Pharmacodynamics of carbenicillin in hepatic and renal failure. *Ann. intern. Med.*, **73**, 173–178.

JUSKO, W.J., LEWIS, G.P. & SCHMITT, G.W. (1973). Ampicillin and hetacillin pharmacokinetics in normal and anephric subjects. *Clin. Pharmac. Ther.*, **14**, 90–99.

MITCHARD, M., ANDREWS, J., KENDALL, M.J. & WISE, R. (1977). Mecillinam levels following intravenous injection: a comparison with pivmecillinam. *J. Antimicrob. Chemother.*, **3**, Suppl. B, 83–88.

NAUTA, E. & MALTIE, H. (1975). Pharmacokinetics of flucloxacillin in healthy subjects on chronic intermittent haemodialysis. *Br. J. clin. Pharmac.*, **2**, 111–121.

NAUTA, E., MALTIE, H. & GOSLINGS, W. (1973). Pharmacokinetics of cloxacillin in patients on chronic dialysis. *Chemotherapy*, **19**, 261–271.

ROHOLT, K. (1977). Pharmacokinetic studies with mecillinam and pivmecillinam. *J. Antimicrob. Chemother.*, **3**, Suppl. B, 71–81.

SCHREINER, G.E. & TEEHAN, B.P. (1972). Dialysis of poisons and drugs. *Trans. Am. Soc. Art. Org.*, **18**, 563–580.

WILLIAMS, J.D., ANDREWS, J., MITCHARD, M. & KENDALL, M.J. (1976). Bacteriology and pharmacokinetics of the new amidino penicillin—mecillinam. *J. Antimicrob. Chemother.*, **2**, 61–69.

NALOXONE MODULATES THE PERCEPTION OF ITCH IN MAN

Naloxone, a pure opiate antagonist, can alter the subjective assessment of pain, thus providing evidence that endorphins may modulate pain in man (Lasagna, 1965; Buchsbaum, Davis & Bunney, 1977; Levine, Gordon, Jones & Fields, 1978; Levine, Gordon & Fields, 1978a; Levine, Gordon & Fields, 1979). The hyperalgesia caused by naloxone in patients with dental pain appears to be due entirely to the abolition of the placebo response (Levine *et al.*, 1978a). The present study was designed to assess the effect of naloxone on the related sensation, itch. Both itch and pain are transmitted to the dorsal horns of the spinal cord by small diameter (c) fibres (Zotterman, 1939), and are probably integrated at a common site at each spinal segment (Graham, Goodell & Wolff, 1951). Furthermore, there is evidence that pain may be modulated by an enkephalin system in the interneurones of the substantia gelatinosa in each dorsal horn (Hökfelt, Ljungdahl, Terenius, Elde & Nilsson, 1977; Jessell & Iversen, 1977). In these experiments the effect of naloxone on nocturnal itch was studied in patients with cholestatic liver disease who had severe protracted itching.

Twenty patients with cholestatic liver disease were studied (age range 29 to 71 years). Thirteen were female. The diagnosis was established by compatible biochemical tests, liver biopsy and/or cholangiography. They had been itching for between 1 month and 17 years (mean 3.2 years). The itch was constantly present although six patients volunteered that it was worse at night. Patients with mild itching were excluded from the trial. Three patients, who had received cholestyramine continuously for between 4 months and 3 years, and four patients who took regular night sedation (diazepam or nitrazepam), continued to receive therapy. D-penicillamine treatment was continued in six patients with primary biliary cirrhosis. The study was approved by the hospital ethical practices committee and informed consent was obtained from each patient. The patients were told they would receive an agent that reduced itch in a proportion of patients (placebo) and a drug whose effect was being evaluated (naloxone). A randomized double-blind placebo controlled design was used. The code was not broken during any experiment. Drugs were administered intravenously at 18.00 h in equal volumes (5 ml) of either naloxone (2 mg) or saline (0.9% w/v). The injections were indistinguishable colourless liquids and produced no immediate effect that could be identified. All the patients completed the study. The experiments were performed between May and September 1979. Nocturnal itching was assessed on 4 consecutive nights. Night 1 and night 3 were control nights. On night 2 and night 4 patients received either placebo or naloxone. The last eight patients also received a placebo on night 1 to access the reproducibility of the placebo response. Itching was assessed at 9.00 h the following morning by the visual analogue scale validated for the assessment of pain (Joyce, Zutshi, Hrubes & Mason, 1975; Scott & Huskisson, 1976). This was a 10 cm horizontal line on a white card marked at the left end 'none' and at the right end 'unbearable'. The patient assessed the previous night's itching by marking a point along this line. The visual analogue scales were later estimated to within 1 mm. Patients could not refer to earlier assessments. The results were expressed as the change in itch score between the treatment night and the previous night. Nocturnal scratch was estimated in the first 12 patients on nights 2, 3 and 4. Electronic movement meters were attached to each arm on retiring to sleep and removed on waking. In previous experiments this

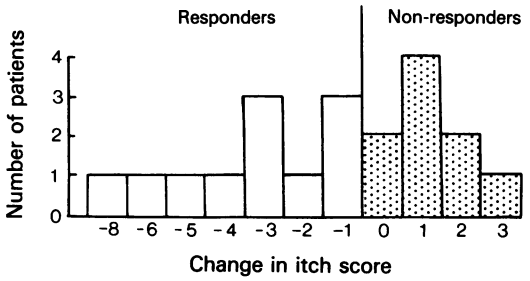

Figure 1 The change in itch score induced by placebo. Nine patients rated itch unchanged or worse following placebo (non-responders) whereas eleven rated itch improved after placebo (responders). The distribution of these patients suggests they may form two populations. The reproducibility of the placebo response was assessed by giving the final eight patients an additional placebo on night 1. Seven responded the same way after each placebo, one placebo responder became a non-responder (no difference between response to first and second placebo compared to control night; paired t-test, $t = 0.147$, $P > 0.5$).

arm movement was shown to be correlated with the subjective assessment of itch (Summerfield & Welch, 1980).

Analysis of the whole group showed that the mean change in itch score induced by naloxone (−0.95) was not different from that caused by placebo (−1.33) (paired t-test $t = 0.152$, $P > 0.5$). However, there appeared to be two groups as judged by their response to placebo (Figure 1). These groups were similar with respect to mean age, sex and duration of illness. Two patients in each group took regular night sedation. Most patients defined as placebo responders reported that the itch was worse on naloxone than placebo, whereas placebo non-responders tended to rate itch improved after naloxone (Figure 2). Furthermore, the magnitude of the placebo response was significantly correlated with the itch score change between naloxone and placebo ($r = 0.57$; $P < 0.01$). Figure 3 shows that the enhancement of itch by naloxone in placebo responders appears to be due to the abolition by naloxone of the placebo induced reduction in itch score ($0.05 > P > 0.02$). In contrast, naloxone caused a significant reduction in itch score in the placebo non-responders ($0.05 > P > 0.02$). Consequently, while the response to placebo was significantly different in the placebo responders and the placebo non-responders (t-test on changes in individual itch scores after placebo; $t = 5.19$, $P < 0.01$), naloxone caused a similar reduction in itch score in both groups (t-test on changes in individual itch scores after naloxone; $t = 1.01$, $0.5 > P > 0.2$). Neither naloxone nor placebo altered nocturnal scratching in 12 patients as judged by movement meter estimations. The arm movement on the control night (72 ± 20 min/8 h; mean ± s.e. mean, $n = 12$) was similar on the placebo night (73 ± 22 min/8 h) and on the naloxone night (75 ± 15 min/8 h). No difference was apparent between placebo responders and non-responders. The upper limit of the normal range of nocturnal arm movement in patients with non itchy

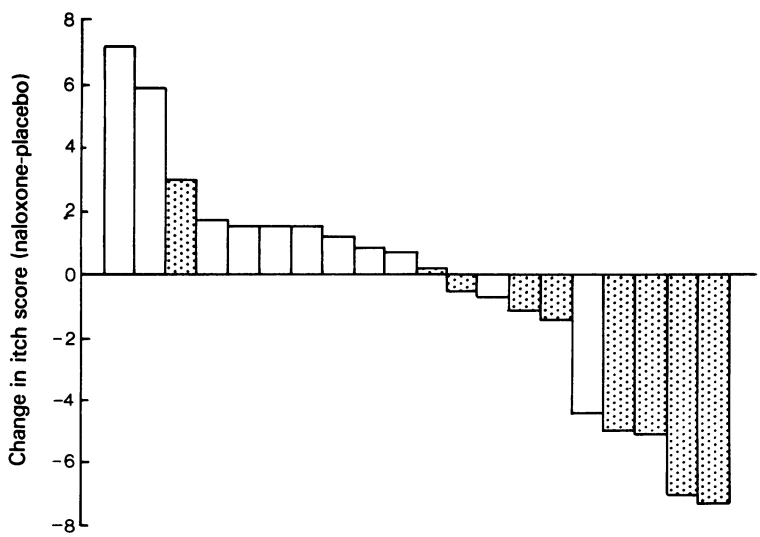

Figure 2 The change in itch score calculated as the difference between the itch score on the naloxone night and the placebo night for each patient. Positive differences indicate the itching was rated worse on naloxone. On the basis of their response to a placebo the patients were classified as 'placebo responders' (□) or 'placebo non-responders' (▨). After naloxone most placebo responders rated the itch as worse but most placebo non-responders rated the itch as improved (groups significantly different by t-test on individual difference scores; $t = 2.89$, $P < 0.01$).

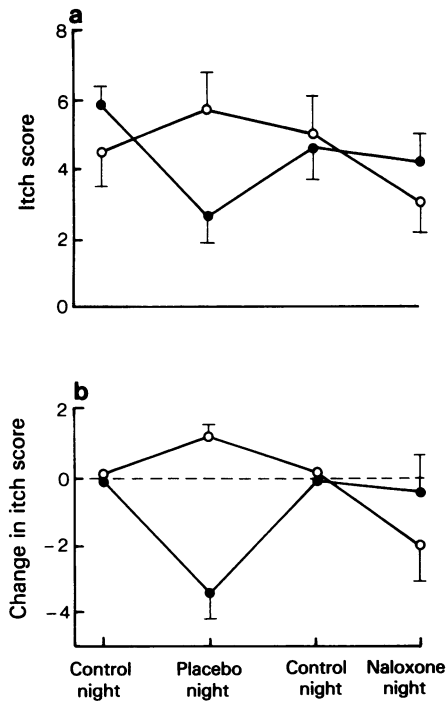

Figure 3 The effect of placebo and naloxone on itch score. The mean itch score (a) and the change in itch score (b) with standard error bars during the four nights of the study is plotted for placebo responders (●) and placebo non-responders (○). In placebo responders, the placebo induced reduction in itch score was abolished by naloxone (paired t-test on changes in individual itch scores on placebo or naloxone; $t = 2.62$, $0.05 > P > 0.02$). In contrast the itching of placebo non-responders diminished after naloxone ($t = 2.76$, $0.05 > P > 0.02$).

liver disease is 43 min/8 h (mean+2 s.d.). (Summerfield & Welch, 1980).

These data suggest that naloxone modulates itch sensation in man. The effect is only apparent when placebo responders are separated from non-responders. The placebo response has been demonstrated in a variety of conditions (Beecher, 1955) and in painful states appears to be mediated by an endorphin system (Levine *et al.*, 1978; Levine *et al.*, 1978a). In this study placebo responders reported significantly greater itch after naloxone than after placebo. This appeared to be due to the abolition of the placebo response. However, placebo non-responders reported less itch after naloxone than after placebo. These results differ from those observed in dental pain where the effect was restricted to placebo responders (Levine *et al.*, 1978a). However, a bidirectional response to naloxone has been reported in a study of experimental pain (Buchsbaum *et al.*, 1977). Patients with liver disease have a reduced opiate tolerance probably due to enhanced cerebral receptor sensitivity (Laidlaw, Read & Sherlock, 1961). This could account for the naloxone effect being observed after the assessment period of 15 h in this study. This is much longer than the duration of action of intravenous naloxone in normal subjects (Levine *et al.*, 1978a).

Finally, the effect of naloxone on itch must be reconciled with its apparent failure to influence scratch. Scratch, the response evoked by itch, can be a spinal reflex in experimental animals (Sherrington, 1906). There is some evidence that scratch during sleep may also be a spinal reflex (Savin, Paterson, Oswald & Adam, 1975). If this is so, then scratch during sleep may not be influenced by the processes modulating the perception of itch.

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References

BEECHER, H.K. (1955). The powerful placebo. *J. Am med. Ass.*, **159**, 1602–1606.

BUCHSBAUM, M.S., DAVIS, G.C. & BUNNEY, W.E. (1977). Naloxone alters pain perception and somatosensory evoked potentials in normal subjects. *Nature*, **270**, 620–622.

GRAHAM, D.T., GOODELL, H. & WOLFF, H.G. (1951). Neural mechanisms involved in itch, 'itchy skin' and tickle sensations. *J. clin Invest.*, **30**, 37–49.

HÖKFELT, T., LJUNGDAHL, Å., TERENIUS, L., ELDE, R. & NILSSON, G. (1977). Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: Enkephalin and substance P. *Proc. Nat. Acad. Sci.* **74**, 3081–3085.

JESSELL, T.M. & IVERSEN, L.L. (1977). Opiate analgesics inhibit substance P release from rat trigeminal nucleus. *Nature*, **268**, 549–551.

JOYCE, C.R.B., ZUTSHI, D.W., HRUBES, V. & MASON, R.M.

(1975). Comparison of fixed interval and visual analogue scales for rating chronic pain. *Eur. J. clin. Pharmac.*, **8**, 415–420.

LAIDLAW, J., READ, A.E. & SHERLOCK S. (1961). Morphine tolerance in hepatic cirrhosis. *Gastroenterology*, **40**, 389–396.

LASAGNA, L. (1965). Drug interaction in the field of analgesic drugs. *Proc. Roy. Soc. Med.*, **58**, 978–983.

LEVINE, J.D., GORDON, N.C. & FIELDS, H.L. (1978a). The mechanism of placebo analgesia. *Lancet*, **ii**, 654–657.

LEVINE, J.D., GORDON, N.C. & FIELDS, H.L. (1979). Naloxone dose dependently produces analgesia and hyperalgesia in post-operative pain. *Nature*, **278**, 740–741.

LEVINE, J.D., GORDON, N.C., JONES, R.T. & FIELDS. H.L. (1978). The narcotic antagonist naloxone enhances clinical pain. *Nature*, **272**, 826–827.

SAVIN, J.A., PATERSON, W.D., OSWALD, I. & ADAM, K. (1975). Further studies of scratching during sleep. *Br. J. Derm.*, **93**, 297–302.

SCOTT, J. & HUSKISSON, E.C. (1976). Graphic representation of pain. *Pain*, **2**, 175–184.

SHERRINGTON, C.S. (1906). Observations on the scratch reflex in the spinal dog. *J. Physiol.*, **34**, 1–50.

SUMMERFIELD, J.A. & WELCH, M.E. (1980). The measurement of itch with sensitive limb movement meters. *Br. J. Derm.* (in press).

ZOTTERMAN, Y. (1939). Touch, pain and tickling; an electrophysiological investigation on cutaneous sensory nerves. *J. Physiol.*, **95**, 1–28.

EVALUATION OF A SIMPLE METHOD TO CHECK COMPLIANCE WITH ANTIHYPERTENSIVE DRUG THERAPY

There are many ways of improving patient compliance (Blackwell, 1972). These include interrogation and education, tablet counting, stool and urine markers and drug detection. There is evidence that patient education alone may fail to improve compliance (Sackett, Haynes, Gibson, Hackett, Taylor, Roberts & Johnson, 1975) and drug checks on urine and blood have been recommended as the most certain means of monitoring whether a patient takes his prescribed drugs. Treating hypertension is an important example of patient compliance presenting a problem to the clinician. Untreated patients with moderate to severe hypertension often feel well and feel less well when given the complex drug regimens which may be needed to achieve satisfactory blood pressure control. Consequently, poor compliance may be understandable. However, the doctor frequently fails to recognize this reason for the patient's poor response and proceeds to prescribe more drugs. Methods of recognizing poor compliance are therefore of interest.

Simple methods of detecting hydrochlorothiazide and methyldopa in urine are available (Lowenthal, Briggs, Mutterperl, Adelman & Creditor, 1976). We now report the evaluation of a simple technique, using solvent extraction and thin-layer chromatography for the monitoring of a number of commonly prescribed β-adrenergic receptor blocking drugs and the vasodilator, hydralazine, in urine.

The method involved taking 4 ml urine which was made alkaline with 0.05 ml of 7M NaOH and extracted with 4 ml diethyl ether: dichloromethane (4:1). The organic phase was aspirated, evaporated to dryness, redissolved in two drops of methanol and spotted on to a silica gel chromatography plate. Appropriate drug standards were spotted alongside and the plate developed in ethyl acetate: methanol 40:5) for a hydralazine compliance check and ethyl acetate: methanol: concentrated ammonia (40:5:5) for a check of the β-adrenoceptor blockers. After development the drugs or their metabolites were identified either by their fluorescence under ultra violet light (254 nm) or by the colour produced on treatment with a visualizing agent (Table 1). The method is sensitive enough to allow detection of the drugs studied if they are taken daily at the recommended doses. The unchanged drug is detected except in the case of metoprolol and hydralazine when a metabolite is the compound visualized. Full experimental details are given in an earlier methodological paper (Jack, Dean & Kendall, 1980).

The reliability of the method was tested by examining batches each consisting of sixteen urine specimens, eight obtained from patients taking a particular drug under supervision and eight from volunteers taking no drug. The specimens were randomized and tested for the drug in question by the method described above. The procedure was repeated for each of the drugs studied, namely, propranolol, oxprenolol, metoprolol, acebutolol, nadolol and hydralazine. In all, six batches of sixteen urine specimens were tested in this way.

As a further, more stringent, test of reliability fifty urine specimens were collected from patients taking the above drugs under supervision in hospital, about eight specimens for each drug, and these were tested