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Intravenous dexketoprofen induces less injection pain than racemic ketoprofen

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SUMMARY

What is known and objective: **Ketoprofen has high analgesic efficacy against inflammatory and nociceptive pain. Additionally, when ketoprofen is administered in conjunction with an opioid during pain management, it prevents the development of opioid-induced hyperalgesia. The main limitation for racemic ketoprofen IV administration is venous irritation. Dexketoprofen is the active enantiomer of racemic ketoprofen and has a similar analgesic efficacy in a dose proportion of 1 : 2, but it causes fewer adverse effects than racemic ketoprofen. It has been claimed that dexketoprofen may cause less frequent and less severe injection pain than racemic ketoprofen. In this study, we compared the injection pain of IV administered racemic ketoprofen and dexketoprofen in elective surgical patients.**

Methods: **The ethics committee of our institution approved this randomized, double-blinded, two-treatment, two-period, crossover clinical comparison of ketoprofen and dexketoprofen. A total of 221 ASA I-III adult patients, aged 20–75 years, were initially IV administered either 0·5 mg/kg racemic ketoprofen followed 2 h later with 0·25 mg/kg dexketoprofen (group 1) or vice versa (group 2). Both compounds were diluted in 20 mL of normal saline and were injected over 6 min. Patients reported injection pain on an 11-point numerical rating scale (NRS) (0 = no pain, 10 = most pain).**

Results and discussion: **Significantly less injection pain was reported after dexketoprofen administration. A total of 201 of 209 patients reported pain during racemic ketoprofen injection, and 157 of 210 patients reported pain during dexketoprofen injection, respectively. Moderate or severe pain was reported by 90 (41%) patients during racemic ketoprofen administration and by 43 (20%) during dexketoprofen injection ($P = 0{\cdot}001$). The mean of injection pain during racemic ketoprofen injection was 4·2 (SD 2·5) and was 2·5 (2·4) during dexketoprofen injection ($P = 0{\cdot}001$). No serious or unexpected adverse events were reported.**

What is new and conclusion: **Dexketoprofen causes significantly less injection pain than racemic ketoprofen; therefore, it may be a more suitable IV non-steroidal anti-inflammatory than the racemate.**

WHAT IS KNOWN AND OBJECTIVE

Ketoprofen is a commonly used non-steroidal anti-inflammatory drug (NSAID) in children and adults.[1] Ketoprofen has been in clinical use since 1972, and its mechanism of action is the non-selective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes.[2,3] During acute pain management, the most effective administration route is intravenous injection (IV). After IV administration, ketoprofen readily permeates the blood–brain barrier and its retention time in the central nervous system is relatively long, which may explain its rapid onset and prolonged action mediated by central mechanisms.[4]

Ketoprofen is a racemic mixture, and its analgesic efficacy is due to the (*S*)-enantiomer, dexketoprofen. The analgesic action of the (*R*)-enantiomer is considered to be less significant, but causes the majority of adverse effects, that is gastric mucosa irritation.[3,5] Dexketoprofen is half of the corresponding dose of racemic ketoprofen, for example 50 mg dexketoprofen vs. 100 mg of racemic ketoprofen provides similar analgesic efficacy with fewer and less severe adverse effects.[3,5]

When drugs are IV administered, a primary concern is venous irritation.[6] Pain and discomfort at the administration site may delay or terminate drug administration.[7] Additionally, other uncommon adverse effects such as exanthema and urticaria may occur. After parenteral dosing, rare serious complications, including Stevens Johnson's and Nicolau's syndromes, have been reported.[7]

Our previous clinical experience administering dexketoprofen to 500 patients indicated that IV administered dexketoprofen caused less injection site irritation and pain compared with racemic ketoprofen. However, data concerning the venous irritation caused by these two enantiomers are sparse. Therefore, we decided to study whether IV administered dexketoprofen causes less venous irritation than racemic ketoprofen in adults and elderly patients. The primary outcome was the incidence of moderate and severe pain at the injection site, and the secondary outcomes were the incidence and severity of injection pain, the need to terminate the infusion and reoccurrence of pain after continuing the infusion, and adverse effects.

METHODS

The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (no. 80/2011), and was conducted in accordance with the Declaration of Helsinki. The Finnish Medicines Agency was notified (no. 50/2011), and the study was recorded in the European Clinical Trials Database (EudraCT no. 2011-000566-36).

A total of 221 ASA (American Society of Anesthesiologists) physical status classification I-III patients were included in this study. Two age groups of patients were enrolled: 111 adult patients (aged 18–64 years) and 110 elderly patients (aged 65–85 years). The patients came for elective day case surgery without contraindications for ketoprofen as pain treatment. Eligible patients were provided oral and written study information, after which they provided written informed consent.

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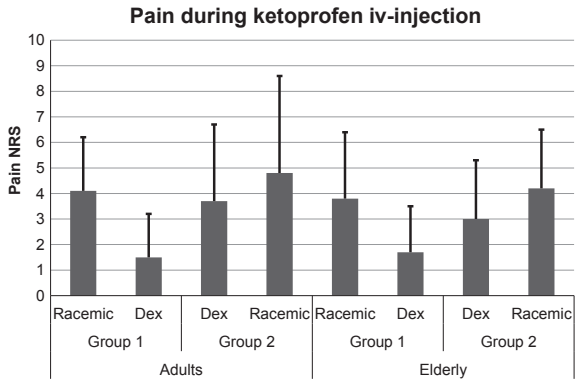

Fig. 1. Injection pain in adult (age 18–64 years) and elderly patients (age 65–85 years). In the group 1, patients (n = 54 and n = 56) received first 0·5 mg/kg racemic ketoprofen and then, at least 2 h later, 0·25 mg/kg dexketoprofen in 20 mL Na0·9 over 6-min injection, and in the group 2 (n = 56 and n = 54), patients received first dexketoprofen and then racemic ketoprofen, respectively. Data are mean and standard deviation. NRS, numerical rating scale for pain.

This study was a controlled, double-blinded, two-period, two-treatment, crossover study. The randomization sequence was computer generated (www.randomization.com), and a sealed, opaque envelop method was used to ensure blinding. A hospital pharmacist who was not participating in the care of the patients prepared the infusions; a similar infusion appearance further ensured blinding. The blinding performance was verified after each study drug infusion by asking the patient and attending nurse to assess which drug was administered. Before surgery, the patients were IV administered 0·5 mg/kg racemic ketoprofen and 0·25 mg/kg dexketoprofen after surgery (group 1) or vice versa (group 2). The study drugs were diluted in physiological saline and administered during a 6-min injection at a rate of 200 ml/h with an infusion pump. After the drug was administered, the IV cannula was flushed with 0·9% saline.

The anaesthetic method, that is general, regional or local anaesthesia, was chosen by the attending anaesthesiologists. The anaesthetic drugs were administered in a separate IV cannula than the study drugs.

During each study drug infusion, the patient was asked to rate the irritation or pain at the injection site using a four-point verbal rating scale (VRS; no, mild, moderate or severe pain/irritation) and a numerical rating scale 0–10 (NRS; 0 = no irritation/pain, 10 = most irritation/pain). If the pain or irritation at the injection site was unbearable, the study drug infusion was terminated and the duration of pain or irritation was recorded. If the pain or irritation was relieved within 5 min, the study drug infusion was continued. If the pain or irritation returned, the study drug infusion was stopped permanently. One week after surgery, the patients were contacted by phone and asked about any infusion-site-related symptoms.

Statistics

Descriptive and statistical analyses were performed using statistical software (IBM SPSS Statistics 19, Armonk, NY, USA). The results are presented as the mean and standard deviation, median, minimum and maximum, or number of cases, as appropriate. A linear mixed model was used to evaluate the effect of the drug, order of drugs and time between the study drug injections on the injection pain experienced by patients. The Pearson's chi-squared test was used to evaluate the distributions of categorical data, and the Student's t-test was used for continuous data. A P-value of 0·05 or lower was considered to be statistically significant.

RESULTS

A total of 221 were included in this study, 111 patients were 18–64 years of age and 110 were 65–85 years of age. One protocol deviation occurred; one patient in the 18- to 64-year-old age group had their drug infusion administered by hand because the infusion pump malfunctioned; the results of this patient are not included. One 62-year-old man did not have the second racemic ketoprofen injection because he had a 900 mL drainage volume after a total knee arthroplasty. The patient characteristics and types of surgery and anaesthesia used are presented in Tables 1 and 2.

Significantly less injection pain was reported after dexketoprofen administration (Fig. 1). A total of 157 of 210 patients reported pain during dexketoprofen injection and 201 of 209 patients during racemic ketoprofen injection (P = 0·001). Moderate or severe pain was reported by 43 patients (20%) during dexketoprofen injection and by 90 (41%) patients during racemic ketoprofen injection (P = 0·001). The mean of injection pain during racemic ketoprofen injection was 4·2 (SD 2·5) and was 2·5 (2·4) during dexketoprofen injection (P = 0·001). The injection pain was severe enough in 14 racemic ketoprofen patients and five dexketoprofen patients (P = 0·034) so that the patients requested a cessation of the injection. In eight cases, the patients did not tolerate the reinstitution of the racemic ketoprofen infusion, but all five dexketoprofen patients (P = 0·045, Fisher's exact test) tolerated a second injection after a 5-min pause.

In a linear mixed model that included the adult patients and all parameters, the drug itself (P = 0·001), order of drugs (P = 0·001) and time between the two injections (P = 0·002) affected the pain experienced during the test drug injection. In elderly patients, the drug (P = 0·001) and the group, that is order of drugs (P = 0·016), were significant factors for pain during the study drug injections.

No serious adverse effects were noted in the study groups. The pain caused cessation of the first study drug infusion in 11 of 211 (5%) patients and the cessation was not related to the drug (P = 0·77) (Table 3). Total of eight patients, five in group 1 and three in group 2, did not tolerate a drug infusion continuation. The drug itself and the order of drugs did not affect tolerance of the drug infusion (P = 0·55) (Table 3).

The blinding performed sufficiently. The attending nurses, blinded to the study drugs, guessed correctly the first drug injection in 61% of cases and the second injection in 70% of cases. The patients guessed the first drug injection correctly in 56% of cases and the second injection in 65% of cases.

At 1 week after surgery, two patients in group 1 and two in group 2 reported pain at the injection site. Two patients had mild pain and two had moderate pain. A total of 58 patients had haematomas at the injection site, but no inflammatory signs or symptoms were reported (Table 4).

DISCUSSION

In the present study, racemic ketoprofen caused more infusion pain or irritation than dexketoprofen. In adult patients, the drug

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Table 1. Patient characteristics in adult (aged 18–64 years) and elderly (aged 65–85 years) patients

Variable	Adult patients (aged 18–64 years) n = 110		Elderly patients (aged 65–85 years) n = 110	
	Group 1 (racemic/dexketoprofen) (n = 54)	Group 2 (dexketoprofen/racemic) (n = 56)	Group 1 (racemic/dexketoprofen) (n = 56)	Group 2 (dexketoprofen/racemic) (n = 54)
Age (years)	52 [19–64]	51 [22–64]	73 [65–84]	72 [65–84]
BMI (kg/m^2)	25·9 [21·0–45·7]	27·5 [20·6–46·6]	27·0 [18·8–40·2]	29·0 [20·1–39·8]
Sex (female/male)	35/19	36/20	31/25	36/18
ASA I/II/III	32/20/2	36/20/–	5/32/19	1/41/12

Data are median [minimum–maximum]. BMI, body mass index; ASA, American Society of Anesthesiologists Physical Status.

Table 2. Anaesthesia and surgical data

Variable	Adult patients (age 18–64 years) n = 110		Elderly patients (age 65–85 years) n = 110	
	Group 1 (racemic/dexketoprofen) (n = 54)	Group 2 (dexketoprofen/racemic) (n = 56)	Group 1 (racemic/dexketoprofen) (n = 56)	Group 2 (dexketoprofen/racemic) (n = 54)
Type of anaesthesia				
General	21	31	10	12
Regional	27	23	39	40
Local	6	2	7	2
Type of surgery				
Urologic/gynaecologic	27	25	10	16
Orthopaedic	15	15	33	31
Plastic	6	5	3	2
Gastrointestinal/inguinal	6	6	8	4
Eye, ear	–	5	2	1
Duration of surgery (hours:minutes)	00:55 [00:09–2:30]	1:05 [00:09–5:15]	1:00 [00:11–4:10]	00:57 [00:19–1:50]
Blood loss (mL)	0 [0–900]	0 [0–900]	0 [0–800]	0 [0–700]

Data are median [minimum–maximum] or number of patients

itself, order of drugs and time between drugs were factors associated with injection pain. In elderly patients, only the drug itself and order of drugs affected the pain experience. The reasons for infusion pain can be hypothesized. Racemic ketoprofen contains the (*R*)-enantiomer, which is thought to cause irritation, specifically in the gastric mucosa.[3,5] When racemic ketoprofen, a weak acid, is administered, the local concentration of ketoprofen at the infusion site is twice the amount compared with when dexketoprofen is administered; therefore, racemic ketoprofen may cause increased irritation or pain. Conversely, when dexketoprofen is administered, only the active enantiomer is present and it is at half the concentration compared with racemic ketoprofen infusions. The dexketoprofen formulation, dexketoprofen trometamol salt, is more water soluble than racemic ketoprofen arginine salt combinations;[5] therefore, the poorly water-soluble ketoprofen molecules may induce more injection pain than the well-soluble dexketoprofen molecules.

The order of drugs affected the injection pain that patients experienced. The patients in the group 1, who received racemic ketoprofen first, thought the injection pain after dexketoprofen injection was considerably less severe than after racemic ketoprofen injection. However, the group 2 patients, who received dexketoprofen first, thought the difference in pain between the injections was less considerable because the patients did not have any earlier injection pain experience to compare the pain caused by the two infusions.

The premedication used may affect the assessment of injection pain. The majority of patients were orally administered 1–2 g paracetamol. Two of 110 patients in group 1 and four of 111 patients in group 2 were only administered diazepam as a premedication. In group 1, pregabalin was administered to one patient and oxycodone–naloxone was administered to two patients. In group 2, no patients received pregabalin and oxycodone–naloxone was administered to two patients. The premedication was determined by the attending anaesthesiologist, and the study protocol did not have any specifications for premedication. There were no differences in premedication between the study groups and the effect of premedication was negligible.

The blinding of the order of study drugs was successful. Only 62% of nurses attending the patients correctly guessed the infused

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Table 3. Pain and tolerance of the study drug infusions in adult (18–64 years) and elderly (65–85 years) patients

	Adult patients (age 18–64 years) n = 110		Elderly patients (age 65–85 years) n = 110	
Variable	Group 1	Group 2	Group 1	Group 2
First drug infusion	Racemic (n = 54)	Dexketoprofen (n = 56)	Racemic (n = 56)	Dexketoprofen (n = 54)
Pain yes/no	52/2	47/9	50/6	46/8
Pain (NRS)	4 [0–8]	3 [0–10]	3 [0–9]	3 [0–7]
Cessation	2	5	4	0
Resume not tolerated	1	3	4	NA
Second drug infusion	Dexketoprofen (n = 54)	Racemic (n = 55)	Dexketoprofen (n = 56)	Racemic (n = 54)
Pain yes/no	31/23	49/6	33/23	50/4
Pain (NRS)	1 [0–5]	5 [0–10]	1 [0–7]	4 [0–9]
Cessation	0	8	0	0
Resume not tolerated	NA	3	NA	NA

Data are median [minimum–maximum] or number of patients. NRS, numerical rating scale for pain.

Table 4. Post-operative symptoms at 1 week after surgery in adult (18–64 years) and elderly (65–85 years) patients

Variable	Group 1 (racemic/dexketoprofen) (n = 110)	Group 2 (dexketoprofen/racemic) (n = 110)
Haematoma at the injection site (yes/no/missing data)	30/77/3	28/82/–
Inflammation at the injection site (yes/no/missing data)	–/107/3	1/109/–
Post-operative pain		
No	42	42
Mild	48	47
Moderate	16	17
Severe	1	4
Data missing	3	1
Post-operative pain NRS	2 [0–9]	2 [0–8]

Data are presented as number of patients or median and [minimum–maximum]. NRS, Numerical rating scale.

drug. Correspondingly, 56% of patients correctly guessed which drug was administered first. During the second drug infusion, the amount of correct answers increased; 71% of nurses and 65% of patients correctly guessed the drug administered.

In the present study, the gender or infusion site did not affect the pain experienced during the study drug infusion. Data concerning venous injection pain are sparse; however, when hypertonic saline intramuscular injection was studied, females experienced more pain and pain in a larger area than males.[8] In a study examining post-operative pain in Finnish patients, it was revealed that females had more pain than males after heterogeneous types of surgery.[9] The site of infusion did not affect pain during the study drug infusions. This is contradictory when compared with propofol, which is an anaesthetic agent that causes significant injection pain in 60% of patients. When propofol is injected, more pain is experienced if the injection is in the peripheral veins of the hand than in the antecubital veins of the arms.[10] The reason for this phenomenon may be the greater size of the veins and a shorter exposure period to propofol. It would have been interesting to compare propofol-induced injection pain to racemic ketoprofen and dexketoprofen injection pain. Initially, this was planned in the present study, but the Finnish Medicines Agency declined this portion of the study plan.

Infusion pain is an important factor when drug feasibility is considered. Compliance to drug therapy increases if drug administration does not cause pain or inconvenience. Intramuscular injections are not used in children because the injection pain may be severe and unpleasant, causing the children to tolerate the pain rather than receive repeated injections.[11] Our clinical experience using dexketoprofen in paediatric patients has been positive. Particularly in children, the use of dexketoprofen should be advocated to provide convenient pain-free treatment of acute pain. Proper drug formulations should be used to ensure adequate pain treatment in all age groups.

WHAT IS NEW AND CONCLUSION

In conclusion, the present study demonstrated that dexketoprofen caused less infusion pain or local irritation; therefore, dexketoprofen may be preferred to the racemic formulation for intravenous NSAID pain management. However, neither dexketoprofen nor racemic ketoprofen infusion caused any long-term adverse effects at the injection site.

CONFLICT OF INTEREST

No conflict of interests have been declared.

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