Br. J. clin. Pharmac. (1984), **17**, 347–351

Changes in circulating androgens during short term carbamazepine therapy

J. M. C. CONNELL, W. G. RAPEPORT, G. H. BEASTALL[1] & M. J. BRODIE

Department of Medicine, Gardiner Institute, Western Infirmary and [1]Endocrine Biochemistry Laboratory, Royal Infirmary, Glasgow

1 Serum concentrations of testosterone, androstenedione, dehydroepiandrosterone sulphate (DHAS), sex hormone binding globulin (SHBG) and luteinising hormone (LH) were measured before, during and after 21 days treatment with carbamazepine (CBZ) 400 mg daily in six healthy male subjects.

2 Induction of hepatic microsomal enzyme activity was confirmed by an increase in antipyrine clearance ($P < 0.02$) and a fall in circulating CBZ concentrations from the seventh to the fourteenth CBZ dose ($P < 0.05$).

3 Within 7 days of starting CBZ there was a rise in SHBG ($P < 0.05$) and a fall in testosterone, free testosterone fraction, DHAS and androstenedione ($P < 0.05$).

4 Testosterone, free testosterone fraction and androstenedione levels rose towards baseline by the end of the treatment period while DHAS concentration remained low ($P < 0.05$).

5 The rise in SHBG and increased androgen catabolism is most likely to be secondary to induction of hepatic monooxygenase activity by CBZ.

6 These changes may be implicated in the production of sexual dysfunction encountered in some epileptic patients on chronic anticonvulsant therapy.

Keywords carbamazepine androgens

Introduction

Diminished libido and impaired spermatogenesis occur in male subjects with epilepsy (Taylor, 1969; Toone *et al.*, 1980), and have been attributed to a reduction in androgenic activity secondary to anticonvulsant therapy (Toone *et al.*, 1980). It has been suggested that this is due to a fall in circulating free testosterone levels secondary to a rise in sex hormone binding globulin (SHBG) concentration, and possibly also to a change in hepatic metabolism of testosterone (Dana-Haeri *et al.*, 1982). Previous reports have, however, been unable to differentiate between these two possible effects and most patients received combination anticonvulsant therapy (Toone *et al.*, 1980; Dana-Haeri *et al.*, 1982). We describe a prospective study of the influence of short term therapy with the anticonvulsant drug carbamazepine (CBZ) on androgen levels and SHBG in a group of healthy male subjects.

Methods

Subjects

Six healthy male Caucasian subjects each ingested CBZ (Tegretol, Geigy) 400 mg at 22.00 h for 21 days. No subject had evidence of hepatic or renal dysfunction. No other drugs were taken prior to or during the study, and subjects were requested to abstain from alcohol during the course of the study. All subjects were non-smokers. Subjects

gave written informed consent prior to entry to study which was approved by the Hospital Ethics Committee.

Protocol

Venous blood (15 ml) was taken for measurement of serum testosterone, dehydroepiandrosterone sulphate (DHAS), androstenedione, SHBG and luteinising hormone (LH) before starting CBZ, after 7, 14 and 21 days of therapy and 3 weeks after stopping CBZ. On each occasion subjects were studied at 09.00 h. Serum and plasma samples were stored at −20°C and all assays performed in a single batch. As an index of hepatic enzyme induction the kinetics of antipyrine were measured in the week prior to CBZ treatment and on the last day of treatment. Antipyrine (600 mg p.o.) was taken at 09.00 h, and saliva collected for antipyrine assay at 3, 5, 8, 12, 24 and 32 h thereafter.

CBZ plasma concentrations were measured 12 and 16 h after the 7th, 14th and 21st doses.

Assays

Serum testosterone was measured in ether extracts of human serum using a radioimmunoassay that employs a rabbit antiserum to testosterone-3-(*o*-carboxymethyloxime)-BSA, an [^{125}I]-histamine-17-testosterone radioligand and a double antibody separation. This antibody cross reacts with 5-dihydrotestosterone (21%). However, as the circulating concentrations of this steroid are very low, this cross reactivity is unimportant when assaying testosterone in serum or plasma. The reference range for adult men is 11–36 nmol/l. Serum androstenedione was quantitated using a similar assay that employs rabbit antiserum to androstenedione-17-carboxythio-ether ovalbumin and (1,2,6,7-[^{3}H])-androstenedione. The appropriate reference range is 2–11 nmol/l. Serum DHAS was estimated in diluted serum using a radioimmunoassay that employs rabbit antiserum to dehydroepiandrosterone-3-hemisuccinate - BSA, (7-[^{3}H](n))-DHAS as radioligand and a double antibody separation. There is cross reactivity with dehydroepiandrosterone (129%) and androstenedione (30%). As serum DHAS concentrations are a thousandfold higher than either of these androgens, such cross reactivity has little practical significance. The reference range is 2–12 nmol/l. Sex hormone binding globulin capacity was determined in serum with a [^{3}H]-dihydrotestosterone (DHT) saturation assay based on that of Rosner (1972). The reference range for adult men is 5–45 nmol/l DHT bound. Serum LH was measured with a conventional double antibody radioimmunoassay using reagents recommended by the UK External Quality Assessment Scheme for gonadotrophins. The reference range for men aged less than 50 years is < 8.0 u/l. All the above assays have intra-assay imprecision in the range 5–10% CV.

Antipyrine was assayed using high pressure liquid chromatography (h.p.l.c.) by a modification of the method of Shargal *et al.* (1979). CBZ concentrations were also measured by h.p.l.c. (Meijer, 1981). Antipyrine kinetics were calculated by linear regression using the method of least squares. Statistical analysis of data was performed using Student's *t*-test for paired values. Correlations were obtained by the Spearman ranking procedure.

Results

The changes seen in SHBG, testosterone, free testosterone fraction, DHAS, androstenedione and LH are shown in Figure 1. SHBG rose within 7 days of starting CBZ ($P < 0.05$); mean SHBG concentration was highest after 14 days treatment, and remained elevated after 21 days treatment. A fall was noted in total testosterone concentration during CBZ treatment, being maximal at 7 days after the start of therapy. Testosterone levels had returned to the pre-treatment baseline after 21 days of CBZ. Free testosterone fraction

$$\text{testosterone} \times \frac{1}{\text{SHBG}}\%$$

fell in parallel with total testosterone ($P < 0.05$), although the magnitude of fall was greater. Again, by the end of the treatment period, free testosterone fraction had returned to the pre-treatment level.

Androstenedione and DHAS concentrations also fell during CBZ therapy ($P < 0.05$). Androstenedione, like testosterone and free testosterone fraction, tended to return to pre-therapy values during continued CBZ treatment. In contrast, mean DHAS concentrations remained low during the entire period of ingestion. Following withdrawal of CBZ, DHAS concentrations returned to pre-treatment levels. No consistent change was seen in LH levels during the study.

In all subjects induction of antipyrine oxidation occurred so that antipyrine half-life fell and clearance rose ($P < 0.02$). There was no change in volume of distribution (Table 1). CBZ concentrations during the study are shown in Figure 2. The fall in mean CBZ concentration at 12 and 16 h between the 7th and subsequent dose ($P < 0.05$) is consistent with autoinduction of CBZ levels between 14th and 21st doses. No relationship between changes in antipyrine metabolism

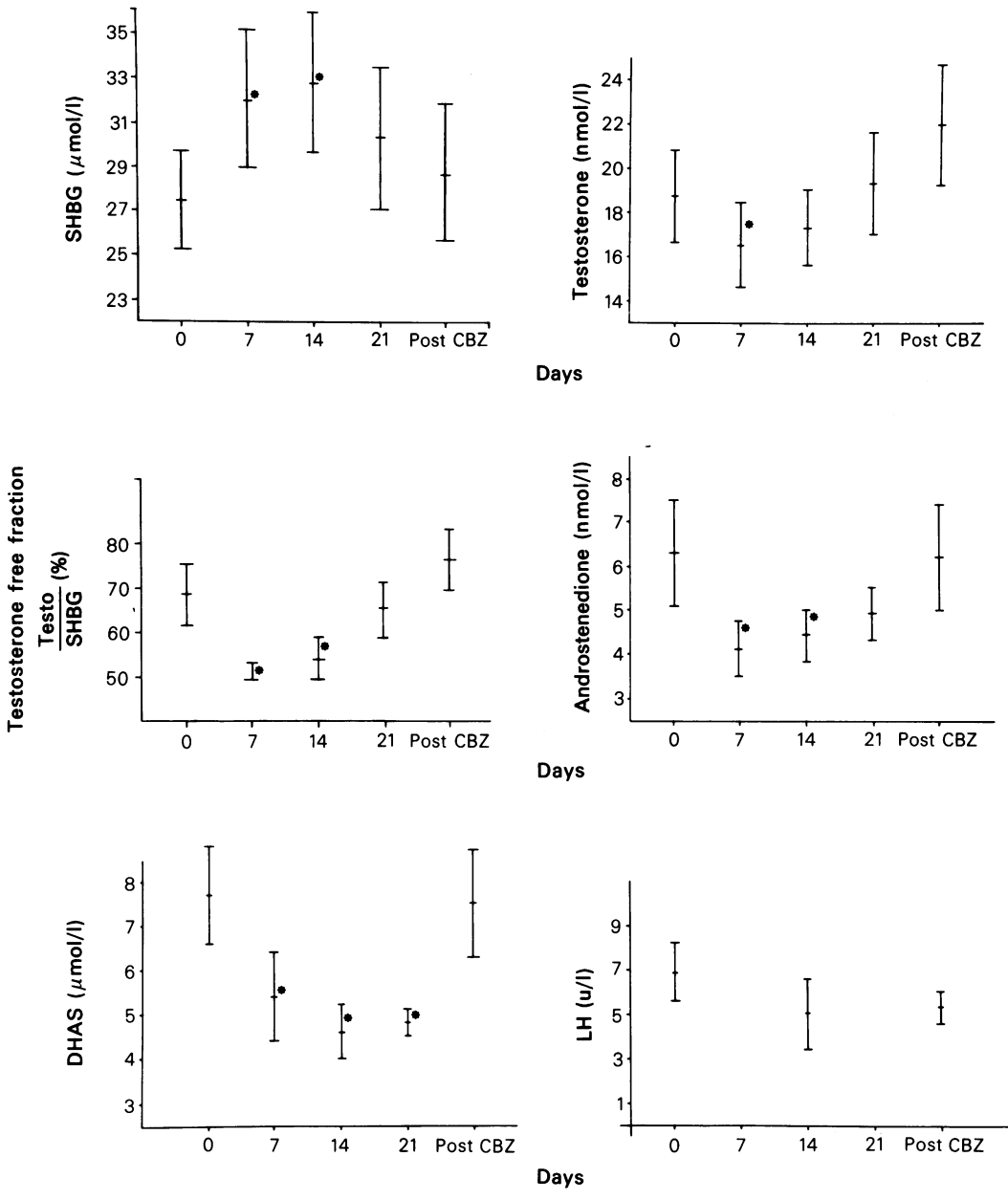

Figure 1 Changes in sex hormone binding globulin (SHBG), testosterone, free testosterone fraction, androstenedione, dehydroepiandrosterone (DHAS) and luteinising hormone (LH) during CBZ therapy. CBZ (400 mg/day) was given from Day 0–Day 21. All values are mean ± s.e. mean. Statistics were obtained using Student's *t*-test for paired values. * $P < 0.05$.

Table 1 Changes in antipyrine kinetic parameters (mean ± s.d.) following treatment with carbamazepine 400 mg daily for 21 days in six healthy male subjects.

	Basal	*21 days*
Elimination half-life (h)	10.4 ± 1.7	6.8* ± 1.2
Systematic clearance (ml min $^{-1}$kg^{-1})	0.79 ± 0.17	1.1* ± 0.3
Volume of distribution (l)	48.4 ± 9.3	45.6 ± 8.4

Statistics are by Student's *t*-test for paired values. * $P < 0.02$

or in CBZ concentrations and in SHBG and androgen levels was observed.

Discussion

CBZ is a first-line anticonvulsant exhibiting dose-dependent enzyme inducing properties (Rapeport *et al.*, 1983). We have shown that shortly after starting CBZ therapy there is a fall in free testosterone fraction in male subjects. This is partly accounted for by a rise in SHBG, which is presumably secondary to an increase in hepatic SHBG synthesis. The time course of the changes seen makes it likely that this rise in SHGB concentration is a primary effect of CBZ on hepatic synthetic enzyme activity rather than a secondary event following an anticonvulsant induced fall in circulating sex hormone concentrations (Toone *et al.*, 1980). Other drugs which induce hepatic monooxygenase synthesis such as phenytoin and rifampicin have also been shown to lead to a rise in SHBG concentrations (Victor *et al.*, 1977; Brodie *et al.*, 1981). In contrast to studies with rifampicin, however, total testosterone levels did not rise in parallel with SHBG during CBZ therapy. This suggests that either testosterone production is inhibited or testosterone disposal enhanced by CBZ. The early rate limiting steps in steroid biosynthesis are catalysed by a mitochondrial cytochrome P450 monooxygenase system (Butt, 1976) and CBZ therapy might, in theory, be expected to lead to an increase in androgen production by inducing the activity of such enzymes in testis and adrenal. The actual fall seen in total testosterone is likely, therefore, to be due to enhanced testosterone disposal. Testosterone undergoes biotransformation by the hepatic microsomal mixed function enzyme system prior to excretion, largely in conjugate form (Vermeulen, 1979). CBZ induction of hepatic microsomal enzymes may increase the activity of this excretory pathway and so lead to a fall in total testosterone (Fingal & Woodbury, 1977).

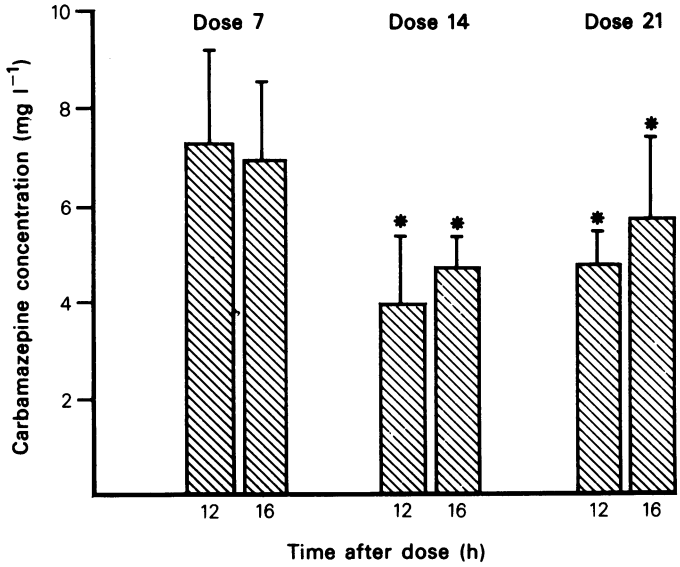

Figure 2 'Steady state' plasma carbamazepine concentrations (12 and 16 h) after the seventh, fourteenth and twenty-first doses. Values shown are mean ± s.e. mean Statistics were obtained using Student's *t*-test for paired values. * $P < 0.05$.

The increase in antipyrine clearance and the demonstration of autoinduction of CBZ metabolism provide confirmation of induction of the hepatic microsomal enzyme system in this study. The maximal changes noted in SHBG and androgen levels in the current study occurred following 7 days treatment, which seem to mirror the time course of induction with CBZ (Rapeport *et al.*, 1983). The marked fall in DHAS and androstenedione concentrations is also likely to be due to enhanced androgen metabolism secondary to hepatic enzyme induction. Unlike testosterone, neither hormone is bound to a high affinity carrier protein such as SHBG, and the changes seen are likely to result from direct effects on the catabolism of these androgenic substances. The maximum change in mean DHAS concentration occurred after 14 days therapy, in comparison with androstenedione and testosterone, where maximum changes were seen after 7 days. This may reflect the much larger circulating pool of DHAS (μM) compared with androstenedione and testosterone (nM).

During continued therapy with CBZ, testosterone concentrations, free testosterone fraction and androstenedione rose towards pre-treatment levels. Although CBZ concentrations fell during the latter part of the study as a result of autoinduction, this seems unlikely to account for this effect in view of the evidence of sustained hepatic microsomal enzyme induction at the end of the treatment period. The secondary rise in testosterone and androstenedione levels may reflect increased testicular steroidogenesis induced by LH stimulation. Circulating testosterone in man is almost wholly of testicular origin; around 30% of androstenedione is derived from the testes. As most DHAS is secreted by the adrenal gland, increased LH activity would not be expected to affect circulating DHAS levels (Vermeulen, 1979). LH levels have been shown to be elevated in subjects taking chronic anticonvulsant therapy (Dana-Haeri & Richens, 1981), and this rise in LH is thought to be secondary to a fall in the free testosterone fraction. We were unable to demonstrate a change in mean LH levels during CBZ therapy in this study, but failure to do so may have been due in part to the pulsatile nature of LH secretion.

We have confirmed that in male subjects complex changes in circulating androgen concentrations occur shortly after the start of CBZ therapy and that these coincide with the induction of hepatic monooxygenase activity. The significance of a sustained fall in circulating adrenal androgens in adult males is unclear. Adrenal androgens may play an important role in the control of linear growth and in the initiation of puberty (Tanner, 1981) and the effect of chronic CBZ therapy on these factors in children and adolescents merits further study.

Our grateful thanks go to Moira Duffy and Carol Downes for secretarial assistance and Geigy Pharmaceuticals for financial support.

References

Brodie, M. J., Boobis, A. R., Gill, M. & Mashiter, K. (1981). Does rifampicin increase serum levels of testosterone and oestradiol by inducing sex hormone binding globulin capacity? *Br. J. clin. Pharmac.*, **12**, 431–432.

Butt, W. R. (1976). *Hormone Chemistry* 2nd edition, Vol. 2, pp. 16–59. Chichester: Ellis Harwood Ltd.

Dana-Haeri, J. & Richens, A. (1981). Effect of antiepileptic drugs on the hypothalmic/pituitary axis. *Br. med. J.*, **282**, 902.

Dana-Haeri, J, Oxley, J. & Richens, A. (1982). Reduction of free testosterone by antiepileptic drugs. *Br. med. J.*, **284**, 85–86.

Fingel, E. & Woodbury, D. M. (1977). In *The Pharmacological Basis of Therapeutics* 5th edition, pp. 1–46, eds Goodman, L. S. & Gilman, A. New York: McMillan.

Meijer, J. W. A. (1981). Antiepileptic drugs: analytical techniques In *Therapeutic Drug Monitoring*, eds. Richens, A. & Marks, V., pp. 349–369. Edinburgh: Churchill Livingstone.

Rapeport, W. G., McInnes, G. T., Thompson, G. G., Forrest, G., Park, B. K. & Brodie, M. J. (1983). Hepatic enzyme induction and leucocyte delta aminolaevulinic acid synthase activity: studies with carbamazepine. *Br. J. clin. Pharmac.*, **16**, 133–137.

Rosner, W. (1972). A simplified method for the quantitative determination of testosterone-estradiol binding globulin activity. *J. clin. Endocrinol. Metab.*, **34**, 983–988.

Shargal, L., Cheung, W. & Yu, A.B.C. (1979). High pressure liquid chromatographic analysis of antipyrine in small plasma samples. *J. pharm. Sci.*, **68**, 1050–1053.

Tanner, J. M. (1981). Endocrinology of puberty. In *Clinical Paediatric Endocrinology*, 1st Edition, ed. Brook, C. G. D., pp. 207–223. Oxford: Blackwell.

Taylor, M. (1969). Sexual behaviour and temporal lobe epilepsy. *Arch. Neurol.*, **21**, 510–516.

Toone, B. K., Wheeler, M. & Fenwick, P. B. C. (1980), Sex hormone changes in male epileptics. *Clin. Endocrinol.*, **12**, 391–395.

Vermeulen, A. (1979). The Androgens In *Hormones in Blood* 3rd Edition, eds. Gray, C. H. & James, V. H. T. pp. 356–416. London: Academic Press.

Victor, A., Lundberg, P. O. & Johansson, E. D. B. (1977), Induction of sex hormone binding globulin by phenytoin. *Br. med. J.*, **2**, 934–935.

(Received July 18, 1983
accepted October 31, 1983)