

Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis

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For a systematic review of postoperative analgesic efficacy and adverse effects of single doses, injected or oral, of pethidine and ketorolac compared with placebo, we sought published randomized studies in moderate to severe postoperative pain. Information on summed pain intensity or pain relief outcomes over 4–6 h was extracted and converted to dichotomous information to produce the number of patients with at least 50% pain relief. This was used to calculate the relative benefit and number-needed-to-treat (NNT) for one patient to achieve at least 50% pain relief. Minor and major adverse effect data were extracted and summarized. For pethidine 100 mg i.m., eight randomized, controlled studies met the inclusion criteria, with 203 patients given pethidine and 161 placebo. The NNT to produce at least 50% pain relief was 2.9 (95% confidence interval 2.3–3.9). At this dose, pethidine produced significantly more drowsiness and dizziness than placebo, with numbers-needed-to-harm (NNH) of 2.9 (2.2–4.4) and 7.2 (4.8–14), respectively. For ketorolac, 14 reports met the inclusion criteria (six i.m. and eight oral). Most i.m. information (176 patients) was available for the 30 mg dose, which had an NNT of 3.4 (2.5–4.9). Most oral information was available for the 10 mg dose, which had an NNT of 2.6 (2.3–3.1). Oral ketorolac 10 mg was consistently at least as effective as ketorolac 30 mg i.m. Only with oral ketorolac 10 mg were there significantly more adverse effects than with placebo, with an NNH for any adverse effect of 7.3 (4.7–17).

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Pethidine is a commonly used postoperative opioid analgesic, and ketorolac is a newer non-steroidal anti-inflammatory drug (NSAID), licensed for short-term use in the management of moderate to severe postoperative pain. Injectable NSAID are a popular alternative to injected opioids in acute pain, even though we lack evidence that NSAID are more effective by injection than by mouth.¹ How effective and safe are they, and how do they compare with opioids used in this pain setting?

It is important to be able to compare the relative efficacy and safety of analgesics to make informed decisions on which analgesic to prescribe. A very large randomized study making direct comparisons between analgesics would provide data on their relative efficacy and safety. Such studies do not exist. The published randomized trials of direct comparisons between analgesics are too small, and hence lack power for their estimates of relative efficacy and safety to be credible.

An alternative method of estimating relative efficacy is

by indirect comparisons of each analgesic with placebo. By pooling data from individual studies of an analgesic vs placebo with similar pain settings, pain outcome measures and study design, we can estimate the number-needed-to-treat (NNT) for at least 50% pain relief. By using these same criteria for each analgesic and by using 50% pain relief as a common descriptor of analgesic efficacy, it is possible to produce a rank order of NNT values that describes clinically relevant pain relief.

The league table of analgesic efficacy² shows the relative NNT values of oral analgesics used for acute postoperative pain. The studies used to produce the NNT values were all single-dose, postoperative, randomized and double-blind. All patients had moderate to severe pain before being treated. Standard pain outcomes and measures of pain were used. Internal validity of the league table is shown by the dose–response rankings within it. To date, the only NNT available for an i.m. analgesic is for morphine 10 mg,³ and the league table needs more i.m. data to be clinically useful

Table 1 Details of i.m. pethidine vs placebo single-dose studies

| Author | Condition and no. of patients | Design, study duration and follow-up | Treatment groups | Outcome measures | Analgesic outcome results (pethidine vs placebo) | Withdrawals and exclusions | Adverse effects | Comment | Quality score |
|---|---|--|---|---|--|---|--|---|---------------|
| Bloomfield <i>et al.</i> , 1983 ³⁵ | Post-partum episiotomy <i>n</i> =20, age >16 yr | RCT, DB, identical ampoules, single dose, parallel group. Assessed at: 0, 0.5, 1, 1.5 h then hourly up to 6 h. Severe stitch pain | 1. Pethidine 100 mg i.m., <i>n</i> =10 2. Placebo, <i>n</i> =10 3. Metkephamid 70 mg i.m., <i>n</i> =10 | 1. PI 4-point standard scale (0–3) 2. PR 4-point non standard scale (0–3) 3. Patient global 10-point non-standard scale (0–10) | 1. 6 h SPID: pethidine 15.5; placebo 9.0 | None | Number of patients reporting AEs: pethidine 6/10; placebo 2/10 | Pethidine 100 mg, more effective than metkephamid 70 mg and placebo | 4 |
| Bloomfield <i>et al.</i> , 1983 ³⁵ | Post-partum episiotomy <i>n</i> =20, age >16 yr | RCT, DB, identical ampoules, single dose, parallel group. Assessed at: 0, 0.5, 1, 1.5 h then hourly up to 6 h. Severe stitch pain | 1. Pethidine 100 mg i.m., <i>n</i> =10 2. Placebo, <i>n</i> =9 3. Metkephamid 140 mg i.m., <i>n</i> =10 | 1. PI 4-point standard scale (0–3) 2. PR 4-point non-standard scale (0–3) 3. Patient global 10-point non-standard scale (0–10) | 1. 6 h SPID: pethidine 13.0; placebo 5.6 | One patient took analgesia within 4 h pre-study dose 12/59 received rescue analgesia | Number of patients reporting AEs: pethidine 8/19; placebo 3/9 | Metkephamid 140 mg more effective than pethidine 100 mg, both more effective than placebo | 4 |
| Calimlin <i>et al.</i> , 1982 ³⁶ | Post-operative not specified | RCT, DB, single dose, parallel group. Assessed at: 0, 0.5, 1, 1.5 h then hourly up to 6 h. At least moderate baseline pain | 1. Pethidine 100 mg i.m., <i>n</i> =11 2. Placebo, <i>n</i> =11 3. Metkephamid 70 mg, <i>n</i> =10 | 1. PI 5-point non-standard scale (0–4) 2. PR 5-point standard scale (0–4) 3. VASPI 100 mm 4. Patient global 5-point scale (1–5) | 1. 6 h TOTPAR: pethidine 9.5; placebo 1.3 2. Global rating pethidine 2.5; placebo 1.3 | Two placebo patients re-medicated in first hour of study and excluded | Number of patients reporting AEs: pethidine 36.4%; placebo 33.3% | Both active treatment groups similar and more effective than placebo | 3 |
| De-Andrade <i>et al.</i> , 1996 | Major orthopaedic surgery <i>n</i> =198; age 18–87 yr | RCT, DB, multi-centre study, single and multiple doses, attempts to blind with use of amber syringes, parallel groups. Assessed at: 0, 0.5, 1 h then hourly up to 6 h. At least moderate baseline pain | 1. Pethidine 100 mg i.m., <i>n</i> =82 2. Placebo, <i>n</i> =35 3. Ketorolac 60 mg i.m., <i>n</i> =81 | 1. PI 5-point non-standard scale (0–4) 2. PR 5-point standard scale (0–4) 3. VASPI 100 mm 4. Patient global non-standard 5-point scale (0–4) | 1. 6 h TOTPAR: pethidine 9.7; placebo 1.7 2. 6 h SPID: pethidine 4.3; placebo –0.1 | 44 patients excluded because of study violations and insufficient sample | No AE data for single dose | Both active treatments similar and more effective than placebo | 5 |

Table 1 Continued

| Author | Condition and no. of patients | Design, study duration and follow-up | Treatment groups | Outcome measures | Analgesic outcome results (pethidine vs placebo) | Withdrawals and exclusions | Adverse effects | Comment | Quality score |
|-------------------------------|---|--|--|---|---|--|---|--|---------------|
| Folsland <i>et al.</i> , 1990 | Major abdominal surgery, $n=129$, Age 17–82 yr | RCT, DB, identical ampoules, single dose, parallel group. Assessed at: 0, 0.5, 1 h then hourly up to 8 h. Moderate to severe baseline pain | 1. Pethidine 100 mg i.m., $n=27$ 2. Placebo, $n=32$ 3. Ketorolac 10 mg i.m., $n=31$ 4. Ketorolac 30 mg i.m., $n=29$ | 1. VASPI 100 mm 2. VASPR 100 mm 3. Patient global 5-point standard scale (0–4) | 1. 6 h VASTOTPAR: pethidine 301; placebo 122.85 2. 6 h VASPID: pethidine 191.7; placebo 77.6 3. Global rating: pethidine 5/27 very good or excellent; placebo 1/32 very good or excellent | One withdrawal because of nausea (pethidine), 2 pethidine withdrawals because of study violations, 3 pethidine, 1 placebo excluded from efficacy analysis because of incomplete data | Number of patients reporting AEs: pethidine 6/32; placebo 1/32 | All active treatments better than placebo. Pethidine 100 mg similar to ketorolac 30 mg | 4 |
| Sherline, 1983 | Post-Caesarean pain, $n=21$, age 18–40 yr | RCT, DB, identical ampoules, single dose. Assessed at: 0.5, 1, 1.5, 2 h and then hourly up to 6 h. Moderate to severe baseline pain | 1. Pethidine 100 mg i.m., $n=11$ 2. Placebo, $n=10$ 3. Piceadol 25 mg i.m., $n=11$ | 1. PI 5-point non-standard scale (0–4) 2. PR 5-point standard scale (0–4) | 1. 6 h TOTPAR: pethidine 19.7; placebo 5.7 | One placebo excluded because of unreliable responses | Number of patients reporting AEs: pethidine 11/11; placebo 4/10 | Both active treatments better than placebo. Pethidine 100 mg similar to piceadol 25 mg | 4 |
| Sunshine <i>et al.</i> , 1984 | Post-Caesarean section or major gynaecological surgery, $n=94$, age 18–75 yr | RCT, DB, single parallel group. Assessed at: 0, 0.5, 1 h then hourly until 4 h. Moderate to severe baseline pain | 1. Pethidine 50 mg i.m., $n=30$ 2. Pethidine 100 mg i.m., $n=32$ 3. Placebo, $n=32$ 4. Flumxin 20, 40 and 80 mg i.m., all $n=32$ | 1. PI 4-point standard scale (0–3) 2. PR DNS scale 3. Patient global, DNS scale | 1. 4 h SPID: pethidine 50 mg 5.64; pethidine 100 mg 4.69; placebo 2.77 | DNS | Number of patients reporting AEs: pethidine 50 mg 5/30; pethidine 100 mg 8/32; placebo 2/32 | All active treatments better than placebo | 2 |
| Wang and Robinson, 1993 | Various post-operative procedures, $n=62$, age 21–70 yr | RCT, DB, identical ampoules, single parallel group. Assessed at: 0.5, 1, 1.5, 2 h then hourly until 6 h. Moderate to severe baseline pain | 1. Pethidine 50 mg i.m., $n=21$ 2. Pethidine 100 mg i.m., $n=20$ 3. Placebo $n=21$ 4. Doxipomine 200 mg i.m., $n=21$ 5. Doxipomine 400 mg i.m., $n=20$ | 1. PI 5-point non-standard scale (0–4) 2. PR 5-point standard scale (0–4) | 1. 6 h TOTPAR: pethidine 50 mg 9.1; pethidine 100 mg 10.3; placebo 5.4 2. 6 h SPID: pethidine 50 mg 6.2; pethidine 100 mg 6.7; placebo 3.3 | Two patients withdrew from doxipomine | AE reported for pethidine 100 mg only | Pethidine 100 mg similar to doxipomine 400 mg, all active groups better than placebo | 4 |

in the postoperative setting. We set out to provide more i.m. NNT data, examining pethidine and ketorolac. Efficacy is only part of the equation, for both prescribers and patients, and we also compared and contrasted the adverse effect profiles of the three i.m. analgesics morphine, pethidine and ketorolac.

Methods

Randomized controlled studies of ketorolac or pethidine vs placebo in postoperative pain were sought. Studies of epidural, intrathecal or i.v. routes using patient-controlled analgesia (PCA) were not included. Several different search strategies were used to identify eligible reports from MEDLINE (1966 to July 1998), EMBASE (1980–1998), the Cochrane Library (1998, issue 2) and the Oxford pain relief database (1950–1994).⁴ Broad free text searches with no restriction to language were undertaken using the terms ‘ketorolac’, ‘Toradol’, ‘pethidine’, ‘postoperat*’, ‘operat*’, ‘postsurg*’, ‘surg*’, ‘dental’, ‘molar’, ‘extract*’, ‘random*’, ‘double blind’, ‘dummy’, ‘study’, ‘trial’, ‘analgesi*’, ‘pain’ and seven brand names (including Meperidine and Demerol). Reference lists of retrieved reports were searched for additional studies. Abstracts and review articles were not considered. Roche Products Ltd (UK) were contacted for ketorolac reports. Authors of articles were not contacted for unpublished reports or additional information from published reports.

Inclusion criteria and data extraction

The criteria for inclusion in the meta-analyses were: full journal publication of randomized controlled trials which included single-dose treatment groups of i.v., i.m. or oral pethidine and placebo, or ketorolac and placebo; double-blind design, baseline postoperative pain of moderate to severe intensity or visual analogue pain intensity of at least 30 mm²; patients of more than 15 yr of age; and standard pain scales. These scales were the four-point pain intensity scale (none, mild, moderate, severe), the five-point pain relief scale (none, slight, moderate, good, complete) or their visual analogue (VAS) equivalents. Study duration had to be 4–6 h, and there had to be sufficient data to allow calculation of total pain relief (TOTPAR) or summed pain intensity difference (SPID) or their visual analogue equivalents (VASTOTPAR and VASSPID).

Each report which could possibly be described as a randomized controlled study was scored independently for quality by two of the authors (pethidine L. A. S. and D. C.; ketorolac D. C. and H. J. M.) using a three-item, 1–5 score, quality scale.⁶ Reports which were described as ‘randomized’ were given one point, and another point if the method of randomization was described and adequate (such as a table of random numbers). Randomization was assumed when stated as such in the report. One point was given when the study was described as ‘double-blind’. When the method of double-blinding was described and

adequate (e.g. tablets of identical colour, shape and taste), another point was given. Finally, reports which described the number and reasons for withdrawals were given 1 point. Thus the maximum score of an included randomized controlled study was 5 and the minimum 1. Authors met to agree consensus. Data extracted from each study were: type of surgery; study treatment groups; number of patients treated; study duration; dose of pethidine or ketorolac and route of administration; and mean or derived 4–6 h TOTPAR, SPID, VASTOTPAR or VASSPID. Where available, information on the type, incidence and severity of adverse effects, including study withdrawals, was also extracted.

Statistical analyses

The proportion of patients in each treatment group who achieved at least 50% of the maximum possible total pain relief (maxTOTPAR) was calculated using verified equations.^{7–9} These proportions were then converted into the number of patients achieving at least 50% maxTOTPAR by multiplying by the total number of patients in the treatment group. Information on the number of patients with at least 50% maxTOTPAR for active and placebo was then used to calculate relative benefit and NNT. Information on adverse effects was used, where possible, to calculate the relative risk and NNH.

Relative benefit and risk estimates were calculated with 95% confidence intervals using a fixed effects model.¹⁰ NNT and NNH with confidence intervals were calculated by the method of Cook and Sackett.¹¹ When relative benefit or risk was statistically significant (95% confidence interval did not include 1), the respective NNT or NNH values are given in the text and tables, and the relative benefits and risks are shown only in the tables. When relative benefit or risk was not statistically significant, it is given in the text and tables, and respective NNT or NNH values were not calculated. Calculations were performed using Excel v 5.0 on a Power Macintosh 8500/150.

All of the data that we were able to extract are shown in Tables 1–6. In principle, however, it is preferable to make conclusions from substantial data,¹² and to emphasize that substantial data are more credible, we have emphasized the rows in the tables where we had at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment.

Results

Pethidine

We identified 24 placebo-controlled pethidine studies but only eight met our inclusion criteria. The citations and reasons for excluding the 16 studies are available at <http://www.jr2.ox.ac.uk/Bandolier/painres/pethketo/pethketo.html>.

Eight randomized studies generating 10 pethidine vs placebo comparisons fulfilled our inclusion criteria; 254

Table 2 Relative benefit and number-needed-to-treat (NNT) for studies of i.m. pethidine compared with placebo. nc=Not calculated because relative benefit not statistically significant. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

| Pethidine dose (mg) | No. of comparisons | No. of patients with at least 50% pain relief | | Relative benefit (95% CI) | NNT (95% CI) |
|---------------------|--------------------|---|---------------|---------------------------|----------------------|
| | | With pethidine | With placebo | | |
| 50 | 2 | 19/51 | 12/53 | 1.7 (0.9–3.0) | nc |
| 100 | 8 | 109/203 | 30/161 | 3.2 (2.3–4.6) | 2.9 (2.3–3.9) |

Table 3 Relative risk and number-needed-to-harm (NNH) for studies of i.m. analgesics compared with placebo. nc=Not calculated because relative benefit not statistically significant. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

| Drug and dose | Adverse effects | No. of studies | No. of patients reporting adverse effects | | Relative risk (95% CI) | NNH (95% CI) |
|------------------|---------------------------------------|----------------|---|---------------|------------------------|----------------------|
| | | | With active | With placebo | | |
| Pethidine 100 mg | Withdrawals because of adverse effect | 3 | 9/65 | 4/77 | 2.2 (0.8–6.4) | nc |
| | Any adverse effect | 7 | 136/201 | 41/139 | 1.7 (1.4–3.0) | 2.6 (2.1–3.6) |
| | Drowsiness/somnolence | 5 | 103/158 | 29/96 | 1.6 (1.2–2.0) | 2.9 (2.2–4.4) |
| | Dizziness/light-headedness | 5 | 27/158 | 3/96 | 6.6 (2.1–21) | 7.2 (4.8–14) |
| | Nausea/vomiting | 4 | 39/147 | 13/86 | 1.4 (0.8–2.3) | nc |
| Morphine 10 mg | Withdrawals because of adverse effect | 6 | 3/195 | 2/192 | 1.2 (0.3–4.5) | nc |
| | Any adverse effect | 15 | 108/320 | 68/295 | 1.5 (1.1–2.0) | 9.1 (5.6–28) |
| | Drowsiness/somnolence | 3 | 49/94 | 15/67 | 2.7 (1.7–4.3) | 3.4 (2.3–6.4) |
| | Dizziness/light-headedness | 3 | 43/80 | 7/79 | 5.7 (2.8–12) | 2.2 (1.8–3.1) |
| | Nausea/vomiting | 6 | 41/166 | 12/164 | 3.3 (1.8–6.0) | 5.9 (4.0–11) |
| Ketorolac 10 mg | Withdrawals because of adverse effect | 2 | 0/70 | 0/74 | | nc |
| | Any adverse effect | 2 | 14/70 | 7/74 | 2.1 (0.9–5.0) | nc |
| | Drowsiness/somnolence | 1 | 6/38 | 5/41 | 1.3 (0.4–3.9) | nc |
| | Dizziness/light-headedness | | | None reported | | |
| | Nausea/vomiting | 2 | 7/70 | 2/74 | 3.7 (0.8–17) | nc |
| Ketorolac 30 mg | Withdrawals because of adverse effect | 3 | 1/119 | 0/119 | | nc |
| | Any adverse effect | 3 | 19/119 | 16/119 | 1.2 (0.6–2.2) | nc |
| | Drowsiness/somnolence | 2 | 9/81 | 10/82 | 0.9 (0.4–2.1) | nc |
| | Dizziness/light-headedness | 1 | 0/41 | 5/41 | 0.1 (0.01–1.6) | nc |
| | Nausea/vomiting | 3 | 19/119 | 15/119 | 1.3 (0.7–2.4) | nc |

patients were given pethidine 50 or 100 mg i.m. and 214 placebo. No studies of oral or i.v. pethidine at any dose met our inclusion criteria. The studies investigated pain relief predominantly after orthopaedic, general or gynaecological surgery. Pain outcomes were over 6 h except for one study which was over 4 h¹³. One report scored 5 points on the quality scale, five reports scored 4, one scored 3 and one report scored 2. Further study characteristics are included in Table 1.

Efficacy

I.m. pethidine vs placebo. In the two comparisons of pethidine 50 mg vs placebo, 51 patients received pethidine and 53 placebo. There was no significant benefit of pethidine over placebo (Table 2).

There were eight comparisons of pethidine 100 mg vs placebo (Table 1); 203 patients received pethidine and 161 placebo. For a single dose of pethidine 100 mg, the proportion of patients with at least 50% pain relief was 43–100% (mean 54%) and 0–70% (mean 19%) for placebo (Fig. 1). Pethidine 100 mg was statistically superior to placebo, with an NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain of 2.9 (2.3–3.9) (Table 2).

Adverse effects

Only for pethidine 100 mg i.m. vs placebo was sufficient information available for analysis of adverse effects. Thirteen patients withdrew from the studies because of adverse effects (Table 3). Nine patients who received pethidine withdrew; nausea was the most frequently reported adverse effect causing premature study termination.^{14 15} Four patients on placebo withdrew, one because of severe drowsiness, and three for reasons that were not specified.^{14 16}

Seven of the eight randomized studies comparing a single dose of pethidine 100 mg with placebo reported adverse effect information. One study provided data only for those patients who received pethidine and not for those who received placebo.¹⁷ Sixty-eight percent (136 of 201) of patients who received pethidine reported an adverse effect compared with 30% (41 of 139) of patients who received placebo. For a single dose of pethidine 100 mg i.m. compared with placebo, the NNH to report any adverse effect was 2.6 (2.1–3.6) (Table 3).

Six of the seven randomized studies reported the frequency and type of individual adverse effects. The adverse effects most frequently reported were drowsiness or somnolence, dizziness or light-headedness and nausea or vomiting.

Table 4 Details of ketorolac vs placebo single-dose studies

| Author | Condition and no. of patients | Design, study, duration and follow-up | Treatment groups | Outcome measures | Analgesic outcome results (ketorolac vs placebo) | Withdrawals and exclusions | Adverse effects | Quality score |
|--|---|--|--|--|--|---|--|---------------|
| Injected Estienne <i>et al.</i> , 1988 | Various major surgery (gynaecological, urological, abdominal), $n=160$ (159 included in analysis), age 18–85 yr | RCT, DB, not identical yellow injectable preparations. Single dose, parallel group. Assessed at 0, 0.5, 1 h then hourly up to 8 h. At least moderate baseline pain, 1 ml injections into vastus laterus | 1. Ketorolac 10 mg i.m., $n=38$ 2. Ketorolac 30 mg i.m., $n=39$ 3. Placebo $n=41$ 4. Pentazocine 30 mg i.m., $n=41$ 1. Ketorolac 10 mg i.m., $n=32$ 2. Ketorolac 30 mg i.m., $n=32$ ($n=29$ analysed) 3. Placebo $n=33$ ($n=32$ analysed) 4. Pethidine 100 mg i.m., $n=32$ ($n=27$ analysed) | 1. PI 5-point (0–4) 2. PR 5-point (0–4) 3. Patient and investigator global rating 5-point (1–5) 4. Would patient take tablets again? 1. VASPI 100 mm 2. VASPR 100 mm 3. Investigator and patient global rating 5-point (0–4) | 1. 6 h SPID: K10 9.2 vs K30 10.7 vs P 6.7 2. 6 h TOTPAR: K10 13.8 vs K30 17.7 vs P 10.2 3. Patient global scores >50%: K10 23/38 vs K30 33/39 vs P 15/41 1. 6 h VASSPID: K10 114.8 vs K30 174.6 vs P 60.9 2. 6 h VASTOTPAR: K10 178.9 vs K30 259.5 vs P 102.5 3. 6 h patient global rating K10 15/32 vs K30 18/29 vs P 9/32 | Mean time to re-medication (h) K10 7.5 vs K30 9/40 vs P 6/41 Study withdrawals because of AEs: not reported No. of patients reporting AEs: K10 8/38 vs K30 2/32 vs P30 1/32 Study withdrawals because of AEs: K30 1/29 vs P 0/32 | No. of patients reporting AEs: K10 8/38 vs K30 2/32 vs P30 1/32 Study withdrawals because of AEs: not reported No. of patients reporting AEs: K10 6/32 vs K30 2/32 vs P30 1/32 Study withdrawals because of AEs: K30 1/29 vs P 0/32 | 2 |
| Folsland <i>et al.</i> , 1990 | Major abdominal surgery, $n=129$ (119 included in efficacy analysis), age 17–82 yr | RCT, DB, not identical yellow injectable preparations. Single dose, parallel group. Single investigator assessments at 0, 30 min, 1 h then hourly up to 8 h. At least moderate baseline pain, 1 ml injections into vastus laterus | 1. Ketorolac 30 mg i.m., $n=38$ 2. Ketorolac 10 mg i.m., $n=38$ 3. Placebo $n=37$ | 1. Verbal ordinal score P1 0–100 2. PI (4-point) (0–3) 3. Patient global rating end of treatment 5-point (0–4) | 1. Global rating good–excellent: KIV: 13/37 vs KIM 9/38 vs P 2/37 | % remedicated at 6 h KIV 78% vs P 95% | No serious adverse effects reported | 5 |
| Parke <i>et al.</i> , 1995 | Major orthopaedic, $n=113$ (112 analysed), age 17–82 yr | RCT, single dose, double-blind, not identical yellow injectable preparations parallel group. Assessments (by patient observed by investigator) at 0, then every 2 min up to 10 min, every 5 min up to 45 min, then 1, 2, 3, 4, 5, 6 h. At least moderate baseline pain | 1. Ketorolac 60 mg i.m. (multiple dose 30 mg) $n=97$ (81 analysed) 2. Pethidine 100 mg i.m., $n=97$ (82 analysed) | 1. PI 5-point (0–4) 2. PR 5-point (1–5) 3. Patient global rating 5-point (1–5) | 1. 6 h SPID: K30 5.9 vs P –0.1 2. 6 h TOTPAR: K30 12.2 vs P 1.7 | 44 excluded for variety of reasons. 200/244 in final analysis. Patients remedicated within 6 h K60 35/81 43% vs P 35/35 (100%) | No AE data for single dose | 5 |
| DeAndrade <i>et al.</i> , 1996 | Major orthopaedic surgery, $n=244$ (200 included in analysis), age 18–87 yr | RCT, DB, multicentre (7 sites), single and multiple dose as required. Not identical yellow injectable preparations. Assessments at 0, 30 min, 1 h then hourly up to 6 h. At least moderate baseline pain within 48 h of surgery | 1. Ketorolac 30 mg i.m., $n=41$ 2. Placebo $n=41$ 3. Ibuprofen arginine 400 mg orally $n=42$ | 1. VASPI 100 mm 2. Patient global rating 5-point (0–4) | 1. NSD between active treatments and placebo, except subgroup analysis 2. No. of patients rating treatment as at least good: K 22/40 vs P 14/41 | No. re-medication with inadequate relief: K 12/41 vs P 17/41 | No adverse effects reported | 4 |
| Laveneziana <i>et al.</i> , 1996 | Hernia repair, $n=125$ (124 included in analysis), age 18–72 yr | RCT, single dose, double-dummy. Not identical yellow injectable preparations parallel group. Assessments (by patient observed by investigator) at 0, 15, 30 min, 1, 2, 3, 4, 5, 6 h. At least moderate baseline pain | 1. Ketorolac 30 mg i.m., $n=30$ 2. Placebo $n=32$ 3. Ibuprofen arginine 400 mg orally $n=30$ | 1. VASPI 100 mm 2. Patient global rating 5-point (0–4) | 1. Derive VASSPID from Fig. 3B or 2 2. No. of patients rating treatment as at least good: K 16/30 vs P 4/32 | No. re-medication with inadequate relief: K 13/30 vs P 21/32 | No adverse effects reported | 4 |
| Pagnoni <i>et al.</i> , 1996 | Caesarean section, $n=92$, age 18 yr + | RCT, single dose, parallel group, single centre, double-dummy. Not identical yellow injectable preparations. Assessments (by patient observed by investigator) at 0, 15, 30 min, 1, 2, 3, 4, 5, 6 h. Baseline pain at least 60 mm VASPI | 1. Ketorolac 10 mg orally $n=37$ 2. Placebo $n=32$ 3. Acetaminophen 600 mg + codeine 60 mg orally $n=27$ 4. Aspirin 650 mg orally $n=32$ | 1. PI (4-point) 0–4 2. PR (5-point) TOTPAR 3. VASPI (0–99) VASSPID 4. Patient global rating (5-point) 0–4 | 1. 6 h SPID: K 5.65 vs P 0.25 2. 6 h TOTPAR: K 12.41 vs P 2.91 3. Hours of 50% pain relief: K 3.07 vs P 0.72 4. Patient global rating: K 2.81 vs P 0.72 | 161/162 available at 1 week follow-up. Results based on data from 128 for efficacy and 142 for safety. No. of patients re-medication K 2.81 vs P 27/32 | No. of patients reporting AEs: K 10/39 vs P 5/34 Study withdrawals for single dose not given | 5 |
| Oral Forbes <i>et al.</i> , 1990 | Impacted lower third molars, $n=128$, age 16–41 yr | RCT, single and multiple dose, DB, double-dummy, parallel group, single nurse observer, assessments at 0, 30 min, 1 h then hourly for 6 h. At least moderate baseline pain | 1. Ketorolac 10 mg orally $n=37$ 2. Placebo $n=32$ 3. Acetaminophen 600 mg + codeine 60 mg orally $n=27$ 4. Aspirin 650 mg orally $n=32$ | 1. PI (4-point) 0–4 2. PR (5-point) TOTPAR 3. VASPI (0–99) VASSPID 4. Patient global rating (5-point) 0–4 | 1. 6 h SPID: K 5.65 vs P 0.25 2. 6 h TOTPAR: K 12.41 vs P 2.91 3. Hours of 50% pain relief: K 3.07 vs P 0.72 4. Patient global rating: K 2.81 vs P 0.72 | 161/162 available at 1 week follow-up. Results based on data from 128 for efficacy and 142 for safety. No. of patients re-medication K 2.81 vs P 27/32 | No. of patients reporting AEs: K 10/39 vs P 5/34 Study withdrawals for single dose not given | 5 |

Table 4 Continued

| Author | Condition and no. of patients | Design, study, duration and follow-up | Treatment groups | Outcome measures | Analgesic outcome results (ketorolac vs placebo) | Withdrawals and exclusions | Adverse effects | Quality score |
|-------------------------------|---|---|--|---|---|--|--|---------------|
| Forbes <i>et al.</i> , 1990 | Impacted lower third molars, <i>n</i> =206, age 16–48 yr | RCT, single and multiple dose, multicentre, DB, double-dummy, parallel group, single nurse observer, assessments at 0, 30 min, 1 h then hourly for 6 h. At least moderate baseline pain | 1. Ketorolac 10 mg orally <i>n</i> =31 2. Ketorolac 20 mg orally <i>n</i> =35 3. Placebo <i>n</i> =34 4. Ibuprofen 400 mg orally <i>n</i> =32 5. Acetaminophen 600 mg orally <i>n</i> =36 6. Acetaminophen 600 mg + codeine 60 mg orally <i>n</i> =38 | 1. PI (4-point) 0–3 SPID 2. PR (5-point) 0–4 TOTPAR 3. VASPI 0–99 4. Patient global rating (5-point) 0–4 | 1. 6 h SPID: K10 5.84 vs K20 5.69 vs P 0.59 2. 6 h TOTPAR: K10 11.84 vs K20 12.57 vs P 1.88 3. Hours of 50% pain relief: K10 3.25 vs K20 3.83 vs P 0.29 4. Patient global rating: K10 2.39 vs K20 2.56 vs P 0.56 | 265/269 available at 1 week follow-up, 206 evaluable for efficacy, 244 evaluable for safety. No. of patients re-medication K10 18/31 vs K20 19/35 vs P 33/34 | No. of patients reporting AEs: K10 5/39 vs K20 8/43 vs P 0/38 Study withdrawals for single dose not given | 5 |
| Fricke <i>et al.</i> , 1993 | Third molar extraction, <i>n</i> =207, age 16 yr + | RCT, DB, single (multiple dose). Assessments at 0, 15, 30, 60, 90, 120, 180, 240, 300, 360 min. At least moderate baseline pain | 1. Ketorolac 10 mg orally <i>n</i> =69 2. Placebo <i>n</i> =69 3. Hydrocodone 10 mg + paracetamol 1 g orally <i>n</i> =69 | 1. VASPI 0–100 2. CATPI (0–4) 3. Overall patient rating end of treatment 5-point (0–4) | 1. 6 h SPID (means only) 2. 6 h TOTPAR 3. 6 h global | Patients receiving rescue analgesia 6 h K 11/30 P 11/30 | No major AEs reported Minor AEs K 43 events in 23/71 patients P 30 events in 20/69 patients | 3 |
| Maslanka <i>et al.</i> , 1994 | Orthopaedic surgery, <i>n</i> =176, age 19–87 yr | RCT, single dose, DB, double-dummy, parallel group, assessments at 0, 30 min, 1 h then hourly for 6 h. At least moderate baseline pain | 1. Ketorolac 10 mg orally <i>n</i> =50 2. Placebo <i>n</i> =25 3. Morphine 10 mg i.m., <i>n</i> =50 4. Morphine 5 mg i.m., <i>n</i> =50 | 1. PI (4-point) 0–4 SPID 2. PR (5-point) 0–4 TOTPAR 3. VASPI 0–99 4. Patient global rating (5-point) 0–4 | 1. 6 h SPID: K 6.9 vs P 2.42, 2. 6 h VASSPID: K 197.4 vs P 77.33, 3. 6 h TOTPAR: K 12.6 vs P 5.0 | 1/176 patients excluded from analysis 105 completed 6 h study: K 33/50 vs P 7/25 | No. of patients reporting AEs: K 18/50 vs P 5/25 5 study withdrawals for AEs: K 3/50 vs P 3/25 | 4 |
| Reines <i>et al.</i> , 1994 | Orthopaedic surgery, <i>n</i> =242, age 18–95 yr | RCT, multicentre, DB, single dose, parallel group. Assessments at 0, 30 min, 1 h then hourly intervals for up to 6 h. Follow-up at 1 week (some treatments taken at home). At least moderate baseline pain | 1. Ketorolac 10 mg orally <i>n</i> =76 2. Placebo <i>n</i> =73 3. Oxycodone + acetaminophen 325 mg orally <i>n</i> =69 | 1. PI (5-point) 0–4 2. PR (5-point) 0–4 TOTPAR 3. Patient global rating (5-point) 0–4 | 1. 6 h SPID: derive from Fig. 1 2. 6 h TOTPAR: P 3.1 vs K 7.6 | 242 patients enrolled, 218 included in analysis | No. of patients reporting AEs: P 22 (30%) vs K 40 (52%) | 3 |
| Norholt <i>et al.</i> , 1995 | Third molar extraction <i>n</i> =300, age 17–40 yr | RCT, multicentre, DB, but not double-dummy, single dose, parallel group. Assessments at 0, 0.5, 1 h then hourly intervals for up to 8 h. Follow-up at 1 week. At least moderate baseline pain | 1. Ketorolac 10 mg orally <i>n</i> =46 2. Placebo <i>n</i> =48 3. Lornoxicam 4 mg orally <i>n</i> =43 4. Lornoxicam 8 mg orally <i>n</i> =45 5. Lornoxicam 16 mg orally <i>n</i> =48 6. Lornoxicam 48 mg orally <i>n</i> =43 | 1. PI (5-point) 0–4 2. PR (5-point) 0–4 TOTPAR 3. Patient global rating (5-point) 1–5 | 1. 6 h TOTPAR: 3.7 vs K 14.1 2. Patient global of good or excellent: P 4/48 vs K 25/46 | 278/300 took part, 22 excluded from analysis. Results for 266 patients | 26 patients reported 37 AEs No treatment related study withdrawals Patients reporting AEs: P 7/48 vs K | 3 |
| White <i>et al.</i> , 1997 | Ambulatory atherosclerotic and laparoscopic tubal ligation, <i>n</i> =252 (10 excluded; protocol violations), adult females | RCT, multicentre, DB, single dose, parallel group. Assessment at 0, 30 min, 1 h then hourly intervals for up to 6 h. Stratification by operation type. At least moderate baseline pain. Escape analgesia permitted at 1 h | 1. Ketorolac 10 mg orally <i>n</i> =82 2. Placebo <i>n</i> =82 3. Hydrocodone 7.5 mg + acetaminophen 750 mg orally <i>n</i> =87 | 1. PI (4-point) 0–3 2. PR (5-point) 0–4 3. Patient global rating (5-point) 1–5 | 1. 6 h SPID split by op. type 2. 6 h TOTPAR split by op. type 3. Global rating 6 h good + K 57/87, P 59/83 | 10 excluded; study violations Patients in study at 6 h K 3/83 P 5/87 | No AEs reported | 3 |

Table 5 Details of pooled analyses of different routes and doses of ketorolac. RB=Relative benefit; NNT=number-needed-to-treat; nc=not calculated because relative benefit not statistically significant. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

| Dose | Route | No. of studies | At least 50% pain relief on ketorolac | At least 50% pain relief on placebo | RB (95% CI) | NNT (95% CI) |
|--------------|-------------|----------------|---------------------------------------|-------------------------------------|----------------------|----------------------|
| 10 mg | I.m. | 2 | 33/69 | 22/73 | 1.6 (1.1–2.4) | 5.7 (3.0–53) |
| 30 mg | I.m. | 5 | 93/176 | 42/183 | 2.3 (1.8–3.1) | 3.4 (2.5–4.9) |
| 60 mg | I.m. | 1 | 45/81 | 0/35 | 40 (2.5–626) | 1.8 (1.5–2.3) |
| 10 mg | I.v. | 1 | 13/37 | 2/37 | 6.5 (1.6–27) | 3.4 (2.1–7.9) |
| 5 mg | Oral | 1 | 21/30 | 17/30 | 1.2 (0.8–1.8) | nc |
| 10 mg | Oral | 8 | 205/410 | 43/380 | 4.3 (3.2–5.8) | 2.6 (2.3–3.1) |
| 20 mg | Oral | 1 | 20/35 | 0/34 | 39 (2.5–632) | 1.8 (1.4–2.5) |

Table 6 Analgesia with single doses of i.m. analgesics for postoperative pain. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

| Drug and dose | No. of studies | No. of patients given drug | NNT (95% CI) |
|-------------------------|----------------|----------------------------|----------------------|
| Pethidine 100 mg | 8 | 203 | 2.9 (2.3–3.9) |
| Morphine 10 mg | 15 | 486 | 2.9 (2.6–3.6) |
| Ketorolac 10 mg | 2 | 69 | 5.7 (3.0–53) |
| Ketorolac 30 mg | 5 | 176 | 3.4 (2.5–4.9) |

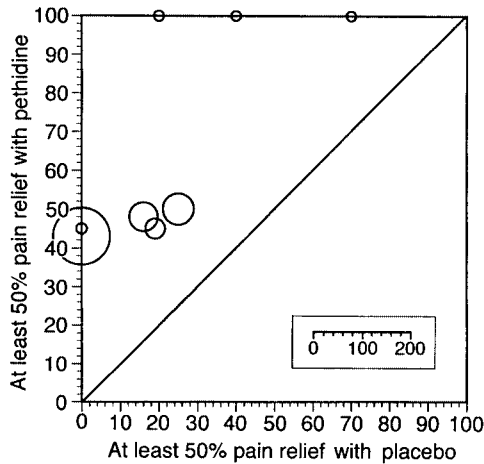


Fig 1 Proportion of patients in each study achieving at least 50% pain relief. Pain relief was over 4–6 h for pethidine 100 mg i.m. in randomized double-blind studies in patients with pain of at least moderate intensity. Point size is linearly proportional to the total number of patients in each study.

Pethidine produced significantly higher incidences than placebo of drowsiness or somnolence (NNH 2.9 (2.2–4.4)) and dizziness or light-headedness (7.2 (4.8–14)). There was no significant difference in the incidence of nausea or vomiting between pethidine and placebo (relative risk 1.4 (0.8–2.3)) (Table 3).

Ketorolac

Fourteen reports met the inclusion criteria. There were six studies of i.m. ketorolac vs placebo and eight of oral ketorolac vs placebo (Table 4). Quality scores were 3 or greater in all but one report. Four reports scored 5 points, four scored 4, five scored 3 and one scored 2 points. One report¹⁸ compared ketorolac 10 mg i.v. (38 patients) with

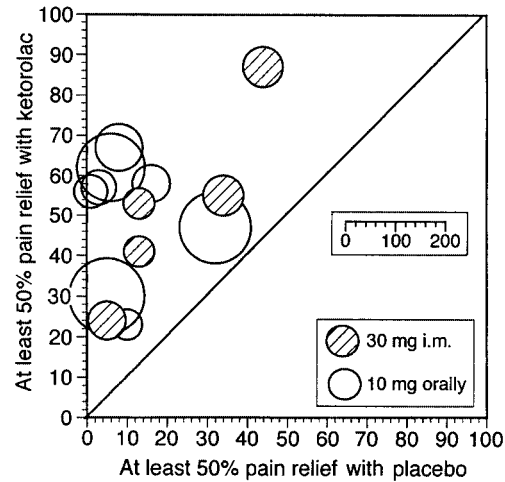


Fig 2 Proportion of patients in each study achieving at least 50% pain relief. Pain relief was over 4–6 h for ketorolac 30 mg i.m. and 10 mg orally in randomized double-blind studies in patients with pain of at least moderate intensity. Point size is linearly proportional to the total number of patients in each study.

placebo (Table 5). Details of the 55 studies excluded from the review are available at: <http://www.jr2.ox.ac.uk/Bandolier/painres/pethketo/pethketo.html>.

Efficacy

I.m. ketorolac vs placebo. Six reports^{14 15 18–21} contained eight comparisons of i.m. ketorolac with placebo, five at 30 mg, two at 10 mg and one at 60 mg. There was a total of 326 patients given i.m. ketorolac and 291 given placebo.

The proportion of patients obtaining at least 50% pain relief was 5–44% for placebo (mean 22%), 22–66% for ketorolac 10 mg i.m., 24–87% for ketorolac 30 mg i.m. (mean 53%) (Fig. 2, Table 5) and 56% for ketorolac 60 mg i.m. The NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain for the two reports of ketorolac 10 mg i.m. was 5.7 (3.0–53), and with increasing dose the NNT decreased (Table 5). For ketorolac 30 mg i.m., studied in five trials and with the most information, the NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain was 3.4 (2.5–4.9).

Oral ketorolac vs placebo. Eight reports^{22–29} involved a total of 410 patients given ketorolac 10 mg orally and 380

given placebo. One report²² also compared ketorolac 5 mg orally (30 patients) with placebo and another²⁴ compared ketorolac 20 mg orally (35 patients) with placebo.

The proportion of patients obtaining at least 50% pain relief was 1–32% for placebo (mean 10%), 70% for ketorolac 5 mg orally, 23–67% for ketorolac 10 mg orally (mean 50%; Fig. 2) and 57% for ketorolac 20 mg orally. The NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain for eight reports of ketorolac 10 mg orally was 2.6 (2.3–3.1), and with increasing dose the NNT decreased (Table 5).

Adverse effects

I.m. ketorolac. One patient who received ketorolac 30 mg i.m. withdrew because of dry mouth¹⁵; with a 10-mg dose, no patient withdrew because of adverse effects (Table 3). At both 10 mg and 30 mg, adverse effects were not considered clinically serious and were described as mild or moderate.

Three studies reported adverse effects after ketorolac 30 mg i.m. (19 of 119 patients; 16%) compared with placebo (16 of 119 patients; 13%).^{18–20} There was no significant difference between ketorolac and placebo when data were pooled for all reported adverse effects (relative risk 1.2 (0.7–2.2)). Two studies reported adverse effects of ketorolac 10 mg i.m. (14 of 70 patients; 20%) compared with placebo (seven of 74 patients; 9%).^{15, 19} There was no significant difference between ketorolac and placebo when data were pooled for all reported adverse effects (relative risk 2.1 (0.9–5.0)).

The adverse effects reported most often were drowsiness or somnolence, dizziness or light-headedness, nausea or vomiting and dry mouth (Table 3), but there were no significant differences between ketorolac and placebo.

Oral ketorolac 10 mg. Four patients withdrew from studies because of adverse effects; three after ketorolac and one after placebo. Two patients who received ketorolac reported nausea and one reported severe headache.^{25–27} One patient who received placebo withdrew with nausea.²⁶

Five studies provided information on the total number of patients who had reported adverse effects.^{23, 24, 26–28} Thirty-one percent (79 of 250) of patients who received ketorolac reported adverse effects compared with 18% (39/218) who received placebo. With a single dose of ketorolac compared with placebo, the NNH for a patient to report any adverse effect was 7.3 (4.7–17).

Six studies reported the frequency and type of individual adverse effects.^{23–28} The adverse effects reported most often were drowsiness or somnolence, dizziness or light-headedness, nausea or vomiting and dry mouth (Table 4), but there were no significant differences between ketorolac and placebo.

Discussion

It was surprising that, despite rigorous searching, there were so few placebo-controlled studies in which pethidine had

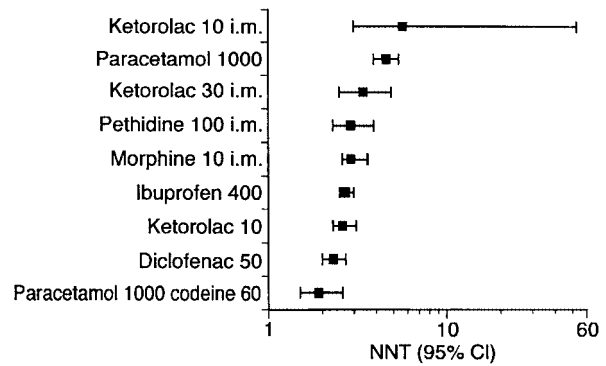


Fig 3 Numbers-needed-to-treat (NNT) (95% confidence intervals) for at least 50% pain relief over 4–6 h in patients with moderate or severe postoperative pain. All doses are oral unless labelled i.m. Data for pethidine and ketorolac from this article, for morphine from McQuay, Carroll and Moore RA³ and for other drugs from McQuay and Moore.²

been given by i.v., i.m. or oral routes, and for both pethidine and ketorolac, so few studies using standard validated methods to test single-dose analgesic efficacy. The reasons are in part historic, because pethidine is an old drug and was not used as often as morphine as a comparator in studies, and partly novelty. Many investigations of ketorolac used outcomes such as opioid-sparing effect rather than categorical or visual analogue scales. The quality of the studies included was high for both pethidine and ketorolac.

Efficacy

Only for injected morphine do we have sufficient data to be confident in our estimates.¹² Table 6 summarizes the analgesic efficacy for the two i.m. opioids pethidine and morphine,³ and the i.m. NSAID ketorolac. There is clearly little difference in efficacy between i.m. morphine 10 mg, pethidine 100 mg and ketorolac 30 mg. A theoretical limitation of this NNT method summarizing efficacy over 4–6 h is that it does not tell us if there are differences between the drugs for time to peak effect or duration beyond 6 h. Clearly, overall the areas under the pain relief vs time curves for these drugs at these doses were comparable. Figure 3 shows the NNT values for these i.m. doses and, for comparison, the NNT values for oral ketorolac, other oral NSAID and paracetamol, alone and in combination with codeine 60 mg.

Ketorolac 10 mg orally and 30 mg i.m. had NNT values (2.6 and 3.4, respectively, compared with placebo) which were similar to aspirin 650 mg³⁰ (4.4), paracetamol 1000 mg³¹ (3.6), ibuprofen 400 mg³² (2.7) and diclofenac 50 mg³² (2.3). The comparisons were with placebo, in patients with moderate or severe pain after surgery, and all used the outcome of at least 50% pain relief over 4–6 h.

We showed that, because confidence intervals of ketorolac 10 mg orally and 30 mg i.m. overlapped, they could not be distinguished in their analgesic efficacy. This is consistent with a review of NSAID which failed to demonstrate any benefit of injected over oral administration.¹ What was interesting in this review was that oral ketorolac appeared

consistently to be at least as potent as i.m. ketorolac (Fig. 3). The reasons for this are not immediately obvious. Use of analgesics by injection is expected to lead to faster increases in blood concentrations and hence faster onset of action. Oral administration is expected to lead to reduced bioavailability, and slower and lower blood concentrations than the same drug and dose given by injection. In addition to the kinetic difference between oral and injected routes, there is also a mechanistic difference between opioids and NSAID. Opioids act via receptors, NSAID by inhibiting enzymes. For ketorolac, the kinetic distinction does not seem to apply. In younger and older volunteers, ketorolac 10 mg orally resulted in more rapid maximal blood concentrations than ketorolac 30 mg i.m.³³ Nor was there any difference in dose-corrected areas under the concentration–time curve, indicating no substantial presystemic elimination with oral administration.

Another possible reason for the apparent effectiveness of oral ketorolac may be that it was given to patients with less severe pain. This is also unlikely. All studies used pain of at least moderate severity as an inclusion criterion. The studies all had a placebo-treated group. If there was any major difference in initial pain intensity between patients who were given oral or injected preparations, then it might be reflected in lower rates of placebo response. This did not occur (Fig. 2). The range of patients achieving at least 50% pain relief with placebo was 5–44% in the injected ketorolac studies (mean 22%) and 1–32% in the oral ketorolac studies (mean 14%).

The most likely explanation is that there is no real difference between oral and i.m. ketorolac over the dose ranges studied. This is supported by a wider review of injected and oral NSAID.¹ To demonstrate a small difference of statistical rather than clinical significance would require many more patients than found in these studies.¹² The practice point is that oral administration is very often simpler than i.m.²

Adverse effects

Table 3 summarizes the adverse effect data for the two i.m. opioids pethidine and morphine, and i.m. ketorolac. The similarity between the incidence of minor adverse effects of morphine 10 mg and pethidine 100 mg at these equi-analgesic doses is to be expected. For the i.m. NSAID ketorolac, there were no significant differences from placebo in the incidence of minor adverse effects at 10 or 30 mg. This is slightly surprising because for oral ketorolac 10 mg compared with placebo, we found a number-needed-to-harm of 7.3 (4.7–17) for one patient to report an adverse effect. Indeed, with aspirin, ibuprofen and paracetamol, there was increased reporting of any adverse effect compared with placebo.^{30–34} The explanation for the greater incidence of adverse effects with 10 mg orally compared with 30 mg i.m. may be that there were too few patients in the i.m. ketorolac analysis to produce accurate estimates of the incidence of adverse effects.

The clinical conclusion is that opioids carry a small but finite risk of serious adverse effects such as respiratory depression, and a greater risk of minor adverse effects than single-dose injected or oral NSAID. Conversely, NSAID carry a risk of renal problems after operation. Analgesia from the injected doses, opioid or NSAID, was equivalent to that achieved with oral NSAID. Higher doses of opioid can produce greater analgesia.³ For patients who cannot swallow, the choice is injected opioid vs injected NSAID. Our information suggests that in patients who can swallow, and in whom NSAID are not contra-indicated, oral NSAID are as effective as injected NSAID, and provide analgesia equivalent to that from conventional doses of injected opioid.

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