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Use of Radiolabel in Drug Development

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ABSTRACT

Radiolabel is a powerful tool for understanding the metabolism and pharmacokinetics of drugs and drug candidates. It is usually faster compared to studies with unlabeled compounds, and can be more specific and more quantifiable. Most common uses include investigation of mass balance and excretion, tissue distribution, and metabolite identification. This presentation gives several examples of the utilization of radiolabel compounds in preclinical studies (compounds A, B, C, and D) to clinical studies (compound E) to standard ADME studies, and to address specific mechanistic issues.

Compound A was given intravenously to intact rats and orally to intact and bile-duct cannulated (BDC) rats. Urine, feces, bile, and plasma were collected for 96 h or 168 h. A total recovery of 92.0, 97.3, and 98.7% of the administered dose was observed in the three groups, respectively. Urinary recovery in the intact group after the oral dose was higher than the BDC rats, suggesting entero-hepatic recirculation. This was confirmed by a shorter plasma half-life in BDC rats.

Compound B showed protein covalent binding when incubated *in vitro* with rat and human liver microsomes. There was protein covalent binding found in the liver samples but much less in blood samples from rats treated with Compound B.

Compound C was given to rats orally to collect plasma and urine for radioanalysis and metabolite identification. Metabolites were separated with HPLC. The metabolites were profiled and quantified based on the radioactivity and the structures were proposed based on LC/MS/MS analyses. Furthermore, the ratio of LC/MS/MS response to the radioactivity for each major metabolite was used to estimate the metabolite concentration in samples collected from a toxicity study.

Compound D was given to a group of 10 rats, one rat per time point, and its distribution to the tissues over the time course of one week was determined using the technique of whole-body autoradiography. The tissue exposure of radioactivity in rats was used for dosimetry calculation to project exposure in humans in the human mass balance/excretion study. The maximum whole-body exposure of a 70-kg human to radioactivity from a 100 µCi PO dose of Compound D was approximately 4.6% of the 3- to 5-rem limit specified for whole-body exposure by the Code of Federal Regulations.

Compound E was spiked into human plasma samples collected in a clinical study to determine unbound fractions and unbound concentrations.

^{14}C label is generally the preferred radiolabel due to its chemical and biological stability. However, ^{3}H label often offers a good alternative in early drug development for its ease of synthesis and lower cost.