Conclusion:

1. Sleep apnea occurs in 63% of all patients admitted to Sleep center, predominantly in men (1: 2), with an average age of 49 ± 8.9, 2. Obesity, high abdominal circumference, daily smoking, and high Malanpatti scores are most risk factors for OSA.

3. Polysomnography showed that OSA patients have decreased sleep quality, changed the normal structure of sleep, more severe apnea, decreased blood oxygen levels, high arousal index, and persistent high systolic blood pressure during the day and night.

4 CPAP treatment of patients with OSA resulted in decreased AHI, increased duration of slow wave sleep, decreased duration of light sleep, normalized heart rate, decreased nocturnal systolic pressure, and decreased mean systolic pressure during the day.

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WHAT IS THE EFFECTS OF PARACETAMOL APPLIED AT DIFFERENT DOSES TO HEAVY METAL LEVELS IN RAT FETUS?

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ABSTRACT

Paracetamol is the first preferred pharmacological agent as a pain reliever and antipyretic in all periods of pregnancy. In this study, we aimed to analyze trace element and heavy metal levels in the placenta, intestinal and kidney tissues of rats in the early development period of paracetamol. Sixteen pregnant rats were randomly divided into four groups; the control group, the 50 mg/kg paracetamol group, the 250 mg/kg paracetamol group, the 500 mg/kg paracetamol group. There was a statistically significant decrease in the placental weight of the experimental groups compared to the control group. However, a statistically significant difference was found in terms of cobalt (Co) and lead (Pb) levels compared to the control group and the groups that received various doses of paracetamol. There were also statistically significant differences in intestinal chromium (Cr), selenium (Se) and cadmium (Cd) levels in the studied groups. In addition, significant differences were detected in all trace elements and heavy metal levels except Cd in the groups studied in kidney tissue ($p < 0.01$ for all).

As a result, it was determined that the use of paracetamol during pregnancy disrupted the current balance due to the increase in dose. In addition, it was observed that the weight of the placenta decreased due to the paracetamol dose, and the placenta Pb and Co levels increased. In other tissues, there was no toxic concentration at heavy metal and trace element levels, but the highest levels were determined in the control group.

Keywords: Paracetamol, Placenta, Fetus, Pb, Co, Chelator

Conflict of Interest: The authors declare that there is no conflict of inter

INTRODUCTION

Paracetamol is used by millions of patients worldwide as one of the most reliable analgesic/antipyretic drugs in medical use, especially in special groups such as children, elderly, pregnant women (Karakuş et al., 2013). Paracetamol, the active metabolite of phenacetin, called coal tar analgesic; Also known as acetaminophen, N-acetyl-p-aminophenol, APAP. Paracetamol is a synthetic non-opioid p-aminophenol derived drug, a synthetic compound with a molecular weight of 151.2 g/mol (Slattery & Levy, 1979).

Especially in the first weeks of pregnancy, drug use affects the development of the baby negatively, causing abnormalities in abortion or organ development, and later on, it may cause physiological anomalies or dysfunctions in the embryo (Ulger & Pratten, 1996).

Pain medications are not very innocent (simple) drugs, and the active ingredients they contain can damage the mother's organs and even create various teratogenic effects on the fetus organs through the placental barrier (Dharmage & Allen, 2011).

Paracetamol, which is preferred as a short-term pain reliever and antipyretic in every period of

pregnancy (Dharmage & Allen, 2011, Robson, 2011), is a 'over-the-counter' medication that is the most widely used and available without a prescription in the world. Therefore, paracetamol takes the first place in cases of overdose use during pregnancy. Overdoses can cross the placenta and cause fetal and maternal hepatotoxicity (Wilkes et al., 2005).

The American Food and Drug Administration (FDA) grouped medicines in 5 categories from A to X, depending on the severity of their teratogenic effects. In our country, the Ministry of Health requires that the pregnancy category in which the drug is included in the drug leaflets should be specified in the warnings section (Şavlı, 2012). Accordingly, paracetamol, which is in category B, can be used in pregnancy when necessary in the group of drugs that have been shown to have a fetotoxic effect with studies conducted in experimental animals, but this effect has not been confirmed by controlled clinical studies in pregnant women (Rebordosa et al., 2009).

Although paracetamol is known as one of the most reliable drugs used during pregnancy, some studies published in recent years have focused attention on paracetamol again (Robson, 2011). In addition, there are data showing that paracetamol adversely affects ossification in experimental fracture models in animals and in studies performed after fracture in humans (Williams et al., 2011, Vestergaard et al., 2012, García-Martínez et al., 2011). In animal studies, no data were found to show that the use of paracetamol in pregnancy increased congenital malformation. However, it has been shown that the use of 2 times the maximum recommended human dose may cause fetotoxicity (Scialli et al., 2010). In addition, there are studies claiming that exposure to paracetamol in the intrauterine period increases the risk of asthma in childhood or adolescence (Eyers et al., 2011, Henderson & Shaheen, 2013).

While daily paracetamol intake of more than 4000 mg may pose a risk of hepatotoxicity in an adult person (Bertolini et al.,2006), in animals, 400-900 mg/kg in rats and 2000 mg/kg in rats and rabbits in oral use (Kaya et al., 2002).

Studies have reported that high doses of paracetamol affect the antioxidant defense system. The head of the most affected organs in the body is the liver and kidney. Causes of hepatotoxicity include oxidative stress, calcium imbalance and covalently binding of NAPQI cellular proteins and hepatocytes to the lipid layers. Oxidative stress is one of the most important mechanisms that cause the formation of paracetamol hepatotoxicity. (Price et al., 1987, James et al., 2003).

Heavy metals such as lead (Pb) are considered toxic to the body. It is more harmful especially in children and it can affect the developing nerves and brain even at very low blood concentration levels (Igbinaduwa et al., 2015, Needleman & Gatsonis, 1990, Ziegler et al., 1978).

Cobalt (Co) is a basic oligoelement that enters the vitamin B12 composition. Food and drinks are the main source of cobalt exposure in the general population. The two main target organs in exposure are the skin and respiratory system. As a result of cobalt margin, allergic dermatitis, rhinitis and asthma may occur. However, cobalt ions can pass through the placenta, accumulate in fetal blood and amniotic fluid, in other words, there is a potential toxicity of cobalt exposure for the fetus (Lauwerys & Lison, 1994, Cai et al., 2012).

In our study, we aimed to investigate the effect of paracetamol given during pregnancy on the placenta by inductive coupled plasma mass spectrometry (ICP-MS) method.

METHODOLOGY

Our study was approved by Erciyes University Animal Experiments Local Ethics Committee's decision dated 16/11/2016 and numbered 16/145. The care, feeding, drug applications of animals and sacrification of animals at the end of the experiment were carried out within the Experimental Research Application and Research Center (DEKAM). In addition, heavy metal and trace element levels in placental tissue were measured at the Yozgat Bozok University Science and Technology Application and Research Center (BİLTEM).

Selection and Mating of Experimental Animals

Within the scope of the study, 16 Wistar Albino female rats with a mean weight of 185-200 gr and at least 8 weeks old, which were not used in any study, were used. Female rats to be used in the study were kept separately from male rats for 20 days. Female rats, which were determined to be pregnant, were placed in the same cage together with male rats (1 female males per 2 females) at 17:00 in order to conceive. The rats were kept in the same cage until 08:00 on the morning of the next day. At the end of this process, vaginal smear samples taken from female rats were examined under a microscope and females with spermium in the vaginal smear were identified as 0.5 days pregnant.

Experimental Groups

Doses to be given in the experimental groups (50 mg/kg, 250 mg/kg, 500 mg/kg) were determined in accordance with the literature. Paracetamol (Doğa Pharmaceutical Raw Material Ltd. Company, Istanbul) was obtained in powder form. The amount of paracetamol at the appropriate dose to be administered per rat was given orally every day prior to administration by gavage between 16.30 and 17.00. Experimental groups:

Control Group: The rats in this group were given orally by 1 ml / day saline (SF) gavage between the hours of 16.30-17.00 on 1-20 days of pregnancy.

50 mg/kg paracetamol group: 50 mg/kg paracetamol application by gavage until the 20th day of their pregnancy.

250 mg/kg paracetamol group: 250 mg/kg paracetamol application by gavage until the 20th day of their pregnancy.

500 mg/kg paracetamol group: 500 mg/kg paracetamol application by gavage until the 20th day of their pregnancy.

Ketamine (75 mg/kg) + xylazine (10 mg/kg) anesthesia was administered to pregnant rats at 8:00 am on the day following the end of SF and paracetamol administration (at the end of the 20th day) in both the control group and the experimental groups. The abdomen of pregnant rats who were under anesthesia

were cleaned with 70% alcohol. The anterior abdominal walls were then removed with a transverse incision. Fetuses located inside the uterus were dissected together with their placenta.

Fetuses taken into the Petri dish were separated from their placenta and the weights of the placenta were weighed and recorded.

Analysis

For the measurement of heavy metal and trace element levels in the placenta, intestinal and kidney tissue, the tissues were preserved in a cold chain environment and transferred to the Science and Technology Application and Research Center (BİLTEM). Here, placental tissue samples were dried and their dry weights were weighed on a precision scale. Samples were burned in a high pressure microwave oven (Ethos, Milestone) using nitric acid (Suprapur® HNO3) and ultrapure water. Inductively coupled plasma chromium (Cr), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), selenium (Se), cadmium (Cd) and lead (Pb) analysis of burned samples mass spectrometry (ICP-MS) was performed on the device.

RESULTS & DISCUSSION

Pregnant rats were kept under constant control and observation from the beginning of the experimental phase of our study (from the time the female and male rats were placed in the same cage) to the sacrification stage at the end of the experiment. No maternal death or behavioral changes were observed in pregnant rats during this period. No significant changes were seen when the water and feed consumption of the control and experimental groups were compared.

In terms of placental weights; There were significant differences between the control group and the experimental groups between 250 mg/kg and 500 mg/kg paracetamol groups ($p < 0.05$) (Table 1).

Table 1:

Placental weights of fetuses

Groups	Control	50 mg/kg Paracetamol	250 mg/kg Paracetamol	500 mg/kg Paracetamol
Placenta weight (gr)	0.56±0.09	0.54±0.08	0.51±0.07	0.49±0.06
Min/Max	0.39/0.79	0.39/0.70	0.42/0.70	0.40/0.61

*One Way Anova test; A value of $p < 0.05$ was considered statistically significant difference.

A statistically significant difference was found in terms of placental cobalt (Co) and lead (Pb) levels when compared with the control group and paracetamol groups at various doses (50 mg/kg, 250 mg/kg and 500 mg/kg) (respectively, $p = 0.045$ and $p = 0.037$). No significant difference was found between other heavy metal and trace element levels (Table 2).

Table 2:

Comparison of control and paracetamol groups in terms of heavy metal and trace elements in placental tissue.

PLACENTA GROUPS	Control (n=8)		50 mg/kg Paracetamol (n=5)		250 mg/kg Paracetamol (n=10)		500 mg/kg Paracetamol (n=7)		Total (n=30)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p
Cr [ppb]	3.740	2.830	4.250	8.040	6.320	7.420	7.870	9.180	5.331	6.675	0.808
Co [ppb]	0.190	0.180	0.510	0.600	0.610	0.540	0.660	0.720	0.449	0.529	0.045 *
Ni [ppb]	1.790	1.240	3.710	4.670	4.420	4.180	8.510	10.340	4.240	5.966	0.391
Cu [ppb]	106.530	86.780	93.870	51.750	78.560	73.100	54.620	36.390	86.315	69.147	0.344
Zn [ppb]	274.930	267.250	213.130	73.360	179.890	110.960	129.930	101.950	209.569	182.188	0.424
As [ppb]	13.370	12.280	5.370	2.190	4.950	3.420	3.860	3.510	7.830	8.685	0.052
Se [ppb]	5.870	5.330	4.530	2.400	3.420	2.630	2.360	1.860	4.285	3.843	0.223
Cd [ppb]	0.020	0.010	0.010	0.020	0.020	0.020	0.030	0.040	0.022	0.023	0.741
Pb [ppb]	1.390	1.570	2.380	1.840	3.000	1.980	2.960	2.440	2.288	1.980	0.037 *

*$p < 0.05$ values were accepted as statistically significant difference, SD-Standard Deviation.

When the control group and paracetamol groups at various doses (50 mg/kg, 250 mg/kg and 500 mg/kg) were compared, statistically significant differences were found in terms of intestinal chromium (Cr), selenium (Se) and cadmium (Cd) levels (respectively, $p = 0.029$, $p = 0.006$ and $p = 0.034$) (Table 3). No significant difference was found in intestinal tissue between other heavy metal and trace element levels. However, in the paracetamol-treated groups, less trace elements and heavy metal levels were detected in the

intestinal tissue compared to the control group. The lowest metal concentrations were detected in the intestine at the dose of 250 mg/kg Paracetamol.

Table 3:

Comparison of control and paracetamol groups in terms of heavy metal and trace elements in intestinal tissue.

BOWEL GROUPS	Control (n=8)		50 mg/kg Paracetamol (n=5)		250 mg/kg Paracetamol (n=10)		500 mg/kg Paracetamol (n=7)		Total (n=30)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p
Cr [ppb]	1.072	0.847	0.305	0.150	0.019	0.001	0.562	0.306	0.674	0.650	0.029
Co [ppb]	0.003	0.003	0.002	0.001	0.001	0.001	0.004	0.004	0.003	0.003	0.116
Ni [ppb]	0.666	1.000	0.072	0.039	0,001	0.001	0.164	0.112	0.351	0.685	0.099
Cu [ppb]	0.163	0.288	0.089	0.110	0.131	0.146	0.348	0.313	0.183	0.243	0.333
Zn [ppb]	0.533	0.604	0.012	0.001	0.404	0.506	0.160	0.151	0.353	0.472	0.231
As [ppb]	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.998
Se [ppb]	0.011	0.013	0.001	0.001	0.001	0.001	0.003	0.004	0.005	0.009	0.006**
Cd [ppb]	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.034*
Pb [ppb]	0.011	0.016	0.006	0.007	0.024	0.016	0.010	0.008	0.014	0.014	0.254

* p <0.05 and ** p <0.01 values were accepted as statistically significant difference, SD-Standard Deviation.

When the control group and paracetamol groups at various doses (50 mg/kg, 250 mg/kg and 500 mg/kg) were compared; there were statistically significant differences in terms of kidney chromium (Cr), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), selenium (Se) and lead (Pb) levels (respectively, p = 0.001, p = 0.001, p = 0.001, p = 0.006, p = 0.004, p = 0.006, p = 0.001, and p = 0.003) (Table 4). In terms of cadmium (Cd) levels, there was no significant difference between the groups in kidney tissue. However, in the paracetamol treated groups, less trace elements and heavy metal levels were found in kidney tissue compared to the control group. At the dose of 250 mg/kg Paracetamol, the lowest metal concentrations were detected in the kidney.

Table 4:

Comparison of control and paracetamol groups in kidney tissue in terms of heavy metal and trace elements.

KIDNEY GROUPS	Control (n=8)		50 mg/kg Paracetamol (n=5)		250 mg/kg Paracetamol (n=10)		500 mg/kg Paracetamol (n=7)		Total (n=30)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p
Cr [ppb]	3.204	1.347	0.523	0.337	0.094	0.194	0.591	0.338	1.092	1.456	0.001**
Co [ppb]	0.011	0.007	0.002	0.003	0.001	0.001	0.004	0.004	0.004	0.006	0.001**
Ni [ppb]	0.631	0.260	0.117	0.094	0.021	0.037	0.154	0.116	0.227	0.286	0.001**
Cu [ppb]	0.398	0.343	0.150	0.224	0.019	0.021	0.256	0.450	0.196	0.315	0.006**
Zn [ppb]	1.585	0.962	0.098	0.113	0.009	0.008	0.396	0.474	0.767	0.987	0.004**
As [ppb]	0.004	0.003	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.002	0.006**
Se [ppb]	0.022	0.013	0.003	0.003	0.001	0.001	0.003	0.002	0.007	0.011	0.001**
Cd [ppb]	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.082
Pb [ppb]	0.024	0.013	0.010	0.008	0.001	0.001	0.018	0.023	0.012	0.016	0.003**

** p <0.01 values were accepted as statistically significant difference, SD-Standard Deviation.

Paracetamol; It has the feature of being the most reliable and frequently used drug in patient populations including special groups such as children, elderly and pregnant (Karakuş et al., 2013). It is a pain medication in the 'B group' in the FDA risk factor category. Although widely used, information about the safety of therapeutic use in pregnancy is limited (Aselton et al., 1985). Paracetamol is an analgesic and antipyretic drug

used since 1893 (Von Mering, 1893). It has been demonstrated by many researchers that its pain relieving effect is achieved by inhibiting COX-1 and COX-2 enzyme as well as inhibition of COX-3 (Botting et al., 2000, Swierkosz et al., 2002, Warner et al., 2004).

Experimental studies show that paracetamol applications affect the ovaries and accordingly, the number of offspring decreases (Holm et al., 2015, Reel et al., 1992). Reel et al., reported that when paracetamol was administered to pregnant mice of Swiss CD-1 genus by diet, they obtained an average of 12 pups in the control group, while they obtained an average of 9 pups in the drug-administered group. They also reported that mice in the group receiving high doses of paracetamol failed to conceive for the fifth time (Reel et al., 1992).

In some experimental animal studies with paracetamol recently; It is reported that even the doses given for treatment cause changes in the cognitive competence and behavior of animals (Viberg et al., 2014, Ilic et al., 2010). These data indicate that there may be different potential mechanisms that may support the effect of paracetamol on neurological development. Get Viberg et al., showed that administration of paracetamol in mice during neonatal brain development later affected cognitive function and changed the analgesic and anxiolytic response in adult male mice (Viberg et al., 2014). Ilic et al. reported that rapidly developing hepatic encephalopathy with general convulsions occurred in Wistar Albino rats, where they produced sudden onset encephalopathy by intraperitoneal administration of 5 mg/kg paracetamol (Ilic et al., 2010). However, in a study by Igbinaduwa et al., Pb levels in various brands of paracetamol were found between 6 and 524 ppb (Igbinaduwa et al., 2015). In their study, Nessa et al., detected various levels of Pb in 39 different pharmaceutical dosage forms (28 tablets, 4 syrups, 6 suspensions and 1 chewing gum) (Nessa et al., 2016). In contrast, pure standard was used in our study. In this case, it indicates the damage caused by different potential mechanisms depending on the dose of paracetamol.

The dose-related pain relieving effect of paracetamol has been described in many studies with inhibition of cyclooxygenase (Botting et al., 2000, Swierkosz et al., 2002, Warner et al., 2004). As a result of this inhibition, accumulation-related increase in the levels of arachidonic (AA) and docosahexaenoic (DHA) acids occurs. As a result, there are serious losses in total fatty acid levels. As a matter of fact, Lim et al., found an increase in AA and DHA levels and a 56% decrease in total fatty acid concentrations as a result of cyclooxygenase inhibition in their study in rats (Lim et al., 2005). In the study of Lawton et al., chicks, an increase in AA levels and an increase in Pb levels were observed in addition to liver damage. As a result, with the decrease in energy intake, it causes the body and liver weight to decrease and thus the weight of the placenta and fetus to decrease (Lawton & Donaldson, 1991).

In experimental animal studies, there are publications reporting that exposure to paracetamol during pregnancy caused short stature in children and placental and fetal weight reduction (Lubawy & Garrett, 1977, Wyskiel, 1998, Burdan, 2003). In a study conducted by Wyskiel, it was stated that administering 50 mg/kg, 100 mg/kg and 200 mg/kg paracetamol three times a day to Wistar rats caused short stature and low birth weight in the fetuses, as well as a decrease in placental weight (Wyskiel, 1998). In our study, besides the decrease in the weight of placenta, it was observed that toxic metal such as Pb and oligometalin such as Co increased. Conings et al., evaluated maternal-fetal, fetal-maternal placental passage in pregnant women using paracetamol and stated that there was a 45% passage through the placenta (Conings et al., 2019). Paracetamol is the most popular analgesic in the world today and is widely used as an over-the-counter drug to relieve common health problems such as fever and various pain and pains in the body (Prescott, 1996). In our study, less trace elements and heavy metal levels were found in the paracetamol-treated groups in the intestinal and kidney tissues compared to the control group. This result is an important finding that paracetamol can be used as a chelator in toxic metal poisoning. The use of paracetamol at a certain level (in normal therapeutic doses) may make the treatment more effective, especially in the removal of toxic levels of metals accumulated in the tissues. As a matter of fact, Chandrathilaka et al., showed that this complex was effective in the chelation of metal ions such as Pb, Cd and Cu, especially in its complex application study on ascorbic acid and paracetamol. On the other hand, it has been found that it is not effective in ions loaded with +3 such as Al (Chandrathilaka et al., 2013). In our study, the lowest metal concentrations in the intestine and kidney tissues in rats were detected in the group receiving 250 mg/kg paracetamol.

CONCLUSION

As a result, it was determined that the use of paracetamol during pregnancy disrupted the current balance due to the increase in dose. An increase in placenta Pb and Co levels related to paracetamol dose was also observed. In other tissues, there was no toxic concentration at heavy metal and trace element levels, but the highest levels were determined in the control group. In our study, it was observed that the placental tissues hold heavy metal levels thanks to the conservative feature, while other tissues involved in the metabolism process such as kidney and intestine do not have this feature. However, it was found that paracetamol may be effective in tissue metal intoxication at normal therapeutic doses. In addition, the most effective dose was 250 mg/kg. In order to understand the mechanisms related to enzyme inhibition, it was suggested to look at AA and DHA levels in such studies.

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ЭФФЕКТИВНЫЙ КОНТРОЛЬ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ С ПРИМЕНЕНИЕМ ТРИПЛИКСАМА

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РЕЗЮМЕ

Актуальность

Согласно данным исследования, проведенного в 2018 году, 1,3 миллиарда человек в мире страдают от артериальной гипертензии (АГ). Цель исследования-оценить эффективность лечения Трипликсамом у пациентов с (АГ) артериальной гипертензией, не контролируемых двухтерапией.

Материал и методы

Среди 235 пациентов, получающих лечение в кардиологической клинике МЦ Эребуни, у которых не было возможности достичь целевых показателей, было проведено ретроспективное исследование. Выбранные в рамках исследования пациенты получили Трипликсамное лечение (Доза трипликсама была выбрана в зависимости от показателя АД).

Результаты и обсуждение

Начальное систолическое артериальное давление (САД) составляло 172,7 мм рт.ст., а диастолическое артериальное давление(ДАД) - 97,3 мм рт. 87% пациентов, включенных в исследование, получили регулярное лечение в различных комбинациях, а 13% - нерегулярное. В результате исследования 89% больных удалось достичь целевых показателей АД, статистически достоверного снижения показателей САД и ДАД средний показатель САД с 172.7 составил 128.1, а ДАД от 97.3 до 79.5 ($p<0.05$).

Заключение

Результаты исследования подтверждают высокую антигипертензионную эффективность Трипликсама у пациентов, не контролируемых двухтерапией, независимо от предшествующей двухтерапии и начального уровня АД.