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Nefopam for the prevention of postoperative pain: quantitative systematic review

M. S. Evans[1]*, C. Lysakowski[1] and M. R. Tramèr[1 2]

[1]Division of Anaesthesiology, University Hospitals of Geneva, Geneva, Switzerland. [2]Medical Faculty, University of Geneva, Geneva, Switzerland

**Corresponding author. E-mail: marc.evans@hcuge.ch*

Nefopam, a centrally acting analgesic, has been used in the surgical setting in many countries since the mid-1970s. However, clinical trials provide contflicting results for its analgesic potency. We performed a systematic search (multiple databases, bibliographies, any language, to January 2008) for randomized, placebo-controlled trials of nefopam for the prevention of postoperative pain. Data were combined using classic methods of meta-analyses and were expressed as weighted mean difference (WMD), relative risk (RR), and number needed to treat/harm (NNT/H) with 95% confidence interval (CI). Nine trials (847 adult patients, 359 received nefopam) were included. Nefopam (cumulative doses, 20–160 mg) was given orally or i.v., as single or multiple doses, or as a continuous infusion. Compared with placebo, cumulative 24 h morphine consumption was decreased with nefopam: WMD −13 mg (95% CI −17.9 to −8.15). Pain intensity at 24 h was also decreased: on a 100 mm visual analogue scale, WMD −11.5 mm (95% CI −15.1 to −7.85). The incidence of tachycardia was increased with nefopam (RR 3.12, 95% CI 1.11–8.79; NNH 7), as was the incidence of sweating (RR 4.92, 95% CI 2.0–12.1; NNH 13). There is limited evidence from the published literature that nefopam may be a useful non-opioid analgesic in surgical patients. The analgesic potency seems to be similar to non-steroidal anti-inflammatory drugs. However, dose responsiveness and adverse effect profile remain unclear, and the role of nefopam as part of multimodal analgesia needs to be established. Data in children are lacking.

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In the early 1970s, nefopam was developed as an antidepressant and was also used as a myorelaxant for the treatment of spasticity.[15] The additional analgesic property was soon recognized,[10] and although the mechanism of analgesia is not completely understood, it appears that nefopam is a centrally acting, non-opioid analgesic that inhibits reuptake of serotonin, norepinephrine, and dopamine.[23]

Nefopam is a benzoxazocine and is a cyclized analogue of diphenhydramine (an antihistamine), and its chemical structure is close to orphenadrin (an antimuscarinic). Nefopam is synthesized in four steps from *O*-benzoyl benzoic acid and is pharmacologically unrelated to any other known analgesic.[13] Plasma half-life is 3–5 h; plasma peak concentrations are reached 15–20 min after i.v. injection, and after 30 min during a continuous infusion. Owing to a first-pass metabolism, oral bioavailability is only 40%. Nefopam undergoes extensive hepatic biotransformation to desmethylnefopam (which seems to be biologically active) and *N*-oxide-nefopam.[2] Protein binding is 75%, and the major route of elimination (87%) is renal whereas a small part (8%) is excreted in the faeces. Ninety-five per cent of an initial dose is excreted within 5 days, 5% as unchanged substance.[13]

Nefopam has been used extensively in many countries for the treatment of acute and chronic malignant and non-malignant pain, often despite the lack of valid clinical trial data. Some studies have suggested that in the surgical setting, nefopam 20 mg was equipotent to morphine 6–12 mg,[26] or to meperidine 50 mg.[28] Some authors also reported on a morphine-sparing effect of 30–50%.[18 20] However, others were unable to confirm these results,[19] and the role of nefopam as an adjuvant to opioid-analgesia in patients undergoing surgery has remained obscure.

Nefopam is generally considered to be safe and well tolerated. Reported adverse effects are mostly minor and include drowsiness, nausea and vomiting, and sweating.[6 14 20] Potentially more serious adverse effects are confusion and tachycardia.[20 30] Unlike non-steroidal anti-inflammatory drugs, nefopam has no effect on platelet function,[5] and, in

contrast to opioids, this drug does not seem to increase the risk of respiratory depression.[11] In this quantitative systematic review, we aimed to quantify the analgesic efficacy and the adverse effect profile of nefopam when used as an analgesic for the prevention of postoperative pain.

Methods

Literature search

MEDLINE, the Cochrane Library, EMBASE, WHOLIS, the African Index Medicus, and LILACS were searched using the term 'nefopam' either alone or in association with 'pain'. Trials studying the anti-shivering effect of nefopam[16] were excluded using the command 'NOT shivering' in the title, abstract, and keywords. Additional trials were identified from the reference lists of retrieved reports. The last search was performed in January 2008. Searches were without language restriction and authors were contacted for supplemental data or specific questions about their trials.

We included trials that compared nefopam with an inactive control group (placebo or no treatment) for the prevention of postoperative pain and that reported on pain outcomes or adverse effects. We limited our search to randomized trials in humans. Data from abstracts, letters, experimental studies in healthy volunteers, narrative reviews, animal studies, and studies with <10 patients per group were not considered.

One author (M.S.E.) extracted information on patients, surgery, anaesthesia, nefopam and postoperative analgesic regimens, pain outcomes, and adverse effects. Two other authors independently checked all extracted data. Appropriate pain outcomes were pain intensity at rest and on movement (or during coughing), and cumulative postoperative morphine consumption.

Continuous outcomes were extracted as means and standard deviations or standard errors. When these data were not reported, we contacted the authors. If they did not respond, and the data were presented graphically, we attempted to extract the data from the graphs. Data from continuous 0–10 cm visual analogue scales for pain intensity were converted to a 0–100 mm scale. Binary outcomes (for instance, adverse effects) were extracted as the presence or absence of the effect. Definitions of adverse effects were taken as reported in the original trials.

We applied a modified four-item, seven-point Oxford scale to assess the adequacy of data reporting (randomization, concealment of treatment allocation, blinding, description of withdrawals) of all included trials.[8] As we included only randomized trials, the minimum score was 1. One author scored all included studies (M.S.E.). Scores were independently checked by the two other authors and discrepancies were resolved by discussion.

Meta-analysis

For continuous outcomes, we computed weighted mean differences (WMD) with 95% confidence interval (CI). For dichotomous outcomes, we calculated relative risks (RR) with 95% CI. If the 95% CI around the WMD or RR did not include 1, we assumed that the difference between nefopam and control was statistically significant at the 5% level. To estimate the clinical relevance of a beneficial or harmful effect, we calculated numbers needed to treat (NNT) or to harm (NNH); a 95% CI around the NNT/H point estimate was computed when the difference was statistically significant.[29] We were using a fixed effect model throughout. Heterogeneity was formally tested using both the conventional χ^2 statistics and the I^2 statistics (i.e. the proportion of total variation in the estimates of a treatment effect that is due to heterogeneity between the studies). Analyses were conducted using Review Manager (version 4.2, Cochrane Collaboration) and Microsoft Excel® 2003 for Windows XP®.

Results

Retrieved trials

We identified 70 trials but subsequently excluded 61 (Fig. 1). Two reports were unavailable,[4 27] and one was excluded as data reporting was inappropriate.[31] One report was published twice.[1 25] We included the more recently published study[1] as the data reported were more complete.

We contacted three authors for supplementary information.[19 20 30] One answered and the data were included in our analyses.[20] One was unable to provide the necessary data, but some information could be extracted from the published figures.[30] Finally, one did not answer, and as no relevant efficacy data could be extracted from the published report, only data on drug-related harm could be used for analysis.[19]

We eventually analysed data from nine valid randomized trials, published between 1974 and 2007, with data from 847 adult patients, of which 359 received nefopam, 136 received another analgesic drug (ketamine, diclofenac, tilidine, propoxyphene, or proparacetamol), and 352 received an inactive control treatment (placebo or no treatment).[1 3 6 12 14 18–20 30] Five studies were performed in France, two in the UK, one in Belgium, and one in the USA. Group sizes ranged from 20 to 102 patients. The median score for quality of data reporting was 4 (range 1–7). Surgery was major abdominal in four trials, episiotomy in two, and hip arthroplasty, gynaecologic or orthopaedic, or dental extraction in one each. All patients underwent general anaesthesia (Table 1).

A large variety of nefopam regimens were tested. In two trials for each regimen, nefopam was administered as a continuous i.v. infusion, as repeat i.v. injections, or as a