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Department of Toxicology, Medical University of Lublin, Poland

MONIKA GAWROŃSKA-GRZYWACZ, MARIOLA HERBET,
JOANNA PAZIK, JUDYTA HAWRYLUK, EWA JAGIEŁŁO-WÓJTOWICZ

Influence of combined administration of Ukrain and tricyclic antidepressants on basic biochemical serum parameters of kidney function in rats

Wpływ łącznego podawania leku Ukrain i tricyklicznych leków przeciwdepresyjnych na podstawowe parametry biochemiczne funkcji nerek w surowicy krwi szczurów

INTRODUCTION

The prevalence of psychiatric disorders in cancer patients is assessed to be between 25% and 60% and the recent reports suggest that major depressive disorder occurs quite frequently among these patients [16]. Traditional pharmacotherapy includes tricyclic antidepressants (TCAs) considered as comparable to or more effective than selective serotonin reuptake inhibitors (SSRIs), amitriptyline in particular. TCAs are also effective and often used as the adjuvant analgesics - the essential tool in the treatment of cancer pain [1, 15]. Evidence gathered over several decades suggests that tricyclic antidepressants are the "gold standard" for the treatment of persistent neuropathic pain [3, 4]. Neuropathy is a common side effect in patients receiving chemotherapy (vinca alkaloids, platinum derivatives or taxanes). Recently amitriptyline was tested as an adjuvant analgesic in the prevention and treatment of chemotherapy-induced neuropathic symptoms [9, 10]. Unfortunately, TCAs are known for a lot of side effects, the most typical atropinic side effects and interactions with other drugs [13, 21]. Literature data also focus on liver dysfunction during TCAs' therapy [12]. Treatment with amitriptyline has resulted in severe cases of hepatotoxicity in patients [21]. However, there is insufficient data on the influence of tricyclic antidepressants on kidney function [11]. These medicines and their metabolites are mainly excreted with urine with long half elimination periods. In addition, the anticholinergic activity of TCAs results in urinary retention which can occur in more than 60% of patients with chronic neuropathic pain [18]. It is proposed that metabolic activation of amitriptyline and subsequent covalently binding of reactive metabolites to cellular proteins of hepatocytes play a causative role in hepatotoxicity [21]. There is a question whether this kind of toxic reaction may take place towards kidney cells in the above-mentioned circumstances (urinary retention, long half elimination periods).

Ukrain (i.e. tiophosphoric acid derivative of alkaloids *Chelidonium majus* L.) is a semi-synthetic cytostatic drug reducing toxic effects of earlier administered cytostatics as well as prolonging and improving quality of patients' lives [5, 8, 14, 20]. The lack of clinical data on simultaneous treatment with Ukrain and TCAs inspired our research. The presented study was aimed to estimate whether, and in what degree, Ukrain with TCAs (imipramine and amitriptyline) influence the serum biochemical parameters indicating kidney function in rats.

MATERIAL AND METHODS

D r u g s a n d c h e m i c a l s. The following substances were used in the study: Ukrain (aqueous high-purity concentrate 1:30, Ukrainian Anti-Cancer Institute, Vienna, Austria), imipramine (IMI) and amitriptyline (AMI) hydrochlorides, both from Sigma-Aldrich GmbH (Germany) and also *aqua pro injectione* (Polfa Lublin, Poland). Ready-made diagnostic kits were used to determine: creatinine and urea concentrations (Cormay Diagnostic S.A., Lublin, Poland) and β2-microglobulin level (IBL, Hamburg, Germany).

A n i m a l s. The study was carried out on male Wistar rats (200-250 g) coming from licensed breeder. The animals were kept at room temperature (20±1ºC) under a natural day-night cycle in constant environmental conditions (humidity, noise). They had access to food and water *ad libitum*. The experiments were approved by the Local Ethics Committee on Animal Experimentation of the Medical University of Lublin.

T r e a t m e n t s. Aqueous solutions of IMI (10 mg/kg), AMI (10 mg/kg) and Ukrain (14 or 28 mg/kg) were prepared *ex tempore* and administered intraperitoneally (ip) once daily for 10 days separated or combined in constant volumes 0.5 ml/100 g of body weight. Our previous research [6, 7] proved the above-mentioned doses of IMI, AMI and Ukrain were effective. The control groups received the same amounts of *aqua pro injectione*.

E x p e r i m e n t a l p r o t o c o l s. The experimental groups consisted of eight animals each. Twenty four hours after the last injection, the animals were decapitated and the blood was taken and centrifuged for 10 minutes at 3000 rpm. Serum was stored at -20ºC until biochemical determinations.

S t a t i s t i c a l a n a l y s i s. Results are expressed as mean ± SEM. Statistical significance among groups was determined by Student's *t*-test and *p*-values less than 0.05 were considered significant.

RESULTS AND DISCUSSION

Clinical practice points out that chemotherapy – fundamental treatment of tumours, goes hand in hand with many other pharmacological therapies of different health problems associated with cancer. Antidepressant drugs, particularly TCAs, cure the major depressive disorder occurring quite frequently among oncological patients [16]. These drugs are also used as adjuvant analgesics to work

against pain in cancer, especially neuropathic pain – common adverse effect of chemotherapy [1, 10]. In case of polytherapy there is always a risk of toxic drug-drug interaction. TCAs pose that risk and may be susceptible to pharmacokinetic interactions when given in combination with inhibitors or inducers of the cytochrome P450 isoenzymes involved in their metabolism [19]. Literature data supply inadequate information about kidney function during monotherapy with TCAs but indicate that patients with renal impairment are hypersensitive to TCAs side effects [11]. Based on the above-mentioned observations we intended to examine whether combined treatment with TCAs and Ukrain influences kidney function in rats. For this purpose we determined basic serum parameters indicating kidney function – creatinine, urea and β2-microglobulin concentrations.

The presented study indicated the 10-day simultaneous administration of Ukrain (14 or 28 mg/kg) and imipramine or amitriptyline (10 mg/kg both) had changed the concentrations of creatinine, urea and β2-microglobulin in serum when compared with groups of rats receiving only Ukrain or only tricyclic antidepressants. In animals treated with Ukrain and IMI only β2-microglobulin concentration remained unaffected (Fig. 3). The combined treatment with Ukrain (28 mg/kg) and IMI resulted in the decrease of creatinine concentration in rat serum in comparison with Ukrain (Fig. 1). However, Ukrain at a dose of 14 mg/kg administered with IMI increased urea level compared with only Ukrain and only IMI groups (Fig. 2). The simultaneous application of Ukrain (28 mg/kg) and AMI decreased creatinine level in comparison with AMI (Fig. 1). The same combination of drugs also decreased urea concentration in rat serum compared with Ukrain and AMI (Fig. 2). In groups of rodents treated with Ukrain (14 mg/kg) and IMI or AMI interesting similarity was noted in relation to urea level (Fig. 2). This concentration was enhanced. However, in rats receiving Ukrain with AMI change wasn't statistically significant because of high SEM value. The combined administration of Ukrain (14 and 28 mg/kg) and AMI to rats caused increase or decrease of β2-microglobulin concentration when compared with Ukrain or AMI, respectively (Fig. 1). In our previous study, we observed the simultaneous treatment with Ukrain and the above-mentioned tricyclic antidepressants adversely affected the concentration of total protein determined in rat serum [6, 7]. These changes may also indicate that such administration unfavorably influences kidney function.

Our research also showed that imipramine (10 mg/kg) decreased creatinine level in rat serum but didn't influence the concentrations of urea and β2-microglobulin (Fig. 1-3). In rats pre-treated with amitriptyline (10 mg/kg) only the increase of β2-microglobulin level was observed (Fig. 3). The 10-day administration of Ukrain (14 or 28 mg/kg) had no impact on the concentrations of any examined parameters indicating renal function (Fig. 1-3).

It was found that the 10-day combined administration of Ukrain and imipramine or amitriptyline affects basic serum biochemical parameters which indicate kidneys functional state in rats. The differences between IMI and AMI in effects on the tested parameters could probably result from various chemical structures of the examined TCAs. Our study showed the observed changes may suggest the possibility of renal disorder when Ukrain and TCAs are administered together for a long time. We hope the results could be considered to use in clinical practice to avoid or limit adverse effect on the kidneys.

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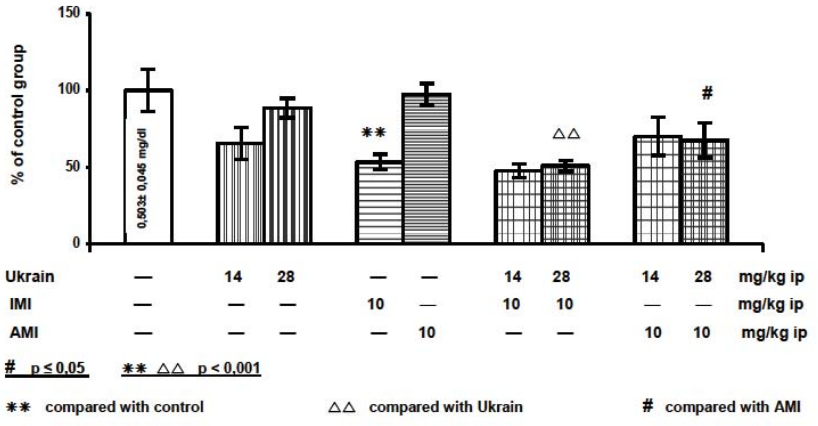
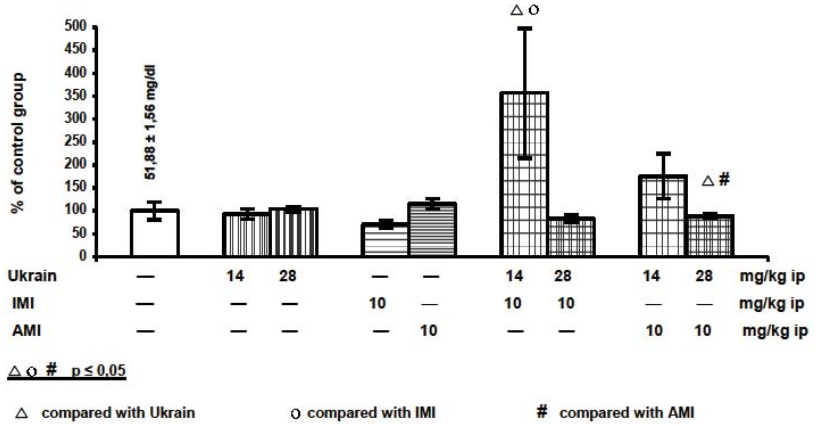
Fig. 1 Effect of 10-day combined administration of Ukrain and IMI or AMI on creatinine level in rat serum



p ≤ 0,05 ** △△ p < 0,001

** compared with control △△ compared with Ukrain # compared with AMI

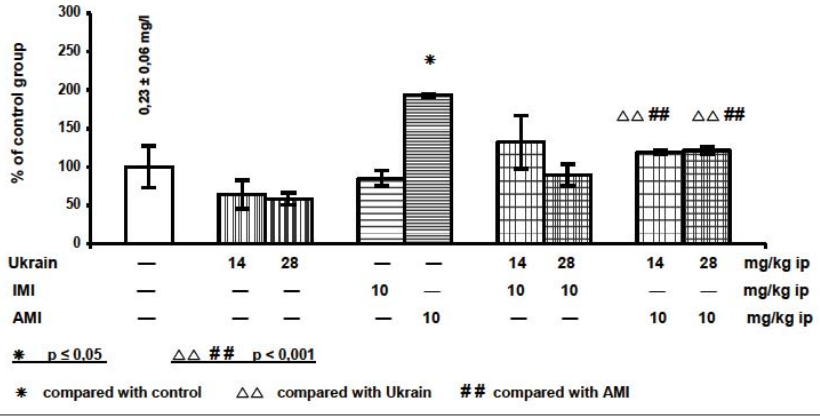
Fig. 2 Effect of 10-day combined administration of Ukrain and IMI or AMI on urea level in rat serum



△ o # p ≤ 0,05

△ compared with Ukrain o compared with IMI # compared with AMI

Fig. 3 Effect of 10-day combined administration of Ukrain and IMI or AMI on β_2-microglobulin level in rat serum



SUMMARY

Our research was aimed to assess the impact of 10-day simultaneous dosing of Ukrain and tricyclic antidepressants, imipramine (IMI) and amitriptyline (AMI), on basic biochemical parameters of renal function in rats. The concentrations of creatinine, urea and β2-microglobulin were determined in animal serum. Based on the results of the study it was found that 10-day combined administration of Ukrain and IMI decreased creatinine concentration (Ukrain 28 mg/kg) and increased urea level (Ukrain 14 mg/kg) in blood serum. The same combination of drugs did not affect the concentration of β2-microglobulin. However, the application of Ukrain and AMI for 10 days resulted in the decrease of creatinine and urea (Ukrain 28 mg/kg) concentrations in the serum of rats. The β2-microglobulin level increased in groups of rodents treated with Ukrain (14 and 28 mg/kg) and AMI compared with Ukrain and decreased in relation to AMI. These adverse fluctuations in the studied biochemical parameters in blood serum of rats may indicate a risk of renal impairment after combined 10-day administration of Ukrain and tricyclic antidepressants. We suppose our conclusions may be useful in clinical practice to avoid the above-mentioned adverse effect.

Keywords: Ukrain, TCAs, nephrotoxicity, rats

STRESZCZENIE

Celem pracy była ocena wpływu równoczesnego 10-dniowego podawania leku Ukrain oraz tricyklicznych leków przeciwdepresyjnych, tj. imipraminy (IMI) oraz amitryptyliny (AMI) na podstawowe parametry biochemiczne świadczące o funkcji nerek szczurów. W surowicy krwi zwierząt oznaczono stężenia kreatyniny, mocznika oraz β2-mikroglobuliny. W oparciu o wyniki przeprowadzonych badań stwierdzono, że 10-cio dniowe stosowanie u gryzoni leku Ukrain

w kombinacji z IMI zmniejszało stężenie kreatyniny (Ukrain 28 mg/kg) a zwiększało poziom mocznika (Ukrain 14 mg/kg) w surowicy krwi. To samo połączenie leków nie wpływało na stężenie β2-mikroglobuliny. Natomiast podawanie szczurom przez 10 dni leku Ukrain w połączeniu z AMI powodowało zmniejszenie stężenia kreatyniny i mocznika (Ukrain 28 mg/kg) w surowicy krwi zwierząt. Z kolei stężenie β2-mikroglobuliny wzrastało w grupach gryzoni poddanych 10-cio dniowemu działaniu leku Ukrain (14 i 28 mg/kg) oraz AMI w porównaniu z lekiem Ukrain a obniżało się w odniesieniu do AMI. Opisane niekorzystne wahania w badanych parametrach biochemicznych w surowicy krwi szczurów mogą wskazywać ryzyko zaburzenia czynności nerek po łącznym 10-cio dniowym podaniu leku Ukrain z tricyklicznymi lekami przeciwdepresyjnymi, co może okazać się przydatne w praktyce klinicznej.

Słowa kluczowe: Ukrain, TLPD, nefrotoksyczność, szczury

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