LETTER TO THE EDITOR

Effect of rosiglitazone on early-morning plasma cortisol levels

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Abstract

OBJECTIVES: PPAR-γ agonists are able to inhibit pituitary tumour development and tumoral hormonal secretion in rodents both in vitro and in vivo. Their use for treatment of Cushing Disease (CD) has been suggested but the clinical experience with the two PPAR-γ agonists commercially available (rosiglitazone and pioglitazone) was not impressive. Short-time treatment has been proposed to be the cause of unsuccessful results on CD in humans. We report here the effect on early-morning plasma cortisol levels of a long-time treatment with rosiglitazone at the highest approved dose.

METHODS: Because PPAR-γ receptors are located in normal corticotroph cells we tested in a placebo-controlled study the influence of rosiglitazone on cortisol secretion. The study enrolled 30 newly diagnosed type 2 patients which were assigned to receive either rosiglitazone (8mg/day) or placebo. Plasma morning cortisol (8.00 a.m.) was measured at the baseline and at the end of the study.

RESULTS: Rosiglitazone vs placebo did not modify the early morning plasma levels of cortisol (13 μg/dl [3–21] vs 11 μg/dl [7–23] [median and range]) after 26 weeks of treatment.

CONCLUSION: The discrepancy between in vitro and animal data on one side and clinical data on the other side warrant further investigations into the mechanisms of action of PPAR-γ agonists on ACTH secretion before other clinical studies will be conducted.

Sir, we read with interest the report by Gruszka et al [4] on the inhibiting effect of rosiglitazone on viability of the estrogens-induced, prolactin secreting rat tumours in vitro. We would like just to warn the reader that clinically trials with PPAR-γ agonists for treatment of pituitary tumours, as suggested by the authors, should be cautiously prepared.

Previous reports have also shown promising effect of PPAR-γ agonists on different pituitary tumours in vitro or when inoculated in rodents [6]. The inhibiting effect shown by rosiglitazone on the ACTH-producing tumors [7] suggested the use of thiazolidinediones (TZD) for treatment of Cushing Disease (CD). However the effects of both clinically approved TZD (rosiglitazone and

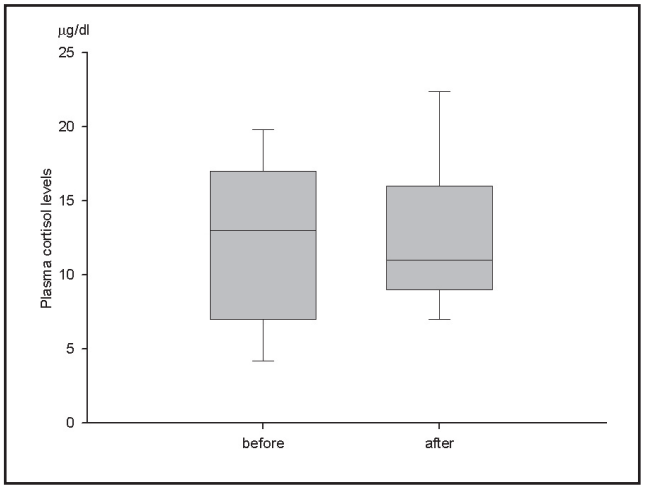

Figure
Early morning plasma cortisol levels before and after treatment with rosiglitazone 8 mg/day versus placebo for 26 weeks in patients with type 2 diabetes (median, 25%–75% and 10%–90%).

pioglitazone) on CD were not impressive [1] if any [2, 9]. It has been suggested that long term treatment with TZD could be more successful for inhibiting the adrenal axis. We would like to report here our experience on the effect of long-time rosiglitazone therapy at maximal dose on early morning cortisol levels.

Taking in account the reported presence of PPARγ receptors in corticotroph cells in normal human pituitary cells [7] we measured the plasma cortisol levels from a double blind, placebo-controlled study on 30 newly diagnosed patients with type 2 diabetes [5, 8]. After 26 weeks of treatment with rosiglitazone in the maximal admitted dose (8 mg/day), plasma cortisol levels at 8.00 a.m. were similar to those in the placebo group (13 µg/dl [3–21] vs 11 µg/dl [7–23] [median and range]) (figure). Our findings are in perfect agreement with the data published for long time treatment with pioglitazone [9].

The inconsistent effects of TZD on HPA axis in humans could rely on the much lower doses used in clinical studies compared to animal experiments. It might be that the inhibitory effects of high doses TZD on the HPA axis observed in animals are modulated by PPAR-γ receptor independent mechanisms already reported for their antitumoral effects [3].

In conclusion we would like to emphasis that further investigations into the mechanisms of action of TZD on ACTH secretion are needed before other clinical studies will be conducted.

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