The Aging Liver
Drug Clearance and an Oxygen Diffusion Barrier Hypothesis

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Contents

Summary .......................................................... 359
1. Aging and the Liver ........................................... 360
   1.1 Morphological Changes ................................... 360
   1.2 Physiological Changes .................................... 361
   1.3 Biochemical Changes ...................................... 361
   1.4 Clinical Implications ..................................... 362
   1.5 Drug Metabolising Enzymes ............................. 362
   1.6 Drug Clearance In Vivo .................................. 363
2. Principles of Hepatic Drug Clearance ....................... 363
3. Physiological Theories of Aging and Hepatic Drug Metabolism ........................................... 364
   3.1 Hepatic Blood Flow ....................................... 364
   3.2 Intrinsic Clearance ...................................... 365
   3.3 Protein Binding .......................................... 365
4. Disease-Based Theories of Aging and Hepatic Drug Metabolism ........................................... 367
   4.1 Intact Hepatocyte Theory ................................. 367
   4.2 Sick Cell Theory .......................................... 367
   4.3 Impaired Drug Uptake Theory ............................ 368
   4.4 Oxygen Limitation Theory ............................... 368
5. Alternative Theories ........................................ 370
   5.1 Hepatocyte Membrane Transporter Change .............. 370
   5.2 Cellular Physico-Chemical Change ....................... 370
6. Dosing Guidelines ........................................... 370
7. Therapeutic Horizons and Conclusions .................... 371

Summary

A change in drug clearance with age is considered an important factor in determining the high prevalence of adverse drug reactions associated with prescribing medications for the elderly. Despite this, no general principles have been available to guide drug administration in the elderly, although a substantial body of clearance and metabolism data has been generated in humans and experimental animals. A review of age-related change in drug clearances established that patterns of change are not simply explained in terms of hepatic blood flow, hepatic mass and protein binding changes. In particular, the maintained clearance of drugs subject to conjugation processes while oxygen-dependent metabolism declines, and all in vitro tests of enzyme function have been normal, requires new explanations.
Reduction in hepatic oxygen diffusion as part of a general change in hepatocyte surface membrane permeability and conformation does provide one explanation for the paradoxical patterns of drug metabolism, and increased hepatocyte volume would also modify oxygen diffusion path lengths (the ‘oxygen diffusion barrier’ hypothesis). The reduction in clearances of high extraction drugs does correlate with observed reduction in hepatic perfusion.

Dosage guidelines emerge from these considerations. The dosage of high clearance drugs should be reduced by approximately 40% in the elderly while the dosage of low clearance drugs should be reduced by approximately 30%, unless the compound is principally subject to conjugation mechanisms. If the hepatocyte diffusion barrier hypothesis is substantiated, this concept may lead to therapeutic (preventative and/or restorative) approaches to increased hepatocyte oxygenation in the elderly. This may lead to approaches for modification of the aging process in the liver.

Prescribing drugs for elderly people is a major professional challenge for many medical practitioners. On one hand, the incidence of most illnesses increases with age; hence, the elderly are likely to benefit from the use of appropriate medications. On the other hand, the elderly more frequently suffer from the adverse effects of drugs. Hurwitz, in a survey of 1268 patients admitted to a general hospital, found that the rate of adverse reactions more than tripled in patients over 70 years old. This trend has also been observed in general practice and possibly to an even greater extent amongst elderly in nursing homes. It has been argued that old age itself is not an independent risk factor for adverse drug reactions but merely a marker for comorbidity, altered pharmacokinetics and polypharmacy, however, this argument was advanced in an attempt to prevent exclusion of older volunteers from clinical trials.

The need to reduce adverse drug reactions has stimulated much research into the effects of age on drug metabolism. It is surprising that despite significant research efforts, the effect of age of hepatic drug metabolism continues to be a controversial issue. The observed changes in the clearance of drugs that undergo hepatic metabolism were originally attributed to changes in hepatic enzyme activity and more recently to altered hepatic size and blood flow. However, it has been recognised that none of these invoked mechanisms fully explain the age-related changes in hepatic drug clearance seen in vivo.

In this paper we present a review of the effects of age on those general aspects of liver function and activity that could impact on drug metabolism and also review the adequacy of current pharmacokinetic theories to explain the effects of age on hepatic drug clearance. This paper focuses on systemic drug clearance because of the inconsistencies in the data available for presystemic clearance and aging. As a result of these reviews, we propose alternative theories which may help explain some of the observed, but unexplained, effects of age on hepatic drug metabolism. If validated, these proposals provide a practical clinical basis for safer prescription choices and drug design as well as dosage guidelines in the elderly.

1. Aging and the Liver

1.1 Morphological Changes

Macroscopically the liver is described as undergoing ‘brown atrophy’ with old age. Initially, aging was found to be associated with a 20% reduction in liver weight in males and an 11% reduction in females. This trend has been confirmed many times in both humans and animals using a