MINISTERIO DE SALUD
INSTITUTO DE SALUD PUBLICA DE CHILE
DEPARTAMENTO CONTROL NACIONAL
AVDA. MARATHON 1000 — FONO: 2391105
CASILLA 48 — DIREC. TELEG. "BACTECHILE"
SANTIAGO

02.DIC.1992 * 15856

Ref.: 3139/92
30 / 11 / 92
EMZ/TTA/mmr

SANTIAGO,

VISTO ESTOS ANTECEDENTES: la presentación del Químico Farmacéutico, Director Técnico, y en representación de la firma Laboratorio Benguerel Ltda., por la que solicita registro del producto farmacéutico FUROSEMIDA 40 mg COMPRIMIDOS, para los efectos de su fabricación y venta en el país, el que será fabricado por Laboratorios Andrómaco S.A., de acuerdo a convenio notarial de fabricación suscrito entre las partes; el Informe Técnico respectivo; y

TENIENDO PRESENTE: las disposiciones del Código Sanitario, decreto con fuerza de ley N° 725 de 1968; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, Alimentos de Uso Médico y Cosméticos y del Reglamento de Farmacias, Droguerías, Almacenes Farmacéuticos y Botiquines Autorizados, aprobados por los decretos supremos N°s. 435 de 1981 y 466 de 1984, respectivamente, ambos del Ministerio de Salud; y en uso de las facultades que me confieren la letra b) del Art. 39° del decreto ley N° 2763 de 1979, el decreto supremo N° 79 de 1980 del Ministerio de Salud y la Resolución N° 027 de 1980 del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I O N

1.- INSCRIBASE en el Registro Nacional de Productos Farmacéuticos, Alimentos de Uso Médico y Cosméticos bajo el N°s32951, el producto farmacéutico FUROSEMIDA 40 mg COMPRIMIDOS a nombre de la firma Laboratorio Benguerel Ltda., para los efectos de su fabricación y venta en el país, en las condiciones que se indican:

a) Este producto será fabricado como producto terminado por el Laboratorio de Producción de propiedad de la firma Laboratorios Andrómaco S.A., ubicado en Avda. Vicuña Mackenna 3451, Santiago, por cuenta de la firma mandante Laboratorio Benguerel Ltda, quien efectuará la distribución y venta, como propietaria del Registro Sanitario.

b) La fórmula aprobada corresponde a la siguiente composición y en la forma que se señala:

Cada comprimido contiene:

Furosemida	40,00 mg
Lactosa monohidrato	170,70 mg
Almidón de Maíz	24,50 mg
Talco	7,35 mg
Estearato de magnesio	2,45 mg

c) Período de eficacia: 36 meses.

d) Presentación: Estuche de cartulina impreso con 10, 12, 20 ó 30 comprimidos en blister pack impreso.

Envase clínico: Caja de cartón etiquetada con 100, 500 ó 1000 comprimidos en blister pack impreso.

Los envases clínicos están destinados al uso exclusivo de los Establecimientos Asistenciales y deberán llevar en forma destacada la leyenda: "ENVASE CLINICO SOLO PARA ESTABLECIMIENTOS ASISTENCIALES".

e) Condición de venta: "BAJO RECETA MEDICA EN ESTABLECIMIENTOS TIPO A Y B".

2.- Los rótulos de los envases y folletos para información médica aprobados, deben corresponder exactamente en su texto y distribución a lo aceptado en el anexo timbrado de la presente Resolución, copia del cual se adjunta a ella para su cumplimiento, sin perjuicio de respetar lo dispuesto en el Art. 46° del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, Alimentos de Uso Médico y Cosméticos.

3.- Las especificaciones de calidad del producto terminado deberán conformar al anexo timbrado adjunto y cualquier modificación deberá comunicarse oportunamente a este Instituto.

4.- La firma Laboratorios Andrómaco S.A. se responsabilizará del almacenamiento y del control de calidad de materias primas, material de envase-empaque, producto en proceso y terminado envasado, debiendo inscribir en el Registro General de Fabricación las etapas ejecutadas, con sus correspondientes boletines de análisis, sin perjuicio de la responsabilidad que le compete a la firma mandante Laboratorio Benguerel Ltda., como propietaria del Registro Sanitario.

5.- La prestación de servicios autorizada deberá figurar en los rótulos, individualizando con su nombre y dirección a la firma fabricante, debiendo anotar además el N° de partida o lote correspondiente.

6.- La Droguería deberá comunicar a este Instituto la comercialización de la primera partida o serie que se fabrique, de acuerdo a las disposiciones de la presente Resolución, adjuntando una muestra en su envase definitivo.

ANOTESE Y COMUNIQUESE

INSTITUTO DE SALUD PUBLICA DE CHILE DEPARTAMENTO

DRA. Q.F. RAQUEL GONZALEZ DIEZ
JEFE DEPARTAMENTO CONTROL NACIONAL
INSTITUTO DE SALUD PUBLICA DE CHILE

DISTRIBUCION:

- Laboratorio Benguerel Ltda.
- Laboratorios Andrómaco S.A.
- Sub-Depto. Q. Analítico
- Sub-Depto. A.R.I.
- Archivo.

Transcrito Fielmente
Ministro Fe.

DEPARTAMENTO
Autorización, Registro, e Inspección
OFICINA DE PARTES

318

Instituto de Salud Pública
Ministerio de Salud

Gobierno de Chile

JMC/JON/RSA/npc
Nº Ref.:MA487399/13

MODIFICA A LABORATORIOS ANDRÓMACO S.A., RESPECTO DEL PRODUCTO FARMACÉUTICO FUROSEMIDA COMPRIMIDOS 40 mg, REGISTRO SANITARIO Nº F-11274/11

RESOLUCIÓN EXENTA RW N° 23022/13
Santiago, 30 de octubre de 2013

VISTO ESTOS ANTECEDENTES: la presentación de Laboratorios Andrómaco S.A., por la que solicita **modificación del período de eficacia** para el producto farmacéutico **FUROSEMIDA COMPRIMIDOS 40 mg**, registro sanitario NºF-11274/11; el Informe Técnico Nº 2660, emitido por la Unidad de Metodologías Analíticas;

CONSIDERANDO: Que, el estudio de estabilidad presentado se realizó con un tipo de envase; y

TENIENDO PRESENTE: las disposiciones de los artículos 94º y 102º del Código Sanitario; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, aprobado por el Decreto Supremo Nº 3 de 2010 del Ministerio de Salud y los artículos 59º letra b) y 61º letra b), del D.F.L. Nº 1 de 2005, y las facultades delegadas por la Resolución Exenta N° 1553 de 13 de julio de 2012, del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- AUTORÍZASE para el producto farmacéutico **FUROSEMIDA COMPRIMIDOS 40 mg**, registro sanitario Nº F-11274/11, concedido a Laboratorios Andrómaco S.A., un Período de eficacia de:

- 36 meses, almacenado a no más de 30º C, para el producto envasado en caja de cartón o estuche de cartulina impreso, debidamente sellado que contiene Blister pack de PVDC transparente ámbar / aluminio termosellable impreso, mas folleto de información al paciente.
- 12 meses, almacenado a no mas de 25° C, para el producto envasado en caja de carton o estuche de cartulina impreso, debidamente sellado que contiene Blister pack de PVC transparente, incoloro o ambar / aluminio termosellable impreso, mas folleto de información al paciente.

2.- El nuevo período de eficacia aprobado deberá consignarse claramente en los rótulos del producto, indicando como "Fecha de Vencimiento", el mes y año de expiración de la eficacia del producto, en todas las series o lotes que se fabriquen con posterioridad a la presente resolución.

ANÓTESE Y COMUNÍQUESE

JEFA SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

DRA. Q.F. HELEN ROSENBLUTH LÓPEZ
JEFA SUBDEPARTAMENTO REGISTRO Y AUTORIZACIONES SANITARIAS
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INSTITUTO DE SALUD PUBLICA

TTA/AMM/TCM/ras
B11/ Ref.: 2077/04

SANTIAGO, 18.05.2004*003925

VISTO ESTOS ANTECEDENTES: la presentación de Laboratorios Andrómaco S.A., por la que solicita **nuevo rotulado gráfico** para el producto farmacéutico FUROSEMIDA COMPRIMIDOS 40 mg, registro sanitario Nº F-11.274/01; y

TENIENDO PRESENTE: las disposiciones de los artículos 94 y 102 del Código Sanitario; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, Alimentos de Uso Médico y Cosméticos aprobados por el decreto supremo Nº 1876 de 1995 del Ministerio de Salud y los artículos 37 letra b) y 39 letra b) del decreto ley Nº 2763 de 1979, y las facultades delegadas por la resolución Nº 102 de 1996, del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- AUTORÍZASE el proyecto de rotulado gráfico para el producto farmacéutico FUROSEMIDA COMPRIMIDOS 40 mg, registro sanitario Nº F-11.274/01, concedido a Laboratorios Andrómaco S.A., el cual debe conformar al anexo timbrado de la presente resolución, sin perjuicio de cumplir lo dispuesto en el artículo Nº 49 del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, Alimentos de Uso Médico y Cosméticos.

ANÓTESE Y COMUNÍQUESE

INSTITUTO DE SALUD PUBLICA DE CHILE
Depto. de Control Nacional
JEFE

DRA. Q.F. PAMELA MILLA NANJARÍ
JEFA DEPARTAMENTO CONTROL NACIONAL
INSTITUTO DE SALUD PÚBLICA DE CHILE

DISTRIBUCIÓN:

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- Unidad de Procesos
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Transcrito Fielmente
Ministro de Fe

S/C

LABORATORIOS ANDROMACO S.A.

INSTITUTO DE SALUD PUBLICA
Departamento Control Nacional
Sección Registro

PROYECTO DE ROTULADO GRAFICO

ENVASE VENTA PUBLICO

FUROSEMIDA COMPRIMIDOS 40 mg

INSTITUTO DE SALUD PUBLICA
DEPARTAMENTO DE CONTROL NACIONAL
REGISTRO Nº F- 11.274/01

MANTENGASE FUERA DEL ALCANCE DE LOS NIÑOS

VENTA BAJO RECETA MEDICA
EN ESTABLECIMIENTOS
TIPO A y B

Rotulado gráfico del estuche:

Cara N° 1:

FUROSEMIDA
40 mg

X Comprimidos

Laboratorios Andrómaco S.A.

Cara N°2:

Cada comprimido contiene:
Furosemida 40 mg
Excipientes c.s.

Registro I.S.P. N° F- 11274/01

DEPARTAMENTO CONTROL NACIONAL
Nº. REF 2077/04
01 MAY 2004
UNIDAD DE MODIFICACIONES

Cara N°3:

Administración y dosis vía oral, según prescripción médica.

Manténgase fuera del alcance de los niños, en lugar fresco y seco, a no más de 25°C.

Venta bajo receta médica en establecimientos tipo A y B.

AV.QUILIN 5273 – TELEFONO 510 8500 – FAX 552 9363
SANTIAGO – CHILE

LABORATORIOS ANDROMACO S.A.

INSTITUTO DE SALUD PUBLICA
Departamento Control Nacional
Sección Registro

Cara N°4:

Elaborado y distribuido en Chile por
Laboratorios Andrómaco S.A.
Av. Quilín 5273, Peñalolen, Santiago.

Aleta superior:

FUROSEMIDA
40 mg

X Comprimidos

INSTITUTO DE SALUD PUBLICA
DEPARTAMENTO DE CONTROL NACIONAL
REGISTRO Nº F-11.274/01

MANTENGASE FUERA DEL ALCANCE DE LOS NIÑOS

VENTA BAJO RECETA MEDICA
EN ESTABLECIMIENTOS
TIPO A - B

Aleta inferior:

Serie:

Vence:

DEPARTAMENTO CONTROL NACIONAL
Nº. REF 2077/04
01 MAY 2004
UNIDAD DE MODIFICACIONES

LABORATORIOS ANDROMACO S.A.

INSTITUTO DE SALUD PUBLICA
Departamento Control Nacional
Sección Registro

Rotulado gráfico del blister:

FUROSEMIDA
40 mg

Comprimidos

Reg. I.S.P. Nº: F-11.274/01

Serie:

Vence:

Laboratorios Andrómaco S.A.

INSTITUTO DE SALUD PUBLICA
DEPARTAMENTO DE CONTROL NACIONAL
REGISTRO Nº F-11.274/01

MANTENGASE FUERA DEL ALCANCE DE LOS NIÑOS

VENTA BAJO RECETA MEDICA
EN ESTABLECIMIENTOS
TIPO A

DEPARTAMENTO CONTROL NACIONAL
Nº. REF 2077/04
01 MAY 2004
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LABORATORIOS ANDROMACO S.A.

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Departamento Control Nacional
Sección Registro

Proyecto de rotulado gráfico del envase clínico:

INSTITUTO DE SALUD PUBLICA
DEPARTAMENTO DE CONTROL NACIONAL
REGISTRO Nº F- 11.274/01

FUROSEMIDA
40 mg

X Comprimidos

MANTENGASE FUERA DEL ALCANCE DE LOS NIÑOS

Cada comprimido contiene:

Furosemida	40 mg
Excipientes	c.s.

Registro I.S.P. Nº F- 11274/01

ENVASE CLINICO SOLO
PARA ESTABLECIMIENTOS
MEDICO -ASISTENCIALES

Envase clínico sólo para
establecimientos Asistenciales

Almacenar en lugar fresco y seco, a no más de 25°C

Serie:

Vence:

Elaborado y distribuido en Chile por
Laboratorios Andrómaco S.A.
Avda. Quilín 5273, Peñalolen, Santiago.

DEPARTAMENTO CONTROL NACIONAL
Nº. REF 2077/04
01 MAY 2004
UNIDAD DE MODIFICACIONES

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Journal of Hepatology

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Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety☆,☆☆

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***Background/Aims*: The most rational treatment of moderate ascites is spironolactone alone or in combination with furosemide. However, it is unknown which of these two treatment schedules is preferable.**

***Methods*: One hundred nonazotemic cirrhotic patients with moderate ascites were randomly assigned to be treated with spironolactone and furosemide (Group 1: 50 patients) or with spironolactone alone (Group 2: 50 patients). If no response was obtained, the doses of diuretics were increased up to 400 mg/day of spironolactone and 160 mg/day of furosemide. In patients of group 2 not responding to 400 mg/day of spironolactone, furosemide was added. In cases with an excessive response, the dosage of diuretics was reduced.**

***Results*: The response rate (98% in Group 1 vs. 94% in Group 2), the rapidity of ascites mobilization and the incidence of complications induced by diuretic therapy was similar in both groups. The need to reduce the diuretic dosage was significantly higher in Group 1 than Group 2 (68% vs. 34%; $P = 0.002$).**

***Conclusions*: In the treatment of moderate ascites, spironolactone alone seems to be as safe and effective as spironolactone associated with furosemide. Since spironolactone alone requires less dose adjustment, it would be more suitable for treating ascites on an outpatient basis.**

***Keywords*: Spironolactone; Furosemide; Ascites; Cirrhosis**

1. Introduction

Ascites is the most frequent complication of cirrhosis and it is associated with a worsening of the prognosis of these patients. The estimated probabilities of survival at 1 and 5 years after the development of ascites are of 50% and 20%, respectively [1,2].

While therapeutic paracentesis is the first treatment of choice in tense ascites, treatment of moderate ascites should initially include both salt restriction and diuretics simultaneously, since a positive response to diet alone is slow, and rare (approximately 14% of cirrhotic patients with ascites) [3–5].

The most rational diuretic treatment of cirrhotics with moderate ascites is spironolactone alone or in combination with furosemide [6–8]. Two different diuretic schedules are usually used in these patients. The first one consists of the administration of increasing doses of spironolactone, adding

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☆ Preliminary results of this study were presented at the 50th Annual Meeting of the American Association for the Study of Liver diseases held in Dallas (November, 1999) and the 35th Annual Meeting of the European Association for the Study of the Liver held in Rotterdam (April–May, 2000).

☆☆ The authors who have taken part in this study have not a relationship with the manufacturers of the drugs involved either in the past or present and did not receive funding from the manufacturers to carry out their research.

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furosemide only to those patients not responding to the highest recommended doses of the former (400 mg/day). The second one consists of starting with the simultaneous administration of furosemide and spironolactone increasing the doses of both diuretics if no therapeutic response is achieved. Although stepwise sequential therapy with increasing oral doses of an aldosterone antagonist may be effective in mobilizing ascites in 60–80% of nonazotemic cirrhotic patients with ascites who did not respond to bed rest and dietary sodium restriction [5,9], to our knowledge in only one study, a relatively low number of cirrhotic patients with ascites and without overt oliguric renal failure has been randomized to be treated with furosemide, combination therapy with furosemide and spironolactone or sequential spironolactone (spironolactone followed by furosemide if necessary) [10]. Therefore, we performed a randomized study comparing spironolactone alone versus spironolactone associated with furosemide, in terms of efficacy and safety, in nonazotemic cirrhotic patients with moderate ascites.

2. Patients and methods

2.1. Patients

We studied 127 consecutive nonazotemic cirrhotic patients admitted to our hospitals for treatment of moderate ascites. The following criteria were required for inclusion in the study: grade 2 ascites, serum creatinine ≤ 1.5 mg/dl, urinary sodium excretion < 50 mmol/day, serum sodium ≥ 125 mmol/l, and serum potassium < 5.5 mmol/l, after 5 days on a 50 mmol/day sodium diet and without diuretics, as well as absence of gastrointestinal bleeding, hepatic encephalopathy, infection, advanced hepatocellular carcinoma, and severe liver disease (serum bilirubin > 10 mg/dl and prothrombin rate $< 40\%$). Patients with respiratory, cardiac or renal disease and those treated with nonsteroidal anti-inflammatory drugs were also excluded.

The cause of cirrhosis was alcoholic in 60 patients, HCV-associated in 41 cases, alcoholic and HCV-associated in 13 cases, alcoholic and HBsAg-associated in six patients, HBsAg-associated in five patients, and cryptogenic in two. Fifty-two of the 127 patients had had ascites in the past. Thirty-nine of them were on low-dose diuretic treatment (spironolactone alone or in combination with furosemide) at admission.

2.2. Study design

To be sure that the effect of previous diuretic therapy washed out, patients were maintained for a minimum of 5 days in hospital on a diet containing 50 mmol/day of sodium and without diuretics. Then, blood samples were drawn to measure liver and renal function tests, plasma renin activity (PRA) and plasma aldosterone concentration (PAC), and a 24-h urine volume was carefully collected to measure urinary sodium excretion. Samples for PRA and PAC were obtained and processed as reported elsewhere [11,12]. Normal values of PRA and PAC in our laboratory for subjects at rest and on a diet containing < 50 mmol/day of sodium are 0.5–2.6 ng/ml/h and 1–16 ng/dl, respectively.

In all patients, the volume of ascites was assessed by an ultrasonographic method ($V = 1/3[\pi d^2(3r - d)]$), were d is the greatest vertical depth of ascites with the patient placed prone on a gurney, and r is the radius of the abdominal cavity calculated by: $r =$ abdominal circumference$/2\pi$ [13].

After baseline measurements, patients were randomly allocated, in separate strata according to the volume of ascites (< 4 l vs. > 4 l), to be treated with increasing doses of spironolactone in combination with furosemide (Group 1) or with spironolactone alone (Group 2). The starting dose of spironolactone (S) in both groups was 100 or 200 mg/day for patients with less or more than 4 l of ascites, respectively. Furosemide (F) in Group 1 was started at a dose of 40 or 80 mg/day on the basis of ascitic volume. These doses were increased, every 4 days, in a stepwise fashion until the highest recommended doses were achieved (400 mg/day of S, and 160 mg/day of F), if there was no response. In patients of Group 2 not responding to 400 mg/day of spironolactone, increasing doses of furosemide were added. In cases with an excessive response, the dosage of diuretics was reduced to the immediately lower dosage.

At baseline and during the study body weight and urine volume were measured daily in every patient. Urinary sodium excretion, and serum concentrations of creatinine, urea, sodium and potassium were measured every 3 days. In those patients in whom potassium levels increased above 5.5 mEq/l, 15 g of a potassium chelant (Resin-Calcium) was administered three times daily. Furthermore, PRA and PAC were measured at the end of each treatment period.

2.3. Definitions

According to the criteria of International Ascites Club [14] the following definitions were used in the study. *Response to treatment*: Mobilization of ascites, defined as decrease of ascites at least to grade 1 (ultrasonography but not clinically detectable ascites), was considered response to treatment. *Lack of response:* Four-day mean weight loss lower than 200 g/day, and urinary sodium excretion < 50 mmol/day. *Refractory ascites:*ascites that cannot be mobilized due to diuretic-resistance (lack of response to dietary sodium restriction and intensive diuretic treatment) or to diuretic-intractability (development of diuretic-induced complications). *Intensive diuretic treatment:*Spironolactone 400 mg/day, alone or associated with furosemide 160 mg/day. *Diuretic-induced complications:* Hepatic encephalopathy (its the development in the absence of other precipitating factors); renal failure (increase in serum creatinine $> 100\%$ to a value above 2 mg/dl in patients with ascites responding to diuretic treatment); hyponatremia (decrease in serum sodium concentration > 10 mmol/l to a level < 125 mmol/l); hypo- or hyperkalemia (decrease of serum potassium concentration to less than 3 mmol/l or increase to more than 6 mmol/l despite appropriate measures to normalize potassium levels). *Excessive response:*mean of the body weight loss greater than 500 g/day or greater than 1000 g/day if peripheral edema was present.

2.4. Statistical analysis

The sample size was calculated to demonstrate that both treatment schedules were equally effective. It was assumed that spironolactone plus furosemide effectivity was about 90% and maximum difference of 15% between treatments was considered as equivalent. With these assumptions and an unilateral alpha error of 0.05 and a beta error of 20%, the sample size obtained was of 50 patients per group.

Unless otherwise stated, results are expressed as mean $\pm$ SD or frequencies. Quantitative variables between groups were compared with Student's t-test for unpaired data (or the nonparametric Mann–Whitney U-test, as required). Frequencies were compared using the χ^2-test (with Yates' correction if necessary). Changes in quantitative variables during treatment within either group were assessed with Student's t-test for paired data (or the Wilcoxon's test if required).

The probability of ascites mobilization was calculated for each group by the Kaplan–Meier method and then compared with the log-rank test. The statistical analysis was performed using the BMDP package (Statistical Software Inc., Los Angeles, CA).

2.5. Ethical issues

Informed consent was obtained from all patients. The study was performed according to the latest revision of the Helsinki Declaration (1989) for human research. The study protocol was approved by the Ethical Committees of the two participant hospitals.

3. Results

Twelve of 127 patients with moderate ascites observed during the study period were not included due to serum

creatinine > 1.5 mg/dl (3 patients), serum sodium < 125 mEq/l (2), advanced hepatocellular carcinoma (2), grastrointestinal bleeding (2), urinary infection (1) and spontaneous bacterial peritonitis (2). Moreover, low sodium diet and bed rest induced ascites mobilization in 15 out of 115 patients (13%) during the previous 5 days before randomization.

Therefore, 100 nonazotemic cirrhotics patients with moderate ascites were randomly assigned to two groups, Group 1 (50 patients) treated with spironolactone and furosemide and Group 2 (50 patients) treated with spironolactone alone. Forty-one of them had had ascites in the past, and 31 were on low-dose diuretic therapy at admission (15 in Group 1, and 16 in Group 2; P = not significant (NS)). The median dose of furosemide and spironolactone in this subset of patients were 40 and 100 mg/day and 30 and 100 mg/day, respectively (P = NS in all cases). Six of 100 patients were not evaluable because of the early development of a severe complication of cirrhosis: three patients from Group 1 (variceal bleeding in two and spontaneous bacterial peritonitis in one) and three from Group 2 (variceal bleeding, sepsis and spontaneous bacterial peritonitis). Therefore, the present study includes 94 evaluable patients, 47 in Group 1 (21 patients with < 4 l of ascites, and 26 with > 4 l) and 47 in Group 2 (17 patients with < 4 l of ascites, and 30 with > 4 l). At baseline, both groups were comparable with respect to clinical features, liver and renal function, PRA and PAC (Table 1). PAC was

Table 1
Baseline clinical features and laboratory tests of patients included in the study

	Group 1: S + F (n = 50)	Group 2: S (n = 50)	P value
Age (years)	58.5 ± 11.3	60.1 ± 9	NS
Gender (male:female)	12:38	13:37	NS
Child–Pugh score (points)	9.1 ± 1.5	8.9 ± 1.3	NS
Ascites in the past (yes/no)	20/30	21/29	NS
Low dose diuretics (yes/no)	15/35	16/34	NS
Body weight (kg)	72.4 ± 13.9	70.4 ± 12.3	NS
Ascites volume (l)	6.2 ± 3.7	6 ± 3.2	NS
Peripheral edema (yes/no)	41/9	40/10	NS
Leukocytes (10^3/mm^3)	5778 ± 3331	5638 ± 2929	NS
Hemoglobin (g/dl)	10.3 ± 1.4	11.1 ± 1.5	NS
Platelets (10^6/mm^3)	114 ± 60	97 ± 51	NS
Prothrombin activity (%)	65 ± 16	68 ± 16	NS
Cholesterol (mg/dl)	116 ± 33	120 ± 29	NS
Albumin (mg/dl)	26.3 ± 4.3	27.4 ± 5.2	NS
Total bilirubin (mg/dl)	2.3 ± 1.6	2.1 ± 1.3	NS
Serum creatinine (mg/dl)	0.81 ± 0.2	0.84 ± 0.2	NS
Serum urea (mg/dl)	26.9 ± 14.6	30.9 ± 16.5	NS
Serum sodium (mmol/l)	135.6 ± 2.5	136.1 ± 3.6	NS
Serum potassium (mmol/l)	3.97 ± 0.4	4.13 ± 0.5	NS
Urinary sodium (mmol/day)	22.9 ± 12.1	18.6 ± 11.5	NS
Plasma renin activity (ng/ml/h)	4 ± 4	3.9 ± 4.4	NS
Plasma aldosterone (ng/dl)	20.5 ± 17.4	24.8 ± 20.2	NS

NS, not significant.

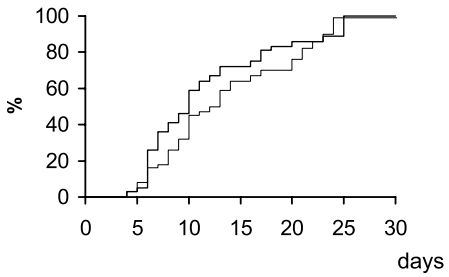

Fig. 1. Cumulative probability of mobilization of ascites in patients treated with spironolactone plus furosemide (Group 1, continuous line) and in those receiving spironolactone alone (Group 2, dotted line) (Kaplan–Meier curves, compared with the log-rank test; P = 0.5).

within the normal range in 40% of cases (40 patients: 19 from Group 1 and 21 from Group 2).

3.1. Effectiveness of treatment

Mobilization of ascites was achieved in 46 out of the 47 patients in Group 1 and in 44 out of the 47 patients in Group 2 (97.9 vs. 93.6%, respectively; P = NS). Seventeen out of the 47 patients from Group 1 responded to 100 mg/day of spironolactone and 40 mg/day of furosemide, 23 to 200 mg/day of spironolactone and 80 mg/day of furosemide, and six to 300 mg/day of spironolactone and 120 mg/day of furosemide. The non-responder patient developed diuretic-induced renal failure. In Group 2, ten out of the 47 patients responded to 100 mg/day of spironolactone, 24 to 200 mg/day, six to 300 mg/day, and three to 400 mg/day of spironolactone. In two other patients from Group 2, furosemide had to be added, but response was achieved only in one. In the three non-responder patients from Group 2, this was due to the development of severe diuretic-induced side-effects: hepatic encephalopathy in one case, and hyponatremia in two (one of them was that who also received furosemide). Thus, the incidence of ascites refractory to diuretic therapy in nonazotemic cirrhosis was 4.25% (four cases: one from Group 1 and three from Group 2).

The cumulative probability of mobilization of ascites was similar in both groups (Fig. 1). The median response time was 9.8 days (range: 4–35 days) in Group 1 and 10.3 days (range: 4–32 days) in Group 2 (NS). The cumulative dose of spironolactone was slightly higher in Group 2 than in Group 1 (Table 2). Moreover, PAC was significantly higher in the group of patients requiring more than 200 mg/day of spironolactone and in non-responders than in those responding to ≤ 200 mg/day of spironolactone (44.4 ± 34.3 ng/dl vs. 19.2 ± 16.2 ng/dl; P < 0.001).

Diuretic treatment induced a marked increase in urinary sodium excretion in both groups of patients. A mild but significant increase in both serum creatinine, and serum potassium was observed in either group. In addition, a mild but significant increase in serum urea and a decrease in

Table 2
Effectiveness and safety items in both therapeutic groups[a]

	Group 1: S + F ($n = 47$)	Group 2: S ($n = 47$)	P value
Loss of body weight (kg)	7.5 (2–17)	6.6 (2–15)	NS
Time to obtain of response (days)	9.8 (4–35)	10.3 (4–32)	NS
Response or Mobilization of ascites (*n*/%)	46/98	44/94	NS
Side effects (*n*/%)	3/7.7	6[b]/13.2	NS
Need to reduce the diuretic dosage (*n*/%)	32/68	16/34	0.002
Spironolactone (mg)			
Cumulative dose	1934 (400–7700)	2445 (400–7800)	NS
Dose/day	148 (83–233)	170 (100–325)	0.037
Dose/liter of ascites	311 (125–1405)	407 (118–1300)	NS
Cumulative dose of furosemide (mg)	480 (80–3080)	240 and 640[c]	-

[a] Median (range).
[b] In one, furosemide was added.
[c] Only two patients of this group received treatment with furosemide.

serum sodium concentration were observed in Groups 1 and 2, respectively (Table 3). When both groups of patients were compared at the end of treatment, no significant differences were found regarding renal function and endogenous vasoactive systems, except for an increase in serum potassium levels in the group of patients treated with spironolactone alone (4.7 ± 0.7 vs. 4.3 ± 0.4 mEq/l; $P < 0.03$) (Table 4).

The percentage of patients in whom diuretic dosage had to be reduced due to an excessive response was significantly higher in Group 1 than in Group 2 (68 vs. 34%; $P = 0.002$). (Fig. 2).

3.2. Diuretic-induced side-effects

The incidence of complications induced by diuretic therapy was similar in the two groups (three cases in Group 1 and six in Group 2; NS). In Group 1, they consisted of muscle cramps in one case, hypokalemia in one, and renal failure in the remaining patient. In Group 2 they were hyperkalemia (three cases), hyponatremia (two cases; one of these also received furosemide) and hepatic encephalopathy (one patient). In the four cases with hypo- or hyperkalemia, potassium levels normalized with appropriate measures. For this reason, these cases were not considered as refractory ascites. In contrast, diuretic treatment had to be discontinued in cases with severe diuretic-induced side effects (namely hepatic encephalopathy, renal failure, and marked hyponatremia).

4. Discussion

Since the study by Pérez-Ayuso et al. [6], showing that spironolactone is more effective than furosemide in nonazotemic cirrhotic patients with ascites, it has been well established that increasing doses of spironolactone alone or associated with furosemide are the most suitable approaches to the treatment of these patients, while the single administration of furosemide is not recommended because this drug alone fails to increase the urinary sodium excretion in approximately 50% of cases [6]. Therefore, two different diuretic schedules are usually used in cirrhosis. The first consists of the administration of increasing doses of spironolactone, adding furosemide only to those patients not responding to the highest recommended doses of the former, whereas the second consists of starting with the simultaneous administration of furosemide and spironolactone, increasing the doses of both drugs if no therapeutic response is achieved.

We report the results of a randomized controlled trial comparing the efficacy and safety of these two treatment schedules. The simultaneous administration of a loop diuretic, such as furosemide, with and aldosterone antagonist, such as spironolactone, may offer three advantages.

Table 3
Serum and urine electrolytes, serum urea and creatinine before and after diuretic therapy in responding patients

	Group 1: S + F ($n = 46$)			Group 2: S ($n = 44$)		
	Baseline	After	P value	Baseline	After	P value
Serum creatinine (mg/dl)	0.8 ± 0.2	0.94 ± 0.4	0.0005	0.83 ± 0.2	0.91 ± 0.2	0.0007
Serum urea (mg/dl)	25.9 ± 13.8	34 ± 18.5	0.001	29.6 ± 12.3	31.4 ± 16.3	NS
Serum sodium (mmol/l)	135.6 ± 2.4	134.9 ± 3.2	NS	136.1 ± 3.6	134.7 ± 3.9	0.003
Serum potassium (mmol/l)	4 ± 0.4	4.3 ± 0.4	0.0007	4.1 ± 0.5	4.7 ± 0.7	0.00005
Urinary sodium (mmol/l)	23 ± 12.5	90.5 ± 70.2	0.00005	20.4 ± 14.5	101 ± 49.8	0.00005

Table 4
Body weight, serum and urine electrolytes, serum urea and creatinine, PRA and PAC after diuretic therapy in responding patients of either group

	Group 1: S + F ($n = 46$)	Group 2: S ($n = 44$)	P value
Body weight (kg)	64.9 ± 12.9	63.8 ± 10.6	NS
Serum creatinine (mg/dl)	0.94 ± 0.4	0.91 ± 0.2	NS
Serum urea (mg/dl)	34 ± 18.5	31.4 ± 16.3	NS
Serum sodium (mmol/l)	134.9 ± 3.2	134.7 ± 3.9	NS
Serum potassium (mmol/l)	4.3 ± 0.4	4.7 ± 0.7	0.03
Urinary sodium (mmol/day)	90.5 ± 70.2	101 ± 49.8	NS
PRA (ng/ml/h)	4 ± 5.1	3.6 ± 2.6	NS
PAC (ng/dl)	31 ± 25.3	43.5 ± 51.9	NS

First, it could lead to an earlier onset of diuresis. Second, it may reduce the incidence of hyperkalemia that is frequently observed when aldosterone antagonists are given alone. Third, it may increase the efficacy of aldosterone antagonists by increasing the delivery of sodium to the distal tubule [5,15]. Despite these theoretical advantages, in the present study, spironolactone alone has proven to be as effective as the combined therapy in terms of response rate in nonazotemic cirrhotic patients with moderate ascites. The percentage of ascites mobilization obtained with spironolactone alone in the present study (94%) was virtually the same as that observed in the above mentioned study by Pérez-Ayuso et al. [6] (95%), as well as in the study by Fogel et al. [10] comparing three treatment schedules: sequential treatment (spironolactone followed by furosemide if necessary), combination treatment (spironolactone plus furosemide from the onset) and furosemide alone. Similar results were obtained in the study by Gatta et al. [5] when stepwise sequential therapy with increasing oral doses of an spironolactone followed by furosemide if necessary was used in nonazotemic cirrhotic patients with ascites. Moreover, the rapidity to ascites mobilization was also similar in patients receiving spironolactone alone or associated with furosemide. This was probably due to the specific design of the present study. In fact, in 68% patients from group 1 reduction of diuretic dosage was performed in order to avoid an excessive diuresis, that could lead to

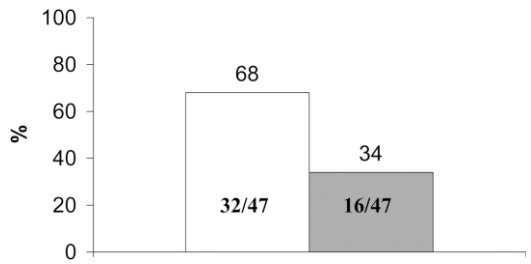

Fig. 2. Need to reduce the diuretic dosage due to an excessive response (weight loss > 500 g/day or > 1000 g/day if peripheral edema is present) in patients treated with spironolactone plus furosemide (empty bars) and those receiving spironolactone alone (dashed bars) ($P = 0.002$).

diuretic adverse events. Taking into account that in nonazotemic cirrhotic patients with ascites, the distal tubule reabsorbs almost all the sodium delivered, defining the final amount of sodium in the urine [16], it is not surprising to observe that the administration of spironolactone alone is followed by a good natriuretic response in most patients.

The observation that the effective dosage of aldosterone antagonists depends on plasma aldosterone levels was already demonstrated in previous investigations [5,6,9]. The finding of a markedly increased PAC in nonresponders to aldosterone antagonists, as compared to responders, probably reflects different degrees of reduction in the effective arterial circulating volume in these patients [17,18]. On the other hand, 40% of the patients included in the present study had a PAC concentration within the normal range. An increased tubular sensitivity to aldosterone in cirrhotic patients with ascites could explain why patients without hyperaldosteronism respond to spironolactone [19]. Another possibility is that although the supine PAC is normal, it is well documented there is an exaggerated response of the renin-angiotensin-aldosterone system in cirrhotic patients to assuming the upright posture, and the response to spironolactone could be dependent on this effect [20]. This finding confirms the clinical feeling that spironolactone is effective in cirrhosis with ascites even in the absence of hyperaldosteronism, because this diuretic is known to induce a negative sodium balance in most cirrhotics without hepatorenal syndrome and it is well established that approximately one-third of these patients have normal PAC [6,19,21].

Refractory ascites in cirrhosis denotes a condition in which the fluid overload is unresponsive to sodium restriction and diuretic therapy, or a condition in which the drug therapy necessary to mobilize ascites cannot be administered because of serious side effects. Although refractory ascites implies a poor prognosis, only few studies have been carried out in series of consecutive patients with cirrhosis and ascites in order to observe the true incidence of refractory ascites. In the present study, the incidence of refractory ascites to diuretic therapy was 4.25%, a figure which compares well with the 5–10% incidence reported in previous studies [5,9,22,23]. Interestingly, in our study all cases of refractory ascites were due to diuretic-intractability because of either diuretic-induced renal failure, severe hyponatremia or encephalopathy. By contrast, accordingly to the recommendations of the Ascites Club [14], the five patients in the present study who developed hypo or hyperkalemia, and muscle cramps induced by diuretics were not considered as refractory ascites since they were resolved with appropriate measures.

The use of diuretics in cirrhosis may be associated with several complications, such as renal failure, hepatic encephalopathy, electrolyte and acid-base disorders, gynecomastia, and muscle cramps. In most studies, the average prevalence of diuretic-induced complications in cirrhotic patients ranged between 20 and 40% depending on the type

and dose of diuretics used and the clinical status of patients included [24–26]. Interestingly, in the present study the incidence of diuretic-induced side effects was much lower (9.6%), without differences between patients treated with spironolactone alone and those treated with the combined therapy. This figure compares well with the prevalence of diuretic-induced adverse effects in nonazotemic cirrhotic patients with moderate ascites who were treated by stepped-care medical treatment [5,16]. The low incidence of diuretic-induced side effects observed in our study could probably be explained by the fact that the trial was performed in hospitalized patients in whom a close monitoring of daily body weight, and assessment of serum sodium, potassium, urea, and creatinine levels three times a week was performed. In fact, in about 50% of cases, we needed to reduce the diuretic dosage due to an excessive diuretic response, thereby probably avoiding a higher incidence of diuretic-induced side-effects. The need to reduce the diuretic dosage was significantly higher in patients treated with spironolactone associated with furosemide (68%) than in those treated with spironolactone alone (34%). Since spironolactone alone requires less dose adjustment, it would be more suitable for treating ascites on an outpatient basis.

In conclusion, spironolactone alone seems to be as safe and effective as spironolactone associated with furosemide, in terms of response rate and rapidity of moderate ascites mobilization in nonazotemic cirrhotics. Furthermore, since spironolactone alone requires less dose adjustment, it would be more suitable to be used on an outpatient basis.

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