REVIEW

Clinical and Pharmacological Significance of Extrahepatic Drug Metabolism in Man

Dr David Kyegombe*

Human population is exposed to an ever increasing number of substances in its environment. These foreign compounds (xenobiotics) and drugs gain access to the human body through skin, gastrointestinal tract, respiratory system and in case of the foetus, via the placenta. These extrahepatic organs and tissues, to a limited extent, act as mechanical barriers against substances potentially harmful to the human body. This partial protection is greatly enhanced and supplemented by metabolism of the chemical substances by drug metabolising enzymes. The liver is by far the principal organ for biotransformation of drugs and xenobiotics. However significant activities of drug metabolising enzymes have been demonstrated in mammalian extrahepatic tissues[1,2]. There is extensive clinical and pharmacokinetic evidence that various types of hepatic dysfunction result in reduced drug elimination and increased drug action, ranging from modest to major[3]. The presence of drug-metabolising enzymes in extrahepatic tissues in animals has underlined their beneficial function as the first line detoxification defence against body exposure to toxic substances while at the same time it also highlights some harmful effects. However similar studies in humans remain extremely limited and this review sets out to discuss some of the available human data.

EXTRAHEPATIC DRUG METABOLISM IN MAN

It has been reported that aryl hydrocarbon hydroxylase (AHH), an enzyme found in human skin, metabolises a number of aromatic hydrocarbons from the environment and may serve as a protective system against the carcinogenic effects of these xenobiotics[4,5]. The activity of this enzyme system can be greatly enhanced by the hydrocarbons thus stimulating their own metabolism. This has been demonstrated by the increased enzymatic breakdown of the carcinogen, 3-4 benzpyrine, found in tobacco smoke, in the placenta of women who smoke during pregnancy[6,7]. Indeed placental AHH activity has been suggested as a practical biochemical index to measure the exposure of foetus to maternal cigarette smoke. Furthermore, induction of AHH activity in peripheral lymphocytes, monocytes and macrophages shows good correlation with cigarette consumption[8]. With greater refinement these indices may be useful in evaluating the cancer risk among smokers and those exposed to carcinogenic hydrocarbons. It is interesting to note that organic hydrocarbons have been shown to induce mixed function oxidase (MFO) enzymes much more in the intestines and lungs than in the liver[9].

* Assistant Professor
College of Medicine & Medical Sciences
Arabian Gulf University.
State of Bahrain

Other studies have revealed that the human placenta had significant activities of oxidative, reductive and hydrolytic enzymes as well as UDP-glucuronyl transferase enzyme system[10]. The possible function of these drug-metabolising enzymes in extrahepatic tissues may be even more important in the placenta where the organ plays a supplementary metabolic role to the foetal liver, the enzyms of which are under-developed and at a stage of foetal development when the foetus is more sensitive to chemical substances than the adult species[11]. Studies of this nature may be a vital starting point in investigating drug-induced foetal abnormalities.

Franklin and Kyegombe[10] measured the activities of drug-metabolising enzymes in subcellar fractions of human liver, renal cortex, lung, gastric mucosa, colonic mucosa, spleen and prostate freshly obtained at surgery. It was shown that generally the enzymes representing the major classes of enzyme systems of oxidation, reduction, hydrolysis and conjugation could be detected in most of the extrahepatic tissues, but at levels markedly less than those of liver. However, the activity of L-leucyl-B-naphthylamide-splitting enzyme, which is considered to be involved in the metabolism of exogenous insulin, was many times higher in the renal cortex than in the liver. The clinical significance of this interesting observation is not clear. The investigators further demonstrated that these extrahepatic drug-metabolising enzymes could not be induced by phenobarbitone, while the hepatic ones could. The variations in the influence of enzyme inducers on different tissue enzymes suggests an interesting prospect of studying the specific sequence of events of enzyme induction in man. The variations in normal activity and in the inducibility of certain enzymes in extrahepatic tissues may partly explain the occurrence of certain cancers, drug idiosyncrasy, organ-specific drug toxicity, allergic reactions and other generalised adverse drug effects, consequent to the formation of toxic or reactive metabolites within the cells of extra hepatic tissues. For example, the nitroso and hydroxylamine metabolites resulting from the reduction of nitro-groups have been shown to cause methaemoglobinaemia while the products of certain azo-dyes (butter yellow) have been known to cause cancers in animals[12].

The biotransformation of xenobiotics in the intestinal mucosa may explain the carcinogenesis in the gut. This raises some interesting medical possibilities concerning the peculiar epidemiology of cancer of the mouth (India), oesophagus (China), stomach (Japan) and colon (USA). It is generally suspected that exogeneous factors play a role in the pathogenesis of gastro-intestinal cancer. These factors may be the highly reactive intermediate metabolites of xenobiotics such as superoxides and hydrogen peroxides[13]. It has been shown that gastro-intestinal mucosal tissue can metabolise chemical carcinogens such as, benzpyrene[14],[15], nitrosamines[14], dimethyl-hydrazine[16] and aflatoxin[14]. Paradoxically cancer of the jejunum and ileum are rare in humans although the activities of drugs-metabolising enzymes in these tissues are markedly higher than those in the colon and stomach.

The presystemic metabolism of xenobiotics during the intestinal first pass have a significant detoxification function. For example it has been shown in normal humans that doses of oral tyramine below 500 mg have no effect on systemic blood pressure. However, 5 mg of oral tyramine in patients on monoamine oxidase inhibitors may be sufficient to produce a hypertensive crisis due to reduced intestinal first pass deamination[17],[18]. Another consequence of intestinal drug metabolism is to reduce the bioavailability of such drugs as morphine[19], isoprenaline[20] and oestrogens[21].

It should be noted that some drug metabolism is carried out by the microflora normally found in the human gut[8]. The metabolism of orally administered substances by the microflora may lower the drug bioavailability while the active metabolites produced could be absorbed, thus giving rise to unpredictable pharmacological effects. Furthermore, drugs such as chloramphenicol, stilboestrol and long acting sulphonamides when eliminated as conjugates are hydrolysed by bacterial enzymes in the lumen, and the parent compounds so released may be re-absorbed thus setting up an entero-luminal circulation with prolongation of plasma half-lives.

Certain surgical or therapeutic procedures do alter extrahepatic drug metabolism in man. It is well known that prolonged antibiotic therapy or intestinal resection affect the metabolism of certain drugs by altering the distribution and/or species of the intestinal microflora[22]. Finally some intestinal diseases can affect intestinal biotransformation. For example gluten-sensitive enteropathy will reduce the intestin-

al metabolic capacity by reducing the total enterocyte mass.

Recent studies in rabbits suggest that paracetamol is metabolised to highly reactive metabolite(s) in the kidney. These metabolites undergo covalent binding to renal cellular proteins, especially in the inner medulla making this region particularly susceptible to papillary necrosis seen in analgesic nephropathy[23]. During normal therapeutic dosage, the kidney is protected from tissue damage by glutathione which conjugates the toxic metabolites. The mechanism in this respect is probably similar in man according to clinical observations[24].

Organ disease or removal may affect the metabolism and pharmacological effects of drugs which are specifically concentrated in certain target organs. Liver disease (necrosis, cirrhosis, infection etc) may compromise the organ's role as a major metabolic site[25] thus shifting the dependance for drug detoxification more to the extrahepatic sites. Normal plasma half-lives of drugs have been registered in patients with cirrhosis and known to have received no enzyme inducer[26] and this could be explained partly on the basis of compensatory extrahepatic metabolism. Some clinical conditions such as renal disease, malabsorption, cardiovascular disease and pregnancy may alter body tissue metabolism of chemical agents as a result of changes in the dynamics and volume of distribution of drugs in the various body fluid compartments[27].

Another pharmacologically interesting suggestion is that some drug metabolites are formed in-situ, and by virtue of being chemically similar to the parent drug tend to compete with it for receptor sites, thus resulting in altered pharmacological effects of the parent drug[28].

CONCLUSION

The liver is the major organ for the extensive biotransformation of substances foreign to the human body. However extrahepatic metabolism supplement the liver to various degrees depending on the chemical nature of the substrate, its route of entry into the body and inducibility of the metabolising enzymes. The impact of extrahepatic drug metabolism on biochemical pharmacology and environmental medicine is now beginning to have important implications for clinical medicine. More human studies will be needed before we can make a more definite evaluation of the significance of the subject.

REFERENCES

1. Gram TE. Extrahepatic Metabolism of drugs and other foreign compounds. Lancaster : MTP Press, 1980.

2. Rydstrom J, Montelius J, Bengtsson M. Extrahepatic Metabolism and Chemical Carcinogenesis. Amsterdam: Elsevier Science Publishers, 1983.

3. Klotz U, McHorse TS, Wilkinson GR, et al. The effect of cirrhosis on the disposition and elimination of mepheridine in Man. Clin Pharmacol Ther 1974;16:667-675.

4. Alvares AP, Kappas A, Levin W, Conney AH. Inducibility of benzo (3,4) pyrene hydroxylase in human skin by polycyclic hydrocarbons. Clin Pharmacol Ther 1973;14:30-40.

5. Nebert DW, Winter J, Gelboin HV. Induction of 3,4 benzpyrine hydroxylase in placenta of smoking mothers. Cancer Res 1969;29:1763-1769.

6. Welch RM, Harrison YE, Gomm BW, et al. Stimulating effect of cigarette smoking on the hydroxylation of 3,4 Benzpyrene and the N-Demethylation of 3-Methyl Monomethylaminoazo-benzene by enzymes in human placenta. Clin Pharmacol Ther 1969;101:100-109.

7. Vaught JB, Gurtoo HL, Parker NB, et al. Effect of smoking on Benzo(a)pyrene metabolism by human placental microsomes. Cancer Res 1979;39:3177-3183.

8. Gahmberg CG, Sekki A, Kosunen TU, et al. Induction of aryl hydrocarbon hydroxylase activity and pulmonary carcinoma. Int J Cancer 1979;23:302-305.

9. Koivusaari U, Lang M, Hietanen. Differences in the response of hepatic and intestinal drug metabolising enzymes in rats following carbon tetrachloride and/or phenobarbital treatment. Acta Pharmacol Toxicol (Copenh) 1980;46:37-42.

10. Franklin CS, Kyegombe DB. The distribution and induction of some drug-metabolising enzymes in man. Brit J Pharmacol 1973;47:616.

11. Wilson JG, Scott W, Ritter E, Fradkin R. Comparative distribution and embryotoxicity of methotrexate in pregnant rats, rhesus monkeys. Teratology 1979;19:71-79.

12. Huggins C, Grand LC, Fukunishi R. Aromatic influences on the yields of mammary cancers following administration of 7,12, dimethylbenz (a) anthracene. Proc Nat Acad Sci (USA) 1964;51:737-742.

13. Sipes IG, Gandolfi AJ. Biotransformation of toxicants. In: Klaassen CD, Amdur MO, Doull J, eds. Casarett and Doulls Toxicology. New York: Macmillan Publishing Co, 1986;64-98.

14. Autrup H, Harris CC, Wu SM, et al. Activation of chemical carcinogens by cultured human fetal liver oesophagus and stomach. Chem Biol Interact 1984;50:15-25.

15. Cohen GM, Grafstrom RC, Gibby EM, Smith L, Autrup H, Harris CC. Metabolism of benzo(a)pyrene and 1-naphthol in cultured human tumorous and non-tumorous colon. Cancer Res 1983;43:1312-1315.

16. Schwenk M. Use of human intestinal epithelial cells for drug metabolism studies. Naunyn-Schmeideb Arch Pharmacol (Suppl) 1986;332:240-250.

17. Bieck PR, Antonin KH. Monoamine oxidase inhibition by tranylcypromine: Assessment in human volunteers. Eur J Clin Pharmacol 1982;22:301-308.

18. Bieck PR, Schick CH, Aichele G, et al. Oral tyramine pressor tests and tyramine kinetics in subjects treated with different MAO-inhibitors. In: Shagass C, Josiassen RC, Briger WH, Weiss KJ, Stoff D, Simpson GM, eds. Biological Psychiatry. New York: Elsevier Science Publishing Co Inc, 1985;335-337.

19. Villar E, Sanchez E, Tephyl TR. Morphine metabolism II. Studies on morphine glucuronyl-transferase activity in intestinal microsomes of rats. Drug Metabol Dispos 1974;2:370-375.

20. George CF, Blackwell FW, Davies DS. Metabolism of isoprenaline in the intestine. J Pharm Pharmacol 1974;26:265-267.

21. Schwenk M, Schiemenz C, Lopez del Pin V, Remmer H. First-pass biotransformation of ethinylestradiol in rat small intestine in situ. Naunyn-Schmeideb Arch Pharmacol 1982;321:223-225.

22. Scheline RR. Drug metabolism by intestinal microorganisms. J Pharm Sci 1968;57:2021-2037.

23. Saker BM, Kinacid-Smith P. Papillary necrosis in experimental analgesic nephropathy. Br Med J 1969;1:161-162.

24. Prescortt LF. Pharmacokinetic drug interactions. Lancet 1969;2:1239-1243.

25. Kyegombe DB, Al-Mofleh I, Al-Khuwaitir S, Muhamoud A. Effect of Murine Schistosomiasis on hepatic cytochrome P-450 and microsomal protein. Liver 1986;6(3):167-172.

26. Levi AJ, Sherlock S, Walker D. Phenylbutazone and isoniazid metabolism in patients with liver disease in relation to previous drug therapy. Lancet 1968;1:1275-1279.

27. Rowland M, Blascheke TF, Meffin PJ, Williams AL. In:Benet LZ,ed. Symposium on influence of disease states on drug pharmacokinetics. Washington D C: American Pharmaco-kinetics. American Pharmacological Association 1967; 53-63.

28. Rehavi M, Paul SM, Skolnick P, Goodwin FK. Demonstration of specific high affinity binding sites for (3H) imipramine in human brain. Life Sci 1980;26:2273-2279.