

Median Effective Dose (ED_{50}) of Nefopam and Ketoprofen in Postoperative Patients

A Study of Interaction Using Sequential Analysis and Isobolographic Analysis

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Background: The analgesic efficacy of ketoprofen has been shown after moderate- and severe-pain surgery, and the analgesic efficacy of nefopam has been shown after moderate-pain surgery. The aim of this study was to define the median effective analgesic doses of each drug and to determine whether the interaction of nefopam and of ketoprofen is synergistic.

Methods: Seventy-two patients scheduled to undergo moderately painful surgery were enrolled in one of three groups. The dose of nefopam and ketoprofen received by a particular patient was determined by the response of the previous patient of the same group, using an up-and-down technique. Initial doses were 18 and 40 mg, with dose adjustment intervals of 2 and 5 mg, in the nefopam and ketoprofen groups, respectively. The initial doses of nefopam and ketoprofen were 8 and 20 mg, respectively, in the nefopam-ketoprofen group, with the same dose adjustment intervals. Analgesic efficacy was defined as a decrease to less than 3 on a 0-10 numeric pain scale, 45 min after the beginning of drug infusion.

Results: The median effective analgesic dose (median value and 95% confidence interval) of nefopam and ketoprofen were, respectively, 28 mg (17-39 mg) and 30 mg (14-46 mg). The median effective analgesic dose of the combination was 1.75 mg (0.9-2.3 mg) for nefopam and 4.3 mg (2.2-6.5 mg) for ketoprofen.

Conclusion: The isobolographic analysis demonstrated that the combination of the two drugs produces effective analgesia with an important synergistic interaction.

BALANCED analgesia, *i.e.*, the use of combinations of drugs from different pharmacologic classes, is expected to improve analgesia and to decrease the incidence and the severity of adverse effects of each individual drug.¹ Because traditional postoperative analgesics (*i.e.*, morphine, nonsteroidal antiinflammatory drugs [NSAIDs], and paracetamol) have their own analgesic limitations and adverse effects, such as nausea and vomiting, inhibition of platelet function, and impairment of renal function, or limitation of dosing due to liver toxicity, the use of nefopam, a nonnarcotic analgesic, may be useful. Nefopam is a racemic mixture of two enantiomers with

little differences in their pharmacokinetic and pharmacodynamic properties.² Nefopam acts centrally³ by inhibiting serotonin, dopamine, and norepinephrine re-capture.⁴⁻⁶ Nefopam also modulates glutamatergic transmission by inhibiting *N*-methyl-D-aspartate receptors.^{7,8} Nefopam decreases c-Fos immunoreactive expression in the dorsal horn of rats 1 h after intraplantar injection of formalin.⁹ Several studies have demonstrated its efficacy in the postoperative period.¹⁰⁻¹² Nefopam also decreases shivering threshold in volunteers¹³ and proved to be efficacious to treat postanesthetic shivering in patients.¹⁴ The usual intravenous dose is 20 mg. In a precedent study, we determined the median effective analgesic doses (E_{50} = analgesic efficacy in 50% of patients) and 95% confidence intervals (CIs) of nefopam, morphine, and their combination in patients with moderate pain.¹⁵ The E_{50} s of nefopam and of morphine were 17 mg (95% CI, 15.4-18.6 mg) and 5 mg (95% CI, 4-6 mg), respectively, when the drugs were administered alone and 13.5 mg (95% CI, 9.8-17.2 mg) and 4.5 mg (95% CI, 3.3-5.7 mg), respectively, when the two drugs were combined. The interaction was found to be infraadditive.¹⁵

Nonsteroidal antiinflammatory drugs are potent analgesic drugs widely used in the postoperative period.¹⁶⁻¹⁸ They act at both the central and the peripheral level, mainly by decreasing prostaglandin production.^{18,19} In animal studies, the combination of morphine and of various NSAIDs has shown synergy.^{20,21} Ketoprofen is an NSAID widely used to treat postoperative pain and with a potent morphine-sparing effect.^{16,22} However, because the morphine-sparing effect does not necessarily mean synergy, we decided to compare the effects of the combination of nefopam (a drug with a central mechanism of action) and ketoprofen (a drug with partly a peripheral mechanism of action). For that purpose, we first used the Dixon up-and-down method to determine the ED_{50} ^{23,24} followed by an isobolographic analysis.²⁵⁻²⁷

Materials and Methods

Patient Selection

After ethical committee approval (Cochin-Port-Royal Hospital, Assistance Publique-H  pitaux de Paris, Paris, France) and patient written informed consent were obtained, 72 patients with American Society of Anesthesiologists physical status I or II were enrolled. All patients

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were scheduled to undergo surgery that was considered moderately painful (such as inguinal hernia repair surgery or minor ear, nose, and throat surgery). Noninclusion criteria were as follows: (1) contraindications to the use of nefopam and ketoprofen including pregnancy, (2) age younger than 18 yr, (3) intraoperative regional anesthesia, and (4) postoperative pain score of less than 3 on a numeric pain scale (NPS; 0 = no pain, 10 = the worst possible pain) at the time of arrival in the postanesthesia care unit (PACU).

Anesthetic Protocol

The evening before surgery, patients were instructed on how to use the NPS. All patients received general anesthesia with propofol or thiopental and desflurane or isoflurane. The opioids authorized were alfentanil, remifentanil, and sufentanil. All patients received 1 mg droperidol intravenously at the end of surgery.

Analgesic Protocol

The study was double blind, randomized, and prospective. Participants were allocated to one of three groups using a computer-generated table. Blinding was ensured by using blinded syringes freshly prepared by an anesthesiologist not involved in any other part of the study, including patient pain assessment. Immediately after patients' arrival in the PACU, pain intensity was assessed using a NPS. Analgesia was assessed by one of the following two investigators: N. D. or H. M. As soon as the pain score was 3 or greater (defined as T0), the patient was definitely included and received analgesia as defined by the protocol. At T0, patients in the nefopam group received nefopam in a 20-ml syringe as a continuous intravenous infusion over 20 min and 125 ml intravenous saline as a short perfusion over 10 min. Patients in the ketoprofen group received intravenous ketoprofen in a short perfusion of 125 ml over 10 min and saline in a 20-ml syringe as a continuous intravenous infusion over 20 min. Infusions were needed for both drugs to avoid the occurrence of adverse effects. The dose of ketoprofen or of nefopam received by a particular patient was determined by the response of the previous patient within the same group, using an up-and-down sequential allocation technique.²³ In the nefopam group, the first patient received 18 mg nefopam. The dose adjustment interval was 2 mg. In the ketoprofen group, the first patient received 40 mg ketoprofen. The dose adjustment interval was 5 mg. Dose adjustment intervals were defined according to the expected SE of the E_{50} .^{23,24} Patients in the nefopam-ketoprofen group received nefopam in a 20-ml syringe as a continuous intravenous infusion over 20 min and ketoprofen intravenously in a short perfusion of 125 ml over 10 min. The first patient received 8 mg nefopam and 20 mg ketoprofen considering *a priori* a 1:2.5 potency ratio (approximately half the initial dose of each component). The dose adjust-

ment interval was 2 mg for nefopam and 5 mg for ketoprofen. The efficacy of the study drug was assessed using the NPS 45 min after the beginning of drug infusion.^{10,16} Two outcomes were considered: (1) effective: NPS of 3 or lower out of 10 at T45 (a result defined as effective directed a decrement [2 mg nefopam in the nefopam group, 5 mg ketoprofen in the ketoprofen group, and 2 mg nefopam and 5 mg ketoprofen in the nefopam-ketoprofen group] for the next patient); and (2) ineffective: NPS of greater than 3 out of 10 at T45 (a result defined as ineffective directed an increment [same intervals as above] for the next patient).

At 45 min, participants who reported ineffective analgesia were given rescue analgesia and morphine titration was started according to the usual rules of our PACU.

Adverse Effects

Known adverse effects of nefopam (sweating, nausea, vomiting, dizziness, tachycardia, dry mouth, high blood pressure, local pain due to drug infusion) and of ketoprofen (nausea, vomiting, dizziness, gastrointestinal pain, headache, intravenous injection pain, skin rash or pruritus) were collected at 30, 45, and 60 min after the beginning of infusion and every 30 min after, upon discharge from the PACU.

Statistical Analysis

Only patients with a pain intensity of 3 or greater at the time of arrival in the PACU were selected to entry in the study. We first determined the median dose of each drug (E_{50}) leading to satisfactory analgesia in 50% of these patients. This probability of having an NPS score of less than 3 after drug injection was modeled using the Dixon up-and-down sequential allocation technique.^{23,24} The up-and-down method estimates the threshold for an all-or-none response, usually defined as the point above which 50% of the subjects respond to the stimulus and below which 50% of the subjects do not respond. Briefly, a first dose is given to the first patient, and the next doses are given according to the following rule: If the subject responds positively, the dose is decreased one step for the next subject, and conversely, if the subject does not respond, the dose is increased one step. After the E_{50} of each drug was determined, the drugs were administered in combination in a fixed ratio determined by the ratio of the ED_{50} s, and the up-and-down procedure was used again to determine the E_{50} of the combination. Because the Dixon method lets one determine only the median dose and its SD and does not allow one to draw the entire dose-probability curve, we searched for interaction using a classic isobolographic analysis.²⁸ *Isobolographic analysis* is a graphical method that allows the determination of how two (or even more than two) drugs behave when used in combination.²⁵⁻²⁷ An *isobole* is the contour that joins experimentally determined dose pairs producing a fixed re-

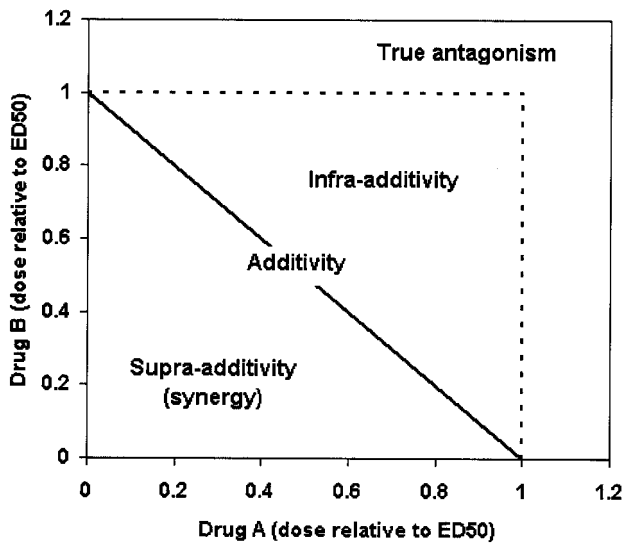


Fig. 1. Isobolographic representation of drug–drug interaction. An isobole is the *straight line* joining the dose pairs producing a fixed response (median effective dose [E_{50}] in this example). The additivity of two drugs combined in a dose ratio corresponding to their respective E_{50} is tested by plotting on the graph the points whose coordinates are the doses leading to E_{50} . The combination is said to be additive if the point lies on the isobole, supraadditive (synergistic) when the coordinates are under the isobole, and infraadditive (antagonistic) when the coordinates are above the isobole. The effect of a drug A may be considered the combined effect of half A and half A or one third A and two thirds A, for example.

sponse, and *isobolograms* are diagrams of isoboles plotted on a cartesian graph. Additivity is considered when it not possible to differentiate between the two drugs (normalized by their relative potency). In the classic representation of Loewe,²⁶ additivity of the drugs is represented by a straight line on the isobologram. It is then possible to qualify the combination as additive, supraadditive (synergistic), or infraadditive (fig. 1). Ninety-five percent confidence contours of the joint action were drawn by joining the 95% CIs of each axis of the isobologram. The combination of the two drugs was considered additive if these contours overlapped and was considered supraadditive or infraadditive otherwise.

The three groups were compared for demographic data using the chi-square test or analysis of variance as appropriate. The occurrence of adverse events and side effects was compared between groups using the Fisher exact test. E_{50} s are presented with their 95% CIs.

Results

The demographic data (age, sex ratio, body weight, type and duration of surgery) of the three groups were similar (table 1). No patient received alfentanil. The numbers of patients given remifentanyl were similar in the three groups (table 1). No patient was excluded

Table 1. Demographic Data of the 72 Patients

	Nefopam (n = 24)	Ketoprofen (n = 24)	Nefopam plus Ketoprofen (n = 24)
Sex, M/F	16/8	11/13	15/9
Age, yr	40 ± 13	43 ± 13	47 ± 15
Body weight, kg	73 ± 16	68 ± 13	70 ± 14
Duration of surgery, min	104 ± 62	123 ± 54	135 ± 85
Total dose of remifentanyl (No. of patients)	1.95 ± 0.31 mg (8)	1.84 ± 0.42 mg (9)	1.86 ± 0.38 mg (5)
Total dose of sufentanyl (No. of patients)	30 ± 9.4 µg (12)	35 ± 9.8 µg (11)	35 ± 10.6 µg (19)
Surgery			
Orthopedic	8 (33%) Removal of orthopedic material (n = 6) Tendon repair (hand) Tenolysis	5 (21%) Removal of orthopedic material (n = 4) Tendon repair (hand)	4 (17%) Removal of orthopedic material (n = 3) Toe exostosis
Ear, nose, and throat	8 (33%) Ear surgery (n = 6) Teeth extraction (n = 2)	9 (37%) Ear surgery (n = 7) Teeth extraction (n = 2)	6 (25%) Ear surgery (n = 2) Teeth extraction (n = 2) Salivary gland removal (n = 2)
Abdominal plus urogenital	8 (33%) Hernioraphy (n = 4) Cholecystectomy* (n = 2) Closure of colostomy Splenectomy* (partial)	10 (42%) Hernioraphy (n = 7) Cholecystectomy* (n = 2) Splenectomy* (partial)	14 (58%) Hernioraphy (n = 7) Cholecystectomy* (n = 2) Closure of colostomy (n = 2) Surrenalectomy* (n = 2) Appendectomy
NPS			
T0	6 (4–8)	5 (5–6.5)	5 (4–6)
T 45 min	5 (2–6)	2.5 (1–5)	3 (1–4)

Numerical pain scale (NPS) ranges from 0 = no pain to 10 = worst possible pain. Data are expressed as mean ± SD and count (percent) as appropriate, or as median and interquartile range for the NPS. No significant difference was observed among the three groups.

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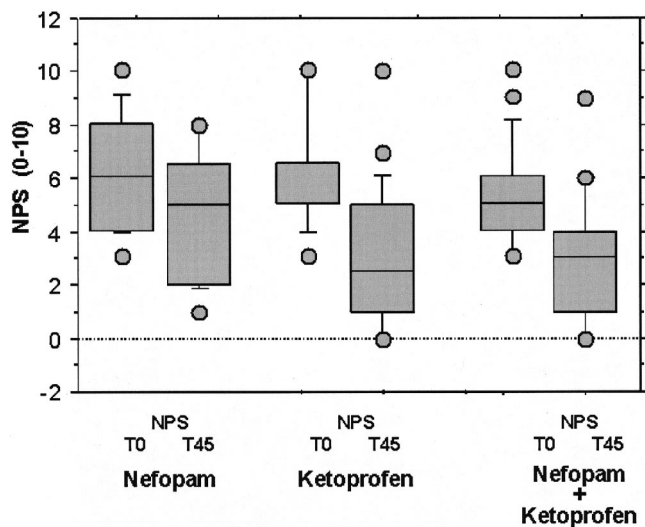


Fig. 2. Numeric pain scale (NPS; from 0 to 10) in the three groups before drug administration (T0) and 45 min after (T45). Box plots are represented as the median and 25th–75th percentiles (box), 10th–90th percentiles (bars), and outliers (circles). Analgesia at T45 was lower (although not significant) in the nefopam group than in the other groups, likely because the starting dose was far from the median effective dose in this group, leading to ineffective analgesia for the first patients (fig. 3).

because of an NPS score of less than 3, and all patients included completed the study. At the time of arrival in the PACU at T0, the patients' pain intensities as assessed by the NPS were similar in the three groups (table 1 and fig. 2).

The E_{50} s of nefopam and ketoprofen were 28 mg (17–39 mg) and 30 mg (14–46 mg), respectively. The E_{50} s of the drug combination were 1.75 mg (0.9–2.3 mg) for nefopam and 4.3 mg (2.2–6.5 mg) for ketoprofen, thus demonstrating an important synergistic effect of the combination. The sequences of effective and ineffective analgesia are shown in figure 3 and the isobolographic representation in figure 4.

In the PACU, we did not observe gastric pain, skin rash or pruritus, bradycardia, or hypotension in any patient. No significant difference was observed between groups in the incidence of sweating, nausea, vomiting, dry mouth, headache, sedation, dizziness, or tachycardia. Patients in the ketoprofen group reported pain related to the intravenous injection significantly more often (table 2).

Discussion

We have defined the median effective analgesic dose of nefopam and ketoprofen administered alone and in combination in the postoperative period after moderately painful surgery. The combination of nefopam and of ketoprofen showed an important synergistic effect.

We used the up-and-down allocation technique to determine the E_{50} of the drugs, and in a second stage, we used a classic isobolographic technique to assess the

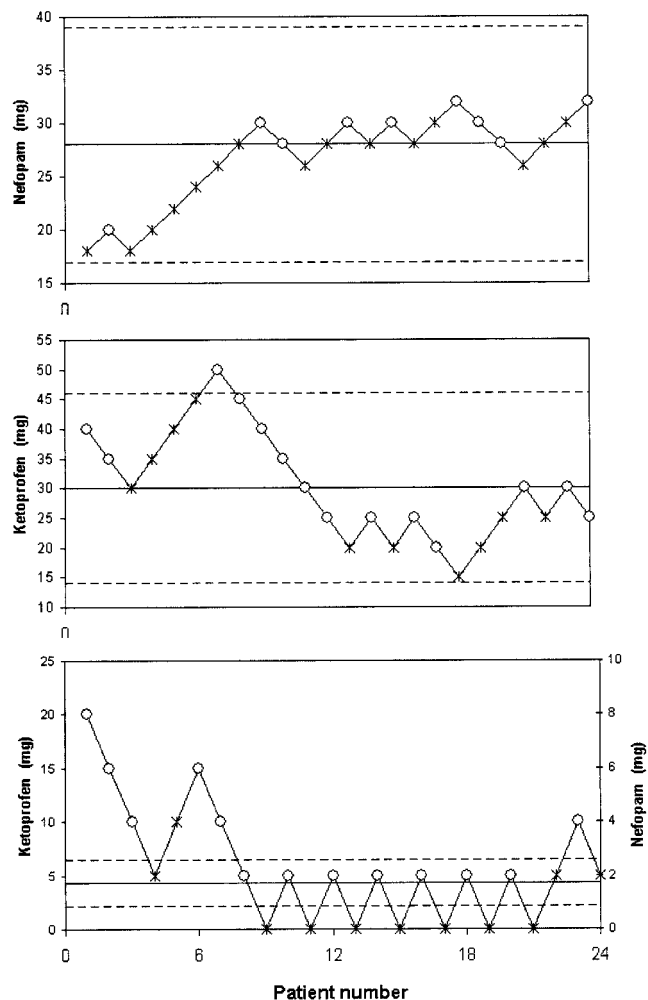


Fig. 3. Sequence of dosing in the three groups of patients receiving nefopam, ketoprofen, and a combination of nefopam and ketoprofen in a 2.5/1 ratio. The quality of analgesia was measured on a numeric pain scale (from 0 to 10) and was defined as ineffective (numeric pain scale score ≤ 3) or effective (numeric pain scale score > 3). Stars are failures (ineffective analgesia), and open circles are success (effective analgesia). In each graph, the horizontal lines are the median effective dose (thick line) and its 95% confidence interval (dashed lines).

synergy of the combination of the drugs. The Dixon up-and-down technique allows determination of E_{50} with a lower number of patients than conventional techniques. It is why this technique is widely used to calculate the minimum local analgesic concentration of drugs used in regional anesthesia and particularly in obstetrics.²⁹ In a second step, we used an isobolographic analysis to compare the E_{50} of the drugs alone and in combination (fig. 1). Curiously, isobolographic analyses of analgesic drug combinations have been used widely in animals but very little in humans. Based on several previous studies,^{15,20,21,30} we wanted to know whether the combination of ketoprofen and of nefopam was synergistic.

In a previous study,¹⁵ we found an E_{50} of nefopam of 17 mg (15.4–18.6 mg) in similar patients, *i.e.*, patients

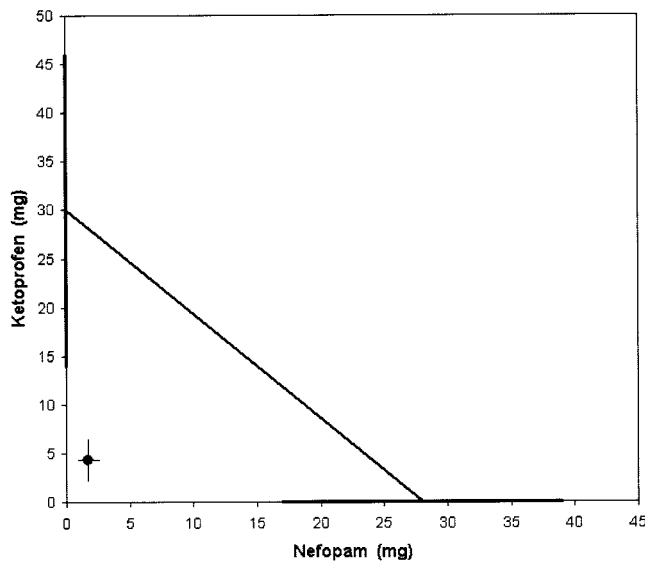


Fig. 4. Isobolographic representation of ketoprofen and nefopam effect in combination. The line joining the median effective dose (E_{50}) of each drug (nefopam on the x-axis and ketoprofen on the y-axis) is the isobole and is defined as representing pure additivity of the combination. ED_{50} s are represented with their respective 95% confidence intervals (thick lines). The E_{50} of the combination of both drugs (given in a 2.5/1 ratio) is represented by the closed circle with its 95% confidence intervals.

with moderate pain in the immediate postoperative period. In the current study, we measured an E_{50} of 28 mg (17–39 mg), which is also higher than the 20 mg recommended by the manufacturer. This higher E_{50} of nefopam in the current study as compared with the preceding study can be explained by the fact that we measured the intensity of pain 45 min after a 20-min infusion in the current study as compared to 30 min after the beginning of a 15-min infusion in the first study. However, the CIs are relatively large, and the difference between the two

Table 2. Incidence of Adverse Events

	Nefopam (n = 24)	Ketoprofen (n = 24)	Nefopam plus Ketoprofen (n = 24)
Sweating	3 (12%)	0	1 (4%)
Nausea	1 (4%)	2 (8%)	1 (4%)
Vomiting	0	1 (4%)	0
Dizziness	4 (17%)	0	2 (8%)
Dry mouth	10 (42%)	8 (33%)	6 (25%)
Local pain due to infusion	0	7 (29%)*	2 (8%)
Headache	0	1 (4%)	2 (8%)
Gastric pain	0	0	0
Pruritus	0	0	0
Skin rash	0	0	0
Hypertension	0	1 (4%)	3 (12%)
Tachycardia	3 (12%)	0	0

Adverse events have been collected every 30 min in the postanesthesia care unit until discharge (all patients stayed for at least 60 min in the postanesthesia care unit). If an adverse effect was noted at any time during this period, it was considered a positive occurrence. Results are expressed as number of patients (percent). * $P < 0.05$ vs. nefopam and nefopam-plus-ketoprofen groups.

studies must be analyzed cautiously. If nefopam were used as a sole drug, it would be necessary to use higher dosages to obtain correct analgesia in more than 90% of the patients.

The E_{50} of ketoprofen, a drug that is routinely used in the postoperative period, has never been estimated. We calculated an E_{50} of 30 mg. This result is in accordance with our practice of using a dose of 50 mg.³¹ These findings confirm the efficacy of ketoprofen, like most NSAIDs, in the postoperative period.³²

The E_{50} of nefopam and ketoprofen in combination was 1.75 mg (0.9–2.3 mg) for nefopam and 4.3 mg (2.2–6.5 mg) for ketoprofen, thus demonstrating an important synergistic effect of the combination. By acting partly at the site of inflammation, ketoprofen has a mechanism of action different from the mechanism of action of other analgesic drugs acting centrally like nefopam. This is why we studied the combination between ketoprofen and nefopam. Nefopam increases the inhibiting tone of serotonergic and norepinephrine descending pathways by inhibiting the synaptosomal uptake of dopamine, norepinephrine, and serotonin.⁴ This is consistent with the findings of Buritova and Besson,⁹ who demonstrated an effect of nefopam on the expression of c-Fos immunoreactive protein at the spinal cord level. Ketoprofen, like other NSAIDs, partly acts at the peripheral site of inflammation,^{16,18,33,34} although a central action is also present.^{18,19,34} Thus, ketoprofen and nefopam, which act on different effectors and by different pathways, show synergistic action when used in combination. In previous studies, we examined the potential synergy between morphine and nefopam, two drugs mainly acting at the central level,¹⁵ and between tramadol and morphine,³⁰ two drugs acting centrally. None of these combinations showed a synergistic effect, but rather infraadditivity. The combination of nefopam and ketoprofen is then the first combination demonstrating a synergistic effect in humans.

As expected, we did not observe severe adverse effects. The low incidence of sweating in the nefopam group (which is the most common adverse effect observed with this drug) may be explained by the slow rate of injection (20 mg over 20 min). The only difference between the groups was that patients receiving ketoprofen alone had a greater incidence of pain at the site of injection (29% of the patients) than the patients in the other groups. The combination of drugs did not reduce the incidence of adverse effects, likely because of the relatively low incidence of adverse effects observed with these agents (table 2). However, it seems always beneficial to use the minimal dose of each drug,³⁵ and the combination is then expected to decrease the incidence and severity of these adverse effects.

In conclusion, this study is the first to define the median effective analgesic dose (E_{50}) of ketoprofen (30 mg) after moderately painful surgery. Moreover, the

combination of nefopam and ketoprofen exhibited an important synergistic effect. We postulate that the different sites of action of the two drugs may explain these results. Further studies comparing the combined effects of opioids, NSAIDs, and paracetamol are needed to better understand the interactions of such drugs and to better treat the patients.

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