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A COMBINATION OF ANALGESIC AND ANTAGONIST IN POSTOPERATIVE PAIN

BY

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Clinicians often hesitate to give adequate doses of narcotic analgesics such as morphine and pethidine because these compounds are known to have a marked respiratory depressant effect. As a result there has been considerable interest in the possibility of combining a dose of one of these analgesics with a small quantity of one of the specific narcotic antagonists. The latter substances are known to exert a much greater antagonism to the respiratory depressant effect than to the analgesic action of the narcotics.

When deciding on such a combination the first prerequisite is that the antagonist should have few undesirable effects of its own and the second is that the antagonist and the analgesic should have approximately the same length of action.

Although the narcotic antagonists nalorphine and levallorphan themselves possess slight respiratory depressant activity, this is insignificant in the doses in which they are used clinically. Levallorphan was chosen for clinical trial because, even in large doses such as are rarely used in therapy, it is tolerated without undesirable side effects by both conscious and unconscious patients (Swerdlow, 1958). Pethidine was selected as the analgesic most likely to have a suitable length of action for combination with levallorphan.

Having decided on the combination of drugs we set out to establish whether, using the two drugs together in suitable proportions, the presence of the antagonist influences the following:

- the respiratory depressant effect of pethidine;
- the analgesic activity;
- the incidence of side effects.

Accordingly, the following studies were carried out.

Influence on Respiratory Depression

In order to study the influence of levallorphan on the respiratory depressant effect of pethidine, it

was necessary first to establish the optimal proportions of the two drugs. Accordingly preliminary tests were carried out in 25 individuals who were about to undergo surgical operations. The patients were premedicated with a barbiturate and atropine (0.25–0.5 mg), pethidine-like drugs being deliberately avoided. Anaesthesia was induced with thiopentone. The patient was intubated after relaxation had been achieved with suxamethonium and anaesthesia was maintained with nitrous oxide and oxygen. When breathing had become regular and tranquil, an intravenous dose of pethidine 1–2 mg/kg was given, accompanied by, or followed by, a dose of levallorphan. Various ratios between 80:1 and 35:1 were studied. After this the respiratory rate and minute volume were measured at intervals. It was found that the ratio of pethidine to levallorphan of 80:1 had no greater respiratory depressant effect than the ratio of 35:1 and as a result the 80:1 ratio was chosen for the main test.

For this test two groups, each of 15 patients, were studied under accurately standardized conditions and the results have been reported in detail elsewhere (Hossli and Bergmann, 1959). In brief, the patients were anaesthetized as described above and, when breathing had become regular, each patient was given an intravenous injection of pethidine 1 mg/kg alone or combined with levallorphan in the ratio of 80:1. The respiratory rate and minute volume were measured every minute for 20 minutes, and figure 1 shows our findings. Statistical analysis of the figures for the respiratory rate, minute volume and alveolar ventilation at 2, 3, 6, 12 and 20 minutes after giving the pethidine or pethidine plus levallorphan showed that, compared with the initial readings, all these figures were reduced more by pethidine than by pethidine with levallorphan. The difference was statistically significant on all occasions except for

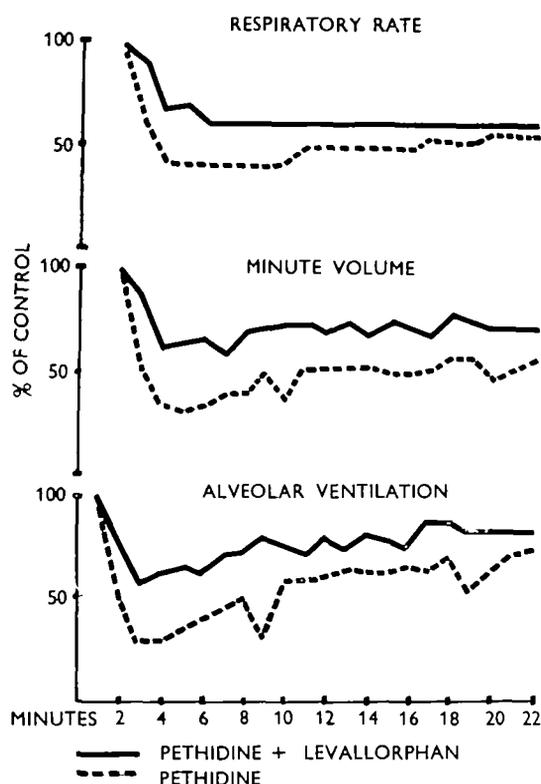


Fig. 1

readings for minute volume and alveolar ventilation at 12 minutes.

It was thus shown that pethidine with levallorphan in the proportion of 80:1 causes significantly less respiratory depression than does pethidine alone.

Effect on the Analgesic Activity

In order to compare the analgesic activity of pethidine with that of pethidine plus levallorphan a double blind control study was carried out in 96 individuals who needed a narcotic analgesic for the relief of postoperative pain. Sixty-four of these patients had undergone major thoracic or abdominal operations, 4 had had minor abdominal operations (appendicectomy or laparotomy) and the remaining 28 had undergone operation for hernia, sympathectomy, mastectomy or operations on the limbs. A dose containing 50, 75 or 100 mg of pethidine, alone or with levallorphan (ratio 80:1), was given according to the patient's

need. Ampoules were labelled with code numbers in order that the trial should be blind to all concerned in it.

Before the administration of any analgesic the severity of the pain was recorded, based on the patient's own statement and also on the impression of the observer, using the following scheme: no pain 0; mild pain 1; moderate pain 2; severe pain 3; intolerable pain 4.

After the injection the severity of the pain was recorded by the same method at 30-minute intervals for a period of 4 hours. A calculation was made at each half-hourly period of the difference between the score for pain at that moment and the score for the initial pain. The sum-total of these differences was taken to be the figure representing the "total analgesic activity" of a single dose of the drug concerned.

If it was necessary to give additional doses to the same patient, then ampoules with the same code number were used throughout. The sizes of additional doses were adjusted, if necessary, to the patient's response and a repeat dose of analgesic was given only if the effect of the previous dose had worn off.

It would have been desirable to have had all the observations carried out by the same individual. However, as this was not possible, care was taken to ensure that the same observer made all the observations in a given patient over the whole 4-hour period.

Results.

In total, 219 doses of analgesic were given. On breaking the code, it was found that 49 patients had been given a total of 154 injections of pethidine plus levallorphan. The content of pethidine was 50 mg on 65 occasions, 75 mg on 43 occasions and 100 mg on 46 occasions. The other group, given pethidine alone, comprised 47 patients who had been given a total of 137 injections; the dose was 50 mg on 51 occasions, 75 mg on 52 occasions and 100 mg on 34 occasions. The number of doses given to single individuals varied from one to seven, the average being 3.1 in the pethidine with levallorphan group and 2.9 in the pethidine group.

In the pethidine with levallorphan group the patient's ages varied between 19 and 73 years (average 47). Their weight varied between 40 and

92 kg (average 65.2). In the pethidine group, the figures were: age between 20 and 79 years (average 49) and weight between 45 and 97 kg (average 68.8). As regards the types of operation, the distribution was similar in the two groups.

In occasional patients it was necessary to interrupt the observations before the end of the 4-hour period for reasons unconnected with the trial. In these patients the pain had not returned to its initial severity at the time when the readings were interrupted. In order not to reduce too much the numbers in each group by omitting these incomplete observations we have also included in the average figures for "analgesic activity" readings taken at 3½ and 3 hours.

In addition, on the very few occasions in which a half-hourly reading was omitted we took for the calculation the lower of the two figures on each side of the missed reading.

Table I shows the findings in the three subgroups, after 50-mg, 75-mg and 100-mg doses of pethidine with or without levallorphan, as well as the number of injections given at each dose level.

As can be seen from this table, the figures show

that there is extraordinarily good agreement in all three groups as regards the average analgesic activity of a single dose of pethidine or pethidine with levallorphan after 3, 3½ and 4 hours. It can also be seen that the average figures for the analgesic effect of a dose increased with the time (that is with the number of observations), and that in general larger doses gave better analgesia than smaller doses.

Statistical analysis of these figures, using the t-test, showed that at the three dose levels there was no significant difference between the average analgesic activity of pethidine and that of pethidine with levallorphan.

On the basis of these findings it can be concluded that the addition of the narcotic antagonist levallorphan to pethidine in the above proportion does not interfere with the analgesic activity of the pethidine.

Influence on the Incidence of Side Effects

As regards the general clinical use of the combination of pethidine with levallorphan an important question is raised. Does the antagonist prevent not

TABLE I
Mean figures for the "analgesic activity" of a single dose of pethidine or pethidine with levallorphan.

	Observation period (hours)	50 mg pethidine		75 mg pethidine		100 mg pethidine	
		A	n	A	n	A	n
Pethidine	3	13.3	51	13.0	52	15.1	34
	3½	14.6	47	14.7	49	17.1	33
	4	14.8	37	16.1	41	18.5	29
Pethidine + levallorphan	3	13.5	65	13.2	43	14.4	46
	3½	15.0	61	14.6	41	16.0	44
	4	16.4	49	15.8	40	17.6	38

A=average analgesic activity of a single dose.
n=number of injections.

TABLE II
Incidence of side effects after pethidine and pethidine with levallorphan.

	Total no. of patients	Total no. of injections	*Patients with side-effects	Nature of side effects					
				Nausea		Vomiting		Sweating	
				P	n	P	n	P	n
Pethidine	51	162	15*	11	12	9	11	2	3
Pethidine + levallorphan	53	171	16*	10	15	4	4	6	8

(* Some patients experienced more than one side effect.)

P=number of patients.
n=number of injections.

only respiratory depression but also other undesirable effects of pethidine, especially nausea and vomiting? In our study in postoperative patients we recorded the presence or absence of nausea and vomiting and, as far as possible, other side effects that might have been associated with medication. Some additional patients were included who could not be used for assessment of the analgesic effect.

Table II shows the incidence of nausea, vomiting and excessive sweating in the two groups. A breakdown into three dose levels is omitted, as it was not possible to show that there was a relationship between the presence of such side effects and the size of the dose. It was found that the incidence of nausea was the same in the two groups. Vomiting was somewhat less common in the pethidine with levallorphan group, whilst excessive sweating was rather more frequent. However, these differences were not statistically significant.

No other significant side effects were observed. In the pethidine with levallorphan group each of the following were observed on one occasion: restlessness, tachycardia, arrhythmia, vertigo, palpitations and flushing. In two patients in the pethidine series there was a considerable rise of blood pressure (possibly a result of hypoventilation).

DISCUSSION

The results of our previous investigation confirmed the protective effect of levallorphan against the respiratory depressant effect of pethidine.

The study in postoperative pain showed that, in the dose ratio of 80:1, the analgesic effect of pethidine on postoperative pain is not reduced by levallorphan. As regards the incidence of side effects other than respiratory depression, this was similar in the two groups. Although we found that the incidence of vomiting after pethidine with levallorphan was somewhat reduced and excessive sweating was slightly increased, the differences were not statistically significant.

When using pethidine the addition of a small dose of levallorphan provides a greater margin of safety and permits the administration of adequate doses without the fear of inducing serious respiratory depression. The following two cases which occurred fairly recently in our clinic illustrate the fact that severe respiratory depression may occur

even when using pethidine in the usual therapeutic doses.

A woman, aged 39 years, had been admitted to hospital for an operation. Some hours after the operation she was found to be unconscious, cyanosed and with dilated pupils; spontaneous respiration was absent. Oxygen was applied immediately and an endotracheal tube was passed. Ten minutes later, regular spontaneous respiration had returned and after 4 hours the patient had recovered completely. Later it was discovered that because of postoperative pain she had been given an intramuscular injection of pethidine 100 mg about 30 minutes before the above incident occurred.

A man, aged 73 years, with emphysema had been subjected to prostatectomy. During the night the patient was erroneously given pethidine 100 mg intravenously instead of Novalgine. The physician, who was called immediately, observed that the patient had slow, gasping respiration, was unconscious and had constricted pupils (the clinical appearances seen in morphine poisoning). Oxygen was administered and an endotracheal tube was passed. However, it was necessary to administer levallorphan 2 mg before spontaneous respiration improved and the reflexes returned. One hour later the patient was again conscious.

These two experiences confirm the fact that there is variation in individual sensitivity to respiratory depressant substances and that even therapeutic doses can cause serious complications. Without rapid medical assistance the apnoea might well have resulted in death, or at least in severe hypoxic damage.

SUMMARY

The authors describe a series of studies designed to establish whether the addition of a small quantity of the narcotic antagonist levallorphan reduces the respiratory depressant action of pethidine. They also investigated the effect on analgesic activity and on the incidence of side effects.

The study of respiratory depression was carried out in two groups of anaesthetized patients. When anaesthesia was established each patient was given a dose of pethidine 1 mg/kg alone or mixed with levallorphan in the proportion of 80:1. The results showed that there was a statistically significantly smaller reduction of the respiratory rate, minute volume and alveolar ventilation in the pethidine plus levallorphan group.

To investigate the analgesic activity two groups of patients with postoperative pain were treated in a blind control study with either pethidine or

pethidine with levallorphan in the above proportion. It was found that the average analgesic activity was almost the same with the two types of treatment. The incidence of side effects between the two groups was insignificantly different.

The authors conclude that the addition of levallorphan in the above proportion gives almost complete protection against the respiratory

depressant effect of pethidine without diminishing the analgesic effect and without increasing the incidence of side effects.

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 FILM REVIEW

"THAT THEY MAY LIVE"

This film is excellent not only from the teaching point of view but also in its presentation and production. It is dramatic and holds the interest of the viewers throughout. There is a tendency to react against the presentation of medical techniques which picture teaching accompanied by all the trappings commonly employed by the commercial film industry. For example, music and the employment of over-dramatic situations sometimes detract from useful teaching films. Nevertheless these are so skilfully employed in the production under review that they positively add to the teaching value of the film.

The film shows the experiences of a newspaper reporter who visits the University of Saskatchewan Hospital with the intention of writing up modern methods of artificial respiration. He sees a demonstration of mouth-to-mouth resuscitation carried out on a paralyzed subject and its efficacy contrasted with that of the more usual methods available to the first-aid workers. He sees a class being instructed in the technique with the aid of a wooden "air passage demonstrator" and an

excellent "manikin". The direct mouth-to-mouth method is shown and also the more hygienic use of the Brook Airway. The reporter is then shown a film demonstrating "action shots" of a variety of accidents: a car collision; a drowning incident; a child trapped in an abandoned icebox; an infant suffocated by a plastic bag; an electrocution occurring at the top of a pylon; a choking scene in a restaurant; all of these being dealt with by members of the general public by mouth-to-mouth resuscitation. Finally, the reporter himself on leaving the hospital visits a fun-fair and is called upon to use the technique in the resuscitation of a case of electrocution.

This is quite the best film of its type that the reviewer has seen and should be in wide demand for showing to undergraduates, nurses, ambulance personnel and first-aid workers.

This film is available from Messrs. Smith and Nephew Ltd., Bessemer Road, Welwyn Garden City, Herts, who also supply the airway passage demonstrator and the Brook Airway.

Cecil Gray