Journal of Hepatology 1997; **27**: 505–511
Printed in Denmark · All rights reserved
Munksgaard · Copenhagen

Journal of Hepatology
ISSN 0168-8278

Effect of liver cirrhosis on the systemic availability of naltrexone in humans

Marco Bertolotti[1,2], Anna Ferrari[1], Giovanni Vitale[1], Marina Stefani[1], Tommaso Trenti[1], Paola Loria[2], Francesca Carubbi[2], Nicola Carulli[2] and Emilio Sternieri[1]

[1]*Servizio di Tossicologia e Farmacologia Clinica and* [2]*Divisione di Medicina Interna III, Dipartimento di Medicina Interna, Università di Modena, Modena, Italy*

Background/Aims: **Naltrexone is a competitive opiate antagonist with high hepatic extraction. It is used for detoxification treatment for heroin addicts and has been proposed as a possible treatment of pruritus in cholestasis. Such patients are likely to have impaired liver function, underscoring the need to understand the pharmacokinetic behavior of naltrexone in liver disease. These studies were undertaken to evaluate the effect of liver cirrhosis on the plasma time-course of naltrexone.**

Methods: **A total of 18 patients were investigated: seven migraine patients with normal liver function regarded as controls and 11 patients with liver cirrhosis (six with decompensated disease and five with preserved liver function). A bolus of 100 mg of naltrexone was administered orally in the morning, after an overnight fast. Blood samples were taken in basal conditions and at fixed intervals, up to 24 h after administration. Serum levels of naltrexone and of its major active metabolite, 6β-naltrexol, were assayed by reversed-phase HPLC analysis.**

Results: **In control subjects, circulating concentrations of naltrexone were always much lower than those of 6β-naltrexol (area under the curve: naltrexone, 200±97 ng/ml×24 h; 6β-naltrexol, 2467±730 ng/ml×24 h, $p<0.01$). In severe cirrhosis serum levels of 6β-naltrexol increased more slowly, so that circulating levels of naltrexone during the first 2–4 h after drug intake were higher than those of 6β-naltrexol (6β-naltrexol/naltrexone ratio at 2 h: controls, 10.91±4.80; cirrhosis, 0.39±0.18, $p<0.01$). The area under the curve for naltrexone (1610±629 ng/ml×24 h) was significantly greater than in controls, whereas that for 6β-naltrexol (2021±955 ng/ml×24 h) was not significantly different. Patients with compensated cirrhosis showed an intermediate pattern. No differences in elimination half-life of the two drugs were detected among the groups.**

Conclusions: **Our data suggest the occurrence of important changes in the systemic availability of naltrexone and 6β-naltrexol in liver cirrhosis; such alterations are consistent with lesser reduction of naltrexone to 6β-naltrexol and appear to be related to the severity of liver disease. This must be considered when administering naltrexone in conditions of liver insufficiency.**

Key words: **Liver cirrhosis; Naltrexone; Pharmacokinetics; Systemic availability; 6β-naltrexol.**

NALTREXONE (N-cyclopropyl-methyl-noroxymorphone) is a potent competitive antagonist of opiates at the receptor level (1,2). When administered orally to human subjects, naltrexone can prevent the pharmacological effects of active doses of heroin for 48–72 h (3). Because of these pharmacological properties, naltrexone has been proposed for the treatment of heroin addicts, to prevent relapse. Its efficacy has been documented in clinical studies (1,2,4) and at the present time naltrexone is registered in a number of European countries, including Italy, for this indication. Very recent evidence has suggested its use in former alcohol addicts as well (5).

The pharmacokinetic properties of naltrexone are not completely understood (6); the drug is well absorbed by the gastrointestinal tract and is efficiently

Received 20 December 1996; revised 3 April; accepted 8 April 1997

Correspondence: Marco Bertolotti, MD, Divisione di Medicina III, Dipartimento di Medicina Interna, Policlinico, Via del Pozzo 71, 41100 Modena, Italy.
Tel: 39 (59) 424939. Fax: 39 (59) 363114.

extracted by the liver (7), where it is converted by enzymatic reduction to 6β-naltrexol and to other minor derivatives (2,8). Both the parent drug and its metabolites are conjugated with glucuronic acid and then excreted, mainly by the kidney and to a lesser extent via the biliary route. The elimination half-life has been reported to be 10–12 h, for both naltrexone and 6β-naltrexol (9); although conflicting results have been reported in the literature (2,8), these kinetic properties seem to justify a single daily administration of the drug. Due to the extensive metabolism of naltrexone, it is believed that most of the pharmacological effects still present 12–24 h after drug administration are accounted for by active metabolites, the principal one being 6β-naltrexol (2).

Despite the important role played by the liver and by the kidney in naltrexone disposition, very little information is presently available on the effects of hepatic and kidney disease on naltrexone pharmacokinetics. The issue of liver function is particularly important when we consider that most candidates for naltrexone treatment are likely to be, or to become, chronic liver disease patients. Theoretically, in this condition, alterations in the systemic availability of naltrexone and/or of its metabolites might underlie increased susceptibility to its potential side effects, even if the drug, so far, has proven to be well tolerated in most clinical settings.

Furthermore, recent evidence has suggested the involvement of opiate receptors in the pathogenesis of pruritus in some forms of chronic cholestasis, such as primary biliary cirrhosis (10,11), where the utilization of opiate antagonists has been proposed as a symptomatic treatment (12). Compared to naloxone, the most extensively studied antagonist, naltrexone would present the advantage of longer half-life and, most of all, the possibility of oral administration. Preliminary evidence has encouraged this approach (13).

In order to investigate more systematically the effects of altered liver function on naltrexone pharmacokinetics, we studied a group of patients with a clinical diagnosis of cirrhosis of the liver. The main pharmacokinetic parameters of naltrexone and 6β-naltrexol were analyzed after an oral bolus of naltrexone.

Materials and Methods

Patients and design of the study

In total, 18 patients were investigated. Seven of them (two males, five females, age range 42–73) were migraine patients with normal liver function, as assessed by clinical and laboratory evaluation, and were regarded as controls. Eleven patients had a well-established diagnosis of liver cirrhosis (see Table 1 for clinical relevant data). Six of them (patients 6–11) had decompensated liver disease and were Child-Pugh class C (14). The remaining five (patients 1–5) had a milder, more compensated form of the disease (Child-Pugh class A or B). Patients were investigated as inpatients or as day-hospital patients in the wards of the Department of Internal Medicine of the University of Modena. All subjects gave their informed consent to the design of the study, which was conducted according to the Declaration of Helsinki.

In the morning, after an overnight fast, patients received an oral bolus of 100 mg of naltrexone, as two 50-mg capsules (ANTAXONE®, Zambon Pharmaceuticals, Milan, Italy). Blood samples were collected in heparin-free tubes in basal conditions just before drug administration, and subsequently at fixed intervals (20 min, 40 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h) after naltrexone. The occurrence of side effects was recorded. The morning after the beginning of the study, a serum sample was taken for analysis of liver enzymes.

A subgroup of patients (four controls, two with

TABLE 1

Relevant clinical data of patients with cirrhosis studied

Patient	Age	Sex	AST	ALT	PChe	Child-Pugh score	Etiology of cirrhosis
			mUml		U/ml		
1	29	M	78	106	5.0	5	HBV
2	59	F	62	80	6.8	6	HCV
3	61	F	69	48	4.0	6	HCV
4	65	F	61	68	5.1	7	HCV
5	41	M	144	187	5.3	8	HBV
6	40	M	57	34	2.4	10	Alcoholic
7	62	F	123	52	1.4	10	HCV
8	64	M	158	170	2.0	10	HCV
9	52	M	104	59	1.5	11	HCV
10	70	M	60	42	2.9	11	Alcoholic
11	56	M	32	18	3.2	12	Unknown

AST=aspartate aminotransferase. ALT=alanine aminotransferase. PChe=pseudocholinesterase.

compensated and three with decompensated cirrhosis) also underwent analysis of caffeine kinetics, as an index of hepatic drug-metabolizing capacity. Subjects were given, together with the naltrexone bolus, 100 mg of caffeine; blood was taken at fixed intervals, as described above, and an aliquot of serum was used for the determination of caffeine levels, assayed by enzyme multiplied immunoassay technique (EMIT Bracco-Syva Chemicals, Milan, Italy).

Analysis of serum concentrations of naltrexone and 6β-naltrexol

Blood was collected in polyethylene heparin-free tubes and serum was stored at −20°C until assayed by reverse-phase HPLC, according to Zuccaro et al. (15) with modifications. After solid-phase extraction using Bond Elut C-18 cartridges (Analytichem International, Harbor City, CA, USA), drug assays were performed with a Beckman System Gold high-performance liquid chromatograph equipped with a diode array detector module 168, set at 202 nm (Beckman Instruments, Inc., San Ramon, CA, USA). A reversed-phase C-18 25 cm×4.6 mm Hypersil column (Labservice Analytical, Bologna, Italy) packed with 5 μm ODS was used.

The mobile phase, composed of acetonitrile 18% and 20 mmol/l KH_2PO_4 82% with 0.015% (v/v) triethylamine, pH 3, was pumped at a rate of 1 ml/min. Naloxone (the internal standard), naltrexone and 6β-naltrexol were used as standards. Standards and samples were quantitated according to the analyte/naloxone ratio in a calibration curve. The sensitivity limit of the assay was 10 ng/ml for both drugs. Within-day and between-day precision measurements gave a coefficient of variation of 4.8% and 7.1%, respectively, for naltrexone and 4.2% and 6.9% for 6β-naltrexol (mean of the values obtained at drug concentrations of 10, 100 and 500 ng/ml).

Analysis of the data and statistical evaluation

Maximal drug concentration (Cmax) and time to peak drug concentration (Tmax) were determined by direct analysis of the data. The area under the curve (AUC) was determined by the trapezoidal rule, restricted to the time interval of experimental samples. The elimination half-life (T/2) of naltrexone and 6β-naltrexol was calculated by non-linear regression analysis using a two-compartment, three-exponential model. The elimination half-life of caffeine was calculated by a one-compartment monoexponential model on the decremental portion of the time-course curve.

Data were expressed as the mean±SD. The significance of the differences between groups was investigated by Student's *t*-test for independent data. When

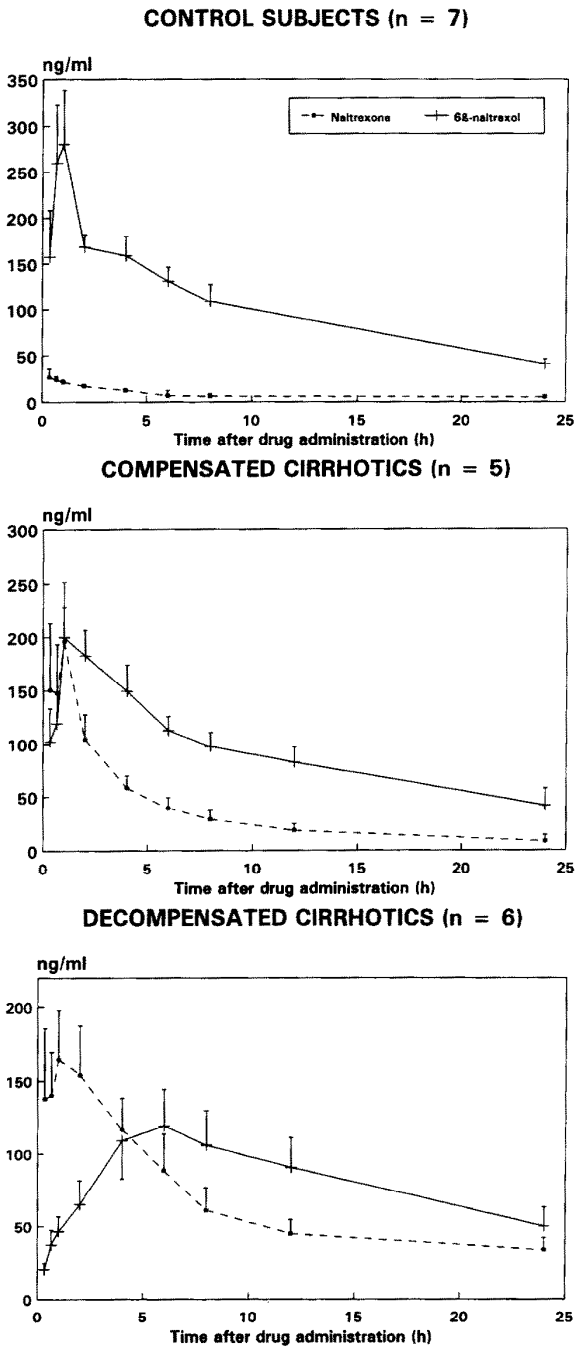

Fig. 1. Time course of plasma levels of naltrexone (broken line) and 6β-naltrexol (continuous line), after oral administration of 100 mg of naltrexone in seven subjects with normal liver function (upper panel), in five patients with compensated (Child-Pugh class A or B) cirrhosis (middle panel) and in six with decompensated (Child-Pugh class C) cirrhosis (lower panel). Data represent mean values and SD.

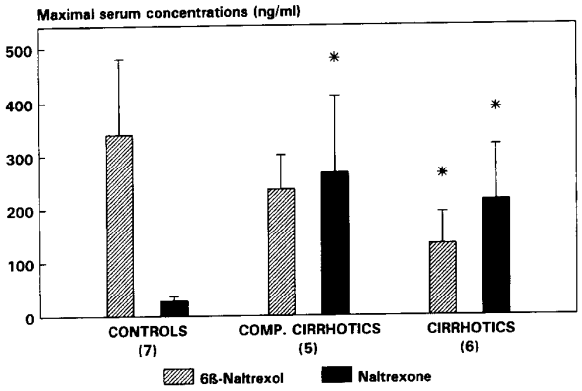

Fig. 2. Maximal serum concentration (Cmax) of naltrexone and 6β-naltrexol in control subjects, patients with compensated and decompensated cirrhosis after oral administration of 100 mg of naltrexone. Data indicate mean value and SD. * p<*0.01 vs controls, Student's* t-*test for unpaired data.*

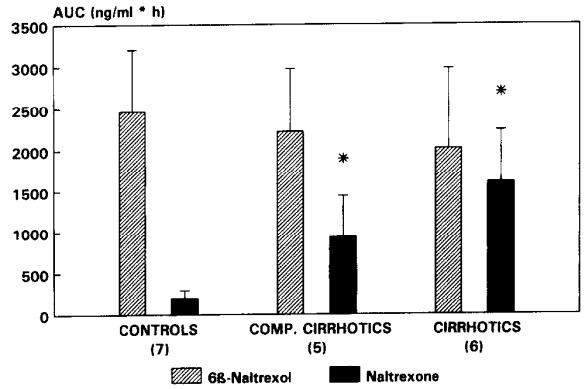

Fig. 3. Area under the curve (AUC) of naltrexone and 6β-naltrexol in control subjects, and patients with compensated cirrhosis and decompensated cirrhosis after oral administration of 100 mg of naltrexone. Data indicate mean value and SD. * p<*0.01 vs controls, Student's* t-*test for unpaired data.*

appropriate, linear correlation and regression analyses were performed using the least-squares method. A level of $p<0.05$ was considered to be statistically significant.

Results

Figure 1 shows plasma time courses of naltrexone and 6β-naltrexol in control subjects, and in patients with compensated (Child A-B) cirrhosis and decompensated (Child C) cirrhosis. In control subjects circulating levels of naltrexone were almost undetectable soon after drug administration, whereas the concentrations of 6β-naltrexol sharply increased over the first 1–2 h; 6β-naltrexol levels were consistently much higher throughout the period of observation. In contrast in patients with decompensated cirrhosis, circulating concentrations of naltrexone were markedly higher, particularly at the earlier time points after drug administration; furthermore, the rise of 6β-naltrexol was much slower, so that plasma levels of naltrexone over the first 2–4 h were higher than those of 6β-naltrexol. Patients with compensated cirrhosis displayed an intermediate pattern, with naltrexone and 6β-naltrexol levels of nearly the same order of magnitude at the earlier time points.

To stress more clearly the different pharmacokinetic behavior, Fig. 2 illustrates the values of Cmax and Fig. 3 shows the values of the AUC in the groups investigated.

Other parameters of naltrexone and 6β-naltrexol pharmacokinetics were investigated in the different groups of patients. The value of Tmax for 6β-naltrexol was significantly higher in patients with decompensated cirrhosis (260±143 min) compared to controls (43±14 min, $p<0.02$) and those with compensated cirrhosis (55±21 min, $p<0.02$), consistently with a delay in the metabolism of naltrexone; differences with regard to naltrexone Tmax were not statistically significant (data not shown). No significant differences in the elimination half-life of parent drug and metabolite could be detected between different groups (naltrexone: controls, 14±12 h; compensated cirrhosis, 17±9 h; decompensated cirrhosis, 28±15 h; 6β-naltrexol: controls, 13±4 h; compensated cirrhosis, 9±4 h; decompensated cirrhosis, 15±7 h). This might be due partly to wide data scatter and, in the case of naltrexone, to the very low serum levels observed in controls, making kinetic evaluation more problematic in this group of subjects.

Figure 4 shows the 6β-naltrexol to naltrexone ratio 2 h after naltrexone administration in all subjects investigated. This parameter was chosen as a means to express, as a single index, the pharmacokinetic behavior, and in particular the different concentration time-course, of the two drugs. Indeed, as is clearly shown, the ratio progressively decreased from subjects with normal liver function to patients with moderate liver disease and to patients with severe liver disease, with almost no overlap among the different patient groups. This confirms the existence of a strict relationship between the degree of liver function impairment and the extent of the changes in drug metabolism.

Linear correlation analysis was performed in the 11 patients with cirrhosis in order to investigate the relationship between liver function, as expressed by the Child-Pugh score, and the main pharmacokinetic par-

ameters of the two drugs: Cmax, Tmax, AUC, half-life of either naltrexone or 6β-naltrexol, and 6β-naltrexol to naltrexone ratio at 2 h. The only two parameters significantly correlated with the clinical score were 6β-naltrexol Tmax ($r=0.80$, $p<0.01$) and the 6β-naltrexol to naltrexone ratio at 2 h ($r=-0.80$, $p<0.01$); we selected the latter parameter, which has the advantage of taking into account the alterations in the time-course of both drugs, for subsequent statistical evaluations.

Figure 5 illustrates the significant correlation between the Child-Pugh score and the 6β-naltrexol to naltrexone ratio at 2 h in patients with cirrhosis.

Finally, a significant correlation was found between the elimination half-life of caffeine and the 6β-naltrexol to naltrexone ratio at 2 h in the nine subjects studied (four controls, two with compensated cirrhosis and three with decompensated cirrhosis). The equation of the regression line was $y=10.30-0.227\times$ ($r=-0.78$, $p<0.02$).

Drug administration was in general very well tolerated. In two patients with decompensated cirrhosis, naltrexone intake was followed by transient nausea and irritability (patient 9) and by tremors (patient 11). In the latter patient, administration of i.m. clonidine helped to resolve the picture. No relevant changes in serum liver enzymes were observed after drug intake.

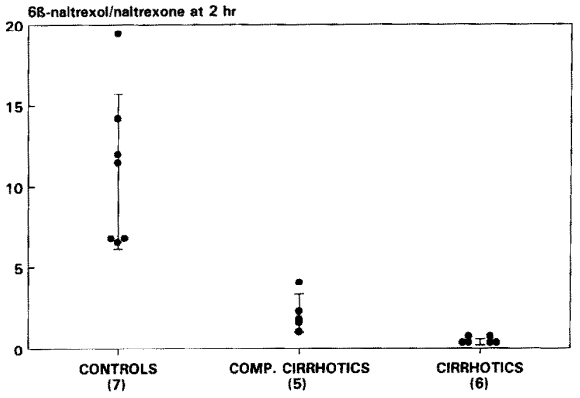

Fig. 4. Plasma 6β-naltrexol/naltrexone concentration ratio 2 h after oral administration of 100 mg of naltrexone in control patients, and patients with compensated and decompensated cirrhosis. Closed circles represent individual data. Bars represent mean±SD. p<*0.01 between controls and either group with cirrhosis and between the two groups with cirrhosis.*

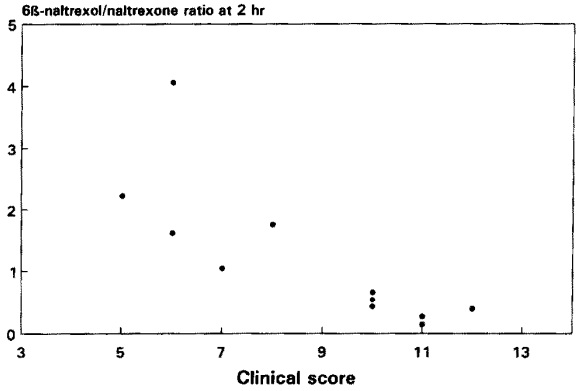

Fig. 5. Correlation between the plasma 6β-naltrexol/naltrexone concentration ratio 2 h after oral administration of 100 mg of naltrexone and the clinical score according to the Child-Pugh grading system (14) in 11 patients with liver cirrhosis. Closed circles represent individual data. Equation of the regression line: $y=4.55-0.387x$; r=−*0.80,* p<*0.01.*

Discussion

The present findings on the plasma time course of naltrexone and its major metabolite, 6β-naltrexol, are consistent with the prompt reductive metabolism of naltrexone in subjects with normal liver function. This is also consistent with previous evidence supporting the occurrence of very efficient first-pass metabolism by the liver (2,7).

At the present time, there is very little evidence on naltrexone pharmacokinetics in liver disease, despite the evident clinical implications of possible changes in drug disposition. As far as we know, this study for the first time provides clear evidence about the changes in naltrexone bioavailability in conditions of impaired liver function. The systemic availability of naltrexone is markedly increased in liver cirrhosis, as reflected by the plasma time course of naltrexone and by the data on the AUC and Cmax. On the other hand, the systemic availability of 6β-naltrexol is not significantly affected by liver disease, even if peak drug concentrations are significantly delayed in patients with cirrhosis. According to these findings, the metabolism of naltrexone to 6β-naltrexol appears to be much slower, even if it is complete after an appropriate period of time.

Little is known at present about the metabolic pathways involved in naltrexone metabolism and in particular about the enzyme(s) responsible for reduction to 6β-naltrexol; in particular, the role of microsomal versus non-microsomal enzymes has not been clearly elucidated so far. At any rate, our findings clearly suggest an impairment in the metabolic conversion of naltrexone to 6β-naltrexol in liver cirrhosis, which seems to parallel the extent of severity of liver disease. It must be remembered that in our study we only assayed circulating levels of free naltrexone and 6β-naltrexol,

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.