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Relation between drug elimination kinetics in intact animals and isolated perfused liver systems: phenylbutazone

Recent studies have shown the usefulness of the isolated perfused liver for investigations of the effects of enzyme induction and of distribution of drug on the drug's metabolism (von Bahr, Alexanderson & others, 1970; Nagashima, Levy & Sarcione, 1968; Levy & Nagashima, 1969). If a drug is eliminated only by biotransformation in the liver, good agreement between its *in vitro* and *in vivo* elimination rate constants may be obtained by correcting for the difference in drug distribution (liver: extrahepatic sites) in the perfused liver system and in the intact animal (Nagashima & others, 1968). This approach has been used successfully with bishydroxycoumarin and has yielded similar "true" elimination rate constants *in vitro* and *in vivo* even though the "apparent" elimination rate constants in perfused rat liver systems were three to four times higher than in the intact animals (Nagashima & others, 1968). The results to be reported here show that there is also a good quantitative correlation between *in vitro* and *in vivo* elimination rate constants in animals pretreated for various lengths of time with phenobarbitone, a potent microsomal enzyme inducing agent.

The elimination rate constant of phenylbutazone was determined in male Sprague-Dawley rats weighing 200 to 300 g and in isolated perfused livers obtained from similar animals. The intravenous dose (50 mg/kg) and the amount of drug in the

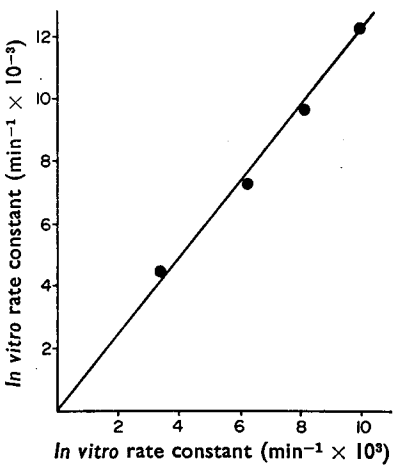

FIG. 1. Relation between *in vitro* and *in vivo* elimination rate constants of phenylbutazone in isolated perfused liver and in intact rats, respectively. From left to right, the data points represent values from control animals and from animals pretreated for 1, 2, and 3 days with phenobarbitone. The results are calculated from the experiments shown in Table 3 in the work of von Bahr & others. The points represent the mean values in these experiments.

perfusion system (5 mg in about 100 ml diluted blood) yielded similar drug concentrations in the plasma. Other details of the experiments are reported elsewhere (von Bahr & others, 1970). Some of the animals were pretreated for 1, 2, or 3 days with daily intraperitoneal doses of phenobarbitone, 80 mg/kg.

Pretreatment with phenobarbitone increased the elimination rate constant of phenylbutazone up to three-fold, depending on the length of the pretreatment. Fig. 1 shows that there is a good correlation between the *in vitro* and *in vivo* elimination rate constants. The average ratio of these constants, *in vitro*: *in vivo*, is 1·24. This ratio depends of course on experimental conditions, such as the volume and composition of the perfusion fluid and (sometimes) the perfusion rate (Nagashima & others, 1968; Nagashima & Levy, 1968).

The experimental results now available show that effects on drug metabolism due to changes in drug distribution, resulting from changes in plasma protein concentration, and drug metabolizing activity, due to enzyme induction, are reflected to the same degree in intact animals and in isolated perfused liver systems in the case of drugs, like phenylbutazone and bishydroxycoumarin, which are eliminated solely by biotransformation in the liver. If the animal excretes part of the drug in an unchanged form, similar correlations should be possible by using the *in vivo* drug biotransformation rate constant rather than the elimination rate constant. These findings encourage further use of the isolated perfused liver for drug metabolism studies.

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