DESFERAL PROTECTION AGAINST ACUTE NITROFURANTOIN TOXICITY IN ALBINO RAT LUNGS

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ABSTRACT

The study was carried on 70 male Albino rats which were divided into 4 groups. The first group (0), consisted of 10 rats, was given distilled water by intraperitoneal route and was used as negative control group. Each of the other three groups consisted of 20 rats. In group 1, rats were given single S.C. injection of N, N-dimethylformamide used to dissolve nitrofurantoin and was used as positive control group. In group 2, rats were given single S.C. injection of nitrofurantoin (200 mg/kg) dissolved in N, N-dimethylformamide and diluted by distilled water. In group 3 rats were given two I.P. injections of desferal (each of them 100 mg/kg) in addition to the single injection of nitrofurantoin, the first were given 1 hour before nitrofurantoin and the other dose was given 12 hours after the first dose. Groups 1, 2 and 3 were divided into two equal subgroups a and b (10 rats each). Rats of subgroups (a) were killed one day after N, N-dimethylformamide or nitrofurantoin injections whereas they were killed two days after these injections in subgroups (b). After sacarification of rats, blood samples were taken then centrifuged and sera were analysed for reduced glutathione. Rats were dissected and lungs were obtained. Lung homogenates were used for measuring the levels of malondialdehyde (MDA) and reduced glutathione (GSH). It was found that N, N-dimethylformamide has no significant effect on studied biochemical parameters when compared with –ve control group. The mean level of lung MDA was found to be significantly higher (compared with control groups) in rats injected with nitrofurantoin but the increase was more in rats of subgroup 2a. In rats received desferal with nitrofurantoin injection, the mean level of lung MDA was found to be significantly lower than its mean level in group 2. On the other hand the mean levels of reduced GSH in lung and serum were found to be significantly lower (compared with control groups) in rats of subgroup 2b. In rats received desferal with nitrofurantoin injection and killed after 2 days, the mean levels of reduced GSH in lung and serum were found to be significantly higher than their mean levels in group 2b.

INTRODUCTION

Nitrofurantoin is used for prophylaxis and treatment of urinary tract infection. Adverse drug reactions to nitrofurantoin include pulmonary reactions, hepatic toxicity, blood dyscrasias and peripheral neuropathy (Holmberg et al., 1980). Pulmo-

nary toxicity from nitrofurantoin therapy has been described in two forms, acute and chronic lung disease (Cooper et al., 1986). Results from both in vivo (Boyd et al., 1979) and in vitro (Martin et al., 1985) studies have suggested that nitrofurantoin induced pulmonary toxicity is exerted via oxidant stress.

The exact mechanisms by which nitrofurantoin damages the lung remain unclear. Nitrofurantoin activation under aerobic conditions may proceed via one electron reduction of the nitro group to the nitro-anion radical. This anion radical is auto oxidized rapidly in the presence of molecular oxygen to regenerate the parent compound and the superoxide anion (Trush et al., 1982). The superoxide anion may dismutate, either spontaneously or in the presence of superoxide dismutase to form hydrogen peroxide (Martin, 1983).

Hydrogen peroxide (H2O2) was shown to be reduced to highly reactive hydroxyl radical (-OH) in iron catalyzed Fenton type reaction (Walling, 1975). Thus by chelating iron in a catalytically inactive form, which is achieved by deferrioxamine, it would be possible to block the generation of (-OH) (Burkitt et al., 1993).

The lung contains intracellular antioxidant enzymes to maintain a normal redox state (Cantin et al., 1987). Disequilibrium, either through increased oxidant stress or decreased antioxidant resources, can result in a series of pathophysiological events in the lung that culminate in cellular death and pulmonary dysfunction (Heffner and Repine, 1989).

The aim of the present work is to evaluate the protective effect of desferal against nitrofurantoin induced acute pulmonary toxic effects in albino rats.

MATERIAL AND METHODS

Drugs:

Nitrofurantoin macrocrystals "Macrofuran 100 mg capsule" (Kahira pharma, Cairo, Egypt) was purchased. Each capsule was evacuated and dissolved in 3 ml. N, N- dimethylformamide according to Barry and Lasner (1976) then diluted with distilled water to give a final concentration of 20 mg/ml. It was injected in a dose 200 mg/kg S.C. which is known to induce acute pulmonary toxicity according to Zacharias and Pang (1992).

Deferoxamine methansulphonic 500 mg vial (Novartis pharma AG, Basle, Switzerland) was dissolved in 5 ml. distilled water. It was given in two doses each of them 100 mg,/kg intra-peritoneal (I.P.) as in the study of Towner et al. (2002).

Animals:

The study was carried out on 70 adult male albino rats obtained from animal

house of Mansoura Faculty of Medicine. Their weight ranged from 195 - 220 g. The rats were housed in metallic cages at room temperature with day and night light rhythm. Animals fed a mixture containing bread, bran and ground maize as well as thoroughly washed leafy vegetables and free water supply. They were allowed to acclimatize to their new environment for 10 days prior to the study.

Rats were classified into 4 groups; group (0) consisted of 10 rats and other three groups named group 1, group 2 and group 3, each of them consisted of 20 rats. Group (0) was given distilled water by intraperitoneal (I.P.) route and was used as negative control group. In group 1, rats were given single S.C. injection of N, N-dimethylformamide in the same dose used to dissolve nitrofurantoin and was used as positive control group. In group 2, rats were given single S.C. injection of dissolved nitrofurantoin (200 mg/kg). In group 3 rats were given two I.P. injections of desferal (each of them 100 mg/kg) in addition to the single S.C. injection of nitrofurantoin; the first were given 1 hour before nitrofurantoin injection and the other dose was given 12 hours after the first dose.

Groups 1, 2 and 3 were divided into two equal subgroups a and b (10 rats each). Rats of subgroups (a) were killed one day after N, N-dimethylformamide or nitrofurantoin injections whereas they were killed two days after these injections in subgroups (b).

Samples collection :

Rats were sacrificed by cut throat then a blood sample (3 ml.) was taken from the cut throat then centrifuged and the collected sera were analyzed for the level of serum reduced glutathione (GSH).

Each rat was dissected after taking the blood sample and lungs were immediately excised. Lungs were rinsed with ice cold saline to remove excess blood then minced and homogenized in 0.02 M sodium phosphate buffer pH 7.4 (1:10 w/v) using a Potter-Elvehjem smooth glass homogenizer with a motor driven teflon pestle. Lung homogenates were used for biochemical assessment of nitrofurantoin induced pulmonary toxicity by measuring the levels of malondialdehyde (MDA) and reduced glutathione (GSH) in lung tissue.

Biochemical studies :

Serum reduced glutathione (GSH) was determined enzymatically by the glutathione-reductase 5, 5'-dithiobis (2-nitrobenzoic acid) recycling assay according to method described by Tietze (1969). Serum reduced GSH was expressed as nmol. / ml.

Malondialdehyde (MDA) contents in lung homogenates were measured spec-

trophotometrically (at 535 nm) according to the method of Lowry et al. (1951). Malondialdehyde level was expressed as nmol. / mg protein of lung tissue.

Reduced GSH contents in lung homogenates were measured according to the method of Kuo and Hook (1982) which was based on conversion of 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) to 5-thio-2-nitrobenzoate (TNB). Formation of TNB was measured by spectrophotometry at 412 nm. Reduced GSH level was expressed as µmol. / g protein of lung tissue.

Statistical analysis:

Statistical analysis was done by using the Statistical Package for Social Science (SPSS) program version 12. The following statistical parameters were utilized: arithmetic mean (x), standard deviation (± SD) and Student t-test. Significance was considered at P value less than 0.05.

RESULTS

The mean levels of lung MDA, lung reduced GSH and serum reduced GSH in +ve control subgroups (1a and 1b) showed no significant differences when compared with each other and when compared with their mean levels in -ve control (0) (Tables 1, 2 and 3).

Lung MDA mean level in rats of subgroups 2a and 2b (injected with nitrofurantoin) was significantly higher when compared with both control groups (1a and 1b respectively as well as group 0). This increase was significantly more in rats of subgroup 2a than in rats of subgroup 2b. In rats of subgroups 3a and 3b (received desferal with nitrofurantoin injection) the mean level of lung MDA was significantly lower than its mean level in rats of subgroups 2a and 2b respectively, but still insignificantly higher than its mean level in control groups. Comparison between mean lung MDA levels in subgroups 3b versus 3a revealed no significant differences (Tables 1 - 4).

There was significantly lower mean level of lung reduced GSH in rats of subgroup 2b when compared with control groups (0 and 1b) as well as subgroup 2a. In rats of subgroup 3b the mean level of lung reduced GSH was significantly higher than its mean level in rats of subgroup 2b, but still significantly lower than its mean level in control groups and subgroup 3a. On the other hand, mean level of lung reduced GSH in other subgroups 2a, and 3a showed no significant differences when compared with control groups and when compared with each other (Tables 1 - 4).

There was significantly lower mean level of serum reduced GSH in rats of subgroup 2b when compared with control

groups as well as subgroup 2a (injected with nitrofurantoin and killed after 1 day). In rats of subgroup 3b the mean level of lung reduced GSH was significantly higher than its mean level in rats of subgroup 2b, but still insignificantly lower than its mean level in control groups and subgroup 3a. On the other hand, mean level of serum reduced GSH in other subgroups 2a, and 3a showed no significant differences when compared with control groups and when compared with each other (Tables 1 - 4).

DISCUSSION

The significantly increased level of malondialdehyde (MDA) in lung tissue as well as significantly decreased levels of reduced glutathione in lung tissue and serum in this study suggests that nitrofurantoin can induce pulmonary toxicity via oxidant stress mechanisms. These mechanisms are not attributed to N, N-dimethylformamide solvent used to dissolve nitrofurantoin which was found to have no significant effect on the biochemical parameters measured in the present study.

The above suggestion is based on the fact that, the increased lipid peroxidation (assessed by increased level of MDA) and decreased reduced GSH in tissues are considered as sensitive indicators of oxidative stress (Tom and Montgomery, 1980).

These findings are on coordinance with the studies of Dunbar et al. (1984) and Hoener et al. (1989) who observed a depletion of reduced GSH with concurrent increases in oxidized sulfhydryls (GSSG) in nitrofurantoin perfused lung and liver respectively. The findings of the present study coincide with those of Zacharias and Pang (1992) who provided in vivo evidence for substantiating lipid peroxidation as a possible cause of lung damage following single subcutaneous injection of nitrofurantoin in rats.

When desferal was given with nitrofurantoin in the present study a significantly lower level of MDA in lung tissue as well as significantly higher levels of reduced GSH in lung tissue and serum were observed compared with their levels in rats given nitrofurantion alone. These levels of the biochemical parameters which were near their levels in control groups, suggest that desferal had played a role in minimizing the oxidative stress induced by nitrofurantoin.

According to Walling (1975) hydrogen peroxide (H2O2) produced in the course of nitrofurantoin activation; was shown to be reduced to highly reactive hydroxyl radical (-OH) in iron catalyzed Fenton type reaction. Thus the protective effects of desferal against nitrofurantoin induced oxidative stress may be explained partially on the basis of its ability to form complex-

es with iron, thereby reducing -OH radical generation. Another supposed mechanism is that of Caraceni et al. (1995) who stated that desferal is not only an iron chelator but it also scavenges directly the hydroxyl radical (-OH) as well as the superoxide radical.

This protective effect of desferal coincides with findings of Younes and Siegers (1985) and Kohen and Chevion (1985) who observed that desferal prevented the toxicity of carbon tetrachloride and paraquat which are free radical generating toxins. Wronska-Nofer et al. (2000) found also that iron chelation with desferal abolished cadmium provoked lipid peroxidation thus attenuating oxidative stress.

In contrast to these findings, the study of Kiyose et al. (1999) who demonstrated that desferal stimulates the formation of nitroxide free radicals and promotes lipid peroxidation during in vitro study of its effect on Ca2+-ATPase of skeletal sarcoplasmic reticulum. They supposed that this effect may occur only with prolonged clinical use of this chelator.

It is concluded that nitrofurantoin can induce pulmonary toxicity via oxidant stress mechanisms. It can be concluded also that iron chelator; desferal is effective in minimizing these oxidant stresses by reducing hydroxyl radical generation or scavenging them.

Accordingly, it is recommended that desferal can be given to the patients receiving repeated courses or high doses of nitrofurantoin to minimize or abolish its possible adverse toxic effects specially on the lung. It is recommended also that estimation of serum reduced GSH in these patients can be used as indicator for development of nitrofurantoin toxic effects.

Table (1): Comparison between levels of lung MDA, lung reduced GSH and serum reduced GSH in different subgroups of the study versus those in control group (0).

Parameters \ Groups		Group (0)	Group (1)		Group (2)		Group (3)	
			Subgroup 1a (killed after 1 day)	Subgroup 1b (killed after 2 days)	Subgroup 2a (killed after 1 day)	Subgroup 2b (killed after 2 days)	Subgroup 3a (killed after 1 day)	Subgroup 3b (killed after 2 days)
Lung MDA nmol/mg	Mean	1.066	1.069	1.064	1.778	1.4	1.097	1.079
	± SD	± 0.048	± 0.053	± 0.053	± 0.050	± 0.096	± 0.032	± 0.028
			↑	↓	↑	↑	↑	↑
	P		0.835	0.942	< 0.001*	< 0.001*	0.061	0.421
Lung reduced GSH umol/g	Mean	1.727	1.751	1.733	1.757	1.057	1.748	1.647
	± SD	± 0.047	± 0.062	± 0.061	± 0.045	± 0.061	± 0.052	± 0.054
			↑	↑	↑	↓	↑	↓
	P		0.293	0.816	0.242	< 0.001*	0.403	0.016*
Serum reduced GSH nmol/ml	Mean	19.395	19.41	19.18	19.435	13.565	19.425	18.975
	± SD	± 0.673	± 0.638	± 0.734	± 0.474	± 0.387	± 0.500	± 0.508
			↑	↓	↑	↓	↑	↓
	P		0.967	0.507	0.872	< 0.001*	0.908	0.063

* Significant if P < 0.05 ↑ = higher Insignificant if P > 0.05 ↓ = lower

Group 0: - ve control

Group 1: + ve control injected N, N-dimethylformamide S.C.

Group 2: injected single dose dissolved nitrofurantoin S.C.

Group 3: injected single dose dissolved nitrofurantoin S.C. + 2 doses desferal I.P.

Table (2): Comparison between levels of lung MDA, lung reduced GSH and serum reduced GSH in rats of subgroups (a) killed after 1 day.

PARAMETERS \ GROUPS		SUBGROUP 2A VERSUS SUBGROUP 1A	SUBGROUP 3A VERSUS SUBGROUP 1A	SUBGROUP 3A VERSUS SUBGROUP 2A
Lung MDA		↑	↑	↑
	P	< 0.001*	0.131	< 0.001*
Lung reduced GSH		↑	↓	↓
	P	0.824	0.922	0.631
Serum reduced GSH		↑	↑	↓
	P	0.930	0.959	0.968

* Significant if P <0.05. ↑ = higher

Insignificant if P >0.05 ↓ = lower

Table (3): Comparison between levels of lung MDA, lung reduced GSH and serum reduced GSH in rats of subgroups (b) killed after 2 days.

Parameters \ Groups		Subgroup 2b versus subgroup 1b	Subgroup 3b versus subgroup 1b	Subgroup 3b versus subgroup 2b
Lung MDA		↑	↑	↓
	P	< 0.001*	0.508	< 0.001*
Lung reduced GSH		↓	↓	↑
	P	< 0.001*	0.004*	< 0.001*
Serum reduced GSH		↓	↓	↑
	P	< 0.001*	0.476	<0.001*

* Significant if P <0.05. ↑ = higher
Insignificant if P >0.05 ↓ = lower

Table (4): Comparison between levels of lung MDA, lung reduced GSH and serum reduced GSH in rats of subgroups (b) versus those in rats of subgroups (a).

Parameters \ Groups		Subgroup 1b versus subgroup 1a	Subgroup 2b versus subgroup 2a	Subgroup 3b versus subgroup 3a
Lung MDA		↓	↓	↓
	P	0.846	<0.001*	0.239
Lung reduced GSH		↓	↓	↓
	P	0.612	<0.001*	0.002*
Serum reduced GSH		↓	↓	↓
	P	0.420	<0.001*	0.059

* Significant if P <0.05. ↑ = higher
Insignificant if P >0.05 ↓ = lower

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الوقاية بالديسفيرال ضد التأثير السمى الحاد لعقار النيتروفيورانتوين فى رئة الجرذان البيضاء

المشتركون فى البحث

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أجريت هذه الدراسة على ٧٠ من ذكور الجرذان البيضاء والتى تم تقسيمها إلى ٤ مجموعات، المجموعة الأولى (0) وتضم ١٠ جرذان أعطيت ماء مقطر عن طريق الحقن البريتونى وأستخدمت كمجموعة ضابطة سالبة، المجموعات الثلاثة الأخرى (١) و (٢) و (٣) يضم كل منها ٢٠ جرذاً، أعطيت الجرذان فى المجموعة (١) والتى أستخدمت كمجموعة ضابطة موجبة جرعة واحدة من مادة الدايميثيل فورماميد تحت الجلد والتى استخدمت لإذابة عقار النيتروفيورانتوين، وأعطيت الجرذان فى المجموعة (٢) جرعة واحدة من عقار النيتروفيورانتوين (٢٠٠مجم/كجم) تحت الجلد بعد إذابتها فى مادة الدايميثيل فورماميد وتخفيفها بالماء المقطر، أما الجرذان فى المجموعة (٣) أعطيت جرعتين من الديسفيرال عن طريق الحقن البريتونى كل منهم (١٠٠مجم/كجم) بالإضافة إلى جرعة النيتروفيورانتوين، الجرعة الأولى من الديسفيرال أعطيت قبل جرعة النيتروفيورانتوين بساعة واحدة أما الجرعة الثانية من الديسفيرال أعطيت بعد ١٢ ساعة من الجرعة الأولى، تم تقسيم كل من المجموعات (١) و (٢) و (٣) إلى مجموعتين فرعيتين متساويتين (أ) و (ب) يضم كل منها ١٠ جرذان ، تم ذبح الجرذان فى المجموعات الفرعية (أ) بعد يوم واحد من حقن مادة الدايميثيل فورماميد أو النيتروفيورانتوين أما الجرذان فى المجموعات الفرعية (ب) فتم ذبحها بعد يومين من الحقن، بعد ذبح كل جرذتم أخذ عينة دم وفصل المصل لاستخدامه فى قياس مستوى الجلوتاثيون المختزل، ثم تم تشريح كل جرذ واستئصال الرئتين وتقطيعهما إلى قطع صغيرة وطحنهما حتى أصبحوا نسيج متجانس أستخدم لقياس مستوى المالون داى ألدهايد والجلوتاثيون المختزل، وجد أن حقن مادة الدايميثيل فورماميد لم يحدث تغيير ذو دلالة إحصائية فى المعايير الكيميائية التى تم دراستها بالمقارنة بالمجموعة الضابطة السالبة، كما وجد أن مستوى المالون داى ألدهايد فى نسيج الرئة أظهر إتفاعاً ذو دلالة إحصائية فى الجرذان التى تم حقنها بعقار النيتروفيورانتوين فقط أى المجموعة (٢) عند مقارنته بمستواه فى المجموعة الضابطة وكان هذا الارتفاع أكثر فى جرذان المجموعة الفرعية (٢أ) ولكن فى الفئران التى تم حقنها بالديسفيرال مع عقار النيتروفيورانتوين أى المجموعة (٣) أظهر مستوى المالون داى ألدهايد إنخفاضاً ذى دلالة إحصائية عند مقارنته بمستواه فى جرذان المجموعة (٢)، وأظهر مستوى الجلوتاثيون المختزل فى المصل ونسيج الرئة إنخفاضاً ذى دلالة إحصائية فى الجرذان التى تم

حقنها بعقار النيتروفيورانتوين وتم ذبحها بعد يومين أى المجموعة الفرعية (٢ب) عند مقارنته بمستواه فى المجموعة الضابطة ولكن فى الفئران التى تم حقنها بالديسفيرال مع عقار النيتروفيورانتوين وتم ذبحها بعد يومين أى المجموعة الفرعية (٣ب) أظهر مستوى الجلوتاثيون المختزل فى المصل ونسيج الرئة إرتفاعاً ذى دلالة إحصائية عند مقارنته بمستواه فى جرذان المجموعة الفرعية (٢ب).

وعلى ضوء هذه النتائج ينصح الباحثان بإعطاء الديسفيرال للمرضى الذين يعالجون بجرعات عالية أو متكررة من عقار النيتروفيورانتوين لتقليل أو منع تأثيره السمى وخاصة على الرئة كما ينصح أيضاً بقياس مستوى الجلوتاثيون فى مصل هؤلاء المرضى كمؤشر لحدوث هذه الآثار.