

## The use of injectable nonsteroidal anti-inflammatory drugs in local accident & emergency practice

CH Chung

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**Objective:** To review the utilization of injectable NSAID in local A&E practice. **Materials and Methods:** NSAID utilization data, in relation to type and specialty, were retrieved through the hospital and central pharmacy computer systems of the Hospital Authority. **Results:** A&E departments were the main users of injectable NSAID. Their expenditure exceeded other forms of NSAID and narcotic analgesics. **Conclusion:** It seems that the use of injectable NSAID in local A&E practice may be excessive. The oral route should be the first consideration, as fast acting oral preparations are now available. As there are risks of severe local complications, stringent justifications should be confirmed before intramuscular administration. (*Hong Kong j.emerg.med.* 2002;9:65-71)

**Keywords:** Adverse drug reaction, diclofenac, drug administration, intramuscular, ketorolac

### Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are a group of medications that have analgesic, anti-inflammatory and antipyretic properties. They are useful analgesics for musculoskeletal or joint pain, soft tissue injury, acute gout, headache, post-operative pain, dysmenorrhoea, renal and even biliary colic. Efficacy among NSAID is comparable or even better than narcotic analgesics.<sup>1-7</sup> In contrast to narcotic analgesics, NSAID do not cause respiratory depression, physical dependence, sedation or psychomotor effect.<sup>7</sup> There is also administrative convenience as, unlike narcotic analgesics, NSAID are not controlled medications. As a result, NSAID are very popular analgesics within local Accident & Emergency (A&E) departments – nearly all of which are under the Hospital Authority. However, they may have adverse effects on the gastrointestinal tract, liver, kidney and the central nervous system, especially in

the elderly. They may also result in bleeding tendency and cause allergic reactions.<sup>8-10</sup> In addition, there have been sporadic reports on local reactions to NSAID injections.<sup>11-19</sup> A survey on the consumption of different forms of NSAID in local A&E departments may give an idea of the pattern of their utilization. This result may help to formulate future policies.

### Materials and methods

Data on the utilization of injectable NSAID within the Hospital Authority, especially in regard to type of drug and specialty, were retrieved through the hospital and central pharmacy computer systems. Consumption of different forms of NSAID by the A&E department of North District Hospital (NDH) was reviewed for seven months from April to October 2001.

Medical literature was searched through Medline and EMBASE concerning adverse local drug reactions and efficacy comparison of oral and parenteral preparations of the following NSAID: diclofenac, ketorolac, ketoprofen, piroxicam, tenoxicam, metamizole sodium and phenylbutazone. Relevant articles were retrieved through hospital library

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Correspondence to:  
Chung Chin Hung, FRCS(Glasg), FHKAM(Surgery), FHKAM(Emergency Medicine)  
North District Hospital, Accident and Emergency Department, 9 Po Kin Road, Sheung Shui, N.T., Hong Kong  
Email: [chunch@ha.org.hk](mailto:chunch@ha.org.hk)

network. Further articles were obtained from cited references.

## Results

The consumption of parenteral NSAID, mainly through the intramuscular (IM) route, by different specialties within the Hospital Authority for the financial years 1998/1999, 1999/2000 and 2000/2001 is shown in Figure 1. There were four NSAID injectable preparations within the Hospital Authority (Table 1) and their usage is shown in Figure 2. The choice varied among hospitals and among specialties, and only diclofenac and ketorolac were available at North District Hospital (Figures 3 & 4). The

expenditure of different forms of NSAID by the A&E department of NDH for the seven-month period from April to October 2001 is shown in Figure 5. During the same period, diclofenac injection, ketorolac injection, methylsalicylate compound ointment (topical) and diclofenac potassium (oral) were always present within the 'top 30 drug expenditure' list of the A&E department of NDH, while diclofenac diethylammonium gel (topical) and dologesic (oral) occurred intermittently and very low on the lists.

## Discussion

Nonsteroidal anti-inflammatory drugs are a group of unrelated organic acids that have analgesic, anti-

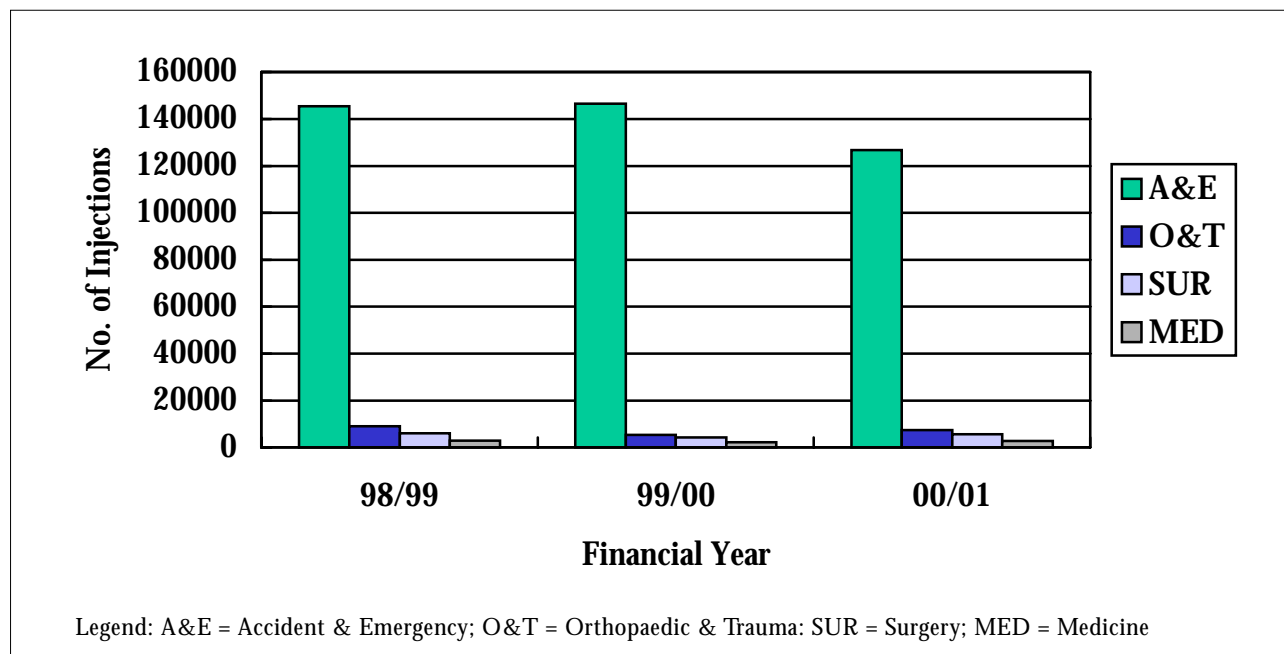


Figure 1. NSAID injections by specialty within Hospital Authority.

Table 1. NSAID injectable preparations available in Hong Kong.

Generic name	Trade name	Dose & preparation	Manufacturer	Use in HA
Diclofenac Na	Voltaren	75 mg/3 ml	Novartis	Yes
Ketoprofen	Orudis	100 mg/2 ml	Aventis pharma	Yes
Ketorolac	Toradol	30 mg/1 ml	Roche	Yes
Piroxicam	Feldene	20 mg/1 ml	Pfizer	Yes
Phenylbutazone	Trabit	400 mg (twin amp)	Mepha	No
Metamizole Na	Sulpyrin/Metilon	0.5 mg/2 ml	CCPC/Daiichi	No

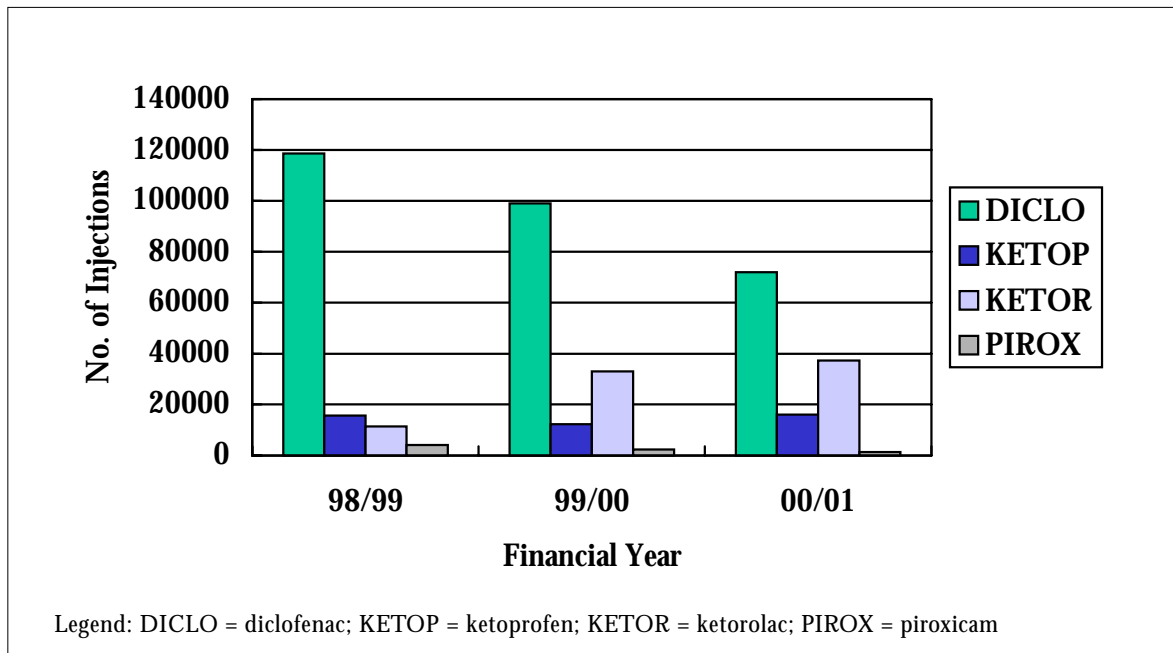


Figure 2. NSAID injections by drug type within Hospital Authority.

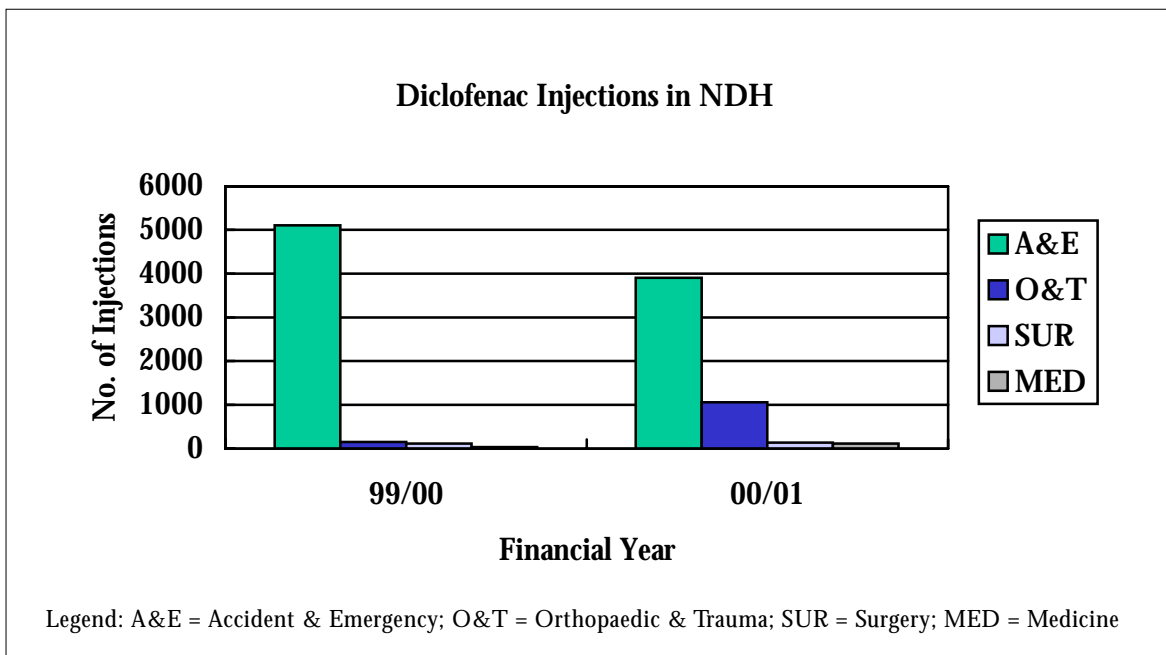


Figure 3. Diclofenac injections at North District Hospital.

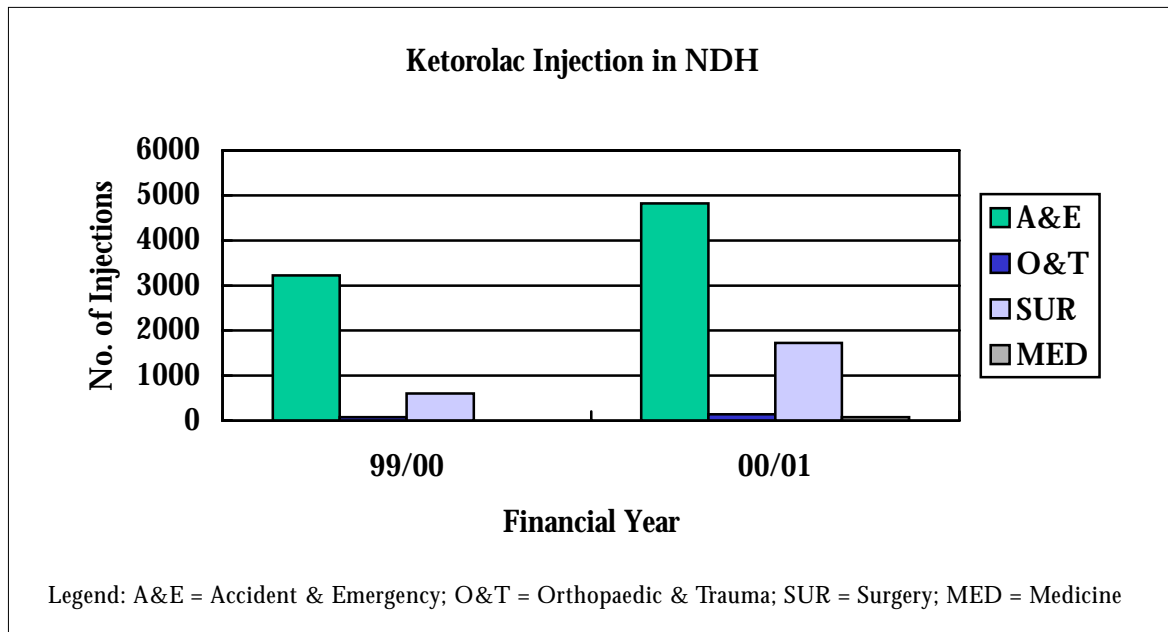


Figure 4. Ketorolac injections at North District Hospital.

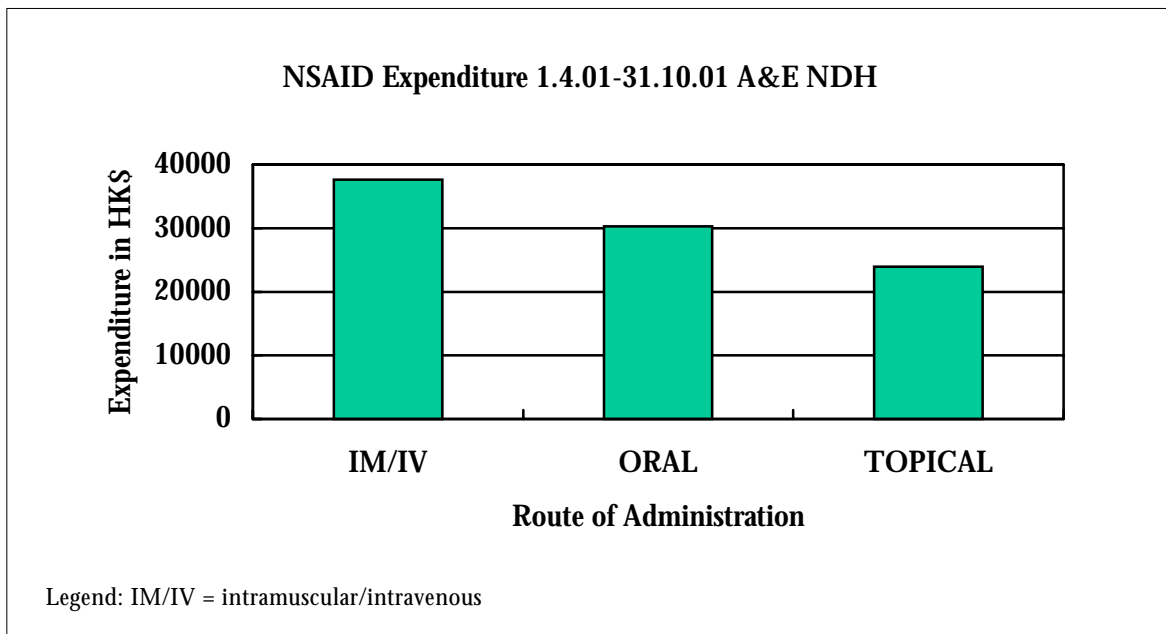


Figure 5. NDH A&E NSAID expenditure 01.04.2001 - 30.10.2001.

inflammatory and antipyretic properties. They inhibit the enzyme cyclo-oxygenase, which synthesizes prostaglandins and thromboxanes from arachidonic acid. There are two forms of cyclo-oxygenase – COX-1 and COX-2. COX-2 is the form induced in the presence of inflammation. Inhibition of COX-2 is thought to be responsible for some of the analgesic, anti-inflammatory and antipyretic effects of NSAIDs. On the other hand, inhibition of COX-1 is thought to produce some of their toxic effects, especially those on the gastrointestinal tract. Most of the NSAID currently available for clinical use inhibit both COX-1 and COX-2 e.g. diclofenac or predominantly COX-1 e.g. ketoprofen.<sup>20</sup> They can be administered through different routes – intravenous, intramuscular, oral, rectal, topical and even sublingual. COX-2 selective NSAID is supposed to have fewer gastrointestinal side effects than non-selective NSAID. Parenteral form of COX-2 NSAID e.g. meloxicam, is now available. Its role still awaits further confirmation.<sup>20,21</sup>

Renal colic is among the most excruciating types of pain a human being can experience. NSAID are very effective for its management.<sup>2</sup> Ureteric stone obstruction stimulates renal prostaglandin synthesis, resulting in increased renal blood flow, diuresis, increased intrarenal pressure, distension of the collecting system or renal capsule and the pain of renal colic.<sup>1,20,22</sup> By inhibiting prostaglandin synthesis, NSAID diminish renal blood flow, diuresis, ureteral smooth muscle activity and local ureteral inflammation.<sup>1,2</sup>

Concern over the high incidence of reported adverse effects with ketorolac trometamol has led to its withdrawal from the market in some countries while in others its permitted dosage and maximum duration of treatment has been reduced.<sup>23</sup> Ketorolac has a narrow therapeutic margin and its risk becomes clinically important as doses increase, in elderly patients and when used for longer than five days. It is indicated for the short-term management of moderate to severe acute pain. On the other hand, ketorolac is the only NSAID approved for intramuscular or intravenous administration for acute pain in the United States.<sup>2</sup>

Medical literature search retrieved reports on adverse local reactions for diclofenac injections only. A review of 10,167 cases of IM diclofenac injection showed an incidence of pain at the injection site (5.6%), abscess formation (0.05%) and necrosis (0.02%).<sup>24</sup> Local irritations<sup>1</sup> and causalgia<sup>17</sup> have occurred with IM injection of diclofenac. The association of life threatening streptococcal myositis, necrotizing fasciitis or tissue necrosis with IM diclofenac have been documented by several case reports.<sup>11-16,18,19</sup> Death as a result has been reported.<sup>18,19</sup>

Intramuscular diclofenac was shown to result in local reddening and induration in nearly all subjects in comparison with 19.4% in IM piroxicam.<sup>16,25</sup> In addition, creatine phosphokinase (CPK) level also rose much more dramatically after IM diclofenac, in comparison with IM piroxicam or IM ketorolac.<sup>6,14,25</sup> In addition, clinical studies using ketorolac have shown that repeated intramuscular administration after surgery does not produce significant injection site pain or damage.<sup>26</sup> As IM ketorolac, piroxicam and diclofenac are equally effective in the treatment of renal colic,<sup>1,4</sup> it may be appropriate to avoid the latter for analgesia. Moreover, the 3-ml volume of IM diclofenac will by itself produce more pain than the 1-ml volume of IM ketorolac or piroxicam. The rare but severe local complications preclude further use of IM diclofenac.<sup>1</sup>

Sublingual piroxicam has been shown to be as effective as parenteral diclofenac sodium in renal colic.<sup>1</sup> Diclofenac dispersible have a faster onset of action and superior efficacy compared with IM ketorolac in the management of pain after orthopaedic surgery.<sup>27</sup> The absorption and pharmacokinetics of the oral and intramuscular doses of ketorolac are similar.<sup>6</sup> Oral ketorolac 10 mg was shown to be as effective as ketorolac 30 mg IM in acute postoperative pain.<sup>3</sup> Diclofenac and indomethacin suppositories can often be an effective alternative, though the onset of action may be a bit slower than the intravenous route.<sup>16,28</sup> Severe hypersensitivity reactions are about a hundred times more frequent with parenteral administration than with oral or rectal application combined.<sup>9</sup>

When intramuscular NSAID injection is contemplated, the risk-benefit should be assessed. There is rarely any absolute need for intramuscular injections of NSAID.<sup>1</sup> Alternative routes of administration should be considered,<sup>18,19</sup> although there are concerns in using a suppository in adults or the inability to take oral medication as a result of vomiting.<sup>20</sup> As ketorolac can be given intravenously, it has definite advantage over diclofenac. However, when the intramuscular route is selected, meticulous injection technique and dosage recommendations must be adhered to. If the injection is unduly painful, administration should be discontinued. It is important to emphasize the manufacturer's instruction that IM diclofenac is to be given only by deep intragluteal injection into the upper outer quadrant, for a maximum of two injections daily (one into each buttock, separated by an interval of a few hours) for two days.<sup>18</sup>

Because of the risk of serious adverse effects, including local aseptic tissue necrosis,<sup>29</sup> the use of IM phenylbutazone and metamizol is justified only in severe pain unresponsive to other drugs.

Cost may also be a consideration in this era of 'value for money'. The cost of a NSAID injection within the Hospital Authority was around \$7.5. For oral or rectal NSAID preparations, the range was from seven cents to more than three dollars. For topical NSAID, the range was from two to nineteen dollars.

In conclusion, it seems that the use of injectable NSAID in our local A&E departments may be excessive, although there may be a decreasing trend. The oral route should be the first consideration, as fast acting oral preparations are now available. Stringent justifications should be confirmed before intramuscular administration.

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