Acute Effect of Some Combinations of Analgesic and Non-Analgesic Drugs in Cancer Patients

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Received: June 6, 1969

Summary. Analgesic effect and side effects were evaluated by means of a conventional scoring system in cancer patients who received single doses of the following drugs: 1. Meperidine 50 mg i.m.; the same drug at the same dose in combination with either a serotonin antagonist, methysergide 1 mg, or a stimulant of the central nervous system, amiphenazol 30 mg; and NaCl. 2. Aspirin 1 g orally; another serotonin antagonist, benzpiperilone 450 and 600 mg; and lactose. 3. Paracetamol 500 mg and 1 g orally; the same drug at the same doses in combination with an anticholinergic drug, etybenzatropine 0.5 and 1 mg; and lactose. None of these combinations produced a significantly higher analgesic effect than the analgesic drugs alone, except for the last one, but even here the difference was of doubtful significance. Amiphenazol reversed the slight hypotensive effect of meperidine but did not modify other side effects of meperidine. Methodological reasons and some possible pharmacological effects are discussed in regard to these negative results.

Analgesics are often combined with other analgesics and drugs which are devoid of any analgesic properties. The advantages of these combinations over the analgesics given alone have been questioned (LASAGNA [9]). If the doses of the ingredients are low, a slight increase of the analgesic power can be due to an additive effect rather than to a higher efficacy. This is probably what happens with mixtures of codeine and aspirin or mafenamic acid (Cass [1]). Indeed, one large scale study has shown that mixtures of aspirin, phenacetin and caffeine did not have a stronger analgesic effect and a lower incidence of side effects than aspirin alone (DeKORN FELD [4]). The confusion between the diminished perception of pain and the decreased wakefulness of the patient may explain some apparently better results when oral analgesics are combined with barbiturates (MacDONALD [10]). On the other hand, a few controlled studies on narcotic analgesics with phenothiazines, i.e. promethazine (KEATS [7]) and trifluoperazine (LASAGNA [9]), or narcotic antagonists (LASAGNA [9]), did not show any potentiation of the analgesic effect or any inhibition of the respiratory depression due to the narcotics. These negative results are, however, limited to the usual combinations of analgesic drugs. The present study was planned to compare other types of drugs: two serotonin antagonists, methysergide and benzpiperilone, a stimulant of the central nervous system, amiphenazol, and an anticholinergic drug, etybenzatropine. All these compounds, except the second one, did not manifest any analgesic properties in animal studies and were combined with standard analgesics.

Patients

All patients had chronic pain due to osseous or abdominal metastases of various types of cancer and were hospitalized in the same ward. Twelve of them were selected for the first trial, eleven for the second and twenty six for the third. Their ages ranged from 21 to 86 (median 62) and their weight from 34 to 82 kg (median 54). They were informed of the purpose of the study and were selected on a voluntary basis. One patient in the first trial and six in the third were excluded because they were no longer available for study after they had received the first dose.

Method

All patients were interviewed by the same investigator under double blind conditions, before and one-half, one, two and three hours after administration of the drug. Pain was defined as very severe (score = 4), severe (3), moderate (2), slight (1) and absent (0). The relief of pain was defined by the patient himself as follows: pain has disappeared (~4), is much less intense (+3), less intense (~2), slightly less intense (~1) than before administration of the drug, unchanged (0), more intense (~1 to ~3). In order to check the validity of the two scales, both questions were asked one after another during each interview of the first trial. In the other trials, the first question was asked before and the second only after the drug was given. Sedation ("Are you sleepy?"") and absence of discomfort ("Do you feel well?") were scored on the same scale as pain. Gastralgia and nausea were noted systematically. Blood pressure was taken with a sphygmomanometer in the lying position.

The scores of each interview were analyzed by means of an analysis of variance. If a drug had been given more than once to the same patient, the results were analyzed separately. A signed rank test (WILCOXON) was applied when the effect of two drugs was compared in the same patients; in this case, the results obtained in the same patient after the same drug were averaged.
Drugs

All drugs were coded and the order of administration was fixed before each trial by a latin square design. They were given by the nurse at least five hours after the last administration of any analgesic. Some patients received more than one sequence of drugs, others less than one, but a least two drugs within one week.

1. Meperidine 50 mg was compared with meperidine 50 mg + methysergide 1 mg, meperidine 50 mg + amiphenazol 30 mg, and with NaCl 0.9%. Each drug was given by intramuscular injection. 2. Aspirin 1 g was compared with benzpiperilone 450 mg and 600 mg, and with lactose. The drugs were given orally, in the form of three identical capsules, at least two hours after the last meal. A higher dose (900 mg) of benzpiperilone was given to the first three patients only; all three had severe nausea. The code was broken, the dose reduced to 600 mg and a new code was chosen. The combination of aspirin and benzpiperilone was not tested. 3. Paracetamol 500 mg was compared with paracetamol 500 mg + etybenzatropine 0.5 mg and lactose in one third of the patients. In the remaining patients, the doses of paracetamol and paracetamol + etybenzatropine were doubled. The low and the high doses were not given to the same patients and the drugs were coded independently for each part of the trial.

Results

1. The analgesic effect of meperidine and its combinations with methysergide and amiphenazol is shown in Fig. 1. The results were comparable whether the patients were asked to define the intensity of their pain (Fig. 1, left), or to evaluate directly the relief of pain (Fig. 1, right). The F values between individual scores and drugs were 3.13 (df 3.56; p<0.05) after one hour and 3.89 (p<0.05) after two hours for pain level scores and respectively 2.73 (p<0.10) and 4.01 (p<0.05) for pain relief scores. The results were not significant after three hours (p>0.10). The combination of meperidine with methysergide or amiphenazol did not change significantly the intensity and the duration of the analgesic effect of meperidine, as shown by signed rank tests between scores obtained in the same patients.

Nausea was severe enough after benzpiperilone 900 mg, to stop the trial with that dose. No sedation occurred after any of these drugs (Table 2).

3. Paracetamol alone and its combination with etybenzatropine had a definite analgesic effect (Fig. 2). The differences between pain relief scores after placebo and the high doses of the active drugs (1 g and 1 g + 1 mg) were significant, one-half to three hours after the drugs had been administered (F = 3.79 to 10.42; df 2.32; p<0.05); the low doses (500 mg and 500 mg + 0.5 mg) did not give significant results. The high dose

1 Dolosal® (Specia).
2 Deseril® (Sandoz).
3 Daptazol® (Nicholas).
4 Ponalid® (Sandoz).