Drug – induced hepatotoxicity

Lecture 7

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Drug - induced hepatotoxicity

Criteria

1. Mimic all liver diseases.
2. Careful history & investigations.
3. Prothrombin time is used for early diagnosis of iatrogenic liver dysfunction.

Also is prognostic in acute & chronic liver diseases.

Because t1/2 of vitamin K - dependent factors is short.

4. Genetic & environmental factors contribute.
5. ↑risk in old age.

6. Withdrawal is the main ttt.
7. Drugs used should be totally excreted by kidney.
8. Reaction onset: usually 5 days - 3 months.
9. Course after cessation: < 2 weeks (hepatocellular).
   < 4 weeks (cholestatic).
10. Reaction after re - administration: 1 day - 2 weeks (hepatocellular).
    1 day - 3 months (cholestatic).

Mechanism

1. Dose or duration - dependent.
2. Hypersensitivity reaction.
   Drug or its reactive metabolites → antibodies.
3. Idiosyncrasy: commonest….. in phase IV clinical trials.

Types of liver injury

A) Mild ↑ liver enzymes (ALT & AST) without manifestations.

e.g. statins , oral antidiabetics.

B) Hepatitis (hepatocellular):

1. Acute: inflammation or necrosis.

↑liver enzymes + manifestations.

e.g. acetaminophen, aspirin, diclofenac.

2. Fulminant (acute liver failure, encephalopathy):

↑↑ ALT or ALT/ alkaline phosphatase > 5.

↑↑Prothrombin time

3. Chronic: ↑ enzymes and/ manifestations > 3 months.

e.g. phenytoin, valproate, propylthiouracil, α methyl dopa, amiodarone (serious, after stopping, may need transplantation) & halothane.

C) Cholestasis:

↑bilirubin, alkaline phosphatase & GGT.

If > 3 months: chronic.

e.g.antiepileptics as phenytoin & carbamazepine, phenothiazines, haloperidol, TCA, naproxen, estradiol, oral contraceptives, androgens, anabolic steroids, carbimazole, rifampin, tetracyclines, cotrimoxazole, erythromycin estolate, Augmentin. ?

D) Fatty liver (steatosis):

With or without hepatitis.

Mild ↑ liver enzymes (ALT & AST) + enlarged liver.

May → cirrhosis or acute liver failure.

e.g. methotrexate, corticosteroids, valproate, tetracyclines, amiodarone, Reye,s syndrome, allopurinol, herbs,…. ?

E) Cirrhosis:

By B (chronic),C or D.

e.g. amiodarone, α methyl dopa, methotrexate.

F) Granuloma:

e.g. phenytoin, allopurinol.

G) Tumors:

e.g. sex hormones & oral contraceptives.

In D – G: abdominal ultrasonography.

Hepatic encephalopathy

Mechanism

Gut bacteria on dietary proteins, produce:

a. Urease : proteins into ammonia.

b. Glutaminase: glutamine into glutamate & ammonia.

Normally, ammonia is converted into:

1. In liver → urea.

2. In brain astrocytes → + glutamate (by glutamine synthetase) → glutamine.

In hepatic encephalopathy:

1. ↑ammonia.
2. ↓glutamate.
3. ↑GABA ergic tone.

This → brain edema & neuropsychiatric manifestations.

In fasting: glycogenolysis is not sufficient to ↑blood glucose.

So ↑gluconeogenesis → ↓amino acids, ↑ammonia & sarcopenia.

Precipitating factors

1. GIT infection.
2. ↑dietary proteins.
3. GIT bleeding.
4. Hypokalemia.