SOME EFFECTS OF NALORPHINE ON THE BEHAVIOUR OF HEALTHY HUMAN VOLUNTEERS

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SOME workers have claimed that nalorphine is as potent an analgesic as morphine and does not lead to addiction.

Lasagna and Beecher (1954) found that, in patients after operation, 15 mg. nalorphine hydrochloride had approximately the same analgesic effect as 10 mg. morphine. This dose, however, produced unpleasant mental side-effects in some patients and six healthy male volunteers given 10 mg. of the drug became sleepy, dizzy and nauseated, and showed evidence of mental change.

Huggins and Moyer (1955) reported that twenty-three out of thirty patients, given nalorphine without the previous administration of morphine or a similar analgesic, experienced hallucinations.

Keats and Telford (1956) found that nalorphine was at least as potent an analgesic as morphine post-operatively and went so far as to say that it represents a long-sought potent non-addicting analgesic. They did, however, think that it might be more liable than morphine to produce side actions.

The possibility of the existence of a potent non-addictive analgesic warranted further investigation; but, in view of reports of serious side effects, it was thought wise, before attempting a clinical trial, to determine on healthy volunteers the ability of nalorphine to raise the pain threshold and, at the same time, to investigate the incidence of side-effects.

METHODS

Selection of Volunteers

Sixteen students who had recently taken part in an experiment to determine the ability of dipipanone hydrochloride to raise the threshold to ischaemic pain, and for whom controls were therefore readily available, were asked to give their services for a similar experiment with nalorphine. The author also took part in the experiment.

Doses and Administration

Doses of 6·7 and 15·0 mg. were chosen for statistical convenience, and given by subcutaneous injection in a volume of 1·0 ml. The ampoules in which the drug was supplied were identical in appearance, and the volunteers were unaware of the doses used. Since the side-effects to be expected were not known, the low dose was always given first.

Procedure

The subjects attended the laboratory on days convenient to them. On the first two days of the experiment they attended in small groups of three or four; but the effects on behaviour were so marked on these occasions that they attended one at a time thereafter so that physical restraint, when necessary, would be easier.

https://doi.org/10.1192/bjp.103.433.850 Published online by Cambridge University Press

The method of estimating the ability of nalorphine to raise pain threshold was based on that described by Keele (1952) using ischaemic pain.

When it became apparent that severe emotional disturbances and aberrations of behaviour were to be expected, a magnetic-tape sound recorder was made available so that sound recordings could be made throughout the experiment for analysis later.

On the first occasion on which the tape recorder was used it was installed in a soundproof room a few yards from the room in which the experiments were taking place. When a subject was behaving abnormally he was taken to the recorder and asked to record his subjective observations. This method, however, resulted in loss of spontaneity which outweighed the advantage gained by cutting out extraneous sound. The recorder was therefore transferred to the laboratory and equipped with a remote control switch which was operated by the author so that recording could begin immediately any abnormality of behaviour was observed. The quality of the recordings suffered as a result of the transfer of the recorder to a room which was not soundproof, and unfortunately, in the time available, it was not possible to devise a method by which the subjects were in complete ignorance of the fact that their speech was being recorded.

At the beginning of each experiment, before the drug was given, the subjects announced their names, ages, status, and habits regarding alcohol and tobacco. This short announcement then acted as a control with which later recordings could be compared.

Results

The effect of 6·7 mg. nalorphine on the behaviour of the first subject was so dramatic that attention was immediately focused upon this aspect of the action of the drug rather than upon any analgesic activity it might possess. Indeed in the majority of subjects the effect of the drug on behaviour was such as to make estimations of rise in pain threshold quite unreliable.

In all thirty-three experiments were carried out on seventeen subjects. One subject, a Sinhalese, had a severe vaso-vagal attack after the low dose, and it was thought unwise to let him proceed to the high dose.

Fifteen minutes after injection of 6·7 mg. nalorphine the first subject began to laugh uncontrollably. He began to shout and insisted on imposing his opinions in a loud voice on everybody in his vicinity. He became extremely garrulous and his speech was incoherent. There was a marked increase in psychomotor activity and the subject made decidedly improper advances to three girls, having to be dragged off one of them. About an hour after injection he became hysterical and begged to be reassured that he would eventually return to normal. A quarter of an hour later he had an almost uncontrollable desire to go out in the street and expose himself and was most insistent that he should not be left alone.

The activity of the drug manifested itself in very marked waves during which the subject was fully aware that his behaviour was abnormal but was powerless to control it. His own written description of his experiences is quoted here verbatim.

"I have felt a slight derealized feeling suddenly in the Common Room. This continued until I was in the expt. room. I was seized by laughter and funny thoughts and had two readings when I was terribly amused. Garrulous. Time sense for readings and counting power lost. Came in waves. Saying things

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I don't want to or ought not to. Awkward socially. I then felt as if I wanted to see people and they to see me. I went to buy my lunch tickets talking loudly with my keeper Dr. Cahal. Everyone turned and looked in the Hall of the School. I tried to make love to the lady at the desk and to a blonde bit in the Pharmacology dept.—pardon the expression madam. Everyone in the Pharm. dept. talked to me and I told them about the drug. Dr. Mogey wanted me to take a viva but I did not feel up to it in any way. Mike and Neville came and I talked to them. They did not respond to me as I would have liked. We had coffee—I told them I could kill someone and if this drug were used—I think this is important. I feel I have no soul. I suddenly got a shock that this feeling was my own Psychiatric disorder and would never end—all my inner personality came out. Almost wept but was reassured that this was the drug. Mike and Nev were annoyed at my garrulness. I decided to go and see Albert Hemingway and Prof. Durward—they stopped me. I went to the Bog in the Med. School and was garrulous in the corridor and assured a nice chap in the VIth yr that I was under the drug and not from the Tunbridge (a public house—D.A.C.). I am being to recover now. On returning I wanted to speak to a chap who works in the Med. School but decided he might think I was balmy. Feeling has worn off suddenly on writing this—went very quietly and suddenly. I do apologize to people of Pharmacology Dept. for any inconvenience caused by me whilst under this drug. Insistence of speaking—interrupt others sentences—very rude—I don't usually do it. Hear things very well. See v. well. Never lost conscious. Perfectly aware that I was being fool all the time but could do nothing about it. That's why Mike and Nev. annoyed me. I feel now as if I want to retrace my steps and apoligize. Slight frontal headache—somewhat tired and exhausted as if I have created a great artistic work. (Mike and Nev are ?? inhibited because of me making a fool of myself.) 11.15 Cannot remember how long I have been normal think it must have been at least since 10.50 because I tried to take a reading then—forgetting."

In contrast to this subject others were lethargic, depressed and averse to any form of physical activity. They lay around in chairs and on camp beds often apparently asleep, but all subjects who were affected in this way maintained that although they felt tired they were prevented from sleeping by flight of ideas, sometimes of a most bizarre character.

There was no obvious connection between the dose and the type of response elicited. Some were "elated" on the high dose and depressed on the low one, whilst the converse was true in other subjects. Again, some subjects experienced both elation and depression on the same dose on the same occasion.

Five subjects experienced waves of pathological laughter, one on the low dose only, two on the high dose only, and two on both doses.

Recall of very early childhood memories was reported quite spontaneously by four subjects. Others indulged in childish horseplay, and four other volunteers had to be physically restrained from open acts of hostility towards a senior member of the staff.

No hallucinations were reported but dream states in which vivid visual images were experienced when the eyes were closed were reported by three subjects. These images disappeared as soon as the eyes opened.

Distortions of time and space were common but only one subject reported any distortion of the body image.

On every occasion on which the drug was given a curious aphasia was observed. This, when combined with the flight of ideas which was frequently observed, led to complete incoherence of speech. In the middle of a sentence a

subject would be unable to think of a word and, after hesitating, would move to another topic of conversation. He would then recall the missing word and proceed with the earlier topic. This led to a curious "back and forth" quality in speech which was likened by one observer to a gramophone needle repeatedly sticking in the groove of a record. This effect was sometimes heightened by a kind of confabulation in which some garrulous subjects, when blocking in speech occurred, repeated over and over words which came easily to mind.

Sixteen of the seventeen subjects taking part in the experiment said that on the whole the subjective effects of the drug were pleasant. Many expressed the opinion that they felt sure that they could easily become addicted to it. The subject who found the effects unpleasant was the Sinhalese already referred to who had a severe vaso-vagal attack. He was, incidentally, the only non-European involved in the experiment.

The effects of nalorphine on behaviour were so marked and of such a nature as to make the experiments on its ability to raise the threshold to ischaemic pain completely unreliable. A full analysis of these results is therefore not given. On the basis of these experiments, however, a subcutaneous dose of 6·7 mg. does not produce any more rise in threshold to ischaemic pain than 1·0 ml. of 0·5 N-saline.

Discussion

Although these effects of nalorphine on human behaviour have already been described by other authors, it is felt that sufficient stress has not been laid upon these undesirable effects in the past. The suggestion that nalorphine may be a potent non-addicting analgesic makes it important to realize that profound disturbances of behaviour may occur when it is administered to patients who have not previously had large doses of major analgesics. Even a clinical trial of nalorphine as an analgesic is contraindicated in view of the results described in this paper.

The effects of nalorphine on behaviour are markedly similar in many respects to those of cannabis indica and are equally unpredictable. Although it has not been possible to establish a relation between the dose and the type of response elicited, a strong impression has been gained that the response is affected by the basic personality of the subject. Further investigation along these lines might be profitable.

The spontaneous recall of childhood memories prompted the suggestion that the effects of nalorphine might be similar to those of LSD. I therefore took 60 mg. of LSD25 by mouth to compare the subjective effects of these drugs and found them totally dissimilar. In general the subjective effects of nalorphine are pleasant, but this can certainly not be said of the effects of LSD25.

The waves of activity of nalorphine are difficult to explain. Similar effects have been noted with LSD25, and with cannabis indica, whilst Isaacs (1956) has observed that apomorphine causes waves of nausea and vomiting.

Finally, it is felt that these results cast some doubt upon the wisdom of the routine clinical use of mixtures of morphine and nalorphine, but do not contraindicate its use in acute poisoning by morphine or other major analgesics.

Summary

1. The effects of nalorphine on the behaviour of healthy human volunteers who have not previously had a major analgesic are described.

2. Because of the effects on behaviour it has not been possible to confirm or deny the claim that nalorphine is a potent analgesic.

3. The effects of nalorphine on behaviour are felt to be so undesirable as to preclude its use as a major analgesic even if it is shown to be such a drug.

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https://doi.org/10.1192/bjp.103.433.850 Published online by Cambridge University Press