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Effect of gamma-irradiation on disposition of the local anaesthetic, carbisocaine in rabbits

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Abstract—^{14}C Labelled carbisocaine, a local anaesthetic agent, has been administered intravenously in a dose of 2 mg kg^{-1} to rabbits 7 days after whole-body ^{60}Co gamma-irradiation with a dose of 5 Gy (1·9 Gy min^{-1}) and to control rabbits. The plasma carbisocaine concentration-time courses were approximated by biexponential equations. The estimated pharmacokinetic parameters obtained when the data were fitted to an open two-compartment model were significantly different for the irradiated group relative to control animals, indicating a radiation-induced slower elimination rate of carbisocaine: AUC: 0·37 vs 0·29% dose min mL^{-1}, CL_{tot}: 109·8 vs 155·4 mL min^{-1}, Vd_{ss}: 27·6 vs 33·2 mL kg^{-1}, k_{el}: 0·0259 vs 0·0307 min^{-1}, MRT: 251·7 vs 214·6 min. The total excreted amount of ^{14}C radioactivity in the irradiated group was lower in comparison with controls: 6·5 vs 8·7% in bile and 18·3 vs 23·7% in urine. However, lower carbisocaine concentrations were recorded in the heart, lungs, liver, and kidneys of irradiated rabbits compared with controls.

Recent experience has shown that radiation casualties are often combined with mechanical or thermal trauma and therefore parenteral administration of local anaesthetics in treatment of these cases is indicated. The use of local anaesthetics may occasionally be associated with side effects arising from their action on the cardiovascular and central nervous systems. These effects may be enhanced by irradiation; however, the limited knowledge of radiation-induced changes in pharmacodynamics and pharmacokinetics of local anaesthetics (Thiel & Boehme 1987) does not allow valid conclusions to be made. As a model drug for studying the effects of irradiation on the disposition of local anaesthetics, we selected carbisocaine, *N*-[2-(2-heptyloxy-phenylcarbamoyloxy)-propyl]-diethylammonium chloride (Beneš et al 1978, 1979), a prospective agent intended to be used for regional anaesthesia. Pharmacokinetics of carbisocaine in rats and mice (Bezek et al 1988) and the rate and extent of carbisocaine absorption after subcutaneous administration to rats (Kállay et al 1990) have been described. Our present aim was to study the effect of sublethal whole body gamma-irradiation on the pharmacokinetics of intravenously administered carbisocaine in rabbits.

Materials and methods

[^{14}C] Carbisocaine (Elbert et al 1983), specific radioactivity 1·86 GBq g^{-1}, radiochemical purity ≥97%, as checked by TLC, was used. Chinchilla rabbits from our own stock were divided into two groups: controls (1·75 2·6 kg, n = 7) and irradiated group (2·30–2·65 kg, n = 8). The rabbits were whole-body irradiated from a ^{60}Co source with a dose of 5 Gy (1·9 Gy min^{-1}). Carbisocaine was administered on the 7th day after irradiation. The animals were anaesthetized with pentobarbitone (initial dose 30 mg kg^{-1} i.v.) and restrained horizontally on a heated table. A solution of mannitol (3%) in 0·9% NaCl (saline) was infused at a rate of 0·65 mL min^{-1} during the experiment. The anaesthesia was maintained by further 10 mg kg^{-1} (average) doses of pentobarbitone for the course of the experiment. (No evidence of respiratory deficiency was seen on this regimen.) A cannula attached to a three-way stopcock was inserted into the right jugular vein. After laparotomy a cannula was inserted into the bile duct. For sampling urine both ureters were cannulated. Carbisocaine in a dose of 1 mg kg^{-1} was administered intravenously 30 min after completion of surgery in a volume of 2 mL kg^{-1}. Blood samples were taken from the jugular vein at selected times. Five hours after administration of the drug (sufficient to obtain the terminal part of the concentration time curve) the rabbits were killed by pentobarbitone overdose and the heart, lungs, liver, and kidneys were dissected.

A liquid-liquid extraction procedure was used for determination of [^{14}C]carbisocaine in plasma (Ščasnár et al 1985). For the determination of total ^{14}C radioactivity 25% KOH in 20% ethanol (1:2) was added to portions of plasma, bile and urine samples. After 48 h the digests were mixed with liquid scintillator SLD 31 (Spolana, n.p., Neratovice, Czechoslovakia). Samples of organs (1–2 g) were digested in the same way (1:5, w/v) and treated as above. A Packard TriCarb 300 CD liquid scintillation spectrometer with external quench correction (Packard Instruments, Downers Grove, IL, USA) was used for ^{14}C radioactivity determination.

Inspection of the plasma concentration curves revealed that a biexponential equation could be fitted to the data. The parameter estimates of the equation were calculated by a least squares non-linear regression algorithm (Peck et al 1984). Consequently a linear open two compartment pharmacokinetic model was fitted to the plasma data. The following compartment model parameter estimates were calculated (Gibaldi & Perrier 1982): area under the curve (AUC), total body clearance (CL_{tot}), terminal elimination half-life ($t_{\frac{1}{2}}$), elimination rate constant (k_{el}), and steady state volume of distribution (Vd_{ss}). From non-compartmental pharmacokinetic parameters the mean distribution residence time (MRT) (Rescigno & Gurpide 1973) was calculated. The parameter estimates for irradiated and control animals were compared (Hauck & Anderson 1984).

Results and discussion

The carbisocaine plasma-concentration time courses for control and irradiated rabbits are shown in Fig. 1. The parameter estimates of the biexponential equation approximating these time courses for animals of the control group and those for the irradiated group are given in Table 1. The coefficients of variation of the parameter estimates were less than 15%, except for parameter C_1 in rabbit number 7 from the irradiated group (CV = 32·2%).

The calculated pharmacokinetic model parameters for both the non-irradiated and irradiated groups are listed in Table 2. It can be seen that the exposure to radiation induced a slight, but significant, alteration of all parameter estimates of the two-compartment model applied to carbisocaine pharmacokinetics, except $t_{\frac{1}{2}}$. The area under the carbisocaine plasma concentration curve was greater in the irradiated than in the non-irradiated animals. Total body clearance, the basic pharmacokinetic parameter derived from AUC and dose (CL_{tot} = Dose/AUC), was decreased corresponding to the increased AUC. The

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Table 1. Parameter estimates of the biexponential equation describing carbisocaine plasma concentration time data after its intravenous administration as bolus to control rabbits and rabbits on the 7th day following a whole-body irradiation with a dose of 5 Gy.

Rabbits	C_1 (% dose mL^{-1})	λ_1 (min^{-1})	C_2 (% dose mL^{-1})	λ_2 (min^{-1})
Control group (n = 7)				
Mean ± s.d.	0·0085 ± 0·0031	0·1051 ± 0·026	0·0007 ± 0·0001	0·0035 ± 0·0005
Irradiated group (n = 8)				
Mean ± s.d.	0·0072 ± 0·0029	0·1501 ± 0·061	0·0011 ± 0·0002	0·0034 ± 0·0005

terminal elimination half-life, on the other hand, was not significantly different between the groups. The elimination rate constant was decreased in irradiated rabbits compared with controls, as was the volume of carbisocaine distribution at steady state.

Similar findings, particularly the decreased clearance and elimination rate constant of gentamicin, were reported in rats following whole-body gamma-irradiation with a dose of 6 Gy (Trnovec et al 1980).

The mean residence time of carbisocaine (interval of time that a drug introduced into the plasma spends in the central and peripheral compartments before irreversibly leaving the central compartment) was significantly prolonged in the irradiated group (cf. Table 2). The tissue concentrations of carbisocaine 5 h after its administration are given in Table 3. Lower concentrations of carbisocaine were found in organs of irradiated compared with control rabbits. The calculated tissue-to-plasma ratios were lower for the irradiated group and reflect mainly the marked elevation of plasma carbisocaine concentration. The calculated changes of model parameter estimates are in accord with experimental data for plasma and tissue concentrations. The decreased volume of carbisocaine distribution in steady state in irradiated rabbits is the result of higher plasma carbisocaine concentrations and its decreased tissue level.

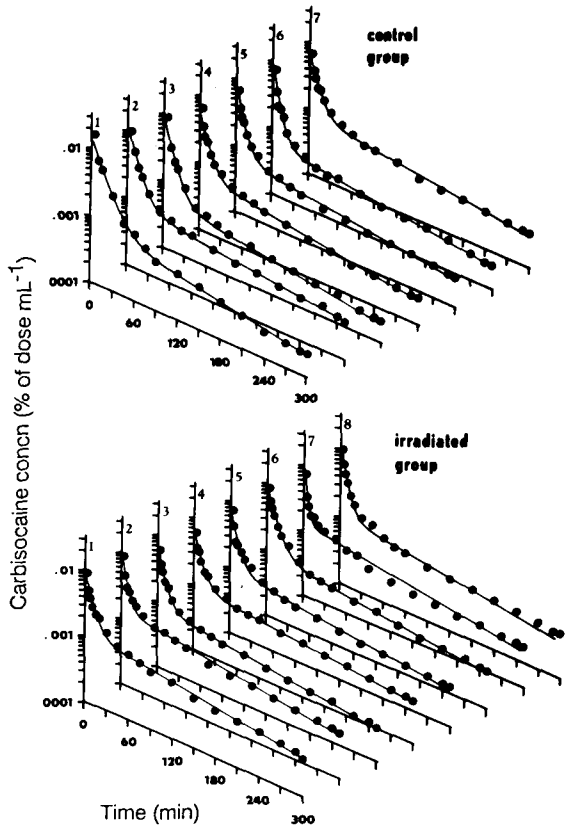

FIG. 1. Carbisocaine plasma concentrations after its intravenous administration to control rabbits and to rabbits on the 7th day following a whole-body irradiation with a dose of 5 Gy. The curves are non-linear least-squares regressions for the biexponential equation.

Table 2. Parameter estimates of carbisocaine pharmacokinetics in control rabbits and rabbits on the 7th day following a whole-body irradiation with a dose of 5 Gy.

Parameter	Control group	Irradiated group	P
AUC (% dose min mL^{-1})	0·2903 ± 0·0878[1]	0·3706 ± 0·409	0·787*
CL_{tot} (mL min^{-1} kg^{-1})	155·4 ± 25·3	109·8 ± 12·2	0·927*
$t_{\frac{1}{2}}$ (min)	203·9 ± 28·0	207·4 ± 27·3	0·015
Vd_{ss} (mL kg^{-1})	33·15 ± 8·79	27·62 ± 4·62	0·979*
k_{el} (min^{-1})	0·0307 ± 0·0063	0·0259 ± 0·0063	0·400*
MRT (min)	214·6 ± 51·2	251·7 ± 35·7	0·473*

[1] All data are the mean ± s.e.m. * Probability that the ratio of the respective pharmacokinetic parameters of the irradiated and control rabbits is lower than 0·8 or higher than 1·2. Asterisk indicates a statistically significant value.

Table 3. Tissue distribution and total excreted amount of carbisocaine 5 h following its intravenous bolus administration in control rabbits and in rabbits on the 7th day following a whole-body irradiation with a dose of 5 Gy.

Parameter	Control group	Irradiated group	P
Heart (% dose g^{-1})	0·00148 ± 0·0003[1]	0·0011 ± 0·0002	0·735*
tissue/plasma	5·7 ± 1·2	2·7 ± 0·6	0·987*
Lungs (% dose g^{-1})	0·0214 ± 0·0054	0·0144 ± 0·0024	0·407*
tissue/plasma	76·6 ± 16·5	30·5 ± 6·6	0·979*
Liver (% dose g^{-1})	0·0013 ± 0·0002	0·0010 ± 0·0002	0·834*
tissue/plasma	4·9 ± 0·7	2·3 ± 0·4	0·997*
Kidneys (% dose g^{-1})	0·0020 ± 0·0005	0·0013 ± 0·0002	0·700*
tissue/plasma	7·4 ± 1·6	3·3 ± 0·5	0·994*
Excretion Bile (% of dose)	8·73 ± 1·43	6·50 ± 1·05	0·220*
Urine (% of dose)	23·69 ± 2·60	18·32 ± 0·99	0·508*

[1] All data are the mean ± sem. * See footnote for Table 2.

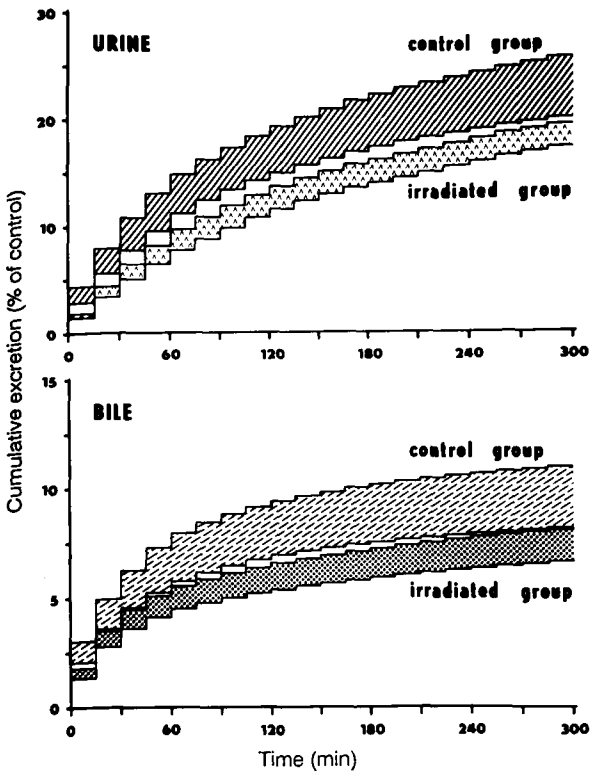

FIG. 2. Excretion of total ^{14}C radioactivity in urine and bile from control rabbits and rabbits whole-body irradiated with a dose of 5 Gy, after intravenous administration of [^{14}C]carbisocaine on the 7th day following irradiation. The interval between the upper and lower boundaries of the data represent the mean ± s.e.m.

Elimination of the carbanilate-type local anaesthetics from the body was found to be mainly due to hepatic metabolism (Štefek & Bezek 1985). Ionizing radiation may damage the activity of hepatic drug metabolizing enzymes and it can be assumed that elevated plasma carbisocaine is a consequence of its inhibited biotransformation. The decreased distribution volume of carbisocaine in irradiated animals may reflect radiation-induced alterations in plasma and tissue binding of the drug. The rate of elimination of ^{14}C radioactivity in the bile and urine in course of the experiment is given in Fig. 2. The cumulative amount of eliminated ^{14}C radioactivity is shown in Table 3. It can be seen that elimination of ^{14}C radioactivity, representing the sum of labelled metabolites and a small amount of unchanged drug, is decreased in the irradiated group. The lower elimination rate of ^{14}C in irradiated rabbits may reflect radiation-induced changes of type I and type II biotransformation steps in the liver (Shysh & Noujaim 1970; Yukawa & Nakazawa 1974; Sokol et al 1975).

In conclusion, after whole-body gamma-irradiation of rabbits, changes in the disposition of the local anaesthetic carbisocaine were observed. Although the values of two pharmacokinetic parameters describing drug elimination, e.g. CL_{tot} and k_{el}, were decreased in the irradiated group, our data indicate that probably the dosage of carbanilate-type local anaesthetics need not be reduced in cases of sublethal irradiation, since the concentration of the drug was lower in sites of possible side-effects in irradiated animals (e.g. heart) in comparison with the values found in intact animals.

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