Opioid peptides and primary biliary cirrhosis

J R Thornton, M S Losowsky

Abstract

Patients with liver disease have increased plasma concentrations of the endogenous opioid peptides methionine enkephalin and leucine enkephalin. As an initial investigation to determine whether opioid peptides contribute to any of the clinical manifestations of hepatic disease nalmefene, a specific opioid antagonist devoid of agonist activity, was given to 11 patients with cirrhosis. They all experienced a severe opioid withdrawal reaction on starting the drug. In the nine patients with primary biliary cirrhosis pruritus was greatly alleviated, fatigue seemed to improve, and plasma bilirubin concentration, which had been rising, showed a modest fall in all except one patient.

These results indicate that blocking opioid receptors has an effect on some of the metabolic abnormalities of liver disease.

Introduction

Opioid peptides are the naturally occurring counterparts of opiate drugs. More than 10 of these peptides have been identified.[1] They have multiple actions, which are exerted via at least three classes of receptors: μ, δ, and $\varkappa$.[1] Knowledge of the metabolism of these peptides, particularly at sites outside the central nervous system, is rudimentary. The plasma concentrations of the pentapeptides methionine enkephalin and leucine enkephalin are raised appreciably in patients with liver disease, and the increase is proportional to the severity of the disease.[2-5] In contrast the plasma concentration of the much larger opioid peptide, β endorphin, is not increased in cirrhosis.[6]

As an initial investigation to determine whether increased activity of opioid peptides contributes to some of the clinical manifestations of liver disease we gave nalmefene (IVAX Laboratories, Miami, Florida), a specific opioid antagonist with no agonist action,[7] orally to patients with cirrhosis. Nalmefene is a more potent antagonist than naloxone at all three main types of opioid receptors.[7] When 300 mg nalmefene was given orally to healthy people it produced only occasional, minor side effects.[8]

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Patients and methods

The study was approved by the Leeds Eastern Health Authority's ethical committee. We studied 11 patients. Nine of them had primary biliary cirrhosis, with histological appearances of the liver compatible with or diagnostic of this disease, and all nine had mitochondrial antibodies. One patient had cryptogenic cirrhosis, and one had alcoholic cirrhosis. This last patient had abstained from alcohol for 17 months. The table gives further baseline data on the patients.

In an attempt to perform a placebo controlled, randomised, double blind crossover trial we gave nalmefene or placebo to five of the patients on an outpatient basis. Three of them took the placebo for two weeks without any change in their symptoms or results of standard liver function tests. However, the two patients given nalmefene, in the lowest available dose of 5 mg, experienced a florid reaction after the first dose, which took three days to subside. They were unwilling to take further doses as outpatients, and consequently the trial proceeded on an inpatient, unblinded basis.

To try to minimise the reaction produced by nalmefene the 11 patients were given clonidine, a drug that ameliorates the symptoms of withdrawal of opiates in heroin addicts.[9-11] The dose of nalmefene was gradually increased over seven to 10 days from 5 mg twice daily to 20-40 mg thrice daily. Clonidine 100 μg thrice daily was given on the first three days of treatment with nalmefene and was reduced to 75 μg thrice daily on day 4, 50 μg thrice daily on day 5, and 25 μg thrice daily on day 6 and was stopped on day 7. Pulse rate and arterial pressure were monitored every hour for the first 12 hours on day 1 and every four hours thereafter.

All nine patients with primary biliary cirrhosis had pruritus. Four of them found that their itching was only partially alleviated by cholestyramine, and the remaining five were unable to take this drug because it worsened their steatorrhoea. To assess whether nalmefene was beneficial in alleviating these patients' itching any antipruritic drugs were stopped three weeks before the study. Pruritus was measured daily for two weeks before the study and then for two weeks at one, three, and six months; patients scored their pruritus on a visual analogue scale consisting of a 10 cm line ranging from "no itching" to "very itchy." Fatigue was assessed similarly, with a 10 cm scale ranging from "no energy" to "plenty of energy."

Plasma bilirubin and albumin concentrations and alanine aminotransferase and alkaline phosphatase activities were measured twice immediately before nalmefene was started and again at one, three, and six months. The nine patients with primary biliary cirrhosis had had all these measurements taken a median of six months (range five to seven months) before the study.

Details of 11 patients with cirrhosis before treatment with nalmefene

Case No	Type of cirrhosis	Sex	Age (years)	Ascites	Plasma bilirubin (μmol/l)	Plasma albumin (g/l)	Plasma creatinine (μmol/l)	Plasma methionine enkephalin (pmol/l)	Plasma leucine enkephalin (pmol/l)	Other medical problems	Continued treatment
1	Primary biliary	F	67	No	173	41	91	295	660		
2	Primary biliary	F	41	No	139	34	77	240	575		
3	Primary biliary	F	47	No	108	44	83	335	615		
4	Primary biliary	F	59	No	80	28	67	215	430		
5	Primary biliary	F	48	No	78	37	90	190	295	Cholecystectomy	
6	Primary biliary	F	70	In past	74	42	104	165	490		Spironolactone
7	Primary biliary	F	61	No	59	37	64	130	385		
8	Primary biliary	F	53	No	23	43	71	120	235		
9	Primary biliary	M	69	No	11	37	102	125	330	Previous myocardial infarct	Frusemide, glyceryl trinitrate
10	Alcoholic	M	59	Yes	26	40	143	445	965	Diabetes	Spironolactone, glibenclamide
11	Cryptogenic	M	34	No	22	33	104	270	315	Splenorenal shunt, hepatic encephalopathy	

Data are expressed as medians with ranges. The significance of differences was determined by Wilcoxon's signed rank sum test.

Results

All the patients experienced a considerable reaction, which began within an hour of the first doses of the two drugs. The cerebral effects were invariably unpleasant and sometimes included visual or auditory hallucinations. Two patients' written accounts of these disturbances were: "Heavy, trembling limbs. Dream-like state. No energy. No concentration. Heavy eyelids. Wanted to sleep but couldn't. Didn't want to be bothered by anyone. Couldn't think. No appetite"; and, "Cold sweat. Dizzy. Very dry mouth. My mind felt white inside. Slept really badly, just cat napped. Too pepped up."

All of these patients experienced anorexia, nausea, colicky abdominal pain, and constipation. Over the first 12 hours of day 1, compared with the same period of the preceding day, the median pulse rate fell from 74 (range 68-82) beats/min to 61 (58-65) beats/min (p<0·01), systolic arterial pressure rose from 118 (113-164) mm Hg to 132 (126-180) mm Hg (p<0·01), and diastolic arterial pressure rose from 78 (70-91) mm Hg to 83 (79-97) mm Hg (p<0·05). During the first day that they were taking nalmefene the patients were pale and had cool skin.

Despite this reaction all of the patients continued taking the drugs, except for the patient with cryptogenic cirrhosis, who refused further drugs after three days. Most of the patients' withdrawal symptoms settled within two or three days, though four patients had intermittent abdominal pain for up to two months. Nalmefene was stopped in the patient with alcoholic cirrhosis after six days because it did not improve his
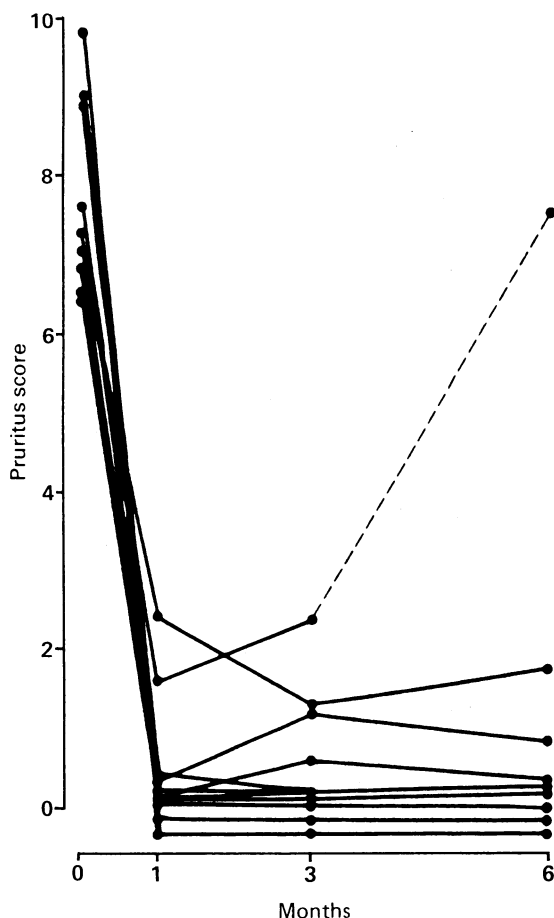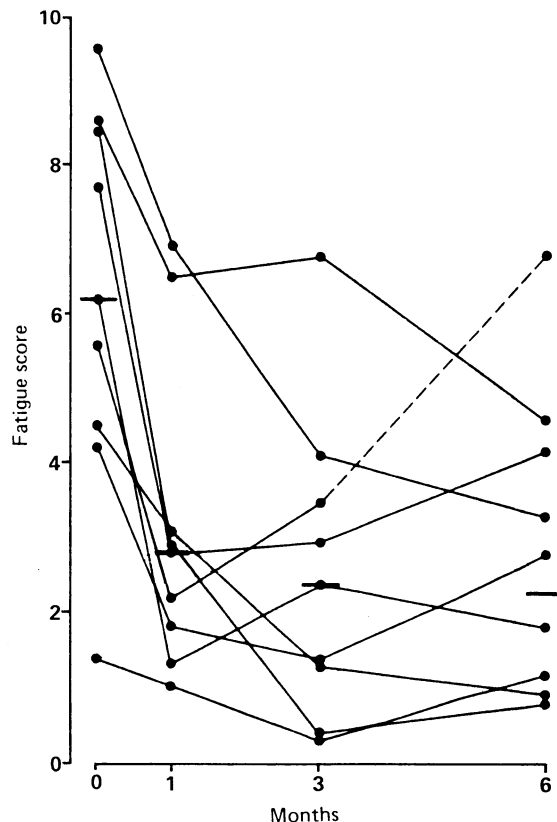

FIG 2—Effect of nalmefene on fatigue scores. ----=Drug stopped. Horizontal bars are median values

worsening ascites. It was also withdrawn in case 3 after four months because, although the patient felt better when taking the drug, her bilirubin concentration, after an initial fall, began to rise, and we could not exclude the possibility that this effect was drug induced. The remaining eight patients continued taking nalmefene for over six months.

All nine patients with itching noticed an immediate, considerable improvement in this symptom. At one month their pruritus score had fallen from 7·6 (6·4-9·8) to 0·2 (0-2·4; p<0·001), and this improvement was sustained at three months (0·2 (0-2·6); p<0·001) and six months (0·3 (0-1·8); p<0·001) (fig 1). The patients' sense of fatigue also improved: before taking nalmefene their score was 6·2 (1·3-9·6), at one month it was 2·6 (1·0-6·9; p<0·01), at three months it was 2·4 (0·6-6·8; p<0·01), and at six months it was 2·3 (0·8-4·6; p<0·01) (fig 2).

Plasma bilirubin concentration, which had risen from 60 (8-122) μmol/l to 72 (11-173) μmol/l (p<0·05) in the six months before the patients were given nalmefene, fell to 54 (11-162) μmol/l at one month (p<0·01), 58 (11-143) μmol/l at three months (p<0·05), and 48 (14-138) μmol/l at six months (p<0·02) (fig 3). Plasma albumin concentration and alkaline phosphatase and alanine aminotransferase activities did not alter significantly at any time during the study.

The three patients with the lowest baseline bilirubin concentration (cases 7-9) took nalmefene 20 mg thrice daily throughout the study. The six other patients were discharged from hospital taking nalmefene 40 mg thrice daily. Fatigue responded least well in case 2, and so the dose of nalmefene was increased at three months to 60 mg thrice daily with some apparent benefit (fig 2).

FIG 1—Effect of nalmefene on pruritus scores in nine patients with primary biliary cirrhosis. ----=Drug stopped

Discussion

All the patients experienced a considerable reaction when first given nalmefene and clonidine. Clonidine, even in larger doses than those that we gave, has not been reported to produce adverse reactions in patients

with liver disease.[12][13] Moreover, the same reaction occurred in the two patients initially given nalmefene alone. These effects were thus clearly a consequence of nalmefene's antagonist action at opioid receptors and not side effects because they were invariable, were temporary, have not been observed when nalmefene has been given to patients with various other diseases, and occurred at a dose one sixtieth of that which produces only occasional, minor cerebral effects, such as feelings of light headedness, in healthy subjects.[8] Similarly, the opioid antagonist naloxone has minimal or no subjective effects in normal subjects, even at high doses,[14] whereas much smaller quantities are sufficient to precipitate intense withdrawal symptoms in opiate addicts.[15]

Increasing evidence suggests that a sustained rise in plasma concentrations of pentapeptide enkephalins allows them to penetrate the blood-brain barrier,[17-20] though such a rise is not always shown after a single bolus injection.[16] Like opiate drugs, opioid peptides produce cerebral dependence when given continually,[21] even when given by a peripheral route.[22] Because our patients had raised plasma concentrations of at least two opioid peptides it is not surprising that they experienced an apparent withdrawal reaction when given an opioid antagonist.

The patients' immediate response to nalmefene has many similarities to the withdrawal reaction seen in opiate addiction.[9-11] In both reactions unpleasant cerebral disturbances, anorexia, nausea, abdominal pain, sweating, pallor, and a rise in arterial pressure occur. Arterial pressure rose in the patients with cirrhosis despite the hypotensive action of clonidine given concomitantly. Whereas heart rate rises in opiate addicts during withdrawal, our patients experienced a relative bradycardia. This was probably at least partly caused by the clonidine. Constipation was a surprising but temporary effect in our patients. With the exception of intermittent, colicky abdominal pain all the adverse effects resolved within the first week and were often minimal after two or three days, which

allowed clonidine to be tailed off and stopped after six days.

The cause of pruritus in cholestasis is uncertain. Methionine enkephalin may be excreted in bile.[2] We hypothesise that biliary excretion may be quantitatively more important for those opioid peptides comprising 10 or more amino acids, which, unlike methionine enkephalin,[2] are fairly resistant to enzymatic breakdown,[23][24] and that plasma concentrations of these larger peptides may therefore be increased in patients with cholestasis. These larger peptides are potent releasers of inflammatory mediators from mast cells, including histamine.[25-28] The alleviation of the patients' pruritus by nalmefene was considerable, apparent after the first dose, and sustained. The patients scratched themselves repeatedly before nalmefene was given but almost stopped doing so after starting to take the drug, and their scratch marks disappeared. This effect of nalmefene therefore seems to be more than a placebo reaction. It is probably a consequence of the inhibition of opioid peptides, which cause pruritic substances to be liberated, because unpublished trials of nalmefene in itchy skin disorders have not shown any direct antipruritic action of the drug.

The alleviation of fatigue by nalmefene was less impressive. Conceivably the high plasma methionine and leucine enkephalin concentrations in patients with cirrhosis[3-5] may contribute to fatigue in liver disease by a direct action on the central nervous system[17-20] and this fatigue may have been alleviated by blocking opioid receptors with nalmefene. An improvement in the patients' sleep after their pruritus had been relieved may also have played a part. A placebo response cannot, however, be excluded.

Plasma bilirubin concentration had been rising in most of the patients with primary biliary cirrhosis. It fell in all of them when they started taking nalmefene and six months later remained below the baseline value in eight of them. This finding suggests that there may be a metabolic contribution to the cholestasis of primary biliary cirrhosis that is caused by increased activity of opioid peptides. One patient, however, developed deepening jaundice three months after starting nalmefene. This was probably coincidental because it continued to worsen when the drug was stopped and she had had a bilirubin concentration of over 100 μmol/l before starting nalmefene, which often indicates rapidly progressive cholestasis.[29]

The patients' plasma albumin concentrations and alkaline phosphatase and alanine aminotransferase activities did not alter significantly with nalmefene. This suggests that the drug affects some of the metabolic abnormalities of liver disease without affecting the disease process itself.

The doses of nalmefene were empirical, and we did not measure the plasma concentrations of the drug. Nalmefene is eliminated predominantly in urine, partly after conjugation with glucuronic acid in the liver.[30] There are no reports of hepatotoxicity caused by nalmefene.

From these results we recommend that nalmefene is started in hospital, that the initial dose is as low as possible, and, perhaps, that a higher dose of clonidine than we used is given for the first few days. Under these conditions it should be possible to determine whether opioid peptides contribute to other manifestations of liver disease[2][3] and to evaluate the possible value of nalmefene in liver disease.
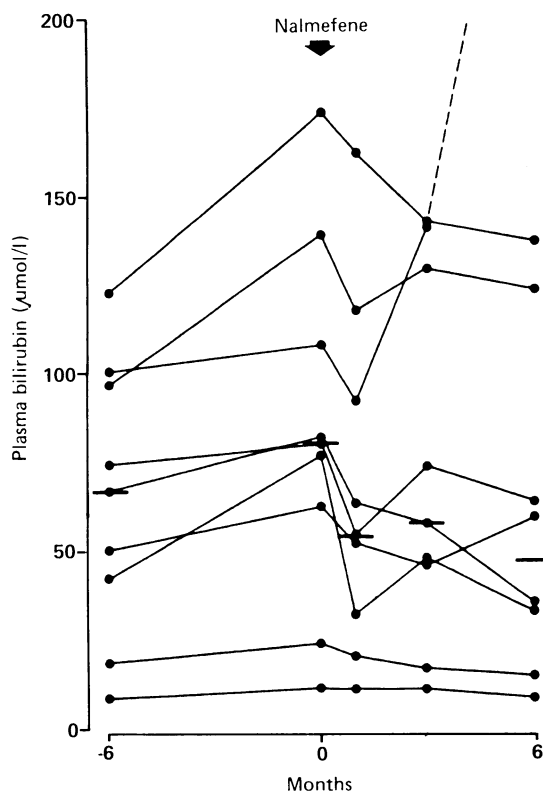

FIG 3—*Plasma bilirubin concentrations in nine patients with primary biliary cirrhosis before and after starting nalmefene. ----=Drug stopped. Horizontal bars are median values*

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Computerised updating of clinical summaries: new opportunities for clinical practice and research?

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Abstract

A new type of clinical summary, produced by copying standard descriptions of diseases on to a computer screen and editing them to match a patient's findings and diagnoses, was updated and reprinted as the patient's condition changed in the ward or as an outpatient. When this method was used to produce typed medical discharge summaries over a three month period, 73 out of 91 (80%) were sent out within a week after discharge compared with five out of 56 (9%) conventionally typed summaries received in a single general practice.

Even completely new computerised summaries are quicker for the secretary to produce than conventional summaries, and the computerised summaries are designed to be scanned rapidly for relevant information. They can also be used to collect data automatically for research, clinical audit, and resource management.

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Introduction

Few computer systems have been designed to help hospital doctors and secretaries avoid tedious repetition and to save time when clinic letters and discharge summaries are being dictated and typed. Word processing software can reduce the amount of dictating and typing required by allowing the copying of standard paragraphs into a document, but this approach has been applied to medicine only in a limited way, for copying simple phrases into standard letters.[1] This technique is difficult to apply when there are many diagnoses because the conventional letter or summary does not give the findings and the management of each diagnosis together in single blocks of text that can be transferred conveniently. Instead, the details of a single diagnosis are dispersed in different sections describing the history, examination, and investigations. This problem can be overcome by using a special format for the clinical summary and for the standard text.

Methods

The software system used in the study was an application of Lotus Symphony run on an IBM PC AT microcomputer. The format of the summary was based on three columns: findings, diagnoses, and management. Each column was divided into blocks of text, which were aligned horizontally and represented a single diagnosis (table I). The summary was drafted by copying the standard blocks of text from a library of entries held on a computer disk into the summary, which was then printed out. The entries on this printout were then edited by the doctor until they represented the patient's details (table II) and the changes were entered into a computer file by the secretary.

The doctor was able to check for clinical omissions and other errors as he edited the summary. This could be done while the patient was still in the ward, when any missing information was easily available. The consultant, other doctors, nurses, paramedical staff, and students caring for the patient could thus refer to the summary and comment or ask about its contents. When the patient was seen in a follow up clinic or readmitted the summary could be updated and reprinted.

ASSESSMENT OF THE SYSTEM

The new summaries were produced for all routine and emergency patients admitted to a medical department under the care of two consultant physicians over three months. The time from discharge of the patient to completion of the final summary was recorded in three different groups of patients: those admitted under the care of the two consultants who were using the new system; those admitted during the same period