Unexpected outcome (positive or negative) including adverse drug reactions

Spironolactone, a possible selective androgen receptor modulator, should be used with caution in patients with metastatic carcinoma of the prostate

Santhanam Sundar, Peter D Dickinson

Oncology Department, Nottingham University Hospitals NHS Trust, Nottingham, UK

Correspondence to Dr Santhanam Sundar, santhanam.sundar@nuh.nhs.uk

Summary

The authors report the case of an 80-year-old man who had heavily pretreated castration refractory carcinoma of the prostate and heart failure. Following the introduction of spironolactone to manage his heart failure, the patient experienced clinical and biochemical progression of his prostate cancer. Within 2 weeks of withdrawing spironolactone the patient's prostate-specific antigen returned its previous level. This is the first reported case of clinical and biochemical progression of prostate cancer following the introduction of spironolactone. The authors propose that spironolactone is a selective androgen receptor modulator. Spironolactone should be used in caution with men with prostate cancer, and should not be used to treat oedema, hypokalaemia and hypertension associated with the newly licensed hormonal therapy abiraterone acetate.

BACKGROUND

In 2010, nearly 2 million prescriptions were issued for spironolactone in England.¹ Prostate cancer is the most common male cancer and excellent long-term survival rates have lead to a high prevalence of prostate cancer, particularly in the older population (In the UK, 10 year estimated prevalence is 181 000 cases).² Hence spironolactone, by chance alone, is likely to be prescribed to many patients with prostate cancer who are at risk of various cardiac problems by virtue of ageing.

Furthermore, abiraterone, a newly licensed hormonal therapy, is associated with mineralocorticoid excess and spironolactone has the potential to be used with this new therapy currently under review by the National Institute of Clinical Excellence in the UK.

Abiraterone is a selective irreversible inhibitor of 17α hydroxylase/C17,20-lyase (cytochrome P450c17 (CYP17)). Inhibition of CYP17 prevents the conversion of pregnenolone to dehydroepiandrosterone (DHEA) and the conversion of progesterone into androstenedione. DHEA and

Figure 1 The effect of abiraterone acetate on adrenal steroid hormone synthesis.

Figure 2 Change in PSA following the introduction and withdrawal of spironolactone.

androstenedione are potent androgens and are precursors of testosterone. Androgen ablation plays an important role in the treatment of prostate cancer and androgens synthesised in the adrenal glands have been shown to be responsible for prostate cancer progression.

Abiraterone's selective inhibition of the 17α hydroxylase pathway leads to diversion of the steroid hormone synthetic pathway via 11β hydroxylase. This diversion leads to increased levels of deoxycorticosterone and corticosterone which can lead to mineralocorticoid based side effects such as hypertension, fluid retention and hypokalaemia. These side effects can be reduced by administering prednisolone alongside abiraterone. Figure 1 summarises the effects of abiraterone on the steroid pathway.

As would be expected predicted from its unique mechanism of action, mineralocorticoid related adverse events were commonly observed with abiraterone acetate in a phase III placebo-controlled randomised trial.³

As the use of abiraterone becomes more widespread, treatment related oedema, hypokalaemia and hypertension will become more prevalent. Researchers involved in the development of abiraterone acetate advise against the use of spironolactone to manage treatment related hypertension, stating that spironolactone can act as an agonist on the androgen receptor causing tumour progression.⁴

Spironolactone, a potassium sparing diuretic, is widely used in clinical practice to treat heart failure, oedema and ascites. It is an aldosterone antagonist which exerts its diuretic effect by binding to intracellular receptors in the distal renal tubule. The actions of spironolactone are not limited to this single mechanism. Spironolactone is also an antiandrogen which binds to the androgen receptor.⁵ This antiandrogen effect has been used to benefit in the treatment of

hirsutism⁶ and acne.⁷ Spironolactone has also been shown to inhibit cytochrome P450 which is necessary for the synthesis of androgens in the adrenal glands and testis⁸ and reduces the production of cortisol and aldosterone.⁹

The antiandrogenic effects of spironolactone make it potentially useful in the treatment of prostate cancer. Spironolactone has been shown to reduce levels of testosterone, androstenedione and dehydroepiandrosterone in castrated men with prostate cancer.¹⁰ Consistent with the antiandrogenic activity of spironolactone, there is a report of a clinical and prostate-specific antigen (PSA) response in a man with prostate cancer treated with spironolactone.¹¹

This paper documents the first reported case of clinical and biochemical progression of prostate cancer following the treatment with spironolactone. This unexpected proandrogenic affect potentially offers a unique insight into the pharmacology of spironolactone.

CASE PRESENTATION

Here we report the case of an 80-year-old man with metastatic castration refractory carcinoma of the prostate. The patient initially presented with a PSA of 22 $\mu\text{g/l}$ and biopsy proven Gleason 9 adenocarcinoma of the prostate. During the course of his illness, the patient received numerous lines of treatment for prostate cancer including indefinite goserelin injections, bicalutamide, diethylstilboestrol, cyproterone acetate, eight cycles of docetaxel chemotherapy, six cycles of mitoxantrone chemotherapy, oral daily metronomic cyclophosphamide and dexamethasone.

In addition to metastatic prostate cancer, the patient developed congestive cardiac failure during the last year of his illness. A transthoracic echocardiogram confirmed dilated cardiomyopathy with a poor left ventricular ejection

fraction. His serum brain natriuretic peptide (BNP) was raised (8406 pg/ml). A consultant cardiologist managed his cardiac failure. The patient's heart failure was initially treated with intravenous furosemide, ramipril and digoxin. This resulted in a good symptomatic response and a corresponding fall in BNP was noted. He was subsequently started on spironolactone.

INVESTIGATIONS

Within 1 week of starting spironolactone the patient had significant clinical and biochemical progression of his prostate cancer; his PSA rose from 95 µg/l to 205 µg/l, his alkaline phosphatase increased from 741 u/l to 884 u/l, and he developed significant bone pain (figure 2).

DIFFERENTIAL DIAGNOSIS

There was no change in any other therapy, including ongoing hormone therapy, and the patient did not have any urinary tract infection, bladder catheterisation or any other procedures that could have caused the PSA to be falsely raised. There was no change in analgesics immediately before this episode.

OUTCOME AND FOLLOW-UP

Spironolactone was withdrawn and within 2 weeks his PSA fell to 116 µg/l, his alkaline phosphatase fell to 553 u/l and his bone pain resolved. The rise and fall in the patient's PSA in relation to his treatment with spironolactone is demonstrated in figure 2. Six weeks after the spironolactone was discontinued, the patient's PSA was 76.6 µg/l and alkaline phosphatase was 879 u/l. No other medication changes in his were made during this period.

It was concluded that spironolactone was responsible for the flare of the patient's PSA and symptoms because of the temporal relationship between the introduction of spironolactone and clinical progression, and the subsequent resolution of symptoms and fall in PSA following withdrawal of the drug. The patient was not re-challenged with spironolactone again.

DISCUSSION

In addition to the well-documented antiandrogenic activity, there is experimental evidence to suggest that paradoxically spironolactone also has pro-androgenic activity; the growth of androgen-sensitive cells has been shown to increase in the presence of spironolactone.¹² We believe that it was this positive androgenic effect of spironolactone which was responsible for the flare of disease activity seen in the patient described here.

The previously published antiandrogenic characteristics of spironolactone, and the case reported here with pro-androgenic activity, suggest that spironolactone is a compound which can exhibit both agonist and antagonistic effects on the androgen receptor. On this evidence, we propose that spironolactone belongs to a new class of drugs called selective androgen receptor modulator (SARM) with pharmacological similarity to the well-known selective oestrogen receptor modulators (SERMs), such as tamoxifen. SERMs have both pro-and antioestrogenic properties on different tissues; tamoxifen has antioestrogenic effects in breast tumours, but pro-oestrogenic effects in the uterus and in bones. This differential effect is due to

the drug causing slightly different conformational changes in the oestrogen receptor which affects the receptor's subsequent interaction with co regulators.^{13 14} The expression and activity of these co regulators varies between cell types and tissues. The cellular and molecular environment which would influence spironolactone's differential action needs further experimental work.

As a result of the case discussed here, we believe that spironolactone should be used with caution in patients with carcinoma of the prostate. As the use of abiraterone acetate increases, there will be an increase in the incidence of treatment related oedema, hypokalaemia and hypertension; we recommend that spironolactone is not prescribed in this situation and the use of alternative medication should be considered. Similarly, particularly as the incidence of both prostate cancer and heart failure increase with age, spironolactone should be used with caution to manage heart failure in men with both pathologies.

Learning points

- ▶ Spironolactone has the potential to cause clinical and biochemical progression of prostate cancer.
- ▶ Abiraterone acetate increases the production of mineralocorticoids, which is associated with treatment related oedema, hypokalaemia and hypertension.
- ▶ Spironolactone should not be used to treat oedema, hypokalaemia and hypertension associated with abiraterone treatment in men with prostate cancer.
- ▶ We propose that spironolactone be classified as a SARM.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Prescription Cost Analysis, England – 2010. <http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england--2010> (accessed 7 November 2011).
2. Cancer research UK: Cancerstats. Incidence and prevalence of prostate cancer. <http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence> (accessed 7 November 2011).
3. **Scher HI**, Logothetis C, Molina A, *et al*. Improved survival outcomes in clinically relevant patient subgroups from COU-AA-301, a phase III study of abiraterone acetate (AA) plus prednisone (P) in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel-based chemotherapy. *J Clin Oncol* 2011;**29**(suppl 7; abstr 4).
4. **Attard G**, Reid AH, de Bono JS. Abiraterone acetate is well tolerated without concomitant use of corticosteroids. *J Clin Oncol* 2010;**28**:e560–1; author reply e562.
5. **Eil C**, Edelson SK. The use of human skin fibroblasts to obtain potency estimates of drug binding to androgen receptors. *J Clin Endocrinol Metab* 1984;**59**:51–5.
6. **Cumming DC**, Yang JC, Rebar RW, *et al*. Treatment of hirsutism with spironolactone. *JAMA* 1982;**247**:1295–8.
7. **Muhlemann MF**, Carter GD, Cream JJ, *et al*. Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol* 1986;**115**:227–32.
8. **Menard RH**, Guenther TM, Kon H, *et al*. Studies on the destruction of adrenal and testicular cytochrome P-450 by spironolactone. Requirement for the 7α-thio group and evidence for the loss of the heme and apoproteins of cytochrome P-450. *J Biol Chem* 1979;**254**:1726–33.
9. **Ye P**, Yamashita T, Pollock DM, *et al*. Contrasting effects of eplerenone and spironolactone on adrenal cell steroidogenesis. *Horm Metab Res* 2009;**41**:35–9.
10. **Walsh PC**, Siiteri PK. Suppression of plasma androgens by spironolactone in castrated men with carcinoma of the prostate. *J Urol* 1975;**114**:254–6.

11. **Rybikowski S**, Maurin C, Deturmeny J, *et al.* [PSA and spironolactone]. *Prog Urol* 2010;**20**:154–7.
12. **Luthy IA**, Begin DJ, Labrie F. Androgenic activity of synthetic progestins and spironolactone in androgen-sensitive mouse mammary carcinoma (Shionogi) cells in culture. *J Steroid Biochem* 1988;**31**:845–52.
13. **McKenna NJ**, O'Malley BW. An issue of tissues: divining the split personalities of selective estrogen receptor modulators. *Nat Med* 2000;**6**:960–2.
14. **Osborne CK**, Zhao H, Fuqua SA. Selective estrogen receptor modulators: structure, function, and clinical use. *J Clin Oncol* 2000;**18**:3172–86.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Sundar S, Dickinson PD. Spironolactone, a possible selective androgen receptor modulator, should be used with caution in patients with metastatic carcinoma of the prostate. *BMJ Case Reports* 2012;10.1136/bcr.11.2011.5238, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow

Keep up to date with all published cases by signing up for an alert (all we need is your email address) <http://casereports.bmj.com/cgi/alerts/etoc>