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MINIREVIEW

PHARMACOKINETICS OF VINYL CHLORIDE

HERMANN M. BOLT
Institute of Toxicology, University of Tübingen, Wilhelmstraße 56, D-7400 Tübingen 1, Germany

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Abstract—So far, all studies on pharmacokinetics of vinyl chloride *in vivo* used rats. Consistent evidence shows that, above a concentration of "saturation" which on inhalation exposure is reached at about 250 ppm vinyl chloride in the atmosphere, non-linear (dose-dependent) pharmacokinetics apply. Two different models describing the pharmacokinetics of vinyl chloride have been published. They show that vinyl chloride can leave the body very rapidly via expiration by lung. However, special conditions apply if rats are exposed to atmospheric vinyl chloride; the compound equilibrates with the organism within 15–30 min, and from this equilibrium it is removed by metabolism. This probably involves formation of the reactive epoxide. Along with the biochemical data on vinyl chloride's interaction with the organism that have been recently elaborated, it is apparent that pharmacokinetic research contributes to the understanding of a variety of properties of this important industrial compound.

INTRODUCTION

The detection of carcinogenic effects of vinyl chloride on the liver (Potter, 1976) has focussed attention on metabolism and disposition of this important industrial chemical in the living organism (Leibman, 1977). Many publications deal with aspects of mutagenicity of this compound (Bartsch & Montesano, 1975) or with the molecular mechanisms by which vinyl chloride may exert its mutagenic or carcinogenic effects (Van Duuren, 1975; Barbin *et al.*, 1975; Laib & Bolt, 1977). However, it has to be considered that biological action of a xenobiotic does not only depend on the biochemical target mechanisms of the latter, but is also largely influenced by pharmacokinetic factors. The aim of the present minireview is to present the data for the pharmacokinetic behavior of vinyl chloride which are available at present. So far all studies have been performed with rats.

DOSE-DEPENDENCE OF DISPOSITION OF VINYL CHLORIDE

It has been stressed, particularly by Gehring and his coworkers (Heiner *et al.*, 1975; Gehring *et al.*, 1976; Watanabe *et al.*, 1977), that metabolism of vinyl chloride *in vivo* is a saturable process. This has been recently confirmed (Bolt *et al.*, 1977). As rats metabolize vinyl chloride according to first-order kinetics only if atmospheric concentrations below 250 ppm vinyl chloride are applied. If this concentration is exceeded, non-linear pharmacokinetics apply which are consistent with the theoretical consideration (Gehring *et al.*, 1976) of saturation of the metabolizing enzymes. However, Henschler (1977) did not observe a saturation of vinyl chloride metabolizing enzymes in the isolated perfused rat liver preparation, even if such high concentrations as 20000 ppm vinyl chloride were applied in the carbogen mixture used for oxygenation of the perfusion medium in the "artificial

A reasonable explanation for the discrepancy between conditions *in vivo* and in the isolated perfused liver is difficult to give and will deserve further studies.

That metabolism of vinyl chloride is dose-dependent can also be inferred from a comparison of the routes for elimination of the compound after different dosage schedules, i.e. comparison of exhalation of unmetabolized vinyl chloride and excretion of urinary metabolites.

Table 1 compiles the data given in the literature. If a low dose, up to 1 mg/kg, of vinyl chloride is administered in oily solution, either via stomach tube or by i.p. injection, a considerable portion is excreted as urinary metabolites. In contrast, when the dose is increased to 100 mg/kg and over, the bulk of vinyl chloride given is exhaled as the unchanged compound. This very much favours consideration of a saturable metabolism of vinyl chloride under *in-vivo* conditions.

Another conclusion can be drawn from the figures of Table 1, as the data of Green & Hathway (1975) show that the route of elimination of vinyl chloride depends on the route of administration of the substance. Administration into the splanchnic area, by p.o. or i.p. dosing, favours urinary excretion of metabolites which is even more pronounced after oral administration. This very much suggests a first-pass effect and is consistent with the potency of liver to rapidly metabolize vinyl chloride if the latter is present in a comparably low concentration.

PHARMACOKINETIC MODELS FOR VINYL CHLORIDE

Pharmokinetic surveys on vinyl chloride have been published by Withey (1976) and by Bolt *et al.* (1977). Both approaches, although very different in concept, lead to similar conclusions as to the rate of exhalation of vinyl chloride. Withey (1976) exposed rats to a gas

Table 1. Exhalation of unmetabolized vinyl chloride and urinary excretion of metabolites after administration of dissolved vinyl chloride to rats by various routes

Vinyl chloride dose given	Oral dose exhaled ($F_{e,o}$)	Oral dose urine ($F_{u,o}$)	p.o. dose exhaled ($F_{e,p}$)	p.o. dose urine ($F_{u,p}$)	i.v. dose exhaled ($F_{e,i}$)	i.v. dose urine ($F_{u,i}$)	References
250 μg/kg	3.7	75.1	43.2	43.1	99	0.5	Green & Hathway (1975)
50–100 μg/kg	1.2	59–68	–	–	–	–	Watanabe *et al.* (1976)
100 mg/kg	67	11		–	–		Watanabe *et al.* (1976)
300 mg/kg	92	–					Feron *et al.* (1975)
450 mg/kg	91.9	5.4	96.2	2.6	–		Green & Hathway (1975)

kept constant, and he monitored blood concentrations of unmetabolized vinyl chloride. Between 500 and 14,000 ppm in the atmosphere, the ratio

$$\frac{\mu g\ VC/ml\ blood}{\mu g\ VC/ml\ air}$$

which is equivalent to Ostwald's solubility coefficient, was constant and amounted to 2.61. The equilibrium between vinyl chloride in the atmosphere and in blood was attained after 30 min of exposure.

Withey (1976) also determined the kinetics of vinyl chloride in rat blood after i.v. administration of the compound. He obtained a biphasic plasma concentration curve which was consistent with a two-compartmental open-ended model shown in Fig. 1. The rate constants shown in the figure are the means of 4 experiments described after i.v. dosing. The mean rate constant for the partial process of exhalation was 0.046 min^{-1}, equivalent to a $t_{1/2}$ of 15.8 min. The model does not take into account metabolism of vinyl chloride which is justified as so far as Table 1 shows that, after an i.v. dose, the overwhelming portion of vinyl chloride is exhaled. However, the present biochemical data strongly suggest that vinyl chloride must be metabolized in order to become effective as a chemical mutagen or carcinogen (see the review of Bartsch and Montesano, 1975). Also, it has to be considered that exposure of an individual to an atmosphere containing vinyl chloride will result in adjustment of equilibrium between vinyl chloride in the gas phase and in the organism (Withey, 1976; Buchter *et al.*, 1977). Under those steady-state conditions the only way for the organism to remove vinyl chloride from the equilibrium is by metabolic conversion. This has been considered when attempting another approach to the biodynamics of vinyl chloride (Bolt *et al.*, 1977).

As shown in Fig. 2, rats were exposed to vinyl chloride in a closed system. The concentration of vinyl chloride was measured in the gas phase and kept below the saturation point of 250 ppm. By means of new and potent inhibitors of oxidative drug metabolism (Bolt *et al.*, 1976) it was possible to completely block biotransformation of vinyl chloride. These experimental conditions permitted determination of the equilibrium constant and the rate constants k_{12} and k_{21} of Fig. 2. With animals not pre-treated with inhibitor an exponential decline of atmospheric vinyl chloride in the closed exposure system is observed which is due to metabolism. The first authors reporting about this parameter of metabolism of vinyl chloride were Heimer *et al.* (1975). From this parameter the constant k_{23} of Fig. 2 was derived (Bolt *et al.*, 1977). Finally, the rate of appearance of radioactivity in urine after application of ^{14}C-vinyl chloride to the system gave constant k_{30}. The data obtained with the model of Fig. 2 are comparable with Withey's basic results. This refers to the rate of exhalation of vinyl chloride from the animal into the atmosphere (k_{21} of Fig. 1 = 0.031 min^{-1}, k_{21} of Fig. 2 = 0.056 min^{-1}) as well as to the distribution between vinyl chloride in the gas phase and in the animal. Withey (1976) as mentioned above obtained a ratio between concentration of vinyl chloride in blood and in the atmosphere of 2.61, whereas the calculation of the "constant of equilibrium" (Bolt *et al.*, 1977)

$$K = \frac{\text{nl gaseous VC per g body wt}}{\text{nl gaseous VC per ml air}}$$

$$= \frac{k_{12}}{k_{21}} \quad \text{(cf. Fig. 2)}$$

under steady-state conditions resulted in 2.86.

CONCLUSIONS

Different conclusions may be drawn from the pharmacokinetics of vinyl chloride. However, it has to be kept in mind that disposition of vinyl chloride is dose-dependent and hence the "linear" pharmacokinetic assessment of metabolism (Fig. 2) refers only to the lower dose range i.e. below 250 ppm in the gas phase. But this is, from the standpoint of occupational medicine, the more interesting one. As has been pointed out by Oehme *et al.* (1976), the non-linear pharmacokinetic behaviour in the higher dose range is of basic importance for interpretation of toxicological studies because an increase of the dose of vinyl chloride does not necessarily imply a parallel increase in formation of the ultimately mutagenic or carcinogenic metabolites.

It has been stressed (Bolt *et al.*, 1977) that, due to the relatively short half-life of vinyl chloride and its metabolites in the organism, no significant cumulation of vinyl chloride or its major metabolites is to be expected on repeated administration of vinyl chloride. This is in marked contrast to the behaviour of the closely related trichloroethylene in the organism, where trichloroethanol and especially trichloroacetic acid are retained for a considerable period of time (Leibman *et al.* 1972; Muller *et al.*, 1974). The rapid elimination of vinyl chloride and its major metabolites from the organisms may be consistent with the current theory that a reactive short-lived metabolite which occurs in low concentrations only, may be responsible for the toxic effects of vinyl chloride.

The pharmacokinetic model of Fig. 2 also reveals the basic difference which exists between inhalation of vinyl chloride and other experimental routes of application. Exposure to a vinyl chloride-containing atmosphere results in a rapid equilibration of vinyl chloride with the organism. If, for toxicological considerations, the actual dose of atmospheric vinyl chloride acting on the organism is calculated as the dose which is taken up from the atmosphere, after equilibrium with the organism has been attained, uptake is only "due to metabolism" (k_{23} of Fig. 2), and all of this dose is metabolized, probably very

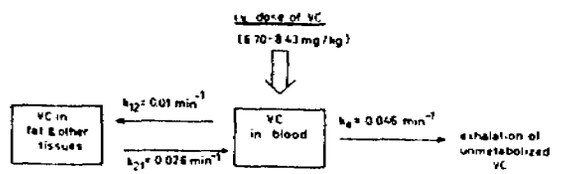

Fig. 1. Two-compartment open-ended model for vinyl chloride in the rat, according to the calculations

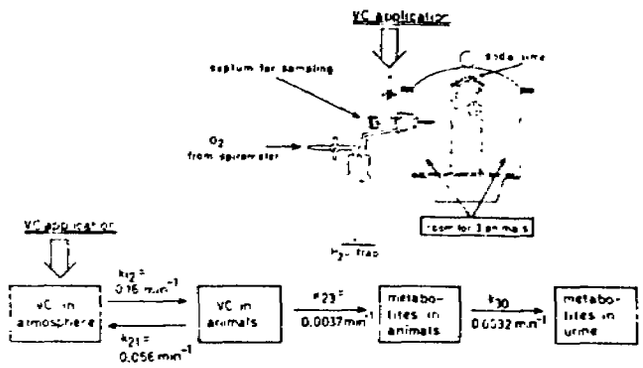

Fig. 2. Pharmacokinetics of vinyl chloride on exposure in a closed system: model of Bolt *et al.* (1977). The model includes metabolism of vinyl chloride. The rate constants are calculated after exposures to initial concentrations below 250 ppm vinyl chloride. For details, see text.

metabolism of vinyl chloride is very likely according to recent biochemical investigations (Van Duuren, 1975; Gneim *et al.*, 1975; Bonse *et al.*, 1975; Reynolds *et al.* 1975; Kappus *et al.*, 1975, 1976; Watanabe *et al.*, 1976; Norpoth *et al.*, 1976; Henschler, 1977; Green & Hathway, 1977).

By contrast, if the animal is not held in a closed system and a vinyl chloride dose injected, the ratio of k_{23}:k_{21} (Fig. 2) implies that more than 90% of the dose is exhaled and only a minor portion transformed to the ultimately toxic metabolites. This fully agrees with the experimental data of Table 1. However, after oral application a first-pass effect for metabolism in liver has to be considered. These theoretical considerations are not limited to vinyl chloride, but refer also to other volatile xenobiotics. Thus, a given oral dose of carbon tetrachloride is much more toxic, if the animals are kept in a closed atmosphere (unpublished results). Another conclusion may be based on the rate of entry of atmospheric vinyl chloride into the organism, i.e. its equilibration is achieved. Figure 3 shows this process which has been visualized using rats pre-treated with an inhibitor of vinyl chloride metabolism (Bolt *et al.*, 1977). The data are consistent with those obtained by Withey (1976). It can be seen that after 10 min the process is nearly completed. Within the first 3 min nearly 50% of the equilibrium dose are taken up; in the first minute, about 18% are taken up. Although an extrapolation from animal data to man is difficult, these figures may be important for assessment of occupational peak concentrations occurring in vinyl chloride plants. As uptake of vinyl chloride from air is a time-dependent process, a very short peak concentration may be of only low impact, but as the elevated concentration is maintained only for a few minutes, considerable amounts of additional vinyl chloride may be taken up by the individual. These few examples serve to show that, in addition to the biochemically-orientated research that is essential for a more complete understanding

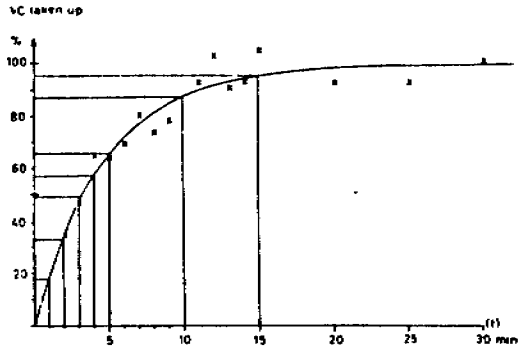

Fig. 3. Uptake of vinyl chloride from the gas phase by rats pre-treated with an inhibitor of vinyl chloride metabolism (6-nitro-1,2,3-benzothiadiazole; see Bolt *et al.* 1977). Amount taken up to achieve equilibrium between gas phase and animals is set to 100%.

vinyl chloride, determination and consideration of the pharmacokinetic behavior of this compound is also necessary and helps to interpret toxicological data.

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