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ORIGINAL ARTICLE

Eplerenone reverses spironolactone-induced painful gynaecomastia in cirrhotics

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Abstract
Purpose To investigate the efficacy and safety of aldosterone antagonist, eplerenone in the treatment of spironolactone-induced painful gynaecomastia in cirrhotic patients.
Methods A number of 19 consecutive patients with cirrhosis due to alcohol abuse or chronic hepatitis B, who had been administered spironolactone and suffered from painful gynaecomastia, have been included in the study. Substitution of spironolactone with eplerenone was followed for 3 months under close inspection. Age and gender, along with Child–Pugh stage of cirrhosis, pain (in a 1–5 visual analogue scale), Na^+, K^+, FSH, LH, 17 (OH) progesterone, DHEA-S, testosterone, and prolactin were measured at the beginning and the end of the study.
Results All 19 patients expressed alleviation of pain ($P < 0.001$). Two patients deteriorated and two other ameliorated as far as the Child–Pugh score is referred. All biochemical and hormonal parameters remained unchanged.
Conclusion In cirrhotic patients with painful gynaecomastia, the use of eplerenone instead of spironolactone might reverse pain and seems to be safe and clinically acceptable option.

Keywords Eplerenone · Spironolactone · Cirrhosis · Gynaecomastia

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Background and purpose

One of the main therapeutic goals in cirrhotic ascites is to combat secondary aldosteronism. Spironolactone has been extensively used for this purpose, despite its potential side effects, including hyperkalemia, gynaecomastia, and impotence. Recently, a second aldosterone antagonist, eplerenone has been introduced mainly for the treatment of essential hypertension and congestive heart failure. However, until now, there are no data published concerning the efficacy and safety of eplerenone in the treatment of cirrhotic ascites. In one of the previous works, we have reported the efficacy of eplerenone to reverse spironolactone-induced painful gynaecomastia only in four cirrhotic patients with chronic hepatitis B [1]. Therefore, we have now conducted an observational study in order to further support the efficacy of eplerenone in alleviating painful gynaecomastia in cirrhosis.

Material and methods

For the purposes of the study, 19 consecutive patients with painful bilateral gynaecomastia and cirrhosis were included in the study. All patients were treated with spironolactone (50–100 mg b.i.d.) plus furosemide (20–40 mg b.i.d.) for at least 6 months. A switch of spironolactone to eplerenone at 50 mg b.i.d. was introduced. In all the patients, spironolactone was substituted by eplerenone (100 mg of aldosterone was considered equivalent to 50 mg of eplerenone). Substitution of spironolactone with eplerenone lasted for 3 months during which the patients were under close inspection. Age and gender was recorded for every patient. Child–Pugh stage of cirrhosis, the presence or the absence of gynaecomastia, and pain (in a 1–5 visual analogue scale; 1: no pain and 5: unbearable pain) were also recorded at the

beginning and the end of the study. Moreover, K^+, Na^+, FSH (follicle-stimulating hormone), LH (luteinizing hormone), 17 (OH) progesterone, DHEA-S (dehydroepiandrosterone sulphate), testosterone, and prolactin were measured at the beginning and the end of the study.

Informed consent was obtained from each patient included in the study and the study protocol was approved by the Scientific Committee of the University Hospital of Alexandroupolis.

For comparisons between values at the beginning and the end of the study, the Wilcoxon's paired test was used. All tests are two-tailed. All means include at least three significant digits and are accompanied by their standard deviation values. The level of statistical significance was set to $P = 0.05$. The statistical package Statistica 6.0 was used for all computations.

Results

All 19 patients were males and their mean age was 64.4 ± 13.3 years. Among them, 12 were alcohol abusers and 7 suffered from chronic hepatitis B.

All 19 patients reported relief of pain and regression of gynaecomastia ($P < 0.001$). As far as the severity of cirrhosis is referred, two patients deteriorated (from Child–Pugh stage B to C) and two other ameliorated (from Child–Pugh stage C to B). All biochemical and hormonal parameters remained unchanged (Table 1).

Discussion

In the present study, we investigated the efficacy and safety of eplerenone in reversing spironolactone-induced painful gynaecomastia in patients with cirrhosis. All patients who received eplerenone instead of spironolactone expressed relief of pain and significant regression of gynaecomastia. However, the clinical severity of the underlying cirrhosis during the study period remained unchanged.

Although spironolactone is the current drug of choice for the treatment of cirrhotic ascites, the potential serious side effects might limit its use. More specifically, gynaecomastia is dose- and time-dependent and may be clinically pronounced. A number of mechanisms have been proposed to explain this phenomenon including a dose-dependent reduction of microsomal cytochrome P450, alterations in the testosterone/oestrogen ratio, a peripheral conversion of testosterone to oestradiol, a decrease in testosterone or increase in oestrone, and oestradiol serum levels [2].

In contrast to spironolactone, eplerenone is 40 times less potent in blocking aldosterone activation of the mineralocorticoid receptor and 370 times less potent in blocking dihydrotestosterone activation of androgen receptors. The limited sexual side effects of eplerenone have been documented in the EPHESUS (eplerenone post acute myocardial infarction heart failure efficacy and survival study) [3]. In this study, the incidence of gynaecomastia in men was 0.5% (comparable with placebo). In contrast, in the RALES (randomized aldactone evaluation study) [4], the evaluation of spironolactone, gynaecomastia as well as breast pain was significantly more frequent (9% in treated patients vs. 1% in the placebo group). In our study, eplerenone was not accompanied by any side effects, serum electrolyte, or hormonal changes.

In conclusion, we report for the first time that a highly selective aldosterone antagonism, by means of eplerenone, could be a more appropriate therapeutic tool in comparison with spironolactone in cirrhotic patients with ascites. Further studies are needed to establish the efficacy and safety in this group of patients.

Table 1 Comparison between biochemical and clinical parameters at the beginning and at the end of the study

	Beginning of the study	End of the study	*P*
Child–Pugh score	8.45 ± 1.32	8.45 ± 1.32	1.000
Serum K^+ concentration (meq/l)	4.82 ± 0.87	4.27 ± 0.53	0.104
Serum Na^+ concentration (meq/l)	136 ± 5	140 ± 3	0.060
FSH (mU/ml)	6.61 ± 5.21	5.74 ± 4.20	0.597
LH (mU/ml)	7.89 ± 5.47	5.22 ± 2.30	0.073
Testosterone (ng/ml)	3.62 ± 2.16	2.89 ± 2.41	0.367
DHEA-S (μg/ml)	64.5 ± 48.9	54.8 ± 45.6	0.560
17 (OH) PG (ng/ml)	2.94 ± 4.99	0.75 ± 0.49	0.091
Prolactin (ng/ml)	9.41 ± 4.05	8.49 ± 3.18	0.580
Pain due to gynaecomastia	3.00 ± 0.84	1.00 ± 0.00	0.001

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