Research Article

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Study the Histopathological Effect Associated with Oral Overdose of Opioid Derivatives - on Liver and Kidney Tissue in Male Rats

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Abstract

The current study aimed to ascertain the impact of acute codeine dose (0.50 and 1 ml/ 250g), on the histolopathological profile of the liver and kidney in male rats. A synthetic antispasmodic substance with comparatively low toxicity is opioid derivatives (Codeine), In present study results found that normal histological structure, except Some minor changes were shown in the control group (antihistamine syrup, which does not contain codeine), while the groups II and III contain overdose treatment of codeine were reveal that the over dose of codeine involved inflammation cells infiltrations in the liver parenchyma, congestion of blood vessel, fatty degeneration, cytoplasmic vacuolation, and pyknotic of hepatocytes nuclei. However, renal damage profiles were seen in the kidneys of treated rats, kidney reveal necrosis, cytoplasmic degeneration of lining of the renal tubules, and enlarged lumen intracellular space. Red blood cells flooded the intertubular gaps and congested the renal blood vessels. conclusion that opioid derivatives (Codeine) poisoning caused renal and hepatocellular damage.

Keywords: Codeine, Liver, Kidney, rats.

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Introduction

The danger of an acute dose of pulmocodin lies in the compounds that make up it, which include codeine. Generally, codeine is a centrally-acting narcotic opioid that has been licensed for use as an antitussive. It is a pharmacological and toxicologically active alkaloid found in the opium poppy. Throughout human history, the opium poppy has been utilized for its hypnotic and therapeutic characteristics, including its analgesic, anti-tussive, and anti-diarrheal effects (1). The Greek word "kodeia" for poppy head is where the name "codeine" came from. Pierre Robiquet isolated codeine later in 1832 in France while extracting morphine (2). Opioids reduce pain perception and strengthen the powerful feeling of pleasure or well-being via interacting with receptors in the spinal cord and brain. Users became more and more drawn to these euphoric and sedative effects, which contributed to the abuse of opioids. (3). The liver's cytochrome p450 enzyme system processes codeine, and the kidneys are responsible for excreting the byproducts. Its biotransformation takes place in the liver, where phase I processes (mainly O- and N-demethylation) and phase II reactions (largely conjugating O- and N-demethylated molecules) are used to produce eleven and twelve metabolites, respectively (4). The severity of the morphological changes caused by intravenous codeine abuse in the liver tissue, they have been shown in a variety of human and animal investigations and consist of vesicular degeneration, lipid alterations, decreased glycogen content in hepatocytes, and vascular abnormalities. (5). Chronic and acute codeine administration can result in a variety of diseases, including respiratory depression due to a direct influence on the heart rate depression and the brain due to vasodilation of the gastrointestinal tract and peripheral arteries (6). Nevertheless, some researchers claimed that the length of time and frequency of medication administration determined how anesthetic, sedative, and narcotic substances affected renal functioning. (7). According to (8), subcutaneous narcotic medications can cause renal tubular dysfunction, subtle hyperglycemia, gradual renal insufficiency, and systemic amyloidosis. The current study investigates and determine the connection between histological alteration in the liver and kidney after repeated administration of an addictive codeine drug to rats as a model to determine the reason for drug users' hepatic and renal damage.

Materials and methods

Test subjects' animals: A total of 15 rats (weighing 250 g) were used in the current stud). All rats were subjected to laboratory settings. The animals were kept in typical household cages that had adequate ventilation, temperature, and lighting (a "12-hour dark-light cycle"). The codeine used in the current study is part of the components of plumcodeine antitussive syrup. Samarra drugs factory – Iraq- SDI) used in this research., each 5 ml contains 12.5 mg of codeine, during our study, (0.50 and 1 ml/250g) codeine dose was given to rats by the gastric tube orally.

Experimental design of research:The experiment was carried out on fifteen of male rats that were divided into three groups (five

animals in each group). Group I (control group) was given antihistamine syroup, it does not contain codeine in its composition, which includes (Glyceryl gluatacolate, chlorpheniramine maleate, and phenylephrine HCL), which is represented by Tussilet cough syrup, does not contain codeine in its composition, Group II administrated codeine orally at a dose amount of 0.5ml/250g/day, two time daily, While the Group III through oral administrated codeine in a dose amount of 1ml /250g/day, two time daily after 30 days, this dosage is comparable to human addictive dosages.

Light microscopy processing: After 30 days of therapy, liver and kidneys were quickly removed after the rats were murdered under diethyl ether anesthesia. For light microscope preparations, specimens were fixed in 10% formalin, then dehydrated in a graded series of ethanol (70%, 85%, 95% and 100%), clearing by xylin encased in paraffin wax and sectioned at 4um thickness. Mallory stain was used to stain slides for histological study. (9).

Results

light microscope results:

Throughout the experiment, there was no fatalities. noticed in either the control or treated groups, group I (control) Sections of liver tissue of control group showed that, semi normal structure of hepatocytes and central veins that were organized in the hepatic cord around blood sinusoids (Fig. 1-A). Histological analysis of the livers of Groups II and III revealed a variety of negative effects on morphology and histopathology, which increased with increasing dose quantity. Group II was found a little enlarged and cirrhotic, few of hepatocytes showed ballooning degeneration, veins congestion and few of inflammatory infiltrate showed diffuse between liver lobular (Fig.1-B, C and D). While group III reveal enlarged and cirrhotic, sinusoidal dilatation, aggregation of Kupffer cells, fibrosis, more of hepatocyte's degeneration and hemorrhage (Fig. 1- E, F and G). Sections of kidney tissue of control group that revealed a semi-normal shape of focal tubules and glomerulus. (Fig.2- A). Groups II showed cytoplasmic degeneration and necrosis of **renal** tubules epithelial, with a few interstitial heamorrahge. While, group III showing the acute necrosis of renal tubules epitheliual, acute haemorrage, and hypertrophy of renal tubular epithelial.

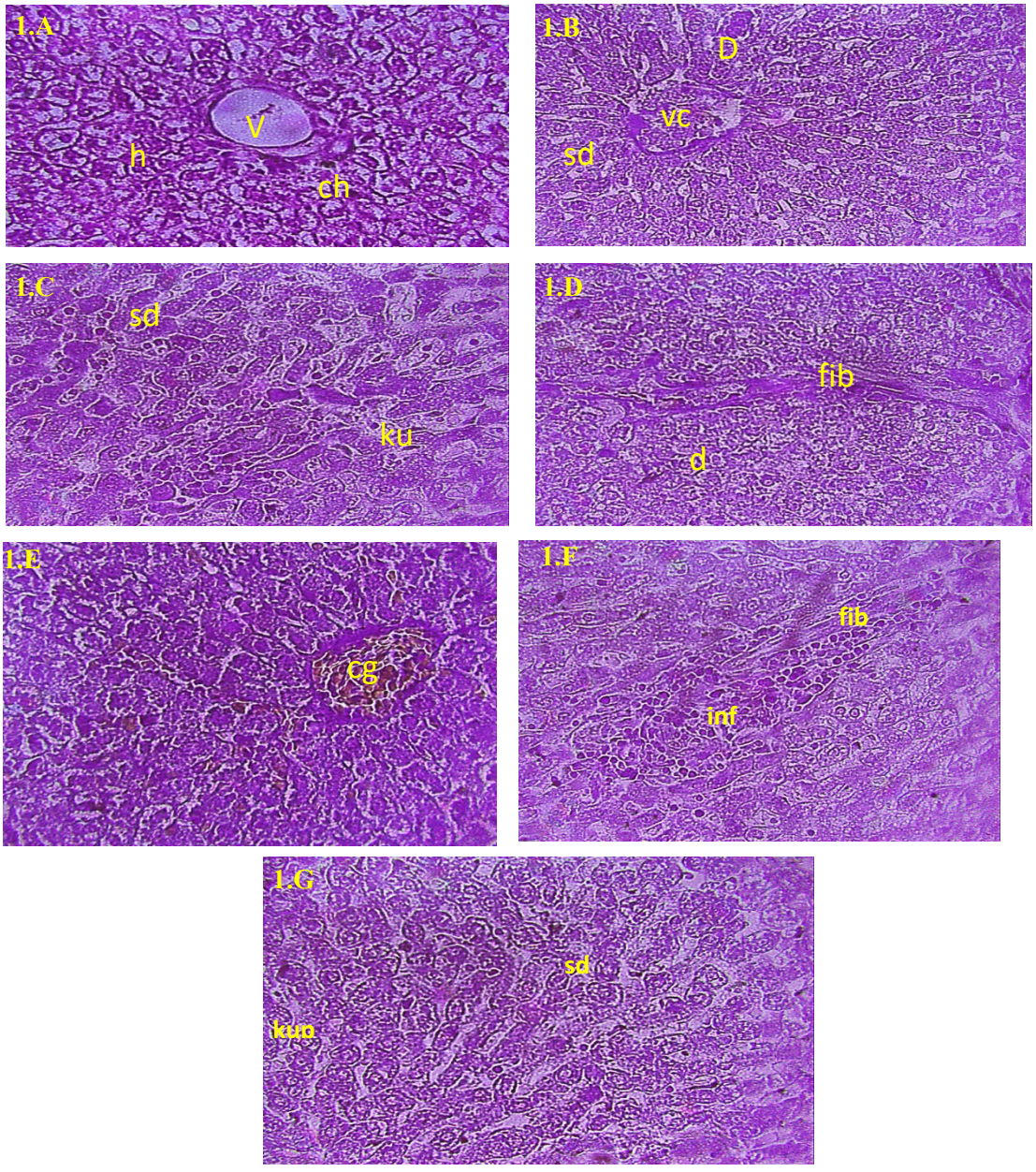

Figure 1. (1.A.) Section in control rats livers central veins (V) as well as hepatocytes (h), There was arranged in hepatic cord around blood sinusoids (ch) and few degeneration of hepatocytes (Mallory stain 400X). (1. B, C and D) group II showing few of hepatocytes showed ballooning degeneration (D), veins congestion (VC), aggregation of kupffer cells (kup) and sinusoidal dilatation (SD) (Mallory stain 400X). (1. E. F. and G) group III showing Sinusoidal dilatation (sd), aggregation of Kupffer cells (kup) , fibrosis (fib), more of hepatocytes degeneration (d), inflammation infiltration cells (inf) and congestion (cg) (Mallory stain, 400X original magnification).

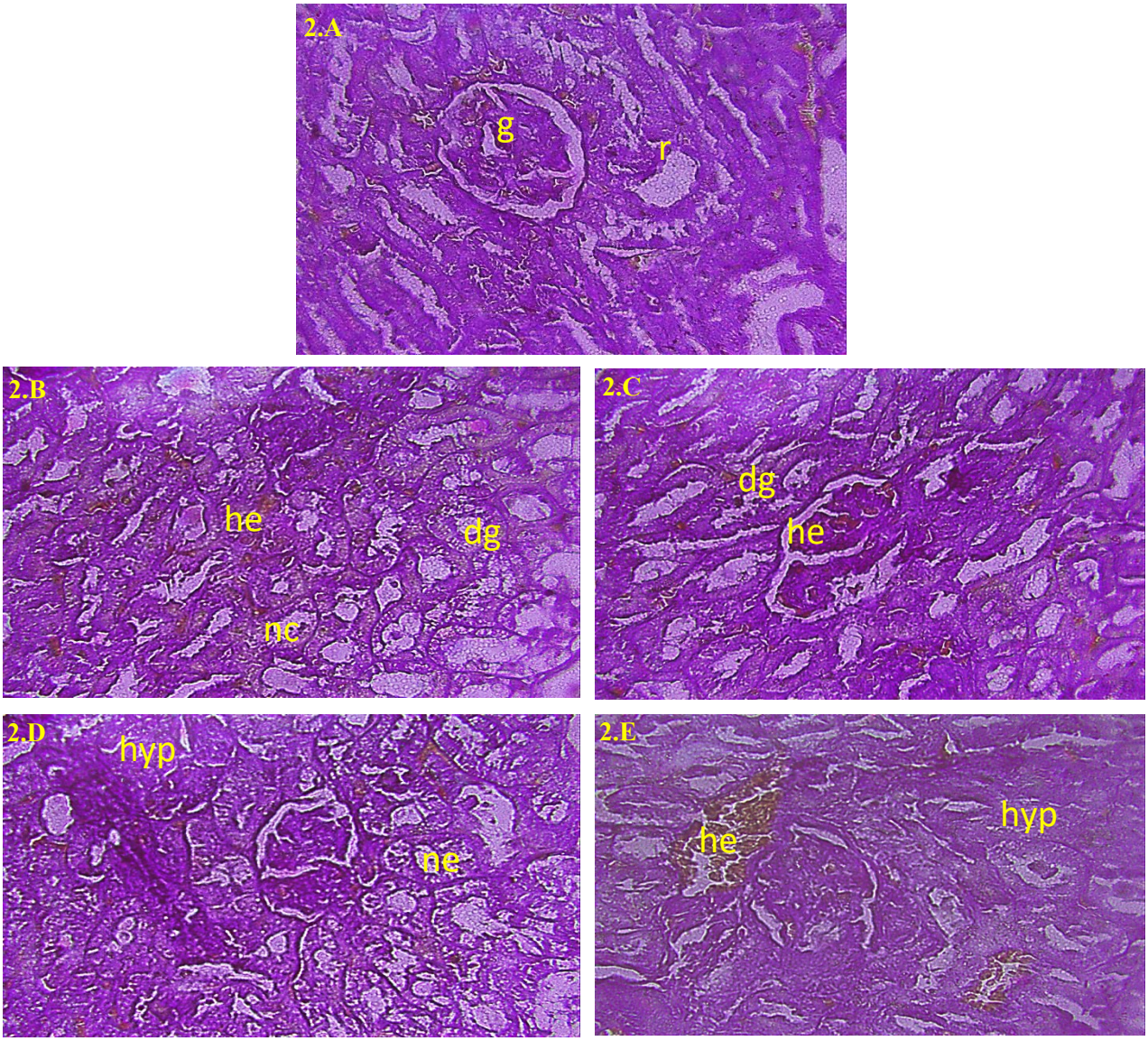

Figure 2. (2.A.) The section in the control rats' kidneys contains normal glomerulus (g) and renal tubules (r) . (2.B.) (Mallory stain 400X). (2. B. and C) group II showing renal tubule epithelial degeneration (dg) and necrosis (nc). Few interstitial hemorrhages (He) (Mallory stain 400X). (2. D and E) group III showing acute necrosis of renal tubules epitheliual (ne), acute haemorrage (he), hypertrophy of renal tubular epithelial (hyp) (Mallory stain, 400X original magnification).

Discussion

Current study results revealed that liver and kidney tissue in the control group the presence of normal histological structure except for some minor changes, while groups II and III which treatment with an overdose of codeine, reflected different histopathological conditions in both the liver and the kidneys, which increased in severity. Hepatic and renal addiction, and its effect on metabolic profiles is quite scant, it's crucial to look into and comprehend how cough syrup affects these metabolic patterns. Although opioids have been widely used for a long period, their long-term effects, particularly at the histological profile, are unknown. (12). One of the natural plant alkaloids known as codeine is found in opium extracts and is commonly used to treat coughs and mild to moderate pain. Despite its widespread usage, codeine has not been linked to blood enzyme increases throughout therapy for a long time, and there have been no compelling reports of idiosyncratic acute, clinically obvious liver impairment linked to its use. (13). As with other opiates, codeine produces respiratory depression and physical and psychological addiction (14). Following parenteral and oral administration, codeine and its salts are effectively absorbed. Codeine is largely processed in the liver by endoplasmic reticulum enzymes, where it passes through partial conjugation with glucuronic acid, O-demethylation, and N-demethylation. Most of the drug's excretion is found in the urine as inactive metabolites, with trace levels of free and conjugated morphine also present. The feces contain very small levels of codeine and its metabolites (15). morphine and its derivatives have been widely employed as opioid analgesics for the treatment of both acute and chronic pain (16). All morphine derivatives undergo liver metabolism before being eliminated by the kidneys; nevertheless, this process can result in hepatotoxicity and nephrotoxicity (17). However, the lethal dose of codeine in rats is 427 mg/kg body weight orally, 130 mg/kg intraperitoneally, 229 mg/kg subcutaneously, and 75 mg/kg intravenously, while in the mice, the corresponding lethal dose values are 250 mg/kg (18). According to a time- and dose-dependent leakage of lactate dehydrogenase, codeine was caused cytotoxicity in isolated rat hepatocytes (19). Cell death started at doses of 0.5 or 1.25 mM after 60 minutes from treatment with codeine, and viability fell to less than 10% after 120 to 150 minutes. Metyrapone, a cytochrome P450 metabolism inhibitor, was added, which prevented hepatotoxicity, proving that a codeine metabolite produced by P450 was the cause of the cytotoxicity (20). The different doses of codeine (2.5 mg/250 g and 5.55mg/250g) exhibited a variety of negative impacts on the liver's histology, including vacuolation, hyperplasia, hypertrophy, degeneration, and necrosis. These effects got worse as the dose level grew. These findings supported those of. (21), who found that varying dosages of opium derivatives caused histological alterations in the liver of mice. In systems are said to be involved in the metabolism of drugs and xenobiotics, making them particularly vulnerable to the harm caused by these chemical insults (10). Both organs use resident acetyltransferases, sulfotransferases, glutathione transferases, and CYP450 enzymes to digest medicines. (11). Research on the impact of cough syrup overdose and its association with

addition to causing histological lesions inflammatory infiltration, necrosis, hyperpigmentation, degeneration, and vessel congestion, the administration of morphine and its derivatives like codeine and tramadol also revealed pathocytological changes like torn and convoluted nuclear membranes, the distance between nuclei and irregular chromatin. Our findings agree with those of earlier research (22). The metabolism and excretion of morphine are carried out by the liver and kidneys, (23 and 24). During its metabolism, morphine has the potential to be toxic to the kidneys and the liver (25). Long-term usage of LAAM has been linked to renal damage, including focal cortico-medullary mineralization, focal tubular epithelium renewal, and mineral/crystal deposition in the intertubular region of the kidney (26). In the tubular cells of the kidneys, they manifested histopathologic alterations (27).

Conclusion: The present study contends that hepatic and renal damage is observed in the histological assessments following an overdose of cough medicine containing codeine. The long-term consequences of these immediate harmful effects could, be severe. Therefore, it is crucial that knowledge about the potential consequences of an overdose be made widely available to reduce misuse of these syrups, especially among adolescents and young adults.

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دراسة التأثير المرضي النسجي المصاحب للجرعة الحادة عن طريق الفم للمشتقات الأفيونية على أنسجة الكبد والكلى في ذكور الجرذان

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الخلاصة

هدف الدراسة الحالية الى دراسة تأثير جرعتي الكودايين الحادة (0.50 و 1 مل / 250 غم)، على الصور المرضية النسجية للكبد والكلى في ذكور الجرذان المختبرية. تعد مشتقات الافيون (الكودائين) مواد اصطناعية مضادة للتشنج ذات سمية منخفضة نسبيًا. بينت نتائج الدراسة الحالية تراكيب نسيجية طبيعية باستثناء بعض التغييرات الطفيفة في مجموعة السيطرة التي جرعت بشراب مضاد للهستامين خالي من الكودايين. بينما اظهرت المجموعات المعالجة بشراب مضاد الهستامين الحاوي على الكودايين بالجرعة المفرطة من الكودائين تسببت في ارتشاح الخلايا الالتهابية واحتقان الاوردة اضافة الى حالات التنكس الدهني والتفجي السايتوبلازمي وتضخم نوى الخلايا لنسيج الكبد. ايضا لوحظ تلف لنسيج الكلية للجرذان المعاملة بالجرعتين من الكودائين تضمنت نخر وتنكس سايتوبلازمي في بطانى النبيبات الكلوية اضافة الى توسع القنوات داخل النبيبات الكلوية مع نزف لخلايا الدم الحمراء بين النبيبات مع حالات من الاحتقان الوريدي. اثبتت نتائج بحثنا الى استنتاج نهائي مفاده ان لمشتقات الافيوم من الكودائين وتحت ظروف الجرعات الحادة والمفرطة تأثير واضح من خلال تلف انسجة الكبد والكلية.

الكلمات المفتاحية: كودايين, كبد .كلية .جرذ.