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Nutritional status of female rats after acute intoxication with ethyl alcohol and treatment with ketoprofen lysine salt or ketoprofen

Barbara Nieradko-Iwanicka[1*], Kinga Ruszel[2]

[1] Hygiene and Epidemiology Department, Medical University of Lublin, Poland
[2] Doctoral School, Medical University of Lublin, Poland

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ABSTRACT

Ketoprofen lysine salt (KL) is a new non- steroidal anti-inflammatory drug (NSAID) competing with ketoprofen (K) on the market. The former is believed to have gastroprotective properties and both to kill acute pain. In East Europe binge drinking and taking NSAIDs after is common. Some people use NSAIDs to treat the discomfort when they sober up. Vomiting after alcohol intoxication and gastritis after use of NSAIDs may produce malnutrition. The aim of the study was to compare nutritional status in female rats treated with KL or K after acute intoxication with ethyl alcohol. In this animal model we wanted to mimic human cases of NSAIDs use on the day(s) after binge drinking. The experiment was carried out on 36 female Wistar rats divided into 6 groups of 6: 1. treated with 50% etanol; 2. 0.9% NaCl; 3. 0.9% NaCl and K; 4. 50% etanol and K; 5. 0.9% NaCl and KL; 6. 50% etanol and KL.

On day 7 animals were sacrificed. Their body, liver and kidney mass was recorded. The blood was obtained to measure blood morphology and biochemical parameters. K and alcohol in group 4 limited body mass gain ($p<0.05$ *vs* ethanol-group 1) and lowered albumin concentration ($p<0.05$ *vs* control-group 1). There was also a statistically significant decrease in the level of serum albumin of rats receiving KL (group 5) compared to the saline (group 2).

K affects the nutritional status more than KLS after alcohol intoxication.

INTRODUCTION

Ketoprofen (K) has an inhibitory effect on cyclooxygenase-1 (COX-1) and COX-2, which determines its well-known anti-inflammatory effect [1]. Ketoprofen lysine salt (KL) is a new non-steroidal anti-inflammatory drug (NSAID). It is a salt, unlike the vast majority of NSAIDs, which are weak acids. Due to L-lysine salification, it is characterized with an increased solubility and faster gastric absorption (when compared with K) [2]. Indeed, Cimini *et al*. conducted an experiment on a human gastric epithelial cell line first exposed to KL and then damaged with ethanol. Their results showed the gastroprotective effect of this product [3]. Furthermore, anecdotal evidence recommends KL as the drug of choice on the day after alcohol overdose.

Although males consume alcohol more often than women do [4], women have lower activity of alcohol dehydrogenase and lower distribution volume. In addition, they become intoxicated with ethanol more easily and need more time to metabolize alcohol. There is a greater pain sensitivity among women compared with men, and women use NSAIDS more often than men [5]. Both KL and K can be purchased over the counter in Poland [4]. Some people use NSAIDs to treat the discomfort when they sober up. However, vomiting after alcohol intoxication and gastritis after use of NSAIDs may produce malnutrition. According to the World Health Organisation, malnutrition means deficiencies or excesses in nutrient intake, imbalance of essential nutrients or impaired utilisation of nutrients at cellular level.

Alcohol is an addictive neurotoxin. It is a source of 'empty calories: yielding 7 kcal per 1 g. It is consumed worldwide, especially in Europe. Recommendations on alcohol consumption are controversial. Some support moderate consumption as it has a beneficial cardiovascular effect or lowers the risk of all-cause mortality. At the same time, there is evidence that alcohol use is associated

* **Corresponding author**
e-mail: barbara.nieradko-iwanicka@umlub.pl

with an increased risk of cancer, neurological diseases, and injuries [6-8]. Data on alcohol use in Poland indicate that measured in litres of pure alcohol *per capita*, consumption levels were at 9.70 l/person in 2021. There are calculations indicating an increasing share in the total consumption of strong alcohols (40% or more ethanol) – from 34.6% in 2018, to 39.2% in 2021, which is accompanied by a decrease in the share of beer from 57.9% to 52.5% [9]. The public health experts recommend not drinking alcohol and if one drinks, one should do so in moderation. Moderate alcohol use means no more than one alcohol equivalent per day for a non-pregnant woman and no more than two for a man [10].

Alcohol use may affect nutritional status too, as 1g of pure ethanol yields 7 kcal of energy when metabolized [11]. On performing nutritional assessment in humans, anthropometric parameters such as: height, body mass, waist and hip circumference are acquired. In children, head, mid-arm and chest circumference measurements are taken as well. With this basic data, body mass index (BMI) and waist to hip ratio (WHR) can be calculated. Centile charts used to interpret anthropometric parameters in children.

In hospitalized patients, Nutritional Risk Score (NRS2002) is routinely employed by physicians and nurses for systematic assessment of nutritional status. During qualification to intravenous nutritional treatment or *via* percutaneous gastrostomy, physicians are obliged to report total protein, albumin, glucose, alanine transaminase, aspartate transaminase, bilirubin, total cholesterol, red blood cell, white blood cell and platelet counts in peripheral blood, as well as creatinine, urea, calcium, phosphorus, magnesium, sodium and potassium levels in the blood serum.

AIM

The aim of the study was to compare nutritional status in female rats treated with KL or K after acute intoxication with ethyl alcohol. In this animal model, we wanted to mimic human cases of NSAIDs use on the day(s) after binge drinking.

MATERIALS AND METHODS

The investigated products were K and KL. K was used in the form of Ketonal solution for injection in ampoules 50 ml/mL (Sandoz GmbH, Wien, Austria). KL was utilized as KETONAL SPRINT and was available in the form of granules (Sandoz GmbH, Wien, Austria). In order to prepare the KL solution, 0.9% NaCl was used (B. Braun, Melsungen AG, Hessen, Germany). Ethyl alcohol was purchased from Polmos (Lublin, Poland) as 95% Spiritus. The 50% ethanol solution was prepared with saline. The doses of the investigated products were chosen following previous experiments carried out in our department [4], and the dose of alcohol was intended to produce the animal model of binge drinking in an adult human. This style of drinking is common in East Europe. On the day after, the majority of users suffer from hangover and headaches. The doses of K and KL used in our experiment are respective to the recommended painkilling doses of these medicines in humans. When planning the study, these doses were converted to the body weight of rats.

The experiment was carried out on 36 randomly selected non-pregnant female Wistar rats, the weight of which before the beginning of the experiment was 190-205 g. The animals were bred at the Experimental Medicine Centre (EMC) at the Medical University of Lublin, Poland. The original source of the herd was Charles River Laboratories (Cologne, Germany). They were 7 weeks old. The experiment was conducted in accordance with European law regulations at EMC. Standard laboratory conditions prevailed in the EMC with a temperature of 21-22°C, a 12-hour light/dark cycle and a relative air humidity of 55–60%. The animals had free access to sterile water (sterilized *via* ultraviolet light) and rodent feed purchased from Altromin International (Lage, Germany). The investigated products were administered by gavage through a gastric tube. The animals were divided into 6 groups of 6 each:

1. Group 1 was treated with 50% ethanol (5 mL/kg b.w. on day 1).
2. Group 2 was treated with 0.9% NaCl (5 mL/kg b.w. on day 1).
3. Group 3 received 0.9% NaCl (5 mL/kg b.w.) on day 1 and K (8 mg/kg b.w.) on day 2-6.
4. Group 4 received 50% ethanol (5 mL/kg b.w.) on day 1 and K (8 mg/kg b.w) on day 2-6.
5. Group 5 received 0.9% NaCl (5 mL/kg b.w.) on day 1 and KL (12.8 mg/kg b.w.) on day 2-6.
6. Group 6 received 50% ethanol (5 mL/kg b.w.) on day 1 and KL (12.8 mg/kg b.w.) on day 2-6.

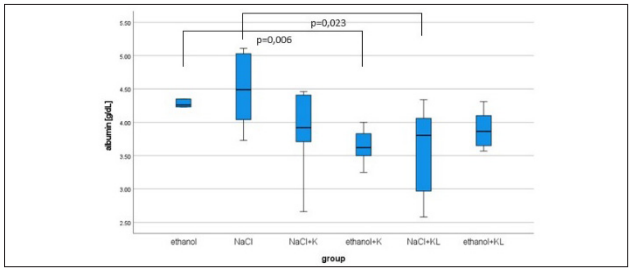
On day 7, all animals were decapitated with a guillotine. We used no anaesthetic in order to prevent possible interactions with blood tests results. This was tested at the Vet Diagnostyka laboratory, Lublin, Poland. In order to determine blood counts, 200 µL of blood was drawn for EDTA. The morphology parameters were measured with an automatic haematological analyser. The rest of the blood was allowed to clot and was centrifuged in order to obtain blood serum. Alanine transaminase and asparagine transaminase activity, cholesterol, glucose, albumin, total protein and creatinine concentrations were measured in the blood sera. An ErbaMannheim XL-60 automated biochemical analyser was used. The data were analysed using IBM SPSS Statistics v.25 software. Comparisons between the analysed groups were made using two-way ANOVA. The significance level was $p < 0.05$.

The project was approved by the Local Ethical Committee for Animal Experiments in Lublin (70/2021 issued on 8 Nov. 2021). The experiment was conducted by way of an internal grant of the Medical University in Lublin awarded to Barbara Nieradko-Iwanicka (DS. 755/2023) in 2023. Both authors had training in conducting experiments on animals and had the permission of the University and EMC authorities to conduct the experiments making up this study.

RESULTS

K and alcohol in group 4 limit the weight gain of animals to the greatest extent ($p < 0.05$ *vs* ethanol-group 1). There was no statistically significant differences between the groups in liver and kidney mass. Significantly lower albumin concentration was observed in the blood serum

of rats exposed to ethanol and K (group 4) compared to those exposed to ethanol only (group 1) ($p<0.05$). There was also a statistically significant decrease in the level of serum albumin of rats receiving KL (group 5) compared to the group receiving saline (group 2) (Figure 1). There was neither significant differences between the groups in terms of alanine transaminase (ALT) nor asparagine transaminase (AST) activity. Similarly, there was no significant differences in the concentrations of total protein, cholesterol, glucose and creatinine in the examined sera. Moreover, there were no differences between the study groups in terms of the count of white blood cells, red blood cells, haemoglobin concentration or the number of platelets per 1 mm^3 of the blood (Table 1).



n = 6, mean (M)±standard deviation (SD); Kruskal-Wallis' test

Figure 1. The effect of ketoprofen (K) and ketoprofen lysine salt (KLS) on serum albumin concetration in female rats after intoxication withethanol

DISCUSSION

Ketoprofen is well absorbed after oral administration. Peak plasma concentrations in humans are reached within 1 h 22 min after oral administration. The half-life (T1/2) in the blood is 2 h, and as much as 99% of K is bound to plasma proteins, mostly albumin. Ketoprofen is metabolized in the liver mainly by glucuronidation. The majority of metabolites are excreted in the urine, and does not accumulate [1]. In the case of laboratory animals, exposure to K albumin determination may be questionable. However, serum albumin level is a part of standard nutritional assessment in hospital practice.

Table 1. The effect of Ketoprofen lysine salt (KL) and ketoprofen (K) on the nutritional status of mice after acute intoxication with ethyl alcohol

		Ethanol (n=6)	NaCl (n=6)	NaCl+K (n=6)	ethanol+K (n=6)	NaCl+KL (n=6)	Ethanol+ KL (n=6)
Body mass day 1 [g]	Mean±SD	205.33±4.16	193±11.19	199.5±14.92	190.67±6.68	199±17.36	199±17.74
	95%CI (lower-upper)	194.99-215.68	181.26-204.74	183.84-215.16	183.65-197.68	177.44-220.56	180.38-217.62
Body mass day 7 [g]	Mean±SD	215.67±21.2	207.83±12.45	213±16.42	195±7.51	210±20.77	210±17.49
	95%CI(lower-upper)	163.01-268.32	194.77-220.9	195.77-230.23	187.12-202.88	184.21-235.79	191.64-228.36
Body mass gain: day 7-day 1 [g]	Mean±SD	16.33±8.08	14.83±4.26	14.83±6.91	5.33±2.73*	10.8±3.7	11±3.9
	95%CI (lower-upper)	-3.75-36.41	10.36-19.31	7.58-22.09	2.47-8.20	6.2-15.4	6.91-15.09
Liver mass [g]	Mean±SD	8.43±0.76	8.5±1.32	9.02±0.85	7.93±0,69	8.92±0.45	8.65±0.91
	95%CI (lower-upper)	6.54-10.33	7.11-9.89	8.13-9.91	7.21-8.65	8.36-9.48	7.69-9.61
Kidney mass [g]	Mean±SD	0.77±0.06	0.75±0.08	0.9±0.11	0.75±0.08	0.86±0.21	0.82±0.12
	95%CI (lower-upper)	0.62-0.91	0.66-0.84	0.79-1.01	0.66-0.84	0.6-1.12	0.69-0.94
Albumin [g/dL]	Mean±SD	4.42±0.07	4.48±0.55	3.85±0.66	3.64±0.26*	3.72±0.67#	3.89±0.28
	95%CI (lower-upper)	4.1-4.44	3.91-5.05	3.15-4.54	3.36-3.91	2.88-4.56	3.6-4.19
ALT [U/L]	Mean±SD	75.67±23.86	55.17±10.85	55.67±20.45	57.5±6.95	54.6±7.92	60.5±13.87
	95%CI (lower-upper)	16.39-134.94	43.78-66.56	34.2-77.13	50.21-64.79	44.76-64.44	45.95-75.05
AST [U/L]	Mean±SD	258.67±85	237.33±88.2	249.17±105.96	248.8±100.37	202±48.1	193±112.33
	95%CI (lower-upper)	47.41-469.93	144.77-329.9	137.97-360.37	181.72-350.37	142.27-261.73	75.12-310.88
Cholesterol [mg/dL]	Mean±SD	70.33±5.86	64.17±15.79	75.17±17.09	72.5±3.99	68.4±23.07	76.17±10.17
	95%CI (lower-upper)	55.78-84.89	47.59-80.74	57.23-93.1	68.32-76.68	39.75-97.05	65.5-86.84
Glucose [mg/dL]	Mean±SD	93.33±3.79	101.33±9.33	101.67±12.31	107.5±4.64	95±25.03	113.5±12.6
	95%CI (lower-upper)	83.93-102.74	91.54-111.13	88.75-114.58	102.63-112.37	63.92-126.08	100.28-126.72
Creatinine[mg/dL]	Mean±SD	0.21±0.02	0.22±0.03	0.22±0.03	0.22±0.02	0.23±0.04	0.21±0.02
	95%CI (lower-upper)	0.16-0.26	0.19-0.24	0.19-0.24	0.19-0.24	0.18-0.27	0.18-0.23
Leucocytes [10^3uL]	Mean±SD	8.52±4.63	9.67±3.56	9.11±2.01	12.53±3.02	11.7±0.93	11.2±2.60
	95%CI (lower-upper)	-2.99-20.04	5.92-13.41	6.99-11.22	9.36-15.70	10.59-12.91	8.46-13.93
Erythrocytes [10^6/uL]	Mean±SD	7.19±0.25	7.86±0.25	6.85±1.30	7.17±0.88	6.32±3.18	6.23±2.78
	95%CI (lower-upper)	6.55-7.83	7.59-8.12	5.48-8.22	6.24-8.09	2.37-10.27	3.31-9.15
Haemoglobin [g/dL]	Mean±SD	15±-.79	15.87±0.48	13.7±2.43	14.3±1.78	15.54±1.24	14.78±1.6
	95%CI (lower-upper)	13.03-16.97	15.37-16.37	11.15-16.25	12.43-16.17	14-17.08	13.11-16.46
Platelets [10^6/dL]	Mean±SD	0.987±0.0291	0.933±0.0180	1.098±0.272	1.287±84	1141±0.199	1.189±0.98
	95%CI (lower-upper)	0.263-1.710	0.743-1.123	0.812-1.383	1.198-1.375	0.893-1.389	1.086-1.292

*p<0.05 *vs* ethanol (group 1); # p<0.05 *vs* NaCl (group 2); Kruskal-Wallis test, Dunn's test

Minor amounts of alcohol have no effect on body weight, but ingestion of moderate amounts leads to an increase in body weight, *via* a lipid-oxidizing suppressive effect. In contrast, chronic intake of excessive amounts leads to a decrease in body weight. This effect is due to increased lipid oxidation and energy expenditure [11].

NSAIDs are contraindicated after acute alcohol intoxication due to the synergism of their gastrotoxic effects. However, anecdotal evidence suggest that K or KL are effective in controlling headaches the day after an alcohol overdose in humans.

In our experiment, female rats were used as a model of human females who become intoxicated with ethyl alcohol and utilize NSAIDs (K or KL) for pain relief on the day after. We found that ethanol and K brought about significant reduction in weight gain in the course of the experiment due to ethanol's negative effect on metabolism and K's effect via COX-1 and COX-2 inhibition [1]. The lysine in KL is believed to produce some gastroprotective effect, as the results obtained on gastric cell lines show [3]. There are several drugs with added lysine (for example, in the form of lysine clonixinate). In related experiments, such drugs were compared with paracetamol/codeine (500 mg + 30 mg) in relieving postoperative pain and were shown to produce more painkilling effect and less side effects than the comparator [12]. KL falls into the growing group of medicinal drugs combined with lysine [13].

In 2021, Kuczyńska *et al*. attempted to confirm the gastroprotective effect of KL in an animal model. They chose male rats and administered K or KL after ethanol intoxication by gavage. The outcome of the work demonstrated that infiltration with lymphocytes, plasmocytes and eosinophils occurred in the gastric mucosa of male rats exposed to ethanol and K, as well as in groups exposed to KLS (with saline or with ethanol). Kuczyńska *et al*. Also recorded lower body mass in the group of animals exposed to KL and ethanol than in all other groups [4]. In our study, all animals consumed similar amount of animal feed and water, but weight gain (body mass on day 7 – body mass on day 1) was significantly lower in the group exposed to ethanol and K when compared with the group intoxicated with alcohol only. We did not measure the amount of animal feed consumed by the animals used in the experiment, but we did not notice any significant change in their feeding behaviour – ie. no anorexia. The rats did not vomit. So this route of energy loss can be excluded, although it is common in humans after alcohol intoxication.

In this study, we chose to utilize female animals following the data demonstrating a higher prevalence of pain states and greater pain sensitivity in women compared with men. It is known that sex hormones influence pain sensitivity, and the activity of cytochrome P450 in females is greater than in males, and this suggests that drugs are more rapidly metabolized in females than in males [5]. Women also are known to usually start using painkillers earlier than men as a part of self-treatment before they go to see the doctor [14]. In our experiment, in rats exposed to K and ethanol, KL plus alcohol produced the highest serum glucose levels. Fang *et al*. searched six databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CBM, CNKI and VIP) for evidence on the effect of NSAIDs on diabetes type 2 patients. They found in their meta-analysis that the antidiabetic effect of salicylates is in a dose-dependent manner [15]. Alcohol consumed with a meal including carbohydrates is the preferred fuel. This may initially lead to elevation in blood glucose levels [16], but alcohol also inhibits gluconeogenesis and glycogenolysis. Indeed, in acute intake without food, it may provoke hypoglycaemia. The highest risk of hypoglycaemia is in diabetic patients treated with sulphonylurea, especially in cases of depleted glycogen stores.

Another NSAID: a cyclooxygenase-2 inhibitor celecoxib was tested on rats in related work, and it was shown that it is able to reverse non-alcoholic steatohepatitis in a type 2 diabetes mellitus model [17]. In the case of K and ethanol elevating blood glucose level in our rats, it was most probably due to the effect of diet and ethanol, not the investigated product.

In our study, ethanol together with K significantly reduced serum albumin concentration when compared with ethanol, and KL intake reduced albumin concentration significantly vs control. In the study by Kuczyńska *et al*., KL together with ethanol significantly decreased serum albumin in comparison with control groups [4].

One of the most common causes of liver failure and ascites in Central Europe is alcohol abuse. An ascites due to hepatic causes (most often due to alcoholic cirrhosis) is usually the first symptom of the decompensation of cirrhosis. It manifests itself in 5-10% of all people who abuse alcohol. Within 10 years, it is found in 60% of all people with previously compensated cirrhosis. Ascites is a sign of high portal pressure. It is estimated that 15% of all people with ascites due to liver cirrhosis will die within a year and 44% within 5 years. The causes of high mortality include bacterial infections of the peritoneum, the development of the hepatorenal syndrome, malnutrition and sarcopenia, and electrolyte disorders. Distinguishing ascites due to hepatic causes from other causes (cardiac, renal, cancerous, infectious) is based on the calculation of the serum-ascites albumin gradient (SAAG). A SAAG >1 g/dL indicates that the cause of ascites is portal hypertension - most often alcoholic cirrhosis of the liver [18].

More than 99% of K is bound to plasma proteins, mainly albumin [1]. In our study, neither K nor KL affected serum cholesterol level. There is evidence, however, that NSAIDS may dose-dependently accelerate the process of free radical formation in low-density lipoproteins (LDL). However, similar pro-oxidant activity was not found in relation to celecoxib (even when used in doses exceeding therapeutic doses), as well as non-selective NSAIDs like K, dexketoprofen and naproxen [19]. K is conjugated in the liver and is minimally metabolized by hydroxylation, which significantly reduces the risk of adverse pharmacokinetic interactions with other concomitantly administered drugs. The resulting metabolites have no pharmacological activity. K is rapidly eliminated primarily through the kidneys. Its half-life in plasma is approximately 1.5 hours. In the case of KL, 60-80% of the dose is excreted in the urine in the form of a glucuronide metabolite within 24 hours. In our experiment, none of the drugs affected the activity of liver enzymes or the creatinine concentration in the blood serum.

In the Kuczyńska *et al*. study, the serum urea concentration was decreased in the group exposed to ethanol and KL. Related studies indicate that alcohol has a diuretic effect, and that NSAIDs may impair kidney function. We, however, did not record any changes in the basic blood morphology parameters in female rats used in our study, but Kuczyńska *et al*. noticed differences in total lymphocyte count and the percentage of neutrophils among the groups [4]. What is more, their recent study revealed that K was more effective as a painkiller for male rats than KL [20].

Apart from the effect of the investigated medicinal products, the effect of ethyl alcohol on the internal organs cannot be neglected. The National Institute of Public Health National Institute of Hygiene - National Research Institute in Poland undertook surveys on risky alcohol drinking in 2018 and 2022. Both studies were conducted using the computer-based guided personal interview technique (CAPI) on 3,000 and 2,000 people, respectively, in representative samples of Polish residents aged 20 or more. The respondents answered questions regarding: thoughts related to drinking too much alcohol, number of occurrences of feeling guilty about drinking, as well as the occurrence of critical comments about the topic of drinking alcohol. A respondent answering affirmatively to at least one of the questions was treated as a risky drinker.

Among both men and women, this percentage was lower in 2022 than in 2018 (16.7% in 2022 vs 21.3% in 2018 for men and similarly 4.3% *vs* 6.0% for women). Analysis of changes broken down into age groups indicates that the positive trend was most pronounced in groups 30-39 and 70-79 among men and 20-29 among women. [9]. The damaging action of ethanol could be attributed to the increase of reactive oxygen species, which plays a key role in the increase of lipid peroxidation products, including malonyldialdehyde and 4-hydroxy-2-nonenal [21].

CONCLUSIONS

Ketoprofen affects the nutritional status more than KL after alcohol intoxication.

ORCID iDs

Barbara Nieradko-Iwanicka https://orcid.org/0000-0002-4839-6003
Kinga Ruszel https://orcid.org/0000-0002-9633-4288

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