


# Evaluation of Rennessans (Iodine Complex Molecule) Safety in Human Beings: An Open-Labelled Clinical Study

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## Abstract

Extensive studies on evaluation of effectiveness/toxicity of different oral doses of iodine have not been explored yet. An open-labeled phase I clinical studies were conducted using iodine complex based research compound called Rennessans. Study groups were observed for development of any adverse/serious adverse events and alteration in laboratory values of vital organs, TSH and T4 hormones before and after the administration of the products. Out of 31 consented individuals, 24 healthy individuals participated in the study. Rate of occurrence of mild Adverse Events (AEs) in group A was 8.3% while in Group B it was 33.33% but these Adverse Events were self-resolving. After completion of study treatment blood serum iodine was reported to 3522.88 µg/l while mean urine iodine concentration (MUIC) was greater than 2000 µg/l. Hormonal and vital organ's testing revealed that all parameters of TSH and T4, LFT, CBC, RFT remained unaltered except from ALT-SGPT (*P-value* = .006) and AST-SGOT (*P-value* = .02). From all of these findings, it can be inferred that the use of Rennessans formulations did not pose any sort of risk to human body and can be considered safe through this pilot study.

## Keywords

Renessans, iodine complex, potassium iodide, phase I clinical study, healthy volunteers

## Introduction

Iodine is vital for thyroid hormones synthesis. These hormones play important role in metabolism, growth and different body functions.<sup>1</sup> Deficiency of these hormones may cause goiter, hypothyroidism, abortion, stillbirth, congenital abnormalities, prenatal mortalities of fetus, and impaired mental health.<sup>2</sup> Whereas, its abundance can also lead to goiter or increase in thyroid volume due to failure of homeostatic function of body, an overt hypothyroidism, thyroid autoimmunity, iodine-induced hyperthyroidism, and Grave's disease.<sup>3</sup>

In human beings, it is present in quantity of 15–50 mg of which almost 80% resides in thyroid gland. The total daily requirement for iodine intake in adults is about 150 µg/day,<sup>4</sup> whereas upper limit for its use is 1100 µg/day according to US Food and Nutrition Board of Institute of Medicine. The upper limit is defined as the quantity of iodine which does not pose

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any risk or damage to human body. However, doses above upper threshold are also well tolerated in body.<sup>2</sup> The main source of iodine comes from diet rich in iodine like seaweed, seafood, milk, and iodine salts.<sup>5</sup>

The ingested iodine is mainly absorbed in the intestine<sup>1</sup> where more than 90% of the absorbed iodine is excreted from the body through urine within 12–24 hours.<sup>5</sup> Usually, the iodine required for removal of iodine deficiency is taken in the form of sodium or potassium salts of iodine or iodates. When used within limits, the use of iodine in these forms of salts is considered safe and has no negative effect on human body.<sup>6</sup> However, when an excess amount of the iodine is consumed, different auto-regulated compensatory mechanisms are switched on inside human body to keep balance of the iodine for proper functioning of thyroid. The amount of iodine taken by thyroid gland not only depends upon iodine intake but also on the intra-thyroid iodine concentration. At a normal or low dose of iodine, the production of T3 and T4 corresponds to the intake of the iodine. However, at dose above the normal level, thyroid intake of iodine may decrease but, the process of organification may increase due to presence of abundant intra-thyroid iodine.<sup>7</sup> At very large doses, excess iodine may stop production of thyroid hormones and this phenomenon is called as “Wolff-Chaikoff Effect.”<sup>8</sup> In addition to this, Eftychia *et al.*,<sup>7</sup> (2017) narrated that thyroid may adopt different protective mechanism in presence of excessive iodine in which “thyroid auto-regulation” is one of them.<sup>7</sup> In this process, thyroid gland regulates iodine metabolism independent of TSH and other hormonal or physiological factors. This help to maintain normal thyroid function without being affected by fluctuation of daily iodine intake.

Iodine and its complexes with different salts like potassium iodide, sodium iodide, and povidone-Iodide are well known for their antibacterial and antiviral effects.<sup>9-11</sup> Micro Technologies of Iodine Medical Private Limited (MTI Medical Pvt. Ltd) organization has developed a research product named as *Renessans* having iodine complex comprising iodine (100 mg), potassium iodide (143 mg), and ascorbic acid (5 mg). Although, the *Renessans* product in varying strengths has tested and found effective previously<sup>12</sup>; however, structured safety evaluation is yet to be performed. The aim of the current study was to analyze the safety profile of 2 dosage forms of *Renessans* in healthy individuals by observing adverse event and impairment/malfunctioning of human body organs. If the safety is established, these formulations could become a readily available rich source of micronutrients particularly for iodine deficient patients. Because iodine has antimicrobial properties,<sup>4</sup> these products may pave the path for oral pharmacotherapy for bacterial, viral, or other types of infections, as iodine acts generically against such infections. The significance of this discovery gains importance as iodine in these formulations is widely available and inexpensive, whereas the production of such medicaments is also cost-effective.

## Research Methodology

The study was conducted in accordance with the International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice [GCP-E6 (R2)], local and ethical guidelines of respective institutes for the research in human beings.

The protocol and other essential documents were submitted and approved by Ethical Committee of University of Lahore (Letter ref. no. IREC-2021-12 H dated: 30Aug2021), Lahore General Hospital (Letter ref. no. 00-118-20, dated 11Sep2020), National Bioethical Committee (NBC) of Pakistan (Letter ref. no.4-87/COVID-34/NBC/20/297, dated: 10 Sep 2020) and Drug Regulatory Authority of Pakistan (DRAP) (Letter ref. no. F. No.03-47/2020-DD (PS), dated: 19Oct2020).

## Clinical Setting

Research was conducted at Lahore General Hospital, Post Graduate Medical Institute Lahore, Punjab, Pakistan, which is located at Ferozpur Road, Ismail Nagar, Lahore, Punjab, 54000

**Study Design.** The study design was an open labeled phase I clinical study in which healthy volunteers coming to Lahore General Hospital were included in the study. There were 24 healthy volunteers enrolled in the study comprising of 12 males and 12 females, who were divided randomly into two groups, that is, group A having 12 participants (6 males and 6 females) and group B having 12 participants (6 males and 6 females). The study participants were enrolled in almost 2 months of time and this safety study was completed in 3 months including their all follow-up visits. The participants were included in the study with the following inclusion and exclusion criteria as shown in [Figure 1](#):

## Inclusion Criteria

The volunteers aged 18 years or above years, willing to give consent for participation in the study at their own will and follow study procedures throughout experiment, and were enrolled in the study. Participants showing absence of any health issues during clinical examination and through medical history were selected for inclusion in the study. Females with childbearing potential were included in the study only on the basis of negative pregnancy test and they agreed to use contraceptive methods during entire duration of the study.

## Exclusion Criteria

All those participants who had co-morbidities such as any pre-existing cardiac or pulmonary disease, diabetes, arrhythmias, pre-existing hepatic or renal disease, or thyroid dysfunctions were not included in the study. Also, those female who were

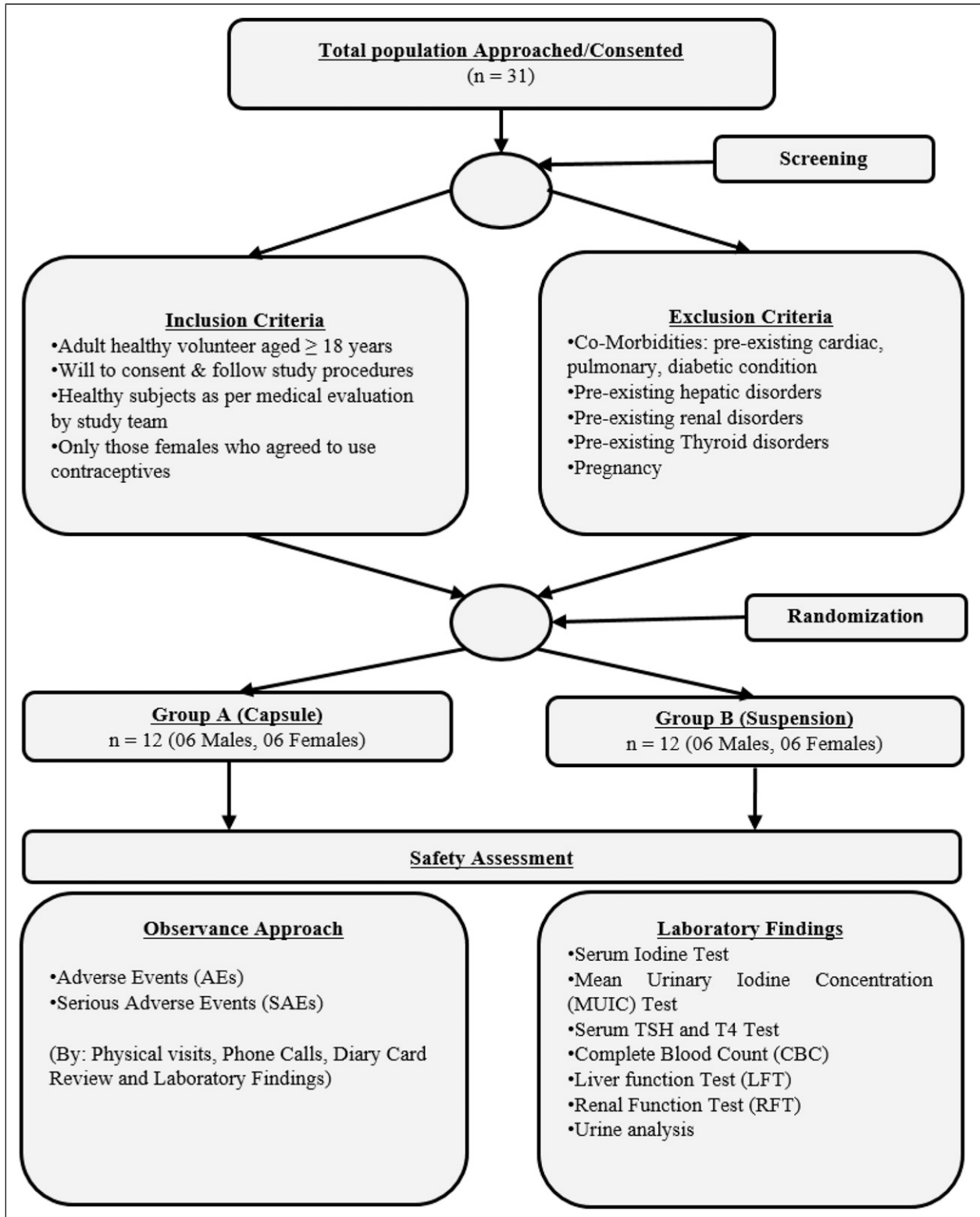


Figure 1. Flow Chart of Inclusion/Exclusion Criteria and study procedures.

**Table 1.** Timelines of Biochemical Test in Phase I Clinical Study.

Tests with timelines					
Sr no	Before the Dose	3rd day	6th day	21st day	6 <sup>th</sup> week
1	CBC			CBC	
2	LFTs			LFTs	
3	RFTs			RFTs	
4	Urine Analysis			Urine Analysis	
5	ECG			ECG	
6	X-ray			X-ray	
7		*MUIC	MUIC	MUIC	
8			Serum iodine test		
9	Serum TSH			Serum TSH	Serum TSH
10	Serum Free T4			Serum Free T4	Serum Free T4

Abbreviation: CBC: Complete Blood Count, LFTs: Liver Function Test, RFTs: Renal Function Test, ECG: Electrocardiogram, TSH: Thyroid Stimulating Hormone, MUIC: Mean Urinary Iodine Concentration.

either pregnant or planned to become pregnant in near future were not included in the study.

### Informed Written Consent

The participants provided their free informed consent to participate in the studies as per inclusion and exclusion criteria. The document has complete information about the study, participant's role and responsibility, risk associated with participation, confidentiality, and participant's right to withdraw from the study. It was clearly stated that participants had right to withdraw their consent at any time during the study.

### Data Collection

A comprehensive case report (CRF) form was developed for the collection of essential data in an organized manner. This CRF was approved by the concerned ethical committees; National Bioethical Committee (NBC) and the DRAP. Patient progress notes, lab reports, and case reports forms served as primary source data for the study. On CRF, questions related to demographics of the patients, vital sign measurements, medical history, physical examination, electrocardiogram, and other information related to adverse event and serious adverse events were collected on different timelines as per studies plan.

### Procedure

Healthy volunteers were offered consent form for participation in the study. After they consented, the data related to demographics and medical history was evaluated as per inclusion/exclusion criteria. Baseline tests including electrocardiogram (ECG), blood chemistry, liver and renal function test, and urine analysis was done only for study subjects. Those participants who passed screening test were divided randomly into group A and group B where Group A received Renessans capsule (equivalent to 200 mg of iodine) and Group

B received Renessans suspension 40 ml (equivalent to 200 mg of iodine) three times a day orally for five days. Enrolled volunteers were admitted in hospital's specialized care unit for five days where Renessans products were administered to provide continuous care to the participants and monitor any change in their health status. The participants were provided with normal diet but it was ensured that this diet did not contain excess of iodine since oral diet rich in iodine can affect its level in the body. Laboratory tests and information regarding any adverse event was collected on specified timelines as outlined in Table 1 and evaluated against the predefined criteria of adverse/serious adverse events (Annexure-A). After day-05, volunteers went back to their home and diary card was provided to note any change in their health status. These volunteers were called again to hospital on day-21 and 6th week after administration of Renessans products for comparative analysis and health status of volunteers. In the final analysis, the data of those participants who did not qualify inclusion/exclusion criteria was excluded.

### Safety Assessment

Safety assessment was done by evaluating the development of adverse event or serious adverse event and observing laboratory tests conducted on the enrolled subjects.

### Development of Adverse Event or Serious Adverse Event

One of the primary focus of safety assessment was to evaluate the occurrence of adverse event or serious adverse after the administration of the product. It was done by examining the participating subjects on every visit and reviewing their diary cards provided to them to note any health illness on it when they are at home.

**Safety assessment through laboratory findings:** Safety assessment of subjects was also evaluated through laboratory

tests and any change in the normal laboratory values. For this purpose, following tests were conducted:

### *Laboratory Test of Specific Interest*

**Serum Iodine Concentration Test:** This test is performed to evaluate iodine concentration in the blood serum. In the current study, it was performed on day-06 morning, that is, immediately after finishing 5 days' treatment of *Renessans* product.

**Mean Urinary Iodine Test (MUIC):** MUIC test is well accepted and readily available biomarker to check iodine status in humans since the drug is largely excreted by urine.<sup>13</sup> It was performed at three time frames, that is, on day-03, day-06, and lastly on day-21 to evaluate the iodine status during, immediately after finishing, and washout period of *Renessans* administration.

**Serum TSH and T4 Test:** *Renessans* product has high concentration of iodine. When ingested, it can affect the normal TSH and T4 functioning as iodine regulate these two hormones.<sup>7</sup> For this purpose, serum TSH and T4 test were conducted on three time frames, that is, on day-0, day-21, and on 6th week.

### *Laboratory Tests to evaluate vital function of body*

**Complete Blood Count:** This is a most commonly prescribed laboratory test to provide information blood cells which include red blood cells (RBC), hemoglobin, and hematocrit. Also, it gives information about white blood cells (WBC) which is indicator of immunity. This test helps in diagnosis of anemia, infections, allergies and different blood related complications.<sup>14</sup> In the current study, the test was performed on day-0 and day-21.

**Liver Function Test:** This test is a helpful screening tool to access the liver function. Since liver has to perform different biochemical processes including metabolism, synthesis, complexation, and excretion, this test may provide preliminary picture of liver malfunctioning, but this test alone may not be sufficient for clinicians to reach final diagnosis.<sup>15</sup> Bilirubin, conjugated bilirubin, unconjugated bilirubin, ALT-SGPT, AST-SGOT, gamma GT, protein, albumin, and globulin were observed before and after administration of *Renessans* product, that is, on day-0 and day-21.

**Renal Function Test:** This test is used to assess the normal functionality of the kidney. Most commonly used biomarkers are serum creatinine, serum urea, and serum blood urea nitrogen (BUN). Any deviation from the normal values of the stated biomarkers provide hint about kidney malfunctioning or related diseases.<sup>16</sup> In the current study, the test was performed before and after the administration of the product, that is, on day-0 and day-21.

**Urine Analysis:** It is an ancient diagnostic screening test which helps clinicians to obtain initial information about

urological function. It may also provide valuable information of kidney, liver, or other metabolic diseases.<sup>17</sup> To know the effect of *Renessans* product on urine chemistry, we performed urine analysis on day-0 and day-21.

### *Statistical Analysis*

R software (version 4.1.2/1) was used for statistical analysis. Data being represented here is given in terms of mean  $\pm$  SD (Standard Deviation). Laboratory finding before and after the administration of the drug was done using pair t-test through R by considering 95% confidence interval. Whereas significance of serum TSH and free T4 was evaluated through analysis of variance (ANOVA) where these values were compared at the start of medication, during the medication and after the medication. Adverse event and serious adverse events were estimated in percentage of occurrence in enrolled population using Microsoft excel 2016.

## **Results**

### *Demographics and Clinical presentation*

Thirty one healthy volunteers were approached for study participation and out of these 24 volunteers remained in the study and completed their required visit till 6th week as per the study plan. From the 7 volunteers who could not become the part of the study, 2 individuals withdrew their consent and five individuals were found to not meet the study protocol. The summary of demographic details of Group A and Group B are given in [Table 2](#).

### *Serum Iodine*

After taking *Renessans* products (capsule and suspension) three times a day for five days, [Table 3](#) serum iodine concentration was found to be as following for all enrolled subjects:

### *Urinary Iodine Test*

The testing equipment available in Pakistan had a limitation of allowing detection of urine concentration up to 2000  $\mu\text{g/l}$  so the results are shown here with qualitative statement in [Table 4](#). Whereas, on day-21, the results obtained were lesser in quantity than 2000  $\mu\text{g/l}$  that is why its results are mentioned in numeric form in [Table 5](#).

### *Occurrence of Adverse Event and Serious Adverse Events*

Evaluation of patient safety through the occurrence of any adverse event or serious adverse event was one of the study's main objectives. Therefore, predefined list of adverse events was developed before the start of study attached as Annexure-A. From the 24 enrolled subjects who took *Renessans* products three

**Table 2.** Demographic Details of participants of Group A and Group B

	Group A – Renessans capsule (n=12)	Group B – Renessans suspension (n=12)
<b>Mean Age (years)</b>	36.7	30.06
<b>Median</b>	34 (29–49)	28 (23–41)
<b>Sex (Male/Female)</b>	6/6	6/6

**Table 3.** Serum Iodine Test Results.

Product	Normal range of serum iodine ( $\mu\text{g/l}$ )	Mean $\mu\text{g/l}$	SD	Minimum $\mu\text{g/l}$	Maximum $\mu\text{g/l}$
Renessans (capsule and suspension)	30.48–80.01	3522.88	1703.21	574	7074

**Table 4.** MUIC Test Results in Healthy Volunteers.

Product	Normal range of MUIC ( $\mu\text{g/l}$ )	Day-3 ( $\mu\text{g/l}$ )	Day-6 ( $\mu\text{g/l}$ )	Day-21 mean ( $\mu\text{g/l}$ )
Renessans (capsule and Suspension)	100–199	>2000	>2000	188.75

**Table 5.** MUIC Test Results on Day-21.

Product	Normal range of MUIC ( $\mu\text{g/l}$ )	Mean ( $\mu\text{g/l}$ )	SD	Minimum ( $\mu\text{g/l}$ )	Maximum ( $\mu\text{g/l}$ )
Renessans (capsule and Suspension)	100–199	188.75	279.27	19.6	1420

**Table 6.** Summary of Adverse Events reported in Phase-I study.

Subject Number	Group A	Group B	Type of adverse event	Outcome
A0002	✓		Burning of mouth, throat and stomach	Resolved
B0001		✓	Burning of mouth, throat and stomach	Resolved
B0003		✓	Burning of mouth, throat and stomach	Resolved
B0004		✓	Burning of mouth, throat and stomach	Resolved
B0010		✓	Burning of mouth, throat and stomach	Resolved

Assessment of safety of organs through laboratory tests.  
Hematological assessment through Complete Blood Count.

times a day for five days, only five patients experienced Adverse Event which fell in the category of “Burning of Mouth, throat and Stomach” from the established list. However, all adverse events were self-resolving and did not require any medical treatment for its resolution. Collectively, occurrence of the adverse event remained 20.83% among 24 healthy volunteers from both groups of the study. It was interesting to note that, the occurrence of adverse event was much higher in Group B, that is, 33.33%, in comparison of Group A which was 8.33%. It is noteworthy, that there had been no Serious Adverse Event reported in any group of the study. The summary of adverse events is described in [Table 6](#).

Effect of Renessans formulations (suspension and capsule) on hematological profile of all subjects determined through Complete Blood Count before and after the administration of the drug is given in [Table 7](#).

### *Liver Function Test of Healthy Volunteers*

The liver’s bilirubin, conjugated bilirubin, unconjugated bilirubin, ALT-SGPT, AST-SGOT, gamma GT, proteins, albumin, and globulin were measured through Liver Function Test (LFT) on day-0 and day-21 before and after administration of the Renessans products. The test was carried out to determine the effect of iodine intake on the normal function of the liver using the earlier stated biomarkers. The results obtained and their reference values are mentioned in [Table 8](#).

### *Renal Function Test of healthy Volunteers*

Renal Function Testing was carried out to assess the effect of iodine on normal urological function using serum urea, BUN, and creatinine indicators, as any imbalance in these parameters

**Table 7.** Complete Blood Count Test Results.

Complete blood count test				
Indicators with reference Values	Before (mean $\pm$ S.D.)	After (mean $\pm$ S.D)	Paired t-test	P-value
RBC				
Male: 4.5–6.5 $\times 10^{12}/l$	5.30 $\pm$ .793	5.20 $\pm$ .84	–1.5574	.133
Female: 4–6 $\times 10^{12}/l$				
HCT				
Male: 38–52%	43.6 $\pm$ 4.42	43.2 $\pm$ 4.18	–.83803	.4106
Female: 36–46%				
MCV				
Male & Female: 75–95 fl	83.2 $\pm$ 8.87	83.7 $\pm$ 9.04	1.2196	.235
MCH				
Male and Female: 26–32 pg	27.6 $\pm$ 3.67	27.9 $\pm$ 3.29	1.2383	.2281
Hb				
Male: 13–18 g/dl	14.4 $\pm$ 1.55	14.1 $\pm$ 1.81	–1.2638	.219
Female: 11.5–16 g/dl				
MCHC				
Male and Female: 30–35 g/dl	32.96 $\pm$ 1.68	32.7 $\pm$ 1.25	–.723	.477
Platelets				
Male and Female: 150–400 $\times 10^9/l$	331 $\pm$ 93.8	302 $\pm$ 101	–1.297	.2075
WBC				
Male and Female: 4–11 $\times 10^9/l$	8.21 $\pm$ 2.04	11.7 $\pm$ 18.16	.80461	.4293
Neutrophils				
Male and Female: 40–75%	59.8 $\pm$ 6.52	60.7 $\pm$ 7.01	.65119	.5214
Lymphocytes				
Male and Female: 20–50%	31.0 $\pm$ 6.18	30.2 $\pm$ 7.10	–.64754	.5237
Monocytes				
Male and Female: 02–10%	5.96 $\pm$ 1.83	6.29 $\pm$ 1.68	.94054	.3567

RBC=Red Blood Cells, HCT= Hematocrit, MCV= Mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin, MCHC= Mean Corpuscular Hemoglobin Concentration, WBC= White Blood Cells.

indicates renal malfunction. The parameters were observed in both groups of the study before and after administration of Renessans products. Table 9 shows the obtained results with reference values.

### Urine Analysis

Urine analysis was performed before and after the administration of the investigational product. Table 10 provides results of quantifiable elements of the analysis, whereas Table 11 provides summary of the qualitative elements of the urine analysis.

Because iodine is primarily excreted through urine, urine analysis was performed before and after the use of study drugs in both groups of the study. Quantifiable parameters such as specific gravity and urine pH were assessed and reported in Table 10, whereas qualitative parameters such as color, turbidity, the presence of glucose, ketones, proteins, hemoglobin, urobilinogen, bilirubin, nitrates, leukocytes, pus cells, red blood cells, epithelial cells, amorphous cells, organisms, yeasts, and crystals were also measured to see if there was any change that could indicate the effect of Renessans on urine

composition. The qualitative parameters obtained before and after the use of study drugs are reported in Table 11 with their reference characteristics and ranges. However, we did not find any difference in either quantifiable or qualitative elements of urine analysis after study drug administration.

### Effect of Iodine Concentration on Serum TSH and T4 Test

Serum TSH and T4 were determined at three time frames: on day-0 before the administration of Renessans, on day-21 after administration of the drug, and on 6th week at the end of study. The outcome of the observations is displayed in Table 12 and 13.

### Discussion

In human beings, iodine and its other salts remain in quantity of .02 mg/kg of the body weight or roughly it can be said 15–20 mg<sup>6</sup>(7). Except from the radioactive form of iodine which is used for diagnosis purposes, different studies have reported that iodine and its salts are safe for human use even in high

**Table 8.** Liver Function Test Results.

Liver function test				
Indicators with reference Values	Before (mean ± S.D)	After (mean ± S.D)	Paired t-test	P-value
Bilirubin				
Male: .10–1.20 mg/dl	.596 ± .341	.659 ± .559	.69251	.4956
Female: .1–.9 mg/dl				
Conjugated bilirubin				
Male: up to .30 mg/dl	.238 ± .106	.242 ± .114	.21384	.8326
Female: <.5 mg/dl				
Unconjugated bilirubin				
Male and Female: .10–1.00 mg/dl	.362 ± .25	.321 ± .182	–1.1096	.2786
ALT-SGPT				
Male: up to 45.00 U/L	36.5 ± 18.7	29.6 ± 15.2	–2.9968	.0064
Female: < 34.00 U/L				
AST-SGOT				
Male: up to 35.00 U/L	32.6 ± 15.0	26.0 ± 6.64	–2.401	.02483
Female: < 31.00 U/L				
Gamma GT				
Male: up to 55.00 U/L	27.1 ± 12.2	27.1 ± 10.9	.00	1
Female: < 38.00 U/L				
Total protein				
Male and Female: 6.00–8.50 g/dL	7.67 ± .412	10.5 ± 14.0	.98137	.3366
Albumin				
Male and Female: 3.50–2.50 g/dL	4.18 ± .282	5.46 ± 6.51	.95426	.3499
Globulins				
Male and Female: 1.80–3.50 g/dL	3.51 ± .496	3.51 ± .46	.089755	.9293

ALT-SGPT= Serum Glutamic-pyruvic transaminase, AS-SGOT= Serum Glutamic-oxaloacetic transaminase, Gamma GT= Gamma-Glutamyl Transpeptidase.

**Table 9.** Renal Function Tests Results.

Renal function test				
Indicators	Before (Mean±S.D.)	After (Mean±S.D.)	Paired t-test	P-value
Serum Urea				
Male and Female: 10–50 mg/dL	20.1 ± 4.96	21.2 ± 5.50	.90501	.3748
Serum BUN				
Male and Female: 08–22 mg/dL	9.29 ± 2.44	9.71 ± 2.84	.62184	.5402
Serum creatinine				
Male: .72–1.25 mg/dL	.732 ± .188	.751 ± .257	.44043	.6637
Female: .6–1.11 mg/dL				

BUN= Blood Urea Nitrogen.

**Table 10.** Urine Analysis Results of Quantitative Parameters.

Urine analysis				
Indicators	Before (Mean±S.D)	After (Mean±S.D)	Paired t-test	P-value
Specific gravity				
1.005 to 1.030	1.03 ± .0059	1.02 ± .00658	–1.7325	.09658
Urine pH				
4.5–7.8	5.79 ± .487	5.83 ± .620	.3366	.7395



**Table 11.** Urine Analysis Results Qualitative Parameters.

Sr No	Descriptive indicator	Reference normal results	Results obtained
1	Urine color	Yellow	Within reference ranges for all 24 subjects
2	Turbidity	Nil	
3	Glucose	Nil	
4	Ketones	Nil	
5	Proteins	Nil	
6	Hemoglobin	Nil	
7	Urobilinogen	Normal	
8	Bilirubin	Nil	
9	Nitrites	Negative	
10	Leukocytes	Nil	
11	Pus cells	1–6 (Range)	
12	Red blood cells	Nil	
13	Epithelial cells	1–4 (Range)	
14	Amorphous cells	Nil	
15	Casts	Nil	
16	Organisms	Nil	
17	Misc	Nil	
18	Yeas	Nil	
19	Crystals	Nil	

**Table 12.** Serum TSH Test Results.

Parameters	(Mean $\pm$ S.D.) Day-0 ( $\mu$ IU/mL)	(Mean $\pm$ S.D.) Day-21 ( $\mu$ IU/mL)	(Mean $\pm$ S.D.) 6th week ( $\mu$ IU/mL)	F value	P-value
Serum TSH					
Age (21–54 years) .4–4.2 $\mu$ IU/mL	1.53 $\pm$ .76	1.46 $\pm$ .81	1.53 $\pm$ .92	1.002	.372

**Table 13.** Serum T4 Test Results.

Parameters	(Mean $\pm$ S.D.) Day-0 (ng/dL)	(Mean $\pm$ S.D.) Day-21 (ng/dL)	(Mean $\pm$ S.D.) 6th week (ng/dL)	F Value	P-value
Serum T4					
Age (20 and above years) .8–2.7 ng/dL	.93 $\pm$ .10	.91 $\pm$ .06	.93 $\pm$ .06	.796	.455

doses. However, there is not much literature available on its safety evaluation.<sup>3,4</sup> Burgi *et al.*, (2001) conducted a study in mice to check lethal dose of iodine and from that he referred that adverse drug reaction due to iodine can occur in human beings at dose of 100 mg/kg of iodate.<sup>5</sup> Mao *et al.*, (2011) wrote that mean lethal dose in human beings maybe 2–4 g in a day; however, toxicity due to iodine in human is very infrequently reported till date.<sup>18</sup> The investigational product *Renessans* (equivalent to 200 mg of iodine) was administered in healthy volunteers three times a day for five days in two dosage forms i.e. suspension and capsule separately. So a total 600 mg/day was given to the individuals in this study. The average

serum concentration in 24 healthy volunteers was evaluated to be 3522.88  $\mu$ g/l after *Renessans* use in the current study, whereas, normal reference range in literature was found to be 30.48–80.01  $\mu$ g/l in human beings.<sup>18</sup> In this study, high serum concentration of iodine drug in human serum was well tolerated by the volunteers as there was no significant change observed at metabolic or physical level in all the individuals. High dose of iodine has strong influence on hormones like TSH and T4;<sup>3</sup> however, in the current studies, the serum TSH and T4 remained within reference normal ranges of TSH (age 21–54 years) .4–4.2  $\mu$ IU/mL and T4 (age 20 and above years) .8–2.7 ng/dL before and after the use of *Renessans* (Table 12 and 13).

There had been no significant change ( $P = .372$ ) observed in TSH values at day-21 (mean value  $1.46 \mu\text{U/mL}$ ) and 6th week (mean value  $1.53 \mu\text{U/mL}$ ), compared to day-0 values of TSH (mean value  $1.53 \mu\text{U/mL}$ ) when measured statistically. Similarly, T4 values at day-21 ( $.91 \text{ ng/dL}$ ) and 6th week ( $.93 \text{ ng/dL}$ ) were not statistically significantly different ( $P = .455$ ) from the Day-0 ( $.93 \text{ ng/dL}$ ) when *Renessans* products were not taken by any group. This non-significant change in TSH and T4 functioning may be due to “Wolff-Chaikoff Effect”<sup>4</sup> where the synthesis of thyroid hormones are inhibited due to presence/exposure to high dose of iodine. Also, potassium iodide might have played its role in regulating iodine organification by influencing  $\text{Na}^+\text{-I}$  symporters where  $\text{K}^+$  acts to regulate  $\text{Na}^+$  import and export through  $\text{Na}^+\text{-I-K}^+\text{ATPase}$  for iodine transport into the cells.<sup>6</sup> In addition to that thyroid auto-regulation might have been another reason as Eftychia *et al.*, (2017) stated that thyroid gland may adopt this procedure as one of the other protective mechanisms when thyroid senses high iodine in the body.<sup>7</sup> This auto-regulation of thyroid gland is independent of TSH functioning and thus it keeps balance of hormone production irrespective of fluctuation in iodine and TSH levels.

Urine iodine concentration test is one of most cost effective, well-accepted, and easy to perform test which is used as a biomarker to check the iodine level in body.<sup>3,19</sup> In a healthy person, almost all of orally taken iodine is absorbed from intestine and more than 90% of it is excreted in urine within 12–24 hours.<sup>3,4,20</sup> For accurate measurement of iodine excretion, 24-hour measurement is required which is not a practical approach so instead a spot urine test from a given population is performed and expressed as median urinary iodine concentration.<sup>4,19,20</sup> According to WHO-Iodine Nutrition Epidemiologic Criteria, population mean urinary iodine concentration is considered adequate in the range of 100–199  $\mu\text{g/l}$  for children and adults. Whereas, 200–299  $\mu\text{g/l}$  and 300  $\mu\text{g/l}$  or above is considered as above the requirement and excessive iodine intake, respectively.<sup>19</sup> In the current study, patients were given approximately 600 mg/day of iodine for five days and their mean serum iodine concentration was 3522.88  $\mu\text{g/l}$  on sixth day whereas, the median urinary iodine concentration (MUIC) on day-3 and day-5 was observed to be greater than 2000  $\mu\text{g/l}$  of iodine for both groups of the study. However, when a washout period of almost 14 days was passed, the mean concentration was found to be 188.75  $\mu\text{g/l}$  on 21st day. Our findings are very much aligned with the available literature that high iodine urinary concentration was noticed within 12–24 hours of iodine intake and after a washout period of 21 days, individuals depicted normal iodine excretion. This means, that almost all of the excessive administered iodine had been excreted out of body and a normal range of iodine was attained in urine of healthy individuals on 21st day and there had been no side effects noticed in the healthy individuals.

The data obtained from our Phase-I study suggested that Iodine Complex based *Renessans* product had a fairly safe profile. Healthy volunteers after using *Renessans* formulations (suspension and capsule) three times a day for five days did not develop any Serious Adverse Event (SAE). Whereas, only 5 out of 24 subjects experienced Adverse Event (AE) which were self-resolving and related to change in taste or burning sensation in mouth, throat or stomach category. There is scarcity of literature where iodine safety is evaluated in human beings when it is used orally, however, Frank *et al.*, (2020) also narrated safe nature of iodine–povidone complex when used in nasal and oral cavities for COVID-19 patients.<sup>21</sup> It is noteworthy that in our study, the occurrence of Adverse Events remained considerable high in Suspension Group (Group B), that is, 33.33% in comparison of Capsule group (Group A), that is, 8.33%. This may be because of the fact that in suspension dosage form, the iodine was directly in contact with mucosal membrane when it was administered in the patient whereas in capsule dosage form, the iodine would be released after the capsule shell had undergone disintegration in gut. Also, the fact that the drug in oral liquid dosage forms (syrup or suspension) is readily available and lesser taste masked due to which characteristic taste of iodine (metallic to acidic)<sup>22,23</sup> was observed in Group B.

When iodine is ingested, human cells are exposed to the iodine and its salts which are developed in body fluids. These iodine salts attain oxidizing power due to which they may penetrate cell membrane and destroy cells of host resulting in human intravascular hemolysis. Mao *et al.*, (2011) narrated incidence of 30-year healthy male in which hemolysis occurred after his suicidal attempt with the ingestion of 200 ml iodine tincture where the blood serum iodine concentration was found to be 1,155,901  $\mu\text{g/l}$ .<sup>18</sup> Whereas, in the present study, mean serum iodine concentration was observed 3522.88  $\mu\text{g/l}$  and mean urinary iodine concentration was above 2000  $\mu\text{g/l}$  but still no change in the blood chemistry observed for RBC, HCT, MCV, MCH, platelets, WBC, Neutrophils, Lymphocytes and Monocytes. The “*p*” value greater than .05 in Table 7 for complete blood count showed insignificant change in the above-mentioned blood components before and after the administration of the *Renessans* product. This is a clear indication that blood cells had well tolerated high concentration of iodine in blood serum which is aligned with the literature.<sup>3,18,24</sup>

Liver Function Test is an effective screening tool providing early information about liver health but it does not provide gold-standard diagnosis of liver diseases.<sup>15</sup> Effect of *Renessans* on liver function was assessed through this test in which bilirubin, conjugated bilirubin, unconjugated bilirubin, ALT-SGPT, AST-SGOT, Gamma GT, protein, albumin, and Gglobulin were tested before and after the administration of the product. Except for ALT-SGPT and AST-SGOT, all of the

parameters observed in the test remained within their referenced normal ranges (Table 8). The “p” value of these biomarkers were also greater than .05 which indicated that there was no significant change occurred in these after the use of study medication. In literature, there is no reference data found which can tell effect of iodine or its complexes at the experimental dose in human beings; however, Sani *et al.*, (2021) narrated that they also did not observed significant change in liver biochemistry when they used 2000 mg/kg povidone iodine in cockerels.<sup>25</sup> There is also a similarity between Sani *et al.*, (2021) and the current study in that both studies observed an increase in the values of the studied parameters of this test when iodine was used, despite the fact that they remained within their normal reference ranges. On contrary to all other parameters, serum ALT-SGPT and AST-SGOT had significant changes where the “p” value of ALT-SGPT was .006 and ALT-SGOT was .024. It happened because there were five volunteers who had ALT-SGPT and AST-SGOT values out of range at the time of study induction; however, these values did not impose any health issue and the volunteers were evaluated and considered healthy for study participation as per investigational team opinion. Interestingly, when their test was repeated on day-21, two subject’s ALT-SGPT and AST-SGOT values came in normal ranges. So the significant result of these two indicators were considered as an independent event because the subjects had out of range values at the start of the study and it was not related with the use of investigational product as evaluated by the investigators. Mao *et al.*, (2011) mentioned that after poisoning with iodine tincture 200 ml (serum iodine concentration 1,155,901 µg/l),<sup>18</sup> the subject showed higher bilirubin, conjugated bilirubin, ALT and AST values, but this might be due to injury associated with alcohol as there was no relationship established by author in that case study. Also, Burgi *et al.*, (2001) mentioned that very high dose of iodine may result in hepatic injury in animal<sup>6</sup> but there had not been any details for this finding. Whereas, the current study revealed that a dose up to serum concentration of 3522.88 µg/l did not produce effect on liver functioning. This is in alignment with the results of a study in which “p” value remained insignificant for ALT, AST, total bilirubin, and direct bilirubin when 150 µg/day iodine supplement was given orally for 90 days. The metabolism of iodine takes place in thyroid gland in human beings and the fluctuation of iodine in blood modulate the release and functioning of thyroid hormone (T3 and T4) in connection with TSH hormone whereas the metabolism of T3 and T4 take place in liver.<sup>26</sup> In the current study, an insignificant change was evaluated in levels of TSH (P = .372) and T4 (P = .455), so there was diminutive chances that liver functions are effected by the Rennsans product.

On an average, a human body excretes 480 µg of iodine in urine and almost 20 µg in stools.<sup>26</sup> Whereas, 90% of ingested iodine is excreted through urine within 12–24 hours.<sup>3,4,19</sup> In the instant study, it has also been observed that median urinary iodine concentration became normal when it was checked on day 21 (mean 188.75 µg/l) whereas it was greater than

2000 µg/l on day-06 which meant that iodine was largely excreted via urine and achieved its normal state in the body without disturbing any kidney function measured through renal function test. In this test serum urea, serum BUN and serum creatinine were evaluated and found within normal reference ranges before and after the use of Rennsans (Table 9). The “p” values of serum urea (.3748), serum BUN (.5402) and serum creatinine (.6637) also remained greater than .05 which meant that there had been no change observed in these kidney bio-indicators. This is in contrary to a case reported by Kim *et al.*, (2017) in which a 47-year-old person had poisoning of 10% povidone–iodine and his serum BUN reached and creatinine reached up to level of 124 mg/dL and 6.3 mg/dL, respectively.<sup>27</sup> However, our results are aligned with Daei *et al.*, (2018) who used a different strength of iodine (150 µg/day) for a period of 90 days, but he also reported that there were no changes occurred in serum urea, creatinine, and other biochemical elements of his study.<sup>28</sup> Urine analysis was also performed to further evaluate the effect of iodine on urine composition. This test had quantitative component in which urine specific gravity and pH were evaluated (Table 10) whereas qualitative component compared the urine color, turbidity, glucose in urine, ketones, proteins, hemoglobin, bilirubin, nitrates, leukocytes, pus cells, red blood cells, epithelial cells, amorphous cells, organisms, yeast, and crystal with their reference ranges/characteristics (Table 11). Like renal function test, the mean value of urine specific gravity and pH remained within their normal reference ranges (Table-10) and their “p” values of .096 and .739 respectively, also remained insignificant which assured that there had been no deleterious effect of iodine on these elements of the urine analysis. There is scarcity of literature to compare effect of iodine on both quantitative and qualitative parameters of urine analysis; however, we did not observe any significant change in these parameters when Rennsans capsule and suspensions were used in healthy volunteers.

## Conclusion

The Rennsans product is evaluated to be safe in healthy human beings. The product having iodine strength of almost 200 mg after being administered three times a day for five days, achieved fairly high concentration of serum iodine in body, that is, 3522.88 µg/l and urinary iodine excretion greater than 2000 µg/l. At this concentration, no significant change in the body thyroid functioning was observed through serum TSH and T4 biomarkers. Also, the vital organ functionality tests like liver function test, renal function test, blood chemistry, and urine analysis remained stable when checked before and after the administration of Rennsans product in healthy volunteers. With the exception of self-resolving adverse events which occurred in only five participants, other physical and clinical conditions of all participants remained stable. All these findings led to a conclusion that Rennsans product would be safe to be used in healthy humans.

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The clinical study was approved by: Institutional Research Ethics Committee of Faculty of Pharmacy, University of Lahore: Letter No. IREC-2021-12 H dated: 30Aug2021. Ethical Review Committee of Lahore General Hospital Lahore: Letter No. 00-118-20, dated 11Sep2020. National Bioethics Committee (NBC) of Pakistan: Letter No. 4087/COVID-34/NBC/20/297 dated: 10Sep2020. Drug Regulatory Authority of Pakistan (DRAP): Letter No. F. No. 03-47/2020-DD (PS), dated: 19Oct2020

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