# Thyroxin, glucose, body growth rate and non-protein nitrogen constituents in albino rats treated with excess potassium iodate

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**Abstract:** The study was aimed to determine median lethal dose ($LD_{50}$) of potassium iodate and to assess its toxicity in albino rats. The oral $LD_{50}$ was found to be 752 mg $kg^{-1}$ body weight. A dose of 1/5 $LD_{50}$ potassium iodate was then given to animals ($n = 36$). Control animals ($n = 36$) received distilled water. Means were compared by independent-samples *t*-test. Growth rates of experimental animals were decreased, particularly at the first two weeks (27.5 and 24.2%, $p = 0.009$ and 0.000, respectively). Significant increase in serum thyroxin was observed at the second and third weeks ($p = 0.007$ and 0.046, respectively). Mean glucose levels were significantly decreased with maximum difference of 26.3% at the fifth week (106.1 ± 4.9 *v* 78.2 ± 4.2, $p = 0.002$). Urea was decreased (max difference = 23.6%, mean = 35.6 ± 1.8 *v* 27.2 ± 1.7, $p = 0.007$) whereas uric acid and creatinine were increased (max difference = 25.4%, mean = 1.77 ± 0.08 *v* 2.22 ± 0.12, $p = 0.011$ and 19.6%, 0.56 ± 0.03 *v* 0.67 ± 0.03, $p = 0.022$, respectively).

**Keywords:** albino rats; body growth rate; glucose; non-protein nitrogen constituents; potassium iodate toxicity; thyroxin.

**Reference** to this paper should be made as follows: Yassin, M.M., Abd El-Aziz, I.I. and El Mabhouh, F.A. (2008) 'Thyroxin, glucose, body

growth rate and non-protein nitrogen constituents in albino rats treated with excess potassium iodate', *Int. J. Food Safety, Nutrition and Public Health*, Vol. 1, No. 2, pp.137–149.

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## 1 Introduction

Iodine is an essential element that is necessary for normal thyroid function. The recommended daily allowance of iodine is 150 µg per day for adults, 220 µg for pregnant or lactating women and lower amount for children (John, 1998; Elizabeth et al., 2004). To prevent iodine deficiency disorder in human population, iodine is added to the table salt and sometimes to bread (World Health Organisation/United Nations Children's Fund/International Council for Control of Iodine Deficiency Disorders Consultation, 1996). The amount of iodine added to the salt ranging from 20 to 80 mg of iodine per kg salt in the form of potassium salt of iodide or iodate (Burgi, Schaffner and Seiler, 2001). However, the use of iodate instead of iodide for iodisation of salt has been recommended for certain conditions, in which iodide loss from the salt may occur, as in moist, exposed to heat, sunlight or acidic condition (Diosady et al., 1998).

Uncontrolled addition of iodate to table salt and bread or human exposure to high doses of iodate could be toxic. Several iodate poisoning cases in humans via oral route were reported (Singalavanija, Dongosintr and Dulayajinda, 1994; Tong, 1995; Singalavanija, Ruangvaravate and Dulayajinda, 2000). Oral exposures of several animal species to high doses, exceeding the human intake from fortified salt by orders of magnitude, pointed to corrosive effects in the gastrointestinal tract, hemolysis, nephrotoxicity and hepatic injury (Burgi, Schaffner and Seiler, 2001). The oral $LD_{50}$ of iodate have been reported to be in the range of 500–1100 mg $kg^{-1}$ body weight for mice; iodides were three times more toxic than iodate (Gosselin et al., 1976). In rats, the oral $LD_{50}$ of potassium iodate was recently estimated to be 675 mg $kg^{-1}$ body weight (Locklear and Ritter, 2003). However, these figures required further confirmation for testing iodate toxicity in albino rat.

Research on iodate toxicity has been focused on physiology and histology of the retina (Yoon and Marmor, 1993; Mizota and Adachi-Usami, 1997; Ohtaka et al., 2006). However, the existing data of iodate toxicity on other organs are limited

(Sherer, Thrall and Bull, 1991). Additional toxicity data were needed for complete risk assessment of potassium iodate. The current study is aimed to determine the oral $LD_{50}$ of potassium iodate in albino rat which enable us to choose the dose of potassium iodate to be tested for iodate toxicity on some physiological and biochemical parameters in albino rats. The findings can then be extrapolated to human beings to assess the potential hazards in the human populations due to excess iodate intake.

## 2 Materials and methods

### *2.1 Experimental animals*

Male albino rats weighing $120 \pm 20$ g were used in the present study. They were purchased from animal breeding unit in Biology Department, Faculty of Science, Islamic University of Gaza. Animals were left for one week before experimentation to adapt to laboratory conditions. They were kept in plastic cages with wire mesh covers. The dimensions of each cage were $40 \times 30 \times 17$ cm and were freshly spread by wood chips to absorb urine of animals. A commercial balanced diet (Anbar) and water were provided *ad libitum* all over the experimental period.

### *2.2 Experimental design*

The study had two phases: the first was to determine the oral $LD_{50}$ of potassium iodate and the second was to assess its adverse effects.

#### *2.2.1 Determination of $LD_{50}$ of potassium iodate*

A total number of 90 rats were used. Animals were divided into nine groups (ten rats group$^{-1}$). Animals were fasted overnight. The first eight groups (I-VIII) were administered different single doses of potassium iodate ranging from 675 to 850 mg kg$^{-1}$ body weight as follows:

| *$LD_{50}$ determination groups* | *KIO3 dose (mg kg$^{-1}$ body weight)* |
|---|---|
| Group I | 675 |
| Group II | 700 |
| Group III | 725 |
| Group IV | 750 |
| Group V | 775 |
| Group VI | 800 |
| Group VII | 825 |
| Group VIII | 850 |
| Group IX control group | distilled water |

The ninth group (control animals) was given distilled water. Potassium iodate was purchased from Riedel de Haen. Potassium iodate was dissolved in distilled water and given orally to rats using a special stomach tube with a smooth tip to protect the interior lining of the oral and buccal cavity from injury. The animals were observed for mortality during the 48 hours observation period. The $LD_{50}$ was determined by graphical method (Manna et al., 2004).

### *2.2.2 Potassium iodate toxicity experiments*

Depending on the value of the oral $LD_{50}$ for potassium iodate that have been determined here and on the literature (Webster, Stohlman and Highman, 1966; Singalavanija, Ruangvaravate and Dulayajinda, 2000), a dose of 150 mg $kg^{-1}$ body weight potassium iodate (1/5 $LD_{50}$) was given to animals to assess iodate toxicity. Animals were divided into two groups: control and experimental groups. Each group comprised 36 rats. Six rats were housed in each cage. Experimental groups were orally administrated potassium iodate daily for an overall experimental duration of 6 weeks. Control animals were given distilled water.

## 3 Morphological studies

### *3.1 Growth rate*

Body weights of control and experimental animals were daily monitored. A digital balance (Accurat 5000, Australia) was used; weights were recorded to the nearest grams and growth rates were calculated.

### *3.2 Mortality rate*

The percentage of mortality was calculated.

## 4 Physiological and biochemical analysis

### *4.1 Blood sampling and processing*

Animals from both experimental and control groups were decapitated weekly. Blood was then collected in centrifuge tubes. Blood was allowed to clot and then centrifuged at 3,000 rpm for 15 min. Clear serum samples were separated in glass tubes, labelled for subsequent analysis.

### *4.2 Determination of serum thyroxin*

Serum thyroxin (T4) was determined by fluorescence polarisation immunoassay, using Abbott IMx T4 assay, following the instruction manual, according to the method described by Dandliker and his colleagues (Dandliker, Kelly and Dandiker, 1973).

### *4.3 Determination of serum glucose and non-protein nitrogen constituents (urea, uric acid and creatinine)*

Serum glucose was determined after enzymatic oxidation of glucose in the presence of glucose oxidase according to Trinder method (Trinder, 1969). The kit used was purchased from Dialab. Non-protein nitrogen constituents were analysed using DiaSys reagent kits. Serum urea was determined by urease–glutamate dehydrogenase/UV method (Gutmann and Bergmeyer, 1974). Serum uric acid was measured by enzymatic photometric test using 2,4,6-tribromo-3-hydroxylbenzoic acid, according to the method described by Fossati, Prencipe and Berti (1980). Serum creatinine was determined without protein precipitation according to the method described by Bartels, Bohmer and Heierli (1972).

## 5 Statistical analysis

Data were statistically analysed using SPSS computer program version 13.0 for windows (Statistical Package for Social Sciences Inc, Chicago, Illinois). Means were compared by independent-samples *t*-test. Probability values ($p$) were obtained from the student's table of '$t$' and significance was at $p < 0.05$.

Percentage difference was calculated according to the formula:

$$\text{Percentage difference} = \frac{\text{Mean of treated} - \text{Mean of control}}{\text{Mean of control}} \times 100.$$

Logarithmic scale of oral $LD_{50}$ of potassium iodate and serum thyroxin level was plotted using Microsoft Excel program version 11.0.

## 6 Results

### *6.1 Oral $LD_{50}$ of potassium iodate*

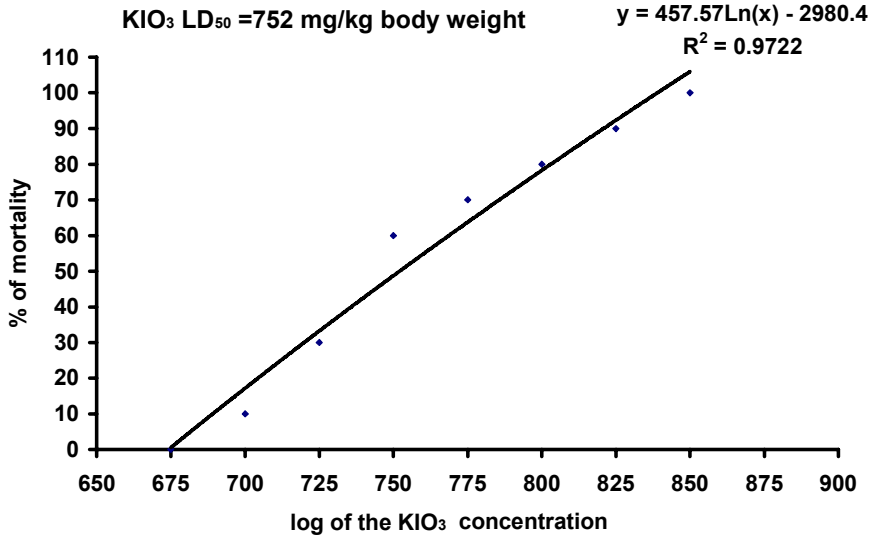
The experimental trials for oral $LD_{50}$ determination of potassium iodate after 48 hours of administration in albino rats revealed that the mortality commenced at 700 mg $kg^{-1}$ body weight, recording mortality percentage of 10% (Table 1). Increasing potassium iodate dose to 725, 750, 775, 800 and 825 resulted in mortality percentages of 30, 60, 70, 80 and 90%, respectively, i.e. the mortality rate was a function of dose increase. The maximum concentration of potassium iodate that kills all rats in the group was found to be 850 mg $kg^{-1}$ body weight. The calculated oral $LD_{50}$ of potassium iodate in albino rats from the linear regression was found to be 752 mg $kg^{-1}$ body weight (Figure 1).

**Table 1** Mortality percentage of male albino rats after 48 hours of oral administration of different doses of potassium iodate

| *Group* | *potassium iodate dose (mg kg$^{-1}$ body weight)* | *Number of animals died/total* | *Percentage of mortality* |
|---|---|---|---|
| Group I | 675 | 0/10 | 0 |
| Group II | 700 | 1/10 | 10 |
| Group III | 725 | 3/10 | 30 |
| Group IV | 750 | 6/10 | 60 |
| Group V | 775 | 7/10 | 70 |
| Group VI | 800 | 8/10 | 80 |
| Group VII | 825 | 9/10 | 90 |
| Group VIII | 850 | 10/10 | 99.99 |
| Group IX control group | Control | 0/10 | 0 |

Note: the number of animals administered potassium iodate was ten in each group (I to VIII). Control animals were given distilled water and their number was also ten.

**Figure 1** Logarithmic scale of oral $LD_{50}$ of potassium iodate in albino rat




## *6.2 Morphological studies*

### *6.2.1 Growth rate*

As shown in Table 2, administration of 150 mg kg$^{-1}$ body weight potassium iodate (1/5 $LD_{50}$) generally caused significant decrease in body growth rate (g day$^{-1}$) of albino rat recording percentage decreases of 27.5, 24.2, 19.9, 12.3, 23.4 and 11.3% at the 1st, 2nd, 3rd, 4th, 5th and 6th weeks of the experiment, respectively, compared to control animals.

**Table 2** Body growth rate (g $day^{-1}$) of control and potassium iodate-treated (150 mg $kg^{-1}$ body weight) albino rats at different time intervals

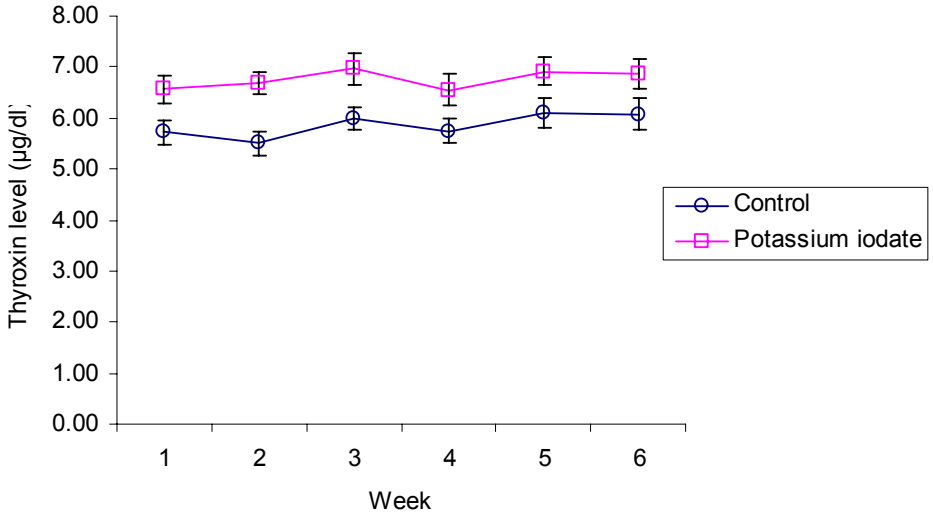
| *Experimental period (week)* | *Control* | *Potassium iodate* | *% difference* | *p value* |
|---|---|---|---|---|
| 1 | 4.37 ± 0.29 | 3.17 ± 0.22 | –27.5 | 0.009 |
| 2 | 4.91 ± 0.09 | 3.72 ± 0.17 | –24.2 | 0.000 |
| 3 | 4.37 ± 0.17 | 3.50 ± 0.23 | –19.9 | 0.012 |
| 4 | 3.42 ± 0.10 | 3.00 ± 0.17 | –12.3 | 0.061 |
| 5 | 2.90 ± 0.08 | 2.22 ± 0.12 | –23.4 | 0.001 |
| 6 | 2.48 ± 0.10 | 2.20 ± 0.10 | –11.3 | 0.075 |

Note: the number of animals was six per time interval for each control and potassium iodate-treated groups. All values are expressed as means ± SE. $p < 0.05$: significant.

### *6.2.2 Mortality rate*

The daily oral administration of potassium iodate at a dose of 150 mg $kg^{-1}$ body weight to albino rats for six weeks did not show any mortality.

**Figure 2** Serum thyroxin levels (µg $dl^{-1}$) in control and potassium iodate-treated (150 mg $kg^{-1}$ body weight) albino rats at different time intervals (see online version for colours)




The number of animals was six per time interval for each control and potassium iodate-treated groups.

**Table 3** Serum glucose levels (mg $dl^{-1}$) in control and potassium iodate-treated (150 mg $kg^{-1}$ body weight) albino rats at different time intervals

| *Experimental period (week)* | *Control* | *Potassium iodate* | *% difference* | *p value* |
|---|---|---|---|---|
| 1 | 96.4 ± 4.4 | 81.4 ± 2.6 | –15.6 | 0.015 |
| 2 | 109.8 ± 5.5 | 83.8 ± 3.7 | –23.7 | 0.003 |
| 3 | 108.4 ± 4.3 | 91.0 ± 3.3 | –16.1 | 0.009 |
| 4 | 109.8 ± 4.1 | 92.5 ± 2.4 | –15.8 | 0.004 |
| 5 | 106.1 ± 4.9 | 78.2 ± 4.2 | –26.3 | 0.002 |
| 6 | 98.5 ± 5.5 | 81.7 ± 4.1 | –17.1 | 0.035 |

Note: the number of animals was six per time interval for each control and potassium iodate-treated groups. All values are expressed as means ± SE. $p < 0.05$: significant.

## *6.3 Physiological and biochemical parameters*

### *6.3.1 Serum thyroxin*

The level of thyroxin (T4) increases in response to daily potassium iodate intake (Figure 2). Such hormonal change was significant only during the 2nd and 3rd weeks of the experiment ($p = 0.007$ and 0.046, respectively).

### *6.3.2 Serum glucose*

Table 3 showed significant decreases of mean glucose levels in potassium iodate-treated animals compared to controls, recording a maximum percentage difference of 26.3% at the fifth week of the experiment (mean = 106.1 ± 4.9 *v* 78.2 ± 4.2, $p = 0.002$).

### *6.3.3 Non-protein nitrogen constituents*

#### *6.3.3.1 Serum urea*

Table 4 pointed out that oral administration of potassium iodate lowered serum urea concentration with percentage decreases of 12.1, 23.1, 12.3, 23.6, 10.6 and 12.2% during the weekly intervals examined. However, this change was significant at the 2nd and 4th weeks of the experiment ($p = 0.009$ and 0.007, respectively).

#### *6.3.3.2 Serum uric acid*

As depicted from Table 5, daily treatment of animals with potassium iodate caused progressive increase in uric acid concentrations that reaches its maximum value of 25.4% at the end of the 5th week ($p = 0.011$). *Such elevation fall down at the end of the 6th week showing percentage increase of 13.3% (p = 0.080).*

#### *6.3.3.3 Serum creatinine*

The change of serum creatinine concentration upon potassium iodate intake was less than that observed with uric acid (Table 6). The increase in creatinine fluctuates across the experimental period reaching its maximum percentage of 19.6% at the end of the 4th week ($p = 0.022$).

**Table 4** Serum urea concentrations (mg $dl^{-1}$) in control and potassium iodate-treated (150 mg $kg^{-1}$ body weight) albino rats at different time intervals

| *Experimental period (week)* | *Control* | *Potassium iodate* | *% difference* | *p value* |
|---|---|---|---|---|
| 1 | 38.7 ± 2.0 | 34.0 ± 2.4 | –12.1 | 0.168 |
| 2 | 37.2 ± 2.2 | 28.6 ± 1.5 | –23.1 | 0.009 |
| 3 | 35.8 ± 2.3 | 31.4 ± 1.6 | –12.3 | 0.142 |
| 4 | 35.6 ± 1.8 | 27.2 ± 1.7 | –23.6 | 0.007 |
| 5 | 35.0 ± 1.8 | 31.3 ± 2.1 | –10.6 | 0.207 |
| 6 | 36.1 ± 2.1 | 31.7 ± 2.3 | –12.2 | 0.186 |

Note: the number of animals was six per time interval for each control and potassium iodate-treated groups. All values are expressed as means ± SE. $p < 0.05$: significant.

**Table 5** Serum uric acid concentrations (mg $dl^{-1}$) in control and potassium iodate-treated (150 mg $kg^{-1}$ body weight) albino rats at different time intervals

| *Experimental period (week)* | *Control* | *Potassium iodate* | *% difference* | *p value* |
|---|---|---|---|---|
| 1 | 1.78 ± 0.11 | 1.99 ± 0.14 | 11.8 | 0.277 |
| 2 | 1.93 ± 0.10 | 2.14 ± 0.13 | 10.9 | 0.233 |
| 3 | 1.83 ± 0.08 | 2.11 ± 0.10 | 15.3 | 0.047 |
| 4 | 1.74 ± 0.09 | 2.15 ± 0.11 | 23.6 | 0.017 |
| 5 | 1.77 ± 0.08 | 2.22 ± 0.12 | 25.4 | 0.011 |
| 6 | 1.95 ± 0.07 | 2.21 ± 0.11 | 13.3 | 0.080 |

Note: the number of animals was six per time interval for each control and potassium iodate-treated groups. All values are expressed as means ± SE. $p < 0.05$: significant.

**Table 6** Serum creatinine concentrations (mg $dl^{-1}$) in control and potassium iodate-treated (150 mg $kg^{-1}$ body weight) albino rats at different time intervals

| *Experimental period (week)* | *Control* | *Potassium iodate* | *% difference* | *p value* |
|---|---|---|---|---|
| 1 | 0.55 ± 0.03 | 0.59 ± 0.03 | 7.3 | 0.344 |
| 2 | 0.48 ± 0.01 | 0.53 ± 0.04 | 10.4 | 0.271 |
| 3 | 0.54 ± 0.02 | 0.59 ± 0.04 | 9.3 | 0.318 |
| 4 | 0.56 ± 0.03 | 0.67 ± 0.03 | 19.6 | 0.022 |
| 5 | 0.56 ± 0.02 | 0.62 ± 0.04 | 10.7 | 0.255 |
| 6 | 0.58 ± 0.04 | 0.65 ± 0.03 | 12.1 | 0.180 |

Note: the number of animals was six per time interval for each control and potassium iodate-treated groups. All values are expressed as means ± SE. $p < 0.05$: significant.

## 7 Discussion

Available studies on iodate toxicity are insufficient, restricted to retina and do not meet current standards of toxicity testing, mostly because they did not separate iodate-specific effects from the effects of an overdose of any form of iodine. Earlier studies reported some features and discrepancy of potassium iodate toxicity (Webster, Stohlman and Highman, 1966). The oral $LD_{50}$ of iodate varies in mice to be in the range of 500–1100 mg $kg^{-1}$ body weight (Burgi, Schaffner and Seiler, 2001). In rats, the oral $LD_{50}$ of potassium iodate is just recently estimated to be 675 mg $kg^{-1}$ body weight (Locklear and Ritter, 2003). On the light of the previous data and to determine the dose required for assessing iodate toxicity, it seems reasonably to determine the oral $LD_{50}$ of potassium iodate in male albino rats.

The recommended level of iodine in humans is between 20 and 80 mg $kg^{-1}$ of salt (equalling 28–110 mg iodate per kilogram of salt). Given a maximal daily salt intake of 15 g; this results in a low human exposure of at most 440–1700 mg of iodate per day (9–34 mg $kg^{-1}$ per day assuming body weights of 50–70 kg). The dose used here for the toxicity experiments was 150 mg $kg^{-1}$ body weight potassium iodate (1/5 $LD_{50}$), i.e. around five times higher than that recommended for humans.

Oral administration of potassium iodate (150 mg $kg^{-1}$ body weight) to albino rats generally caused significant decrease in the growth rate all over the experimental period of six weeks compared to control animals. Such reduction in the body weight may be a secondary result to increase thyroxin synthesis observed in this study as a result of potassium iodate administration. Thyroid hormones potentiate the respective stimulatory effects of epinephrine, norepinephrine, glucagon, cortisol and growth hormones on lipolysis provoking loss of adipose tissue. In addition, changes in carbohydrate and protein metabolism may also contribute to body weight reduction (Berne and Levy, 1998).

As discussed above, there was a general increase of serum thyroxin in response to potassium iodate treatment. This increase is probably attributed to excess iodate intake available to thyroid gland from continuous administration of potassium iodate. Elevation of thyroxin in rats upon administration of iodine or iodide was reported (Sherer, Thrall and Bull, 1991; Thrall, Sauer and Bull, 1992). Less increment in thyroxin levels noted in the last three weeks of the experiment may be induced by feedback mechanism exerted on the thyroid gland probably through the hypothalamus-pituitary axis (Sherer, Thrall and Bull, 1991). All the steps of the biosynthesis of thyroid hormones are stimulated by thyroid stimulating hormone and inhibited by excess iodine (Cavalieri, 1997).

The overt decrease of serum glucose recorded in potassium iodate-treated animals was in one way or another related to increase of thyroxin level. Thyroid hormones are known to stimulate almost all aspect of carbohydrate metabolism including rapid uptake of glucose by the cell. This action may be in part a secondary effect of increase insulin secretion induced by thyroid hormones (Guyton and Hall, 2006). In addition, oxygen consumption is increased by thyroid hormones leading to stimulate glucose oxidation. All these effect probably results in decreasing glucose level in blood (Berne and Levy, 1998; Larsen et al., 2003).

In our study, a dose of 150 mg $kg^{-1}$ body weight potassium iodate provoked general decrease in serum urea concentrations. The effect of iodine and its derivatives iodide and iodate on urea concentration in animals was monitored. In a comparative toxicity study

induced by iodine and iodide in rats (100 mg $l^{-1}$), it was concluded that the blood urea nitrogen values were relatively constant and did not vary much with treatment in compare with control group (Sherer, Thrall and Bull, 1991). In another study, an increase in urea nitrogen value in blood of experimental animals that given higher dose of iodide (164 mg animal $daily^{-1}$) for three weeks was reported (Fitzgerald, 2004). The discrepancy in such results and that presented in this study may be explained on the basis of different doses and experimental conditions and protocols used. Decrease in serum urea observed here may be due to impairment in its synthesis as a result of impaired hepatic function and/or due to disturbance in protein metabolism.

In contrast to urea, serum uric acid concentration was increased in potassium iodate-treated rats. Uric acid is the final breakdown product of purine metabolism. Purines, such as adenosine and guanine from tissue destruction, are converted into uric acid, primarily in the liver. Uric acid is transported in the plasma from the liver to the kidney, where it is filtered by the glomerulus (Ganong, 1997). Elevated plasma uric acid concentration is associated with increased catabolism of nucleic acid or decreased its excretion by kidney (Bishop, Fody and Schoeff, 2005). In general, elevated creatinine concentration is associated with abnormal renal function, especially as it relates to glomerular function (Bishop, Fody and Schoeff, 2005). Enhancement of thyroid hormones biosynthesis by potassium iodate administration is believed to decrease muscle mass which may lead to increase in serum creatinine followed by creatininurea (Ganong, 1997).

In conclusion, the oral $LD_{50}$ of potassium iodate in male albino rats was estimated to be 752 mg $kg^{-1}$ body weight. Administration of 150 mg $kg^{-1}$ body weight (1/5 $LD_{50}$) potassium iodate caused body weight loss. Serum thyroxin level was increased and serum glucose level was decreased. Urea concentration was decreased whereas uric acid and creatinine concentrations were increased. Consequently, one can say that potassium iodate at this dose level could be toxic. Further research is needed to test other different doses.

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