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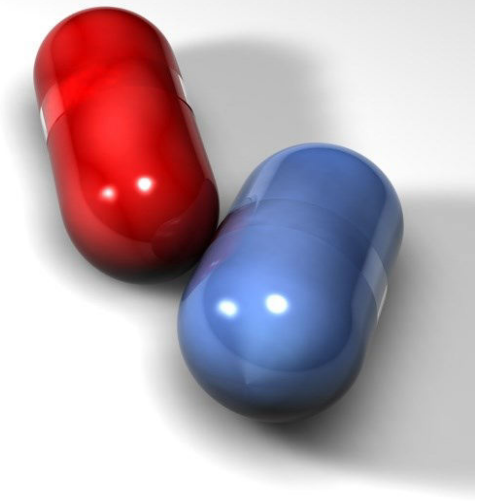

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Letter to the Editor

Reporting a lethal drug interaction occurred during evaluation of insulin resistance in mice polycystic ovary model

Sir,

Hormonal and metabolic imbalance can effect women's health and reproductive system from the view point of endocrinology (Borna et al., 2012; Boroujeni et al., 2016). Polycystic ovary syndrome is an example of such endocrinology disorders. Type 2 diabetes, obesity, metabolic syndrome, hypertension and so on are considered as risk factors of polycystic ovary syndrome. Metformin is used for the treatment of polycystic ovary syndrome, because of insulin resistance in such patients (Keshavarz et al., 2017; Yari et al., 2017). The exact etiology of polycystic ovary syndrome is not clear, because metabolic disorders (e.g. insulin resistance) and hormonal disorders (e.g. hyperandrogenism) are simultaneously observed.

Since insulin resistance in previous murine models of polycystic ovary syndrome has not been evaluated, we were trying to approve this research modeling through empirical administration of insulin glargine. The mice model of polycystic ovary syndrome through testosterone enantate has been previously validated histologically and biochemically by some researchers (Ahmadi et al., 2017; Kalhori et al., 2014).

For the current experimental study 22 female and 7 male mice were used. The animals were grown and kept in animal laboratory of Razi Herbal Medicine Research Center, Lorestan University of Medical Sciences considering ethical guidelines of working with laboratory animals (ethical code: IR.LUMS.REC. 1396.351). Their thermos contained dextrose 5% in water (D5W) instead of distilled water which was free access for the mice in order to prevent unwanted hypoglycemia related death. The mice divided into 4 groups: Group 1: Polycystic ovary syndrome modeling group, administered with 2 mg/100 g testosterone enantate soluted in olive oil; Group 2: Female insulin susceptibility control group, administered with 1 unit/18 g insulin glargine; Group 3: Male insulin susceptibility control group, administered with 1 unit/18 g insulin glargine; and Group 4: Female group for combined administration of testosterone enantate and insulin glargine in order to induce hyperinsulinemia and insulin resistance (which finally showed a lethal drug interaction). All the administrations were daily for 2 weeks. Death in 1st 48 hours of starting insulin administration considered as insulin susceptibility. For Group 1, insulin administration were performed after this two week procedure. In order to analyze the data Fisher's exact test was used.

In the polycystic ovary syndrome modeling group (Group 1), all the animals survived after 2 weeks administration of testosterone enantate, and also survived after empirical administration of insulin. Three out of 7 animals in the female insulin susceptibility controls (Group 2), died in the 1st 48 hours. All the male insulin susceptibility controls (Group 3), survived after insulin administration. In the combined administration group (Group 4), all the mice died after 1st administration. Insulin resistance in the modeling group was higher in comparison to the female controls, but it was not statistically significant ($p=0.19$). The results of Group 4 showed a drug interaction of testosterone enantate and insulin glargine. This result was statistically significant in comparison to other groups ($p<0.05$) (Table I).

The non-significant statistical result of Group 1 versus Group 2 showed that this method of empirical insulin administration could not show the insulin resistance of polycystic ovary syndrome model. This might be due to our low sample size or low power of analysis. Investigation of serum insulin level was our financial limitation. On the other hand, our significant results of Group 4 versus the other groups showed that this dose of combined administration of testosterone enantate and insulin glargine could be at least the absolute lethal dose (LD_{100}) of this combination. Based on Food and Drug Administration (FDA) suggested formula, the ratio of mice mg/kg to human mg/kg is 37/3 (Ahmadi et al., 2015). Our dose for testosterone enantate and insulin glargine were 2 mg/100 g and 1 unit/18 g respectively (= 20 mg/kg and 55 unit/kg). The human equivalent would be 1.62 mg/kg and 4.46 unit/kg. Hence for a 62 kg individual who has administered an injection of testosterone enantate 100 mg, 276 units of insulin glargine will be a killing dose, but this nevertheless shows that testosterone enantate can increase the hypoglycemic effect of insulin (Kapoor et al., 2006) and in such conditions insulin dose should be adjusted.

Table I

Summary of the findings (above) and analysis (below)

	Group 1		Group 2		Group 3		Group 4	
	Survived	Dead	Survived	Dead	Survived	Dead	Survived	Dead
Number	7	0	4	3	7	0	0	8
Inter-group comparison of significance								
p value	Group 1		Group 2		Group 3		Group 4	
Group 1								
Group 2	0.19							
Group 3	1		0.19					
Group 4	0.0002[a]		0.02[a]		0.0002[b]			

[a]Significant and conclusive; [b]Significant but not conclusive (because of male/female bias)

The highlights of our study fall into some categories. The most important one is that this model of insulin resistance evaluation is not successful. The drug interaction of testosterone enantate and insulin glargine is statistically approved. Testosterone can reduce insulin resistance and increase hypoglycemia. This give us clue that testosterone administration is not a suitable modeling for polycystic ovary syndrome in laboratory animals, because testosterone will not induce insulin resistance and these are mutually exclusive. It shows the unknown etiology of polycystic ovary syndrome.

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Seyyed Amir Yasin Ahmadi[1], Afshin Hasanvand[2], Amin Hasanvand[3], Mandana Beigi Boroujeni[4], Fatemeh Yari[4,5]

[1]Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Science, Tehran, Iran; [2]Student Research Committee, Lorestan University of Medical Science, Khorramabad, Iran; [3]Department of Pharmacology, Lorestan University of Medical Science, Khorramabad, Iran; [4]Razi Herbal Medicine Research Center, Lorestan University of Medical Science, Khorramabad, Iran; [5]Department of Reproductive Health, Lorestan University of Medical Science, Khorramabad, Iran.

Corresponding author:
email: yari1672@yahoo.com; Tel/Fax: +98 66 33 120 192; Mobile phone: +98 916 361 3621

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