Efficacy of Glucuronates Versus Placebo in Chronic Hepatitis: A Randomized, Double-Blind Study

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ABSTRACT

This randomized, placebo-controlled, double-blind, six-parallel-group study assessed how adults with alcohol-induced chronic hepatitis responded to betaine glucoronate, diethanolamine glucuronate, and nicotinamide ascorbate (Jetepar). Two hundred patients participated in 4-week study; 100 received Jetepar in capsule, syrup, or intravenous (IV) form daily, and 100 received placebo in capsule, syrup, or IV form daily. Results of physical examination and laboratory analysis performed at the start and end of the study indicated that Jetepar was more effective than placebo in improving blood chemistry parameters (phosphatase, bilirubin, and triglyceride levels) and urinalysis values (bilirubin and urobilinogen levels) and in reducing jaundice, edema, itching, headache, anorexia, dyspepsia, nausea, and vomiting. Hepatomegaly and megalosplenia also improved slightly in patients taking Jetepar. Patients given placebo worsened. The drug was well tolerated, and no differences in therapeutic effect were noted among the three forms.

Keywords: alcoholic hepatitis; serum enzymes; glucuronic acid; betaine; diethanolamine; nicotinamide; ascorbic acid.

INTRODUCTION

Liver diseases are an important cause of morbidity and mortality worldwide. Many toxic and viral factors produce acute or chronic liver damage, which leads to end-stage liver disease. Excessive alcohol intake is one such factor.

Normally, the main pathways for ethanol metabolism in the liver are (1) alcohol dehydrogenase (ADH); (2) the microsomal oxidizing system of the endoplasmic reticulum; and (3) catalase localized in the peroxisomes of the hepatocytes. Excessive alcohol intake stimulates oxidation in the cytosol and leads to enhanced production of acetaldehyde (which is toxic), reduction of acetate, changes in intracellular redox potential (which may cause fatty liver), collagen formation, and impaired glucoronation.[1] Liver damage after excessive alcohol intake can be defined by three major lesions: fatty liver, acute and chronic hepatitis, and cirrhosis.

Alcoholic hepatitis in an inflammatory lesion characterized by leukocyte infiltration, continuous hepatocellular necrosis, and finally fibrosis. It is believed to be the main condition preceding cirrhosis and liver failure,[2] but severe steatosis with perivenular fibrosis and sclerosing hyaline necrosis may also contribute to cirrhosis.[3] Management is difficult, because no specific drugs are available and because it is difficult to convince alcoholics to stop drinking. Prolonged abstinence is the pivotal factor in treating patients with alcoholic liver disease. Nutritional supplementation in the malnourished alcoholic patient has also been shown to be effective.[4] Drug therapies such as propylthiouracil, insulin and glucagon, D- penicillamine, hepatoprotective agents, and antioxidant protective agents[5] have been tried with overall doubtful results.

With the aim of improving the general condition of patients with alcoholic hepatitis, we set up a clinical trial with a drug[1] used successfully in other cases of hepatitis.[6,9] The drug composition complies with a rationale for supplying the liver with a detoxifying substrate (glucuronic acid), a lipotropic agent (betaine), two catalyzers (nicotinamide and ascorbate, the latter a potent antioxidant), and a substance useful for phosphorylation in many biologic processes (diethanolamine [Jetepar®]).

METHODS

Study Design

A randomized, placebo-controlled, double-blind, six-parallel-group comparison study was devised to comply with the Good Clinical Practice (GCP) procedures issued by the Italian Ministry of Health in agreement with the European Community. The hospital's ethics committee approved the study protocol, and patients gave informed written consent before starting the study.

Placebo or Jetepar was administered daily as follows:

- 30 patients: 800 mg (two capsules twice daily) of Jetepar
- 30 patients: placebo capsules
- 30 patients: 840 mg (two cps twice daily) of Jetepar syrup
- 40 patients: 1050 mg (one 10-ml vial) of intravenous (IV) Jetepar
- 40 patients: placebo vial
- 30 patients: placebo syrup

Table 1 shows the composition of the pharmaceutical forms of Jetepar.

Table 1. Composition of Pharmaceutical Forms of Jetepar

Formulation	Betaine Glucuronate	Dietanolamine Glucuronate	Nicotinamide Ascorbate	Excipients
Capsule	150 mg	30 mg	20 mg	Magnesium oxide 35 mg; maize starch 78 mg magnesium stearate 7 mg; talc 10 mg; cocoa 20 mg; lactose 45 mg; gelatin 79.542 mg; E171 (titanium bioxide) 0.324 mg; E172 (red iron oxide) 0.81 mg; E172 (black iron oxide) 0.324 mg
Syrup (100 ml)	3.750 g	1 g	5 g	Sorbitol solution 65.780 g; bitter extract (orange oil, bergamot oil, raspberry oil, gentian extract, ethanol 45%) 0.23 g; caramel 0.34 g; purified water 41.7 g
Injectable solution (10 ml)	750 mg	200 mg	100 mg	Sterile saline to make 10 ml

The trial lasted 4 weeks (the first patient was enrolled in July 1994 and the last patient in December 1994), during which time no drug either complementary to Jetepar or possessing Jetepar-like activity was administered. Baseline laboratory values were determined during visit 1 on the day before drug administration began or on the same day; laboratory analysis was repeated at visit 2 (t_{28}) or on the day of drop-out. Pre-existing illnesses and those appearing during the study were treated as necessary.

Patients

Two hundred adult patients (143 men, 57 women), 26 to 65 years of age (49.8 ± 7.87 years), with chronic alcoholic hepatitis were randomized for study entry. Inclusion criteria were a history of chronic alcohol consumption (>80 g/d for more than 2 years) with clinical signs, laboratory results, and ultrasound findings indicating chronic liver disease. Patients with viral, infective, parasitic, auto-immune, metabolic, and drug-induced hepatitis were excluded from the study.

Clinical Evaluation

All patients underwent a complete physical examination at the beginning and end of the study. Routine hematologic tests (hemoglobin, hematocrit, platelet and red blood cell [RBC] counts, mean corpuscular volume [MCV], and white blood cell [WBC] count with differential) and urinalysis (pH, protein, bilirubin, urobilinogen hemoglobin, nitrites, ketone, glucose and WBC) were performed at these times. Blood chemistry measurements were carried out (one-stage prothrombin time as per Quick's test; total, direct, and indirect bilirubin; total protein; alpha, beta, and gamma globulin; urea; glucose; albumin; total and high-density lipoprotein [HDL] cholesterol; triglycerides; alkaline phosphatase; alanine aminotransferase [ALT]; aspartate aminotransferase (AST); gamma-glutamyl transferase [γ-GT]; and creatinine). All analyses were performed by the hospital's central laboratory according to Good Laboratory Practice standards.

At both visits (the day preceding the start of drug administration, or days 1 and 28), clinicals also rated the severity of hepatitis symptoms (megalosplenia and hepatomegaly [both by ultrasound], ascites, hemorrhagic diathesis, dyspepsia, vomiting, nausea, anorexia, jaundice, itching, edema, headache, spider nevi) by scores from 0 to 2.

At the end of the trial, clinicians evaluated adverse effects, scoring them as "slight," "moderate", or "severe" and tentatively determining their possible relationship to hepatitis symptoms or intercurrent illness. Finally, clinicians estabilished the "overall clinical assessment" (OCA) on (1) the drug's therapeutic effect based on clinical and laboratory results (scores: "high", "moderate", "slight", "absent") and (2) side effects possibly related to treatment (scores 0, "absent" or "not interfering"; 1, "interfering"; 2, "prevailing").

Statistical Analysis

We compiled descriptive statistics of demographic and baseline characteristics for all patient groups. We then compared characteristics measured on a continuous scale, by split-plot analysis of variance (ANOVA), taking into account *P* values in the interaction "times x treatments" to evaluate the significance of differences in the trend between groups. Categorical data (i.e., symptomatology scores and scores for urinary findings or OCA) were analyzed by means of the Wilcoxon test and the X^2 or Fisher test, respectively. Two-sided probability values <.05 were considered statistically significant.

RESULTS

One day 1, all 200 patients included in the trial had a history of classic alcohol intake and showed laboratory and ultrasound findings of chronic liver disease. The second examination was performed on day 28 (range, 27-30 days). Compliance was very high; only 2 patients (1 in the drug group and 1 in the placebo group) did not take a total of eight capsules, corresponding to a lack of 2 treatment days.

Efficacy

Table 2 shows the patients' serum enzyme levels. Note the high values of alkaline phosphatase, ALT and AST, and γ-GT. Treatment with Jetepar significantly reduced these values from baseline, particulary the capsules and syrup; the IV solution was less effective. These values increased in patients receiving placebo.

Table 2. Serum Enzyme Levels in Jetepar-Treated and Placebo Patients

Variable,IU/L	Day 1 (Mean ± SD)	Day 28 (Mean ± SD)	P*
Alkaline phosphatase			
Jetepar capsule	171.6+35.61	143.0+31.68	
Placebo capsule	174.7±29.85	177.2±29.75	<.001
Jetepar syrup	191.2+19.91	163.7±22.59	
Placebo syrup	179.7+19.95	182.8+21.11	<.001
Jetepar IV solution	190.8+16.53	180.0±30.33	
Placebo IV solution	187.0±14.33	186.7±20.89	.006
Alanine aminotransferase			
Jetepar capsule	88.5±43.04	62.5±27.69	
Placebo capsule	75.3+32.54	75.0±30.48	<.001
Jetepar syrup	89.9+31.55	60.7±16.07	
Placebo syrup	72.5±17.60	76.6±21.62	<.001
Jetepar IV solution	66.8±20.01	61.4±28.45	
Placebo IV solution	69.9±22.40	72.7±22.83	.008
Aspartate aminotransferase			
Jetepar capsule	81.2±54.55	55.3±27.70	
Placebo capsule	76.9±32.64	78.3+33.16	.003
Jetepar syrup	98.5±38.26	61.8+17.34	
Placebo syrup	79.7±18.33	83.3+21.59	<.001
Jetepar IV solution	69.0±19.75	61.3+20.92	
Placebo IV solution	73.6±23.78	77.2±22.90	.001
Gamma-glutamyl transferase			
Jetepar capsule	131.4±63.60	87.7±41.65	
Placebo capsule	126.2+57.50	127.7±54.36	<.001
Jetepar syrup	112.7+42.18	76.3±21.89	
Placebo syrup	91.0±24.83	92.9±24.95	<.001
Jetepar IV solution	93.4±26.34	79.0±22.02	
Placebo IV solution	98.1±27.87	100.3±29.83	<.001

*Statistical significance for comparison of "times x treatments" for each drug form (split-plot ANOVA).

No significant change was noted in serum protein, total protein, alpha, beta, and gamma globulin, and albumin after administration of either Jetepar or placebo.

Total, direct, and indirect bilirubin values (Table 3) showed a consistent reduction with oral Jetepar - about 45%, 43%, and 42%, respectively, on day 28- with a lesser decrease noted with syrup. With IV treatment, reduction never exceeded 14%. Placebo patients showed an increase up to 21%, except for the group given capsules. All means were statistically different from baseline values. Fair increases in RBC, hematocrit, hemoglobin, and platelet count occurred with Jetepar; MCV decreased (Table 4). Triglyceride levels decreased significantly in patients receiving Jetepar (Table 3).

Table 3. Cholestatic and Lipid Indexes in Jetepar-Treated and Placebo Patients

Variable, mg/dL	Day 1 (Mean ± SD)	Day 28 (Mean ± SD)	P*
Bilirubin, total			
Jetepar capsule	2.84±1.44	1.50±0.59	
Placebo capsule	2.78±1.30	2.79+1.31	<.001
Jetepar syrup	3.44±1.12	2.08±0.92	
Placebo syrup	2.58±0.80	2.85±0.93	<.001
Jetepar IV solution	2.88±0.89	2.46±0.92	
Placebo IV solution	2.74±0.55	3.20±0.95	.001
Bilirubin, direct			
Jetepar capsule	1.88+1.03	1.06±0.49	
Placebo capsule	1.89±0.98	1.88+1.08	<.001
Jetepar syrup	2.44±1.06	1.38±0.74	
Placebo syrup	1.73+0.61	1.89±0.70	<.001
Jetepar IV solution	2.04±0.74	1.75±0.85	
Placebo IV solution	2.04±0.53	2.47±0.80	.001
Bilirubin, indirect			
Jetepar capsule	0.98±0.62	0.44±0.30	
Placebo capsule	0.89±0.59	0.91±0.53	<.001
Jetepar syrup	1.00+0.33	0.70±0.35	
Placebo syrup	0.86±0.44	0.96±0.35	.001
Jetepar IV solution	0.81±0.38	0.69±0.33	
Placebo IV solution	0.70±0.19	0.76±0.31	.046
Triglycerides			
Jetepar capsule	202.5±25.70	171.7+13.35	
Placebo capsule	200.3±22.13	197.6+18.32	<.001
Jetepar syrup	203.5±8.87	179.6±27.29	
Placebo syrup	199.7±7.07	205.4±14.94	<.001
Jetepar IV solution	200.2±18.37	189.4±22.63	
Placebo IV solution	202.1±8.20	203.3±12.27	<.001

*Statistical significance for comparison of "times x treatments" for each drug form (split-plot ANOVA).

Table 4. Hematologic Findings in Jetepar-Treated and Placebo Patients

Variable	Day 1 (Mean ± SD)	Day 28 (Mean ± SD)	P*
Red blood cell count (x 10^6/μL)			
Jetepar capsule	3.634±0.45	3.983±0.40	
Placebo capsule	3.755±0.49	3.827±0.41	.001
Jetepar syrup	3.507±0.42	4.028±0.44	
Placebo syrup	3.643±0.34	3.700±0.37	.001
Jetepar IV solution	3.852±0.40	4.026±0.50	
Placebo IV solution	3.828±0.25	3.803±0.40	.047
Mean corpuscular volume (fL)			
Jetepar capsule	106.3±3.50	103.6±2.93	
Placebo capsule	106.1±3.58	105.0+3.18	.002
Jetepar syrup	107.7±3.18	104.6±3.40	
Placebo syrup	108.4+3.64	107.8±4.24	.003
Jetepar IV solution	111.5+5.28	107.9±5.36	
Placebo IV solution	110.2+5.35	108.8±4.51	<.001
Platelets (x 10^3/μL)			
Jetepar capsule	76.9+21.19	87.4±21.46	
Placebo capsule	94.3±32.72	89.6±27.49	<.001
Jetepar syrup	103.9±20.76	114.9+19.62	
Placebo syrup	108.7±20.09	104.5±17.77	<.001
Jetepar IV solution	117.7+17.91	123.2±17.54	
Placebo IV solution	118.6+11.29	114.5+12.80	.001

*Statistical significance for comparison "times x treatments" for each drug (split-plot ANOVA).

Jaundice, edema, anorexia, itching, dyspepsia, vomiting, nausea, and headache improved in all patients receiving Jetepar (Tables 5 and 6). The difference between the drug-treated and placebo patients was statistically significant (*P*<.001). This was true for jaundice (41 in the drug group vs 8 in the placebo group), headache (45 vs 14), and itching (40 vs 12). Twice as many placebo patients as drug-treated patients had edema, anorexia, dyspepsia, nausea, and vomiting.

Table 5. Clinical Symptoms

	Jaundice			Edema			Anorexia			Itching		
	Var. t_{28} vs t_0	P t_{28} vs t_0	P J vs Pl	Var. t_{28} vs t_0	P t_{28} vs t_0	P J vs Pl	Var. t_{28} vs t_0	P t_{28} vs t_0	P J vs Pl	Var. t_{28} vs t_0	P t_{28} vs t_0	P J vs Pl
Jetepar (no. of patients)	>15 <41	(44) .001	<.001	> 2 <12	(86) .018	<.001	> 9 <65	(26) <.001	<.001	>14 <40	(46) <.001	<.001
Placebo (no. of patients)	>26 < 8	(66) .005		>11 < 2	(87) <.001		>33 <29	(38) .775		>26 <12	(62) <.001	

Var.= t_{28} symptom changes vs t_0; J = Jetepar; Pl= Placebo; < = improved or disappeared; > = worsened, followed by total number of respective patients. *P* = statistical significance (Wilcoxon test for comparison of t_{28} vs t_0; Fischer's Exact Test for comparison of J vs Pl).

Table 6. Clinical Symptoms

	Dyspepsia			Vomiting			Nausea			Headache		
	Var. t_{28} vs t_0	*P* t_{28} vs t_0	*P* J vs Pl	Var. t_{28} vs t_0	*P* t_{28} vs t_0	*P* J vs Pl	Var. t_{28} vs t_0	*P* t_{28} vs t_0	*P* J vs Pl	Var. t_{28} vs t_0	*P* t_{28} vs t_0	*P* J vs Pl
Jetepar (no. of patients)	> 5 <64	(31) <.001	<.001	>13 <36	(51) .002	<.001	>11 <69	(20) <.001	<.001	>11 <45	(44) <.001	<.001
Placebo (no. of patients)	>19 <26	(55) .364		>29 <15	(56) .095		>33 <31	(36) .748		>23 <14	(63) .264	

Var.= t_{28} symptom changes vs t_0; J = Jetepar; Pl= Placebo; < = improved or disappeared; > = worsened, followed by total number of respective patients. *P* = statistical significance (Wilcoxon test for comparison of t_{28} vs t0; Fischer's Exact Test for comparison of J vs Pl).

Table 7 summarizes results of urinalysis. The most significant results were seen in bilirubin level after Jetepar syrup and IV administration and in urovilinogen concentration after syrup. In fact, both degradation products of hemoglobin were reduced or disappeared totally in a significant number of patients, whereas the patients who received placebo exhibited worsening. Hematuria was also significantly reduced in patients treated with Jetepar syrup, although not in those receiving capsules.

Table 7. Urinary Parameters in Drug-Treated and Placebo Patients*

	Bilirubin				Urobilinogen		Blood	
	Jetepar Syrup	Placebo Syrup	Jetepar IV	Placebo IV	Jetepar Syrup	Placebo Syrup	Jetepar Syrup	Placebo Syrup
Present at day 1	21	15	16	4	5	4	11	2
Present at day 28	17	17	12	12	0	5	4	5
Disappeared	7	4	8	1	5	2	9	1
Appeared	3	6	4	9	0	3	2	4
Unchanged	1	0	1	3	0	2	0	1
Improved	12	3	4	0	0	0	2	0
Worsened	1	7	3	0	0	0	0	0
*P**	.014		.005		.046		.034	

. Treatment with Jetepar capsules and placebo capsules did not significantly (results not reported).
*P was calculated considering disappeared, appeared, unchanged, improved, and worsened cases.

Table 8. Overall Clinical Assessment of Drug and Placebo Efficacy

Score	Capsules*	Syrup*	IV Solution*
High	1/0	0/0	1/0
Moderate	22/0	14/2	15/0
Slight	4/8	6/5	9/10
Absent	3/22	10/23	15/30
Total of patients	30/30	30/30	40/40
P		<.001	

*Number of patients in the drug and placebo groups, respectively.

Table 9. Pre-Existing and Intercurrent Adverse Events After Drug and Placebo Administration

Treatment	Adverse Events					Pre-Existing and Intercurrent Events Illness and Therapy
	Type and No. of Cases	Severity	Outcome	Relationship to Jetepar	Therapy	
Jetepar capsules	Headache, 4	Slight	S3, T1	1, not related;	Aspirin	1, mental depression (Prozac®)
	Diarrhea,1	Slight	S	3, unknown		
	Ear buzzing,1	Slight	S	Unknown		BPCO (Bisolvon®, Tachipirina®)
	Dizziness,1	Slight	S	Unknown		Fever (aspirin)
Jetepar syrup	Headache, 2	Slight	S	Unknown		1, hypertension (Adalat®)
	Diarrhea, 2	Slight	S	Unknown		1, mental depression (Prozac®)
	Dizziness, 3	Slight	S	Unknown		2, mental depression (Prozac®)
						1, cystitis (Noroxin®)
						2, hypertension (Enapren®)
Jetepar IV solution	Headache,1	Slight	S	Unknown		Hypertension (Enapren®)
	Diarrhea, 5	Slight	S	Unknown		2, mental depression (Prozac®)
	Abdominal cramps, 2	Slight	S	Unknown		
	Dizziness, 4	Slight	S	Unknown		1, mental depression (Prozac®)
Placebo capsules	Headache, 3	Slight	S	Unknown		Psoriasis (cortisone ointment);
	Diarrhea, 2	1, moderate	1, T	Unknown	Imodium®	hypertension (Adalat®)
		1, slight	1, S	Unknown		1, fever (aspirin); 1, fever
	Ear buzzing, 2	Slight	S	Unknown		(Tachipirina®)
Placebo syrup	Ear buzzing,1	Slight	S	Unknown		
Placebo IV solution	Dizziness, 2	Slight	S	Unknown		

*S = symptom that spontaneously disappeared within 2 hours and 1 day; T = symptom that disappeared after therapy in the displayed number of patients.

The OCA (comprehensive laboratory results and objective clinical symptoms on physical examination on day 28) indicated significantly different results with active drug compared with placebo ($P<.001$) (Table 8). The statistical difference between groups was highly significant. Jetepar capsules appeared to be slightly more active than the syrup and IV solution.

Tolerability and Safety

Table 9 shows pre-existing and intercurrent adverse events. With one exception, all symptoms were slight and disappeared in most patients within a few hours. One patient was given aspirin for a headache. No statistical significance in frequency of side effects was noted among the groups. No respiratory, cardiac, or blood pressure changes occurred with either drug or placebo.

Pre-Existing and Intercurrent Diseases

Pre-existing and intercurrent diseases (Table 9) were hypertension (4 patients) and mental depression (5). Cystitis (26), fever (8), arthralgia (2), cough (4), and bronchitis (1) occurred during the trial. All patients were treated accordingly. One case of cystitis and one case of cough lasted 21 days; all other illnesses lasted only a few days.

DISCUSSION

Data suggest that Jetepar has a positive effect on clinical and laboratory parameters. Transaminases, alkaline phosphatase, and γ-GT are routinely used to assess liver function and can be correlated with the severity of necrosis, alcohol consumption, and cholestasis. The disease worsened in the placebo patients.

Jetepar reduced the concentration of serum enzymes (up to 37%), particularly AST, ALT, and γ-GT. Thus, the formation of oxalacetic acid and of pyruvic acid and the tranfer of the gamma-glutamyl group from peptides such as glutathione to other amino acids were enhanced. Jetepar also decreased high triglyceride levels to near-normal values. Total and direct serum bilirubin were affected positively, with a mean reduction of 32% in Jetepar-treated patients. The capsule and syrup caused the greatest effect (approximately 43%). Jetepar had a particularly strong effect on jaundice, anorexia, itching, dyspepsia, nausea, and headache, especially when compared with placebo.

Both oral forms appear to be more potent than the IV form, probably as the results of a more persistent serum concentration of active ingredients. Nevertheless, the difference in overall therapeutic activity between oral and IV forms does not seem high.

It is difficult to estabilish which biochemical component of Jetepar is responsible for its therapeutic activity.

Glucuronic Acid

Of the many chemical reactions taking place in the liver cell mitochondria and smooth endoplasmic reticulum, the most important is the glucuronic conjugation.

The essential substrate for conjugation in uridine diphosphate glucuronate (UDPG), which is normally synthesized from glucose with steps involving adenosine triphosphate (ATP) and nicotamide-adenine dinucleotide (NAD). Normally, liver cells can handle this process of energy transformation required for glucuronization, but the process is reduced in impaired cells.

When exogenous glucuronic acid is supplemented, this becomes the preferred substrate for UDPG formation without the need for energy from ailing mitochondria. Both factors are important under normal conditions but become crucial when the liver's capacity to carry out biotransforming processes is limited by functional insufficiency or when the organism must dispose of excess exogenous or endogenous toxic substances.

Betaine

In severe liver disease, fat metabolism is impaired. Lipids accumulate in the hepatocytes and cause subsequent degeneration, which has adverse effects on liver function. Betaine clears the liver cells of fat, as do the lipotropes methionine and choline, which divert fatty

acids toward the phospholipid metabolic pathway.

Betaine, instead of being merely a metabolic by-product of choline oxidation, may be an important methylating agent when normal methylating pathways are impaired by alcohol ingestion.[10] Research indicates the important role of betaine in liver metabolism.[11] Barak and co-workers[12] were able to prove that 0.5% betaine given to ethanol-fed animals prevented the formation of a fatty liver and stimulated the formation of S-adenosylmethionine in the liver. The decrease of S-adenosylmethionine allows folate co-factors to be channeled through the pathway forming N-5methyltetrahydrofolate (the major circulating form of folate) and away from processes that form purines and pyrimidines.

Diethanolamine

Diethanolamine drives fats into the phospholipid pathway and helps clear fat from the liver. Experimental data in rats[13] proved that a diethanolamine-supplemented diet, containing 30% hydrogenated coconut oil, significantly lowered liver lipid levels and liver, aortic, and serum cholesterol levels. Other experiments in rats showed diethanolamine's protective effect against acute ethanol-induced intoxication.[14] Furthermore, diethanolamine acts as an intermediate-level energy carrier and supports high-level energy carriers in the chemical reactions involved in detoxification.

Nicotinamide

The transformation of both exogenous and endogenous toxic substances into molecules ready to be glucuronized is usually an oxidative process and requires energy and catalyzers. The glucuronoconjugation that follows these transformations also requires energy. Nicotinic acid and ascorbic acid (see below), two catalyzers, play an important role. Nicotinamide is an essential component of co-enzymes (NDA and nicotinamide-adenine dinucleotide phosphate [NADP]) that act as hydrogen carriers. In both co-enzymes, nicotinamide directly participates in the transfer, a process fundamental to intermediate metabolism. Enzymes with pyridine co-ferment are present in many dehydrogenases: a classic example is metabolic pathways that produce energy. Some dehydrogenases have NAD and others have NADP as co-enzymes. Furthermore, NAD is the coenzyme of galactose-isomerase, an enzyme that converts galactose-1-phosphate to glucose-1-phosphate, which is subsequently polymerized to glycogen.

Ascorbic Acid

Ascorbic acid is essential for the detoxifying process. It is the catalyst the redox reactions, which allow the synthesis of chemical energy donors such as ATP, UTP, and NADH. Ascorbic acid is not synthesized by humans, and persons with alcoholic liver disease have a consistently reduced intake.[15] Ascorbic acid has at least two benefits; its acts against acetaldehyde and against free radicals, the latter action being greatly increased in alcoholics.[16]

In the liver, alcohol is oxidized by ADH in the hepatocyte cytosol to acetaldehyde with simultaneous reduction of NAD to NADH. Ascorbic acid is a highly reactive substance, more toxic than ethanol, that is metabolized to acetate by the mitochondrial isoenzyme of aldehyde dehydrogenase (ALDH). Factors that increase ethanol oxidation or reduce acetaldehyde clearance produce increased acetaldehyde levels in the liver and greater injury-forming stable and unstable adducts with proteins, glycoproteins, and membrane phospholipids.

The protective effect of ascorbate on acetaldehyde actions was first proved experimentally in mice by Moldowan and Acholonu[17]: the vitamin protected animals from disulfiram-ethanol-induced mortality. Disulfiram, an inhibitor of ALDH, was used because it produces a several-fold increase in blood acetaldehyde than after alcohol. In humans, the disulfiram-ethanol interaction is known as the "Antabuse® syndrome", which is manifested clinically by nausea, facial flushing, headache, tachycardia, and hypotension.[18]

Ascorbate, a water-soluble antioxidant, has not only a number of well-defined biologic activities (such as acting as a co-substrate in procollagen, catecholamine and carnitine biosynthesis), but it also very effectively scavenges a wide array of reactive oxygen species.[19] These toxic substances unsettle vital cell functions and provoke hepatocyte swelling. Activity of the mitochondrial electron transport chain is impaired, and some vital intracel-

lular signaling systems (ie, protein kinase) become inappropriately upregulated. Free radical formation results in increased lipid peroxidation, exacerbating membrane injury of liver cells. Thus, profound changes occur in lipid, carbohydrate, and protein metabolism, leading to ketosis, accumulation of triglycerides and lactate, and, very occasionally, to hypoglycemia in acute alcoholic state.

Like glutathione, ascorbate may directly reduce free radical reactive oxygen species with the concurrent formation of dehydroascorbate through the semidehydroascorbate free radical. The metabolism of ascorbate and glutathione is linked in other respects. Glutathione may reduce the semidehydroascorbate free radical with the formation of a glutathione radical.[20]

Ascorbate supplementation is also vital because glutathione, the other detoxifying agent, is reduced or even suppressed under extreme conditions, as proved in rats.[21] Suppression of glutathione synthesis by chronic alcohol abuse may contribute to the increased susceptibility of alcoholics to the hepatotoxic effects of acetaminophen.

Finally, low serum levels of ascorbic acid were found in 106 patients with delirium tremens and alcohol withdrawal syndrome.[22] A 500-mg oral dose or 1000-mg IV dose of ascorbic acid for 7 days was recommended.

SUMMARY

The results of this study, as well as of previous trials[6,9] in other types of hepatitis, support the efficacy of Jetepar in liver diseases induced by infection or of toxic origin (endogenous or exogenous). Because Jetepar has metabolic activity, it is also effective in nonalcoholic hepatitis. Although it cannot have a resolvent action in very severe illness, Jetepar can help to restore liver function.

The physiologic and multiple biochemical actions of its active components indicate that symptoms tentatively reported as side effects are not signs of low tolerability. This hypothesis is also based on the lower incidence of such effects in Jetepar-treated patients compared with those given placebo.

In conclusion, clinical and statistical results show that Jetepar is more effective than placebo in altering biochemical variables and resolving many symptoms of alcoholic hepatitis. Its beneficial effect arises from its composition, because it contains substances supportive of liver functions impaired by toxic substances in general and chronic alcohol consumption in particular. Jetepar capsules, syrup, and IV-injection solution were well tolerated.

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