Journal of Hepatology, 1992; 16: 241–250

Letters to the Editor

HEPAT 01151

Epomediol ameliorates pruritus in patients with intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and mild biochemical cholestasis that appear in late pregnancy. After delivery, pruritus vanishes and laboratory alterations return to normal. Fetal distress is the most serious consequence of ICP (1,2). No drug has yet consistently improved pruritus, the biochemical cholestasis, and fetal prognosis in patients with ICP.

Epomediol is a terpenoid compound which reverts cholestasis induced by ethinyl-estradiol in the rat, apparently by recovering liver cell plasma membrane fluidity (3–5). Since ICP could also be related to an abnormality in liver cell membrane fluidity caused by maternal estrogens, or some cholestatic estrogen metabolite, we assessed the efficacy and safety of epomediol on ICP, in carefully monitored hospitalized patients.

Seven patients with ICP of early onset (weeks 25–32 of pregnancy) received epomediol (Clesidren^{R}, Camillo Corvi S.p.A., Piacenza, Italy), 900 mg/day for 15 days, and 4 additional patients received 1200 mg/day for 15 days. Pruritus diminished significantly in patients treated with either 900 or 1200 mg epomediol/day (Table 1).

A relapse in the severity of pruritus was observed in 6 patients after epomediol was discontinued. No significant changes were detected in liver function tests during or after treatment with epomediol. All these tests returned to normal values within a month after delivery. Epomediol was well tolerated and no adverse reactions were detected during or after treatment. Most patients reported mild sedation after the second or third day from the first dose of epomediol. Blood cell counts, serum levels of hemoglobin, creatinine, glucose, protein, cholesterol, triglycerides and urine profile did not change. Delivery occurred between weeks 36 and 39 of pregnancy. Eleven babies were born, with Apgar score over 7 at 5 min. Six months after delivery all of them were thriving normally.

In 3 patients examined, fasting serum epomediol levels

TABLE 1

Effect of 2 doses of epomediol administered during 15 days, on pruritus and on serum levels of bilirubin, bile salts, alanine aminotransferase (ALT), and alkaline phosphatases (AP), in patients with intrahepatic cholestasis of pregnancy

Parameter	Treatment group	Days of treatment			
		0	5	10	15
Pruritus score (0 to 4)	Epo 900	3.7 ± 0.1[c]	2.5 ± 0.3	2.0 ± 0.3	1.4 ± 0.2[a]
	Epo 1200	3.5 ± 0.2	2.2 ± 0.6	1.2 ± 0.4	1.0 ± 0.3[a,b]
Bilirubin (mg/dl)	Epo 900	0.8 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.2
	Epo 1200	1.5 ± 0.4	1.0 ± 0.3	0.9 ± 0.3	1.1 ± 0.4
Bile salts (μmol/l)	Epo 900	36 ± 8	33 ± 13	57 ± 21	51 ± 25
	Epo 1200	58 ± 12	117 ± 28	78 ± 22	72 ± 19
ALT (kU/l)	Epo 900	151 ± 26	110 ± 21	101 ± 13	104 ± 48
	Epo 1200	193 ± 46	152 ± 40	134 ± 44	104 ± 44
AP (IU/l)	Epo 900	160 ± 17	152 ± 24	172 ± 17	202 ± 31
	Epo 1200	212 ± 25	199 ± 24	185 ± 13	232 ± 26

Epo 900 = epomediol 900 mg/day/15 days; $n = 7$.
Epo 1200 = epomediol 1200 mg/day/15 days; $n = 4$.
Normal range for laboratory tests: bilirubin, 0.4–1.1 mg/dl: bile salts, 2–11 μmol/l; ALT, 10–40 kU/l; AP, < 170 IU/l in non-pregnant women.
[a] $p < 0.05$ in comparison with values observed before treatment (intragroup analysis of variance for non-parametric data).
[b] $p < 0.05$ in comparison with Epo 900 (intergroup analysis of variance for non-parametric data).
[c] Mean ± S.E.

TABLE 2

Serum levels and urinary excretion of epomediol and its main metabolite in 3 patients with intrahepatic cholestasis of pregnancy during oral epomediol administration (1200 mg/day for 15 days)

Days of treatment	Serum levels (μg/ml)		Urinary excretion (mg/12 h)	
	Epomediol	Metabolite M1	Free Epo	Total Epo
1	7.9 ± 2.7[a]	0.3 ± 0.1	0	0
2	7.8 ± 2.5	0.5 ± 0.2	20.7 ± 5.1	497 ± 100
3	8.8 ± 2.7	0.5 ± 0.3	25.3 ± 7.7	609 ± 200
5	7.7 ± 2.8	0.5 ± 0.3	10.5 ± 3.0	457 ± 187
8	8.3 ± 2.6	0.4 ± 0.2	22.0 ± 0.3	585 ± 21
10	10.8 ± 3.7	0.6 ± 0.2	15.4 ± 4.0	753 ± 369
15	7.8 ± 2.6	0.4 ± 0.1	18.7 ± 6.5	506 ± 185
Range	3.3–18.2	0.1–1.2	4.7–36.5	210–1123

[a]Mean ± S.E.M.

reached maximal values on the third day of treatment and remained stable throughout the 15-day treatment period, indicating an adequate intestinal absorption of epomediol (Table 2).

A similar observation was done with urinary excretion of the drug. Epomediol in blood appeared largely in excess over its main metabolite. In the samples of amniotic fluid examined, only total epomediol was detected and in a concentration of 0.52 μg/ml or less.

In the present pilot study, the amelioration of pruritus was greater than in a group of 9 patients who received a placebo (6) ($p < 0.05$, intergroup analysis of variance for non-parametric data). The lack of biochemical improvement in patients treated with epomediol could be due to the brevity of the treatment period. Alternatively, pruritus was attenuated through some extrahepatic effect of epomediol. A placebo effect seems unlikely because pruritus improved more in patients treated with the higher dose of this drug. In conclusion, epomediol can be considered a satisfactory alternative in the treatment of pruritus in patients with ICP, with the advantage of its oral administration and excellent tolerance.

This study was supported by grant 467/88 from Fondecyt, Chile.

Manuel C. Gonzalez[a], Joaquin Iglesias[c], Claudio Tiribelli[d], Jose Ribalta[a], Humberto Reyes[a,b], Ismael Hernandez[b], Marcelo Bianchi[b], Francisco Andrighetti[b] and Claudina Molina[c]

Departamentos de [a]Medicina, [b]Preclínicas, and [c]Obstetricia, Facultad de Medicina, Universidad de Chile (División Oriente), Hospital del Salvador, Santiago de Chile, Chile and [d]Istituto di Patologia Speciale Medica, Universita Degli Studi di Trieste, Trieste, Italy

References

1 Svanborg A. A study of recurrent jaundice in pregnancy. Acta Obstet Gynaecol Scand 1954; 33: 434–44.
2 Reyes H. The enigma of intrahepatic cholestasis of pregnancy: lessons from Chile. Hepatology 1982; 2: 87–96.
3 Zuin M, Dioguardi ML, Festorazzi S, Podda M. Effects of epomediol on bile flow and composition in normal rats and in rats with ethinyl estradiol induced cholestasis. Il Farmaco 1981; 36: 383–9.
4 Miccio M, Orzes N, Lunazzi GC, Gazzin B, Corsi R, Tiribelli C. Reversal of ethinyl estradiol-induced cholestasis by epomediol in the rat. Biochem Pharmacol 1989; 38: 3559–63.
5 Barrera G, Parola M. Effect of epomediol on the ATPase and adenylate cyclase activities in plasma membranes isolated from rat liver. Pharm Res Commun 1984; 16: 1133–40.
6 Ribalta J, Reyes H, Gonzalez MC, Iglesias J, Arrese M, Poniachick J, Molina C, Segovia N. *S*-adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: a randomized, double-blind, placebo-controlled study with negative results. Hepatology 1991; 13: 1084–9.

HEPAT 01156

Hepatitis C virus, autoimmune liver disease and cryoglobulinaemic hepatitis

Dr. Magrin and colleagues reported (J Hepatol, 1991; 13: 364–7) the association of hepatitis C virus (HCV) infection and autoimmune chronic active hepatitis (AI-CAH) in a group of fifteen Italian patients. On the basis of this association and the efficacy of α-interferon treatment, the Authors hypothesized the existence of a clinically and etiologically distinct subset of AI-CAH. Another study reports evidence of geographical hetero-