

## COMPARISON OF NEFOPAM AND PETHIDINE IN POSTOPERATIVE PAIN

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### SUMMARY

A double-blind, between-patient, two-dose comparison was performed with pethidine and nefopam in 100 subjects, the majority of whom were recovering from upper abdominal surgery. Either 15 or 30 mg of nefopam or 50 or 100 mg of pethidine were given by i.m. injection in a random order. All assessments were made by the same observer on the first day after operation, at least 4 h after the previous analgesic injection. Nefopam 15 mg was equipotent with pethidine 50 mg, peak analgesia being achieved 1 h after the i.m. injection. Pethidine 100 mg provided significantly better pain relief than nefopam 30 mg, the latter being not more effective than nefopam 15 mg apart from the duration of analgesia which was longer. The incidence of nausea and vomiting was similar after both drugs. Sweating and tachycardia were observed more frequently after nefopam, whereas sedative side-effects were more common after pethidine.

Nefopam HCl is a new non-narcotic analgesic with a unique heterocyclic structure (Klohs et al., 1972). The analgesic action of nefopam has been confirmed by several studies (Tobin and Gold, 1972; Cohen, 1974; Workmon and Winter, 1974). It seems to have no depressant action on the central nervous system, unlike most other potent analgesic agents. On the contrary, Gassel (1973) has demonstrated enhanced reflex activity after nefopam. Gasser and Belville (1975) found no respiratory depression after giving nefopam in therapeutic dosages. Klotz (1974) was unable to demonstrate any habituation or dependency after long-term administration of nefopam in human volunteers. In the study of Sunshine and Laska (1975) nefopam 20 mg was found to be approximately equipotent with morphine 12 mg.

We have compared nefopam with our conventional postoperative analgesic, pethidine, in patients with pain following surgery.

### PATIENTS AND METHODS

The study was designed as a double-blind comparison between two doses of nefopam and pethidine, the patients being randomly assigned to one of the four treatment groups. Each patient received only one dose of the test drug, which was given by an i.m. route. Altogether 100 patients participated in the study in the II Surgical Clinic of Helsinki University Central Hospital. All the patients were in a good or fair general condition (ASA classification 1 or 2) and

informed consent was obtained from them. During the preceding 6–20 h, all the patients had undergone a surgical procedure.

A careful history of any previous allergy, the psychic condition and current medication was obtained before the administration of the test drug, with special attention being paid to analgesics and sedatives. None of the patients had received analgesics or sedatives for at least 4 h before receiving the test. All the test drugs were administered i.m. by the same person from identical coded ampoules containing 2 ml of injectate. Thus each patient received either 15 or 30 mg of nefopam or 50 or 100 mg of pethidine.

A pre-injection assessment of pain intensity (PI) was made by one observer: 0 = no pain, 1 = slight, 2 = moderate, 3 = severe pain. Only patients with moderate or severe pain were included in the study. The same PI scale was used by the observer at each subsequent observation period.

The patients were asked at each time of observation after injection for a subjective assessment of pain relief: 0 = none, 1 = slight, 2 = moderate, 3 = complete (Pain Relief Score (PRS)). Any other apparent effects of the drugs were noted also. The timing of the interviews were before treatment and at 30 min, 1, 2, 3, 4, 5 and 6 h after the test injection. To measure the severity of side-effects, an arbitrary scoring scale was used as follows: 0 = no effect, 1 = mild, 2 = moderate, 3 = severe. An increase of 0–20% in the heart rate was considered mild, 20–40% moderate and more than 40% severe. If pain was not relieved by the test drug after 30 min or if the pain returned later to the level experienced before treatment, the patient received a conventional analgesic and the

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TABLE I. *The characteristics of the different patient groups (mean and range, or  $\pm$  SEM)*

| Treatment        | No. of patients | Sex M/F | Age (yr)      | Weight (kg)    | Height (cm)      | Initial pain intensity |
|------------------|-----------------|---------|---------------|----------------|------------------|------------------------|
| Nefopam 15 mg    | 25              | 13/12   | 40<br>(22-67) | 73<br>(50-102) | 172<br>(159-190) | 2.60<br>$\pm$ 0.10     |
| Nefopam 30 mg    | 25              | 6/19    | 46<br>(19-76) | 63<br>(42-112) | 165<br>(148-181) | 2.40<br>$\pm$ 0.09     |
| Pethidine 50 mg  | 26              | 10/16   | 44<br>(20-75) | 68<br>(39-104) | 165<br>(150-183) | 2.54<br>$\pm$ 0.10     |
| Pethidine 100 mg | 24              | 11/13   | 45<br>(16-72) | 70<br>(53-130) | 168<br>(140-186) | 2.63<br>$\pm$ 0.10     |

score of pain intensity for the remainder of the study period was considered to be the same as that before the conventional analgesic.

Pain intensity differences (PID) were calculated from initial pain intensity minus pain intensity at each observation period after administration of the drug. The sums of pain intensity differences (SPID) were defined as the summation of pain intensity differences weighted by the length of the observation period.

#### Statistical tests

One-way analysis of variance was used for a comparison of the physical characteristics of the patients. To test the significance of differences in the scored data of the test groups (PI, PID scores and mean severity of side-effects), the Kruskal-Wallis non-parametric rank test, corrected for ties, was used. The same test was applied to continuous data (SPID).

#### RESULTS

The physical characteristics of the patients in the different treatment groups are shown in table I. The groups were comparable in all respects.

None of the patients had a history of taking narcotics, stimulants or antihistamines. Only a few patients in each group had ever used sedatives, tranquillizers or anti-inflammatory agents. There was no previous long-term use of analgesics before the present admission to hospital. Consumption of alcohol was similar in all groups. Previous allergic reactions among the patients were rare and mainly to penicillin. Mean PI scores are shown in table I. The small variations between the groups were not statistically significant.

The categories of operation are shown in table II.

In respect of PID, the peak effect of both doses of pethidine and the smaller dose of nefopam occurred after 1 h, whereas the peak effect of nefopam 30 mg appeared after 2 h. At 1 h, pethidine 50 mg and both

TABLE II. *Surgical procedures and analgesics administered*

| Operative procedure | Treatment group |       |           |        |
|---------------------|-----------------|-------|-----------|--------|
|                     | Nefopam         |       | Pethidine |        |
|                     | 15 mg           | 30 mg | 50 mg     | 100 mg |
| Abdominal           | 23              | 22    | 21        | 19     |
| Thoracotomy         | 1               | —     | 1         | —      |
| Nephrectomy         | —               | 1     | 1         | —      |
| Miscellaneous       | 1               | 2     | 3         | 5      |
| Total               | 25              | 25    | 26        | 24     |

doses of nefopam showed an equal analgesic effect, whereas the effect of pethidine 100 mg was clearly greater, although only the difference between this and nefopam 30 mg was statistically significant ( $P < 0.05$ ) (fig. 1). At 2 h, pethidine 100 mg was not significantly superior to the other treatments. At 3 h, however, it was found to differ significantly from nefopam 15 mg ( $P < 0.01$ ).

The pattern of PRS was similar to that of PID (fig. 2). However, no statistically significant differences between the treatment groups could be demonstrated until 3 h, when pethidine 100 mg gave significantly better pain relief than did nefopam 15 mg ( $P < 0.01$ ). Thereafter, nefopam 30 mg appeared to have the longest analgesic effect and was significantly superior to nefopam 15 mg ( $P < 0.05$ ), but not to both doses of pethidine.

SPID values for pethidine were greater than those for nefopam: 4.46 for the 50-mg and 6.02 for the 100-mg dose of pethidine; 3.84 for the 15-mg and 5.44 for the 30-mg dose of nefopam. However, a statistically significant difference occurred only between the high dose of pethidine and the low dose of nefopam ( $P < 0.05$ ).

No pain relief had occurred, after 30 min, in two patients receiving nefopam 15 mg, in one patient receiving nefopam 30 mg and in two patients

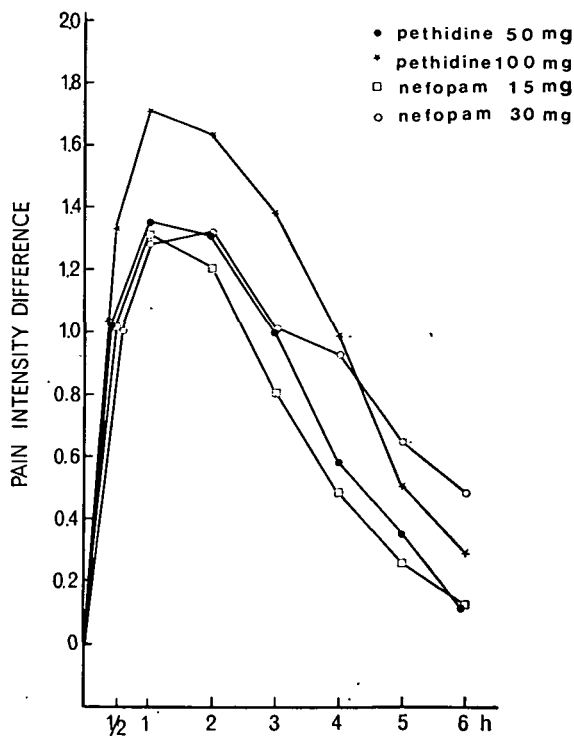


FIG. 1. Mean pain intensity differences in different treatment groups.

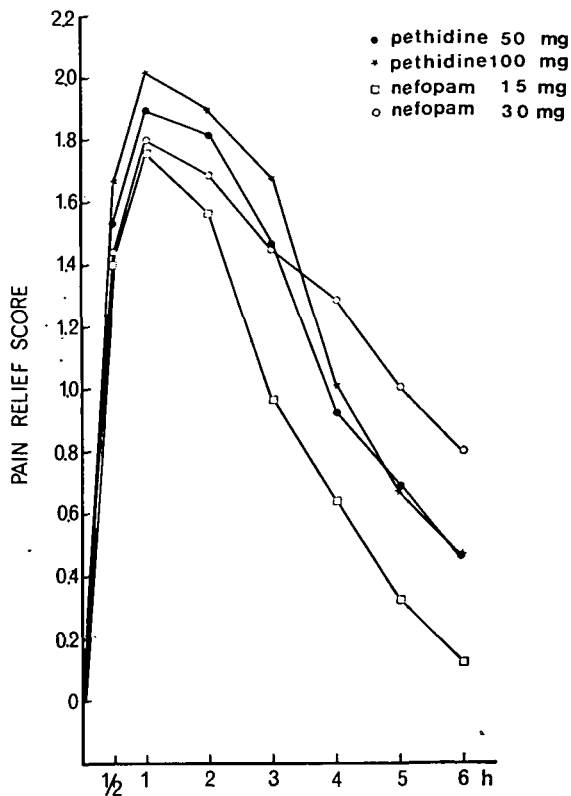


FIG. 2. Mean pain relief scores (patients' assessments).

receiving pethidine 50 mg, whereas after pethidine 100 mg every patient reported at least slight relief at that time. During the remainder of the 6-h period of study, 17 patients who received pethidine 100 mg, 16 who received pethidine 50 mg, 15 who received nefopam 30 mg and 19 patients who received nefopam 15 mg required additional pain relief with conventional analgesics (narcotics or spasmolytics, or both). The peak number of all side-effects occurred 30 min after the administration of the test drug and side-effects had almost disappeared after 1 h, except sedation or drowsiness, the mean severity of which was greater after both doses of pethidine as compared with nefopam (fig. 3). The difference between pethidine 100 mg and nefopam 30 mg was statistically significant at 30 min and 1 h after the injection ( $P < 0.01$ ).

The mean severity of nausea and vomiting was about the same for both drugs, but nefopam 30 mg caused significantly more nausea than did nefopam 15 mg, which was almost devoid of this side-effect ( $P < 0.01$ ) (fig. 4).

More sweating occurred in the patients who received nefopam as compared with those who

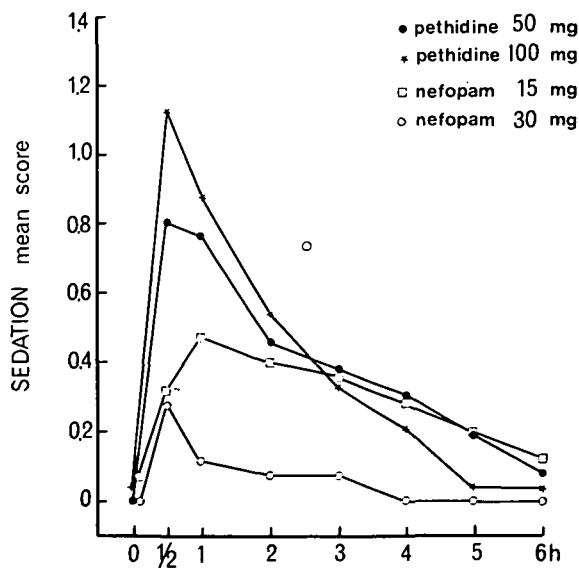


FIG. 3. Mean severity scores for sedation.

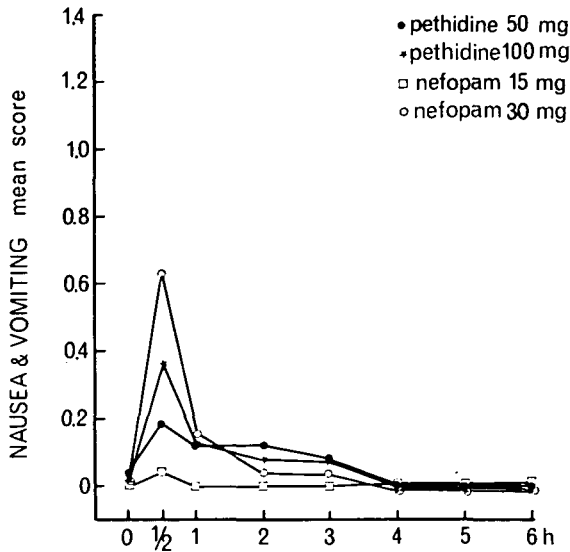


FIG. 4. Mean severity scores for nausea and vomiting.

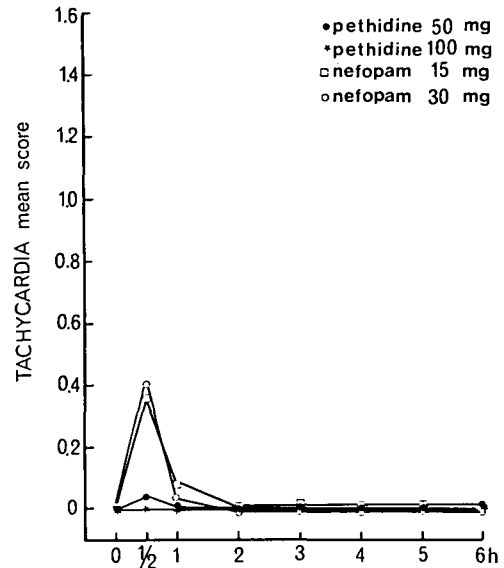


FIG. 6. Mean severity scores for tachycardia.

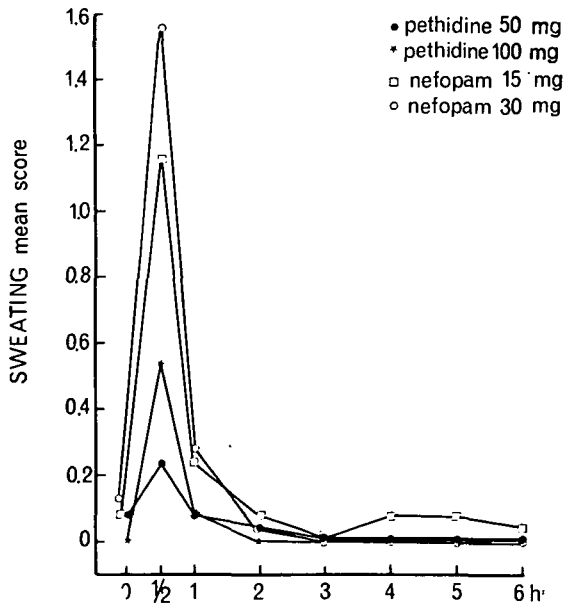


FIG. 5. Mean severity scores for sweating.

received pethidine ( $P < 0.01$ ) (fig. 5). A similar pattern was observed in respect of tachycardia ( $P < 0.05$ ) (fig. 6). No adverse effects were observed with either of the test drugs.

#### DISCUSSION

In the present study, the peak effect of nefopam 15 mg was approximately equipotent with pethidine

50 mg, whereas pethidine 100 mg had a significantly greater analgesic effect than nefopam 30 mg, which did not seem to be more effective than nefopam 15 mg. In fact, at 1 h after the injection nefopam 15 mg seemed to be even more effective than nefopam 30 mg (PID 1.32 and 1.28 respectively). The difference between pethidine 100 mg and nefopam 30 mg was statistically significant ( $P < 0.05$ ) whereas that between pethidine 100 mg and nefopam 15 mg was not. However, after the larger dose of nefopam the peak effect remained almost unchanged during the following hour (PID 1.28 at 1 h compared with 1.32 at 2 h). In our experience the analgesic effect of nefopam 30 mg therefore seemed to be less than expected on the basis of the study by Sunshine and Laska (1975) who found that nefopam 20 mg was equipotent with morphine 12 mg, which in turn is generally considered to be equipotent with pethidine 100 mg. On the other hand, PID for pethidine 100 mg in this study was comparable with that for morphine 12 mg reported by Sunshine and Laska during the maximal analgesic effect. It seems as if the dose-response curve of nefopam is less steep than that of the narcotics at higher doses.

By definition, two factors contribute to SPID for an analgesic: the sum of different PID values during the study and the length of the period of observation. The relatively long duration of action seems to be a major factor determining SPID for nefopam, whereas

that for pethidine is influenced more by the high peak effect of the drug. Therefore, in contrast to PID, SPID showed only an insignificant difference between the higher doses of pethidine and nefopam. SPID did not show significant reduction and no estimate of relative potency for nefopam could be obtained.

Nausea and vomiting in this study were less frequent than in the study of Gasser and Bellville (1975), who administered nefopam 20 mg and 40 mg. On the other hand, Sunshine and Laska did not report any episodes of nausea following nefopam in the dose range 10–20 mg. Our observations agree with these findings. The sedative effect of pethidine was comparable to that found by Takki and Tammisto (1973). The absence of sedation and drowsiness and the high frequency of sweating and tachycardia in the nefopam groups suggests that nefopam might have a sympathomimetic action. The present findings indicate that nefopam 15 mg offers a good non-narcotic alternative for relief of moderate pain after operation. Doubling the dose, however, does not seem to provide better analgesia and is associated with a higher frequency of undesirable side-effects.

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## COMPARAISON DU NEFOPAM ET DE LA PETHIDINE POUR LE SOULAGEMENT DES DOULEURS POST-OPERATOIRES

## RESUME

On a procédé à la comparasion, entre malades, de deux doses de péthidine et de néfopam, au cours d'une étude à double inconnue effectuée sur 100 sujets, dont la plupart étaient en cours de récupération après une intervention chirurgicale à la part supérieure de l'abdomen. On leur a administré au hasard, par injection intramusculaire, soit 15 ou 30 mg de néfopam, soit 50 mg ou 100 mg de péthidine. Toutes les évaluations ont été faites par le même observateur au cours de la première journée qui a suivi l'opération, au moins 4 h après l'injection analgésique précédente. Quinze milligrammes de néfopam ont été équipotentiels à 50 mg de péthidine, l'analgésie maximale étant obtenue 1 h après l'injection intramusculaire. Cent milligrammes de péthidine ont apporté un soulagement très significatif de la douleur, soulagement supérieur à celui apporté par 30 mg de néfopam, cette dernière dose n'ayant pas un effet supérieur à celui résultant de 15 mg de néfopam, sauf en ce qui concerne la durée de l'analgésie qui a été plus longue. L'incidence des nausées et des vomissements a été similaire après l'un ou l'autre de ces médicaments. On a observé que la transpiration et la tachycardie étaient plus fréquentes après l'injection de néfopam alors que les effets secondaires sédatifs étaient plus courants après l'injection de péthidine.

## VERGLEICH ZWISCHEN NEFOPAM UND PETHIDIN BEI POSTOPERATIVEN SCHMERZEN

## ZUSAMMENFASSUNG

Ein Doppelblind-Vergleich zwischen Patienten und mit zwei Dosen wurde mit Pethidin und Nefopam bei 100 Personen durchgeführt, von denen die Mehrheit Operationen im oberen Unterleib hinter sich hatten. In wahlloser Reihe wurden entweder 15 oder 30 mg Nefopam oder 50 oder 100 mg Pethidin intramuskulär verabreicht. Alle Bewertungen wurden vom selben Beobachter am ersten Tag nach der Operation vorgenommen, wenigstens 4 Stunden nach der vorherigen schmerzstillenden Injektion. 15 mg Nefopam waren gleich wirksam wie 50 mg Pethidin, wobei der Höhepunkt der schmerzlindernden Wirkung 1 Stunde nach der intramuskulären Injektion eintrat. Ein hundert mg Pethidin erwiesen sich als wesentlich schmerzlindernder als 30 mg Nefopam, welche Dosis nicht wirksamer war als 15 mg Nefopam, nur dass die Wirkungs-dauer länger war. Die Häufigkeit von Schwindel und Brechreiz bei beiden Drogen gleich. Schweissausbruch und Tachykardie traten häufiger mit Nefopam auf, während die sedativen Nebenwirkungen bei Pethidin häufiger waren.

## COMPARACION ENTRE NEFOPAM Y PETHIDINA PARA DOLOR POSTOPERATORIO

## SUMARIO

Se llevó a cabo una comparación de dos dosis entre pacientes, mediante pruebas de doble anonimato, con pethidina y nefopam en 100 individuos, la mayoría de los cuales se recuperaban de cirugía al abdomen superior. Se suministraron inyecciones intramusculares en orden irregular ya fuera con 15 o 30 mg de nefopam o 50 mg o 100 mg de pethidina.

Todas las evaluaciones fueron realizadas por el mismo observador en el primer día después de la operación, por lo menos 4 h después de la última inyección analgésica. Nefopam 15 mg resultó equipotente a petidina 50 mg, alcanzándose una analgesia máxima 1 h después de la inyección intramuscular. Petidina 100 mg proporcionó un alivio de dolor significativamente mayor que nefopam

30 mg, este último siendo no más efectivo que nefopam 15 mg, aparte de la duración de la analgesia, la cual perduró durante más tiempo. La incidencia de náusea y vómitos resultó semejante después de ambas drogas. Se notó sudor y traquicardia con más frecuencia después de nefopam, mientras que los efectos posteriores del sedante fueron más comunes después del suministro de petidina.