7.3.3. Ageing

The biological and physiological consequences of aging can dramatically affect the pharmacokinetic profile of a medication (177). This can have serious implications for pharmacotherapy in the elderly. For example, increased gastric pH, decreased GI motility, and reduced intestinal blood flow can affect the rate and extent of drug absorption following oral administration. The shift in body composition (increased body fat, reduced total body water) with age can affect V_D and $t_{1/2}$ of both lipophilic (↑ distribution) and hydrophilic (↓ distribution) compounds. Likewise, alterations in cardiac output, organ mass, and organ function collective reduce the ability of aging individuals to clear medications. The pharmacokinetics of a drug is also subject to changes in pediatric subjects, where drug metabolism enzyme expression is considerably different from adult humans (178,179). In recent years, considerable research is devoted in understanding the pharmacogenomics of drug metabolizing enzymes in children also (180). Several other factors related to absorption, distribution, and excretion could also contribute to pharmacokinetic differences in children (181).

The expression of CYP enzymes changes markedly during development. CYP3A7 is the predominant CYP isoform expressed in fetal liver. CYP3A7 peaks shortly after birth, and rapidly declines to undetectable levels, being replaced primarily with CYP3A4. Distinct isoform-specific developmental expression of CYPs has been noted postnatally in the following order of appearance: CYP2E1, CYP2D6, CYP3A4, CYP2C9/19, and CYP1A2 (180). CYP2E1 expression surges within hours after birth, CYP3A4 and CYP2C appear during the first week of life, and CYP1A2 appears at one to three months of life.

8. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODELING OF PRECLINICAL DATA

PK/PD modeling was traditionally been utilized only during phase 2 to phase 4 trials, using clinical PK and efficacy data. Today, PK/PD modeling is also combined with computer simulations to design trials, prior to initiation of the clinical trials. Although the use of preclinical pharmacokinetic–pharmacodynamic modeling and simulation in drug development is presented in Chapter 6, the topic will be briefly discussed here.

In recent years, modeling approaches have been applied to preclinical studies to predict first in human (FIH) or Proof of Concept (POF) dosing regimens. This approach is popularly becoming known as Computer Assisted Trial Design (CATD) or Computer Assisted Drug Development (CADD). Typically, for phase 2 to 4 trial designs, CATD simulates virtual clinical trials under various design scenarios to predict the outcomes of real-life clinical trials, based on mathematical models that reflect the following: