Radiation-induced changes in gentamicin pharmacokinetics

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Summary. Decreased clearance of i.v. or intratracheally administered gentamicin was observed in rats following single whole-body irradiation, 6 Gy ^{60}Co, reaching its lowest rate on the 7th post-irradiation day. Simultaneously the absorption rate of gentamicin from the lungs was found to be increased.

Although radiation injury and antibiotic treatment may coincide, no data about radiation-induced changes in pharmacokinetics of antibiotics, particularly of the aminoglycoside type, have been published. The absorption of gentamicin from the lungs into the systemic circulation has been established[2]. The aim of the present work was to study the pharmacokinetics of i.v. and intratracheally administered gentamicin in irradiated rats.

Material and methods. White, male rats, weighing 197–236 g were whole-body irradiated from a ^{60}Co source with a dose of 6 Gy[3]. Gentamicin sulfate (Gentamycin, Pharmachim, Bulgaria) was administered i.v. or intratracheally in a dose of 8 mg per rat to groups of 12–19 rats on days 3, 7, 10, 14, 17, 21, and 24 after irradiation. Blood samples were taken from the retroorbital venous plexus at fixed intervals and gentamicin was determined in heparinized plasma by the plate diffusion method using *Staphylococcus aureus* MAU 78/71 NCTC 6571, as described previously[2]. The time dependences of the logarithm of gentamicin concentration in plasma were approximated by functions composed from 1 or 2 exponential terms using the Monte Carlo and least-square methods. Total body clearance Cl was calculated from the relationship $Cl = k_{el} \cdot V_d$, where k_{el} is the elimination rate constant and V_d is the volume of distribution of gentamicin[4].

Results. After i.v. administration of gentamicin, approximation of the time-dependence of gentamicin plasma concentration with a double exponential function gave a lower sum of squares of deviations between experimental and smoothed values in all instances than with a monoexponential function. The k_{el} was significantly lower ($p \leq 0.05$) on the 3rd and 7th post-irradiation days than the control value. The Cl of gentamicin was decreased from the 3rd to the 17th post-irradiation day (figure 1).

After intratracheal administration of gentamicin, the limited number of time intervals at which blood samples were taken allowed only an approximation to a one-compartment model with first order rate absorption. The absorption rate constant of gentamicin was increased (figure 2) and Cl decreased on the 7th post-irradiation day (table).

Discussion. Impaired gastric emptying, intestinal motility and reduced absorption rate of water[5] or metabolic enzyme activity[6] are the most common mechanisms of radiation-induced changes in the kinetics of drugs. As gentamicin is neither absorbed from the gut nor metabolized, other factors must be considered. Clearance is the product of distribution volume and elimination rate constant and its decrease may depend on the change either of the former or of the latter, or both factors may be involved. V_d of drugs depends on the range of their plasma and tissue binding. The binding of gentamicin to plasma proteins was reported to be insignificant[7], yet there is sufficient evidence on the interaction of gentamicin with tissue substrates[8]. The renal clearance of gentamicin is a further factor to be considered. Early changes in renal morphology and function after comparable radiation doses were observed[9–12]. The increase in the gentamicin absorption rate on the 7th post-irradiation day correlates well with morphological changes in the lungs of rats following a single exposure to 651 or 2000 R[13,14]. Destruction of the air-blood barrier was observed between the 4th and 7th post-irradiation days[13–15].

Total body clearance of intratracheally administered gentamicin, 8 mg/rat, at various times after a single whole-body irradiation, ^{60}Co 6 Gy. The values are statistical estimates from 12–19 experiments and their 95% confidence intervals

	Clearance (ml/min/100 g b.wt)	
Controls	0.76 ± 0.13	
Days after irradiation		
3	0.58 ± 0.11	
7	0.41 ± 0.08	$p \leq 0.05$
10	0.55 ± 0.11	
14	0.81 ± 0.18	
17	0.68 ± 0.32	
21	0.69 ± 0.28	
24	0.74 ± 0.26	

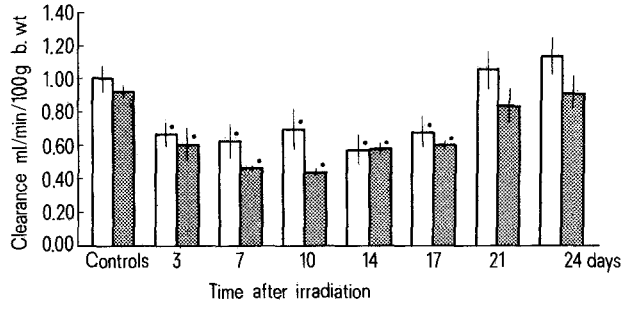

Fig. 1. Total body clearance of i.v. administered gentamicin, 8 mg/rat, at various times after a single whole-body irradiation, ^{60}Co 6 Gy. Approximation with 1-compartment, white, with 2-compartment model, shaded columns. Each value is a statistical estimate from 12–18 experiments ± 95% confidence intervals and significant differences at $p \leq 0.05$ are marked with a dot.

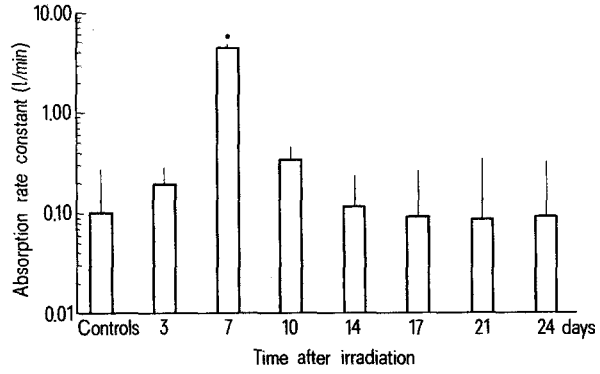

Fig. 2. Absorption rate of intratracheally administered gentamicin, 8 mg/rat, at various times after a single whole-body irradiation, ^{60}Co 6 Gy. Each value is a statistical estimate from 12–19 experiments ± 95% confidence intervals and significant difference at $p \leq 0.05$ is marked with a dot.

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Effects of a mammalian cholesterol biosynthesis inhibitor on adipocyte ultrastructure and metamorphosis in *Rhodnius prolixus* (Hemiptera)[1]

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Summary. A potent inhibitor of cholesterol biosynthesis in rodents [BMVA; 5-(4-biphenylyl)-3-methylvaleric acid] inhibits metamorphosis of 4th stage larvae of the blood-sucking bug *Rhodnius prolixus.*

It is well documented that the adipocytes of the haemophagus insect undergo a sequence of alterations in subcellular organization following a single nutrient meal[2]. The nutrient meal provides the necessary stimulus which initiates protein synthesis in the adipocyte[3]. Larval development and metamorphosis are dependent not only upon nutritional factors, but also upon the availability of the molting hormone (ecdysone) which restores the capacity of protein synthesis in the epidermal cells and ventral abdominal muscles. It is also well documented that dietary sources of sterols in the insect serve not only as structural components of cells and tissues, but also as precursors of essential metabolites and regulators (e.g. hormones)[4–6].

The biphenylyl methylated derivative of valeric acid (BMVA) appears to be a potent inhibitor of cholesterol biosynthesis in rodents[7,8]. The administration of BMVA to 4th instar larvae of *Rhodnius prolixus* interferes with molting and metamorphosis.

Materials and methods. 4th instar larvae of *Rhodnius prolixus* Stål (Hemiptera, Reduviidae) used in these studies had been starved for 2 months previously to reduce the large quantities of fat normally found in the insect adipocyte, allowing more critical electron microscopic observation. Employing an artificial feeding technique and heparinized human whole blood[9], 3 groups of insects (each group consisting of 55–60 larvae) received BMVA at concentrations of 10.5, 21.0, and 42.0 mg per 100 ml blood. A 4th group of insects was fed blood alone and served as a vehicle control. A minimum increase of $2\frac{1}{2}$ times the original body weight was the criterion used to ensure sufficient abdominal distention to provoke hormonal activation, initiating the molting phase. The onset of molting was recorded.

For ultrastructural investigations, 4 insects from each of the 4 experimental groups were sacrificed at 12 h and at daily intervals after feeding until day 6. The body cavity was cut open along the dorsal-ventral midline and Dalton's fixative (1% osmium tetroxide in dichromate buffer at pH 7.4) injected within. The upper cuticle was subsequently detached together with the net-like array of fat body. After 1h of fixation, the tissue was dehydrated in graded ethanol concentrations and 2 changes of epoxy propane and infiltrated with an epon-araldite mixture. Ultra-thin sections were cut and stained with uranyl acetate (30% w/v in ethanol) and Reynolds lead citrate[10]. Electron micrographs were taken at various levels of magnification for critical observation of fat body ultrastructure. For light microscopic investigations, epon-araldite embedded tissues were sectioned at 1 µm and stained with alkaline toluidine blue O[11]. The periodic acid Schiff reagent was utilized to determine visually the glycogen content in the adipocytes[12].

Results. 4th instar larvae of *Rhodnius prolixus* in all groups ingested approximately 2.7–3.1 times their body weight of human blood. The insects from all groups lost weight at a similar rate during the initial 5 days following feeding. In subsequent days, the weight loss in controls reached a maximum of 38% of the original weight recorded immediately after feeding. The rates of decrease in the mid- and low-dose groups were similar, although on day 6 insects in the mid-dose group lost significantly more weight. Similarly, an accelerated weight loss was observed in the high-dose insects from the 6th day on, reaching almost half of the original weight noted after the blood meal.

No significant differences among groups were observed regarding the normal onset and duration of molting. The 1st molt occurred between the 13th and 15th day after feeding in all groups. The remaining insects molted between the 13th and 23rd day after feeding. In this series of experiments, the most significant drug-related morphological effect was the inhibition of growth and development. All but one insect in the control group, and all the low-dose insects molted normally. In the mid-dose group 76% molted, while only 11% underwent ecdysis after receiving 42.0 mg BMVA/100 ml blood.

The electron microscopic investigations revealed that the general architecture of the fat body tissue and cells was well preserved in all groups, at all time intervals studied. In the 4th instar insects starved for 2 months, the adipocyte nuclei were generally ovoid in shape with well defined nucleoli and chromatin material. Chromatin was peripherally associated with the nuclear membrane and was scattered in clumps about the nucleoplasm and around the nucleolus (figure 1). The cytoplasm contained rough-surfaced endoplasmic reticulum consisting of single strands of cisternae concentrated mostly in the proximity of the plasma and