Biotransformation of drugs has been shown to serve a key function in total pharmacokinetics. Changes in the pharmacokinetic behaviour of drugs are likely to occur, when drug metabolism has been altered. This, in addition, has been demonstrated to result in pharmacological and toxicological implications.

It was first demonstrated by experiments in vivo, that ethanol acts as an potent inhibitor of certain reactions in the biotransformation of drugs (SCHÜPPEL 1967). The microsomal compartment seems to be affected exclusively, for oxidative C-hydroxylation and N-/O-desalkylation turned out to be materially altered by ethanol in vivo. Hydroxylation of pentobarbital and phenazon as well as N-demethylation of phenazon and aminopyrine are considerably diminished under the acute action of ethanol. This results in a prolonged decrease of blood levels of these drugs and a derangement of the elimination pattern of typical metabolites in the urine compared to normal.

This can be shown for the elimination of pentobarbital from the blood of rats, being dosed additionally with ethanol in a single moderate dose (3ml/kg). The first order kinetics of pentobarbital elimination changed to a zero order and was markedly delayed. This delay in the elimination from the blood fits to the prolongation in sleeping time, observed in the rats tested. This increase is in good keeping with the dose of ethanol used.

Further studies revealed a lowered blood level for the main metabolite of aminopyrine, 4-aminooantipyrine, derived by N-demethylation. Correspondingly a reversal of the normal elimination pattern of this metabolite was found in the urine following dosage of ethanol.

Later we were able to show by experiments in-vitro, that microsomal N-demethylation activity is materially inhibited by ethanol. This inhibitory action of ethanol can be related to its binding to the microsomal hydroxylating enzyme system (SCHÜPPEL 1969). Kinetic experiments demonstrated a competitive type of inhibition, so that strength of inhibition is only determined by the concentration ratio of ethanol and the drug respective at the site of the enzyme. If molar concentrations are considered, it can be calculated, that this ratio will range from $10^{-5}$ to $10^{-9}$ and even lower, assuming a molecular weight of 300, a dose of 100 mg - 1 mg/70 kg and a blood-alcohol-level between 50 mg% and 100 mg%. This ratio enables ethanol to act as a potent inhibitor of the reactions outlined above.

As ethanol itself is metabolized in vivo, concentration of ethanol is there-
fore decreasing after absorption is complete. That causes the inhibition due to ethanol to be a reversible one in vivo. Other reactions of drug metabolism, however, are not affected by ethanol in vivo at all. So will be esterolysis or conjugations. Only those drugs, which have to be metabolized via microsomal oxidations, will be altered in their pharmacokinetic behaviour, the others, in contrast, are not affected. But there are peculiarities to note: drugs with a mixed metabolic elimination pattern, comprising both microsomal oxidations along with other types, which do not interfere with ethanol, are expected to show special changes in pharmacokinetics during acute action of ethanol. Owing to depression of the first pathways the other will be increased for compensation. This increase is only an indirect one and not due to direct enzymatic activation or even induction. By this mechanism more drugs, as judged directly by their metabolic fate in the body, are prone to interact with ethanol on a pharmacokinetic level. Thus a metabolic mechanism, by which ethanol may alter pharmacokinetics of drugs according to their biotransformation pattern, offers a valuable tool to elucidate mechanisms of drug-ethanol-interaction on a pharmacokinetic level.

We have chosen different hypnotic agents to prove this concept in rats. The fate of most hypnotics in the body has been well established, so that valid conclusions can be drawn. In addition, duration of action and the course of metabolic inactivation are closely related in these drugs and can readily be assessed by measuring the sleeping time after dosage of a drug or a combination of it. In the experiments one dose of a hypnotic drug was each matched with two different doses of ethanol, besides a control group, in order to follow up possible additional or potentiating effects due to ethanol. Ethanol was given in moderate doses only by oral route (1.5 and 3.0 ml/kg as 10/20 Vol% solutions), not sufficient to cause apparent sedative or narcotic effect by its own.

There are considerable variations in the responses of various hypnotics to additional ethanol dosage. Some drugs were potentiated by the doses of ethanol used, but other failed to show any effect. Taking into account the fate of the drugs used, there seems to exist a strong correlation between the individual pattern of inactivation and the increase of the duration of action due to ethanol ("intensifying index").

Barbiturates, which have - except of barbital - to be metabolized by microsomal oxidation only, show considerable increase of sleeping time, when combined with moderate doses of ethanol. Correspondingly, a prolonged de-
crease of blood levels under the same conditions has been demonstrated for pentobarbital before in rats (SCHÜPPEL et al. 1967) and mice (SEIDEL 1967). Barbital does not undergo oxidation or any other biochemical changes and increase of sleeping time under the acute action of ethanol is only slight, compared to other barbiturates. Thiopental even fails to show any effect of ethanol corresponding to the different mode of inactivation in vivo. The same holds true for hydroxydione, 4-hydroxy-butyric acid-ethylester and propanidid, all drugs being inactivated by hydrolysis and/or conjugation. As ethanol does not interfere with these latter reactions, pharmacokinetics of these drugs will not be changed in a similar manner by ethanol. This has been shown by SEIDEL (1967) for thiopental and barbital in mice.

The results presented give strong evidence for pharmacokinetic factors to act in certain types of drug-ethanol-interactions, not fully recognized at the present time.

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