Pharmacokinetics and Toxicokinetics in Drug Safety Evaluation

1 INTRODUCTION

Among the cardinal principles of both toxicology and pharmacology is that the means by which an agent comes in contact with or enters the body (i.e., the route of exposure or administration) does much to determine the nature and magnitude of its effects (Goldstein et al., 1974; Pratt and Taylor, 1990). Accordingly, an understanding of route(s) of administration and their implications for absorption is essential. The therapeutic index (calculated based on plasma and therefore absorbed levels) is the ratio between what levels cause adverse effects and the levels which have the desired therapeutic effect.

Safety assessment studies usually involve a control group of animals (untreated and/or dosed with formulation only) and at least three treated groups receiving "low," "intermediate," and "high" dose levels of the drug entity of interest via a route approximately that used in humans (as closely as possible). Frequently there will also be recovery groups to determine if any observed effects are reversible (and if so, to what extent). In most instances the high dose level is expected to elicit some toxic effects in the animals, often expressed as decreased food consumption and/or below-normal body weight gain, and has been selected after consideration of earlier data, perhaps from dose range-finding studies, or at least to a dose as high as possible by the intended route. The other two dose levels are anticipated not to cause toxic effects. Generally, but not always (e.g., nonsteroidal anti-inflammatory drugs

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