Current Practice

DISEASE OF THE DIGESTIVE SYSTEM

Drugs and the Liver

SHEILA SHERLOCK,* M.D., F.R.C.P., F.R.C.P.ED., F.A.C.P.(HON.)

The last quarter-century has seen the introduction into clinical practice of large numbers of new and potent therapeutic agents. Many of them have unexpected effects on the liver, which sometimes have little clinical significance but which may be fatal (see Table). Many of the hepatic sequelae, and unfortunately most of the serious ones, cannot be predicted on the basis of previous tests of toxicity on animals.[1] The rarity of some, and their close resemblance to naturally occurring acute virus hepatitis, may make it difficult to identify the drug with the untoward reaction.

Classification of Drug Jaundice

Type	Examples	Dose Dependent	Prognosis
Haemolytic	Phenacetin		
Conjugation	Novobiocin	Yes	Good
Competition excretion	Cholecystographic media	,,	,,
Direct hepatotoxins ..	Tetracycline	,,	Depends dose
	Cytotoxic drugs		
Hepatitic	M.A.O. inhibitors	No	20% mortality
	Halothane		
Cholestatic			
Steroid	Methyl testosterone	Partly	Good
Sensitivity	Chlorpromazine	No	Usually good
Hypersensitivity ..	Sulphonamides	,,	,, ,,
	P.A.S.		
	Erythromycin estolate		

Drug Detoxication

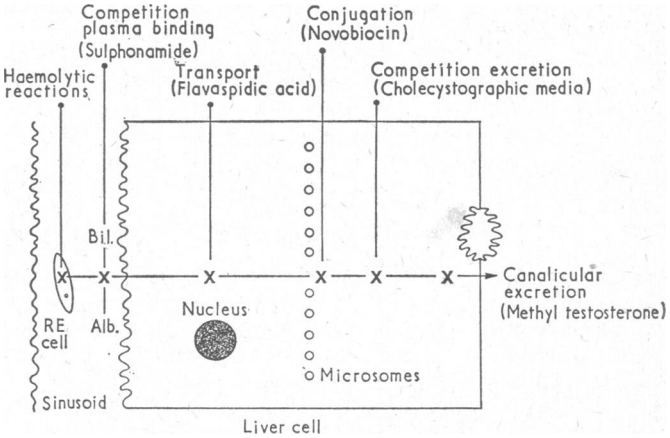
Many drugs are metabolized by the liver, so making them more polar—i.e., water soluble—for extraction into the bile. This is done by oxidizing, reducing, hydrolysing, or conjugating enzymes which are largely located in the hepatic microsomes, part of the smooth endoplasmic reticulum of the liver cell.[2] Metabolism of the drug may make it more potent (e.g., phenylbutazone) or less potent (e.g., pethidine) or even produce a toxic derivative (e.g., chloramphenicol). Sometimes metabolism by the liver is necessary to make the drug clinically effective (e.g., cyclophosphamide).

Much discussion concerns the effect of certain drugs in patients with underlying liver disease. It is common knowledge that morphine may precipitate coma in patients with cirrhosis and that paraldehyde causes profound sleep in some patients with liver disease. It is difficult to show that the half-life of these and other drugs is increased in patients with cirrhosis, though recent investigations have shown that this is probably so.[3] Any drug should be given with caution to patients with underlying liver disease. If sedation of the patient is mandatory then half the usual dose of butobarbitone (which is excreted by the kidney) or an antihistaminic, such as promethazine, may be used.

The rate at which a drug is metabolized by the liver may be increased by the process of enzyme induction. A great many drugs cause an activation of the microsomal enzymes of the endoplasmic reticulum, which can actually be shown to hypertrophy after their use.[2] This may explain why certain drugs, particularly barbiturates and meprobamate, become less effective and have a shorter duration of action with repeated use. Even patients with underlying liver disease are able to improve their hepatic metabolism to some extent by this method.[3] This is probably the process by which the alcoholic becomes increasingly tolerant of alcohol. In the later stages, however, when liver damage has occurred, alcohol tolerance is diminished, probably owing to the reduction in the amounts of hepatic detoxicating enzymes, particularly alcohol dehydrogenase, in cirrhotic liver.[4] Enzyme induction is nonspecific and is not confined to the enzymes actually concerned in the metabolism of the drug being administered. This principle of nonspecific enzyme induction has been applied therapeutically. A patient with deep, unconjugated hyperbilirubinaemia was given phenobarbitone in order to induce the enzymes which metabolize bilirubin and did indeed show a marked reduction in icterus.[5]

Drugs which Interfere with Bilirubin Metabolism

Drugs can interfere with the handling of bilirubin at all points in its passage from the reticulo-endothelial cell into the bile (see Fig.). Drugs causing haemolysis increase the load of unconjugated bilirubin on the liver cell. Drugs such as sulphonamides or salicylates compete with serum albumin for binding with bilirubin. Flavaspidic acid, the active principle of male fern, interferes with the transport of bilirubin through the hepatic cell. Novobiocin inhibits the conjugation of the bilirubin as a glucuronide. All cholecystographic media compete with the conjugated bilirubin for excretion into the biliary canaliculus. Drugs which are C-17-substituted testosterone



Diagrammatic representation of a liver cell showing the passage of bilirubin from the reticuloendothelial cell to the bile canaliculus. X marks the point at which various drugs can interfere with bilirubin metabolism.

* Professor of Medicine, Royal Free Hospital, University of London.

derivatives interfere with excretion at a biliary canalicular level and cause a cholestatic (obstructive) jaundice. This cholestasis is associated particularly with such drugs as methyl testosterone and norethandrolone, but probably applies to almost all orally active anabolic or androgenic agents.[6]

These reactions are, by and large, mild, reversible, and of little importance. They assume clinical significance in two circumstances. In the newborn the microsomal enzymes are slow to develop and there is difficulty in conjugating bilirubin. Neonatal jaundice and its complication kernicterus can therefore develop. Any of the drugs which interfere with bilirubin metabolism at premicrosomal or microsomal levels can potentiate kernicterus, and these are to be avoided. Patients with underlying defects of bilirubin metabolism, such as Gilbert's syndrome of unconjugated hyperbilirubinaemia, or with hepatocellular impairment (recovering hepatitis, cirrhosis) may well show overt jaundice when these drugs are given.

Direct Hepatic Toxicity

Certain substances produce a predictable liver injury when given to human subjects or to experimental animals. Other organs suffer in company with the liver and in most instances renal damage is more important than hepatic. Nausea, vomiting, and diarrhoea reflect gastrointestinal injury, and confusion and coma signify central nervous system involvement.

Carbon tetrachloride is a good example. It can be taken accidentally or suicidally. Renal damage is usually more important than hepatic, and haemodialysis may be life-saving. This and other similar solvents may be incriminated as causes of industrial liver injury. In general, permanent liver damage due to these chemicals is unusual and progression to cirrhosis is rare. Screening in factories where the workers are exposed to hepatotoxins should include regular testing of the urine for bilirubin and estimation of serum transaminase and pseudocholinesterase values.

The tetracyclines depress hepatic metabolism. In the usual therapeutic dosage and under normal circumstances they are quite safe. Their use in the last trimester of pregnancy has been associated with the development of acute fatty liver, a particularly serious complication of pregnancy. Intravenous tetracycline should be avoided in large doses (greater than 3 g. a day), especially when protein synthesis is deficient or stressed, as in malnutrition or pregnancy.[7] Overdose of such drugs as paracetamol or ferrous sulphate is associated with hepatic necrosis.

Cytotoxic drugs are hepatotoxic, but it is difficult to separate this effect from the hepatic change induced by the disease for which the drug is being given.[8] The clinical picture of a hepatitis can be produced by 6-mercaptopurine, methotrexate, or 5-fluoro-2-deoxyuridine. In addition, cytotoxic drugs may damage vascular endothelium and cause injury to the central hepatic veins within the lobule. A Budd–Chiari (hepatic venous occlusion) syndrome is thus produced.[9] Local irradiation to the liver can have similar effects.

Hepatitis-like Reactions

These reactions cannot be distinguished from ordinary acute virus hepatitis. Since there is no specific diagnostic test for this common virus infection, the possibility of a coincident and unrelated virus hepatitis can never be completely excluded. The reaction is unrelated to dose or to duration of therapy. It may be more frequent after multiple exposures. The hepatitis can develop as long as three weeks after stopping the drug. The incidence is low, but the condition has a high mortality of about 20%. It cannot be predicted from preliminary animal testing, as only humans seem to be affected.

This reaction was originally associated with cinchophen. It seems possible that some instances of delayed chloroform poisoning were of this type. More recently this hepatitic reaction has been associated with the hydrazine amine oxidase inhibitors, particularly with iproniazid (Marsilid), pheniprazine (Cavodil), phenoxypropazine (Drazine), phenelzine (Nardil), and isocarboxazid (Marplan). Some of these drugs are no longer used because of this unfortunate complication, even though it is rare. Isonicotinic acid hydrazide (isoniazid), although a hydrazine, has fortunately been recorded to cause this reaction only exceedingly rarely. Other non-hydrazine drugs have been related, such as ibufenac.[10]

The position of the anaesthetic halothane is particularly difficult to assess. At least 30 million halothane anaesthetics have been given and there are fewer than 100 reported cases of an associated hepatitic reaction. There are many other causes of postoperative jaundice, and the close resemblance to natural acute viral hepatitis always makes the relation of the anaesthetic to the jaundice difficult to determine. The position could be clarified if "challenge" experiments were possible. These are not ethically justifiable with such a potentially serious reaction (20% mortality). On two occasions they have been done by chance[11 12] and once by an anaesthetist using himself as the subject.[13] The results in these "challenge" tests clearly suggest a relationship between the anaesthetic and a hepatitic reaction. The problem seems to be one of individual sensitivity. The hepatitic reaction is independent of dose, mode of administration of the anaesthetic, or the surgical procedure being performed. It is not particularly apt to affect those having hepatobiliary operations or those with underlying liver disease. It seems more frequent after multiple exposures. Patients having gynaecological, orthopaedic, or plastic surgical treatment may therefore be particularly at risk.

The first anaesthetic is followed within five days by fever, leukocytosis, bile in the urine, and a slight rise in serum bilirubin level. Jaundice develops some one to two weeks after this first exposure or after the second anaesthetic. It is probably unwise to give repeated halothane anaesthetics within six months of each other, especially if the first has been followed by an otherwise unexplained febrile reaction. The rarity of this reaction to halothane is emphasized by the findings of the National Halothane Study conducted in the United States.[14] Eleven thousand necropsies within six weeks of general anaesthesia were scrutinized. In 82 patients massive hepatic necrosis was present, but in only nine could this be explained in no other way than by the anaesthetic. Seven of the nine patients had received halothane and in five of these on more than one occasion.

Sensitive-type Cholestasis

This type of cholestatic (obstructive) jaundice is usually associated with the phenothiazines, of which chlorpromazine is a good example. The reaction is unrelated to dose and can follow only one tablet given as much as four weeks previously. The usual onset is within one to three weeks of starting the drug. Sensitivity rashes, blood dyscrasias, eosinophilia, and, frequently, recurrence on regiving all suggest that this is a hypersensitivity type of reaction. It cannot be predicted on the basis of tests on animals.

The severity of the illness is very variable. Usually the jaundice is mild and transient, lasting only a few days. Sometimes it is deep and surgical obstructive jaundice is simulated. Care has to be taken that the patient does not undergo a laparotomy, and here a careful history of previous drug therapy is very important. Very rarely the cholestatic jaundice persists for more than three years, but ultimate complete recovery is usual.[15]

The reaction seems to be associated with all the phenothiazine drugs, including chlorpromazine (Largactil), promazine

(Sparine), prochlorperazine (Stemetil), pecazine (Pacatal), and trifluoperazine (Stelazine). One drug does not seem more likely to be causative than another. The frequency depends on how much of the agent is being used in the community concerned.

Other Types of Hypersensitivity Jaundice

The reaction to para-aminosalicylate is particularly complex. It is probably the commonest drug used in antituberculous chemotherapy to be associated with a hepatic reaction. Sometimes the reaction is a generalized hypersensitivity one with rashes, eosinophilia, and jaundice. Alternatively (and more frequently) the picture may resemble the sensitivity, chlorpromazine type of cholestasis.[16] Sulphonamides are in a similar position.[17] A complex hepatitic and cholestatic reaction can follow treatment with other antituberculous drugs, including pyrazinamide, ethionamide, and cycloserine. Tolbutamide, chlorpropamide, and methimazole can also cause a cholestatic drug reaction.[18]

Erythromycin estolate can cause a cholestatic type of jaundice, sometimes with a generalized hypersensitivity reaction,[19] and commoner after multiple exposures. Neither antibiotic base itself nor erythromycin stearate is hepatotoxic. As erythromycin seems effective in the stearate form, there seems little indication nowadays to use the estolate, which is potentially hepatotoxic.

The liver may be involved in other hypersensitivity reactions, —for instance, to penicillin or to the anticoagulant phenindione.

Oral Contraceptive Drugs

The "pill" is composed of an oestrogen and a progestogen. Either or each is usually a C-17-substituted compound of testosterone and as such has potentially cholestatic properties. The rarity of cases of jaundice among the many millions of women taking the pill has various possible explanations. In part it is due to the very small dose of cholestatic drug consumed. In part it is related to the underlying susceptibility, possibly genetic, of the women being treated. It is interesting that the only large series of patients reported with jaundice complicating oral contraceptive therapy have come from Scandinavia and Chile.[20] It is from these countries that the largest series of patients with cholestatic jaundice of the last trimester of pregnancy have been described. Moreover, about half the patients who react to the pill have suffered from this condition. This suggests that the sufferers have an undue sensitivity both to some steroid contained in the pill and to one produced during pregnancy. The end result is cholestasis of variable severity. Oral contraceptives should not be given to patients who have experienced jaundice or itching in the last trimester of pregnancy. Patients with underlying liver disease may also react abnormally, and "the pill" should not be prescribed for patients with underlying liver disease or within six months of recovery from virus hepatitis.

Most instances of jaundice associated with the pill are seen in the first three cycles of administration. If jaundice is seen after this it is probably not related to the pill.

Nonspecific Changes in Liver Function due to Drugs

Transient changes in serum transaminase levels may be seen after many drugs. They follow the start of oral contraceptive therapy in a high proportion of patients. They may follow the administration of certain hypotensive and vasodilator drugs, some anti-inflammatory agents, and carbenoxolone sodium, and they may be found in workers exposed to hepatotoxic substances. If the drug is continued the biochemical changes usually revert to normal. Fluctuations in serum enzyme levels may be found in untreated, apparently normal persons, and it is exceedingly difficult to know the significance of these reactions in those taking various drugs. The serum enzymes concerned are virtually specific for liver injury, and elevation of the level presumably reflects a hepatic disturbance. The prognostic importance is uncertain. In doubtful cases the drug must be stopped and further investigations of liver function undertaken.

Conclusions

Before a drug is given its possible hepatotoxic effects must be considered. Particular attention must be paid to the individual patient being treated, particularly to the age, underlying liver function, and the disease present. A drug should not be given if it carries even a small risk of causing a hepatic reaction and there is an equally effective therapeutic alternative.

A careful history of drug therapy, with identification of the drugs being given, is essential in any patient developing liver damage or jaundice.

All possible untoward drug reactions, however well recognized the association may be, should be reported to the Medical Assessor, Committee on Safety for Drugs, Queen Anne's Mansions, Queen Anne's Gate, London S.W.1. Postage prepaid letter cards are available for reporting.

REFERENCES

1. Sherlock, S., *Medicine (Baltimore)*, 1966, **45**, 453.
2. Remmer, H., *Progress in Liver Diseases*, ed. H. Popper and F. Schaffner, 1965, **2**, 116. Grune and Stratton, New York.
3. Levi, A. J., and Sherlock, S., *Gastroenterology*, 1967, in press.
4. Leevy, C. M., *Proceedings of the Third World Congress of Gastroenterology*, Tokyo, 1966, in press.
5. Whelton, M. J., Krustev, L. P., and Billing, B. H., *Amer. J. Med.*, 1968, in press.
6. Sherlock, S., *Diseases of the Liver and Biliary System*, 4th edition, 1968. Blackwell's Scientific Publications, in press.
7. Kunelis, C. T., Peters, J. L., and Edmondson, H. A., *Amer. J. Med.*, 1965, **38**, 359.
8. Hersh, E. M., Wong, V. G., Henderson, E. S., and Freireich, E. J., *Cancer (Philad.)*, 1966, **19**, 600.
9. Reed, G. B., jun., and Cox, A. J., jun., *Amer. J. Path.*, 1966, **48**, 597.
10. Thompson, M., Stephenson, P., and Percy, J. S., *Ann. rheum. Dis.*, 1964, **23**, 397.
11. Tygstrup, N., *Lancet*, 1963, **2**, 466.
12. Wilpert, L., and Creutzfeldt, W., *Germ. med. Mth*, 1967, **12**, 360.
13. Belfrage, S., Ahlgren, I., and Axelson, S., *Lancet*, 1966, **2**, 1466.
14. *J. Amer. med. Ass.*, 1966, **197**, 775.
15. Read, A. E., Harrison, C. V., and Sherlock, S., *Amer. J. Med.*, 1961, **31**, 249.
16. Simpson, D. G., and Walker, J. H., ibid., 1960, **29**, 297.
17. Dujovne, C. A., Chan, C. H., and Zimmerman, H. J., *New Engl. J. Med.*, 1967, **277**, 785.
18. Popper, H., Rubin, E., Gardiol, D., Schaffner, F., and Paronetto, F., *Arch. intern. Med.*, 1965, **115**, 128.
19. McKenzie, I., and Doyle, A., *Med. J. Aust.*, 1966, **1**, 349.
20. Orellana-Alcade, J. M., and Dominguez, J. P., *Lancet*, 1966, **2**, 1278.