROPic changes, and focal hyaline cast formation.Comparative studies showed that the nephrotoxicity of meloxicam (concerning biochemical as well as histopathological changes) was more or less similar to that of etodolac.203Summary4-Follow up studyFollow up of etodolac and meloxicam toxicity revealed that both drugs induced hepatotoxicity, nephrotoxicity, and genotoxic changes which were more or less reversible on follow up for 4 weeks.5-Apoptotic effect (DNA fragmentation) HepatotoxicityAcute toxicity studyThere is a significant lower mean value of maximal optical density of acute meloxicam toxicity group than controls at intact DNA. While there is a significant higher mean value of maximal optical density of acute etodolac and meloxicam toxicity group than controls at 600, and a significant higher mean value of maximal optical density of acute meloxicam toxicity group than controls at 400 and 200 base pair.Chronic toxicity studyAt the end of the 2nd week, etodolac and meloxicam treated rats experienced the highest apoptotic changes when compared with those in control rats. The previously mentioned changes became less pronounced at the end of the 4111 week of each drug administration.Comparative studies showed that meloxicam induced a significant higher mean value of maximal optical density when compared to etodolac.However, at the end of the follow up period, both drugs

showed a non significant mean value of maximal optical density indicating that these effects of apoptotic changes were reversible.NephrotoxicityAcute toxicity studyThere is a significant lower mean value of maximal optical density of acute etodolac and meloxicam toxicity group than controls at intact DNA.204SummaryWhile there is a significant higher mean value of maximal optical density of acute etodolac and meloxicam toxicity group than controls at 600, 400 and 200 base pair.Chronic toxicity studyAt the end of the 2nd week, etodolac and meloxicam treated rats experienced the highest apoptotic changes when compared with those in control rats. The previously mentioned changes became less pronounced at the end of the 4th week of each drug administration.Concerning the 2 weeks and the follow up studies meloxicam induced a significant higher mean value of maximal optical density when compared to etodolac.At the end of the follow up period, however, both drugs showed a significant mean value of maximal optical density indicating residual apoptotic changes at the renal but not hepatic level.205ConclusionConclusion•from the results of the present study, it can be concluded that acute and short—term chronic toxicity with etodolac and meloxicam can induce genotoxicity, hepatotoxicity and nephrotoxicity.•The toxic effects of both drugs were mote or less reversible.•Meloxicam is slightly more toxic than etodolac as regard hepatotoxicity and nephrotoxicity.•The heptotoxicity and nephrotoxicity of etodolac and meloxicam may decrease by time.•Both etodolac and meloxicam can induce apoptosis in kidney and liver, the apoptotic effects being more pronounced in the kidney and this toxic effect is less reversible in the kidney.