Anti-arthritic propionic acid derivatives and 17-oxosteroid measurements – a direct interference

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Summary: Many drugs interfere with the assay of urinary 17-oxo and oxogenic steroids. Some propionic acid derivatives, in particular, tiaprofenic acid, have now been shown to affect this assay. Care should be taken when interpreting results in patients on these drugs.

Introduction

The 24 h urinary excretion of 17-oxo and oxogenic steroids is often used in the investigation of adrenal disease, the 17-oxosteroids reflecting androgen production. The assay involves the formation of a chromogen with 17-oxosteroids by the Zimmerman reaction (Callow *et al.*, 1938). Although a number of drugs are known to interfere with this reaction (Varley *et al.*, 1976; Gray *et al.*, 1969) interference by propionic acid derivatives has not been reported. We report here a patient in whom tiaprofenic acid (Surgam TM), a new anti-arthritic propionic acid derivative, was shown to interfere directly in this reaction.

Case report

A 61 year old woman was discovered to be hypertensive when she complained of blurred vision. She also had severe, longstanding, painful osteoarthritis of both hips and took paracetamol and dextropropoxyphene (Distalgescic) and 600 mg/d of tiaprofenic acid, with good analgesic effect. Examination showed that she had truncal adiposity and a buffalo hump, although there were no striae, hirsuties or virilization. The blood pressure was elevated, 220/110 mm Hg lying and 190/120 mm Hg standing. She had grade 3 hypertensive retinopathy. Although she had normal blood urea, electrolytes and glucose, Cushing's syndrome was suspected. The morning serum cortisol was 390 nmol/l (normal range 280–650 nmol/l), but the 24 h urinary 17-oxosteroids were grossly elevated at 295 μ mol/d (normal range 17–70 μ mol/d) and 17-oxogenic steroids were also elevated at 93 μ mol/24 h

(normal range 17–52 μ mol/d). A computed tomographic (CT) scan of the abdomen identified 2 normal adrenals; no ovarian masses could be demonstrated on pelvic ultrasound. The low and high dose dexamethasone suppression tests achieved complete suppression of serum and 24 h urinary cortisols (measured by radio-immunoassay), but the urinary oxo- and oxogenic steroids remained grossly elevated.

Drug studies

In view of the normal serum cortisol, the absence of a source of excess endogenous androgens and lack of virilization, it was suspected that tiaprofenic acid might be interfering with the assay for oxo- and oxogenic steroids. The drug was stopped and the patient's 24 h urinary oxo- and oxogenic steroids returned to normal within 2 d. Subsequently, in 4 other patients, administration of tiaprofenic acid 600 mg/d was found to raise the 24 h urine oxosteroids to twice normal within a day. Thus the phenomenon appears to be universal in all patients to whom the drug is given. Also, the abnormality disappeared within 2 d of stopping the drug, and was suspected to be due to the parent drug, although the possibility of interference from its metabolites could not be excluded. This was confirmed by *in vitro* tests with tiaprofenic acid, which showed that with Zimmerman reagent it produced a chromogen with a broad peak of absorbance (maximum at 550 nm); dehydroepiandrosterone and other androgens produce a maximum at 515 nm (Gray *et al.*, 1969). The normal suppression of urine cortisol by dexamethasone (Liddle, 1960) confirms that the drug is interfering directly in the oxosteroid assay and is not affecting the pituitary-adrenal axis.

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We also examined other propionic acid derivatives *in vivo* for interference in the assay. No reaction was found with ketoprofen or ibuprofen, but fenbufen produced a labile chromogen that faded rapidly. Naproxen was found to react weakly, producing a chromogen with peak absorbance at approximately 550 nm. We subsequently learned that the interference by naproxen in the oxosteroid assay was documented by Syntex Pharmaceuticals in 1974 but not published.

The sodium borohydride used in the first step of the oxogenic steroid assay (Gray *et al.*, 1969) reduces these propionic acid derivatives so that they no longer can react with Zimmerman reagent. Thus the oxogenic steroid result will be unaffected provided that an adequate excess of sodium borohydride is used.

References

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Discussion

Many other drugs can interfere directly with the assay for oxosteroids (Varley *et al.*, 1976; Gray *et al.*, 1969). Oestrogens and reserpine produce falsely low results; high results are seen with penicillin, cloxacillin, erythromycin, nalidixic acid, quinidine and spironolactone.

In the interpretation of urinary oxo- and oxogenic steroids, the possibility of interference by drugs should be kept in mind to avoid subjecting patients to expensive and time consuming investigations. Tiaprofenic acid must now be added to the already long list of substances that interfere with the oxosteroid assay.

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