

A prospective, randomised clinical trial comparing oral diclofenac potassium and intramuscular diclofenac sodium in acute pain relief

一個比較口服雙氯芬酸鉀與肌肉注射雙氯芬酸鈉對減輕急性痛楚的前瞻性隨機化臨床試驗

MK Ho 何文錦 and CH Chung 鍾展鴻

Objectives: To compare the efficacy of oral (PO) diclofenac potassium (Cataflam®) and intramuscular (IM) diclofenac sodium (Voltaren®) in acute pain relief, with a hypothesis of equivalence between the two. **Patients and methods:** In this prospective randomised single center clinical study, adult Chinese patients attending the emergency department and suffering from renal colic, acute musculoskeletal injury or arthritis were enrolled. They were randomly assigned either 75 mg of IM Voltaren® or 75 mg of PO Cataflam®. Pain was assessed by the Visual Analogue Scale (VAS) and evaluations were performed at baseline, 30 minutes, 1 hour and 2 hours after treatment. Blood pressure, pulse rate and respiratory rate were also recorded at similar time intervals. **Results:** We recruited 46 cases in the Voltaren® group and 45 cases in the Cataflam® group. Both treatment groups showed statistically highly significant reduction ($P < 0.0001$) in pain VAS, systolic blood pressure and pulse rate compared with the baseline. Voltaren® was statistically more effective in pain relief at 30 minutes ($P = 0.012$) and 1 hour ($P = 0.010$) but not at 2 hours ($P = 0.311$) compared with Cataflam®. The changes in blood pressure, pulse rate and respiratory rate were not statistically significant between the two treatment groups at all time points. **Conclusion:** IM Voltaren® was more effective in acute pain relief compared with PO Cataflam®. (*Hong Kong j.emerg.med.* 2004;11:69-77)

目的：比較口服雙氯芬酸鉀(確特快®)與肌肉注射雙氯芬酸鈉(服他靈®)對減輕急性痛楚的功效，假設兩者效力相等。病者及方法：這是一個前瞻性隨機化單一醫療中心的臨床研究，招募因腎絞痛、急性肌肉骨骼受傷或關節炎到急症室求診之華裔成年病者。他們被隨機化分派接受 75 毫克肌肉注射「服他靈®」或口服 75 毫克「確特快®」。以視覺化模擬比例尺於開始時，用藥後三十分鐘、一小時及二小時評估痛楚的程度，並同時記錄各時段的血壓、脈搏率和呼吸率。結果：共招募了 46 名病者於「服他靈®」組及 45 名病者於「確特快®」組，兩組病者用藥後，對於減輕痛楚，收縮壓及脈搏率均顯示比開始時有統計學上高顯著性的改善 ($P < 0.0001$)。「服他靈®」止痛功效於用藥三十分鐘 ($P = 0.012$) 及一小時後 ($P = 0.010$) 在統計學上是比「確特快®」強，但於用藥後二小時則沒有差別 ($P = 0.311$)。在所有時段，兩組的血壓、脈搏率及呼吸率的變化，均沒有統計學上顯著性之差別。結論：在減輕急性痛楚方面，肌肉注射「服他靈®」比口服「確特快®」為有效。

Keywords: Analgesia, non-steroidal anti-inflammatory agents, pain measurement, urinary calculi, wounds and injuries

關鍵詞：止痛、非類固醇抗炎藥、量度痛楚、尿結石、傷口及創傷

Correspondence to:

Ho Man Kam, MBChB(CUHK), MRCP(UK), MRCSED
North District Hospital, Accident and Emergency Department,
9 Po Kin Road, Sheung Shui, New Territories, Hong Kong
Email: homk@netvigator.com

Chung Chin Hung, FRCS(Glasg), FHKAM(Surgery), FHKAM(Emergency
Medicine)

Introduction

Diclofenac, a non-steroidal anti-inflammatory drug (NSAID), acts by inhibiting cyclo-oxygenase and lipoxygenase pathways. It is widely used for acute pain relief because of its analgesic and anti-inflammatory

properties.¹⁻³ It is superior to narcotic analgesics because it does not cause respiratory depression, physical dependence, sedation or psychomotor effect.

In patients with renal colic, various clinical trials have demonstrated that NSAID are at least comparable to and frequently superior to many narcotics and spasmolytic combinations.⁴⁻¹¹ For patients with musculoskeletal pain such as back pain, soft tissue injury, joint injury and arthritis, NSAID have also been shown to be effective and well tolerated analgesics.¹²⁻²⁶ However, there is no international standard on the route of NSAID use; both parenteral and oral (PO) routes are used for acute pain relief.

It is widely believed in the local Chinese population that intramuscular (IM) injection of analgesic is superior to other routes of administration because of rapid onset of action and more potent analgesic effect. Thus IM Voltaren[®] has become one of the most commonly used NSAID in our Accident & Emergency (A&E) Department for acute pain relief in patients with renal colic, musculoskeletal injury and arthritis. One local study in A&E departments showed that the use of IM NSAID might be excessive.²⁷

Nevertheless, there is rarely any absolute indication for the use of NSAID through the IM route. Besides, pharmacokinetic and pharmacodynamic studies²⁸⁻⁴¹ only showed equivocal evidence concerning the superior effect of IM versus PO route.

In addition, it is not uncommon to encounter reports of adverse effects of IM injection in the medical literature. A review of 10,167 cases of IM diclofenac showed an incidence of six abscesses (0.05%), three necrosis (0.02%) and pain (5.6%) at the injection site.⁴² The complications due to IM diclofenac in literature review ranged from mild local reaction to severe fatal reaction: erythema and fever, neurogenic pain, streptococcal myositis, muscle damage, tissue necrosis and the Nicolau syndrome, ischaemic stroke, hypoxic brain damage, anaphylactic shock, and even death.⁴³⁻⁵⁷

Furthermore, the difference in cost may be a big concern in view of tight budgets in this cost-conscious era. The cost of a Voltaren[®] injection in the Hospital

Authority is around \$7.5 compared with the oral preparation Cataflam[®] which is around \$3 for the same dosage. Thus the shift of administration of NSAID from IM to PO route may reduce drug expenditure. Therefore many authors^{43,46,50-55} advocated the use of alternative routes of diclofenac administration instead of the IM route.

Diclofenac potassium (Cataflam[®]), the only available fast acting NSAID in our department, has been shown to be rapidly and completely absorbed in the gastrointestinal tract with measurable plasma levels in some subjects within 10 minutes of dosing. Peak plasma level is achieved in 20 minutes to 2 hours. The onset of absorption of Cataflam[®] is much faster than enteric coated diclofenac sodium. Less than 10% of all subjects treated with enteric coated diclofenac reach measurable plasma level within 15 minutes compared with 95% after treatment with Cataflam[®] (Ciba-Geigy, information on file). Marzo et al³⁴ demonstrated that Cataflam[®] was rapidly absorbed and useful for quick relief of pain. Therefore, it is an alternative drug of choice for rapid pain relief.

To date, no studies have been documented in the literature comparing the efficacy of PO versus IM diclofenac for acute pain relief. Therefore, we designed a prospective randomised clinical trial to compare the efficacy of Cataflam[®] and Voltaren[®] for acute pain relief and in an attempt to show equivalence.

Study design and method

This was a single centre, prospective randomised clinical trial performed at the A&E Department of North District Hospital under the supervision of the investigators.

Patients enrolled in the study were Chinese adults aged above 18 years and of either sex, who attended the A&E Department of North District Hospital during the scheduled study period from September 2002 to May 2003, and who were mentally fit for consent and pain score assessment. The inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and Exclusion criteria of the study**Inclusion criteria for patient enrollment**

Patient with either one of the following diagnoses: -

- Acute renal colic: -
 - i) Compatible clinical signs and symptoms and urine analysis; or
 - ii) Confirmed presence of stone by visualisation of compatible opacities in abdominal radiography or ultrasonography.
- Acute painful musculoskeletal injury: sprain or contusion.
- Acute painful arthritis including gouty arthritis.

Plus the following conditions: -

- The baseline Visual Analogue Scale (VAS) must be >25 mm on a 100 mm divided line.
- The condition as judged by the attending doctor according to his usual practice that rapid pain relief was required.

Exclusion criteria for patient enrollment

- <18 years old.
- Known allergic history to diclofenac or any NSAID.
- History of gastrointestinal bleeding or peptic ulcer.
- History of asthma.
- History of renal failure.
- Patient on anticoagulant or with history of bleeding tendency.
- Pregnant or lactating mother.
- Contraindications for oral medication.
- Immediate admission required for further management.
- Concomitant treatment of diclofenac during the previous 24 hours.
- Skeletal fracture or joint dislocation.
- Septic arthritis or joint effusion.

Those eligible patients would be informed about the study and invited to participate in the study after detailed and clear explanation about the study had been provided. Time was allowed for consideration before giving informed written consent.

An assigned nursing staff who was not involved in the trial performed randomisation. Patients enrolled into the study would be stratified into four groups before randomisation: clinical renal colic, confirmed renal colic, acute musculoskeletal injury, acute arthritis or gout. The patients were then further stratified into subgroups of male or female and case numbers were assigned consecutively. Block randomisation was used in each of the eight subgroups to assign the treatment regimen for each case number. It was written inside a sealed envelop with corresponding case number in the cover. Patients enrolled in each subgroup would receive consecutive case numbers and receive either treatment.

No change in treatment regimen was allowed once the patient was enrolled into the study.

The patients were randomly allocated to one of the two treatment regimens: 75 mg IM Voltaren®, the reference treatment, or 75 mg PO Cataflam®, the study treatment. All data were recorded in a separate case report form for each patient with patient gum label affixed. Baseline demographic data including name, age, sex, date of attendance, inclusion criteria met and duration of pain experienced were recorded.

The primary end-point of the study was the extent of pain relief by the two treatment regimens. Patients enrolled were requested to assess the pain intensity by using Visual Analogue Scale (VAS) on a 100 mm divided line with point 0 indicating no pain and point 10 as maximal pain. They had to score at different time intervals at baseline, 30 minutes, 1 hour and

2 hours after treatment in four separate sheets. This was to reduce bias by avoiding reference to previous assessment. Secondary clinical variables including blood pressure, respiratory and pulse rates were also recorded at baseline, 30 minutes, 1 hour and 2 hours after administration of the medications.

The study ended after the pain assessment at 2 hours after treatment. The patient was then assessed by the attending doctor for the need of rescue narcotic analgesic if sufficient pain relief had not been achieved. The decision on subsequent management would depend on the usual practice and judgement of the attending doctor. The patient acceptance of the treatment and the final outcome of the patients were also noted at the end of the study.

Adverse effects to treatment either locally to IM injection or systemic effects reported by patients were recorded. In patients who developed allergic reaction to diclofenac, the protocol treatment would be terminated immediately irrespective of the severity of the allergic reaction and the attending doctor would treat the patients as appropriate.

Statistical methodology

The SPSS version 10.0 software programme was used for statistical analysis. The data was entered into the computer in spreadsheet format by the investigators for analysis. The homogeneity of the baseline descriptive variables of the two treatment groups was compared by Student's t-test for continuous variable and Chi-square test for discrete variables. Analysis of change in pain intensity on VAS at different time intervals after treatment, compared with the baseline, was performed by Student's t-test and ANOVA. Subgroup analysis was performed by Kruskal-Wallis test. The within group and between group differences were analysed and compared. In addition, 95% confidence intervals on between group differences in proportion to pain relief were estimated.

Ethical consideration, consent and confidentiality

Approval had been given by the Ethics Committee of New Territories North Cluster for conducting this clinical trial. A written consent was obtained from each patient before the start of the study. Those who were

not willing to participate would be treated as normal routine without penalty or delay in treatment. All information of the participants would be kept confidential and would be accessed by the investigators only.

Results

We recruited a total of ninety-one cases into the study from September 2002 to May 2003. There were 46 cases in the IM Voltaren® treatment group and 45 cases in the Cataflam® treatment group. The number of cases in each subgroup is shown in Table 2. The demographic data with regards to sex (Pearson Chi-square=0.231), age, pain duration before attending the A&E Department and baseline outcome variables were comparable in both treatment groups (Table 3).

Following the administration of treatment, both groups showed highly statistically significant reduction ($P<0.0001$) in pain VAS with time compared with baseline (Table 4, Figure 1). The change in systolic blood pressure and pulse rate with time as compared with baseline also showed highly statistically significant reduction ($P<0.0001$) in both treatment groups. In the between group analysis, there were statistically significant differences in 30 minutes ($P=0.012$) and 1 hour ($P=0.010$) pain VAS between IM Voltaren® and PO Cataflam® treatment groups. However, there was no statistically significant difference in baseline ($P=0.396$) and 2 hours ($P=0.311$) pain VAS between the treatment groups (Table 5, Figure 2). Similar statistically significant

Table 2. Number of cases in each treatment group

		IM Voltaren®	PO Cataflam®
Clinical renal colic	M	4	6
	F	0	2
Confirmed renal colic	M	5	2
	F	0	2
Musculoskeletal injury	M	14	10
	F	8	8
Arthritis	M	11	10
	F	4	5
Total		46	45
M: F		2.83: 1	1.65: 1

Table 3. Demographics and baseline outcome variables of the treatment groups

	IM Voltaren® Mean (SD)	PO Cataflam® Mean (SD)	P value* (95% CI of difference)
Age	53.196 (16.26)	52.12 (14.01)	0.734 (-5.24, 7.41)
Pain duration	30.65 (31.91)	32.87 (31.13)	0.738 (-15.4, 10.92)
Baseline VAS	77.94 (19.19)	81.02 (15.06)	0.396 (-10.23, 4.11)
Baseline SBP	146.87 (25.14)	147.49 (26.53)	0.909 (-11.38, 10.14)
Baseline DBP	80.39 (14.75)	79.91 (13.47)	0.872 (-5.41, 6.34)
Baseline PR	78.696 (14.51)	79.78 (12.37)	0.703 (-6.71, 4.54)
Baseline RR	18.22 (2.61)	17.53 (2.28)	0.187 (-3.4, 1.71)

VAS=visual analogue scale; SBP=systolic blood pressure (mmHg); DBP=diastolic blood pressure (mmHg); PR=pulse rate (beats per min); RR=respiratory rate (breaths per min).

*Independent t-test

Table 4. Reduction in pain VAS with time in the treatment groups

Time interval	IM Voltaren®		PO Cataflam®	
	Mean (SD)	95% CI of difference	Mean (SD)	95% CI of difference
Baseline - 30 minutes VAS	26.83 (18.25)*	21.41, 32.24	18.93 (19.02)*	13.22, 24.65
Baseline - 1 hour VAS	38.69 (24.73)*	31.35, 46.04	28.67(22.96)*	21.78, 35.56
Baseline - 2 hours VAS	46.44 (25.47)*	38.87, 54.00	44.22 (25.98)*	36.42, 52.03

*Paired t-test: P< 0.0001

Table 5. Between group differences in pain VAS at different time points for the treatment groups

Time point		Mean (SD)	Mean difference (P value)*	95% CI of the difference
Baseline VAS	IM Voltaren®	77.94 (19.19)	-3.09 (0.396)	-10.28, 4.12
	PO Cataflam®	81.02 (15.06)		
30 minutes VAS	IM Voltaren®	51.11 (18.36)	-10.98 (0.012)†	-19.53, -2.43
	PO Cataflam®	62.09 (22.41)		
1 hour VAS	IM Voltaren®	39.24 (24.19)	-13.12 (0.010)†	-23.03, -3.20
	PO Cataflam®	52.36 (23.4)		
2 hours VAS	IM Voltaren®	31.50 (25.55)	-5.30 (0.311)	-15.629, 5.029
	PO Cataflam®	36.8 (23.99)		

*Independent t-test; †Statistically significant

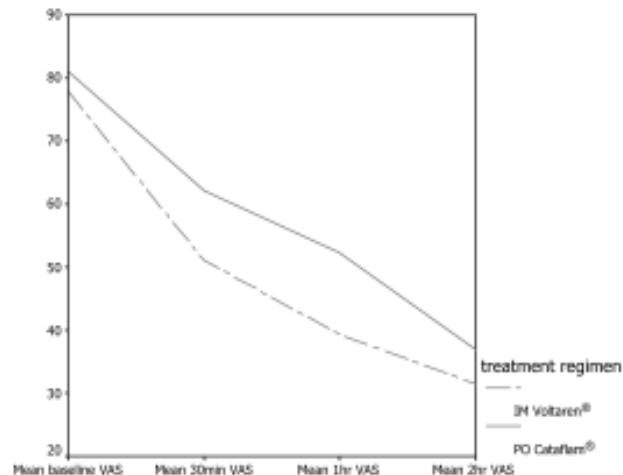


Figure 1. Change in pain VAS with time in the treatment groups.

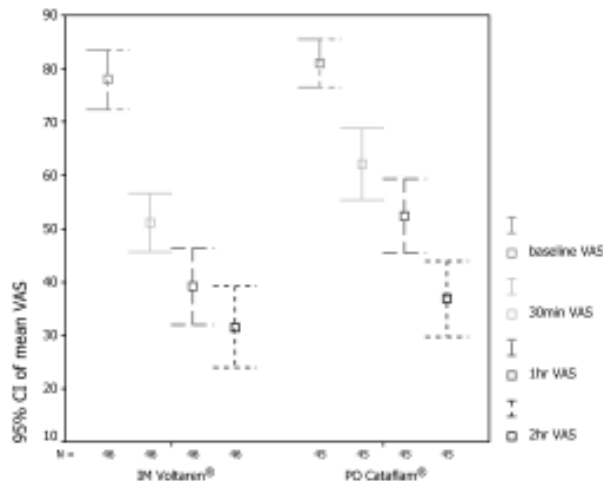


Figure 2. 95% CI of mean VAS at different time points for the treatment groups.

difference between the two treatment groups in overall pain VAS with time was also demonstrated by Repeat Measure ANOVA analysis ($P=0.033$). However, the changes in blood pressure, pulse rate and respiratory rate with time compared with baseline between the two treatment groups were not statistically significant at all time points.

Subgroup analysis was performed by Kruskal-Wallis non-parametric test because of small sample size in each subgroup. It showed statistically significant difference in 1 hour pain VAS between IM Voltaren® and PO Cataflam® treated groups for those patients with confirmed renal colic ($P=0.041$) and arthritis ($P=0.038$). There was no statistically significant difference in the baseline, 30 minutes and 2 hours pain VAS between the treatment groups in all subgroups of patients. The changes in pain VAS with time for subgroups of patients in the two treatment groups were shown in Figures 3 and 4.

There was no adverse effect noticed in both treatment groups. Three patients in the IM Voltaren® treatment group needed rescue analgesic compared with two in the PO Cataflam® treatment group. All patients were discharged with pain relief after treatment except one in the IM Voltaren® treatment group who was admitted into hospital because of chest pain which was not related to the treatment received. More patients in the IM Voltaren® treatment group rated the acceptance of treatment as satisfactory or good (Table 6).

Discussion

In our locality, renal colic, acute musculoskeletal injury and arthritis are common painful conditions requiring IM NSAID in the A&E Department. With conflicting evidences for the superior effect of IM NSAID, its excessive use may not be justified.²⁵ Superiva et al⁴ compared piroxicam fast-dissolving dosage form (FDDF) versus IM diclofenac sodium in the treatment of acute renal colic. He concluded that piroxicam FDDF was as effective as parenteral diclofenac. Therefore, with the development of fast absorption oral NSAID, it may be possible to change

our practice of using IM NSAID. Cataflam® was the only available fast acting NSAID in our department, and had been claimed to be rapidly and completely absorbed and useful for quick relief of pain.^{33,34} It had become an alternative drug of choice for rapid pain relief.

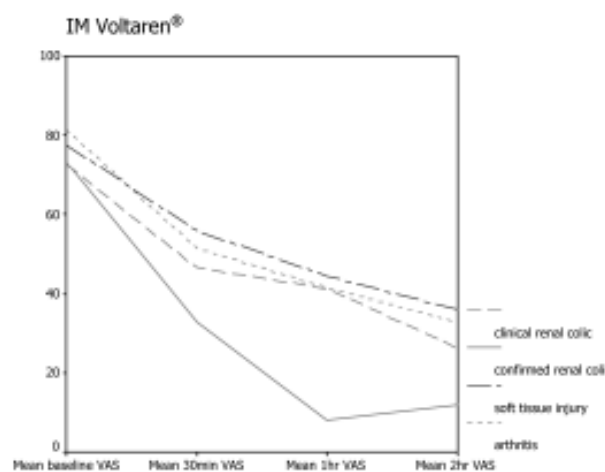


Figure 3. Change in pain VAS with time for subgroups of patients treated with IM Voltaren®.

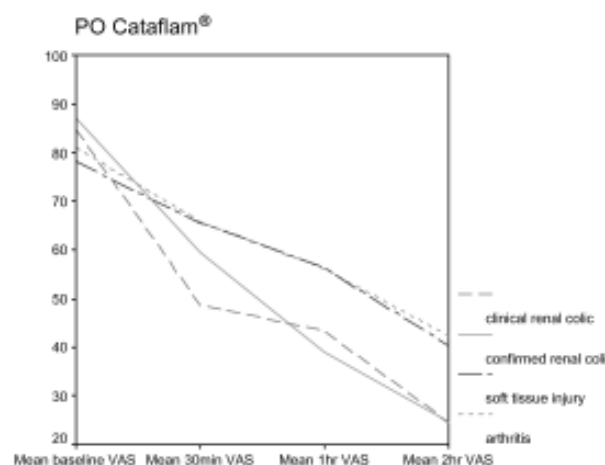


Figure 4. Change in pain VAS with time for subgroups of patients treated with PO Cataflam®.

Table 6. Patient acceptance of treatment for the treatment groups

Patient rating	IM Voltaren®	PO Cataflam®
Poor	2.2%	0%
Fair	8.7%	22.2%
Satisfactory	34.8%	33.3%
Good	41.3%	33.3%
Excellent	13.0%	11.2%

This study showed that either Voltaren® or Cataflam® was effective for pain relief with time. ($P < 0.0001$) This was consistent with the results of other studies for patients with renal colic,⁴⁻¹¹ musculoskeletal injuries,¹⁴⁻²¹ and arthritis.^{25,26} Systolic blood pressure and pulse rate, which would be influenced by the stress of pain, also showed statistically significant reduction with time. ($P < 0.0001$) However, the between group analysis demonstrated that there was statistically significant difference in pain VAS at 30 minutes ($P = 0.012$) and 1 hour ($P = 0.010$) between the two treatment groups. Thus, IM Voltaren® was more effective than PO Cataflam® for rapid pain relief. The difference might be due to the fact that absorption of Cataflam® in the early phase (within an hour) was not fast enough compared with IM Voltaren®. Therefore, relief of pain was less adequate at 30 minutes and 1 hour, probably a result of inadequate plasma level of the drug. Nevertheless, once peak plasma level was achieved, the analgesic effect at 2 hours became similar. In subgroup analysis, the better pain relief for confirmed renal colic ($P = 0.041$) and arthritis ($P = 0.038$) at 1 hour in IM Voltaren® treated groups might be related to the underlying pathophysiology of the painful conditions and absorption of drug. Adequate pain relief can be achieved once sufficient plasma level of NSAID is present to block the cyclo-oxygenase and lipoxygenase pathways. As the absorption of IM Voltaren® might be faster in the early phase, pain reduction at 1 hour was better in those patients with confirmed renal colic and arthritis. In addition, the usual oral dosage of Cataflam® recommended by the drug company was 50 mg instead of 75 mg. Therefore, we would expect an even more significant difference in pain relief between the two treatment groups if a lower dosage of Cataflam® was used.

One of the main limitations in this study was the small sample size in each subgroup. It seriously affected the statistical power in subgroup analysis and control for confounding factors like sex. The original estimated sample size for each treatment group was 102 if we assume the minimum difference of practical interest (equivalence limit) was 0.15.^{58,59} Nevertheless, when the subgroups were combined for analysis, we were able to show statistically significant difference between the two treatment groups in this study. Thus it might be justified to prematurely terminate the study despite

the small sample size achieved. Another limitation was the absence of placebo control in this study. The design of the study was a practicality study in an attempt to show the equivalence of Cataflam® to Voltaren® in rapid pain relief. The negative conclusion in this study indicated that IM Voltaren® was significantly better than PO Cataflam®. The placebo effect of IM injection was excluded in previous studies comparing IM Voltaren® with IM placebo.^{10,11} There was no previous trial comparing the effect of PO NSAID and IM placebo in literature search. Therefore, another trial would be needed to exclude placebo effect in order to confirm the equivalence. Limitation on possible bias in interpretation of pain intensity by VAS had been assessed. Measures like clear explanation on the use of VAS, addition of cartoon picture in the VAS line to help interpretation and avoiding reference to previous VAS score were undertaken to reduce bias.

Patients requesting rapid pain relief expect symptom relief within a short time and early discharge. Our negative study result showed that the analgesic effect of Cataflam® was not equivalent to Voltaren® in the early phase. Therefore, unless a new fast absorbing oral NSAID is available and confirmed by trials to have equivalent effect, we are unable to discourage our practice of using IM NSAID for rapid pain relief.

Conclusion

IM Voltaren® is more effective than PO Cataflam® for rapid pain relief in patients suffering from renal colic and arthritis.

Declaration of conflict of interest

The authors declared no conflicts of interest or sources of funding.

Acknowledgement

We would like to thank all staff of the A&E Department for their help in conducting this study. We are also grateful to Professor Benny Zee of The

Chinese University of Hong Kong for his valuable advice and help to complete the study.

References

- Skoutakis VA, Carter CA, Mickle TR, et al. Review of diclofenac and evaluation of its place in therapy as a nonsteroidal antiinflammatory agent. *Drug Intell Clin Pharm* 1988;22(11):850-9.
- Babic-Naglic D. Voltaren – the gold standard. *Reumatizam* 2000;47(2):29-31.
- Kantor TG. Use of diclofenac in analgesia. *Am J Med* 1986;80(4B):64-9.
- Supervia A, Pedro-Botet J, Nogues X, et al. Piroxicam fast-dissolving dosage form vs diclofenac sodium in the treatment of acute renal colic: a double-blind controlled trial. *Br J Urol* 1998;81(1):27-30.
- Mackway J. Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. *Emerg Med J* 2001;18:462-70.
- Stein A, Ben Dov D, Finkel B, Mecz Y, Kitzes R, Lurie A. Single-dose intramuscular ketorolac versus diclofenac for pain management in renal colic. *Am J Emerg Med* 1996;14(4):385-7.
- Laerum E, Ommundsen OE, Gronseth JE, Christiansen A, Fagertun HE. Intramuscular diclofenac versus intravenous indomethacin in the treatment of acute renal colic. *Eur Urol* 1996;30(3):358-62.
- Al-Waili NS, Saloom KY. Intramuscular piroxicam versus intramuscular diclofenac sodium in the treatment of acute renal colic: double-blind study. *Eur J Med Res* 1999;4(1):23-6.
- Cohen E, Hafner R, Rotenberg Z, Fadilla M, Garty M. Comparison of ketorolac and diclofenac in the treatment of renal colic. *Eur J Clin Pharmacol* 1998; 54(6):455-8.
- Lundstam S, Wahlander L, Kral JG. Treatment of ureteral colic by prostaglandin synthetase inhibition with diclofenac sodium. *Curr Ther Res* 1980;28(3 I): 355-8.
- Vignoni A, Fierro A, Moreschini G, et al. Diclofenac sodium in ureteral colic: a double-blind comparison trial with placebo. *J Int Med Res* 1983;11(5):303-7.
- Simon L. Low back pain. *Eur J Rheumatol Inflamm* 1987;8(1):65-7.
- van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2000;(2): CD000396.
- Ng P, Kam CW, Yau HH. A comparison of ketoprofen and diclofenac for acute musculoskeletal pain relief: a prospective randomized clinical trial. *Hong Kong J Emerg Med* 2001;8(2):73-7.
- Moran M. Double-blind comparison of diclofenac potassium, ibuprofen and placebo in the treatment of ankle sprains. *J Int Med Res* 1991;19(2):121-30.
- Hoogewijs J, Diltoer MW, Hubloue I, et al. A prospective, open, single blind, randomized study comparing four analgesics in the treatment of peripheral injury in the emergency department. *Eur J Emerg Med* 2000;7(2):119-23.
- Bahamonde LA, Saavedra H. Comparison of the analgesic and anti-inflammatory effects of diclofenac potassium versus piroxicam versus placebo in ankle sprain patients. *J Int Med Res* 1990;18(2):104-11.
- Verstraeten A, Bakshi R. Diclofenac potassium for the treatment of traumatic joint distortions: an open multicentre study. *J Int Med Res* 1991;19(2):165-70.
- Bakshi R, Rotman H, Shaw M, Sussman H. Double-blind, multicenter evaluation of the efficacy and tolerability of diclofenac dispersible in the treatment of acute soft-tissue injuries. *Clin Ther* 1995;17(1):30-7.
- Colombo G, Giombini A, Pamich T, Peruzzi E, Pisati R. Diclofenac dispersible provides superior analgesia with faster onset of action compared to naproxen granular in patients with acute, painful, minor sports injuries. *J Sports Med Phys Fitness* 1997;37(3):228-33.
- Moran M. An observer-blind comparison of diclofenac potassium, piroxicam and placebo in the treatment of ankle sprains. *Curr Med Res Opin* 1990;12(4):268-74.
- Green S, Buchbinder R, Glazier R, Forbes A. Interventions for shoulder pain. *Cochrane Database Syst Rev* 2000;(2):CD001156.
- Green S, Buchbinder R, Barnsley L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database Syst Rev* 2002;(2):CD003686.
- Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. *Drugs* 1980;20(1):24-48.
- Shaikh KA, Ali M, Sharafatullah T. Comparative study of diclofenac sodium and flurbiprofen in osteoarthritis. *J Pak Med Assoc* 1996;46(12):270-2.
- McKenna F, Borenstein D, Wendt H, Wallemark C, Lefkowitz JB, Geis GS. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. *Scand J Rheumatol* 2001;30(1):11-8.
- Chung CH. A review on the use of injectable nonsteroidal anti-inflammatory drugs in local accident & emergency practice. *Hong Kong J Emerg Med* 2002; 9(2):65-71.
- Kurowski M. Pharmacokinetics and biological availability of diclofenac preparations following intramuscular injection of 75 mg and oral administration of 150 mg of active drug. *Z Rheumatol* 1988;47(1):37-42.
- Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arzneimittelforschung* 2001;51(11):885-90.
- Willis JV, Kendall MJ, Flinn RM, Thornhill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur J Clin Pharmacol* 1979;16(6):405-10.

31. Pinto Pereira LM, Chen D, Clement Y, Simeon D. Analgesic effects of diclofenac suppository and injection after preoperative administration. *Int J Clin Pharmacol Res* 1999;19(2):47-51.
32. Lotsch J, Kettenmann B, Renner B, et al. Population pharmacokinetics of fast release oral diclofenac in healthy volunteers: relation to pharmacodynamics in an experimental pain model. *Pharm Res* 2000;17(1):77-84.
33. Silva LC, Simoes IG, Lerner FE, Belem GR, de Moraes ME, de Nucci G. Comparative bioavailability of two different diclofenac formulations in healthy volunteers. *Arzneimittelforschung* 1999;49(11):920-4.
34. Marzo A, Dal Bo L, Verga F, et al. Pharmacokinetics of diclofenac after oral administration of its potassium salt in sachet and tablet formulations. *Arzneimittelforschung* 2000;50(1):43-7.
35. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997;33(3):184-213.
36. Mustofa M, Suryawati S, Dwiprahasto I, Santoso B. The relative bioavailability of diclofenac with respect to time of administration. *Br J Clin Pharmacol* 1991;32(2):246-7.
37. Willis JV, Kendall MJ, Jack DB. The influence of food on the absorption of diclofenac after single and multiple oral doses. *Eur J Clin Pharmacol* 1981;19(1):33-7.
38. Scholer DW, Ku EC, Boettcher I, Schweizer A. Pharmacology of diclofenac sodium. *Am J Med* 1986;80(4B):34-8.
39. Small RE. Diclofenac sodium. *Clin Pharm* 1989;8(8):545-58.
40. Todd PA, Sorkin EM. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1988;35(3):244-85.
41. Lockey AS. Emergency department drug therapy for status epilepticus in adults. *Emerg Med J* 2002;19(2):96-100.
42. Serratrice G. Study of diclofenac injectable. *Tribune Medicine* 1982;46:43-8.
43. Ali MT, Mathias IM. Continued problems with diclofenac injections. *Anaesthesia* 1991;46(12):1089-90.
44. Barrett PJ, Fayle R. Complications following intramuscular diclofenac. *Anaesthesia* 1992;47(1):83-4.
45. Tweedie DG. Unusual reaction to diclofenac. *Anaesthesia* 1989;44(11):932.
46. Schaad HJ, Zurcher RM. Erythema and fever after diclofenac i.m. *Ther Umsch* 1998;55(9):586-8.
47. Horowitz SH. Iatrogenic causalgia. Classification, clinical findings, and legal ramifications. *Arch Neurol* 1984;41(8):821-4.
48. de Courcy JG, Nicholls BJ. Neurogenic pain associated with diclofenac injection. *Anaesthesia* 1993;48(5):455.
49. Power I. Muscle damage with diclofenac injections. *Anaesthesia* 1992;47(5):451.
50. Pillans PI, O'Connor N. Tissue necrosis and necrotizing fasciitis after intramuscular administration of diclofenac. *Ann Pharmacother* 1995;29(3):264-6.
51. Stricker BH, van Kasteren BJ. Diclofenac-induced isolated myonecrosis and the Nicolau syndrome. *Ann Intern Med* 1992;117(12):1058.
52. Rygnestad T, Kvam AM. Streptococcal myositis and tissue necrosis with intramuscular administration of diclofenac (Voltaren). *Acta Anaesthesiol Scand* 1995;39(8):1128-30.
53. Giovannetti M, Machado MA, Borrelli Junior M, Ikejiri CI, Alonso N, Branco PD. Tissue necrosis: a side effect of sodium diclofenac: report of cases and discussion of the physiopathology. *Rev Hosp Clin Fac Med Sao Paulo* 1993;48(1):39-42.
54. Kornowski R, Pines A, Levo Y. Ischemic stroke following an intramuscular injection of diclofenac. Case report. *Angiology* 1995;46(12):1145-7.
55. Schabitz WR, Berger C, Knauth M, Meinck HM, Steiner T. Hypoxic brain damage after intramuscular self-injection of diclofenac for acute back pain. *Eur J Anaesthesiol* 2001;18(11):763-5.
56. Alkhawajah AM, Eifawal M, Mahmoud SF. Fatal anaphylactic reaction to diclofenac. *Forensic Sci Int* 1993;60(1-2):107-10.
57. Kortelainen ML, Sarkioja T. Fatal complications of intramuscular and intra-articular injections. *Z Rechtsmed* 1990;103(7):547-54.
58. Blackwelder WC, Chang MA. Sample size graphs for "proving the null hypothesis". *Control Clin Trials* 1984;5(2):97-105.
59. Tu DS. Two one-sided tests procedures in establishing therapeutic equivalence with binary clinical endpoints: fixed sample performances and sample size determination. *J Statist Comput Simul* 1997;59:271-90.