genuine acupuncture sessions may have been the result of an order effect. This explanation, however, cannot be used to explain any of the demonstrated superiority of genuine acupuncture over pseudoacupuncture since these sessions were in balanced order of presentation.

The conclusion must be that acupuncture may have analgesic effects. This is consistent with the results of other research on Western populations which has controlled for suggestion¹⁹ and with several recent studies on man and animals which implicate neurophysiological mechanisms.^{1 20 21} The practical value of acupuncture, however, still remains to be established.

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References

- ¹ National Health and Medical Research Council of Australia, *Report on Acupuncture*. Canberra, Australian Government Publishing Service, 1974.
- ² Wall, P D, *New Scientist*, 1974, **64**, 31.
- ³ Bonica, J J, *Journal of the American Medical Association*, 1974, **229**, 1317.
- ⁴ Hardy, J D, Wolff, H G, and Goodell, H, *Pain Sensations and Reactions*. Baltimore, Williams and Wilkins, 1952.
- ⁵ Barber, T X, and Hahn, K W, *Journal of Abnormal and Social Psychology*, 1962, **65**, 411.
- ⁶ Barber, T X, and Cooper, B J, *Psychological Reports*, 1972, **31**, 647.
- ⁷ Gammon, G D, and Starr, I, *Journal of Clinical Investigation*, 1941, **20**, 13.
- ⁸ Wolff, B B, Krasnegor, N A, and Farr, R S, *Perceptual and Motor Skills*, 1965, **21**, 675.
- ⁹ Clark, W C, and Yang, J C, *Science*, 1974, **184**, 1096.
- ¹⁰ Katz, R L, *et al*, in *Advances in Neurology*, Vol 4, ed J J Bonica. New York, Raven Press, 1974.
- ¹¹ Clausen, J, Gjesvik, A, and Urdal, A, *Journal of General Psychology*, 1953, **49**, 261.
- ¹² Matsumoto, J, Ambruso, V, and Levy, B, *International Surgery*, 1974, **59**, 40.
- ¹³ Mann, F B, *Atlas of Acupuncture*. London, Heinemann, 1966.
- ¹⁴ Research Group of Acupuncture Anesthesia, *Chinese Medical Journal*, 1973, No 3, abstr p 35.
- ¹⁵ Siegel, S, *Nonparametric Statistics*. New York, McGraw-Hill, 1956.
- ¹⁶ Beecher, H K, *Science*, 1966, **151**, 840.
- ¹⁷ Keegan, J J, and Garrett, F D, *Anatomical Record*, 1948, **102**, 409.
- ¹⁸ Van Nghi, N, *American Journal of Chinese Medicine*, 1973, **1**, 135.
- ¹⁹ Anderson, D G, Jamieson, J L, and Man, S C, *Canadian Journal of Psychology*, 1974, **28**, 239.
- ²⁰ Linzer, M, and Van Atta, L, in *Advances in Neurology*, vol 4, ed J J Bonica. New York, Raven Press, 1974.
- ²¹ Chiarg, C Y, *et al*, *Scientia Sinica*, 1975, **18**, 651.

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Dreaming, fenfluramine, and vitamin C

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Summary

The effect of increasing doses of fenfluramine on dream patterns was studied in 20 patients receiving a reducing diet with or without a controlled dietary intake of vitamin C daily. The dream pattern was unchanged in six patients and dreams disappeared in another who normally dreamed often. In 13 patients dreams increased in frequency and intensity, and in five the dreams assumed frightening proportions. There was a significant straight-line relation between response and the size of the dose. When placebo tablets were given to four patients their dreams disappeared or assumed their pretreatment normal pattern. Absence of vitamin C from the diet did not significantly affect the dream pattern. That fenfluramine has dose-related cerebral effects should be remembered in patients with a history of mental illness.

Introduction

Fenfluramine hydrochloride has an antiobesity and anorectic action and has been successfully used to treat obesity.^{1 2} It is chemically similar to amphetamine but lacks its central stimulant effects.³ Several studies have shown that the cate-

cholamines are intimately concerned in the sleep mechanism⁴⁻⁶ and that the anorectic action of fenfluramine depends on a direct or indirect serotonin mechanism.⁷ Moreover, the anti-obesity action of fenfluramine may be related to its specific ascorbic acid releasing action,^{8 9} while dietary desaturation of ascorbic acid potentiates the antiobesity action of fenfluramine in man.¹⁰ Administration of vitamin C 2000 mg/day produces better nocturnal sleep and less sleeplessness in young adults than placebo treatment.¹¹ We investigated the effect of fenfluramine on the dream pattern of 20 patients who were receiving a weight-reducing diet and either fenfluramine or placebo tablets.

Subjects and methods

Eighteen women and two men participated. The investigation was part of a larger trial in which the effect of ascorbic acid was examined on the antiobesity action of fenfluramine.¹⁰ The patients were aged 14-63 years (mean 43 years). Each patient received a 4.18-MJ (1000 kcal) reducing diet. Alternate patients received either a controlled intake of 40 mg vitamin C daily, or a diet free of vitamin C. All received fenfluramine in daily doses ranging from 20 to 80 mg/day. The patients completed a daily chart of their weight, sleep and dream pattern, and mood. They were asked to record the number and nature of their dreams each morning on waking.

Placebo tablets were administered double blind to four of the patients for four weeks from the 10th week of the investigation. Some patients received tablets for as long as 17 weeks (see table).

Results

Of the 20 patients, five received other forms of drug treatment consisting of ketoprofen, indomethacin, amitriptyline, or reserpine. None of these patients experienced any change in the nature or increase in the frequency of their dreams while receiving fenfluramine.

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Number and character of dreams recorded each week by 15 patients before and after increasing doses of fenfluramine and placebo tablets. Number of patients taking drug during each 4-week period is indicated at head of column. Placebo tablets were administered from 10th to 14th week of investigation, which lasted up to 17 weeks for some patients

Case No	Dose of Fenfluramine (mg/day)					
	Before treatment (n = 13)	20 (n = 13)	40 (n = 11)	60 (n = 9)	80 (n = 4)	Placebo (n = 4)
1	0, 0, 0	7, 2, 0	7, 7, 5, 5 Very vivid	7, 7, 7, 7 Less vivid		1, 0, 0
2	1, 0, 1, 0	0, 0	7, 4, 0, 0	7, 5, 4, 2	4, 3, 2	0, 0, 0, 1
3	0, 0, 0, 0	7, 7, 7 Frightening	7, 7, 7, 7 Less frightening	7, 7, 7, 7 Very vivid	7, 7, 7 Pleasant	0, 0, 0
4	0, 0, 0	7, 5 Nightmares	3, 3, 3, 3 Nightmares	3, 3 Nightmares		
5	0, 0, 0, 0	0, 0	3, 3, 3 Nightmares			
6	0, 0, 0, 1	0, 0	1, 2, 1 Vivid	1, 2, 2 Very vivid		
7	0, 0, 0	2, 2, 2 Frightening	4, 3, 2 Frightening			
8	0, 0, 0, 0	0, 1, 0	0, 0, 0	2, 3, 3 Pleasant, vivid		
9	1, 0, 0, 0	0, 0, 0	0, 0, 0, 0	7, 7, 7, 7 Pleasant, vivid	7, 7, 7, 7	
10	0, 0, 1, 0	0, 0, 0	0, 0, 0, 0	0, 0, 7, 3 Nightmares, vivid	7	0, 0, 0, 1
11	0, 0, 0	0, 0	3, 1	3, 2		0, 0, 0, 0
12	0, 0, 0	3, 0, 0, 0 Very vivid				
13	0, 0, 0	3, 3 Vivid, pleasant				
14	2, 2, 3, 3	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0		
15	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0		

Two other patients (cases 14 and 15) received no other drugs. One of them did not dream before or after receiving fenfluramine and the other stopped dreaming while on fenfluramine (see table).

None of the remaining 13 patients received any drugs other than fenfluramine or vitamin C. These 13 patients experienced a change in the pattern of their dreaming as the dose of fenfluramine was increased.

Seven of them received a controlled intake of 40 mg vitamin C daily, and six received no vitamin C in their 4-18-MJ diet. There was no significant difference in the dream pattern between these two groups. Seven reported an increase in dream frequency with the smallest dose of fenfluramine (20 mg). Eight of the 11 who received 40 mg fenfluramine daily complained of increased frequency and intensity of dreams. The nine patients to whom 60 mg was administered experienced a pronounced change in their pattern of dreaming. Fenfluramine 80 mg/day was given to four patients all of whom reported frequent dreaming. Three of them were dreaming every night (see table).

Five patients complained that their dreams were terrifying. Three described them as nightmares. The dreams were concerned with day-to-day frightening events seen in great detail. Two had pleasant dreams and one noted a change in quality of dreams from frightening to pleasant as the dose of fenfluramine was increased. All commented that their dreams were very vivid. One experienced such severe nightmares that it became necessary to stop fenfluramine. Five maintained that they slept better, and four of the 13 patients complained of day-time sleepiness while receiving fenfluramine.

Placebo tablets were administered to four patients in place of the

fenfluramine for four weeks. After two nights their dreaming habits returned to the pretreatment pattern in that dreams became much less frequent and vivid. This change was maintained throughout the placebo period. When fenfluramine was resumed at the end of four weeks the dreams rapidly resumed their former frequency and intensity under the influence of the drug (see table).

The responses to each dose of fenfluramine were analysed on the IBM 360/44 computer. A regression line was obtained showing response in dream nights per week against the dose of fenfluramine administered in mg/day (see figure). The data were transformed by arcuate transformation to stabilise variance, and an F test performed on the regression, showed that it was highly significant ($P < 0.0001$). There was no statistical evidence of deviation from a straight line relation, and the intercept of the line was not significantly different from zero. The apparent lack of fit of the regression line to the raw data may have been due partly to the deviation of the data from a symmetrical distribution at some dose levels.

Discussion

Alvi¹² has reported that an evening dose of fenfluramine led to complaints of nightmares on several succeeding nights, and Hooper¹³ described vivid dreams in one out of 46 patients. A similar change occurs in sleep patterns with the related drug 780SE,¹⁴ and Oswald¹⁵ reported the brief occurrence of dreams after sudden withdrawal of fenfluramine. In our four patients dreaming did not increase when they were suddenly transferred to placebo treatment. The low-intensity pretreatment dream pattern was resumed 48 hours after stopping fenfluramine. This corresponds with the metabolic and excretory pattern of fenfluramine, all the drug having been eliminated from the body within 48-72 hours after administration of a single dose of 60 mg.¹⁶ In one patient the normal high intensity pattern was inhibited after administration of fenfluramine.

The fenfluramine-induced changes in dream pattern occurred in 65% (13) of our patients. The occurrence of a significant dose-response relation between fenfluramine and dream frequency has not been reported, although a similar relation has been described after pentazocine.¹⁷ Since fenfluramine did not affect 35% of the patients other factors in addition to dosage of fenfluramine may influence the onset and intensity of dreaming. Four of the patients complained of daytime sleepiness corresponding to the observation of daytime sleepiness in four out of 30 patients by Spence and Medine.¹⁸ The duration of rapid-eye movement (REM), dreaming, sleep is diminished when patients

Regression line showing response in dreams per week against dose of fenfluramine administered to 13 subjects.

receive 80 mg fenfluramine daily. It is associated with an increase in intrasleep restlessness, during which more frequent spontaneous shifts to stage 1 sleep occur.¹⁹ Patients may be more conscious of their dreams during the periods of intrasleep restlessness. Phenothiazines, monoamine oxidase inhibitors, tricyclic antidepressants, amphetamines, and alcohol reduce REM sleep to below normal levels.²⁰⁻²² When these drugs are withdrawn an REM sleep rebound takes place, and the patient spends a higher proportion of the night than usual in dreaming sleep. Dreams become particularly vivid and disturbing.²⁰ Total withdrawal of vitamin C from the diet did not change the dream pattern induced by fenfluramine when compared with the pattern reported by subjects receiving a daily intake of 40 mg with the fenfluramine. Dreaming has not been reported in scorbutic patients,²³ and dreaming is not described as a mental change that accompanies scurvy.²⁴ Our results show that there is a definite relation between the dose of fenfluramine administered and the degree of change in sleep pattern.

Depression and acute psychotic episodes have been reported during or immediately after fenfluramine treatment.²⁵⁻²⁷ It seems that fenfluramine played a part in precipitating psychotic decompensation in three patients, in two of whom there was a previous history of mental illness.²⁸ One patient in our study complained of nightmares while on fenfluramine and developed a severe depressive illness. Fenfluramine was discontinued and her depression rapidly resolved. Hence, as well as its dose-related weight-reducing and anorectic actions, fenfluramine also exerts dose-related central effects, which may assume undesirable toxic proportions. Patients who dream or have nightmares while on fenfluramine may develop an acute psychotic episode. This possibility should be recognised when its use is contemplated in patients with a history of mental disease or in whom the disease is inadequately controlled with other drugs.

References

- ¹ Duncan, E H, *et al*, *British Journal of Clinical Practice*, 1965, **19**, 451.
- ² Brodrin, P, and O'Connor, C A, *Practitioner*, 1967, **198**, 707.
- ³ Le Dauarec, J C, *et al*, *Annals of the Rheumatic Diseases*, 1966, **25**, 425.
- ⁴ Oswald, I, *Pharmacological Reviews*, 1968, **20**, 273.
- ⁵ Jouvet, M, *Science*, 1969, **163**, 32.
- ⁶ Wyatt, R J, *Biological Psychiatry*, 1972, **5**, 33.
- ⁷ Samanin, R, *et al*, *European Journal of Pharmacology*, 1972, **19**, 318.
- ⁸ Odumosu, A, and Wilson, C W M, *British Journal of Pharmacology*, 1974, **50**, 471.
- ⁹ Odumosu, A, and Wilson, C W M, *British Journal of Pharmacology*, 1975, **54**, 226.
- ¹⁰ Wilson, C W M, *et al*, *Recent Advances in Obesity Research*, 1, ed A Howard, p 77. London, Newman Publishing, 1975.
- ¹¹ Wilson, C W M, Greene, M, and Molloy, T, paper presented at 6th International Congress of Pharmacology, Helsinki, 1975.
- ¹² Alvi, M J, *British Medical Journal*, 1969, **3**, 237.
- ¹³ Hooper, A G, *Journal of the Irish Medical Association*, 1972, **65**, 35.
- ¹⁴ Firth, H, *et al*, *British Journal of Pharmacology*, 1970, **39**, 462.
- ¹⁵ Oswald, I, and Chacore, V R, *British Medical Journal*, 1963, **2**, 427.
- ¹⁶ Bruce, R B, and Maynard, W R, *Journal of the Pharmaceutical Sciences*, 1968, **57**, 1173.
- ¹⁷ Paddach, R, *et al*, *Clinical Pharmacology and Therapeutics*, 1969, **10**, 355.
- ¹⁸ Spence, A W, and Medrei, V, *British Journal of Clinical Practice*, 1966, **20**, 643.
- ¹⁹ Lewis, S A, Oswald, I, and Dunleavy, D L F, *British Medical Journal*, 1971, **3**, 67.
- ²⁰ Hartman, E, *Psychophysiology*, 1968, **5**, 207.
- ²¹ Kales, A, *Annals of Internal Medicine*, 1969, **10**, 591.
- ²² Kales, A, *et al*, *Sleep Physiology and Pathology*. Ed A Kales. Philadelphia, Lippincott, 1969.
- ²³ Kinsman, R A, and Hood, J, *American Journal of Clinical Nutrition*, 1971, **24**, 455.
- ²⁴ Wilson, C W M, *Practitioner*, 1974, **212**, 481.
- ²⁵ Oswald, I, *et al*, *British Medical Journal*, 1971, **3**, 70.
- ²⁶ Steel, J M, and Briggs, M, *British Medical Journal*, 1972, **3**, 26.
- ²⁷ Harding, T, *British Journal of Psychiatry*, 1972, **121**, 338.
- ²⁸ Sharman, B J, Leonard, D, and Kidson, M A, *British Medical Journal*, 1974, **3**, 576.

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Influence of simultaneous low amniotomy and oxytocin infusion and other maternal factors on neonatal jaundice: a prospective study

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Summary

In a prospective study of 196 consecutive single births a significant increase in serum bilirubin concentrations was found in infants born after low amniotomy induction and oxytocin infusion compared with those born spontaneously. This relationship was not dose-dependent and may have been associated with artificial interruption of pregnancy rather than the oxytocin itself. Infants delivered after spontaneous labour accelerated by oxytocin showed no such increase. The hormonal surge at the spontaneous onset of labour may affect fetal enzyme induction, but other factors, such as methods of infant feeding and oral contraceptive use, were found not to be significant.

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Introduction

The use of oxytocin infusion to induce labour is now routine in many centres. Simultaneous surgical and medical induction has been advocated,^{1 2} and the interval between induction and delivery has been reduced to about eight hours.^{3 4} Hazards of these procedures, however, include fetal distress and low Apgar scores.⁵ Oxytocin has been implicated in an increased incidence of neonatal jaundice,⁶⁻⁸ though other workers have failed to confirm this.⁹⁻¹¹

We have carried out a prospective study of the factors implicated in neonatal jaundice and report here the results.

Patients and methods

A total of 217 consecutive single deliveries at this hospital were considered for the study. Of these, 21 babies were excluded because of incomplete bilirubin data, birth weight below 2500 g, haemolytic disease, neonatal infection, or discharge from hospital within 48 hours. A further 15 infants were delivered by caesarean section. The remaining 181 babies were divided into three groups: A (54 infants), spontaneous onset of labour, no oxytocin used; B (28 infants), spontaneous onset of labour, oxytocin used to accelerate labour; C (99 infants),