Effect of X-Ray and MRI Contrast Media on Lipid Peroxidation in Rat Kidneys in Health and Disease

E. N. Bolotova, P. V. Sergeev, N. L. Shimanovskii, and M. K. Kerimaliev

UDC 616.61.008.939.15-39]-02:615.849.2]-092.9

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 9, pp. 277-279, September, 1993
Original article submitted March 24, 1993

Key Words: *lipid peroxidation; rat kidneys; contrast media; health and disease*

The introduction into medicine of magnetic resonance imaging with the use of artificial contrast media has raised the problem of side effects. Previously we demonstrated [3] that the rates of absorption of cholecystographic and angiographic x-ray contrast media by kidney slices were reduced in rats with experimental renal disease (glycerin nephritis). Accumulating in the kidneys in low amounts these agents were eliminated from them more slowly than in intact animals. By remaining in the tissue, contrast media may exacerbate pathological processes in the organs responsible for their elimination and cause complications of varying severity.

A rise in the level of lipid peroxidation (LPO) may be one of the mechanisms of the toxic effect of contrast media; a shift of this process may result in changes in cellular, tissue, and organ structure and functions. Our study was aimed at elucidation of the effects of x-ray and MRI contrast media on LPO in rat kidneys *in vivo* and *in vitro* in health and disease (experimental glycerin nephritis, acute CCl_4 poisoning of the liver).

MATERIALS AND METHODS

White outbred male rats weighing 180-250 d kept on a standard diet were used in the experiments. The following agents were under study: ionogenic x-ray contrast media - bilignost 50% and triombrast 76%, manufactured in Kiev, and nonionogenic agents - omnipaque 300 (Nicomed, Norway) and its analog iohexol All-Russian Research Chemical-Pharmaceutical Institute, Moscow); a new Russian MRI contrast medium: gadolinium complex with diethyltriamine pentacetate (Gd-DTPA) and one more MRI contrast medium, $GdCl_3$.

The following doses of contrast media were used *in vivo*: x-ray contrast media 1 ml/kg, Gd-DTPA 0.1 mmol/kg. $GdCl_3$ (characterized by excellent paramagnetic properties but higher toxicity vs. Gd-DTPA [2]) 0.05 mmol/kg. The animals were killed under light ether anesthesia one hour after intravenous injection of the contrast media. *In vitro* all media were used in concentrations of 10^{-4}-10^{-3} M, the incubation time being 30-90 min at 37°C.

Acute liver failure was simulated by a single intramuscular injection to rats of CCl_4 in a dose of 0.4 ml per 100 g weight [6]. Acute kidney failure was induced by a single i.m. injection of 50% glycerin solution (10 ml/kg) [7]. Animals were decapitated under ether 24 h after CCl_4 injection or 72 h after glycerin injection.

The rate of LPO was assessed by spectrophotometry of malonic dialdehyde (MDA) in rat kidney homogenate at wavelength 532 nm [1] using an SF-16 spectrophotometer. MDA content was estimated in nm per gram fresh tissue. Results

Department of Molecular Pharmacology, Russian State Medical University, Moscow

0007-4888/93/0009-1111$12.50

TABLE 1. Effect of Contrast Media (10^{-3} M) on *in Vitro* Lipid Peroxidation in Rat Kindey Homogenate for Various Incubation Periods ($M \pm m$)

Contrast medium	MDA content, nmol/g tissue		
	Incubation time, h		
	0.5	1.0	1.5
Control	10.2±1.3	19.7±1.3	24.7±2.6
Bilignost	12.3±1.1	36.6±1.2*	31.5±1.4
Triombrast	12.9±1.2	30.4±1.2*	38.0±1.3*
Iohexol	11.2±1.2	27.9±3.9	28.6±2.5
Omnipaque	11.9±1.2	27.1±1.4*	28.9±1.2
$GdCl_3$	14.5±1.4	49.3±1.5*	51.1±2.9*
Gd–DTPA	11.7±1.3	24.0±1.2	25.1±1.4

Note. Here and in Tables 2–4 an asterisk shows reliable ($p<0.05$) values.

were statistically processed using the Student *t* test; values at $p \leqslant 0.05$ were considered reliable.

RESULTS

The rate of LPO in rat kidneys was found to depend on the duration of kidney tissue exposure to contrast media, the concentration of medium, and the status of the excretory organs.

Table 1 shows that the spontaneous LPO level in intact rat kidney homogenate increased as a function of the incubation time from 10.2±1.3 to 24.7± 2.7 nmol/g during 0.5-1.5 h of observation; this increase was most strongly expressed during the first hour, and therefore in subsequent experiments we studied the effect of contrast media on LPO after a one-hour incubation of homogenate with the agents. It should be noted that in glycerin nephritis the LPO level in the kidneys increased by 62% but was unchanged in acute CCl_4 poisoning (Tables 2 and 3).

The examined contrast media variously changed the rate of LPO in intact rat kidney homogenate. *In vitro* with contrast media used in a concentration of 10^{-4} M (Table 2) only $GdCl_3$ raised the LPO level (by 52%) in intact rat kidney homogenate; in disease (nephritis) $GdCl_3$ and bilignost raised it by 51 and 38%, respectively, whereas in liver intoxication the rise was by 48 and 93%.

Increasing the contrast media concentration to 10^{-3} M led to a rise of the rate of LPO in rat kidneys $GdCl_3$ was found to be most toxic: it increased LPO in health and disease more than twofold. Other contrast media also influenced lipid peroxidation, though not as much as $GdCl_3$. In disease this effect was more noticeable than in health. For example, bilignost (10^{-3} M) in glycerin nephritis induced twofold rise of the LPO level and raised it 2.6 times in liver intoxication as against a 1.8-fold increase in intact animals.

The nonionogenic contrast media iohexol and omnipaque had the least effect on renal lipid peroxidation *in vitro*. Gd-DTPA, an MRI contrast medium, did not change the lipid peroxidation level.

Studies of rat kidney LPO *in vivo* showed that its levels in homogenate were the same *in vitro* and *in vivo* (control values shown in Tables 2 and 4). Moreover, just as *in vitro*, the level of spontaneous LPO in the kidneys of rats with glycerin nephritis was higher than in intact animals or those with CCl_4 poisoning (Table 4).

The studied contrast media, when injected intravenously, influenced renal lipid peroxidation in the following manner. In intact animals only $GdCl_3$ and bilignost intensified lipid peroxidation (uniformly, by 1.5 times). In rats with glycerin nephritis all the agents except Gd-DTPA changed the level of LPO, $GdCl_3$ and bilignost being most toxic. In animals with acute liver poisoning the LPO level remained unchanged not only after Gd-DTPA injection, but after iohexol and omnipaque as well, whereas bilignost, a hepatotropic agent, was the most active under such conditions and raised the LPO level more than twofold (Table 4).

TABLE 2. Effect of Contrast Media (10^{-4} M) on *in Vitro* Lipid Peroxidation in Rat Kidney Homogenate in Health and Disease ($M \pm m$)

Contrast medium	MDA content, nmol/g tissue		
	intact animals	glycerin nephritis	acute CCl_4 intoxication of liver
Control	19.7±1.3	31.9±1.2	22.2±1.2
Bilignost	22.7±1.3	44.0±2.1*	42.8±1.3*
Triombrast	22.3±2.1	33.8±1.6	23.1±2.4
Iohexol	21.8±1.2	32.6±1.8	22.3±1.4
Omnipaque	22.0±1.5	32.9±1.4	22.6±2.1
$GdCl_3$	30.0±1.8*	62.8±2.1*	32.9±1.3*
Gd–DTPA	20.6±2.2	32.4±1.2	22.8±1.4

TABLE 3. Effect of Contrast Media (10^{-3} M) on *in Vitro* Lipid Peroxidation in Rat Kidney Homogenate in Health and Disease ($M \pm m$)

Contrast medium	MDA content, nmol/g tissue		
	intact animals	glycerin nephritis	acute CCl_4 intoxication of liver
Control	19.7±1.3	31.9±1.2	22.2±1.2
Bilignost	36.6±1.2*	66.4±3.3*	58.8±1.2*
Triombrast	30.4±1.2*	56.5±2.3*	38.4±1.3*
Iohexol	27.9±3.9	51.6±1.2*	28.6±1.2*
Omnipaque	27.1±1.4*	52.9±2.0*	30.4±1.2*
$GdCl_3$	49.3±1.5*	74.8±1.2*	45.7±3.6*
Gd–DTPA	24.0±1.2	38.4±1.2	20.8±1.2

Hence, analysis of the findings has shown $GdCl_3$ to be the most toxic agent, increasing lipid peroxidation by 1.5-2.5 times in rat kidney homogenate *in vivo* and *in vitro* in both health and disease. Bilignost proved similar to it in its effect. The rest of the studied contrast media less strongly affected the LPO level in rat kidneys, the intensity if their effects diminishing in the following order: bilignost>triombrast>iohexol=omnipaque. In disease (glycerin nephritis, acute CCl_4 poisoning of the liver) the effects of the media on the level of LPO were more pronounced. Our data indicating a higher toxicity of ionic as opposed to nonionic x-ray contrast media are in line with the findings of Parevrz *et al.*, who investigated the effects of diatrizoate, an ionic x-ray contrast medium, and the nonionic iopromide on spontaneous lipid peroxidation in the kidneys of rats with glycerin nephritis [5].

The data on contrast media intensified lipid peroxidation should be taken into consideration in the clinical setting, for diagnostic studies making use of contrast media are mainly carried out in patients with visceral diseases, including excretory organ insufficiency, which may result in inversion of contrast medium excretion: for example, cholegraphic iodoxamate, excreted in health by the liver, may be excreted by the kidneys in the case of liver disease, remaining in the body and aggravating the pathological processes in the involved organ [4].

We consider the increased nephrotoxicity of the examined contrast media in experimental diseases of not only the kidneys but also of the liver to be clinically important. Liver intoxication with CCl_4 appears to be associated with disturbances and depletion of the antioxidant system of the whole body, this stepping up the effect of contrast media vis-a-vis LPO induction in the kidneys both *in vivo* and *in vitro*. These data indicate the advisability of using antioxidants for premedication when carrying out contrast examinations of patients with severe pathological changes, which are associated as a rule with intensified lipid peroxidation processes.

From the standpoint of pharmacological inertness, the nonionic agents omnipaque, ultravist, etc., are the safest, but they are expensive and are not yet manufactured in Russia. Our previous data on the effect of iohexol, synthesized at the All-Russian Research Chemical and Pharmaceutical Institute in Moscow, on human and rat blood macro- and microrheology and on lipid peroxidation processes in rat liver and kidney tissue in health and disease prove the advisability of seeking new nonionic contrast media to be used in x-ray diagnosis, as these have proved safer than ionic media.

TABLE 4. Effect of Contrast Media on *in Vivo* Lipid Peroxidation in Rat Kidney Homogenate in Health and Disease ($M \pm m$)

Contrast medium	MDA content, nmol/g tissue		
	intact animals	glycerin nephritis	acute CCl_4 intoxication of liver
Control	20.3±2.3	29.8±2.0	22.0±1.7
Bilignost	30.5±1.4*	50.1±1.4*	53.1±1.4*
Triombrast	27.1±1.4	43.6±1.2*	31.6±1.2*
Iohexol	19.1±3.3	40.4±1.3*	28.4±1.2
Omnipaque	25.6±1.2	42.8±1.3*	26.7±1.0
$GdCl_3$	32.8±1.2*	51.6±1.2*	36.1±1.2*
Gd–DTPA	20.8±1.2	33.4±1.4	25.1±1.4

Currently, methods based on magnetic resonance imaging (MRI) are being increasingly introduced into medical practice. In many cases MRI contrast media are injected to improve the quality of tomograms. Preliminary results of studies of the Russian agent Gd-DTPA, which we have received for preclinical trials, have shown it to be not inferior to magnevist, manufactured by Schering (Germany), in terms of its magnetic resonance characteristics and effects on the blood of human and laboratory animals. The results of the present study have once more demonstrated that Gd-DTPA tested *in vivo* and *in vitro* has no effect on lipid peroxidation level in rat kidneys in health and even in disease, this agreeing with published data on the lower toxicity of MRI in comparison with x-ray contrast media [2].

Comparison of the nephrotoxic effects of one of the safest of the current x-ray contrast media, omnipaque, and of the MRI contrast medium Gd-DTPA has demonstrated the superiority of the latter and its recommended use for clinical examinations in combination with MRI tomography.

REFERENCES

1. Yu. A. Vladimirov and A. I. Archakov, *Lipid Peroxidation in Biological Membranes* [in Russian], Moscow (1972).
2. P. V. Sergeev, V. O. Panov, and N. L. Shimanovskii, *Khim.-Farm. Zh.*, № 5, 540-549 (1989).
3. P. V. Sergeev, E. N. Bolotova, V. S. Veksler, *et al.*, *Ibid.*, № 4, 13-15 (1991).
4. M. Ardity, G. Molino, A. Biondi, *et al.*, *Rays (Roma)*, **10**, № 1, 81-87 (1985).
5. Z. Parevrz, M. A. Phahmen, R. Moncada, *et al.*, *Invest. Radiol.*, **24**, № 9, 697-702 (1989).
6. P. D. Simplicio and G. Segre, *Pharmacol. Res. Commun.*, **9**, № 9, 283-298 (1977).
7. M. Yates, P. Bowner, and J. Emmarson, *Biochem. Pharmacol.*, **33**, № 10, 1695-1696 (1984).