JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205

Volume 14 Issue 09, September 2024

Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

ACTION MECHANISMS OF DRUGS THAT AFFECT THE LIVER AND THEIR PECULIARITIES

Egamberdiyev Jasurbek Jumanazar o'g'li

Andijan State Medical Institute, Uzbekistan

Annotation: This article provides information on the mechanism of action of drugs that affect the liver. The liver performs the function of a filter, being considered one of the most important organs in the body. Therefore, patients who are constantly undergoing treatment in any disease are honored with Tafsia by adding liver-protective drugs. The article was written in a state of widespread use of internet resources.

Key words: liver, drug, artery, blood.

The liver receives approximately 30% of cardiac output. Uniquely it receives both arterial blood from the hepatic artery and venous blood from the portal veins. The portal vein supplies 70–75% of hepatic blood flow but only 50% of oxygen supply, the remaining blood flow and oxygen supply being from the hepatic artery.

Anatomically the liver is divided into two lobes and further into functional lobules based around a central vein, which contains blood from the hepatic arterial and portal venous circulations. Blood arriving to the liver flows into the sinusoids which are spaces lined by hepactocytes. Blood then drains towards the centre of the lobule and the central vein then hepatic vein to return blood back to the heart via the inferior vena cava. It is the portal veins taking blood directly from the gut to the liver which allows for first pass metabolism, making the liver susceptible to ingested drugs as they are absorbed from the gastrointestinal tract and transported to the liver.

The liver metabolises a wide range of drugs the end result being to produce water soluble compounds which can be excreted in the bile. This results from phase 1 reactions mediated by cytochrome p450 including oxidation, reduction and hydrolysis reactions. This is followed by phase 2 reactions which are conjugative.

Cytochrome P450

The cytochrome P450 family are a group of enzymes found mainly in the liver, which perform oxidation and reduction reactions (phase 1) using iron to enhance the water solubility of drugs to aid excretion. CYP450 enzymes are so named as they are bound to membranes within the cell

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 14 Issue 09, September 2024
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

and contain a haem pigment that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide.

There are many different isoforms of CYP450, classified according to their amino acid sequencing into families, subfamilies and individual genes. Their importance can be seen in certain subgroups that lack particular genes. An example pertinent to anaesthesia is deficiency in CYP2D6 which metabolises codeine to morphine, these patients therefore find codeine ineffective. Conversely there is a small subgroup of people of Saudi Arabian and Ethiopian descent with very high expression of 2D6 who metabolize codeine into vast amounts of morphine. An individual more detailed breakdown of CYP450 genes is beyond the scope of this article.

Prevalence of ultrarapid metabolisers[2]

Population	Prevalence of ultrarapid metabolisers
African or Ethiopian	29%
African American	3.4–6.5%
Asian	1.2–2%
Caucasian	3.5–6.5%
Greek	6%
Hungarian	1.9%
Northern European	1–2%

Some drugs can induce or inhibit CYP450 enzymes which have the sequential effect on the metabolism of other drugs, either increasing or reducing it respectively. Possibly the most important example is CYP3A4 which metabolises many substrates and is induced by rifampicin, carbamazepine, phenytonin and dexamethasone. Of interest to anaesthesia this will increase metabolism of opioids, benzodiazepines and local anaesthetics. Another well cited example is the increased metabolism of the oral contraceptive pill and its reduction in efficacy.

A number of non-cytochrome p450 dependent reactions occur in the liver, e.g. oxidation of dopamine and alcohol and hydrolysis of amides and esters (e.g. lignocaine and pethidine respectively). A predominant rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) signals hepatocellular injury or death. This can be caused by drug reactions or toxicity (e.g. paracetamol), viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, ischaemic hepatitis secondary to profound hypotension, and rare causes such as Wilson's disease.

An obstructive pattern has a rise predominantly in alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT); these are canalicular enzymes and suggest cholestasis. This is caused by obstruction, either calculi or tumour (primary biliary, pancreatic or metastases), and

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 14 Issue 09, September 2024
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

liver disease such as primary biliary cirrhosis. Pharmacological causes include antibiotics, anabolic steroids and oral contraceptives.

A mixed pattern can be seen in sepsis, some drug reactions, cholangitis, congestive cardiac failure and alcoholic liver disease. Halothane hepatitis can cause raised liver enzyme assays, raised bilirubin and jaundice. An isolated rise in unconjugated bilirubin may be attributed to Gilbert's syndrome or haemolysis.

The SARS-CoV-2 virus uses angiotensin-converting enzyme 2(ACE-2) receptors to gain entry into cells.[3] Liver particularly in the ductal region has abundance of these receptors, and hence may be susceptible to SARS-CoV-2[4] Elevated LFT have been reported widely in hospitalized patients with COVID-19; the range of elevation is highly variable, from 14 to 58%. Surprisingly, the pattern of elevation mimics hepatocyte damage (AST/ALT higher than bilirubin or ALP) rather than cholangiocytic damage, as would have been expected given that the density of ACE-2 receptors is higher in the ductal system. Additionally low albumin has been seen and is a marker of severe disease. One study reported longer hospital stay in patients with elevated LFT.

An international registry has suggested that as many as 25% of patients with COVID-19 may present with hepatic decompensation in the absence of respiratory symptoms.

The above findings hold important implications for anaesthetists, especially in preoperative assessments.

Absorption

Most drugs given in anaesthesia and intensive care are given intravenously, thus having a bioavailability of 1. However, some may be given orally or nasogastrically and absorbed enterally. The absorption will be affected by delayed gastric emptying or reduced by diarrhoea and increased gastric transit time seen in liver failure. Additionally, if vasopressors are used there may be splanchnic vasoconstriction with associated reduced absorption.

Volume of distribution

Volume of distribution is a theoretical calculated volume within which a dose of a drug is dissolved. Hepatic dysfunction can cause fluid retention and will increase the volume within which drugs are present, particularly those which usually remain in the plasma, thus increasing their volume of distribution and reducing their plasma concentration.

In liver disease, protein synthesis may be reduced. These proteins are important as binding sites for drugs and as such alter the amount of free drug available, volume of distribution, half life and

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 14 Issue 09, September 2024
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

duration of action. An important example is albumin. Hypo-albuminaemia will increase the proportion of free drug which is active; therefore doses of highly protein bound drugs may need to be reduced, for example phenytoin and benzodiazepines, aspirin and warfarin.

Another protein produced by the liver, α_1 acid glycoprotein, binds basic drugs such as carbamazepine, propanolol, alprenolol and imipramine as well as steroids. Bilirubin can also compete for protein binding sites, so raised levels can increase the amount of free drugs; the effect however is less in vivo than in vitro.

Metabolism and elimination

Problems with absorption of enterally delivered drugs have been described. Once absorbed these drugs undergo the 'first pass effect' by the liver before reaching the systemic circulation. In liver failure the degree of metabolism will be reduced, therefore the extraction ratio will also be reduced and more drug will reach the systemic circulation, thus increasing bioavailability.

Metabolism of drugs in liver disease depends on liver blood flow. This can be reduced in a cirrhotic liver as portovenous shunting in the form of varices which are created and blood is diverted directly into the systemic circulation bypassing the liver. Thus first pass metabolism is reduced.

Drug metabolism by the liver may also be reduced by the use of vasopressors on intensive care which reduce liver blood flow due to varying degrees of splanchnic vasoconstriction. The phase 1 and 2 reactions performed by the liver are affected and metabolism – and thus extraction ratios – are reduced.

Drugs can be divided into those with high extraction ratios >0.7, for example fentanyl and morphine and low extraction ratios <0.3 such as lorazepam, diazepam and methadone. Most drugs have low extraction ratios <0.3, that is they have poor permeability and are metabolized by the liver but poorly extracted; therefore clearance is limited by reduced metabolism not by blood flow. Those with high extraction ratios >0.7 are highly permeable and clearance is dependent on blood flow.

Hepatic dysfunction is not uncommon within the intensive care setting affecting 11–54% of critically ill patients depending on definitions used. There is currently no tool akin to renal clearance to indicate degree of liver dysfunction. Therefore clinicians use liver function blood tests, international normalized ratio (INR), serum albumin and clinical scores such as the Child Pugh score act as a surrogate for function. More recently the Model for End Stage Liver Disease (MELD Score) and the MELD-Na have been used to more accurately predict the severity of liver

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 14 Issue 09, September 2024
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

dysfunction. However, their correlation with pharmacokinetic function not well understood.

Due to the alterations discussed in pharmacokinetics in liver dysfunction drug choices, dosages and frequency may need to be rationalized and altered accordingly. For example the induction dose and maintenance dose, for either anaesthesia or sedation, needs to be reduced.

Inhalational agents

Historically inhalational agents, particularly halothane have been implicated in causing hepatitis. The risk is related to the generation of trifluroacteyl chloride (TFA) by metabolism of agents, which is implicated in toxicity.[12] Around 20% of administered dose of halothane is metabolized by the liver, more specifically by cytochrome P450. This is a relatively high percentage when compared to more modern inhalational agents, for example 0.2% isoflurane, 0.02% desflurane and 3% sevoflurane. Even though sevoflurane undergoes 3% metabolism it does not generate TFA and hence is not linked to immune mediated injury. Sevoflurane metabolism produces fluoride which is not linked to hepatotoxicity. Inhalational agents themselves cause a dose dependent reduction in hepatic blood flow (HBF). Isoflurane and sevoflurane result in relatively lower reduction in HBF at 1 MAC as compared to desflurane.

As long as hypotension is avoided and the above effects are kept in mind desflurane is probably the safest choice of inhalational agent due to its low rate of metabolism and rapid and predictable emergence from anaesthesia.

There are two types of halothane hepatitis. Type 1 which is mild, transient and has a relatively high incidence (25–30%). Type 2 caused by oxidative metabolism of halothane in the liver leading to fever, jaundice, and dramatically elevated serum transaminases. The compounds synthesized by oxidation then bind to trifluoroacetylate proteins in the hepatic endoplasmic reticulum causing cellular dysfunction; it is thought to occur in genetically predisposed individuals.

The Committee on Safety of Medicines in 1986 recommended the avoidance of halothane in patients with a history of previous adverse reactions, those who had received halothane within 3 months unless clinically necessary, and those with a history of unexplained jaundice or pyrexia following previous halothane anaesthesia.

IV Anaesthetics: the induction agents have a marked effect on haemodynamics and may cause sudden precipitous fall in blood pressure. In clinical practice a standard induction dose need not be altered. However, they should be titrated slowly to effect. There are no current recommendations on the use of TIVA (Total Intravenous Anaesthesia) in patients with liver disease. Research is sparse and conflicting. Some earlier reports suggested that inhalational

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 14 Issue 09, September 2024
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

anaesthesia results in smaller elevation of liver enzymes than TIVA with propofol-fentanyl.[16] A more recent study however, suggested a slightly lower rate of elevation in LFT after using TIVA.

References:

1. Bernal W. Changing patterns of causation and the use of transplantation in the United Kingdom. Semin Liver Dis. 2003;23:227. \
2. MHRA Drug Safety Update. 2010;vol. 3 [Google Scholar]
3. Hoffmann M., Kleine-Weber H., Schroeder S., et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271–280. e8. 4. Alqahtani S.A., Schattenberg J.M. Liver injury in COVID-19: the current evidence. United Euro Gastroenterol J. 2020 Jun;8:509–519. [PMC free article] [PubMed] [Google Scholar]
4. Huang J., Cheng A., Kumar R., et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. May 2020;10:1002. [PMC free article] [PubMed] [Google Scholar]
5. Xu L., Liu J., Lu M., Yang D., Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40:998–1004. doi: 10.1111/liv.14435. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
6. Moon A.M., Webb G.J., Aloman C., et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry. J Hepatol. May 2020;73:705–708.