Mean (SD) sublingual temperatures (°C) before, immediately after, and one hour after exercise in 10 healthy men given placebo or naloxone five minutes before exercise

	Control	Placebo	Naloxone
Before exercise	36·85 (0·24)	36·64 (0·28)	36·58 (0·29)
Immediately after	37·33 (0·26)	37·16 (0·27)	36·40 (0·54)*
An hour after	36·83 (0·24)	36·67 (0·34)	36·34 (0·41)*

*$p < 0.001$ compared with control and placebo studies.

measured with a simple thermometer before exercise, immediately afterwards, and one hour later. Statistical study of results was performed by two way analysis of variance.

There were no significant differences in maximal heart rate, maximal workload, or duration of exercise until exhaustion when the control, placebo, and naloxone trials were compared. As expected, a rise of body temperature of about 0·5°C was seen immediately after exercise in the control and placebo tests: mean sublingual temperature was 36·85 (SD 0·24)°C before and 37·33 (0·86)°C after exercise in the control test and 36·64 (0·28)°C before and 37·16 (0·27)°C after exercise in the placebo test. Administration of naloxone completely abolished this rise in temperature: before exercise the sublingual temperature in the naloxone test was 36·58 (0·29)°C and after 36·40 (0·54)°C. The difference between the placebo and control tests was significant ($p < 0.001$) (table).

Discussion

Our finding that the rise in body temperature induced by exercise is antagonised by naloxone suggests that endogenous opiates play a part in thermal regulation during muscular exercise.

References

1 Yehuda S, Kastin A. Peptides and thermoregulation. *Neuroscience and Biobehavioral Reviews* 1979;4:459-71.
2 Holaday JW, Loh HH, Li CH. Unique behavioural effects of beta endorphin and their relationship to thermoregulation and hypothalamic function. *Life Sci* 1978;**22**:1525-35.
3 Holaday JW, Wei E, Loh HH, Li CH. Endorphins may function in heat adaptation. *Proc Natl Acad Sci USA* 1978;**75**:2923-7.
4 Clark WG. Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics, and related agents. *Neurosci Biobehav Rev* 1980;**3**:179-231.

(*Accepted 21 November 1984*)

Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs

J N BARNES, A J WILLIAMS, M J F TOMSON P A TOSELAND, F J GOODWIN

Abstract

The pharmacokinetics of a single oral dose of dihydrocodeine were studied in nine patients with chronic renal failure treated by haemodialysis and nine subjects with normal renal function. In the patients the mean peak plasma dihydrocodeine concentration occurred later and the area under the curve was greater than in the normal subjects. Furthermore, the drug was still detectable after 24 hours in all the patients but only three of the normal subjects.

These data, together with those obtained from previously published clinical case reports, contradict the traditional view that the body's ability to cope with opioid drugs is not altered in renal failure.

Introduction

The kidney is the main site for the elimination of many drugs and their metabolites from the body, and renal disease can consequently have important effects on the pharmacokinetics of such drugs. In addition, the pharmacokinetics of these drugs may be altered in uraemia by changes in plasma protein binding and the rates at which they are metabolised.[1 2]

Although opioid drugs and their metabolites are excreted by the kidney[3 4] and some have decreased plasma protein binding in uraemia,[5] it is generally considered to be safe to prescribe them at the normal therapeutic dosage to patients with impaired renal function.[6-8]

This view must now be challenged. There have been several reports of serious narcosis in patients with renal failure treated with opioid drug,[9 10] and evidence that the kidney has an important role in the elimination of opioid narcotics is accumulating.[11 12]

The present study was performed to investigate the effect of end stage renal failure on the pharmacokinetics of a single oral dose of dihydrocodeine, a drug that has hitherto been considered to be safe at the conventional dosage in patients with chronic renal failure receiving maintenance haemodialysis.[13]

Subjects and methods

We studied nine subjects (five men), mean (SD) age 34·2 (4·2) years, with normal renal function and nine patients (seven men), age 40·8 (5·2) years, receiving maintenance haemodialysis. All the subjects attended after an overnight fast, and the patients attended on days when they were not receiving dialysis. A 19 G Butterfly cannula was inserted into a forearm vein in the normal subjects or into a vein on the back of the hand in the patients. Blood samples were taken immediately and without tourniquet for estimating plasma

Department of Nephrology, The London Hospital, E1
J N BARNES, MA, MRCP, lecturer in medicine
A J WILLIAMS, MD, MRCP, senior registrar
M J F TOMSON, MB, BS, house officer
F J GOODWIN, MD, FRCP, consultant nephrologist

Department of Clinical Chemistry, Guy's Hospital, London
P A TOSELAND, PHD, FRCPATH, top grade biochemist

Correspondence to: Dr J N Barnes, Medical Unit, The London Hospital.

concentrations of urea, creatinine, electrolytes, and proteins, liver biochemistry, and dihydrocodeine concentration.

The patients and subjects took dihydrocodeine tartrate 60 mg by mouth with 50 ml of water and remained supine and fasting for four hours. After four hours they were allowed to eat lunch and move about. Blood samples were taken before and half an hour and one, two, three, four, six, and 24 hours after ingestion of the dihydrocodeine. All blood samples were taken into lithium heparin tubes, which were immediately placed on ice. They were then centrifuged at 4°C and 2000 rpm and the plasma separated and stored in plastic tubes at −20°C.

All the tablets used in the study were from the same batch.

The data are presented as mean (SEM) values, and statistical comparisons were made using Student's *t* test for unpaired data. The area under the curves was calculated using the trapezoid method.

DIHYDROCODEINE ASSAY

Two methods of analysis were employed, both of which measured the total concentration of unconjugated active drug present in the plasma, the inactive glucuronide conjugates being removed by the extraction procedure.

Gas liquid chromatography—Figure 1 outlines the extraction procedure. Gas liquid chromatography was performed on 7 μl final solution injected on to an 8 feet (2·44 m) by 2 mm column of 3% SP-2250 operated at 265°C in a Hewlett-Packard 5700 nitrogen detector system. Disopyramide 1 μg/ml of plasma was used as an internal standard.

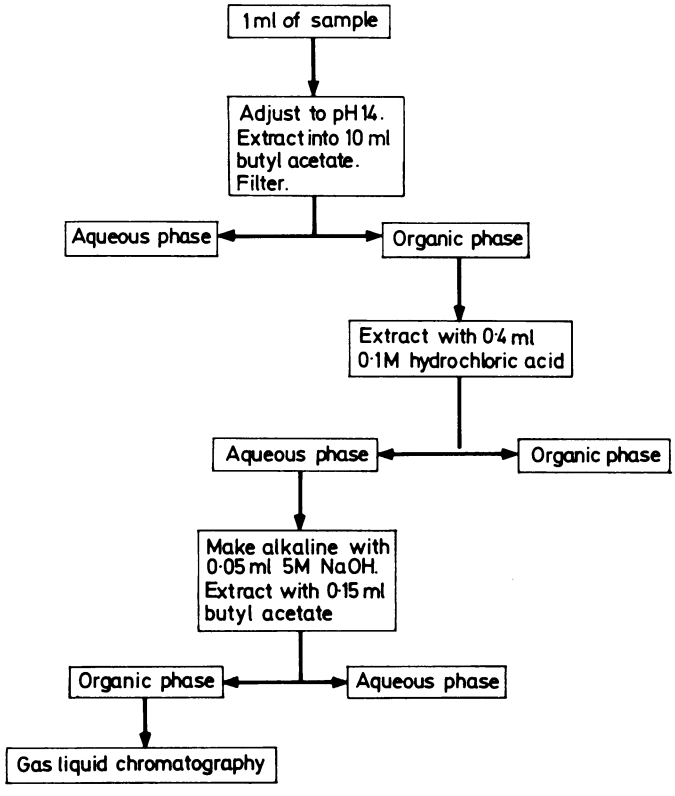

FIG 1—Flow chart of extraction procedure for measurement of dihydrocodeine by gas liquid chromatography.

High pressure liquid chromatography—The same extraction procedure was used up to the stage of acid re-extraction. In this case 0·2 ml of 0·1M hydrochloric acid was used, and the whole product was transferred to a liquid phial of a Hewlett-Packard 1084B automatic high pressure liquid chromatograph. Chromatography was performed on a C18 ODS column in the cartridge form (Brownlee, Santa Clara, California). The eluting phase consisted of an acetonitrile and an aqueous phase at the ratio of 35 to 65. The aqueous phase consisted of a solution of 1·1 g trimethyl chloride, 0·4 ml concentrated sulphuric acid, and 0·5 ml tetraethyl ammonium chloride. The eluent was monitored at 282 nm.

Assay standards were prepared at the time the samples were collected and were stored together with the samples at −20°C.

Results

The mean age of the patients was not significantly different from that of the normal subjects, and one way analysis of variance showed that age was not a confounding factor in the handling of dihydrocodeine. There was no significant difference between the mean (SEM) plasma protein concentration in the normal subjects (69·1 (1·0) g/l) and the patients (66·6 (2·5) g/l). The mean plasma albumin concentration was, however, higher in the normal subjects (45·7 (0·8) *v* 36·5 (0·9) g/l; $p < 0.05$). The mean plasma creatinine concentration was 82·6 (5·9) μmol/l (0·94 (0·07) mg/100 ml) in the normal subjects and 1114·7 (101·2) μmol/l (12·6 (1·1) mg/100 ml) in the patients.

The dihydrocodeine concentration in the plasma samples obtained from the first five subjects studied (three normal, two with renal

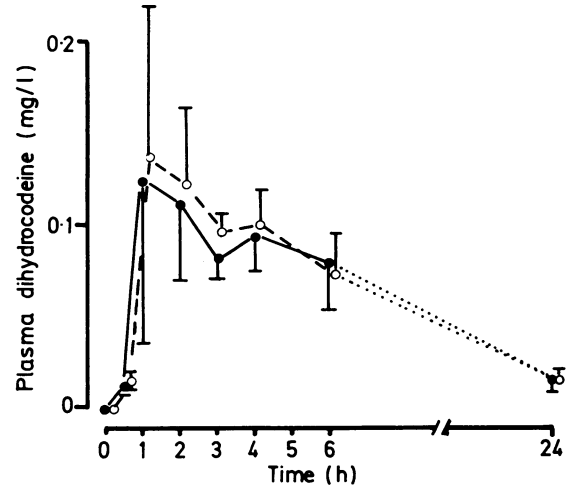

FIG 2—Mean (SEM) plasma dihydrocodeine concentrations in five subjects (three normal, two with renal failure) after receiving 60 mg dihydrocodeine by mouth, measured by gas liquid chromatography (●——●) and high pressure liquid chromatography (O——O).

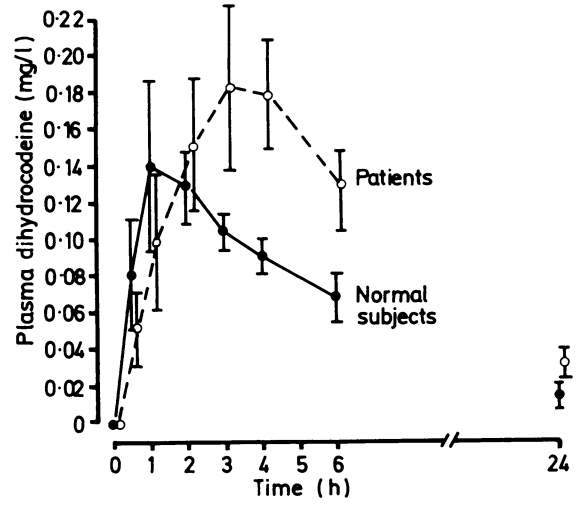

FIG 3—Mean (SEM) plasma dihydrocodeine concentrations in nine subjects with normal renal function and nine patients with chronic renal failure (CRF) after receiving 60 mg dihydrocodeine by mouth. Plasma dihydrocodeine concentrations were significantly higher in the patients at four and six hours ($p < 0.05$), and the area under the curve was greater ($p < 0.05$), than in the normal subjects.

failure) were measured by both gas liquid chromatography and high pressure liquid chromatography; the results were similar (fig 2). Results obtained subsequently are presented for the gas liquid chromatography method.

Figure 3 shows the mean plasma dihydrocodeine concentrations for the patients and the normal subjects. The curves are clearly different. The mean peak blood concentrations occurred after one hour in the normal subjects and three hours in the patients. The area under the curve during the 24 hours of the study was greater in the patients (2·25 (0·39) *v* 1·32 (0·20) mgh/l; $p < 0·05$) and, whereas dihydrocodeine was still detectable after 24 hours in all the patients, it was found in only three of the normal subjects after that time.

Discussion

This study shows that the pharmacokinetics of dihydrocodeine given by mouth differ between subjects with normal renal function and patients with chronic renal failure treated with haemodialysis. The mean peak blood concentration occurred earlier in the subjects, and the area under the curve was less. In addition, the drug was detectable after 24 hours in only three of the nine normal subjects but in all of the patients. Possible explanations for these findings include differences in absorption, the volume of distribution, the rate of metabolism, and the rate of excretion of the drug.

The rate of rise in plasma dihydrocodeine concentration reflects the rate of absorption of the drug but may also be influenced by metabolism and excretion. Many patients receiving chronic haemodialysis have hyperchlorhydria,[14] which might be expected to reduce gastric absorption of a basic drug such as dihydrocodeine. This would be in keeping with the slower rise in plasma dihydrocodeine concentration observed in the patients.

After absorption the plasma concentration of dihydrocodeine is influenced by its volume of distribution as well as by the rates of metabolism and excretion. Metabolic acidosis in the patients with renal failure might reduce the tissue penetration of a basic drug, thus resulting in higher plasma concentrations. In contrast, the lower plasma albumin concentration found in our patients and the decreased plasma protein binding that can occur with some drugs in uraemia might be expected to increase the apparent volume of distribution and result in lower plasma concentrations.

The metabolic fate of dihydrocodeine has not been clearly established. Traditionally opioid drugs have been thought to be metabolised in the liver, and the process by which dihydrocodeine is metabolised may be similar to that for codeine, with N-demethylation to dihydromorphine, O-demethylation to nordihydrocodeine, or conjugation with glucuronic acid. Uraemia can alter the hepatic extraction of some drugs.[15] If the hepatic extraction of dihydrocodeine were reduced in renal failure higher concentrations of the drug would result. Recently, however, attention has focused on the extrahepatic metabolisation of narcotic drugs and in particular metabolisation within the kidney.[12 16] Failure of such metabolisation might account for some of the differences in plasma concentrations between our groups.

Finally, the kidney is the major organ for excreting opioid drugs,[3 4] possibly by tubular secretion as well as glomerular filtration. Clearly, failure of renal excretion of the parent drug or its metabolites could be an important factor in explaining the differences between the patients and the normal subjects.

In conclusion, this study was designed to examine the traditionally held view that the pharmacokinetics of dihydrocodeine are unchanged in renal failure.[6 7 13] It shows clearly that this is not true. More detailed analysis of the altered pharmacokinetics of dihydrocodeine in renal failure is required, with studies using intravenous doses of the drug. The present observations, however, suggest that the kidney has an important role in the handling of opioid drugs and that the contraindications for prescribing dihydrocodeine and related drugs and the recommendations regarding their dosage in patients with renal failure require urgent review.

We thank Miss Christine Taylor for her help in the preparation of this manuscript.

References

1 Reidenberg MM. The binding of drugs to plasma proteins and the interpretation of measurements of plasma concentrations of drugs in patients with poor renal function. *Am J Med* 1977;**62**:466-70.
2 Reidenberg MM. The biotransformation of drugs in renal failure. *Am J Med* 1977;**62**:482-5.
3 Adler TK, Fujimoto JM, Way EL, Baker EM. The metabolic fate of codeine in man. *J Pharmacol Exp Ther* 1955;**114**:251-62.
4 Hug CG, Mellett LB, Cafruny EJ. Stop flow analysis of the renal excretion of tritium-labeled dihydromorphine. *J Pharmacol Exp Ther* 1965;**150**:259-69.
5 Olsen GD, Bennett WM, Porter GA. Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. *Clin Pharmacol Ther* 1975;**17**: 677-84.
6 Brenner BM, Rector FC. *The kidney*. Philadelphia: W B Saunders, 1981:2681.
7 Bennett WM, Aronoff GR, Morrison G, *et al*. Drug prescribing in renal failure: dosing guidelines for adults. *Am J Kidney Dis* 1983;**3**:155-75.
8 Cheigh JS. Drug administration in renal failure. *Am J Med* 1977;**62**:555-63.
9 Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *Br Med J* 1983;**286**:438-9.
10 Don HF, Dieppa RA, Taylor P. Narcotic analgesics in anuric patients. *Anaesthesiology* 1975;**42**:745-7.
11 McQuay H, Moore A. Metabolism of narcotics. *Br Med J* 1984;**288**:237.
12 Moore RA, Sear JW, Baldwin D, *et al*. Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984;**35**:641-8.
13 Datapharm Publications Limited. ABPI. *Data sheet compendium 1983-1984*. London: Datapharm Publications Limited, 1983:357-8. (Manufacturer's data sheet.)
14 Ventkateswaran PS, Jeffers A, Hocken AG. Gastric acid secretion in chronic renal failure. *Br Med J* 1972;iv:22-3.
15 Bianchetti G, Graziani G, Brancaccio D, *et al*. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokinet* 1976;**1**:373-84.
16 Schali C, Roch-Ramel F. Transport and metabolism of (3H) morphine in isolated, nonperfused proximal tubular segments of the rabbit kidney. *J Pharmacol Exp Ther* 1982;**223**:811-5.

(*Accepted 28 December 1984*)

100 YEARS AGO

At the meeting of the Odontological Society of Great Britain, held on the 1st instant, Dr. St. George Elliott exhibited three very curious and interesting specimens of Japanese artificial teeth. The Japanese, he said, were the only nation outside the limits of Western civilisation who understood the fitting of artificial teeth. They had derived most of their scientific and technical knowledge from the Chinese, but in this matter they were in advance of their teachers, for the Chinese had no idea of fitting an artificial denture. They could, indeed, carve a row of incisors, and fasten them to the teeth on each side; but these productions were only intended for ornament, not for use, whilst those of Japanese manufacture were thoroughly efficient. Thus a Japanese physician who came to Dr. Elliott for a set of teeth, remarked that, though the foreign teeth were more natural in appearance, those of home-manufacture were quite as good from a practical point of view; and, in proof of this, he took up a piece of hard "rock-candy," and crunched it between his false teeth. These dentures were made on wooden bases; the front teeth were made from quartz-pebbles ground down, but the process of mastication was performed by copper-nails, which occupied the place of the molars. It was an interesting fact, also, that the fixing of dentures by means of suction had been known to the Japanese for at least two hundred years. The base-plates were carved by hand, the process being as follows. An impression of the mouth was taken in wax, and from this a model was made, also in wax. The model was then coated all over with red pigment, and the plate, after being roughly shaped, was placed on the model thus coloured. The red patches on the under surface of the plate were then carefully cut away, until at last it fitted the model exactly. It was then tried in the mouth in the same way, the gums being covered with the pigment, and any inaccuracy readily detected. Dr. Elliott stated that one of these dentures had been in use for fifteen years. (*British Medical Journal* 1885;i:89.)