18 Clinical Pharmacology in Drug Labeling. The Impact of Drug Metabolism and Clinical Pharmacology on Recommended Dose of Drugs

STUART DOMBEY
QuatRx Pharmaceuticals, Ann Arbor, MI, USA

18.1 INTRODUCTION

The main principle of drug labeling is to provide the prescriber with sufficient objective information to make informed prescribing decisions. The structure of US drug labels has evolved over time, and in 2006 new regulations were put in place to make the organization and chapter headings of drug labels consistent and easier to understand for both the patient and physician. Nevertheless, the labels have lengthened and the composite book of US labels (the 2011 edition of the PDR) has grown to over 3250 pages of labeling information on over 1116 of the most commonly prescribed drugs. Issues of dosing, drug metabolism, and clinical pharmacology have to be carefully reviewed for any drug prescribed to avoid unwanted consequences. Important issues

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are addressed as "black box warnings" although there is some dispute whether or not this information is used in a consistent manner [1]. The length of the label may also reflect a defensive legal side as well as the more helpful informational aspect. Despite the carefully crafted labeling information, drugs are increasingly prescribed off label, which means using approved drugs in unapproved situations [2].

Modern drugs are fully investigated before approval and marketing and tend to be very robust in dose and rarely need dose modification. This chapter discusses how we reached this state and provides some examples from the past of drugs that were inappropriately dosed or that required dose modification based on variations in drug metabolism or excretion. Recommended drug doses are currently based on a full development program providing appropriate doses to maximize efficacy and minimize safety issues. In addition, a full drug development program uses clinical pharmacology to investigate pharmacokinetics and pharmacodynamics, including potential metabolic variability and drug–drug interactions. The full description of the efficacy, safety, and clinical pharmacology information collected is then presented in the drug labeling for the use of physicians and patients. Whether or not this information leads physicians to make dosing modifications for individual subjects is discussed.

Before considering the impact of drug metabolism, it is worth considering how recommended drug doses are decided; and the factors that may influence that decision both before and after regulatory approval. For new drugs or old drugs for new indications, the process of drug development leads to a choice of dose, dosing interval, and method of administration. Appropriate formulations are then manufactured to satisfy those needs and the definitive clinical trials are usually carried out using those formulations, which are then taken through to marketing.

Selection of new drugs usually involves a choice from a range of chemicals with different physical and chemical properties, leading to potential benefits in terms of absorption, distribution, and elimination. Once selected, the chemical is tested in animals to determine the nature of any toxicity at high doses and the serum levels of drug that are associated with those toxicities. This allows the first use in man using appropriate algorithms to compare kinetics in different species and choosing a dose with an adequate safety margin [3]. From that point clinical pharmacology guides the process, but the minimum dose is considered from observation of efficacy and the maximum dose from the appearance of toxicity or maximum tolerability. This is made easier for drugs with a clear surrogate end point such as measurement of serum cholesterol or blood pressure, but it is harder for drugs with more subjective end points, such as pain, or psychiatric disorders. Thus, at the end of the development program, a recommended dose range is chosen together with appropriate formulations and a full label to guide prescribing.

The basis for the dose range is supported by clinical trials in predominantly healthy subjects, that is, those with the disease of interest but otherwise healthy. Additional studies provide information on absorption, distribution, and elimination; potential interaction with food; drug–drug interactions; and pharmacokinetics in the presence of renal and hepatic impairment. The product is then launched and subsequent information becomes available through postmarketing surveillance, phase 4 clinical trials, and other sources of information. This ultimately leads to changes in the label providing guidance to physicians and users. Thus, information from real world use leads to continuing updates to prescribing information as the product life cycle continues.

18.2 RECOMMENDED DOSE OF DRUGS

The dose of drug chosen, for marketing, at least for small molecules, is usually an arbitrary or compromise dose, dependent on number preferences. For example, a dose of 10 mg of drug a day could have been in a range of 5–15 mg and the number preference was to make a 10-mg dosage form rather than 7.5-, 8-, or 12.5-mg dose. These decisions are to some extent made by market comparisons and also by the risk–benefit profile (lower doses sacrifice efficacy for safety, whereas higher doses are more likely to be efficacious at the potential risk of higher adverse event rates). This lack of precision rarely matters because the variability of serum levels of the same drug in the same individual is usually greater than a small difference in the dose of drug. However, there are a small number of drugs that are very sensitive to variations in serum level, and they may have to be monitored carefully, either by measuring the serum drug level or by measuring the pharmacological action of the drug. Some examples are warfarin, phenytoin, and digoxin.

The US label for warfarin actually lists seven different oral presentations between 1 and 10 mg, as well as a parenteral form, and states that dosage needs to be individualized for each patient by regular measurement of clotting through the INR (international normalized ratio) [4].

Phenytoin has only one slow release form of 100 mg with an initial recommended dose of 300 mg/day and subsequent adjustments up to 600 mg/day. That allows dose adjustment with the objective to prevent seizures without inducing phenytoin toxicity. Because of the narrow therapeutic range, it is advisable to measure phenytoin serum levels until the dose is stable. It appears that the wide interindividual variability is due to CYP2C9 and CYP2C19 variants [5].

Digoxin is similar in its narrow therapeutic range and the manufacturer provides four solid oral doses staged by doubling the previous dose (62.5, 125, 250, and 500 μg) as well as a liquid capsule and a parenteral form. In the 1970s, the Burroughs Wellcome Company changed the formulation of the branded Lanoxin (digoxin) tablet, unintentionally, making it more bioavailable. This resulted in a number of cases of digoxin toxicity and shows that dose cannot be considered independently of formulation and actual bioavailability [6].

For the vast majority of small molecule drugs, there is a wide therapeutic range so that dose selection is less critical. This has led to a number of examples of excessive recommended doses of drugs continued over many years. The recommended dose of estrogens, for example, was excessive for many years, probably because estrogens were first used in the 1940s and were not subjected to current standards of clinical pharmacology. A paper in 1948 [7] described the dose of ethinyl estradiol (which had just become available in Britain) at around 1 mg/day, whereas the current tablet size is 0.03 mg. It is not clear that the lowest effective dose of the various forms of estrogen has even now been reached, leading to confusion in the literature about the efficacy and hazards of estrogen use in women at different times of pre- and postmenopause [8].

The dose of captopril was initially 150 mg three times daily in the majority of preapproval studies and was initially approved at that level. It was subsequently used at doses closer to 25 mg two or three times daily. The adverse effect profile was reviewed soon after the launch of captopril and showed that rash and taste disturbance were clearly dose-related adverse effects when compared to doses >150 mg/day and <150 mg/day, and the efficacy was maintained at the lower dose [9].

Another area to consider in initial drug dosing is the first-time use in humans. The FDA provides extensive guidance on estimating the initial human dose [3]. This has been an area of relative safety, but a recent experience with a biological has inspired a fresh look at first in man dosing. Tegeneron 1412 is a monoclonal antibody to CD28, which was studied in animals and then caused severe life threatening reactions in all four of the initial volunteers, who were all dosed at the same time. A representative critique suggests that further nonclinical work should have been carried out before initiating human dosing and the initial dose was too high [10].

On the basis of this history, regulators have clarified and expanded the clinical pharmacology requirements for new drugs and new formulations to lead to a fuller understanding of desirable dosing. This leads to a large amount of information to include in the label for drugs that is designed to help good prescribing.

18.3 FORMULATION AND METHOD OF ADMINISTRATION

The concept of a dose is based on the formulation and method of administration. Some drugs such as fenofibrate have been reformulated to have different doses in the different formulations each providing similar activity. Fenofibrate is a relatively insoluble molecule, so altering the physical properties, such as by micronizing the active pharmaceutical ingredient changes the bioavailability. This leads to different dosages depending on the type of formulation with doses of 48 and 145 mg for the Tricor brand; 130 mg for the Antara brand; 160 and 200 mg for the Lofibra brand; and 45–135 mg for Trilipix a delayed release form. In addition, the absorption of fenofibrate is increased by 35% when given with food for all of the brands except Trilipix.

18.4 AGE

An understanding of dosing is needed at both ends of the age spectrum. It has been traditional in children to use drugs studied in adults and adjust the dose in some nonspecific way. Since 1997, the pharmaceutical industry has been encouraged to carry out studies in children because of the Food and Drug Administration Modernization Act (FDAMA), which provides additional six months of marketing exclusivity in return. This has provided more appropriate information to prescribe in children based on actual pediatric experience in the disease of interest.

As individuals get older, their renal function deteriorates leading to a need for specific dosing guidance. Groups of interest are subjects with ages from 65 to 75, 75 to 85 and older than 85 [11]. One of the first drug problems in the elderly occurred with the drug benoxaprofen, a nonsteroidal anti-inflammatory agent. Benoxaprofen was initially approved at a single dose of 600 mg/day but turned out to have a much longer half-life in the elderly population, particularly, in subjects over 80 years of age. A series of subjects, all aged over 80 years, had cholestatic jaundice and died probably related to the excessive benoxaprofen serum levels seen in this population [12]. A study suggested that the drug was being overdosed particularly in the elderly [13]. This episode led to the requirement for pharmacokinetic studies in the elderly to ensure the dosing is consistent with the younger population and adverse events are kept to a minimum [14].

18.5 SIZE AND WEIGHT

Most labeling is silent on dose adjustments for weight or BMI (body mass index). However, some attempts have been made to study different doses for different sized people. A study of heparin suggested that if doses were modified, it would lead to more rapid anticoagulation and reduced bleeding, but the concept has not been widely adopted [15]. Anticancer drugs are usually prescribed based on body surface area and are labeled as a dose per meter squared. This concept was started in the 1950s but has been questioned [16]. It has also been suggested that the interpretation of body surface area leads to underdosing of anticancer medication for the treatment of breast cancer, particularly, in subjects of low socioeconomic status [17]. Some other classes of drugs, including anesthetic agents, do have nomograms for modifying dose based on weight or BMI; but the best way of estimating the dose adjustment still has to be established [18].

18.6 RENAL IMPAIRMENT

It is clear that if a drug is excreted by the kidneys, either as the unchanged parent drug or as major metabolites, the plasma, blood, and tissue levels are likely to rise in the presence of increasing renal impairment. That has led the FDA to insist on estimating this increase in subjects with renal impairment for all chronic use drugs whether or not they are renally excreted [19]. The results of these small pharmacokinetic studies are then reported in the label with statements such as "use with caution in subjects with renal impairment."

However, there are some drugs that become toxic as the serum levels increase, and this has led to various methods for monitoring and adjusting dose in response to renal impairment. Aminoglycoside antibiotics have traditionally been used in renal impairment even though they cause both ototoxicity and nephrotoxicity at high systemic levels. An early nomogram for gentamicin was published in 1972 that allows the dose to be modified to maintain efficacy in all degrees of renal impairment and hemodialysis, and the results were very successful in terms of outcome. Another drug that has to be used with caution in subjects with renal impairment is lithium. As lithium toxicity impairs renal function, it exacerbates the problem, and careful monitoring of lithium levels is important. It may be necessary to use hemodialysis to reduce lithium toxicity [20].

Because of the general concerns about using drugs in renal impairment, efforts have been made to offer guidelines for such prescribing that go beyond the approved label [21]. Such advice is almost certainly used in renal units where the issues are fully understood and there is very little margin of error. However, in the more general medical environment, the issues of renal impairment are probably underestimated [22]. Physicians seeking clarity on the appropriate dosing guidance in renal impairment may find confusion in the various official and secondary sources of information [23].

Renal physicians are comfortable using a limited number of drugs in subjects with severe renal failure or on dialysis, but there is some confusion in the general population who may incidentally have mild or moderate renal impairment. Although there are theoretical concerns, it does not appear that there is a major safety issue for the majority of drugs and those drugs that are well known to cause problems have appropriate dose adjustment guidelines. The use of language such as "use with caution" is probably too vague to be useful in practice.

18.7 HEPATIC IMPAIRMENT

Many drugs are metabolized by the liver either into inactive metabolites or into active moiety. It is therefore recommended that such drugs have pharmacokinetic studies in mild, moderate, and severe liver function as measured by the Child-Pugh classification. Unlike renal disease, there is no simple factor that determines the degree of liver function The study design recommended by the FDA [24] involves studying the drug in at least eight usable subjects with the relevant amount of hepatic dysfunction and an age- and sex-matched control group. This provides pharmacokinetic information but does not really address whether or not there are consequences of chronic use in such subjects and whether or not the dose needs adjusting. There are some drugs that may be needed to modulate the hepatic disease such as prednisolone and other drugs that are needed for chronic or acute therapy in subjects who happen to have some degree of hepatic impairment, but in general, it is easier to avoid or reduce the use of therapeutic drugs in subjects with marked hepatic impairment..

A full discussion of the various factors involved in dose adjustments in hepatic dysfunction has been published [25]. They include protein binding as well as increases and decreases in efficacy as a result of potential pharmacokinetic changes in both the parent drug and its metabolites. In addition, safety considerations may be intensified in subjects with hepatic impairment. This is a consideration particularly with antineoplastic drugs, which may also contribute to the hepatic toxicity and resulting dysfunction. However, there is no clarity in dose adjustments for particular drugs even though the pharmacokinetic changes may be clear resulting in a clinical dosage trial in each subject as suggested by some authors [26].

18.8 METABOLIC PATHWAYS

The knowledge of metabolism of individual drugs is a major part of drug discovery and development starting with *in vitro* microsomal studies and following through with extensive study of metabolic pathways and the resulting potential drug–drug interactions. This is discussed extensively in this encyclopedia. Drugs with high potential for interactions are rarely chosen to develop further. However, this is an area where drug labeling is more precise and the results of pharmacokinetic drug–drug interaction studies are accurately presented. There are two potential directions of concern. Does the drug interact with other drugs because of competition, stimulation, or inhibition of a particular pathway that may be needed for the metabolism of the other drug? Alternatively, does the other drug interfere with the metabolism of the new drug because of competition, stimulation, or inhibition of the relevant metabolic substrates? This leads to presentation of the data in the label with statements about the pharmacokinetic changes.

If we use Lipitor (atorvastatin) as an example of a commonly used drug, the dosing consequences from the label can be seen.

Under the heading of drug interactions, we see the following statements:

> The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole).

No numbers are presented to help assess the increased risk. Is it from 0.001% to 0.002%, which is a doubling, but remaining very rare; or is it from 5% to 6%, a smaller increase of the population but one that will affect many more people? Many physicians use fibrates and atorvastatin together and a combination tablet has been under development [27] with results that were encouraging and showed no increase in myopathy in a relatively small study.

The metabolism of modern drugs is well understood allowing fairly accurate statements to be made in the label.

Strong Inhibitors of CYP3A4. Lipitor is metabolized by cytochrome P450 3A4. Concomitant administration of Lipitor with strong inhibitors of CYP3A4 can lead to increase in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4.

Clarithromycin. Atorvastatin AUC was significantly increased with concomitant administration of Lipitor 80 mg with clarithromycin (500 mg twice daily) compared to that of Lipitor alone. Therefore, in patients taking clarithromycin, caution should be used when the Lipitor dose exceeds 20 mg.

Combination of Protease Inhibitors. Atorvastatin AUC was significantly increased with concomitant administration of Lipitor 40 mg with ritonavir plus saquinavir (400 mg twice daily) or Lipitor 20 mg with lopinavir plus ritonavir (400 + 100 mg twice daily) compared to that of Lipitor alone. Therefore, in patients taking HIV protease inhibitors, caution should be used when the Lipitor dose exceeds 20 mg.

Itraconazole. Atorvastatin AUC was significantly increased with concomitant administration of Lipitor 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the Lipitor dose exceeds 20 mg.

So, it is clear that despite the known interaction, it is reasonable to use up to 20 mg Lipitor, and it may even be useful to use higher doses. How are the individual physician and patient to decide? Although no formal survey has been performed discussion with a number of practicing physicians suggests that each subject is considered in a therapeutic environment with reductions in dose to alleviate adverse events and increases in dose to maintain the desired therapeutic effect so the language in the label may be ignored unless issues arise.

Grapefruit Juice It contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L/day).

Does this mean that subjects should not take grapefruit juice or that they should take grapefruit juice to increase the efficacy of Lipitor? The clinical answer suggests that it depends on how the subject is responding although this statement seems to cause concern to subjects on atorvastatin.

Cyclosporine Atorvastatin and its metabolites are substrates of the OATP1B1 transporters. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of Lipitor 10 mg and cyclosporine 5.2 mg/kg/day compared to that of Lipitor alone. In cases

where coadministration of Lipitor with cyclosporine is necessary, the dose of Lipitor should not exceed 10 mg.

The advice is clear but the maximum AUC increase is not mentioned to help understand whether to go to 20 mg Lipitor if the desired efficacy is not achieved.

Rifampin or Other Inducers of Cytochrome P450 3A4 Concomitant administration of Lipitor with inducers of cytochrome P450 3A4 (e.g., efavirenz and rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Owing to the dual interaction mechanism of rifampin, simultaneous coadministration of Lipitor with rifampin is recommended, as delayed administration of Lipitor after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

This is the most specific type of labeling language giving clear and undeniable advice, but this is the most unusual form.

Digoxin When multiple doses of Lipitor and digoxin were coadministered, steady state plasma digoxin concentrations increased by ~20%. Patients taking digoxin should be monitored appropriately.

This advice refers to digoxin rather than Lipitor and clearly implies that the dose of digoxin may need to be lowered but does not advise how best to do that. Discussions suggest that a 20% increase in digoxin serum concentrations are considered generally insignificant and digoxin dosing would not be modified unless there was an evidence of toxicity.

Oral Contraceptives Coadministration of Lipitor and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol. These increases should be considered when selecting an oral contraceptive for a woman taking Lipitor.

The implication is that lower dose oral contraceptives should be chosen, but no comments are made on whether the efficacy of those lower doses will be sustained. This would appear to be a relatively unusual situation, as the vast majority of subjects treated for excess lipids are postmenopausal. However, it becomes a serious issue in those subjects with familial hypercholesterolemia. Other statins are available that are not modulated through cytochrome P450 3A4 and that may be an alternative solution although not specifically mentioned in the label for atorvastatin.

Warfarin Lipitor had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

This is an important labeling statement because it discusses the outcome, that is, prothrombin time, rather than the usual presentation of pharmacokinetic drug levels.

The conclusion is that a good deal of clinical pharmacology takes place to help understand the metabolism of the drug of interest. However, whether that can be translated into practical clinical advice remains unclear, and the physician must then decide on how to deal with each drug–drug interaction issue.

18.9 GENETIC POLYMORPHISM

Variations in cytochrome P450 metabolic pathways are modified by polymorphic genetic variability. These provide opportunities to modify the drug dose and hence individualize drug therapy, to reduce adverse events and maintain efficacy. A review of the subject suggests that adverse events could be reduced, but the practical implications are not contained in current labeling [28]. A more recent paper confirms these findings and argues that science be used prospectively in drug research [29].

Some examples may be helpful. Tramadol is a centrally acting analgesic that is by itself active and has an active metabolite *O*-desmethyl-tramadol (M1). The O-demethylation is catalyzed by cytochrome P450 2D6 and the N-demethylation is catalyzed by CYP2B6 and CYP3A4. There is a wide variability in pharmacokinetics because of CYP genetic polymorphism [30]. This is reflected in the current Tramadol label, which reads as follows:

> "The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown."

Irinotecan is an anticancer drug which can cause toxicity including leucopenia and diarrhea. Irinotecan is metabolized to form an active metabolite SN-38 which is then further metabolized by UDP-glucuronosyltransferase (UGT) 1A1 enzyme. There is genetic polymorphism of the (UGT) 1A1 enzyme [31]. The label states the following:

> "The metabolic conversion of Irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele. In a prospective study, in which Irinotecan was administered as a single-agent on a once-every-3-week schedule, patients who were homozygous for UGT1A1*28 had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*. The disposition of Irinotecan has not been fully elucidated in humans. The urinary excretion of Irinotecan is 11% to 20%; SN-38, $<1\%$; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of Irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of Irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2)."
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> "When administered as a single-agent, a reduction in the starting dose by at least one level of Irinotecan hydrochloride injection should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient

population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment."

It would appear that the science continues to improve to help understand how genetic polymorphism explains differences in toxicity and to some extent efficacy. However, based on these two examples, it is still not possible to adequately label the proposed change in dose with any precision.

18.10 ETHNIC DIFFERENCES

Ethnic factors have become an issue in drug development with a guideline generated from the International Congress on Harmonization (ICH) [32]. It is hard to tease out the effects of ethnic factors from genetic polymorphism as discussed in the last section. Ethnic factors include intrinsic factors such as genetics and metabolism and extrinsic factors such as diet, medical practice, and use of concomitant drugs, tobacco, or alcohol. There are probably no pure ethnic factors but the proportion of the population with a particular genetic polymorphism varies in different ethnic populations. It is clearly desirable to include as diverse a population as possible in clinical trials to help understand and anticipate any ethnic differences, but the practical labeling consequences are less clear. It is apparent that some drugs have been dosed lower in Japan than the United States, but there is greater concordance in dosing between Europe and the United States although there are some exceptions [33]. A full review of the literature underpinning ethnic differences has been carried out, and includes questions on the precision of the ethnic group being tested as well as differences in methodology used in different studies [34]. Modern drug development incorporates a diverse population with multicentered multinational studies becoming the norm in phase 3. However, the interpretation of this diverse data does not lead to individual drug labeling advice.

18.11 INDIVIDUALIZED DRUG THERAPY

Much has been written about personalized medicine but with a few exceptions it remains a dream rather than a reality. Looking at mean differences resulting from drug therapy in clinical trials and comparing with placebo has been the standard for 40 years. Defining subpopulations with the appropriate results from genetic testing of some description will result in several different subpopulations making recruitment for clinical trials more complex. This has been established with a few efficacy markers such as Herceptin targeting HER2, Erbitux targeting EGFR for metastatic colorectal cancer, and Gleevec targeting the cell surface tyrosine kinase receptor in gastrointestinal cells [35]. Whether it is equally possible to target subpopulations who are more likely to have adverse events remains to be seen and will present increasing complexity in clinical trial design. One of the issues is that it may be becoming easier to predict changes in serum level of active drug or active metabolites, as has been discussed, because of increasing knowledge of genetic diversity, but translating these values into meaningful dosing information remains difficult.

18.12 CONCLUSION

The drug development process leads to increasing knowledge about the metabolism of drugs, and this information is usually collected during drug development before drugs being marketed. The drug development process is intended to exclude drugs that have problematic metabolism or drug–drug interactions, and modern drugs are usually robust in their dosing regardless of the medical issues of the subjects taking the drugs. The labeling process is formalized, but it would appear not to be terribly helpful in practice in answering questions about dose modifications. Terms such as *use with caution* are prolific but all drugs should be used with caution so the term is almost meaningless. Questions on particular drug dosing have suggested that labeling be more precise and kept simple but that full information be made available so physicians can make informed decisions [36]. The prospect of individualized medicine remains an opportunity rather than a reality. In addition, it is important that medical professionals get more training on drug use at medical school and through ongoing continuing medical education, so they can make fully informed and appropriate dosing decisions [37,38].

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