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Comparative clinical effects of hydromorphone and morphine: a meta-analysis

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Editor's key points

- Morphine is the standard opioid analgesic for pain control.
- Hydromorphone may have pharmaceutical and clinical advantages.
- Meta-analysis shows a small advantage for hydromorphone for analgesia but not for side-effects.
- Hydromorphone may be worthy of further consideration, but the limited number of studies suggest that more randomized controlled trials are required.

Summary. We have conducted a meta-analysis of the clinical effects of morphine and hydromorphone to compare their benefit in analgesia. Embase and Medline were searched with an end-date of June 2009 for randomized, controlled trials or observational studies that addressed comparative analgesic and side-effects or particular side-effects. Two researchers independently identified included studies and extracted the data. Estimates of opioid effects were combined by using a random-effects model. Meta-analysis of eight studies suggested that hydromorphone (494 patients) provides slightly better (P=0.012) clinical analgesia than morphine (510 patients). The effect-size was small (Cohen's d=0.266) and disappeared when one study was removed, although the advantage of hydromorphone was more evident in studies of better quality (Jadad's rating). Side-effects were similar, for example, nausea (P=0.383, nine studies, 456 patients receiving hydromorphone and 460 morphine); vomiting (P=0.306, six studies, 246 patients receiving hydromorphone and 239 morphine); or itching (P=0.249, eight studies, 405 patients receiving hydromorphone, 410 morphine). This suggests some advantage of hydromorphone over morphine for analgesia. Additional potential clinical pharmacological advantages with regard to side-effects, such as safety in renal failure or during acute analgesia titration, are based on limited evidence and require substantiation by further studies.

Keywords: opioid; pharmacology

Potent opioids such as morphine, hydromorphone, oxycodone, piritramide, meperidine, or members of the fentanyl group are the basic drugs specified in Step III (Freedom from Cancer Pain) of WHO's cancer pain relief ladder.[1] Evidence also supports the moderate use of these drugs in treating non-cancer pain.[2 3] In short-term or chronic pain treatment, being able to choose and rotate multiple opioids is recommended for handling major opioid-induced side-effects.[4 5]

However, only morphine is on WHO's essential drugs list (http://www.who.int/medicines/publications/essentialmedicines/en/ accessed January 27, 2010). This raises the question as to whether this is sufficient or whether other strong opioids are needed in addition to morphine. Hydromorphone, synthesized in Germany in 1924 and introduced in 1926, is a semi-synthetic morphine derivative that differs (Table 1) from morphine in its chemical structure only at position 6 of the benzol ring, where it has a keto-group instead of a hydroxy group (Fig. 1). This makes it 5–10 times more potent than morphine[6] and enhances its distribution into the brain making titration of the effects easier. In addition, due to the keto-group in position 6, hydromorphone is only glucuronidated at position 3, and does not form an active 6-glucuronide metabolite like morphine.[7] Therefore, hydromorphone may be better tolerated than morphine in patients with renal failure because the glucuronides are eliminated via the kidney and those patients may suffer severe opioid side-effects (Table 2). However, the 3-glucuronides (morphine-3-glucuronide, M3G, hydromorphone-3-glucuronide, H3G) have anti-analgesic and neuroexcitatory effects[8–11] not mediated by opioid receptors.[12]

Hydromorphone thus may have advantages over morphine. We have conducted a meta-analysis of the evidence supporting the additional use of hydromorphone as a standard potent opioid and compared this with morphine.

Methods

We searched PubMed and Embase (via DIMDI) databases using Cochrane's search strategy, confining the search to

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Table 1 Key pharmacological properties of hydromorphone and morphine. *K_i values specifying the concentration of competing ligand which would occupy 50% of the receptor if no radio-ligand was present (calculated according to the Cheng–Prusoff equation)

	Hydromorphone	Morphine
Physicochemistry		
Molecular weight	285.388 g mol^{-1}	285.34 g mol^{-1}
pK_a	8.2[43]	8.21[43]
Octanol water partition coefficient	1.28[43]	0.7[43]
Pharmacokinetics		
Plasma elimination half-life	2–3 h[4]	2–3,5 h[4]
Transfer half-life plasma effect site, $t_{1/2,ke0}$	18–38 min[40]	1.6–4.8 h[37]
Volume of distribution, V_d	1.22 litre kg^{-1} [44]	1.0 litre kg^{-1} [44]
Oral bioavailability (immediate-release formulation)	50%[45]	30%[46]
Pharmaceutical formulations		
Oral administration in solutions, capsules, or tablets with either immediate or sustained release	Sustained-release hydromorphone is used once daily	Sustained-release morphine is used every 12 h
I.V.	Lyophilized powder and fluid forms of morphine and hydromorphone	
Suppositories	Available in Canada	Available in Canada and Germany
Transdermal	Possible (no commercial brands available)	
Pharmacodynamics		
[^{3}H] DAMGO replacement (μ-opioid receptor affinity)*	0.6 nM[47]	1.2 nM[47]
[^{3}H] DPDPE replacement (δ-opioid receptor affinity)*	—	68.5 nM[48]
[^{3}H] U69,593 replacement (κ-opioid receptor affinity)*	55 nM	26 nM[49]
[^{3}H] N/OFQ replacement (orphan-opioid receptor affinity)*	—	>10 000 nM[50]
μ-opioid receptor cAMP inhibition	67%[48 49 51]	48%[48 49 51]
δ-opioid receptor cAMP inhibition	65%[48 49 51]	39%[48 49 51]
κ-opioid receptor cAMP inhibition	55%[48 49 51]	26%[48 49 51]
Orphan receptor [^{35}S]GTPγS binding	—	0%[50]

studies published between 1970 and June 2009. Entering the key words 'hydromorphone+morphine' yielded 1535 hits. With 'hydromorphone+morphine+pain' got 520 hits, and with 'hydromorphone *vs* morphine randomized controlled trials', yielded 27 hits. Most were excluded for the following reasons: (i) only *in vitro* assessment or animal data, (ii) hydromorphone was not compared with morphine, and (iii) reviews not containing original controlled data. The references of the studies included were hand-searched to identify any missed papers.

We selected the opioid effects for analysis to be analgesia and side-effects. Side-effects included respiratory depression, psychotropic effects such as sedation, tolerance or addiction to opioid analgesics, nausea, vomiting, constipation, and 'other side-effects' such as blurred vision, decreased heart rate or arterial pressure, itching, or oedema. Meta-analyses were done for opioid effects reported in at least five samples from at least four independent cohorts.

Two investigators, working independently, extracted data from the eligible papers, subsequently cross-checking them, and resolving discrepancies. If data were reported in a format that did not allow inclusion in the meta-analysis, we contacted the authors and asked them to release data. The following data were extracted: first author, year of publication, location, diagnostic status, whether pain was acute or chronic. When more than one study sample was reported, data were treated as subgroups of the same study.

We used the Comprehensive Meta-Analysis software version 2.0 for Windows (Biostat Inc., Englewood, NJ, USA) for the meta-analysis. Heterogeneity of the study sets submitted to meta-analysis was assessed with *Q*-statistics[13] and by calculating the value of I^2,[14] which is interpreted as $I^2>50$ showing a significant heterogeneity and $I^2<25\%$ indicating an insignificant heterogeneity. Clinical data were grouped for acute or chronic pain. Data were analysed within a random-effects framework, and individual study effect sizes were calculated using Cohen's *d*, which quantifies the standardized difference in parameter means between the groups receiving either hydromorphone or morphine normalized at the joint standard deviation, $d=(\text{Mean}_{\text{Morphine}}-\text{Mean}_{\text{Hydromorphone}})/\text{SD}_{\text{Combined}}$. When the direction of this difference *d* is a negative value, then this would indicate an advantage of one medication over another medication. An absolute value of $d=0.2$ indicates a small effect size, 0.5 indicates a medium one, and 0.8 indicates a large one.[15] Effect sizes were pooled using inverse variance methods to generate a summary effect size and its 95% confidence interval (CI). The assumption underlying a random effects framework is that between-study variation is due to both chance or random variation and study effect. The

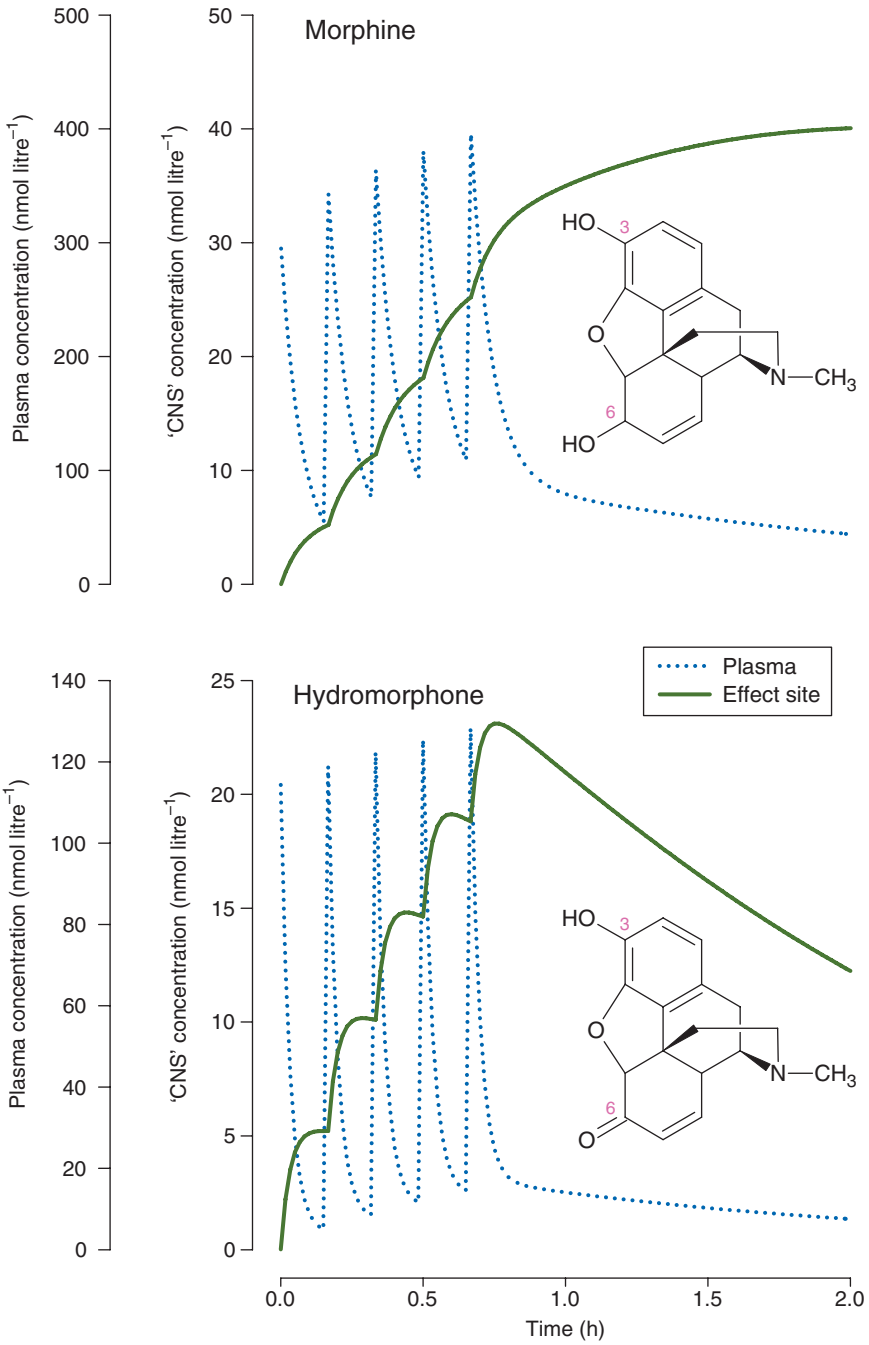

Fig 1 Comparison of simulated time courses of plasma and effect site (CNS) concentrations of morphine (5 i.v. injections of 2 mg morphine hydrochloride at an interval of 10 min during titration of analgesia) *vs* hydromorphone (0.5 mg hydromorphone hydrochloride every 10 min). After the titration injections are stopped, morphine opioid concentrations at the effect site continue to increase for at least an hour, whereas those of hydromorphone quickly decrease. For both opioids, plasma concentrations *vs* time courses were described by a standard three-compartment pharmacokinetic model. Parameter values for the simulations were taken from previous publications.[37 40–42] The k_{e0} transfer half-lives between plasma and 'CNS' effect sites were taken as 166 min for morphine[37] and 28 min for hydromorphone as the mean of the reported range.[40] Note the different scaling of the ordinates for optimum visibility of all curves. In addition, the chemical structures of morphine and hydromorphone are depicted.

significance of the pooled effect size was determined using *Z*-statistics. Forest plots were generated to visualize the standardized difference in means between genotype groups and 95% CI per study. Publication bias was assessed by testing for classic fail-safe N.[16] Although its utility is controversial,[17 18] study quality was judged according to the criteria proposed by Jadad and colleagues,[19] and the appropriateness of allocation concealment was evaluated according to the

Table 2 Side-effects of morphine or hydromorphone in patients with renal dysfunction

Reference	n	Dosing	Route of administration	Diagnose/pain condition	Comments
32	12	20 mg day^{-1} HM	Oral	Chronic pain	Higher H3G concentrations correlated with higher pain scores (r^2=0.578, P<0.001)
34	48	0.5–50 mg h^{-1} HM	I.V./s.c.	Cancer pain	Incidence of agitation=50%, myoclonus=60% with ≥20 mg h^{-1} for ≥15 days
52	2	30 mg day^{-1} M oral	Oral	Cancer pain and vascular pain	Sedation and drowsiness with plasma M6G of 941 nM
53	1	141 mg day^{-1} (total dose 1.547 g) morphine	I.V.	Morphine administered for sedation	
54	1	110 mg M over 31 h	I.V.; PCA	Intra- and postoperative pain	Unconsciousness 31 h after surgery for 45 h
55	1	Controlled release M 60 mg day^{-1}	Oral	Cancer pain	Drowsiness, confusion, and multifocal myoclonus

criteria of Schulz and Grimes[20] as appropriate or inappropriate. In the Jadad system, 1 point for each of the following criteria will be added, so that an overall result of 0–5 can be achieved: randomization, appropriate method of randomization, double-blinding, appropriate method of double-blinding, and adequate description of excluded cases and dropouts.

Results

The final data set consisted of 11 controlled clinical studies (Table 3). We included four studies comparing analgesic effects of hydromorphone and morphine for acute analgesia[21–24] and four studies comparing analgesic effects in chronic pain treatment.[25–28] In addition, three studies were included only with respect to side-effects as the pain data were not suitably reported.[29–31] Study quality was assessed as described above and results are included in Table 3.

Analgesia

Pain data were included from 10 independent samples reported in eight studies,[21–28] comprising 1004 patients, of whom 494 were treated with hydromorphone and 510 with morphine. Patients were enrolled in different clinical settings with varying pain conditions such as chronic cancer pain[25–28] and acute pain.[21–24] The opioids were administered orally,[25 26 28] s.c.,[26 27] and i.v.[21–24] In three studies,[23 26 27] pain was measured by a 100 mm visual analogue scale (VAS), and five studies[21 22 24 25 28] used an 11-point numerical rating scale (NRS). If pain intensity ratings were reported for different time points,[24 27] values were combined.

Hydromorphone provided significantly better analgesia than morphine in acute pain (d=−0.266, P=0.006, Fig. 2). The difference in pain was about −0.4 points at an NRS, calculated as the mean difference, weighted at the study size,[21 22 24 25 28] between ratings after hydromorphone and morphine administration. However, no difference was observed for chronic pain (P=0.889). The apparent advantage in acute pain treatment disappeared with the removal of any study from the analysis, showing that the effect depended on the complete study set (Fig. 3). However, the advantage of hydromorphone was better in higher quality studies, suggesting that it was less likely to be due to poor studies. The advantage for acute pain treatment was reflected in a small overall advantage of hydromorphone over morphine (d=−0.228, P=0.012). Publication bias was not significant (classic fail-safe N: P=0.14). However, the study set was heterogeneous, as indicated by Q=26.5 and I^2=73.6 (P<0.001). When leaving out each study successively, the effects did not substantially change. This also included when leaving out the study with the Jadad score 0,[26] suggesting that the hydromorphone advantage in pain relief was not the result of including a low-quality study. Similarly, a cumulative meta-analysis of the analgesic effects did not suggest a change in the result when including decreasingly scored studies.

Side-effects

Some studies numerically listed side-effects, whereas others merely reported no statistically significant difference without details (see below). Therefore, the numbers of patients differ from those analysed for analgesic effects. Three studies provided data on respiratory depression,[22 29 31] which are insufficient for meta-analysis. Similarly, constipation was reported in only two studies.[25 28] Numerical information about pruritus,[21–25 29–31] nausea,[21–25 28–31] and vomiting[21 22 24 25 28 30] was available from eight, nine, and six studies, respectively.

Nausea was comparable between hydromorphone and morphine in the acute pain group (d=0.097, P=0.346). No statistical difference was seen for either the incidence of vomiting (d=0.175, P=0.306, Fig. 2) or for itching (d=−0.361, P=0.249). Too few studies compared side-effects in the chronic pain setting. However, since separate analyses were predefined for acute and chronic pain, the results drawn from two studies suggested an advantage of hydromorphone over morphine regarding nausea (d=−0.409, P=0.005) and vomiting (d=−0.865, P=0.001)

Table 3 Comparisons of clinical effects of hydromorphone (HM) and morphine (M) included in the meta-analysis. *HM>M: hydromorphone>morphine: clinically favours hydromorphone because producing more analgesia or less side-effects, HM<M, the opposite case. †Data could not be included in meta-analysis of analgesia but were included for side-effects. OME, oral morphine equivalents.[6] ‡Data could not be included in meta-analysis

Reference	Jadad score	*n*	Dosing	Route of administration	Diagnose/pain condition	Analgesia *	Side-effects*	Comments
30	5	61	HM: 49.9 M equivalents; M: 52.6 mg	I.V.	Post-abdominal surgery	HM=M†	HM=M	Treatment similarity also recorded for influences in mood, cognitive functioning, headache, and sleep disturbances‡
21	5	198	Single bolus: HM: 0.015 mg kg^{-1}, M 0.1 mg kg^{-1}	I.V.	Acute pain, presented to ED	HM>M (P=0.002)	HM=M	
22	5	194	Single bolus: HM: 0.0075 mg kg^{-1}, M 0.05 mg kg^{-1}	I.V.	Acute pain, presented to ED	HM=M	HM=M	
23	4	119	PCA: M: 5 mg ml^{-1}; HM: 1 mg ml^{-1}	I.V.	Post-bone marrow transplantation	HM=M	HM=M	Sedation occurred less with morphine P=0.027‡
24	5	50	PCA M: 1 mg ml^{-1}; HM: 0.2 mg ml^{-1}	I.V.	Lower abdominal or pelvic surgery	HM=M	HM=M	
25	5	200	HM:12–108 mg day^{-1}; M: 60–540 mg day^{-1}	Oral	Cancer pain	HM>M (P=0.047)	HM< or >M	HM>M (P=0.028). Fewer events of vomiting and somnolence were recorded under the influence of HM, more events of constipation recorded HM<M (P=0.022)‡
26	0	74	2.5–300 mg HM *vs* 10–2500 mg M	Oral/s.c.	Cancer pain	HM=M	No side-effect profile reported	Higher opioid doses needed when rotating from M to HM than oppositely
27	3	74	Dose ratio 5:1 (no specified doses given)	S.C.	Hospice care, different diagnoses	HM=M	HM=M	
28	3	100	94.4–137.6 mg daily dose M equivalents	Oral	Cancer pain	HM<M (P<0.001)	HM>M (P=0.01)	Nausea and vomiting significantly less under HM, less constipation (P=0.04)‡
29	5	55	M 0.9 mg h^{-1}, HM 0.3 mg h^{-1}	Epidural	Post-major surgery	HM=M†	HM=M	
31	4	90	M: 10 μg kg^{-1} h^{-1}; HM 1 μg kg^{-1} h^{-1}	Epidural	Pre-, peri-, and postoperative: orthopaedic procedures	HM=M†	HM>M (P=0.011)	Fewer patients with itching under HM. Additionally, fewer events of respiratory depression in the HM group (P=0.039)‡, fewer patients with urinary retention under HM (P=0.05)‡

in chronic pain. When pooled with acute pain, the overall effect was non-significant. Publication bias was significant for vomiting (classic fail-safe N: P=0.01), and the study set was heterogeneous for itching and vomiting (Q and I^2 values at P<0.05).

Discussion

Our meta-analyses suggest a slight advantage of hydromorphone for analgesia. However, both opioids are effective analgesics, and neither is without clinically relevant side-effects. An absolute value of Cohen's d of 0.266 for better acute analgesia produced by hydromorphone shows only a small effect size. Indeed, the difference in pain was about 0.4 points at an 11-point NRS, in favour of hydromorphone. This may be clinically significant when considering that the average effect of WHO Step III opioids on chronic non-cancer pain was found to be 1.1 points *vs* placebo.[2] The advantage of hydromorphone over morphine is weakened as three comparative studies, which suggested the clinical equivalence of the two opioids, were not included into the meta-analysis due to unsuitable data reporting. Moreover, the slight

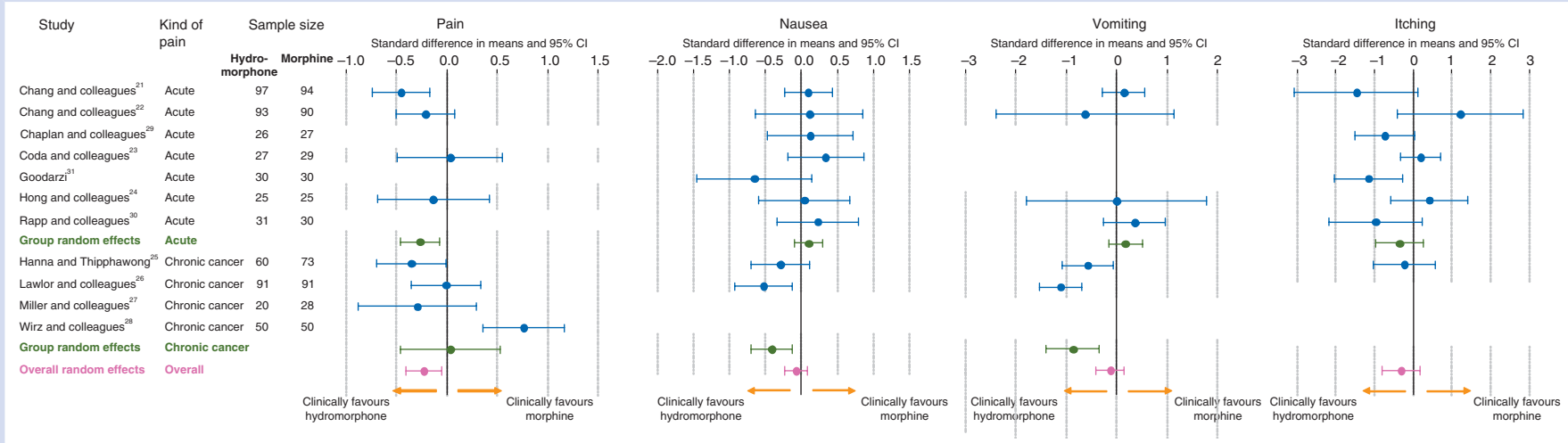

Fig 2 Comparative assessments in various clinical settings of the effects of hydromorphone and morphine on pain, nausea, vomiting, and itching. Meta-analysis indicates that hydromorphone provides significantly lower pain (negative Cohen's *d*) than morphine, whereas for chronic pain both opioids provided similar analgesia. Thus hydromorphone is slightly more advantageous than morphine at providing analgesia in a clinical setting. In contrast, significantly less nausea (negative Cohen's *d*) during chronic pain treatment with hydromorphone cannot be taken as result due to only two studies included in that subgroup. Forest plots show the standardized differences in means between groups with 95% CIs shown for each study.

Fig 3 Comparative assessments of the analgesic effects of hydromorphone and morphine when one study was removed from the analysis (left) and cumulative meta-analysis with successive inclusion of studies with decreasing Jadad's quality rating. The forest plot at the left indicates, for each study, the meta-analysis result that would have been obtained when that particular study had not been included. It shows that the apparent advantage of hydromorphone depends on the completeness of the data set and disappears when either of the included studies was removed. The plot on the right shows the changes in the meta-analysis results when lower Jadad-scored studies were successively included. It indicates that the advantage of hydromorphone is better justified in higher quality studies and was not merely suggested by lower quality studies.

advantage depended on the complete study set, as removing any of the studies eliminated the hydromorphone advantage. However, the advantage was supported by the better quality studies rather than the lower quality ones. The results are based on surprisingly few studies considering the >80 yr of clinical availability of hydromorphone.

Nevertheless, in some populations, hydromorphone has been reported to be better than morphine because it does not have an active, renally eliminated metabolite. Several case reports suggested that morphine's 6-glucuronide metabolite is responsible for sedation and nausea in patients with impaired renal excretory function (Table 3). Hydromorphone, pharmacokinetics, and pharmacodynamics have been studied in a single, controlled study in patients receiving 4 h haemodialysis treatment twice weekly.[32] Between haemodialysis treatments, the half-life of plasma hydromorphone was significantly prolonged ($t_{1/2}$=33.3 h), but was normal during haemodialysis ($t_{1/2}$=3.3 h, P=0.02). McGill Pain Questionnaire and VAS pain scores decreased from 35 items and 5.9 mm between haemodialysis sessions to 15.5 items and 4.4 mm VAS during haemodialysis, respectively. Higher H3G concentrations were correlated with higher pain scores (r^2=0.578, P<0.001). Since no serious side-effects occurred, hydromorphone was concluded as a safe treatment option in haemodialysis patients. However, this finding in haemodialysis patients does not rule out neuroexcitatory symptoms triggered by H3G in renal functional impairment without haemodialysis.[33] In 48 terminally ill hospice patients treated with at least 20 mg h^{-1} continuous parenteral hydromorphone for more than 15 days,[34] agitation had an incidence of 50% and myoclonus an incidence of 60%, when treatment duration was longer.

Other perceived clinical advantages of hydromorphone, such as less sedation and other central nervous side-effects, could not be tested against morphine because the current data are insufficient. Moreover, the common practice of opioid-rotation does not reveal a particular advantage of hydromorphone over morphine due to the lack of randomized controlled trials.[35] The only controlled study covering opioid rotation[26] did not compare side-effect profiles, for which opioid rotation is especially advised.[5] Moreover, in a prospective clinical trial, improvements in pain and side-effects caused by rotation to hydromorphone could not be solely related to a better pharmacokinetic profile of the substance hydromorphone as the technique of opioid-rotation itself and an increase in dosage may influence effective symptom control.[36]

A further possible advantage of hydromorphone over morphine may apply to short-term analgesia. Hydromorphone has a shorter plasma:central nervous effect-site equilibration half-life than morphine (Table 1). The physicochemical properties of morphine in a slow blood–brain barrier transfer half-life of ~166 min.[37] This slow transfer can result in delayed fatal respiratory depression,[38] and suggests that morphine is poorly suited by titration for immediately analgesia. Simulation shows that hydromorphone's effects have a quicker onset time than those of morphine. Importantly, the concentrations at effect site do not increase after titration has stopped as with morphine (Fig. 1). Therefore, hydromorphone may be better suited than morphine for titration of acute analgesia. This theoretical pharmacokinetic–pharmacodynamic modelling-based consideration is also supported by a shorter latency [22.5 (6) min] of the onset of postoperative analgesia after epidural administration of hydromorphone (n=19) when compared with morphine [36.6 (6) min; n=37].[39]

Our meta-analyses suggest a slight advantage of hydromorphone for analgesia but was based on relatively few and heterogeneous studies. Further comparative studies of hydromorphone are needed, despite its clinical use for more than 80 yr. Our comparison does not justify a preference for the current use of morphine, but pharmacokinetic advantages and perceived clinical benefits of hydromorphone with respect to side-effects are based on limited evidence and require substantiation by further clinical studies.

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Conflict of interest

G.G. received a research grant from Mundipharma Research, Limburg, Germany, and has also consulted Pfizer and Grünenthal. J.L. had cooperations and consultations with Mundipharma research more than 5 yr ago and has consulted Pfizer. D.D. is a consultant for Johnson and Johnson Inc. and Masimo Inc. R.-D.T. has received consultancy fees, honoraria, or research support from Astellas, AWD, Dr Kade, Galderma, Grünenthal, Nycomed, Merz, Pfizer, DFG, BMBF, and EU in the past year. H.K. has received honoraria for presentations from Mundipharma, Grünenthal, Janssen in the past years.

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