ANALGESIC ACTION OF PETHIDINE-LEVALLORPHAN MIXTURES IN MAN

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The introduction of specific antagonists to the morphine-like analgesics has suggested the possibility of reducing some of the unwanted actions of these drugs, particularly respiratory depression, without impairing analgesia. The observations described below were made to compare the analgesia produced by pethidine with that produced by pethidine-levallorphan mixtures in normal subjects.

Methods

Table I records experiments done on five normal men, using two methods of assessing analgesia.

TABLE I

Subject	Age (Years)	Ischaemic Pain	Thermal Pain Threshold
S	32	+	
H	29	+	
G	20	+	+
Y	20	+	+
A	32	+	+

Preliminary observations on anaesthetized patients showed that 1 mg. of levallorphan can reverse the respiratory depression produced by about 200 mg. of pethidine (Fig. 1). This dose ratio was therefore used as a guide in subsequent tests, although we cannot be sure that it would be the same at the lower dose levels used in conscious normal subjects.

FIG. 1.—Spirometer tracing showing the reversal of pethidine-induced respiratory depression by levallorphan in man. Before operation; thiopentone-nitrous-oxygen anaesthesia.

Ischaemic Pain Experiments

Hewer and Keele (1948) described a method for testing the power of analgesics to relieve experimentally induced pain in ischaemic muscles. We have modified their method slightly in the present experiments.

A sphygmomanometer cuff was applied to the left arm, with the subject lying on a couch. After a preliminary rest of 5–10 minutes the arm was raised to empty the veins, and the cuff rapidly inflated to 200–220 mm. Hg. With the arm resting on a splint, the subject then squeezed the bulb of a Higginson syringe in time with a metronome set at a rate of 90 beats a minute. When a certain number of contractions had been completed the arm was rested. The pain in the arm gradually increased, and all five subjects were trained to assess its intensity on an arbitrary scale (Fig. 2). An ob-

server questioned the subject at irregular intervals of $\frac{1}{2}$ to 1 minute on the intensity of the pain, to conceal from the subject how long the experiment had been going on. When intolerable pain was reached the cuff was deflated and the pain relieved.

Numerous observations were first made on each subject to determine the number of contractions which would produce intolerable pain in about ten minutes after the last contraction. This time was chosen because it was found that there was difficulty in concentrating on the pain, and subjects got bored with experiments lasting longer than

FIG. 2.—A typical pain-intensity/time diagram. Subject G, 52 contractions. Intravenous injection of saline $2\frac{1}{2}$ minutes after last contraction. The pain became intolerable after 13.9 minutes ($=T_{10}$).

about 20 minutes. Most of the experiments were in fact completed within this time. After a suitable number of contractions had been found, one or more preliminary experiments were done giving intravenous injections of pethidine or a pethidine-levallorphan mixture to familiarize the subject with the procedure. After these trial runs four tests were done on each subject, the injections comprising (a) pethidine 22.5 mg., (b) pethidine 22.5 mg. + levallorphan 0.075 mg., (c) pethidine 22.5 mg. + levallorphan 0.15 mg., (d) physiological saline, each in a volume of 3 ml. Preliminary observations had shown that after 15 mg. of pethidine no analgesia could be detected by this method.

The ratios of pethidine to levallorphan in the mixtures were 300:1 and 300:2, bracketing the ratio of 300:1.5 found at a higher dose level in the preliminary experiments. All injections were given intravenously into the right arm $2\frac{1}{2}$ minutes after the last contraction. The subjects did not know which injection they were receiving on any particular occasion. A Latin square design determined the order of the injections in four subjects; in the fifth subject (A) the order was random.

The analgesic effect of the injection was assessed by the time taken to reach intolerable pain.

Pain Threshold Determinations

An apparatus similar to that devised by Hardy, Wolff, and Goodell (1940) was used to measure thermal pricking-pain thresholds on the skin of the forehead. The threshold was measured before and 30, 60, and 90 minutes after the injection. In subjects G and Y the threshold determinations were combined with the ischaemic pain tests described above; in subject A the experiments were done on separate occasions.

Results

Ischaemic Pain Experiments (Table II).—Analysis of the results of the experiments on the first four subjects, which were arranged in a Latin square, showed that the order in which the different injections were given did not affect the results. The figures for the fifth subject (A) were therefore pooled with those from the other four for statistical analysis. In the experiments in which drugs were injected, the mean

TABLE II

Drug	Mean Time Taken to Reach Intolerable Pain (T ₁₀) (Minutes)	Standard Error of the Difference Between Any Two Means
(a) Pethidine (22.5 mg.)	13.4	0.83
(b) Pethidine: levallorphan (300 : 1)	15.1	
(c) " " (300 : 2)	14.8	
(d) Saline	11.4	

time taken to reach intolerable pain (T₁₀) was significantly longer than in the control experiments when saline was given. From the means it appears probable that the pethidine-levallorphan mixtures were more effective than pethidine in postponing intolerable pain.

Thermal Pain Threshold.—Thresholds were measured before, and 30, 60, and 90 minutes after the injection. The figures given in Table III are changes in the pricking-pain

TABLE III.—Changes in Thermal Pain Following Administration of Pethidine and Pethidine-Levallorphan Mixtures

Drug	Minutes after Injection		
	30	60	90
(a) Pethidine	+12.5	+ 5.6	+ 3.3
(b) Pethidine: levallorphan (300 : 1)	+19.8	+14.1	+10.1
(c) " " (300 : 2)	+13.2	+ 7.2	+ 3.7
(d) Saline	— 0.3	— 0.1	+ 0.7

threshold expressed as a percentage of the pre-injection threshold. The rise in threshold was greatest after 30 minutes; at 60 and 90 minutes the thresholds were returning towards the pre-injection values.

In the statistical analysis of these results it has been assumed that the random error of the pre-injection threshold measurements was the same as the error of the other measurements. All three drug injections significantly increased the threshold, while saline did not. A difference of more than 5.5 between any two drugs is significant at the 5% level. The mixture containing the smaller amount of levallorphan (b) is thus significantly more effective than pethidine and the other mixture (c).

Discussion

Both methods depend largely on the subject's reaction to pain, as well as on the pain sensation and the physical stimulus provoking it. The ischaemic pain method has the advantage that drugs are tested under conditions close to clinical situations; in practice conscious patients nearly always have a pain before they are given a drug to relieve it. The greater precision of the thermal pain threshold method is offset by its dependence on skin temperature (Whyte, 1951; Jackson, 1952), so that changes in blood flow and sweating caused by the drugs may affect the results. Greater apparent analgesia after one injection compared with another might thus be due to changes in the local blood flow rather than to an action in the brain.

The results show that the two pethidine-levallorphan mixtures relieve ischaemic pain more effectively than does pethidine. The mixtures are also no less effective than pethidine in raising the thermal pain threshold. Lasagna and Beecher (1954) have reported similar results using mixtures of morphine and nalorphine in patients with post-operative pain.

In the thermal pain experiments it was surprising that the mixture containing the smaller dose of levallorphan caused the greatest rise in threshold. If this is a real effect, and not due to chance, it might be explained in several ways. The lower dose of levallorphan might cause vasodilatation and/or sweating, and so raise the threshold, while with the higher dose the antagonism for pethidine becomes manifest. On the other hand, Yim *et al.* (1955) have shown in rabbits that levallorphan is a weak analgesic, and this suggests the possibility that the rise in threshold is due to an analgesic

action which is added to that of pethidine. This might be investigated further by using higher doses of suitable pethidine-levallorphan mixtures, and testing analgesia by a different method.

Costa and Bonnycastle (1955) found that, in rats, levallorphan antagonizes respiratory depression produced by pethidine more than analgesia. Our results show that in man the addition of levallorphan does not necessarily impair the analgesic action of pethidine. Whether the addition of levallorphan is of value in clinical practice can only be decided by a trial in patients under clinical conditions.

Summary

A comparison has been made between the analgesia produced by intravenous injections of (a) pethidine 22.5 mg., (b) pethidine 22.5 mg. + levallorphan 0.075 mg. (dose ratio 300 : 1), (c) pethidine 22.5 mg. + levallorphan 0.15 mg. (dose ratio 300 : 2), and (d) physiological saline solution. The effects of these drugs on ischaemic muscle pain and on the thermal pain threshold were measured.

The pethidine-levallorphan mixtures produced no less analgesia than did pethidine; the mixture containing the smaller amount of levallorphan—(b) above—produced significantly greater analgesia than pethidine. This unexpected result is discussed.

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FATE OF BILE PIGMENT IN CHOLERA

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The rice-water stool of cholera is well known to every student of tropical medicine. It is believed to be due to the absence of bile pigment from the intestine caused by congestion and oedema of the mucous membrane of the biliary tract, and thus to obstruction of the flow of bile to the duodenum (Rogers, 1921). De and Chatterji (1935), on the other hand, suggested that this is brought about by the depression of the secretory function of the liver in cholera. It was felt that these explanations were not satisfactory, since we could not detect any obstruction to the biliary flow at necropsy on cholera patients who died in the stage of purging. We found that gentle pressure on the gall-bladder led to the escape of bile into the duodenum. Investigations were therefore undertaken to ascertain the fate of bile pigment in cholera patients.