Inhalation Pharmacokinetics Based on Gas Uptake Studies

IV. The Endogenous Production of Volatile Compounds

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Abstract. A pharmacokinetic description of production, distribution and metabolism of endogenous volatile compounds is presented. This description uses the "gas uptake model" of a closed recirculated atmosphere in which experimental animals are exposed. As an example, the production rates of acetone, under different conditions of stimulation by xenobiotics, are calculated from published experimental data.

The theoretical descriptions may serve as a basis for treating the problem of hydrocarbon exhalation in toxicological experiments with compounds eliciting lipid peroxidation.

Key words: Pharmacokinetics – Gas uptake – Acetone – Hydrocarbons

Introduction

The problem of appropriate determination of pharmacokinetic parameters for endogenously produced volatile compounds has recently been addressed (Frank et al. 1980). Aliphatic hydrocarbons like ethane (Riely et al. 1974) and pentane (Dillard et al. 1977) are experimentally monitored as indicators of lipid peroxidation in experimental animals, and increased acetone exhalation is observed when rats are exposed to various halogenated xenobiotics (Filser and Bolt 1980; Filser et al. 1982). In view of a recent discussion as to reliable quantitative indicators for production of such endogenous compounds in experimental animals which are concurrently metabolized (Frank et al. 1980) the need for a thorough pharmacokinetic assessment of this problem is obvious.

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Therefore, the present paper will present a theoretical pharmacokinetic treatise that demonstrates how to adequately analyze the data material for endogenous compounds when a "closed exposure system" (desiccator jar chamber) is used. The analyses are based on previous pharmacokinetic descriptions for exogenous xenobiotics by Andersen (Andersen et al. 1980; Andersen 1981) and ourselves (Filser and Bolt 1979, 1981; Bolt et al. 1981).

As an example, model calculations are given for acetone produced by control rats and by rats stimulated with vinylidene fluoride (see Filser et al. 1982); the pharmacokinetic parameters of exogenous acetone (Hallier et al. 1981) were entered into these calculations.

Moreover, this paper serves as the theoretical basis for an analysis of endogenous productions of ethane and n-pentane which is published separately (Filser et al. 1983).

**Pharmacokinetic System**

The desiccator jar chamber was used for exposures as previously described. In standard experiments, a 6.4 l system was equipped with 135 g soda lime and occupied by two rats (male Wistar, about 250 g each). Results of experiments run under different experimental conditions were entered into the quantitative correction formulae given in the Appendix.

Throughout an observation period (50 h, or as indicated) the compound studied (acetone) was quantitatively determined in the gas phase of the exposure system, as described by Hallier et al. (1981).

**Pharmacokinetic Modelling**

In order to obtain a suitable pharmacokinetic model, earlier work to analyze inhalation pharmacokinetics is extended for simultaneous production and elimination of a chemical produced by endogenous metabolic pathways. This model is analogous to the two compartment open models used in conventional pharmacokinetic analyses. One compartment is the gas phase which is accessible for analysis. This is formally equivalent to the central compartment in conventional terms. The second or "deep" compartment is the animal which is regarded as a single-homogeneous unit. Formally, both metabolism and production of the chemicals of interest occur in this "deep" compartment. The overall analysis is reminiscent of the development of conventional pharmacokinetic descriptions.

The pharmacokinetic model now used is shwon in Fig. 1. It implies two compartments, the gas phase (Cp1) and the organism (Cp2). Metabolism is dose-dependent for many chemical compounds, also when administered via gas phase (Filser and Bolt 1981); it is therefore generally refered to as the "metabolic rate" $dN_\text{met}/dt$. If only a specially defined dose range is considered metabolic elimination may be described by a first order process, with the rate constant $k_{el}$. 