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TOXICOLOGICAL INTERACTION OF CHROMIUM AND GENTAMICINE SULPHATE ON KIDNEY FUNCTIONS.

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ABSTRACT

The present study was done to explore relation between kidney failure problem in Egypt and chromium toxicity with or without aminoglycoside. Chromium levels in tanning hides dyes and out put of some factories were determined. Area of tainting hides in SOR MAGRY EL AIONE in Egypt used for collection of samples. Samples from certain solutions used in tanning hides, water discharge in these factories, water discharge of Kaha factories and Vetrac Company was used. Nephrotoxic effect of chromium on kidney functions of rabbits treated with and without gentamicin sulfate was studied. Four groups of rabbits each of four rabbits were used in this study. First group was given 1.8 PPM (mean of chromium level in analytic samples) potassium dichromate (VI) for 21 successive days in drinking water. Second group injected intramuscular by gentamicin sulfate (5ml/kg.b w) for seven days. Third group given pot. Dichromate for 21 successive days and gentamicin sulfate for seven days by doses and route as that given to first and second groups. Fourth group kept as control.

Chromium and gentamicin sulfate levels were determined in serum and kidney of treated animals at the end of experiments (21 days). Serum chromium and gentamicn sulfate levels showed marked increase in group taken pot. Dichromate and gentamicin sulfate in comparison to first and second group. Chromium in the kidney tissues was increased in third group in comparison to first group taken pot. Dichromate (VI) Serum urea and Creatinine levels were also monitored. Serum urea and creatinine levels were increased in all groups in comparison to control group. Histopathological alteration of kidney was detected. Kidney in the group taken 1.8 PPM pot. Dichromate showed cellular infiltration and necrosis in renal tubule. Kidney in group taken gentamicin sulfate showed fibrosis in glomerular basement membrane and necrosis. Lesions in kidney of third group (pot. Dichromate & gentamicin sulfate) showed greater marked lesions in the kidney in comparison to first and second group.

INTRODUCTION

Industrial uses of chromium centered on the production of dyes and tainning of hides **(Terry, 1995).** Chromium is an essential trace element. Chromium has many oxidation states, of which the trivalent and hexavalent states are the most stable. Exposure to chromium and its salts takes place via cement, wood ash, plating baths, green baize of gaming tables, matches leather, tanning agent, leather gloves, welding fumes, coated zinc and galvanized iron sheets **(Bang-Pedersen, 1982).** Industrial and agricultural discharge is considering the primary source of metal poisoning **(El Nabawi, et al, 1987).** Several metals are toxic to the kidney either from occupational or environmental exposures **(WHO, 1991).** Chromium is essential for glucose metabolism, but the margin between required concentration and toxic concentration is often small **(Bowen, 1966).** Toxic effect of chromium are mediated via reactive oxygen intermediates during reduction of chromate (VI) to chromate (III) in tissue cells **(Sugiyama, 1992).** Chromium and its salts induce cytotoxicity, these observations suggest that chromium produce reactive oxygen species which may mediate many of the untoward effects of chromium **(Bagchi, et al (1995).** Chromium increased urinary excretion of low molecular weight proteins (B2-Microglobine and retinol-binding protein (RBP) **(Bernard and Lauweryes, 1991).** Such increase may reflect tubular cell dysfunction, or damage or competition for absorption. B2-M is synthesized by all nucleated cells and is present on their membranes as a component of histocompatibility antigens. Healthy subjects excrete little B2-M in urine (L 100 ug/24 hr) but excretion is increased with renal tubular dysfunction **(Goyer and Cherion, 1995).** Chromium enhanced excretion of urinary lipid metabolites **(Bagchi, et al 1995 and Bagchi, et al 1997).** After oral or dermal absorption of chromium (VI) the kidney is the main target organ for chromium accumulation, which might result in acute tubular necrosis in human **(Dartsch, et al., 1998).** Same author adds that kidney epithelial cells are 10 times more sensitive towards chromium than liver epithelial cells and this might explain the known nephrotoxicity in vivo. Chronic renal failure seems to be responsible for marked elevation of serum chromium **(Brodner, et al., 1998)**

Renal, tubular necrosis after ingestion of chromate or dichromate salts has been demonstrated in animals and in humans following acute intoxication **(Lonard and Norseth, 1986).** B-Glucuronidase and renal cell antigen may be increased in workers with chronic exposure **(Mutti, 1989).** Tubular proteinuria was reported after acute exposure to chromium **(Franchini and Mutti, 1988).** Chronic nephrotoxicity of solvents has been investigated in a group of workers in the foot wear industry **(Caudarella, et al 1981)**

Gentamicin is an aminoglycoside antibiotic derived from micromonospora purpurea with bactericidal effect for many gram-negative pathogens **(Black, et al., 1983).** Gentamicin is widely used in veterinary and human medicine Aminoglycosides. Aminoglycoside nephrotoxicity usually develops over 7-10 days, polyuria and renal concentration defect may proceed a fall in glomerular filtration rate **(Bennett, 1986).** Amino-

glycosides inhibited lysosomal phospholipidosis and tubular cell accumulation of phospholipids that interfere with mitochondrial oxidative phosphorylation **(Michael and Richard, 1989).** Administration of gentamicin sulfate caused increase in serum urea with reduction in urea clearance **(Whiting and Simpson, 1983).** Urinary drug level may be diminished in patient with severe depression of glomerular filtration rat **(Stamy, et al 1974).** Thickened glomerular basement membranes showed in ewe administered gentamicin for 7 days **(Brown, et al., 1985).** Aminoglycoside produced tubular cell damage necrosis in proximal tubule and tubular desquamations **(Bennett, 1986 and Ngeleka, et al., 1990).**

MATERIAL AND METHODS

Sampling: Total of twintey samples was collected. Ten samples represent certain dyes used in tanning hides in factories of Sor Magra El Aieon in Egypt . Ten samples from some industrial factory discharge in Kalubia governerate.

Analysis of samples: Dyes and water samples were filtered and 0.1 ml of nitric acid was add to each 100 ml and kept in refrigerator till analysis. All the samples were analyzed for determination of chromium using flame type air- acetylene atomic absorption spectrophotometer **(Tahan, et al, 1994).**

Test Materials

A- Potassium dichromate powdered (K2 Cr2 O7)obtained from ADWIC EL-Nasr pharmaceutical chemicals Company.

B-Gentamicin sulfate was obtained from Alexandria for Pharmaceuticals Alexandria.Egypt

Toxicological study: Sixteen Newzland rabbits (weighted from 900-1200 gm) were divided into four groups each of four rabbits .The first group taken 1.8 ppm (mean level of chromium in examined samples) potassium Dichromate in drinking water for 21 days. The second group given (IM injection of 5 ml / kg. b. w gentamicin sulfate) for 7 days according to **(Reynolds, 1989).** Third group given pot. Dichromate in drinking water for 21 days with gentamicin sulfate for 7 days by same route and doses that given to first and second group. Fourth group was kept as control. All rabbits were slaughtered at the end of study (21 days). Serum and kidney tissue (for residue and pathological examination) was obtained.

Chromium levels were determined in serum and kidney tissue according to **(Bernhad, 1976 and Al-Ghais, 1995)** using flame type air –acetylene atomic absorption spectrophotometer **Tahan et al (1994).** Gentamicin sulfate levels was determined in serum and urine according to **(Kirshbaum and Arret, 1959).** Gentamicin was extracted from kidney homogenate according to **(Haddad et al, 1987)** then determined as mentioned before. Serum urea levels we-re determined according to **(Tabacco, 1979)** and serum creatinine according to **(Husdan and Rapoport, 1968).** Kidney sections submitted for histopathological examination according to **(Druy and Walling, 1979).**

The data obtained in this study were calculated as mean + standard error, and they were statistically analyzed by the student's (t) test .All statistical analysis were carried out according to **(Johnston, 1972)**

RESULTS

The results in table (1&2)indicated that the concentration of chromium in some dyes used in tanning of hides ranged from 0.747 to 8.487ppm with mean value of 1.8 PPM. Chromium level in water out put of some industrial locality ranged from 0.774 to 2.750 PPM with mean value of 1.127 PPM. Such data exceed the permissible limits (0.05 PPM).

Table (1): Concentrations of chromium (PPM) in some tainning hides dyes and some water out put of some industrial locality in comparison to permissible limit.

Hides dye samples	Cr (PPM)	Water discharge of some locality	Cr (PPM)	Permissible limits (p.l) *0.05
1	0.747	Near out put of Kaha factory	0.774	+
2	8.486	Out put of Kaha factory	0.841	+
3	0.84	Near out put of Vetrac factory	0.88	+
4	1.13	Near out put of Vetrac factory	0.938	+
5	1.2	Out put of Vetrac factory	0.949	+
6	1.09	Out put of carpet factory in Moshtohor	1.056	+
7	1.15	Moshtohor out put(EL-Namol canal)	1.0867	+
8	0.78	Moshtohor canal	0.783	+
9	1.3	Out put of tanning hid factory in area of Sore Magra El Aion	1.210	+
10	1.28	Out put of another tanning hid factory in area of Sore Magra El Aion	2.752	+

+ Over permissible limits

- Less than the permissible limits

*According to **WHO, (1984)**

Table (2): Concentration of chromium (PPM) in some dyes and water out put of some industrial locality.

Value	Sampling area	
	Hides dye	Water out put in some industrial locality
Min.	0.747	0.774
Max.	8.487	2.750
Median	1.140	0.943
Mean.	1.8	1.127
SE	0.746	0.186

Serum chromium levels in group taken pot. Dichromate or group taken gentamicin sulfate and pot. Dichromate is presented in table (3).Increase in serum chromium levels was detected in group taken pot. Dichromate and gentamicin sulfate. Serum gentamicin level in group taken both gentamicin and Pot. Dichromate showed high significant increase in comparison to group taken gentamicin sulfate only. Serum gentamicin sulfate was 15.36± 1.3 and 8.53 ± 1.1 respectively as clear in table (3). There is no significant difference in serum gentamicin sulfate in group administered gentamicin sulfate and pot. Dichromate and that administered gentamicine sulfate only. Gentamicin sulfate levels were 22.41± 2.17 and 20.29± 1.33 in third and second group respectively. Effect of pot. Dichromate or gentamicin sulfate or both on serum urea and creatinine levels were detected in table(3). Increase in serum urea levels was showed in group taken pot. Dichromate and group injected by gentamicin sulfate as compared to control group. Urea levels were 40.56± 1.8, 38.56± 1.22 and 25.8± 2.14 mg/dl respectively. Third group that taken pot. Dichromate and gentamicin sulfate showed high significant increase in serum urea level as compared to first and second group (taken pot. Dichromate and gentamicin sulfate only respectively). Serum creatinine levels showed high significant increase in first and second group in comparison to control group. Serum creatinine levels were 3.96± 0.5, 4.92± 0.54 (mg/dl) for first and second group respectively in comparison to 1.72± 0.21(mg/dl)of control group. Administration of Pot. Dichromate and gentamicine sulfate caused increase in creatinine levels as compared to first and second group. Serum creatinine levels were 6.16± 0.69 mg/dl in third group in comparison to 3.96± 0.5 mg/dl and 4.92± 0.54 mg/dl in first and second group respectively.

Table (3): Serum chromium levels (PPM); gentamicin sulfate; urea and creatinine of Newzeland rabbit administered (1.8ppm) pot . Dichromate or gentamicin sulfate (IM 5ml /kg.b.w.) or pot. Dichromate and gentamicin sulfate in comparison to control groupat the end of 21 days of expermental. (Mean ± S.E).

Groups	Treatment	Cr (ppm)	Gentamicin sulfate(ug/ml)	Urea (mg/dl)	Creatinine (mg/dl)
Group1	Daily administration of 1.8 PPM pot. Dichromate in drinking water.	0.282 ± 0.02	------	40.56** ± 1.8	3.96** ± 0.50
Group2	Administration of (5ml/kg.b.w.) gentamicin sulfate for 7 days	----	8.53 ± 1.1	38.56** ± 1.22	4.92** ± 0.54
Group 3	Daily administration of 1.8 PPM pot. Dichromate in drinking water with IM injection of(5ml/kg) gentamicin sulfate for 7 days.	0.68** ± 0.10	15.36** ± 1.3	57.4** ± 3.17	6.16* ± 0.69
Group 4	Control group	.....		25.8 ± 2.14	1.72 ± 0.21

*Significant at p ≤ 0.05 ** High significant p≤ 0.01

- Chromium levels in kidney tissues were showed in table (5). The data indicated an increase in chromium level of kidney in third group(pot. dichromate and gentamicine sulfate)in comparison to first group(pot. Dichromate).Chromium in kidney tissue was 0.346± 0.06 and 0.618± 0.08 PPM in the first and third group respectively. Gentamicin sulfate levels in kidney tissues were cleared in table (4).

Table (4): Residue of chromium levels (PPM) and gentamicine sulfate in kidney of Newzeland rabbit administered (1.8PPM) pot . Dichromate or IM injection of (5 ml /kg) gentamicin sulfate or pot. Dichromate and gentamicin sulfate . (Mean ± S.E)

Groups	Treatment	Cr (ppm)after 21 days of treatment	Gentamicin sulfate(ug/ml) after 21 days of treatment
Group1	Daily administration of 1.8 PPM pot. Dichromate in drinking water.	0.346 ± 0.06	-----
Group2	Administration of (5ml/kg) gentamicin sulfate for 7 days.	------	20.29 ± 1.33
Group 3	Daily administration of 1.8 PPM pot. Dichromate in drinking water with IM injection of(5ml/kg) gentamicin sulfate for 7 days.	0.618* ± 0.08	22.41±2.17
Group 4	Control group		--------

*Significant at $p \leq 0.05$ ** High significant $p \leq 0.01$

Histopathological study revealed that kidney of group taken pot. Dichromate showed renal tubular necrosis cellular and infiltration Fig.(1,2&3). Kidney tissue of second group showed necrosis and fibrosis in glomerular basement membrane Fig.(4,5&6). Kidneys of third group (taken pot. Dichromate and gentamicin sulfate) showed marked necrosis in proximal tubule and thickened in glomerular basement membrane Fig. (7,8&9). Normal kidney of control group showed in Fig.(10&11).

Fig. (1&2): Kidney of rabbit (taken 1.8 PPM pot. Dichromate) showing renal tubular necrosis. (H&E)(X40)

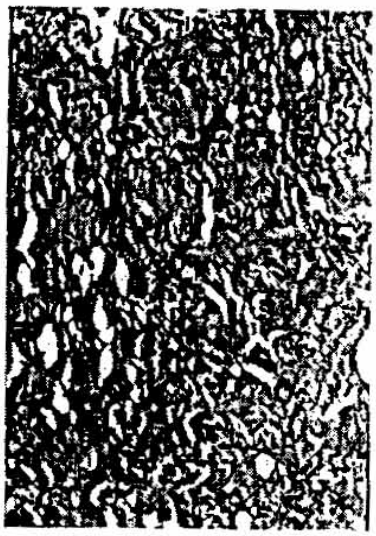

Fig. (3): Kidney of rabbit (taken 1.8PPM pot. Dichromate) showing cellular infiltration sulfate showed necrosis. (H&E) (X 40)

Fig. (4): Kidney of rabbit injected IM 5ml/kg.b.w gentamicine (H&E)(X 40).

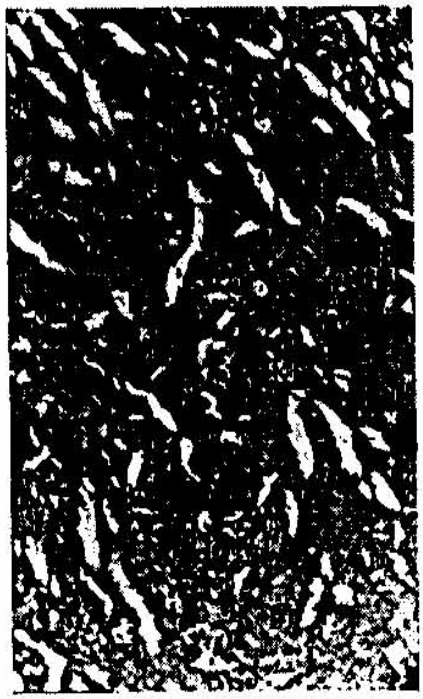

Fig. (5): Kidney of rabbit injected IM 5ml/kg.b.w gentamicine sulfate showed fibrosis in glomerular pasment membrane. (H&E)(X40)

Fig.(6): Kidney of rabbit injected IM (5ml/kg .b. w) gentamicine sulfate showed marked fibrosis .(H&E) (X40)

Fig. (7): Kidney of rabbit (pot. Dichromate &gentamicine sulfate) showed necrosis in proximal tubule. (H&E) (X40)

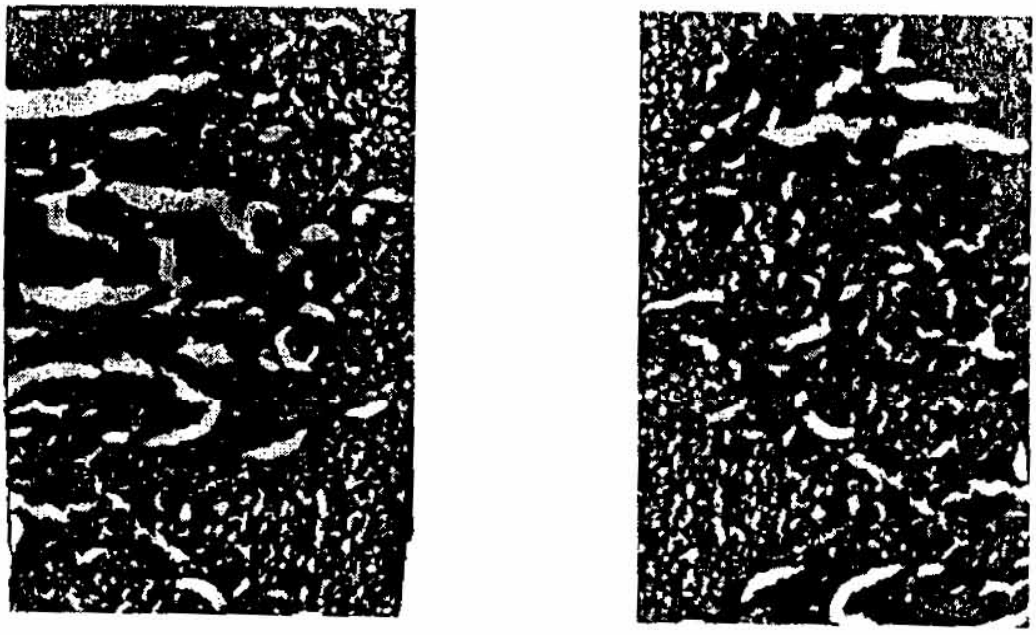

Fig. (8&9): Kidney of rabbit (pot. Dichromate &gentamicine sulfate) showed thickened in glomerular basement membrane. (H&E) (X 40)

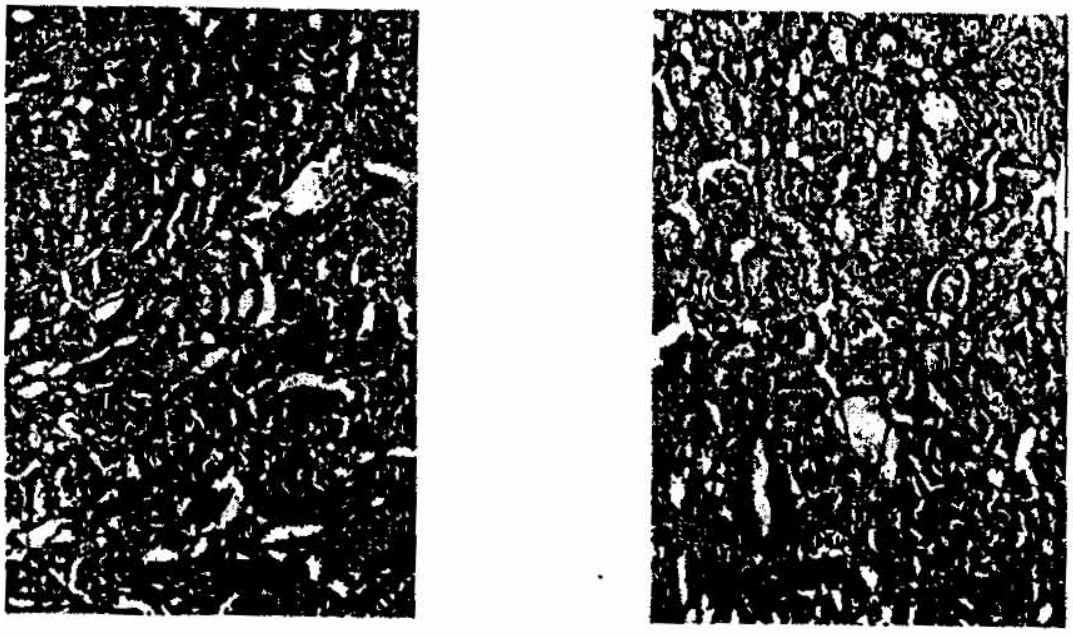

Fig. (10&11): Normal kidney of the control group. H&E (X 40)

DISCUSSION

Chromium is a widely used industrial chemical extensively used in paints, metal finishes, steel including stainless steel manufacturing, alloy cast iron and wood treatment .On the contrary, chromium (III) salts such as chromium polynicotinate, chromium chloride and chromium picolinate are used as micronutrients and nutritional supplements **(Bagchi, et al 2001).**

Industrial and agricultural discharges are consider the primary source of metal poisoning in Egypt **(EL-Nabawi et al, 1987).** The present study indicated that the chromium levels in certain dyes (in leather industry) were reached 0.747 PPM as a minimum level and 8.487 PPM as maximum value with mean value (1.8 PPM) which used as an experimental dose in this study. Chromium in the water discharge of certain factories is higher than the permissible limit as detected by **WHO (1984)** .The present study indicated that leather dye samples contain higher level of chromium. Where industrial uses of chromium centered on the production of dyes and tanning of hides **(Terry, 1995).**

The strong epidemiological occurrence of chromium helps us to study the interaction of chromium and one of common used aminoglycoside (gentamicin sulfate) on the kidney and serum levels of these compounds. Serum chromium level was increased in group taken 1.8 PPM pot. Dichromate in drinking water and 5ml IM injection of gentamicin sulfate than that group taken pot. Dichromate only. This results may be due to nephrotoxic effect of both pot. Dichromate (VI) and gentamicin sulfate **(Lonard and Norseth, 1986, Mutti, 1989, Franchini and Mutti,1988, Bennett,1986, Michael and Richard,1989, Whiting and Simpson,1983).** Exposure to chromium induce an alteration of structure and function of the kidney plasma membrane **(Dey,2001)** Renal failure seems to be responsible for marked elevation of serum chromium **(Brodner, et al 1998).** Serum gentamicin levels increased in group taken pot. Dichromate and gentamicin sulfate in comparison to group taken gentamicin sulfate only. This result may be due to nephrotoxic effects of chromium and gentamicin sulfate **(Langard and Norseth, 1986, Mutti, 1989, Franchini and Mutti, 1988, Bennett, 1986,Michael and Richard, 1989, Whiting and Simpson, 1983).** Such nehrotoxic effect lead to greater marked impairment of renal function as a result of the combination of pot. Dichromate and gentamicin sulfate compared with either test material given alone as first and second group. This explanation is supported by the histopathological finding of kidney in third group (greater marked lesions than other group) as in Fig. (7,8&9) .

Chromium and gentamicin sulfate residues levels in kidney tissues were detected. Chromium showed increase level in group taken pot. Dichromate and gentamicin sulfate. This results were attributed to that kidney is the main target organ for chromium accumulation **(Dartsch et al 1998).** Same author added that up take of Cr. (VI) through the general anion transport system of the cell membrane might be the only facet of cellular uptake and toxification. Concerns residues of gentamicin sulfate (ug/gm) in kidney of rabbits showed no difference between group administered gentamicin sulfate or group administered pot. Dichromate and gentamicin sulfate.

Increase in serum urea and creatinine were detected either in group taken pot. Dichromate or group taken gentamicin sulfate in comparison to control group Third group taken pot. Dichromate & gentamicin sulfate showed marked increase in serum urea and creatinine level. This result agreed with **Beech et al (1977) and Brodner et al, (1998).** This result may be attributed to chromium and aminoglycoside nephrotoxicity **(Langard and Norseth, 1986, Mutti, 1989, Franchini and Mutti, 1988, Bennett, 1986, Michael and Richard, 1989, Whiting and Simpson, 1983).** Chromium caused cytotoxicity by induces an oxidatives stress through enhanced production of reactive oxygen species leading to genomic DNA damage and oxidative deterioration of lipids and proteins. A cascad of cellular events occur including enhanced production of superoxide anion and hydroxyl radicals, increased lipid peroxidation DNA fragmentation, activation of protein kinase c, apoptotic cell death **(Bagchi et al 2001).** Histopathological finding supports this explanation Fig (7,8 & 9).

Results concerning histopathological lesion of kidney rabbits treated with pot. Dichromate was represented by cellular infiltration and renal tubular necrosis. These findings were in agreement with **(Langard and Norseth, 1986 and Dartsch et al, 1998).** Renal lesions in rabbits injected by gentamicin sulfate were represented by fibrosis in glomerular basement membrane and necrosis. These finding are agreed with **Bennett, (1986) and Ngeleka et al (1990).** These result may be explained as chromium (VI) induce an oxidative stress resulting in tissue damaging effects that may contribute to the toxicity of this cations **(Bagchi et al,1997).** Chromium induce an alteration on structure of the kidney **(Dey,2001)** Kidney in rabbits administered pot. dichromate and gentamicin sulfate showed greater marked lesion than first and second group. These results may be due to the augmentation of nephrotoxicity as a result of combination of pot. Dichromate and gentamicin sulfate.

Conclusion: Population that might be at higher risk to a toxic metal that may cause nephrotoxicity such as people or other life stock exposed in the work place to chromium (industrial area of tanning hides or foot wear industry) should be closely monitored for renal effect. Certain drugs (aminoglycoside) augmented the nephrotoxic effect of the toxic metal (chromium).

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الملخص العربي

دراسة التداخل السمي للكروم وسلفات الجنتاميسين وأثرة على كفاءة الكلى .

نبيلة محمود عبد العليم – قسم الطب الشرعي والسموم

كلية الطب البيطرى بمشتهر – جامعة الزقازيق/ فرع بنها

هدف البحث الى دراسة التأثير السام لكل من الكروم وسلفات الجنتاميسين على كفاءة الكلى.تم قياس نسبة الكروم في بعض الصبغات المستخدمة في دباغة وصبغ الجلود وكذلك في مياة صرف بعض هذه المدابغ . كما تم قياس نسبة الكروم في صرف بعض المصانع في محافظة القليوبية وفي مصرف مشتهر (محافظة القليوبية) . .وقد أوضحت الدراسة تواجد الكروم بنسب عالية جدا خاصة في بعض الصبغات المستخدمة في دباغة الجلود حيث أن بعض هذه الصبغات تستخدم تحت مسمي (صبغة ماء الكروم) . أظهرت صبغة ماء الكروم نسبة عالية جدا من الكروم وصلت إلى ٨,٤٨٦ جزء فى المليون .كما تم دراسة التأثير السمي للكروم سداسي التكافؤ (داي كرومات البوتاسيوم) منفردا أو عند تعاطية مع المضاد الحيوي سلفات الجنتاميسيين على الكلي .

تم استخدام عدد ١٦ أرنب قسمت ألي أربعة مجموعات كل مجموعة ٤ أرانب . وضع داي كرومات البوتاسيوم بنسبة ١,٨ جزء في المليون في مياة الشرب للمجموعة الأولي لمدة ٢١ يوم وحقنت المجموعة الثانية بسلفات الجنتاميسيين بمعدل ٥ مجم لكل كيلوجرام من وزن الجسم في العضل لمدة ٧ أيام متتاليين . أما المجموعة الثالثة فقد تناولت ١,٨ جزء في المليون من داي كرومات البوتاسيوم في مياة الشرب مدة ٢١ يوم وحقنت سلفات الجنتاميسيين بجرعة٥ مجم لكل كيلوجرام من وزن الجسم لمدة ٧ أيام . استخدمت المجموعة الرابعة كمجموعة ضابطة . تم أخذ العينات بعد ٢١ يوما فى كل المجاميع.

أوضحت نتائج الدراسة زيادة نسبة الكروم في مصل حيوانات المجموعة الثالثة عن المجموعة الأولي . كما ارتفعت نسبة سلفات الجنتاميسيين في مصل حيوانات المجموعة الثالثة عن الثانية .

أوضحت الدراسة زيادة تركيز الكروم في نسيج الكلي في المجموعة الثالثة (داي كرومات البوتاسيوم مع سلفات الجنتاميسيين) عن المجموعة الأولي (داي كرومات البوتاسيوم) . بينما لم يظهر سلفات الجنتاميسيين في نسيج الكلي أي تغيرات معنوية . سجلت الدراسة زيادة كل من البولينا والكرياتينين في مصل حيوانات المجموعات الأولي والثانية والثالثة عند مقارنتها بالمجموعة الضابطة . وأوضح الفحص الباثولوجي لعينات الكلي تأثير المجموعة الثالثة (داي كرومات البوتاسيوم وسلفات الجنتاميسيين) أكثر من المجموعة الأولي والثانية . حيث حدث موت وتخثر في خلايا أنيبيبات الكلي . وتدل النتائج السابقة أن الكروميوم سداسي التكافؤ له تأثير سمي علي الكلي ويزداد هذا التأثير عند تعاطي المبيد الحيوي سلفات الجنتاميسيين . حيث أن المادتين لهما تأثير ضار علي الكلي .