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A Comparative Study of the Role of Various Antibiotic Drugs in Drug Induced Liver Injury by Hepatotoxicity

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Abstract: ***Medicines associated with side effects include antibiotics, anticoagulants, tranquillisers and non-steroidal anti-inflammatory agents in cases of suspected liver reactions.It is essential to obtain a detailed drug history that includes awareness of the drug's hepatotoxic potential and the timing of drug administration in relation to the emergence of symptoms, previous administration of the antibiotic in question and concomitant drug use.Drug-induced liver injury (DILI) is a leading health problem especially in a globally expanding commercialization of new drugs and the increasing exposure of patients to new compounds. This is expected to increase because of the number of drugs being consumed, prescription and non-prescription, as well as because of the current tendency towards pharmacologically active complementary and alternative medicines, dietary supplements, recreational substances and special diets.***

Keywords: DILI, Xenobiotic, Hepatotoxicity, antibiotics, target organ toxicity

1. Introduction

The rat animals in the experimental groups were treated for drugs, as chemicals (Xenobiotics) that may affect liver function which stimulate the activity of microsomal enzymes (eg.cyt. P450), by a process known as enzyme induction. This is important in determining the degree of hepatotoxicity in the animal study (Conney, 1967). The toxicity of many chemicals results from their metabolic conversion to derivatives that can alter tissue macromolecules by the process of metabolic activation(Mitchell, 1975).Long-term minocycline used as a treatment for acne has also been associated with autoimmune hepatitis, characterized by antinuclear autoantibodies, a lupus-like syndrome, fatigue, rash and arthralgia and hypersensitivity syndrome.All forms of histological injury ranging from cholestasis of amoxicillin to autoimmune hepatitis to telithromycin(Chang and Sciano, 2001).Tissues were homogenized in phosphate buffer for Reduced Glutathione tests (Patterson & Lazarrow, 1955).Long-term minocycline used as a treatment for acne has also been associated with autoimmune hepatitis, characterized by antinuclear autoantibodies, a lupus-like syndrome, fatigue, rash and arthralgia and hypersensitivity syndrome.

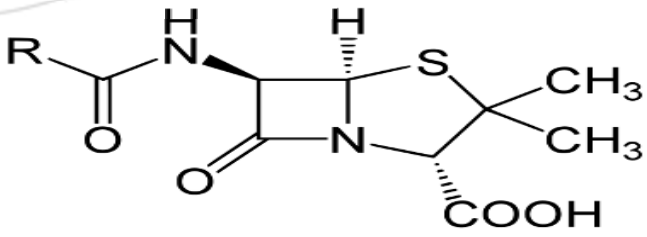
Various types of drug induced liver diseases are acute-dose dependent liver damage, acute fatty infiltration, cholestatic jaundice, liver granulomas, active chronic hepatitis, liver cirrhosis, liver tumors etc. (Bhaskar, R.K., 2016). Drugs metabolized in the liver through the cytochrome pathways may cause liver toxicity when there are polymorphisms in the enzymes (Bissell *et al.,* 2001). Hepatotoxic agents can react with the basic cellular components while available pharmaco-therapeutic options for liver diseases are very limited and there is a great demand for the development of new effective drugs.

Main Antibiotics Used In the Medical Treatment

1. β-Lactams Penicillins

Penicillin is the first generation antibiotic having similar functions but differing in efficacy.Amoxicillin is an antibiotic belonging to the group of penicillin. Other members of this class include ampicillin, piperacillin etc. All of them have similar mechanism of action. The bacteria require cell walls for protection and rigidity. Without cell wall they cannot survive and hence die off. The antibiotic forms differ in the spectrum of action or the microbes to which they are antagonistic. Amoxicillin is effective against many bacteria including H. influenzae, N. gonorrhoea, E. coli, Pneumococci, Streptococci, and certain strains of Staphylococci.Liver injury is extremely rare with ampicillin, and rare with benzylpenicillin (penicillin G).Amoxicillin has little hepatotoxic potential if administered alone in earlier studies.

Chemical Structure of Pencillin



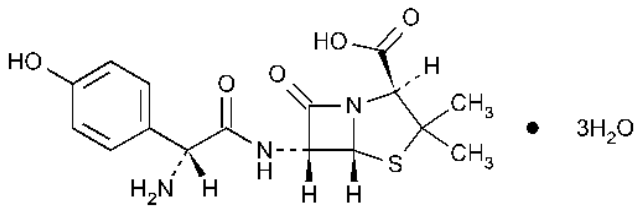
2. Amoxicillin / Clavulanate

Frequency

Primary care physicians must be aware that the combination of the β-lactamase inhibitor clavulanic acid with amoxicillin markedly increases the risk of hepatotoxicity. Thus, amoxicillin/clavulanate is responsible for 13%–23% of drug-induced hepatotoxicity cases and is the leading cause of

hospitalization for adverse hepatic events. Because symptom onset is usually delayed, early diagnosis is difficult.

Chemical Structure of Amoxycillin



Hepatotoxicity is clearly linked to the clavulanic acid moiety, with a 5- to 9-fold increase for the combination versus amoxicillin alone. A recent retrospective case analysis of 800 patients with drug-induced jaundice suggested that amoxicillin /clavulanate was responsible for 32% of cases, giving an estimated incidence rate of 9.91 cases of jaundice per 100 000 prescriptions. Hepatotoxicity associated with amoxicillin/clavulanate usually follows a benign course, with symptoms resolving over several weeks.

Pathology

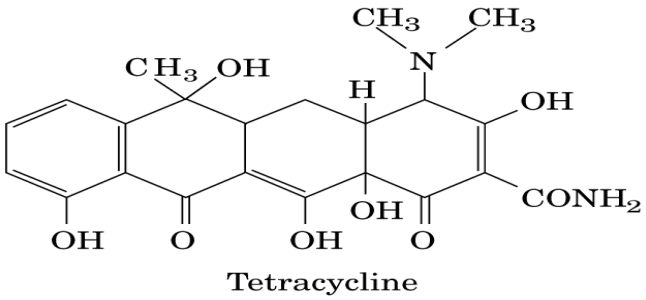
Hepatotoxicity associated with amoxicillin/clavulanate is usually characterized by delayed cholestatic or mixed hepatocellular-cholestatic injury.This ‚hepatotoxic signature" has, however, been challenged with evidence to suggest that while common in older patients, younger patients are more likely to develop hepatocellular injury than cholestatic or mixed injury.

3. Tetracyclines

Pathology

Microvesicular steatosis was the characteristic feature of treatment with intravenous or large oral doses of tetracycline, whereas cholestasis was the predominant clinico-pathological pattern with oxytetracycline and minocycline. Long-term minocycline use as a treatment for acne has also been associated with autoimmune hepatitis, characterized by antinuclear autoantibodies, a lupus-like syndrome, fatigue, rash and arthralgia and hypersensitivity syndrome.

Chemical Structure of Tetracyclin



Tetracycline

Linezolid

Linezolid treatment is most often initiated in the hospital, but, because of its excellent bioavailability in its oral form, linezolid treatment is often extended to home therapy after discharge and, therefore, is under the control of the general practitioner. Thrombocytopenia is itself a common complication in patients with CLD and it is possible that some sort of synergistic effect and/or an enhancement of linezolid toxicity are occurring due to a reduction in its metabolism. Although there is evidence that linezolid accumulates in bile, there are insufficient data to provide specific recommendations about potential side effects at this time.

Penicillin is a narrow spectrum antibiotic effective against most Gram positive and a few Gram negative bacteria. The mode of action is similar with the inhibition of cell wall formation in the microbe.The prophylaxis is easier and treatment can be done by either oral or intravenous methods. The antibiotic has a very low half life requiring it to be administered once in six hours for optimal effect. The hypersensitivity associated with Penicillin has been historical and famous and is reported in numerous cases.Antibiotics can considered as xenobiotics in living body.Biochemical markers are increasingly used to identify the incidence of effects caused by Xenobiotics (Otitju and Onwurah, 2007).

Difference between Amoxicillin and Penicillin

Absorption- Amoxicillin is better absorbed from the gastrointestinal tract compared to other Penicillins such as penicillin V and ampicillin. The levels of drug in blood are high and stable with administration of Amoxicillin.Liver injury is extremely rare with ampicillin, and rare with benzylpenicillin (Penicillin-G). Amoxicillin has little hepatotoxic potential if administered alone. Transient increases in ALT have been reported with oxacillin, carbenicillin and ticarcillin.Severe reactions include cholestasis and acute liver failure, but cases are rare, and deaths due to acute liver failure have not been reported. The hepatotoxicity of therapeutic agents and pharmaceutical chemicals has become an area of intense research interest. Benoxaprofen was removed from prescription drug by clinical evidences of its hepatotoxicity (FDA, 1983; Taggart and Alderice, 1982).

Phamacokinetics

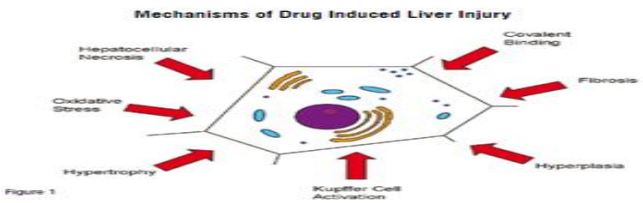
Amoxicillin serum concentrations achieved with the serum concentrations of Amoxycillin and clavulanic most commonly that equivalent to those produced by the oral administration alone. Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal cord. Hepatocellular carcinoma is a cancer arising from the liver. It is also known as primary liver cancer or hepatoma.The liver is made up of different cell types (e.g., bile ducts, blood vessels, and fat-storing cells). However, liver cells (hepatocytes)make up 80% of the liver tissue. Thus, the majority of primary liver cancers (over 90 to 95%) arises from liver cells and is called hepatocellular cancer or carcinoma.Key enzyme systems include

cytochrome P_{450} monooxygenases, phosphoesterases, glutathione-S-transferases, and O-alkyl and O-aryl conjugation which are the marker enzymes for the study.

Sub-chronic Toxicity Study: LD50 and LC 50 values are based on a single dose (LC 50). The toxic effects of antibiotics cause a wide variety of tixic effects from dermal, oral and respiratory exposure.They include carcinogenicity, mutagenicity, teratogenecity, moncogenicity, liver damage, reproductive disorders, nerve damage and allergic sensitization.

Target Organ Toxicity

Unique metabolism and relationship of the liver to the gastro-intestinal tract make it an important target of the toxicity of the drugs and xenobiotics. Therefore examination of blood and liver become significant to help in the diagnosis and treatment of the diseases. The liver undergoes dramatic changes in structure and function during development. The developmental changes that occur in the liver determine the rate and metabolic pathways used in the disposition of drugs and other xenobiotic(Bhaskar, 2012).
In toxicology, liver plays an important role because all substances absorbed by the gastrointestinal tract pass through it before entering into the general circulation.Blood is a highly specialized liquid connective tissue. Some toxicants cause direct injury to liver and others convert the chemicals into toxic substance through metabolic conversion. The classification may focus on the source and the chemical class of the toxicant, on the circumstances of exposure on the type of hepatic lesion produced, on the cell structure damaged or on the molecular or cellular mechanisms involved. Idiosyncratic reaction is attributable to pharmacogenetic differences between individuals (genetic polymorphism in the metabolism of compounds). In the case of severe toxicity the patient may develop liver failure.Cytotoxic injury resembles acute hepatitic and is characterized by damage to the hepatocytes with prominent elevation ofamino transferse. Severe case may result in fulminant liver failure. Due to the presence of different types of cells blood has varied functions and analysis of its components helps in evaluating the abnormal conditions which create pathological conditions in a person (Bhaskar, 2012).



Bhaskar, (2015)

Classification of Drug Induced Liver Injury

1. Predictable Reactions

- Dose related, has a high incidence, and occurs with a short latency within a few days.
- Results from direct toxicity of the drug or its metabolite and is reproducible in animal models
- Classic example is acetaminophen toxicity

2. Idiosyncratic Reactions

- Occur with variable latency (1 week to 1 year or more), with low incidence and may or may not be dose related
- The majority of hepatotoxic drugs cause idiosyncratic reactions
- An alt>3×upper limit of normal (uln), or an alkaline phosphatase (alp)>2×uln has been somewhat arbitrarily identified as a sensitive but not necessarily specific sign of liver toxicity.

3. Immune Mediated Vs Non-Immune Mediated

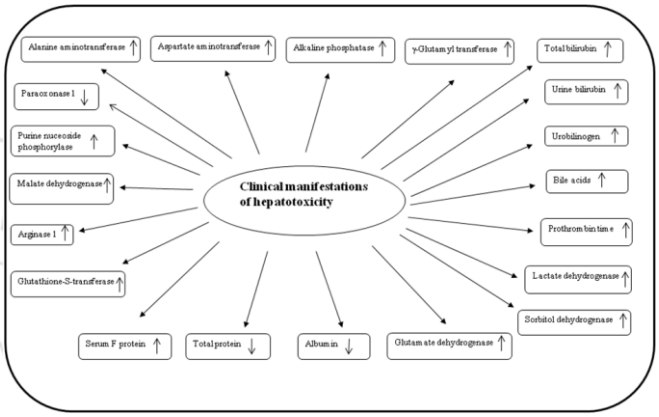


Figure 3 Clinico-biochemical indicators of hepatotoxicity
↑ increased value during hepatotoxicity; ↓ decreased value during hepatotoxicity

Patterns of Abnormality and Clinical Features

1. Hepatitis Pattern

- Hepatocellular injury
- Patient may be asymptomatic or present with fatigue right upper quadrant pain, jaundice or acute liver failure
- Usually poor correlation between degree of ALT elevation and the severity of the liver disease
- Clinical and biochemical parameters often under estimate the degree of liver injury, histology being a more accurate indicator
- A good predictor of mortality in drug-induced hepatitis is Jaundice.
- Hy‟s Law: A consistent serum bilirubin ≥3×ULN in the absence of biliary obstruction or Gilbert‟s syndrome, is associated with a mortality of approximately10% (range, 5–50%)
- The hepatitis pattern of liver injury is most commonly accompanied by acute liver failure, defined as coagulopathy (INR ≥1.5) and hepatic encephalopathy occurring <26 weeks after onset of illness in a patient without pre-existing cirrhosis.This usually has a grave prognosis in absence of liver transplantation.

2. Cholestatic Pattern

- Canalicular cholestasis or ductular injury
- Canalicular cholestasis usually results from inhibition of bilirubin or the bile-salt transport (eg, cyclosporine or oestrogen metabolite) this is referred to as “bland”

cholestasis because histologically there is virtual absence of inflammation or necrosis.

- More commonly, however, cholestasis is associated with some degree of cholangiocyte injury.
- Presentation can mimic biliary obstruction or the course can be more indolent with jaundice and pruritus. Mortality appears tobe less than with the hepatitis pattern (1–7.8%) and death is usually not liver-related, through chronic cholestatic injury can result in ductopenia and rarely, cirrhosis.

• Mixed Pattern

Combination of acute hepatitis and cholestasis. This pattern of liver injury probably has the lowest mortality

• Other Forms of Hepatotoxicity

Granulomas, fibrosis, neoplasms, steatohepatitis and vascular lesions

Drug induced hepatotoxicity is the leading cause of hepatic injury, accounting for approximately half of all cases of acute liver failure (Lee, 2003., Navarro & Senior JR, 2006., Zimmerman, 1978) revealed that Therapeutic agents like acetaminophen, papaverine, tetracycline and nitrofurator are heptotoxic which taken in overdose or in case of poisoning. Antibiotic-induced hepatotoxicity can often be detected early from elevations in serum alanine aminotransferase (ALT) levels.This is frequently observed with amoxicillin/ clavulanate and tetracycline, and was reported for trovafloxacin. Walker, (1997) revealed that in overdose, the analgesic/antipyretic acetaminophen produces centrilobular hepatic necrosis. As most drugs are taken orally the liver is the portal to the tissues for such compounds following absorption from the gastrointestinal tract. The liver is, therefore, a vulnerable organ, being exposed to both the parent drug carried from the G.I. tract via the portal vein and to any metabolites produced which then enter the systemic circulation via the hepatic vein. Chemicals that cause liver injury are called hepatotoxins.More than 900 drugs have been implicated in causing liver injury. chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests(Bhaskar.R.K.2016).Drug induced liver injury is responsible for 5 % of all hospital admissions and 50 % of all acute liver failures (Ostapowicz et al, 2002).

1. Animals and Grouping of Animals

Experimental Part – I

Group-I - C-Control treated with normal feed.
Group-II – T1-Rats fed with 0.200 mg per kg Amoxycillin
Group-III – T2-Rats fed with 0.400 mg per kg Amoxycillin
Group-IV – T3-Rats fed with 0.600 mg per kg Amoxycillin
Group-V – T4 -Rats fed with 0.800 mg per kg Amoxycillin
Group-VI – T5-Rats fed with 1.000 mg per kg Amoxycillin

Experimental Part - II

Group-I - C-Control treated with normal feed.
Group-II - T1-Rats fed with 0.200 mg per kg Penicillin
Group-III - T2-Rats fed with 0.400 mg per kg Penicillin
Group-IV - T3-Rats fed with 0.600 mg per kg Penicillin
Group-V - T4-Rats fed with 0.800 mg per kg Penicillin
Group-VI - T5-Rats fed with 1.000 mg per kg Penicillin

Experimental Part - III

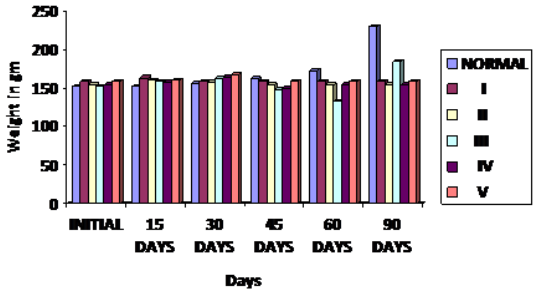
Group-I - C-Control treated with normal feed.
Group-II - T1-Rats fed with 0.200 mg per kg Tetracyclin
Group-III - T2-Rats fed with 0.400 mg per kg Tetracyclin
Group-IV - T3-Rats fed with 0.600 mg per kg Tetracyclin
Group-V - T4-Rats fed with 0.800 mg per kg Tetracyclin
Group-VI - T5-Rats fed with 1.000 mg per kg Tetracyclin

After treatment of specific period, animals were kept starved overnight 89th day of experiments.On next day the animals were sacrificed by decapitation and blood collected by cutting the jugular vein. The liver in each case were dissected out blotted of blood and washed with saline.Biochemical parameters require 1.5 to 50 µ l serum or plasma and are pre-programmed with as many as 20 different clinical chemistry tests.The challenge of clinical pathology laboratory was to develop or adapt procedures designed for human use into reliable tests for the elevation of organ function and toxicity.

Table 1: Weight of Amoxycillin treated experimental rats after 90 days

Period	*Group-1 Control*	*Group-2 T1*	*Group-3 T2*	*Group-4 T3*	*Group-4 T4*	*Group-5 T5*
Initial	152±3.4^{a}	158±3.1^{b}	154±4.2^{b}	152±3.6^{b}	154±4.1^{b}	158±2.3^{b}
15 DAYS	152±3.4^{a}	163±2.6^{b}	160±3.1^{b}	158±2.8^{b}	157±2.2^{b}	160±3.2^{b}
30 DAYS	156±3.1^{a}	158±3.1^{b}	157±3.3^{b}	162±3.1^{b}	164±3.2^{b}	168±3.1^{b}
45 DAYS	162±3.3^{a}	158±3.2^{b}	154±3.2^{b}	148±3.3^{b}	150±3.4^{b}	158±3.2^{b}
60 DAYS	173±3.3^{a}	158±3.1^{b}	154±3.1^{b}	133±3.2^{b}	154±3.1^{b}	158±3.3^{b}
90 DAYS	230±3.1^{a}	158±3.1^{b}	154±3.1^{b}	184±3.1^{b}	154±3.3^{b}	158±3.1^{b}

The Values are average for six rats in each group and are expressed in grams± SEM.Group-1 Control., Group-2 to 6 are tests

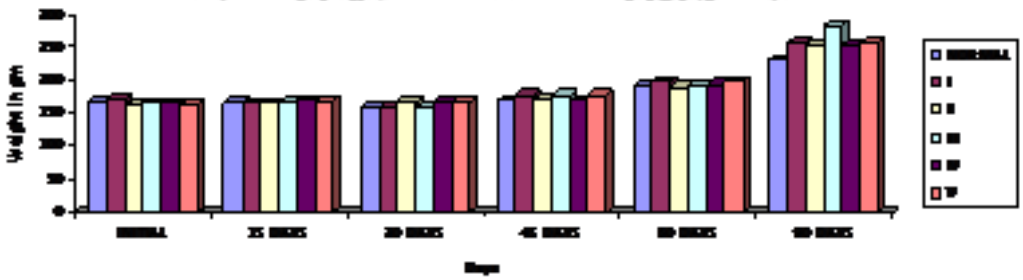


Graph 1: Weight of Amoxicillin treated experimental rats after 90 days

Table 2: Weight of Penicillin treated experimental rats after 90 days

Period	*Group -1 Normal-C*	*Group -2 I*	*Group -3 II*	*Group -4 III*	*Group -5 IV*	*Group - 6 V*
Initial	168±3.0 [a]	172±3.3 [b]	164±3.2 [b]	167±3.5 [b]	166±3.6 [b]	162±3.6 [a]
15 Days	168±3.7 [a]	167±3.2 [b]	166±3.0 [b]	168±3.1 [b]	169±3.1 [b]	168±3.4 [b]
30 Days	160±3.5 [a]	160±3.5 [b]	168±3.4 [b]	160±3.3 [b]	168±3.3 [b]	168±3.3 [b]
45 Days	170±3.4 [a]	178±3.4 [b]	174±3.6 [b]	178±3.2 [b]	170±3.4 [b]	178±3.4 [b]
60 Days	193±3.4 [a]	198±3.3 [b]	191±3.4 [b]	193±3.5 [b]	194±3.2 [b]	198±3.2 [b]
90 Days	233±3.1 [a]	258±3.5 [b]	254±3.5 [b]	284±3.2 [b]	254±3.4 [b]	258±3.3 [b]

The Values are average for six rats in each group and are expressed in grams± SEM.
Group-1 Control., Group-2 to 6 are tests.



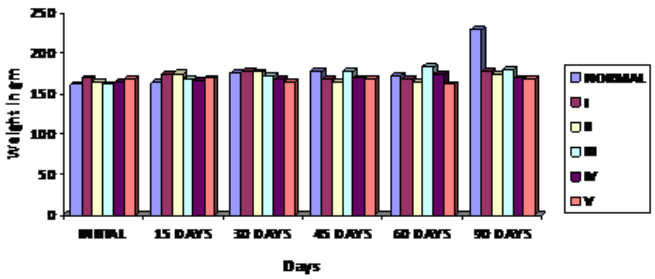
Graph 2: Weight of Penicillin treated experimental rats after 90 days

a- Statistical difference with control group at P < 0.05
b- Statistical difference with test group at P < 0.05.

Table 3: Table-2 Weight of Penicillin treated experimental rats after 90 days

Period	*Group-1 Control*	*Group-2 T1*	*Group-3 T2*	*Group-4 T3*	*Group-4 T4*	*Group-5 T5*
INITIAL	162±3.7 [a]	169±3.3 [b]	164±3.5 [b]	162±3.3 [b]	164±3.6 [b]	168±3.3 [b]
15 DAYS	164±3.8 [a]	174±3.4 [b]	175±3.8 [b]	168±3.5 [b]	167±3.3 [b]	169±3.4 [b]
30 DAYS	176±3.5 [a]	178±3.5 [b]	177±3.5 [b]	172±3.2 [b]	168±3.6 [b]	164±3.5 [b]
45 DAYS	178±3.6 [a]	168±3.7 [b]	164±3.7 [b]	178±3.4 [b]	170±3.5 [b]	168±3.6 [b]
60 DAYS	173±3.2 [a]	168±3.6 [b]	164±3.5 [b]	183±3.3 [b]	174±3.4 [b]	162±3.8 [b]
90 DAYS	230±3.5 [a]	178±3.5 [b]	174±3.4 [b]	180±3.5 [b]	170±3.2 [b]	168±3.5 [b]

The Values are average for six rats in each group and are expressed in grams± SEM.Group-1 Control., Group-2 to 6 are tests.



Graph 3: Weight of Tetracyclin treated experimental rats after 90 days

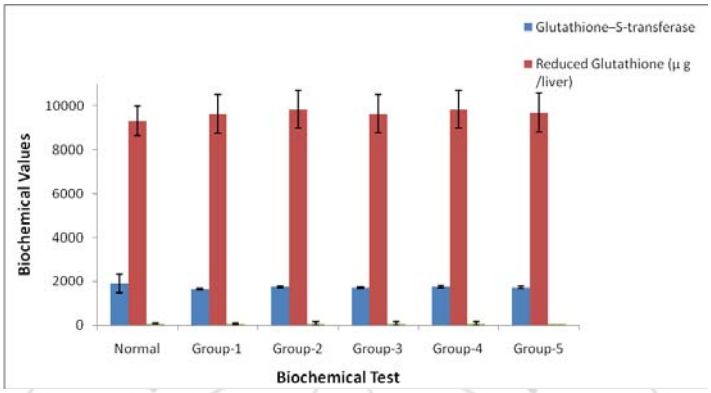
a- Statistical difference with control group at P <0.05
b- Statistical difference with test group at P < 0.05.

Significance: There was an increase in weight in all the groups or extendwhen compared to the normal which was found to be significant.

Table 4: Biochemical analysis of Amoxycillin treated rats

	Glutathione–S-transferase	*Reduced Glutathione (µ g /liver)*	*Lipid Peroxidase*
Group-1 Normal	1909.5±46.5 [a]	9321.3±683.3 [a]	86.0 ±14.50 [a]
Group-2 T1	1649.3±45.0 [b]	9646.5± 888.6 [b]	80.2 ± 36.3 [b]
Group-3 T2	1749.3±46.4 [b]	9846.5± 872.6 [b]	81.4 ± 86.3 [b]
Group-4 T3	1716.3±45.4 [b]	9646.5± 872.6 [b]	81.3 ± 86.3 [b]
Group-5 T4	1748.3±48.4 [b]	9846.5± 862.7 [b]	86.2 ± 85.3 [b]
Group-6 T5	1719.3±45.4 [b]	9716.5± 887.6 [b]	80.8 ± 87.3 [b]

The Values are average for six rats in each group and are expressed in grams± SEM.Group-1 Control., Group-2 to 6 are tests.
a- Statistical difference with control group at P <0.05
b- Statistical difference with test group at P < 0.05.



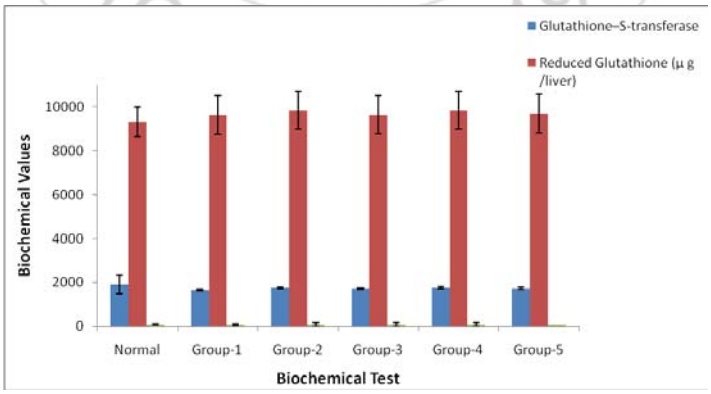
Graph 3: Weight of Amoxicillin treated experimental rats after 90 days

Significance: There was an increase in Glutathione in all the groups or extend when compared to the normal which was found to be significant.

Table 5: Biochemical analysis of Penicillin treated rats after 90 days

	Glutathione–S-transferase	*Reduced Glutathione(µ g /liver)*	*Lipid Peroxidase*
Group-1 Normal	1909.5±46.5 [a]	9321.3±683.3 [a]	86.0 ±14.50 [a]
Group-2 T1	1649.3±45.0 [b]	9646.5± 888.6 [b]	80.2 ± 36.3 [b]
Group-3 T2	1749.3±46.4 [b]	9846.5± 872.6 [b]	81.4 ± 86.3 [b]
Group-4 T3	1716.3±45.4 [b]	9646.5± 872.6 [b]	81.3 ± 86.3 [b]
Group-5 T4	1748.3±48.4 [b]	9846.5± 862.7 [b]	86.2 ± 85.3 [b]
Group-6 T5	1719.3±45.4 [b]	9716.5± 887.6 [b]	80.8 ± 87.3 [b]

The Values are average for six rats in each group and are expressed in grams± SEM.Group-1 Control., Group-2 to 6 are tests.
a- Statistical difference with control group at P <0.05
b- Statistical difference with test group at P < 0.05.



Graph 4: Weight of Tetracyclin treated experimental rats after 90 days

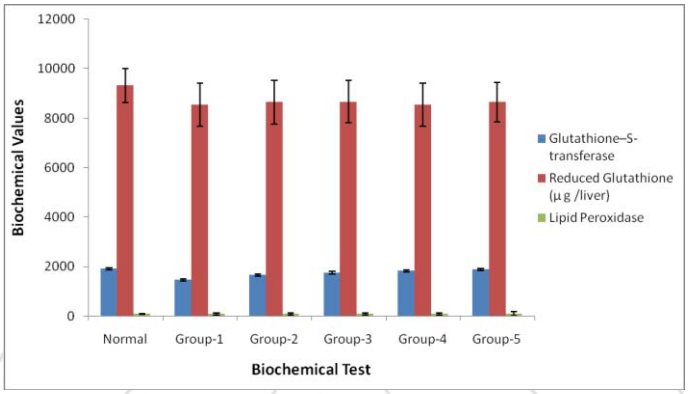
Significance: There was an increase in Glutathione in all the groups or extend when compared to the normal which was found to be significant.

Table 6: Biochemical analysis of Tetracyline treated rats after 90 days

	Glutathione–S-transferase	*Reduced Glutathione (µ g /liver)*	*Lipid Peroxidase*
Group-1 Normal-C	1909.5±45.5 [a]	9321.3±683.3 [a]	86.0 ±14.50 [a]
Group-2 T1	1849.3±45.4 [b]	9146.5± 882.6 [b]	86.2 ± 36.3 [b]
Group-3 T2	1819.3±45.4 [b]	9246.5± 882.6 [b]	85.4 ± 36.3 [b]
Group-4 T3	1816.3±45.4 [b]	9246.5± 882.6 [b]	84.3 ± 36.3 [b]
Group-5 T4	1849.3±45.4 [b]	9346.5± 882.6 [b]	83.2 ± 86.3 [b]
Group-6 T5	1819.3±45.4 [b]	9316.5± 882.6 [b]	82.8 ± 86.3 [b]

The Values are average for six rats in each group and are expressed in grams± SEM.Group-1 Control., Group-2 to 6 are tests.

a- Statistical difference with control group at $P < 0.05$
b- Statistical difference with test group at $P < 0.05$



Significance: There was an increase in Glutathione in all the groups or extendwhen compared to the normal which was found to be significant.

2. Conclusion

Antibiotics are considered as a common cause of drug-induced liver injury (DILI).Hepatotoxicity associated with penicillins is predominantly hepatocellular, although cases of cholestasis with ductopenia.Severe reactions include cholestasis and acute liver failure.Because of the short-term nature of protocols in clinical trials of antibiotics, these changes may remain unseen for a drug later proven to be hepatotoxic. Liver injury is characterized by hepatocellular necrosis and degeneration, such as hepatocyte ballooning, as well as mild inflammatory infiltrates within the portal tracts and cholestasis.Therefore examination of blood and liver in abnormal conditions which create pathological conditions become significant to help in the diagnosis and treatment of the many diseases including cancer.(Bhaskar, 2012).Drugs and other exogenous compounds may affect the liver in various ways (Kshirsagar, 2009).

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