DRUG–DRUG INTERACTIONS

In considering the potential safety and toxicity issues that may be associated with a candidate compound, it is important to look beyond the compound itself. As discussed earlier, the metabolic processes designed to clear xenobiotics from the body can produce compounds (e.g., metabolites) that possess undesirable characteristics. It is also possible that the presence of one compound can cause a second compound to produce side effects that would not occur if it were used alone. In this case, co-administration of the two compounds causes a change in the pharmacokinetic profile of one of the two compounds. These changes could present themselves as higher systemic exposure of the parent compound (e.g., decreased metabolism of the parent compound) or increased production of metabolites (e.g., increased metabolism of the parent compound). In both of these scenarios, a "drug–drug interaction" (DDI) creates an opportunity for side effects to appear.

Consider, for example, a compound that is converted to two metabolites. One metabolic pathway converts 99.99% of the compound to a benign metabolite, while the second metabolic pathway converts the remaining 0.01% to a compound with toxic properties. If a second compound capable of blocking the major metabolic pathway is co-administered, then metabolism of the first compound will be forced into the minor pathway, leading to higher concentration of the toxic metabolite (Figure 8.14). Alternatively,

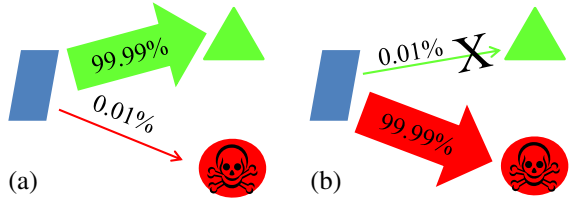

FIGURE 8.14 (a) A compound with the potential to metabolize into a dangerous compound (red) may be safe to use clinically if an alternative, dominant pathway converts it to a safe metabolite (green). (b) Blockade of the metabolic pathway leading to a safe metabolite by another compound, however, can lead to unexpected toxicity as a result of an increase in production of the toxic metabolite (red).

consider a compound that is rapidly metabolized by one metabolic pathway and more slowly by a second pathway. Co-administration of a compound that blocks the fast pathway will lead to a buildup in concentration of the first compound potentially to concentration beyond the established safety window.

Predicting the propensity of a compound to block metabolic pathways can provide substantial guidance as to the likelihood of drug–drug interaction becoming an issue. Compounds that inhibit CYP3A4, a major metabolic