Br. J. Cancer (1986), **53**, Suppl. VII, 265–267

Physiological factors effecting renal radiation tolerance: A guide to the treatment of late effects

M.E.C. Robbins & J.W. Hopewell

CRC Normal Tissue Radiobiology Research Group, Research Institute (University of Oxford), Churchill Hospital, Oxford, UK.

A number of studies have shown a general reduction in renal blood flow (RBF) following irradiation (Dunjic, 1974), most marked in the renal cortex (Scanlon, 1970). Radiation appears to induce changes in the intrarenal distribution of blood flow causing a relative renal cortical ischaemia similar to that seen following a wide variety of nephrotoxic insults. This differential regional ischaemia may explain the selective loss of proximal tubule epithelial cells after irradiation, since these are highly susceptible to ischaemia (Venkatachalam *et al.*, 1978). In addition, a further tubular cell loss may occur as damaged cells die at the first or subsequent division. This may be the result of the natural turnover of tubular cells or through their being stimulated to divide in response to ischaemic injury. Radiation nephropathy is likely to develop as a result of both these processes.

Recent studies (Robbins *et al.*, 1985) have shown that removal of the unirradiated kidney 6 months after unilateral irradiation in pigs resulted in rapid and pronounced increases in the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in previously 'non-functioning kidneys'. These changes in renal haemodynamics suggest that the reduction in GFR and ERPF seen in a unilaterally irradiated kidney must, to some extent, be of functional origin and not simply due to structural occlusive changes. Thus it may be possible, using vasoactive compounds which increase renal haemodynamics, to enhance renal recovery and effectively reduce radiation induced nephropathy. Two such compounds have been studied; (a) the angiotensin converting enzyme (ACE) inhibitor Captopril, and (b) the α-blocker Indoramin. Both have been shown to increase GFR, ERPF and RBF. Since these agents act on the kidney via differing physiological pathways, their use may also provide information concerning the pathogenesis of radiation induced nephropathy.

Materials and methods

Nine female pigs of the Large White strain were used in these studies. The animals were introduced into the animal accommodation when they were ~3 months of age and were allowed a two-week acclimatization period before any experimental procedures were undertaken. Prior to irradiation the position of both kidneys was determined by intravenous pyelography and the position of each kidney included in an 8×12 cm field tattooed on the overlying skin.

All irradiations were carried out using a 250 kVp Maximar unit (1.4 mm Cu HVL) at a dose rate of 0.7 Gy min^{-1}. Each animal was irradiated with a single dose of 10.7 Gy to each kidney. All experimental studies were carried out under anaesthesia, maintained with a gas mixture of 2–3% halothane, 20% nitrous oxide plus oxygen. Following irradiation three pigs received 150 mg indoramin (Wyeth, Wy 21901), and 50 mg captopril (Squibb, SQ 14225) daily for 12 weeks. Three animals received no additional treatment and served as irradiation controls.

Prior to irradiation and at regular intervals following treatment, renal function was determined using [^{99m}Tc]-DTPA and [^{131}I]-hippuran renography to assess GFR and ERPF respectively (Robbins *et al.*, 1984).

Results

The time related changes in renal function following a single dose of 10.7 Gy X-rays to both kidneys are shown in Figure 1. In pigs that received radiation only there was a marked increase in GFR and ERPF 2 weeks after irradiation. After this total GFR and ERPF levels decreased, reaching minimal values by ~8 weeks. At this time GFR and ERPF levels were only 30–40% of those seen in age-related controls. Between 8–16 weeks GFR levels appeared to recover slightly in some of the pigs, whereas ERPF remained at a low level (this trend was confirmed by renograms carried out at longer times after irradiation).

In pigs which received 150 mg indoramin daily for 12 weeks following irradiation the pattern of changes was initially similar to that seen in the irradiation-only group (Figure 1a) i.e. a marked hyperaemia at 2 weeks followed by a decline. However, there was no evidence of recovery in GFR levels evident in some of the irradiation-only pigs. Pigs which received 50 mg captopril

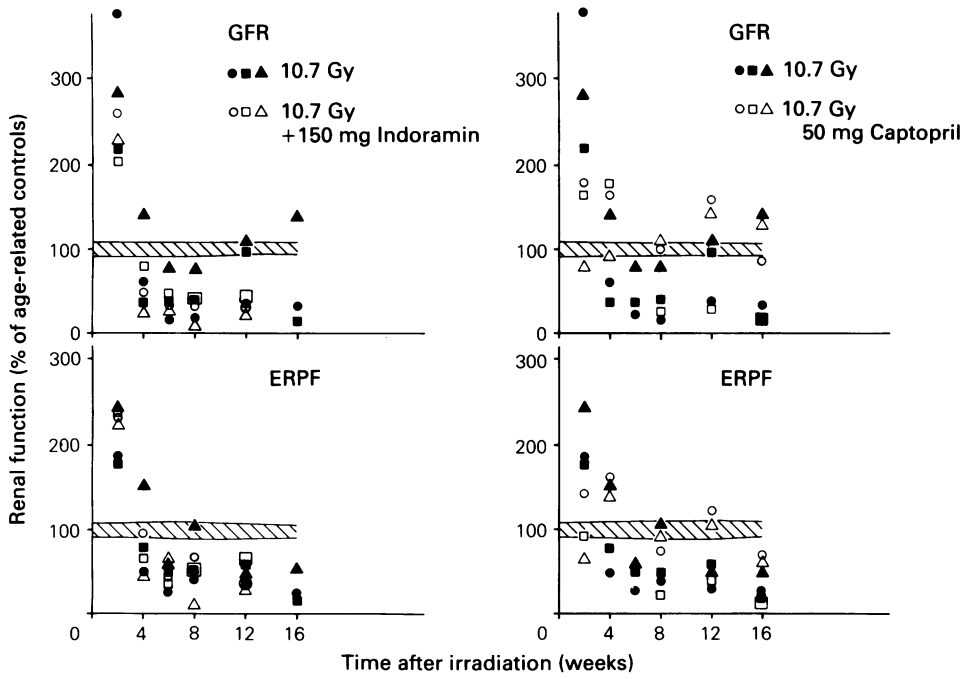

Figure 1 Time-related changes in GFR and ERPF in bilaterally-irradiated pigs compared with (a), pigs which received renal irradiation + 150 mg indoramin and (b), pigs which received renal irradiation + 50 mg captopril daily for 12 weeks. The hatched area represents age-matched unirradiated controls ($\bar{x} \pm 2$ s.e.).

appeared to exhibit a different response. The hyperaemia normally evident 2 weeks after irradiation was markedly reduced. Moreover, in 2 of the 3 pigs receiving captopril the GFR remained at or above that of age-related controls throughout the period of this study (Figure 1b). The results for ERPF show a similar reduction in the hyperaemic response at 2 weeks. In the remaining captopril-treated pig the changes in renal haemodynamics were similar to irradiation-only treated pigs. The spread of data in such a small number of animals in these preliminary findings makes interpretation of the results difficult.

Discussion

The results presented here provide preliminary information concerning the ability of vasoactive compounds to modify the reduction in renal haemodynamics that develops following renal irradiation. The two compounds studied are both widely used in the clinical treatment of hypertension. Captopril, an ACE inhibitor, acts via the blockage of angiotensin II (Ag II) production by inhibition of converting enzyme activity. Ag II preferentially constricts efferent arterioles and also causes a pronounced lowering of the glomerular capillary ultrafiltration coefficient. Stimulation of the renal sympathetic nervous system causes renal vasoconstriction, due to the activation of α adrenergic receptors by norepinephrine released from post-ganglionic sympathetic neurons. This leads to a reduction in both RBF and GFR. This pathway can be blocked by the hypotensive agent indoramin (3-[2-(4-benzamido-piperid-l-yl)ethyl] indole hydrochloride, which has α_1-adrenoceptor blocking properties (Bauer *et al.*, 1984).

Thus the role played by the renin angiotensin system and the renal sympathetic nervous system in the apparent renal vasoconstriction arising after renal irradiation can be investigated using the drugs captopril and indoramin.

The radiation-induced changes in GFR and ERPF observed in bilaterally irradiated pigs which received 150 mg indoramin daily were similar to those seen in pigs which received radiation alone; if anything, the former exhibited a greater decline in renal function. However, two out of the three captopril-treated animals appeared to show a reduced impairment of renal function compared with irradiated controls. It is not known why the remaining pig did not show a similar response. However, plasma renin levels in this pig, measured

10 weeks after irradiation, were markedly higher than in the other two animals, i.e. 10.7 compared with 2.3 and 4.5 pmol $h^{-1}ml^{-1}$, possibly reflecting greater renal damage. Indeed the total renal weight at postmortem of this pig was considerably reduced (~50%), whereas the renal weights of the remaining captopril-treated pigs were similar to those of age-related controls.

These preliminary findings indicate that the application of an appropriate therapeutic drug may prevent or reduce the initial radiation-induced decline in renal haemodynamics. Whether such a procedure will prevent later chronic irreversible changes remains unanswered. However, the renin angiotensin system does appear to play a role in the pathogenesis of radiation damage to the kidney, and is worthy of further study.

We gratefully acknowledge support from the Cancer Research Campaign and the Medical Research Council. We thank E.R. Squibb and Sons Limited and Wyeth Research U.K. for supplying captopril and indoramin respectively. We also thank Nadia Payne at the Middlesex Hospital, London, for determining the plasma renin levels.

References

BAUER, J.H., JONES, L.B. & GADDY, P. (1984). Effects of indoramin therapy on BP, renal function and body fluid composition. *Arch. Intern. Med.*, **144,** 308.

DUNJIC, A. (1974). Blood flow and permeability in liver, kidney and lung. *Curr. Top. Radiat. Res. Quart.*, **10,** 109.

ROBBINS, M.E., SOPER, M. & GUNN, Y. (1984). Techniques for the quantitative measurement of individual kidney function in the pig. *Int. J. Appl. Radiat. Isot.*, **35,** 853.

ROBBINS, M.E.C., HOPEWELL, J.W. & GOLDING, S.J. (1985). Functional recovery in the irradiated kidney following removal of the unirradiated contralateral kidney. (In preparation)

SCANLON, G.T. (1970). Vascular alteration in the irradiated rabbit kidney. *Radiology,* **94,** 401.

VENKATACHALAM, M.A., BERNARD, D.B., DONHOE, J.F. & LEVINSKY, N.G. (1978). Ischaemic damage and repair in the rat proximal tubule: differences among the S_1, S_2 and S_3 segments. *Kid. Int.*, **14,** 31.