



## Abnormal dexamethasone suppression tests in a rifampicin-treated patient with suspected Cushing's syndrome

Nieprawidłowy test hamowania deksametazonem u pacjentów z podejrzeniem zespołu Cushinga leczonych ryfampicyną

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### Abstract

The dexamethasone suppression test is a useful endocrinological test to diagnose Cushing's syndrome. However, its interpretation may be influenced by many factors such as stress, alcohol, failure to ingest the dexamethasone, altered metabolism, drug interaction and obesity. This report illustrates such an instance, whereby the result of the test was erratic due to the anti-tuberculous drug rifampicin. Rifampicin has been found to profoundly attenuate the biological effects of dexamethasone, probably by enhancing its metabolism in the liver. The exact mechanism of the drug interaction remains elusive, though induction of hepatic CYP3A4 enzyme complex is a possible mechanism. In a patient treated with rifampicin, the results of dexamethasone suppression tests thus have no diagnostic value and can be very misleading. (*Pol J Endocrinol* 2010; 61 (6): 706–709)

**Key words:** dexamethasone suppression test, rifampicin, Cushing's syndrome, biological effect, drug interaction

### Streszczenie

Test hamowania z deksametazonem przeprowadza się w celu diagnostyki zespołu Cushinga. Na jego wynik wpływa wiele czynników, takich jak: stres, alkohol, upośledzenie wchłaniania i metabolizmu deksametazonu, interakcje międzylekowe i otyłość. W pracy opisano przypadek wpływu leku przeciwgruźliczego, ryfampicy, na wynik testu. Stwierdzono, że ryfampicina w znacznym stopniu zmienia biologiczny efekt działania deksametazonu, prawdopodobnie przez przyspieszenie jego metabolizmu w wątrobie. Dokładny mechanizm interakcji pozostaje niewyjaśniony, choć prawdopodobna wydaje się indukcja wątrobowego kompleksu enzymu CYP3A4. Test hamowania deksametazonem przeprowadzony u pacjentów leczonych ryfampicyną nie posiada wartości diagnostycznej, a jego wynik może być mylący. (*Endokrynol Pol* 2010; 61 (6): 706–709)

**Słowa kluczowe:** test hamowania deksametazonem, ryfampicina, zespół Cushinga, efekt biologiczny, interakcje międzylekowe

### Introduction

Multiple drugs are often used in a single patient. During treatment, drug-drug interaction occurs when the presence of one drug affects the pharmacodynamics and pharmacokinetics of another drug through absorption, metabolism or disposition and therefore affects the bioavailability, efficacy and toxicity in the patient. We describe a patient with subtle signs of Cushing's syndrome who was also being treated for pulmonary tuberculosis. In this report, we demonstrate an erratic dexamethasone suppression test as a result of concurrent administration of rifampicin that has been recognised to be a liver enzyme inducer. The metabolism of dexamethasone has been accelerated by rifampicin, thus producing falsely abnormal results. Therefore, awareness of this diagnostic pitfall is of paramount importance to avoid unnecessary diagnostic tests and anxiety to the patient.

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### Case report

A 30 year-old Indonesian man, who had been living in Malaysia for the past two years, presented with dry cough of three months' duration associated with intermittent haemoptysis. He had been having fever, night sweats, appetite loss and profound weight loss. There was no history of close contact with tuberculosis. He



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**Figure 1.** The presence of abdominal purplish striae that prompted the initial suspicion of Cushing's syndrome in this patient with pulmonary tuberculosis

**Rycina 1.** Purpurowe rozstępy na skórze brzucha i ud sugerujące wstępne rozpoznanie zespołu Cushinga u chorego z gruźlicą płuc

had an unremarkable medical and surgical history. He was married with two children and indulged in no high risk behaviour. He had no exposure to asbestos at work. He was a heavy smoker but denied consuming alcohol. He had been taking herbal medicine for his cough, but had stopped three weeks prior to admission.

Clinically, he was cachexic with muscle wasting. He was febrile, but his vital signs were normal. Respiratory examination revealed signs of lung consolidation at apical region bilaterally with multiple cervical lymphadenopathies. He was also noted to have subtle features of Cushing's syndrome. Although he did not look cushingoid, there were prominent purple striae noted on the abdominal wall, flank and thighs (Fig. 1). Multiple acnes were also seen on the face and anterior chest wall (Fig. 2). There was no proximal myopathy or thinning of the skin. Other systemic examinations were normal.

The clinical diagnosis considered at the time of admission was pulmonary tuberculosis. Cushing's syndrome was also suspected, despite only subtle clinical signs.

Laboratory investigations revealed mild leucocytosis with normal monocyte count. The renal and liver functions were normal except for hypo-albuminaemia. The erythrocyte sedimentation rate was 78 mm/hour. The Mantoux test was strongly positive but the sputum was negative for acid fast bacilli (AFB). The chest radiograph showed reticulo-nodular opacities over both lung fields, with evidence of bilateral apical pleural thickening. These findings were consistent with secondary tuberculosis (Fig. 3).



**Figure 2.** The multiple acnes on the anterior chest wall

**Rycina 2.** Liczne zmiany trądzikowe na przedniej ścianie klatki piersiowej



**Figure 3.** The AP view chest radiograph of this patient shows the reticulo-nodular shadows of both lung apices which is consistent with secondary pulmonary tuberculosis

**Rycina 3.** Na zdjęciu RTG klatki piersiowej w projekcji przednio-tylnej widoczne smużasto-guzkowe zaciemnienia w szczytach obu płuc odpowiadające obrazowi wtórnej gruźlicy płuc

He was started on anti-tuberculous drugs: isoniazid 300 mg daily, rifampicin 600mg daily, ethambutol 1.2 g daily, pyrazinamide 2 g daily and pyridoxine 10 mg daily.

In view of the possible Cushing's syndrome, he was further investigated while his anti-TB treatment was continued (Table I).

The 1 mg overnight dexamethasone test showed failure of suppression with serum cortisol of 74nmol/L (normal < 50 nmol/L). A further test with low dose DST showed serum cortisol was suppressed. However, in view of a detectable level of ACTH, ACTH-dependent Cushing's syndrome was entertained. We therefore proceeded with high dose DST. The result however

**Table I.** Dexamethasone suppression test (DST) and ACTH level.**Tabela I.** Test hamowania deksametazonem (DST) i stężenia ACTH

Test	Baseline serum Cortisol [nmol/L]	Post test serum Cortisol [nmol/L]	Baseline ACTH [pg/mL]
Overnight 1 mg DST	281	74	
48 hours low dose DST	206	102	11.1
48 hours high dose DST	83	31	< 10.0
6 am	191		
1200 am	55		

failed to confirm our suspicion. The baseline serum cortisol was also found to be low, which again made the diagnosis unlikely. These tests were done on days 6, 11 and 17 respectively. In view of the conflicting results, the basal and midnight serum cortisol were performed and showed an intact diurnal variation of cortisol secretion. An abdominal ultrasound examination excluded adrenal tumour. We could not explain the clinical signs that mimicked Cushing's syndrome, but given the above result we concluded that he did not in fact have Cushing's syndrome. The results were erratic due to concurrent treatment with rifampicin which is a liver enzyme inducer. This mechanism might have caused attenuation of the dexamethasone metabolism, causing a falsely high serum cortisol level in the overnight dexamethasone suppression test. We planned to repeat the test after the anti-tuberculous treatment, but the patient was defaulted from our follow-up.

## Discussion

This patient was admitted with a diagnosis of pulmonary tuberculosis and was found to have subtle clinical signs of Cushing's syndrome — acnes and purplish abdominal and thigh striae. A suspicion of Cushing's syndrome was made and subsequently he was subjected to a series of endocrinological tests using dexamethasone suppression test while he was treated with anti-tuberculous drugs including rifampicin, not realising that it could profoundly affect the interpretation of test results.

Rifampicin is a widely used drug for the treatment of pulmonary tuberculosis. It is known that rifampicin is a potent inducer of the hepatic oxygenase enzymes involved in many drug metabolisms. Patients receiv-

ing rifampicin for the treatment of tuberculosis have increased liver cytochrome P450 activity and intense proliferation of the smooth endoplasmic reticulum [1, 2].

Many reports have found that rifampicin induces profound alterations in cortisol metabolism when administered to patients with primary adrenal failure receiving adequate corticosteroids replacement therapy [3]. The half life and the systemic clearance of hydrocortisol was decreased and increased by about 35% respectively. A study to evaluate the reliability of a standard overnight dexamethasone suppression test on patients taking rifampicin concluded that the dexamethasone test in such patients may mislead physicians into diagnosing non-existent Cushing's syndrome [4].

To the best of our knowledge, there has been no complete report on the bioavailability of dexamethasone in subjects treated with rifampicin. However, a Japanese report found that in patients receiving rifampicin therapy for tuberculosis, the half-life of dexamethasone was decreased three fold and the clearance rate was increased five fold [5]. It appears, therefore, that the removal of dexamethasone by the liver was greatly accelerated compared to that of cortisol and prednisolone, probably by several orders of magnitude, and was the main reason for the failure to suppress serum cortisol, even when an adequate amount of dexamethasone was administered. This suggests that the serum concentration, and presumably the quantity of dexamethasone reaching the pituitary or hypothalamus, in patients receiving rifampicin were not sufficient to inhibit ACTH or CRH secretion. Whatever the mechanism of interaction in patients treated with rifampicin, the dexamethasone suppression test is rendered highly abnormal and if applied in this patient could mislead the physician into diagnosing non-existent Cushing's syndrome. Although no study has had the time required to restore pituitary ACTH suppressibility to normal after discontinuing rifampicin therapy, it would be prudent to stop rifampicin therapy for 15 days before performing a dexamethasone suppression test. This judgment is based on a report on the effect of rifampicin on the metoprolol metabolism [6].

Applying this to our patient, he was treated with rifampicin for pulmonary tuberculosis and subsequently underwent various dexamethasone suppression tests to diagnose Cushing's syndrome. Although the results from overnight DST were consistent with a diagnosis of Cushing's syndrome, he lacked the typical clinical features of Cushing's syndrome. We therefore concluded that these results were misled by the simultaneous administration of rifampicin during the test. Following

that, we decided to review him in six months' time after he had completed his anti-tuberculous treatment, when we planned to repeat the test. However, this patient was lost to our follow-up and we were not able to repeat the test to confirm our suspicion.

Therefore, in screening patients for Cushing's syndrome, it is important to be aware of potential drug-drug interaction with dexamethasone, which may lead to falsely positive and erratic results. Appropriate use of investigations and interpretation of results is of paramount importance to avoid a false diagnosis that will create anxiety in the patient.

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