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# The physiological alterations induced by Sibutramine anti-obesity drug on the functions of the thyroid gland and the liver: An experimental study on Wistar rats

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## Abstract

The present study investigates the safety of Sibutramine anti-obesity drug on the thyroid gland functions as well as the liver functions in adult male Wistar rats. A set of animals were treated with a daily dose of (7 mg/Kg) of Sibutramine for 2 weeks (second group: G II). While, another set were treated with the same dose for 6 weeks (third group: G III), At the end of each treatment periods, the serum parameters were measured (TT3, TT4, cortisol, ALT, AST, ALP & total bilirubin). Significant increases were recorded in means of TT3 and cortisol (1.78±0.025 ng/dl and 8.39±0.53 µg/l respectively) was recorded in the third group (G III) compared to the control group (*t*-Test, P≤0.05 and P≤0.01 respectively). In addition, highly significant decrease was observed in TT4 (1.98 ±0.06 µg/dl) (*t*-Test, P≤0.01). Similarly, highly significant increases was observed in the liver enzymes (ALT, AST & alkaline phosphatase) (184.42±11.60, 263.16±16.20 & 116.28±9.54 IU/l respectively) (*t*-Test, P≤0.01). Also, significant increase was recorded in the total bilirubin (0.65±0.03 mg/dl) (*t*-Test, P≤0.05). The present study clearly showed that the long use of Sibutramine is responsible for inducing serious physiological adverse effects on the thyroid gland functions as well as on the liver functions. Therefore, it can be concluded that the long use of Sibutramine is not therapeutically safe. In addition, it is recommended at the end of this study that Sibutramine should not be prescribed at all for any patient who has a history of hormonal or liver disorders.

**Keywords:** Sibutramine, anti-obesity drug, thyroid gland, liver functions, rat.

## Introduction

Obesity is one of the global epidemic health problems, with global estimation of more than 400 millions obese adults in the last few years (Sharma *et al*., 2008; Panigrahi *et al*., 2009). Meanwhile, obesity is responsible for causing other serious diseases such as cardiovascular diseases, hyperlipidemia, atherosclerosis, diabetes mellitus, thrombosis and fatty liver disease (Pagotto *et al*., 2008; Smith *et al*., 2009; Eroglu *et al*., 2009; Scheen, 2010). Sibutramine is one of the successful and well known anti-obesity drugs which are used clinically since the 90s to treat the abnormal complicated cases of obesity (Smith *et al.,* 2006; Pagotto *et al*., 2008, Viner *et al*., 2009; Scheen, 2010). The mechanism of action of Sibutramine occurs via inhibiting serotonin and noradrenaline reuptake in the hypothalamus, causing appetite suppression and satiety feeling, which in turn reduces the food intake and causes rapid weight loss (Luque & Rey, 1999; Nisoli & Carrubo, 2003). However, this drug is sold in the markets under two brand names Reductil and Meridia (Link *et al.,* 2010). Studies showed that Sibutramine can produce a mean weight loss range between 4.8-8.59 Kg in obese patients if it is used for a period between 3 to 12 weeks (McTigue *et al*., 2003; Keskin *et al.,* 2006; Aberle *et al*., 2009, Panigrahi *et al*., 2009; Scheen, 2010). The drug is available in the pharmacies in the form of (Reductil) capsules which contain the active therapeutic compound known as Sibutramine hydrochloride monohydrate (Strano-Rossi *et al*., 2006). As a result of its rapid therapeutic benefits, Sibutramine was highly recommended and prescribed by many physicians since the 90s (Luque & Rey, 2002; Sharma *et al*., 2008). For *e.g*. Viner *et al*. (2009) documented that the total prescriptions of Sibutramine in the UK during the period extended between Jan 1999-Dec 2006 were 1334 prescriptions for 452 patients, which indicated that there is a rapid increases in Sibutramine prescriptions. Furthermore, in addition to its weight loss effect, Sibutramine has also number of positive physiological effects such as: improving insulin sensitivity, decreasing serum levels of triglycerides and uric acid and maintains insulin mediated muscle glucose uptake (Halford *et al*., 2005; Coletta *et al*., 2006; Smith *et al*., 2009). On the other hand, like any other drugs, Sibutramine has also some side effects such as: increasing blood pressure, dizziness, nervousness and anxiety (Nisoli & Carruba, 2003; Pagotto *et al*., 2008; Sharma *et al*., 2008; Harrison *et al.,* 2010). Despite of these side effects, previous studies reported that Sibutramine was considered as a novel safe drug, but its therapeutic safety was found to be time and dose dependant (Ryan *et al*., 1995; McMahon *et al*., 2002; Sharma *et al*., 2008; Horie *et al*., 2010). However, by 2002 the view toward Sibutramine started to dramatically change, as some studies appeared and reported some cardiovascular side effects such as myocardial infarction occurred in few patients who used Sibutramine for long periods (Eroglu *et al*., 2009; Amundsen *et al*., 2010). But, it is very important to mention the following fact, that the view toward Siburtamine therapeutic safety is still up today surrounded by obscure and uncertainty (Smith *et al*., 2006; Oh *et al.,* 2009; Harrison *et al.,* 2010). Meanwhile, some investigators believed that the cardiovascular

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adverse effects of Sibutramine occurred in obese patients who already have cardiovascular disorders even before using the drug (Halford *et al*., 2005; Panigrahi *et al*., 2009; Horie *et al*., 2010). Despite some countries, Sibutramine is still not licensed in UK for treating the abnormal cases of obese children and obese adolescents (Viner *et al.,* 2009). In addition to UK, Sibutramine (Reductil or Meridia) is still available in the pharmacies of many third world countries such as Egypt, Sudan, Syria, Pakistan and India. This continuation of selling this drug without any restrictions is believed to be due to the obscure image surrounding its safety and not at all due to weak official restrictions in these countries (Tallett *et al*., 2008; James *et al*., 2010). To prove the above real fact, we found during our present study that Sibutramine (Reductil or Meridia) is still available in some Indian pharmacies in Hyderabad up to Nov 2010 (manufactured by Hab. Pharmaceutical & Res. Ltd., Selaqui, Dehradun). So till today, there is a complex doubts between investigators and physicians about the therapeutic benefits and risks of Sibutramine (Horie *et al*., 2010). In our present study it was clearly noted that there is a lack and absence of sufficient information about the hormonal and the hepatic effects of Sibutramine. Therefore, the present study was performed to investigate any potential adverse effects which may result from Sibutramine treatment on the thyroid gland functions, as well as the liver functions in adult male Wistar rats. Biochemical measurements of the serum levels of TT3 and TT4 hormones were carried out to monitor the normal functions of the thyroid gland. Similarly, the serum levels of liver enzymes and total bilirubin were also measured to reflect any alterations in the liver functions induce by this drug. In addition, the serum levels of cortisol hormone were also measured to explain some behavioural observations. During this study, the changes in the animal body weight were not measured as it is not one of the current study objectives and aims and as far as the effect of Sibutramine in producing weight loss is well known and documented by many previous studies (Lugue & Rey, 2002; Nisoli & Carruba, 2003).

## Materials and methods

The present experimental study was performed during the period of June-July 2009 in Experimental animals Dept. at King Fahed Medical Researches Center, King Abdul Aziz University, Jeddah, Saudi Arabia.

*Preparation of Siburtamine dose*

Fifteen mg capsules of Reductil (Sibutramine hydrochloride monohydrate) manufactured by Abbott laboratories Ltd. Co., USA were obtained from some local pharmacies in Jeddah, SA. In the lab each capsule was carefully opened and the powder containing Sibutramine hydrochloride monohydrate was used in preparing the tested dose. Calculated amount of this powder was weighted accurately and then it was dissolved in 1 ml of normal saline to produce a dose of 7 mg/kg body weight. This tested daily dose was selected based on Hansen *et al.* (2010) study. Each animal was given orally this daily dose (7 mg/kg) using gastric feeding tube. The calculation and the preparation methods of this dose were performed as described by Hansen *et al*. (2010).

*Animals & treatment*

Twenty four adult male Wistar strain rats (weighing 120-130 g) were used in this study; the animals were obtained from the animal house unit of King Fahed Medical Researches Center, King Abdul Aziz University, Jeddah. Each animal was housed in a wide proper plastic cage and kept under constant normal temperature (<24°C), 12 h dark/light cycle (Chudasama & Bhatt, 2009). Distilled water and diet were provided daily. Prior the start of the experiments, animals were left for 2 weeks to acclimatize. After the acclimatization period all the animals were fed on a rich fat diet for 4 weeks to become obese animals (weighing between 190-200 g) in order to simulate the cases of obese human individuals when we used the drug and to be exactly like the method used by Chudasama and Bhatt (2009) study which investigated similarly the effects of anti-obesity drugs on experimentally obese rats. After this period, animals were divided in to 3 groups (8 animals in each), the first group (G I ) was the control group, while the second group (G II) and third group (G III) were the treated groups, in which each animal was given a daily dose of 7 mg/kg body weight. In the second group (G II), each animal was given orally the daily dose for treatment period of 2 weeks. While in the third group (G III), each animal was given orally the same dose for treatment duration of 6 weeks. The daily Sibutramine dose was given to each treated animal orally using gastric feeding tube. Animals caring and management experimental protocols were performed according to the method of Tallett *et al.* (2008).

*Blood samples & biochemical measurements*

At the end of each treatment periods, each animal from 3 groups was anesthetized by inhalation of few drops of diethyl ether, blood samples were collected by cardiac puncture according to the method of Hansen *et al*. (2010). Then blood samples were immediately placed in lithium heparin tubes for the biochemical measurements of the thyroid gland hormones (thyroxin TT3 & triiodothyronine TT4), cortisol hormone, total bilirubin and liver enzymes (ALT, AST & alkaline phosphatase) levels in the serum. The blood biochemical measurements were performed in a highly specialist medical lab (AL-Mamlaka Medical Lab, Jeddah, SA). In the laboratory, the blood samples were immediately centrifuged at 3000 rpm for 5 min to collect the serum prior to measure the mentioned parameters. Thyroid hormones and cortisol were measured using Abbott Axsym blood analyzer. Whereas, the liver enzymes and the total bilirubin were measured using Vitros chemistry blood analyzer (model no. 350, Jonson & Jonson, UK).

*Statistical analysis*

Measurement data were expressed as (Mean ± S.E). The results of the tested parameters were statistically

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analyzed by Sigma stat program (v.8), in which *t*-Test has been used to determine the significant differences between each treated group and the control group for each parameter.

*Table 1. The effects of treatment with Sibutramine dose on the serum levels of TT3, TT4 & cortisol hormones in the treated groups (G II & G III) compared to the control group (G I).*

| Blood parameters | Groups | | |
|---|---|---|---|
| | Control group (G I) | Second treated group (G II) | Third treated group (G III) |
| TT3 (ng/ml) | 1.21±0.08 | 2.06±0.03 | 1.78±0.025* |
| TT4 (µg/dl) | 5.20±1.44 | 4.89±0.37 | 1.98±0.062** |
| Cortisol (µg/l) | 0.23±0.06 | 0.27±0.16 | 8.39±0.53** |

*No. of animals in each group was eight (n=8), data are expressed as (Mean±S.E), *Significant difference (P≤0.05) in compared to control group according to t-Test. **Highly significant difference (P≤0.01) in compared to control group according to t-Test).*

## Results

*Effects of Sibtramine on the second treated group (G II)*

*TT3 & TT4 levels:* As shown in the results illustrated in Table 1 the means levels of the 3 hormones in the treated animals of this group were measured, but the recorded changes in the means of these hormones (TT3, TT4 & Cortisol) were found not statistically significant compared to the control group according to *t*-Test (1.82±0.03 ng/ml, 4.89±0.37 µg/dl & 0.27±0.16 µg/L respectively).

*Table 2. The effects of Sibutramine treatment on the serum liver enzymes & total bilirubin in the treated groups (G II & G III) compared to the control group (G I).*

| Blood parameters | Groups | | |
|---|---|---|---|
| | Control group (G I) | Second treated group (G II) | Third treated group (G III) |
| ALT (IU/l) | 48.62 ±1.60 | 50.70±4.65 | 184.42±11.60** |
| AST (IU/l) | 52.68±2.28 | 55.86±3.10 | 263.16±16.20** |
| Alkaline phosphatase (IU/l) | 81.50±5.80 | 83.42±5.30 | 116.28±9.54** |
| Total bilirubin (mg/dl) | 0.03±0.01 | 0.26±0.01 | 0.65±0.03* |

*No. of animals in each group was eight (n=8), data are expressed as (Mean±S.E), *Significant difference (P≤0.05) in compared to control group according to t-Test. **Highly significant difference (P≤0.01) in compared to control group according to t-Test).*

*Liver enzymes levels:* The results of liver enzymes in Table 2 show that treating the animals for 2 weeks with the tested daily dose did not induce any significant alterations in the means levels of liver enzymes. Although there were limited increases in the means levels of ALP, AST and alkaline phosphatase, but these increases were found not statistically significant (50.70±4.65 IU/l, 55.86.±3.10 IU/l & 83.42±5.30 IU/l respectively) compared to the means values in the control group according to (*t*-Test). Similarly, the mean of the total bilirubin also did not significantly change (0.26 ±0.01 mg/dl) compared to the control group according to *t*-Test.

*Effects of Sibtramine on the third treated group (G III)*

*TT3 & TT4 levels:* As shown in Table 1 the long treatment period for 6 weeks with tested dose of Sibutramine induced significant abnormal alterations in the serum TT3 and TT4 levels. Significant increase was recorded in the mean levels of TT3 (1.78±0.025 ng/ml) compared to the control group according to *t*-Test (P≤0.05). Whereas, highly significant decrease was observed in the mean levels of TT4 (1.98±0.06 µg/dl) compared to the control group according to *t*-Test (P≤0.01). While highly significant elevation was also recorded in the mean levels of cortisol (8.39±0.53 µg/l) compared to its mean in the control group according to *t*-Test (P≤0.01).

*Liver enzymes levels:* According to the results illustrated in Table 2 the long treatment with Sibutramine for 6 weeks induced highly significant elevations in the liver enzymes serum levels and in the total bilirubin in the treated animals of this group. The means levels of ALP, AST and alkaline phosphatase were significantly increased (184.42±11.60 IU/l; 263.16.±16.20 IU/l and 116.28±9.54 IU/l respectively) compared to the control group according to *t*-Test (P≤0.01). Similarly, significant increase was also recorded in the mean levels of the total bilirubin (0.65±0.03 mg/dl) compared to the control group according to *t*-Test (P≤0.05).

## Discussion

Sibutramine will remain under complex doubts and disagreement between investigators and physicians as more clinical data are still required to determine its safety and risks (Sharma *et al*., 2008; Luisa *et al.* 2008; Horie *et al*., 2010). The decision of restricting Sibutramine in some European countries was considered in the opinion of many physicians as a wrong decision, as they believed that Sibutramine is a safe and successful anti-obesity drug if it is used for limited therapeutic periods in obese patients who do not have any cardiovascular problems (Horie *et al*., 2010). According to some physicians, Sibutramine was used safely for many years in treating many complicated abnormal obesity cases such as: the genetically obese cases, the obesity cases resulted from endocrinal hormonal disorders and the abnormal obesity cases among the children (Viner *et al*., 2009). According to some physicians these abnormal complicated cases of obesity need Sibutramine therapy for limited therapeutic periods (Astrup *et al*., 2010; Horie *et al*., 2010). Despite of all these facts, recently in Oct 2010, USA food and drug administration (FDA) took a quick decision when it asked Abbott laboratories Ltd. Co. to withdraw Sibutramine (Redictul & Meridia) from the markets based on the cardiovascular risks data (Batty & Czernichow, 2010). But, on the opposite side, Sibutramine is still available today in many third world countries as mentioned before (Batty & Czernichow, 2010). Meanwhile, despite of this

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FDA decision, there was a disagreement between the FDA members itself about this decision, some FDA members voted against the withdrawal decision due to its therapeutic benefits and they suggested that Sibutramine should be allowed to continue marketing with a revised label, including black box warning, to prevent the cardiovascular patients using it (Batty & Czernichow, 2010). However, in regard to the present study, it is also considered as a part of the complex doubts about Sibutramine side effects. In regard to the present data, the hormonal and hepatic results clearly showed that the long use of Sibutramine (for 6 weeks in the third group) induced significant hormonal and hepatic serious adverse effects. The hormonal results showed significant increases in the serum levels of TT3 and cortisol hormones which may reflect the occurrence of abnormal defects in the thyroid and adrenal glands functions. In addition, these abnormal increases in the levels of TT3 and cortisol could explain some of the behavioral abnormalities such as anxiety and aggressiveness which were observed in patients using Sibutramine for long periods. On the other hand, the highly significant decrease observed in TT4 levels may indicate the occurrence of histopathological injuries in the thyroid gland. Meanwhile, during the present study, we believed based on the scientific logic and warning information from the manufacturer that there is a correlation and relationship for sure between the weight loss induced by Sibutramine and the thyroid gland hormones which control the food metabolism. However, despite of that, the hormonal results of TT3 and TT4 were found unfortunately not matching with the previous findings of Keskin *et al*. (2006) on human obese patients, as it reported that Sibutramine treatment with a daily dose of (15 mg) for 3 months in these patients, did not cause any significant changes in the serum levels of TT3 and TT4 hormones. The results of Keskin *et al*. (2006) seem to be strange, as the daily dose was not a low dose and in addition the treatment duration was also not a short one. Keskin *et al*. (2006) study reported some important conclusions, such as that the degree of obesity may affect the thyroid hormones (TT3 & TT4) status and the effects of Sibutramine on the thyroid hormones may be different beyond lowering body weight. On another hand, in regard the present liver parameters results, the highly observed significant increases in the liver enzymes and bilirubin mean levels induced by Sibutramine long treatment can be considered as an evidence which reflect the occurrence of severe defects in the liver functions associated with cellular damages. These present liver results support and correspond with Chounta *et al*. (2005) findings, which reported that long use of Sibutramine was associated with reversible hepatotoxicity. However, regarding the cellular mechanism which can explain how the long treatment with Sibutramine induced these observed adverse hormonal and hepatic effects; the mechanism is regret is still unknown. Despite of that, there is some potential hypothesis. For instance, one of the possible mechanism was mentioned by Solomon *et al*. (2005) as it reported that long treatment with serotonin reuptake inhibitors such as Sibutramine, produces liver injuries via increasing the levels of a very reactive oxygen radicals and the levels of lipid peroxides in the hepatocytes. Such increases is believed to cause marked mitochondrial damages in the target hepatocytes due to the occurrence of cellular oxidative stress which in turn leads to hepatocytes and thyroid gland necrosis. In addition, the second possible mechanism may occur through the accumulation of Sibutramine active metabolites in the thyroid gland cells and liver cells, cytochrome ($P^{450}$ 2B6) is believed to catalyze several toxicants and drugs including Sibutramine into 6 active demethylated metabolites (Strano-Rossi *et al*., 2006; Mo *et al*., 2009). Therefore, long treatment with Sibtramine could cause high accumulation of these demethylated toxicants metabolites in the liver cells and other organs leading to cause hepatocellular and thyroid gland injuries and cells membranes rupture (Chounta *et al*., 2005; Oh *et al.,* 2009).

## Conclusions

The present results showed clearly that the long use of Sibutramine can induce serious physiological adverse effects on the thyroid gland functions as well as on the liver functions. In addition, it can be concluded from the current results that Sibutramine should not be used at all in any obese patient who has clinical history of hormonal or liver disorders. Meanwhile, Sibutramine is believed to be unsafe drug in the long term of use particularly on the functions of thyroid gland and on the liver functions, these current findings are completely opposite to the conclusions of some previous studies which reported that Sibutramine is a safe drug (Ryan *et al.,* 1995). Furthermore, new generation of safe anti-obesity drugs should be discovered by pharmacologists having similar repaid therapeutic benefits of Sibutramine.

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