Short communication

Pharmacokinetics of Ethimizol in Healthy and γ- Irradiated Rats

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Changes in pharmacokinetics of drugs induced by exposure of the organism to ionizing radiation have been studied rarely (Nair 1967), in spite of an increasing interest in the fate and metabolism of drugs under various pathological conditions.

Ethimizol (Vinogradova et al. 1961), bis-methyl-amide of 1-ethylimidazol-4, 5-dicarboxylic acid (1, Fig. 1), is a USSR preparation widely used as a central respiratory analeptic and an anti-inflammatory and anti-allergic agent (Borodkin et al. 1964; Ryzhenkov et al. 1967; Strukov 1973). Ethimizol is indicated in cases of alveolar hypoventilation secondary to CNS damage, poisoning with hypnotics and analgesics or due to other ethiology. Two metabolites of ethimizol, M_1 and M_2, were isolated from rat serum (Šoltés et al. 1983a). Demethylation of ethimizol in the body yielded 1-ethyl-4-carbamoylimidazole (M_1, Fig. 1) (Šoltés et al. 1983b). The mass spectrum of M_2 indicates that the molecular ion ($M^{+\cdot} = 226$) shifted 16 mass units higher than that of ethimizol, suggesting that an oxygen atom had been incorporated into one of the peripheral amide moieties of ethimizol. The aim of this work was to study the pharmacokinetics of ethimizol in healthy and γ-irradiated rats.

Male Wistar rats, weighing 170—200 g, were divided into 3 groups. The first group was not irradiated. Animals of both the second and the third group were whole-body irradiated from a ^{60}Co source with doses of 6 Gy and 9 Gy, respectively. Single ethimizol doses of 10 mg/kg were injected intravenously to all animals 7 days after the irradiation. Similarly as with gentamicin, maximum changes in ethimizol pharmacokinetics can be expected 7 days after the irradiation (Trnovec et al. 1980). Four to 7 rats were killed 5; 10; 15; 30; 60; and 120 min after the administration, respectively and serum concentrations of ethimizol (μg/ml) and the metabolites M_1 and M_2 (relative units/ml) were determined by HPLC (Šoltés et al. 1983a). The equation

$$C(t) = (D/V) \,.\, \exp\left[-(\ln 2/t_{1/2})t\right],$$

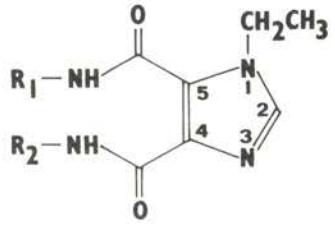

Fig. 1. Structural formulae of ethimizol and its metabolite M_1. Ethimizol, 1: $R_1 = R_2 = CH_3$; 1-ethyl-4-carbamoyl-5-methylcarbamoylimidazole, M_1: $R_1 = CH_3$, $R_2 = H$

where D is the dose of ethimizol, V is the distribution volume of ethimizol and $t_{1/2}$ is the serum half-life of ethimizol, was fitted to ethimizol serum concentration-time data by non-linear regression analysis, and the parameter estimates for V and $t_{1/2}$, including their standard deviations, were obtained for each experimental group. In accordance with the mono-exponential decrease of serum ethimizol and the previously reported data for rats (Trnovec et al. 1982) and humans (Trnovec et al. 1984), a linear open one-compartment model was inferred to the pharmacokinetics of ethimizol in rats of the present study. The total body clearance of ethimizol was estimated using D/AUC, where AUC is the area under the ethimizol serum concentration curve. AUC for ethimizol was estimated using $(D \cdot t_{1/2})/(V \cdot \ln 2)$ and those for M_1 and M_2 using trapezoidal rule. An appropriate t statistics was used to evaluate statistical differences between the pharmacokinetic parameters (Boxenbaum et al. 1974):

$$t = \frac{|\hat{\Theta}_{ij} - \hat{\Theta}_{ik}|}{[(SD_{ij})^2 + (SD_{ik})^2]^{1/2}}$$

where $\hat{\Theta}_{ij}$ is the computer-estimated i-th parameter in study j; $\hat{\Theta}_{ik}$ is the computer-estimated i-th parameter in study k; SD_{ij} is the standard deviation of the i-th estimated parameter from study j; and SD_{ik} is the standard deviation of the i-th computer-estimated parameter from study k. $df =$ (number of data points in the j-th study) + (number of data points in the k-th study) $- NP_j - NP_k$, where df is the number of degrees of freedom, NP_j is the number of parameters in the j-th study and NP_k is the number of parameters in the k-th study.

The concentration-time data of ethimizol and those of the metabolites M_1 and M_2 in serum of non-irradiated and irradiated rats are shown in Fig. 2, and the estimated pharmacokinetic parameters for ethimizol in rats are summarised in Table 1. The absolute distribution volume of ethimizol after a dose of 6 Gy and the relative distribution volume after both doses used (6 Gy and 9 Gy) were significantly larger than the corresponding volumes in non-irradiated animals. It can readily be shown that this difference would be statistically significant even if the

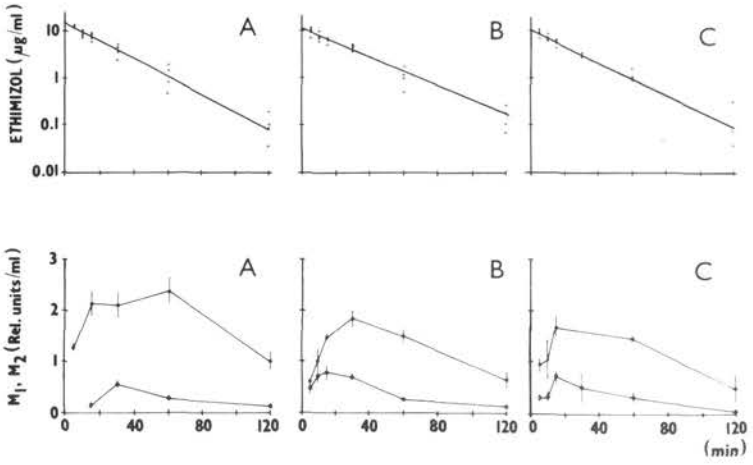

Fig. 2. Upper panel: Serum concentration of ethimizol in rats. Lower panel: Serum concentrations of metabolites M_1 (●) and M_2 (○) in rats (means ± SEM). *A*, non-irradiated rats; *B*, irradiated rats, dose 6 Gy; *C*, irradiated rats, dose 9 Gy.

standard deviations of the parameters compared were twofold underestimated. The increase in the relative volume of distribution is related to the loss of weight of irradiated animals. *AUC* of serum ethimizol in irradiated rats was smaller as compared with non-irradiated animals. A concomitant increase in ethimizol clearance was observed since $Cl = D/AUC$. In general, pathological states, those of radiation ethiology included, may affect the binding of drugs to plasma proteins and the resulting modifications in the free fraction of the drug can cause a change in

Table 1. Pharmacokinetic parameter estimates of ethimizol in rats.

	Non-irradiated rats	Irradiated rats	
		6 Gy	9 Gy
$t_{1/2}$ (min) ± SD	15.9 ± 1.1	20.1 ± 2.2	17.7 ± 2.1
V (ml) ± SD	125.4 ± 15.9	175.3 ± 9.6*	147.4 ± 8.1
V (ml/100 g) ± SD	69.5 ± 2.5	92.3 ± 5.0*	99.3 ± 5.5*
AUC ethimizol (μg . min/ml)	330.2	314.5	256.1
Cl (ml/min)	5.5	6.0	5.8
Cl (ml/min/100 g)	3.0	3.2	3.9
AUC_0^{120} M_1	216.2	150.0	156.5
AUC_0^{120} M_2	28.7	44.5	38.5

* Significantly different from non-irradiated rats at $P \leq 0.05$

the volume of distribution. Distribution can also be influenced by circulatory disorders modifying local blood flows and thus impeding drug entry into the tissues (Barre et al. 1983). AUC_0^{120} of metabolite M_1 in irradiated rats was smaller as compared with non-irradiated rats. The changes in AUC_0^{120} metabolite M_2 were of the opposite nature. These alterations may reflect radiation interference with ethimizol biotransformation.

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Received April 24, 1984/Accepted September 27, 1984