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THE PARACETAMOL AND THEOPHYLLINE CO-ADMINISTRATION - AN AVOIDING TO INTERACTION

Răzvan Gligor[1], Şerban Gligor[2*]
[1]"Vasile Goldis" Western University, Faculty of Medicine, Pharmacy and Dental Medicine, Medicine Department, Arad
[2*]West University, Faculty of Physical Education and Sports, Kinesytherapy Department, Timisoara

ABSTRACT. This paper presents the consequences of Paracetamol and Theophylline co-administration in experimental conditions. For this purpose we used laboratory animals (rats) to whom a single intraperitonealy dose of theophylline (15 mg/kg body weight) has been administered 2 hours after receiving an overdose of paracetamol (1500 mg/kg body weight). Comparatively another xantine base, namely caffeine have been administered intraperitonealy (100 mg/kg body weight). Theophylline showed a high degree of toxicity, increased paracetamol hepatotoxicity, and mortality, perhaps because of generalized convulsions caused by theophylline free, active, in excess. Instead, caffeine significantly reduced the toxicity of paracetamol.

Keywords: theophylline, paracetamol, co-administration, hepatotoxicity, caffeine

INTRODUCTION

Paracetamol is an analgesic-antipyretic drug with a wide therapeutical usage, which implies (when the patient presented disorders are complex) its co-administration with other drugs. This combination may increase efficiency, may counter some adverse effects, or, by contrary, may potentiate it's toxicity. Because the liver damages inflicted by the paracetamol toxicity represents the main cause of the morbidity and mortality associated with this medicine, we've aimed to asses, under experimental conditions, the consequences of paracetamol co-administration, in overdose, with theophylline on paracetamol hepatotoxic effect. (Gunawan B. et al 2004, Kaplowitz N. 2002, Thames G. 1999)

For this purpose laboratory animals receiving intraperitonealy a single dose of theophylline 2 hours after the intraperitonealy administration of a paracetamol overdose have been used. Comparatively another xantine base, namely caffeine, have been used intraperitoneally.

The major aim of this study was to determine the consequences of the theophylline co-administration on the paracetamol hepatotoxicity, comparatively with the caffeine effects.

MATERIALS AND METHODS

The experiments were performed on male, adult Wistar rats, weighing 180 ± 30 g. The animals were maintained in standard laboratory conditions (at a 12 hours light cycle of and at a 20°C ± 2 room temperature) and were fed with a standard balanced regime; 18 hours before the experiment were given only water ad libitum. The experiments described here were performed in compliance with European Communities Council Directive 1986 (86/609/EEC) and ordinance No. 37 of the Romanian Government from 2nd February 2002.

The animals were randomly divided into groups of 20 animals each and were put in separate cages.

To study the consequences of paracetamol and theophylline coadministration we used 4 lots of animals: namely a control group consisting of rats receiving a 0.2 ml/100 g saline solution intraperitonealy (used to determine normal values of biochemical, hematological, pharmacodynamical and morphological parameters), a reference lot for paracetamol consisting of animals receiving intraperitonealy a single dose of 1500 mg paracetamol/kg of body weight, a group composed of animals treated with 1500 mg paracetamol/kg of body weight and two hours later treated intraperitonealy with 15 mg of theophylline/kg of body weight; and a group composed of animals pretreated intraperitonealy with 100 mg/ kg of body weight caffeine and then after one hour treated with a single overdose of paracetamol (1500 mg / kg of body weight, ip).

24 hours following the paracetamol injection, between 8.00 - 10.00 AM, we collected heparinized blood from the retro-orbital plexus, then sacrificed the animals under ether anesthesia. We excised the liver, weighed and examined it macroscopically and then we sampled liver fragments (which we introduced in formalin) for the anatomo-pathological examination.

In the present research we included these following drugs: Paracetamol after dissolution of the preparation Paracetamol®, tablets, from the „Antibiotics SA"; Theophylline from the Miofilin® ampoules from Sicomed SA; caffeine from the Caffeine sodium benzoic®' preparation from „Sicomed SA" and NaCl solution 0,9%; Ser fiziologic vials from „Sicomed SA".

All the drug solutions were prepared right before their usage.

*Correspondence: Serban Gligor, MD, PhD, Lecturer, West University, Faculty of Physical Education and Sport, Kinesytherapy Department, Tel.+40256592.129, Fax.+40256592129, e-mail: gligor_serban@yahoo.com
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METHODS

To assess the effects of the paracetamol co-administration with theophylline we have evaluated a series of biochemical, hematological, pharmacological and hystopathological parameters.

The investigated biochemical parameters included enzymatic determinations (of the aminotransferases - a colorimetric method with 2,4 - dinitrophenyl-hydrazine and of the alkaline phosphatase following the Bodanski method with the respective use of a Specol Spectrophotometer), plasma lipid analysis (of the serum triglycerides by the Tixier method, with phenylhydrazine using the Specol Spectrophotometer), the total serum cholesterol (with the aid of the Watson method), glucose (using the ortotoluidina method) and disproteinemie tests (through evaluation of the Tymol test).

The hematological parameters consited in the determination of the Quick prothrombin time (Soulier method). As pharmacodynamic parameter we assessed the duration of the hexobarbital induced sleep (using a 1% solution, 100 mg/kg of body weight ip, 20 hours following administration of the investigated substance).

As for the morphological parameters we macroscopic examined the liver appearance, sampled the relative weight of the liver (g of liver weight/100 g of body weight) and optical microscopically examined the hepatic tissue (the sampling liver fragments were fixed in a 10% formalin sollution, included in paraffin, than sectioned histological and hematoxylin-eozine stained).

STATISTICAL ANALYSIS

Results are presented as mean ± standard deviation. In order to assess the significance and the degree of statistical significance, data from the experiments were statistically processed using the Student t-test. The minimum level of statistical significance was considered to be $p < 0.05$.

RESULTS AND DICUSSIONS

The results (mean values ± standard deviations) of the biochemical, hematological, pharmacodynamical and morphological parameters investigated in the control group, in the paracetamol reference lot and respectively in the paracetamol and theophylline treated group are presented in Table I and Table II.

Table I Biochemical parameters (mean values ± SD) recorded from the paracetamol reference group, and respectively from the paracetamol and theophylline treated group

	Control group (mean value ± SD)	Paracetamol reference group (1500mg/kgbw ip)	Group treated with paracetamol (1500 mg/kgbw ip) and theophylline (15 mg/kgbw ip)
No. of animals / group	20	20	20
Aminotransferases			
AST (IU/l)	17.06 ± 2.30	136.25 ± 12.80	149.25 ± 9.12* •
ALT (IU/l)	12.93 ± 3.17	138.22 ± 14.07	145.61 ± 4.32* •
Alkaline phosphatase (BU)	31.95 ± 2.26	65.25 ± 5.48	69.55 ± 1.93* •
Plasmatic lipids			
Triglycerides (mg%)	90 ±2.75	105.22 ± 25.98	119.76 ± 12.87
Cholesterol (mg%)	102.00 ± 18.69	114.3 ± 4.90	118.24 ± 8.20
Glycemia (mg%)	98.94 ±2.00	82.10 ± 6.40	97.12 ±2.10
Thymol blood test (MLU)	0.95 ± 0.66	2.05 ± 0.73	3.00 ± 0.10

* $p < 0.05$ vs control; • $p < 0.05$ vs paracetamol reference group

Table II The hematological, pharmacodinamical and morphological parameters (mean values ± SD) and the lethality rate (%) from the paracetamol reference group and respectively from the group treated with paracetamol and theophylline

	Control group (mean value ± SD)	Paracetamol reference group (1500mg/kgbw ip)	Group treated with paracetamol (1500 mg/kgbw ip) and theophylline (15 mg/kgbw ip)
No. of animals / group	20	20	20

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Hematological parameter Prothrombin time (sec)	11.05 ± 1.23	18.79 ± 4.43	18.28 ± 3.13*
Pharmacodinamical parameter Lengths of hexobarbital induced sleep (min)	28.08 ± 2.20	67.70 ± 16.29	30.10 ± 2.24*•
Morphological parameters liver weight (g) / 100 g body weight	4.24 ± 0.30	6.58 ± 0.43	6.70 ± 0.82*
Histopathological changes of the liver fragments	Normal aspect	Hepato-cellular necrosis, Dark intumescences, Acidophilic hepato-epithelials	Accentuation of the typical changes induced by paracetamol, dark intumescences
Lethality (%)	0	30	50

* $p < 0.05$ vs control; • $p < 0.05$ vs paracetamol reference group

Paracetamol has induced cytolytic type hepatotoxicity, whose biochemical markers are the indicator enzymes namely the serum aminotransferases. It was noticed a significant increases in the serum aminotransferases activity, a moderate increases of the alkaline phosphatase activity, a significant prolonged prothrombin time, liver weight increase (hepatomegaly was probably the result of hepatocytes proliferation, as shown Waalker A.M. investigations) (Walker AM 1999), growth duration of hexobarbital sleep, and an increase in mortality; it also noted a slight decrease in blood glucose, perhaps by gluconeogenesis decreasing and by the deficiency of insulin inactivation, and an increase of both cholesterol, and serum triglycerides.

Also, administration in paracetamol overdose induced characteristic histological changes, namely hepato-epitheliums mostly acidofile, kemel picnotic (necrobiosis), cloudy intumescent and mild steatosis with extralobular topography.

The mechanism responsible for producing paracetamol hepatocellular necrosis is not fully elucidated, but it seems that it involves the modification of free sulfhydryl groups (thiol-oxidation) and mitochondrial damages (manifested as studies of Parmar D.V. et al. by a 35% decrease in mitochondrial ATP activity in rats. (Parmar DV et al 1995)

It was shown that each intracellular hepatocytes compartment (mitochondria, nucleus, plasma membrane and cytoplasm) is involved in hepatotoxicity induced by paracetamol. (Holt MP et al 2006)

It seems that in paracetamol hepatotoxicity generation eicosanoids and cytokines would play a role; thus, Bourdi M., Masubuchi Y., et al. (Bourdi M et al 2002) found an increase in IL 4, IL 13 and IL 10 serum concentrations after paracetamol treatment.

Theophylline intraperitoneal administration in rats treated with paracetamol overdose ip caused a very significant increase of mortality rate, probably explained by seizures caused by excess free, active theophylline, existence in conditions of severe liver injury induced by paracetamol. (Lee GA et al 1996)

It was found a sharp increase in serum aminotransferases activity and especially of AST and an obvious hyperglycemia, probably produced as a consequence of theophylline action on medulosuprarenal and that on the release of catecholamines. Regarding the duration of hexobarbital sleep, it was reduced compared with the reference group.

Increased theophylline toxicity in terms of its administration to animals with liver damage due to paracetamol may have on the reduction of theophylline clearance, numerous clinical studies indicated an approximately 50% reduction of theophylline clearance in patients with liver failure. (Mitenko PA et al 1973)

Other possible explanations of this enhancement could be changes in cellular calcium balance produced by the two drugs and increased distribution volume of theophylline, a row existence liver damage, with increasing the amount of free, active theophylline one.

As the combination of caffeine with paracetamol is often used in therapeutics we investigated the effects of this combination when paracetamol is administered in overdose (Table III and Table IV). We found that paracetamol coadministration with caffeine caused an obvious reduction of the paracetamol toxicity compared with reference group. Thus, mortality declined from 30% (as it was in animals treated with paracetamol) at 10%.

Table III Biochemical parameters (mean values ± SD) recorded from the paracetamol reference group and respectively from the group pretreated with caffeine and than treated with paracetamol.

	Control group (mean value ± SD)	Paracetamol reference group (1500mg/kgbw ip)	Group pretreated with caffeine (100 mg/kgbw ip) and than treated with paracetamol (1500 mg/kgbw ip)
No. of animals / group	20	20	20
Aminotransferases			
AST (IU/L)	17.06 ± 2.30	136.25 ± 12.80	76.30 ± 8.40*•
ALT (IU/L)	12.93 ± 3.17	138.22 ± 14.07	57.65 ± 1.21*•
Alkaline phosphatase (BU)	31.95 ± 2.26	65.25 ± 5.48	36.80 ± 1.20
Plasmatic lipids			
Triglygerides (mg%)	90.00 ± 2.75	105.22 ± 25.98	117.72 ± 14.25
Cholesterol (mg%)	102 ± 18.69	114.3 ± 4.90	116.70 ± 2.3
Glycemia (mg%)	98.94 ± 2.00	82.1 ± 6.4	99.32 ± 12.53
Thymol blood test (MLU)	0.95 ± 0.66	2.05 ± 0.73	2.84 ± 1.16

* $p < 0.05$ vs control; • $p < 0.05$ vs paracetamol reference group

Table IV The hematological, pharmacodinamical and morphological parameters (mean values ± SD) and the lethality rate (%) from the paracetamol reference group and respectively from the group pretreated with caffeine and than treated with paracetamol

	Control group (mean value ± SD)	Paracetamol reference group (1500mg/kgbw ip)	Group pretreated with caffeine (100 mg/kgbw ip) and than treated with paracetamol (1500 mg/kgbw ip)
No. of animals / group	20	20	20
Hematological parameter Prothrombine time (sec)	11.05 ± 1.23	18.79 ± 4.43	13.90 ± 2.19*•
Pharmacodinamical parameter Lengths of hexobarbital induced sleep (min)	28.08 ± 2.20	67.70 ± 16.29	30.28 ± 2.12*•
Morphological parameters liver weight (g) / 100 g body weight	4.24 ± 0.30	6.58 ± 0.43	5.21 ± 0.31*•
Histopathological changes of the liver fragments	Normal aspect	Hepato-cellular necrosis, Dark intumescences	Improvement of the hepatic histopathological changes
Lethality (%)	0	30	10

* $p < 0.05$ vs control; • $p < 0.05$ vs paracetamol reference group

Caffeine significantly reduced paracetamol induced liver damage, as established by decreasing the activity of serum aminotransferases, decreased alkaline phosphatase activity, and by reducing prothrombin time. Histological examination of liver fragments showed a reduction of hepatic changes caused by paracetamol, namely less severe liver changes (or

necrobiotics aspects) and aspects of hepato-epithelial regeneration.

The data agree with literature data which showed a net protective effect of caffeine compared to paracetamol induced hepatotoxicity. (Rainska-Gieze GT 1995)

CONCLUSIONS

The combination of paracetamol with theophylline should be avoided because of potential risks.

Theophylline does not produce any improvement of paracetamol-induced liver changes, on the contrary it enhances the paracetamol toxicity in terms of serum transaminase activity and lethality (increased mortality of paracetamol-induced liver damage rats, probably because of seizures caused by excessive free, active, theophylline).

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ABREVIATIONS

AST – aspartate transaminase
ALT – alanine transaminase
ATP – adenosine triphosphate
BU – Bodansky units
IL – interleukin
IU – international unit
MLU – Mc Lagan units
SD – standard deviation