

Research Paper

Effect of Different Concentrations of Aluminum Phosphide and (Sodium Bromide, Calcium Carbonate, and Potassium Nitrate) as Its Possible Antidotes on the Digestive and Reproductive System in a Rat Model


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ABSTRACT

Background: Aluminum phosphide (AIP) is often used as a suicide poison. Considering that there is no effective antidote, the present study aimed to investigate the toxic effect of ALP and evaluate the antidote potency of sodium bromide (NaBr), calcium carbonate (CaCO₃), and potassium nitrate (KNO₃) as antidotes.

Methods: In the first stage, 36 female Wistar rats were divided into six groups to receive AIP in different doses (0–40 mg/kg). After being sacrificed, the rats were histologically evaluated for the esophagus, stomach, pancreas, uterus, and ovary. In the second stage, animals were evaluated regarding the effect of AIP (20 mg/kg) on various fertility hormones, and subsequently, the role of proposed antidotes was investigated to reverse the toxic changes.

Results: Histological findings did not show significant changes in all examined tissues. The studied hormonal changes showed a significant inverse relationship between AIP and luteinizing hormone (LH), prolactin, and estradiol hormones. In the works related to the studied antidotes, the results indicated that prolactin and estradiol decreased and increased, respectively, due to treatment with AIP compared to the control group.

Conclusion: Antidote studies revealed that the prolactin level in rats poisoned with AIP and treated with KNO₃ was not different from the control group, and estradiol also returned to normal and control levels due to the treatment with KNO₃ and NaBr. KNO₃ was an efficient antidote against AIP toxicity regarding prolactin and estradiol among the tested antidotes, while NaBr successfully mitigated the effect of AIP toxicity.

Keywords: Aluminum phosphide (AIP), antidote, calcium carbonate (CaCO₃), potassium nitrate (KNO₃), rice tablets, sodium bromide (NaBr)

Introduction

Aluminum phosphide (AIP) is a solid fumigant widely used since the 1940s and is readily available [1]. In Iran, this combination is known as rice tablets, which can be purchased in local stores [2]. This solid pesticide quickly became one of the most used seed fumigants and is considered an ideal drop killer due to its properties [3]. This substance has become a common cause of poisoning in Iran [4, 5] and is one of the leading causes of suicide in many countries [4, 6]. Poisoning caused by rice tablets is due to the release of phosphine gas [7]. This chemical is typically formulated as pills, granules, or powder and is extremely poisonous and inexpensive. One of its activators, phosphine gas, is created due to a chemical reaction that occurs when it interacts with the humidity of the surroundings [7]. A relatively tiny amount of AIP tablets causes the emission of phosphine gas, which

affects a variety of organs [8]; the heart, digestive system, lungs, and kidneys are the primary organs that are affected by the initial exposure.

Cells undergo an energy crisis as a result of phosphine's non-competitive inhibition of mitochondrial cytochrome oxidase, blockage of the electron transport chain, and oxidative phosphorylation [6]. Phosphonate can immediately disturb the mitochondrial environment by impairing the cytochrome c enzyme's ability to operate. It may also significantly reduce the mitochondrial membrane potential and diminish oxidative respiration by 81% [9]. This poisoning also frequently results in metabolic acidosis, which is carried on by the accumulation of lactic acid brought on by the oxidative phosphorylation block, which results in inadequate blood flow to the tissues [10]. In order to treat AIP poisoning

properly, phosphine absorption and cytotoxicity should be reduced and excretion through the kidneys and lungs should increase [11]. The usual fatal dosage of AIP is between 0.15 and 0.5 grams, and the risk of poisoning with this medication is relatively high [4, 5, 12]. However, there is not a precise remedy for poisoning from rice pills.

There is no proven antidote that has been clinically proven to work [13]. Most AIP toxicity treatments are supportive in nature, such as intra-aortic balloon pumps [14] and extracorporeal membrane oxygenation (ECMO), a recently developed and considerably promising method that offers transient cardiorespiratory support [15-17]. Magnesium sulfate [18-20], melatonin [21], coconut oil [22, 23], acetylcysteine (NAC) [24-27], sodium selenite [28], vitamin E [29, 30], triiodothyronine [31], liothyronine [32], vasopressin and milrinone [31], Laurus nobilis L [33], Aminonicotinamide (6-AN), boric acid [34, 35] and acetyl L-carnitine are among the antidotes investigated in different studies [36]. However, none of these antidotes have been used in clinical settings.

The data offered and the research on potential antidotes suggest that further study is still needed to develop effective antidotes. The impact of AIP poisoning at various dosages as well as the chemicals sodium bromide (NaBr), calcium carbonate (CaCO₃), and potassium nitrate (KNO₃), have been investigated in the current study as potential antidotes on ovarian and digestive system tissues. This is because rice tablets are one of the most frequent causes of acute poisoning and suicide in Iran, and neither the mechanism of action nor the antidote for them has been fully elucidated.

Materials and Methods

Study design

The present study was an *in vivo* study that was

conducted on female Wistar rats poisoned with AIP tablets. This study was performed in compliance with the relevant regulations and institutional guidelines and has been approved by the ethics committee of Tabriz Medical School, Iran, with the ethics code IR.TBZMED.VCR.REC.1399.353. All the ethical principles of working with animals were considered by the researchers. The present study was conducted in two parts. In the first part, the toxicity of different concentrations of AIP was investigated on female rats, and in the second stage, different concentrations of antidotes were investigated.

Toxicity with different concentrations of AIP

In the first part of the study, 36 female Wistar rats were divided into six groups. AIP tablets with different concentrations (0-40 mg/kg) were fed to them. After 24 h of AIP administration, the rats were bled and euthanized under anesthesia, and the tissues of the digestive system (esophagus, stomach, duodenum, and pancreas) as well as the uterus and ovaries were removed and placed in 10% formalin. A block was taken, and a cross-section was prepared; then, hematoxylin and eosin staining were done to carry out histopathological examination.

Therefore, two rats died in the AIP concentration of 40 mg/kg; the AIP concentration for the next phase was equal to 20 mg/kg.

Effect of different concentrations of antidotes on AIP toxicity

A total of 66 female Wistar rats with an approximate weight of 200-250 grams were divided into 11 groups, as presented in Table 1.

Table 1. Prepared groups of treated rats with AIP and antidotes

Group	Treatment
Group 1	Control without intervention
Group 2	AIP - 40 mg/kg body weight as a single dose gavage
Group 3	AIP - 40 and after 20 min low dose NaBr
Group 4	AIP - 40 mg/kg body weight and after 20 min high dose NaBr
Group 5	AIP - of 40 and after 20 min CaCO ₃ with a low dose by gavage
Group 6	AIP - 40 and after 20 min CaCO ₃ with a high dose
Group 7	AIP - 40 and after 20 min KNO ₃ with a low dose
Group 8	AIP - 40 and after 20 min KNO ₃ with a high dose
Group 9	High dose NaBr
Group 10	High dose CaCO ₃
Group 11	High dose KNO ₃

After 24 h, fertility hormones, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH), were measured using the enzyme-linked immunosorbent assay (ELISA) technique.

Tissue sampling for histopathology studies of esophagus, stomach, pancreas, uterus, and ovary

Tissue samples from the esophagus, stomach, pancreas, uterus, and ovary were fixed in 10% buffered formalin. After 24 h, thin sections of the tissues were prepared for

tissue processing. The tissues were dehydrated using alcohol, and then a clarification step was performed using xylol (Tissue Processor Model DS 2080/H, Did Sabz CO., Iran). Finally, the impregnation and molding stages were performed using melted paraffin. After preparing 4–5-micron slices from the molds with a microtome device, they were placed in a 56°C oven for 30 min, and after cooling, the usual hematoxylin and eosin staining was performed.

Evaluation of tissue sections

Prepared slides were examined by a conventional light microscope (OLYMPUS-CH30, Japan) and according to Klopfleisch's [37] study for vascular hyperemia, edema, hemorrhage, amas, and necrosis factors. In all studied cases, in the absence of the desired lesion, the normal state (N), a mild lesion as +1, a moderate lesion as +2, and a severe lesion as +3 were considered.

Data analysis

Statistical analysis of the obtained results was carried out using ANOVA, or Kruskal-Wallis H and Mann-Whitney U tests for parametric and non-parametric data, respectively, using the SPSS (version 22) software. In addition, Pearson's test was employed to investigate the relationship between different parameters.

Results

Histopathological studies of the esophagus, stomach, pancreas, and intestine

The results of the microscopic examination of the examined tissue sections are indicated in Figures 1–4. Esophageal tissue in all groups showed normal tissue structure, and no pathological lesions were observed in the tissue sections studied in the control group and other experimental groups in the squamous epithelium and submucosa of the esophagus (Figure 1).

Pancreatic tissue in all groups showed normal tissue structure, and no pathological lesions were observed in the tissue sections studied in the control group and other test groups in pancreatic acini and islets of Langerhans (Figure 2).

In the stomach tissue of the control group, normal tissue structure was observed (Figure 3). Only in the AIP-4 and AIP-5 groups, there was a mild gastritis with mononuclear mast cells and a small number of eosinophils under the

gastric mucosa, which was not significantly different from the other groups. In other test groups, almost normal tissue structure was observed in the epithelium, gastric glands, and submucosa. There were no other pathological lesions, including edema, hyperemia, hemorrhage, and necrosis.

In the intestinal tissue of the control group, a completely normal tissue structure was observed (Figure 4). In the other test groups, there was mild mononuclear enteritis in the mucosa and submucosa of the intestinal tissue, and no significant difference was observed between the groups. There were no other pathological lesions, including edema, hyperemia, hemorrhage, and necrosis. In addition, the epithelium and glands showed normal structures.

In the control group, the normal structure of uterine and ovarian tissue was observed. Moreover, in other studied groups, common pathological lesions, including vascular hyperemia, edema, bleeding, amas, and necrosis, were not observed, and almost normal structure was seen in all tissue sections (Figure 5).

In the uterine tissue, the normal structure of the epithelium covering the endometrium and uterine glands was observed. In the ovarian tissue, there were active ovarian follicles in different stages of development (Figure 6).

Relationship between the studied parameters and AIP concentration

Pearson's correlation was used to investigate the relationship between the studied hormones and AIP concentration, and the results are indicated in Table 2. Luteinizing hormone (LH), progesterone, and estradiol were found to be inversely related to AIP ($P < 0.05$). However, there was no significant relationship between AIP concentration and FSH or prolactin levels ($P = 0.728$).

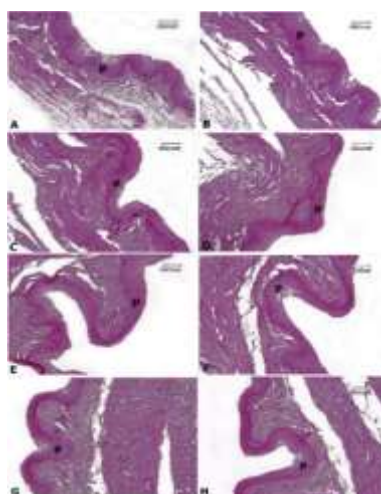


Figure 1. Rat esophagus tissue, A: control group, B: AIP-5 group, C: AIP-4 group, D: A2 group, E: B2 group, F: C2 group, G: AD1, H: AD3. In all groups, an almost normal structure with a fatty esophagus and a normal squamous epithelium (p) is observed—Hematoxylin-eosin staining.

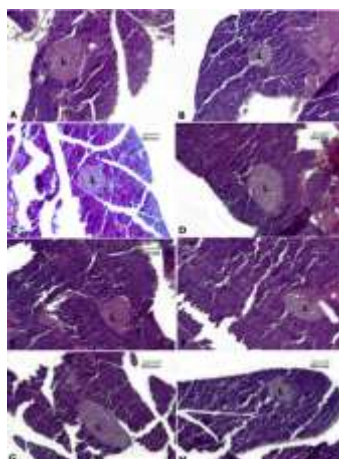


Figure 2. Rat pancreas tissue, A: control group, B: AIP-5 group, C: AIP-4 group, D: A2 group, E: B2 group, F: C2 group, G: AD1, H: AD3. In all groups, normal structure is observed in pancreatic acini and islets of Langerhans (L)—Hematoxylin-eosin staining.

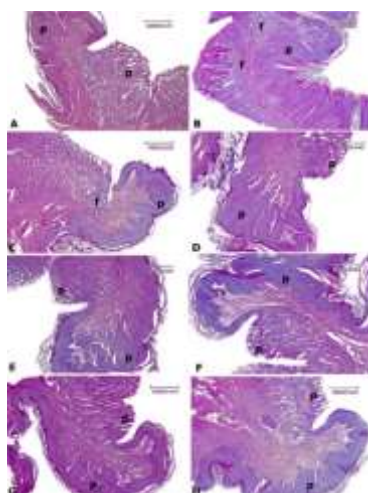


Figure 3. Rat stomach tissue, A: control group, B: AIP-5 group, C: AIP-4 group, D: A2 group, E: B2 group, F: C2 group, G: AD1, H: AD3. In the control group, a normal structure is observed in the mucosa (P) and submucosa of the stomach tissue. Only in the AIP-4 and AIP-5 groups, there was mild gastritis (f) in the submucosa of the stomach. In other test groups, almost normal tissue structure was observed in the epithelium, gastric glands, and submucosa—Hematoxylin-eosin staining.

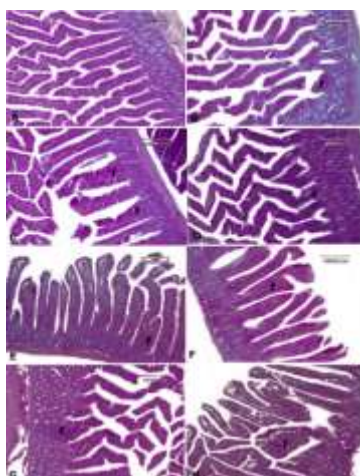


Figure 4. Rat intestinal tissue, A: control group, B: AIP-5 group, C: AIP-4 group, D: A2 group, E: B2 group, F: C2 group, G: AD1, H: AD3. In the control group, normal structure is observed in the intestinal tissue. In the other test groups, mild mononuclear enteritis (f) was present in the mucosa and submucosa of the intestinal tissue—Hematoxylin-eosin staining.

Levels of the hormones as a result of poisoning with AIP and treatment with antidotes

Rats poisoned with AIP were treated with different antidotes. The effect of the studied antidotes is presented in Table 3. According to the obtained results, the levels of

all the examined hormones, including FSH ($P < 0.0001$), LH ($P = 0.001$), prolactin ($P = 0.002$), testosterone ($P < 0.0001$), progesterone ($P < 0.0001$), and estradiol ($P < 0.0001$), had significant differences between different treatments.

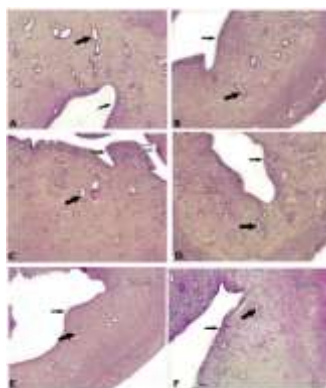


Figure 5. Rat uterine tissue, A: control group, B: AIP-5 group, C: AIP-4 group, D: A2 group, E: B2 group, F: C2 group. In all groups, an almost normal structure is observed, with uterine fat in the normal epithelium (small arrows) and uterine glands (big arrows)—Hematoxylin-eosin staining.

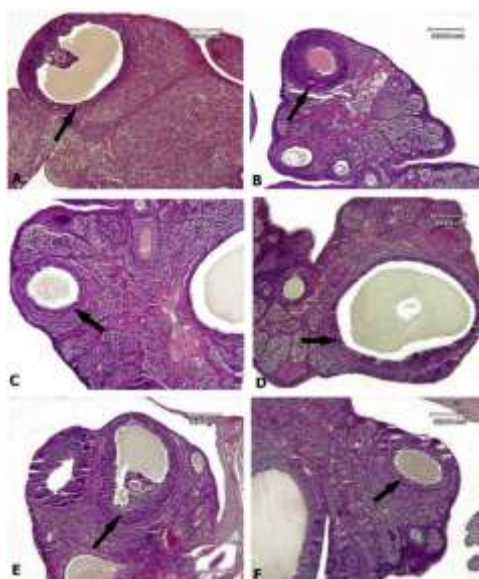


Figure 6. Rat ovary tissue, A: control group, B: AIP-5 group, C: AIP-4 group, D: A2 group, E: B2 group, F: C2 group. An almost normal structure with normal ovarian fat and active ovarian follicles (arrows) is observed in all groups—Hematoxylin-eosin staining.

Table 2. Relationship between the studied parameters and AIP concentration

Correlation to AIP	FSH	LH	Prolactin	Progesterone	Estradiol
Pearson Correlation	-0.066	-0.553	-0.224	-0.751	-0.875
P-value	0.728	0.002	0.234	<0.0001	<0.0001

Table 3. Levels of the hormones as a result of poisoning with AIP and treatment with antidotes

Group	No	Mean	SD	95% Confidence Interval for Mean		P-value	
				Lower Bound	Upper Bound		
FSH	AIP	5	1.30	0.15	1.12	1.48	<0.0001
	AIP-KNO ₃	12	1.33	0.12	1.25	1.41	
	AIP-CaCO ₃	12	1.88	0.58	1.51	2.25	
	AIP-NaBr	12	1.33	0.18	1.21	1.44	
	Control	6	1.33	0.33	0.99	1.68	
	KNO ₃	6	1.12	0.15	0.96	1.27	
	CaCO ₃	6	1.50	0.96	1.40	1.60	
	NaBr	6	1.32	0.15	1.15	1.48	
LH	AIP	5	0.60	0.57	-0.11	1.31	0.001
	AIP-KNO ₃	12	2.00	2.17	0.62	3.38	
	AIP-CaCO ₃	12	3.46	1.84	2.29	4.62	
	AIP-NaBr	12	3.47	3.91	0.99	5.95	
	Control	6	0.90	0.50	0.38	1.42	
	KNO ₃	6	1.73	1.22	0.45	3.01	
	CaCO ₃	6	2.00	0.26	1.73	2.27	
	NaBr	6	6.63	3.75	2.70	10.57	
Prolactin	AIP	5	0.78	0.17	0.57	0.99	0.002
	AIP-KNO ₃	12	2.14	1.39	1.25	3.02	
	AIP-CaCO ₃	12	1.47	0.40	1.21	1.72	
	AIP-NaBr	12	1.27	0.39	1.02	1.51	
	Control	6	3.53	3.17	0.21	6.86	
	KNO ₃	6	0.70	0.18	0.51	0.89	

Testosterone	CaCO ₃	6	2.46	1.31	1.08	3.84	<0.0001
	NaBr	6	1.55	0.65	0.87	2.23	
	AIP	5	0.26	0.09	0.15	0.38	
	AIP-KNO ₃	12	0.32	0.13	0.24	0.41	
	AIP-CaCO ₃	12	0.16	0.06	0.12	0.20	
	AIP-NaBr	12	0.69	0.27	0.51	0.86	
	Control	6	0.53	0.30	0.50	0.56	
	KNO ₃	6	
	CaCO ₃	6	
Progesterone	NaBr	6	<0.0001
	AIP	5	28.66	7.14	19.79	37.53	
	AIP-KNO ₃	12	12.98	9.08	7.21	18.76	
	AIP-CaCO ₃	12	32.72	20.55	19.66	45.77	
	AIP-NaBr	12	39.60	5.80	35.91	43.29	
	Control	6	48.20	1.59	46.53	49.87	
	KNO ₃	6	38.50	15.34	22.40	54.60	
	CaCO ₃	6	2.52	0.28	2.22	2.81	
	NaBr	6	31.60	22.63	7.85	55.34	
Estradiol	AIP	5	16.24	0.34	15.82	16.66	<0.0001
	AIP-KNO ₃	12	22.08	3.84	19.65	24.52	
	AIP-CaCO ₃	12	15.70	2.03	14.41	16.99	
	AIP-NaBr	12	10.65	3.56	8.39	12.91	
	Control	6	8.63	2.64	5.86	11.41	
	KNO ₃	6	16.52	1.64	14.80	18.24	
	CaCO ₃	6	16.90	0.93	15.92	17.88	
	NaBr	6	10.25	1.54	8.64	11.86	

According to the obtained results, the FSH hormone level in the AIP-CaCO₃ group was significantly higher than that in the AIP (P=0.014), AIP-KNO₃ (P=0.001), AIP-NaBr (P=0.001), normal control (P=0.014), KNO₃ (P<0.0001) and NaBr (P=0.010) groups.

The LH hormone was higher in the NaBr group compared to that in the AIP (P=0.003), AIP-KNO₃ (P=0.008), normal control (P=0.003), KNO₃ (P=0.020), and CaCO₃ (P=0.033) groups.

Prolactin hormone in the normal control group was significantly higher than that in the AIP (P=0.011), AIP-CaCO₃ (P=0.028), AIP-NaBr (P=0.011), and KNO₃ (P=0.004) groups.

Progesterone in the AIP-KNO₃ group was significantly lower than that in the AIP-CaCO₃ (P=0.012), AIP-NaBr (P<0.0001), normal control (P<0.0001) and KNO₃ (P=0.006) groups. Moreover, progesterone hormone in the CaCO₃ group was significantly lower than that in the rats receiving AIP (P=0.035), AIP-CaCO₃ (P=0.001), AIP-NaBr (P<0.0001), normal control (P<0.0001), KNO₃ (P>0.0001) and NaBr (P=0.007).

Regarding the estradiol hormone, the results demonstrated that the level of estradiol in rats receiving AIP was higher compared to that in the groups receiving AIP-NaBr (P=0.006), normal control (P<0.0001) and NaBr (P=0.011). On the other hand, it was found that the amount of estradiol in the group treated with AIP-KNO₃ was higher compared to that in the groups receiving AIP (P=0.003), AIP-CaCO₃ (P<0.0001), AIP-NaBr (P<0.0001), normal control (P<0.0001), KNO₃ (P=0.003), CaCO₃ (P=0.007) and NaBr (P<0.0001).

Levels of the examined hormones as a result of AIP poisoning and treatment with different doses of antidotes

Each antidote used in this study was used in two high and low doses. Table 4 shows the results of the evaluation of hormones after poisoning with AIP and treatment with antidotes in high and low doses. According to the results, the levels of all hormones were significantly different between the studied groups (P<0.0001).

Table 4. Levels of hormones investigated as a result of AIP poisoning and treatment with different doses of antidotes.

Group	No	Mean	SD	95% Confidence Interval for Mean		P-value	
				Lower Bound	Upper Bound		
FSH	AIP	6	1.31	0.14	1.17	1.46	<0.0001
	AIP-KNO ₃ -L	6	1.28	0.14	1.13	1.43	
	AIP-KNO ₃ -H	6	1.38	0.09	1.29	1.47	
	AIP-CaCO ₃ -L	6	2.25	0.59	1.63	2.89	
	AIP-CaCO ₃ -H	6	1.50	0.23	1.26	1.74	
	AIP-NaBr-L	6	1.46	0.16	1.29	1.62	
	AIP-NaBr-H	6	1.20	0.10	1.10	1.30	
	Control	6	1.33	0.33	0.99	1.68	
	KNO ₃ -H	6	1.12	0.15	0.96	1.27	
	CaCO ₃ -H	6	1.50	0.10	1.40	1.60	
	NaBr-H	6	1.32	0.15	0.15	1.48	
	LH	AIP	6	0.73	0.61	0.10	
AIP-KNO ₃ -L		6	0.40	0.21	0.18	0.62	
AIP-KNO ₃ -H		6	3.60	2.05	1.45	5.75	
AIP-CaCO ₃ -L		6	4.27	2.31	1.84	6.70	
AIP-CaCO ₃ -H		6	2.64	0.69	1.92	3.37	
AIP-NaBr-L		6	6.00	4.23	1.56	10.44	

	AIP-NaBr-H	6	0.93	0.48	0.43	1.44	
	Control	6	0.90	0.50	0.38	1.42	
	KNO ₃ -H	6	1.73	1.22	0.45	3.01	
	CaCO ₃ -H	6	2.00	0.26	1.73	2.27	
	NaBr-H	6	6.63	3.75	2.70	10.57	
Prolactin	AIP	6	0.77	0.15	0.61	0.93	
	AIP-KNO ₃ -L	6	3.34	0.89	2.41	4.27	
	AIP-KNO ₃ -H	6	0.94	0.20	0.74	1.15	
	AIP-CaCO ₃ -L	6	1.18	0.15	1.02	1.35	
	AIP-CaCO ₃ -H	6	1.75	0.37	1.36	2.14	
	AIP-NaBr-L	6	1.35	0.31	1.02	1.68	<0.0001
	AIP-NaBr-H	6	1.18	0.47	0.69	1.68	
	Control	6	3.53	3.17	0.21	6.86	
	KNO ₃ -H	6	0.70	0.18	0.51	0.89	
	CaCO ₃ -H	6	2.46	1.31	1.08	3.84	
	NaBr-H	6	1.55	0.65	0.87	2.23	
	AIP	6	0.27	0.08	0.18	0.36	
	AIP-KNO ₃ -L	6	0.29	0.05	0.24	0.34	
AIP-KNO ₃ -H	6	0.36	0.18	0.18	0.55		
AIP-CaCO ₃ -L	6	0.15	0.09	0.06	0.24		
AIP-CaCO ₃ -H	6	0.17	0.33	0.14	0.21	<0.0001	
AIP-NaBr-L	6	0.81	0.31	0.48	1.13		
AIP-NaBr-H	6	0.56	0.17	0.39	0.74		
Control	6	0.53	0.30	0.50	0.56		
Progesterone	AIP	6	26.57	8.19	17.97	35.16	
	AIP-KNO ₃ -L	6	20.97	5.25	15.46	26.47	
	AIP-KNO ₃ -H	6	5.00	1.01	3.94	6.06	
	AIP-CaCO ₃ -L	6	13.10	1.42	11.61	14.59	
	AIP-CaCO ₃ -H	6	52.33	1.88	50.36	54.31	
	AIP-NaBr-L	6	45.00	1.45	43.48	46.52	<0.0001
	AIP-NaBr-H	6	34.20	1.42	32.71	35.69	
	Control	6	48.20	1.59	46.53	49.78	
	KNO ₃ -H	6	38.50	15.35	22.40	54.60	
	CaCO ₃ -H	6	2.52	0.28	2.22	2.81	
	NaBr-H	6	31.60	22.63	7.86	55.34	
	AIP	6	16.20	0.32	15.87	16.53	
	AIP-KNO ₃ -L	6	20.70	1.06	19.58	21.82	
AIP-KNO ₃ -H	6	23.47	5.16	18.05	28.89		
AIP-CaCO ₃ -L	6	17.60	0.56	17.01	18.19		
AIP-CaCO ₃ -H	6	13.80	0.26	13.52	14.08		
AIP-NaBr-L	6	13.90	0.43	13.45	14.36	<0.0001	
AIP-NaBr-H	6	7.40	1.52	5.81	8.99		
Control	6	8.63	2.64	5.86	11.41		
KNO ₃ -H	6	16.52	1.64	14.80	18.24		
CaCO ₃ -H	6	16.90	0.93	15.92	17.88		
NaBr-H	6	10.25	1.54	8.64	11.86		
Estradiol	AIP	6	16.20	0.32	15.87	16.53	
	AIP-KNO ₃ -L	6	20.70	1.06	19.58	21.82	
	AIP-KNO ₃ -H	6	23.47	5.16	18.05	28.89	
	AIP-CaCO ₃ -L	6	17.60	0.56	17.01	18.19	
	AIP-CaCO ₃ -H	6	13.80	0.26	13.52	14.08	
	AIP-NaBr-L	6	13.90	0.43	13.45	14.36	<0.0001
	AIP-NaBr-H	6	7.40	1.52	5.81	8.99	
	Control	6	8.63	2.64	5.86	11.41	
	KNO ₃ -H	6	16.52	1.64	14.80	18.24	
	CaCO ₃ -H	6	16.90	0.93	15.92	17.88	
	NaBr-H	6	10.25	1.54	8.64	11.86	

The FSH hormone in rats receiving AIP-CaCO₃-L were significantly higher compared to that in the AIP (P<0.0001), AIP-KNO₃-L (P<0.0001), AIP-KNO₃-H (P<0.0001), AIP-CaCO₃-H (P<0.0001), AIP-NaBr-L (P<0.0001), AIP-NaBr-H (P<0.0001), control (P<0.0001), KNO₃-H (P<0.0001), CaCO₃-H (P<0.0001) and NaBr-H (P<0.0001) groups.

In addition, the LH hormone in rats receiving AIP-NaBr-L was substantially higher compared to that in the AIP (P=0.001), AIP-KNO₃-L (P=0.001), AIP-NaBr-H (P=0.003), control (P=0.002), KNO₃-H (P=0.021) and CaCO₃-H (P=0.039) groups. It was also demonstrated that the rats receiving NaBr-H had a higher level of LH hormone compared to its level in the AIP (P<0.0001), AIP-KNO₃-L (P<0.0001), AIP-CaCO₃-H (P=0.040), AIP-NaBr-H (P<0.0001), control (P<0.0001), KNO₃-H (P=0.004) and CaCO₃-H (P=0.008) groups.

According to the obtained results, the level of prolactin hormone in the rats receiving AIP-KNO₃-L was significantly higher than that in the rats receiving AIP (P=0.008), AIP-KNO₃-H (P=0.017), AIP-CaCO₃-L

(P=0.050), AIP-NaBr-H (P=0.050) and KNO₃-H (P=0.006). In addition, the rats in the control group have a higher level of prolactin hormone in comparison with its level in the AIP (P=0.003), AIP-KNO₃-H (P=0.007), AIP-CaCO₃-L (P=0.021), AIP-NaBr-L (P=0.043), AIP-NaBr-H (P=0.021) and KNO₃-H (P=0.002) groups.

Regarding progesterone hormone, the results indicated that this hormone was significantly lower in the AIP-KNO₃-H group compared to that in the AIP (P=0.004), AIP-CaCO₃-H (P<0.0001), AIP-NaBr-L (P<0.0001), AIP-NaBr-H (P<0.0001), control (P<0.0001), KNO₃-H (P<0.0001) and NaBr-H (P<0.0001). Meanwhile, progesterone in rats receiving AIP-CaCO₃-L was lower than that in the AIP-CaCO₃-H (P<0.0001), AIP-NaBr-L (P<0.0001), AIP-NaBr-H (P=0.005), control (P<0.0001), KNO₃-H (P<0.0001) and NaBr-H (P=0.024). Moreover, progesterone in the rats receiving AIP-CaCO₃-H was significantly higher compared to that in the groups receiving AIP (P<0.0001), AIP-KNO₃-L (P<0.0001), AIP-NaBr-H

($P < 0.0001$), $\text{CaCO}_3\text{-H}$ ($P < 0.0001$) and NaBr-H ($P = 0.006$). This hormone was significantly higher in the AIP-NaBr-L receiving group than in the AIP ($P = 0.025$), $\text{AIP-KNO}_3\text{-L}$ ($P = 0.001$), and $\text{CaCO}_3\text{-H}$ ($P < 0.0001$) groups. It was also significantly higher than AIP ($P = 0.004$) and $\text{AIP-KNO}_3\text{-L}$ ($P < 0.0001$) in control rats. Finally, it was determined that the rats receiving $\text{CaCO}_3\text{-H}$ had lower progesterone levels than that in the AIP ($P = 0.001$), $\text{AIP-KNO}_3\text{-L}$ ($P = 0.024$), $\text{AIP-CaCO}_3\text{-H}$ ($P < 0.0001$), AIP-NaBr-L ($P < 0.0001$), AIP-NaBr-H ($P < 0.0001$), control ($P < 0.0001$), $\text{KNO}_3\text{-H}$ ($P < 0.0001$) and NaBr-H ($P < 0.0001$).

The results related to estradiol hormone showed that rats poisoned with AIP had a lower level of estradiol than $\text{AIP-KNO}_3\text{-L}$ ($P = 0.011$), $\text{AIP-KNO}_3\text{-H}$ ($P < 0.0001$), AIP-NaBr-H ($P < 0.0001$), control ($P < 0.0001$) and NaBr-H ($P < 0.0001$). Rats receiving $\text{AIP-KNO}_3\text{-L}$ had a higher level of estradiol in comparison with $\text{AIP-CaCO}_3\text{-H}$ ($P < 0.0001$), AIP-NaBr-L ($P < 0.0001$), AIP-NaBr-H ($P < 0.0001$), control ($P < 0.0001$), $\text{KNO}_3\text{-H}$ ($P = 0.023$) and NaBr-H ($P < 0.0001$). It was also indicated that rats receiving $\text{AIP-KNO}_3\text{-H}$ had higher estradiol levels than those in other groups except rats receiving $\text{AIP-KNO}_3\text{-L}$ ($P < 0.0001$). In the group receiving $\text{AIP-CaCO}_3\text{-L}$, the amount of estradiol was higher compared to that in the rats receiving AIP-NaBr-H ($P < 0.0001$), control ($P < 0.0001$) and NaBr-H ($P < 0.0001$). Rats receiving $\text{AIP-CaCO}_3\text{-H}$ had a higher level of estradiol in comparison with that in the AIP-NaBr-H ($P < 0.0001$) and control ($P = 0.002$). Rats receiving AIP-NaBr-L had a higher level of estradiol in comparison with that in the AIP-NaBr-H ($P < 0.0001$) and control ($P = 0.001$). Rats receiving $\text{KNO}_3\text{-H}$ have a higher level of estradiol in comparison with its level in rats receiving AIP-NaBr-H ($P < 0.0001$), control ($P < 0.0001$), and NaBr-H ($P < 0.0001$). Finally, it was determined that the group receiving $\text{CaCO}_3\text{-H}$ had a higher level of estradiol in comparison with that in the rats receiving AIP-NaBr-H ($P < 0.0001$), normal control ($P < 0.0001$), and NaBr-H ($P < 0.0001$).

Discussion

The present study aimed to examine the impact of novel antidotes on AIP poisoning in digestive tissues, ovaries, the uterus, and several reproduction hormones in a rat animal model. These antidotes included NaBr , CaCO_3 , and KNO_3 compounds. The findings of our investigation demonstrated that the tissues of the esophagus, stomach, pancreas, uterus, and ovary exhibited no substantial and noteworthy modifications in histological tests. The levels of the LH , progesterone, and estradiol hormones were significantly negatively associated with AIP concentration, whereas hormonal investigations revealed significant variations across groups. Additionally, the FSH , LH , and prolactin hormones in the AIP-CaCO_3 , NaBr , and control groups, respectively, had higher levels than those in the other groups. In contrast to other groups,

progesterone hormone levels significantly decreased in the AIP-KNO_3 and CaCO_3 groups. Regarding the hormone estradiol, the results indicated that the level of estradiol was relatively higher in rats receiving AIP and AIP-KNO_3 .

As mentioned earlier, FSH levels were greater in the AIP-CaCO_3 group than in the other groups. An increase in FSH is a sign of declining ovarian reserve. A decline in ovarian reserve is linked to reduced follicles or eggs, which are frequently of low quality. Statistics show that women with high FSH levels have a poor likelihood of conceiving a child. According to this work, additional substances (e.g., KNO_3 and NaBr) had no discernible impact on the FSH hormone levels compared to the control group. Loeber et al., using immunocytochemistry and radioimmunoassay, aimed to investigate how NaBr affected rat endocrine parameters. The findings of their investigation demonstrated that NaBr directly interferes with thyroid, testicular, and adrenal activities, including the activation of the FSH hormone, at least at high levels. It appears that low doses of NaBr do not have a stimulating effect on FSH , which supports our study because the highest dose we used in this study was 370 mg/kg , which did not have a stimulating effect on FSH . In this study, 0 , 20 , 75 , 300 , 1200 , and $19,200 \text{ mg/kg}$ doses were used, and the effect of NaBr was stimulating only at high doses [38]. In a study on the effects of NaBr on people, with a focus on the endocrine system, Sangster et al. found that the FSH hormone did not alter considerably because of the injection of NaBr [39]. However, we reported that KNO_3 did not alter FSH , and no research has been conducted on this topic. Our investigation into the FSH hormone generally has shown that AIP has no impact on the amount of this hormone.

The LH hormone was also examined in this study, and the findings revealed that AIP had no discernible impact on this hormone. LH aids in the regulation of the menstrual cycle in women. Additionally, ovulation—the release of the egg from the ovary—is brought on by it. Just prior to ovulation, LH levels rise quickly. Only NaBr was able to considerably increase the level of this hormone in our investigation; there was no discernible difference in hormone levels between the other groups. As a result, despite an inverse association between AIP concentration and LH hormone, it can be said that AIP does not significantly affect LH hormone compared to the control group because no additional research in this field has been carried out. Therefore, it is suggested that more studies be conducted in this field.

Prolactin was another hormone examined in this study, and the results demonstrated a significant decrease in this hormone in rats receiving AIP ; therefore, it can be concluded that this hormone is

affected by AIP poisoning. Interestingly, the prolactin hormone in rats receiving AIP treated with KNO_3 was not different from the control group, and it indicates that KNO_3 can neutralize the effect of AIP toxicity on the level of prolactin hormone. Other evaluated compounds did not show such an effect, and the amount of prolactin in rats receiving AIP after treatment with NaBr and CaCO_3 significantly decreased compared to the control group. A decrease in the amount of secreted prolactin can lead to insufficient milk production after childbirth. Most people with low prolactin levels do not have any specific medical problems, although early evidence suggests they may have reduced immune responses to some infections. So far, no study has been conducted regarding the effect of AIP or KNO_3 on the level of prolactin hormone. Therefore, it can be acknowledged that in this study, for the first time, we indicated the reducing effect of AIP on the prolactin hormone and the antidote effect of KNO_3 on the toxicity of AIP regarding this hormone.

Another hormone whose level changed significantly after treatment with AIP in our study was estradiol hormone, which significantly increased after treatment of rats with AIP compared to the control group. Both males and females produce estradiol, the most common type of estrogen in women during their reproductive years. Significant levels of estradiol may lead to acne, decreased libido, osteoporosis, and depression. In addition, its high levels can increase the risk of uterine and breast cancer. Therefore, it can be concluded that the effect of AIP on estradiol can lead to many diseases. On the other hand, based on the findings of this study, the level of estradiol in rats poisoned with AIP and treated with KNO_3 and NaBr was not significantly different from the control group. Therefore, the results of our study indicate the antidote effect of these two substances on the toxicity caused by AIP on the level of estradiol hormone.

Conclusions

Results of our study showed that AIP had no adverse effect on the tissues of the esophagus, stomach, pancreas, uterus, or ovaries of the studied rats. On the other hand, the levels of LH, estradiol, and prolactin hormones showed an inverse relationship with AIP. According to the findings, AIP significantly affected the levels of estradiol and prolactin hormones compared to the control group in such a way that it decreased and increased prolactin and estradiol, respectively. Among the investigated antidotes, KNO_3 was seen as an effective antidote against AIP toxicity in prolactin and estradiol, and NaBr effectively reduced the effect of AIP toxicity.

Data Access and Responsibility

As the principal investigator and corresponding author of the study, Ali Ostadi has full access to all the study's data and bears responsibility for its accuracy and integrity.

Ethical Considerations

Compliance with ethical guidelines: This study was performed in compliance with the relevant laws and institutional guidelines and has been approved by the ethics committee of Tabriz Medical School with the ethics code IR.TBZMED.VCR.REC.1399.353. All the ethical principles of working with animals were considered by the researchers.

Authors' Contributions

All authors were involved in Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Original Draft, as well as Review & Editing.

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Conflict of Interests

There are no conflicts of interest to declare.

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