REVIEW ARTICLE

Drug Safety 2000 Jun; 22 (6): 487-497
0114-5916/00/0006-0487/$20.00/0

Minimising the Adverse Effects of Ketorolac

Douglas J. Reinhart

University of Utah School of Medicine, Department of Anaesthesiology, Salt Lake City, Utah, and Weber State University, Ogden, Utah, USA

Contents

Abstract

Gastrointestinal bleeding and perforation, platelet inhibition with altered haemostasis, and renal impairment are among the list of adverse effects associated with the administration of ketorolac. The incidence of serious adverse events has declined since dosage guidelines were revised. Most of the published literature suggests that the overall risk of gastrointestinal or operative site bleeding related to ketorolac therapy is only slightly higher than with opioids. The risk for adverse events, however, increases with high doses, with prolonged therapy (>5 days) or in vulnerable patients (e.g. the elderly). Acute renal failure has been reported after ketorolac treatment but is usually reversible after discontinuation of the drug. As with other nonsteroidal anti-inflammatory drugs (NSAIDs), ketorolac may trigger allergic or hypersensitivity reactions.

Careful patient selection is essential if use of ketorolac is considered. Contraindications to ketorolac use include a history of, or current risk of, gastrointestinal bleeding, risk of renal failure, compromised haemostasis, hypersensitivity to aspirin (acetylsalicylic acid) or other NSAIDs, labour, delivery and nursing. Ketorolac should be prescribed at the lowest dosage necessary to control pain; the duration of therapy should also be limited to as few days as possible. Practitioners should be familiar with, and follow, label warnings and dosage guidelines.

Ketorolac was first introduced in 1990 in the US. Within 3 years following the launch of ketorolac, 16 million patients had received the drug with 97 mortalities reported, nearly half of which were related to gastrointestinal complications. Table I summarises the findings of the Council of International Organizations of Medical Sciences for adverse events reported for ketorolac.[1] By 1992, the European Union member states were divided over the risk–benefit ratio of ketorolac, and 5 countries (The Netherlands, Greece, Portugal, Germany and France) had instituted a ban on its use.[2] Because of the number of adverse events reported, significant regulatory review began in a number of countries following the release of ketorolac. This review quickly led to a revision of labelling, dosage recommendations and prescribing practices.[3-5] Most of the reports of serious toxicity with ketorolac occurred at high dosages and in patients in whom drug therapy would not currently be recommended, and predated the manufacturer's revised dosage guidelines. Happily, these revised recommendations have resulted in fewer adverse effects.

The tolerability profile of ketorolac parallels that of other nonsteroidal anti-inflammatory drugs (NSAIDs), particularly with respect to effects on haematological and renal function and on the gastrointestinal tract. This review will focus on the incidence of these adverse effects and the means by which clinicians may minimise them.

1. Tolerability of Ketorolac

1.1 Haematological Effects

It is well understood that NSAIDs inhibit the formation of thromboxane A_2, an important mediator of platelet aggregation, through the inhibition of prostaglandin synthesis.[6] A meta-analyses of studies involving the NSAID class showed that their use in association with surgery was not associated with a clinically significant excess of postoperative bleeding or haematoma formation.[7] The antiplatelet effect of ketorolac is well documented and is reportedly similar to that of other NSAIDs.[8-10]

The effects of ketorolac on haemostasis in the clinical setting has been a topic of a growing number of publications. Researchers have reported on the presence or absence of effects on bleeding in the perioperative period in a variety of surgical situations. The question has been raised whether ketorolac may provoke an increase in perioperative surgical site bleeding. There is evidence to both support and refute this notion. In orthopaedics, Thwaites et al.[11,12] reported that ketorolac worsens platelet function during knee arthroscopy when performed under spinal anaesthesia but not when performed under general anaesthesia. Another study found that there is a low risk of significantly increased bleeding associated with concurrent use of low molecular weight heparin and a modest dose of ketorolac after total hip replacement.[13]

Koh et al.[14] studied the effects of ketorolac on coagulation activity in patients undergoing gynaecological surgery. They concluded that there was no difference in blood loss or duration of surgery between patients receiving ketorolac and those who did not. Another group of investigators came to the same conclusion in a study involving open cholecystectomy.[15]

The use of ketorolac in children for perioperative analgesia has been the focus of a number of

Table I. Summary of ketorolac adverse events by body system, March 1990 to June 1994[1]

Body system	Number of events	Proportion of total events (%)
Gastrointestinal	533	27.9
General/nonspecific	366	19.2
Haematological	277	14.5
Urinary	238	12.5
Respiratory	123	6.4
Nervous system	101	5.3
Psychiatric	63	3.3
Cardiovascular	41	2.1
Integumentary	39	2.0
Metabolic and endocrine	37	1.9
Injection site	32	1.7
Hepatobiliary	31	1.6
Musculoskeletal	11	0.6
Reproductive	9	0.5
Neoplasia	9	0.5
Total	1901	100.0

recent publications. The ketorolac dose for patients involved these studies was in the range of 0.75 to 1 mg/kg bodyweight intravenously. Studies involving paediatric surgical procedures such as myringotomy, orthopaedic, plastic/reconstructive or strabismus correction showed no significant increase in perioperative bleeding.[16-18]

The most compelling evidence for significant risk of perioperative bleeding is with children undergoing tonsillectomy.[19] A number of well designed studies concerning ketorolac and tonsillectomies have been published with the conclusion that ketorolac therapy increased the risk of intraoperative and postoperative bleeding.[20-24] Another study contradicted this finding, particularly when ketorolac is given at the end of surgery.[25] A nonopioid, such as ketorolac, is attractive for postoperative analgesia after tonsillectomy, especially in a patient population that may be at risk for airway obstruction, nausea and vomiting. Ketorolac was initially enthusiastically used by clinicians in this setting because of its potent analgesic effects. However, clinical experience and the preponderance of the published evidence indicating increased bleeding has dissuaded many practitioners from using ketorolac specifically for tonsillectomies.

The drug package insert states that ketorolac 'is contraindicated as a prophylactic analgesic before any major surgery and is contraindicated intraoperatively when haemostasis is critical because of the increased risk of bleeding.'[26] The manufacturer strongly advises against the use of ketorolac in any situation where inhibition of platelet function could result in haemorrhage, and tonsillectomy seems to be one of those conditions.

Buck[27] prospectively studied 112 paediatric patients receiving ketorolac as part of their hospitalisation. Data were collected for indication for treatment, dosage, interval, administration of a loading dose, and length of therapy. 110 of the children were given ketorolac for analgesia and 77% of this group received the drug for postoperative pain. Two of the children had bleeding complications that were deemed to be attributable to the ketorolac. One of the 2 children developed lower extremity petechiae and gross haematuria following spinal fusion. The second patient exhibited bleeding from the surgical site 2 days following a similar operation. However, this study was not a randomised controlled trial, which makes it difficult to discern the true cause of increased postoperative bleeding in these patients.

In a 1997 review article concerning the perioperative use of NSAIDs in children, Rømsing[28] concludes that haemorrhagic events in the postoperative period do occur, although the literature remains inconclusive. He further states that 'in order to maximise the benefit of nonsteroidal anti-inflammatory drugs in children, the risks must be recognised and patients, clinical indications, the individual drug, timing and route of administration must be selected carefully. Nonsteroidal anti-inflammatory drugs appear to play a valuable role in the further improvement of postoperative pain relief in children.'

The current US Food and Drug Administration approved ketorolac package insert states that 'Safety and efficacy in paediatric patients (less than 16 years of age) have not been established. Therefore, use of ketorolac tromethamine in paediatric patients is not recommended.'[26] These 2 contradictory statements are cause for clinicians to continually evaluate their indications, dosage selection and administration practices for ketorolac.

Finally, a postmarketing surveillance inception cohort study considered 10 272 courses of parenteral ketorolac versus 10 247 courses of parenteral opioids given in 35 hospitals in the US.[29] The patients were matched by hospital, admitting service and date of initiation of study drug. The conclusion was that the overall association between ketorolac use and operative site bleeding is small. However, 'the risk associated with the drug is larger and clinically important when ketorolac is used in higher doses, in older subjects, and for more than 5 days. Improving physicians' prescribing practices by limiting the dose and duration of ketorolac use, especially in the elderly, should enhance its overall risk-benefit balance.'

1.2 Gastrointestinal Effects

The ulcerogenic potential of NSAIDs has been demonstrated after short and long term drug administration.[3,30] There are 2 proposed mechanisms for NSAID-induced gastrointestinal effects: directly as a topical irritant and systemically by decreasing prostaglandin-dependent gastric acid inhibition.[3,31] Factors in NSAID-induced gastrointestinal tract damage include microvascular aspects, neutrophil recruitment, mucosal prostaglandins, gastrointestinal secretions and bacteria.[32] An important local initiating effect of accumulation of NSAIDs may result in interaction with surface phospholipids, alteration of cellular ATP, and both local and systemic effects of cyclo-oxygenase (COX) inhibition. According to Fosslein,[33] conventional NSAIDs inhibit the synthesis of cytoprotective prostaglandins by COX-1 in the gastrointestinal tract. Surplus arachidonic acid accumulates and enhances the generation of leukotrienes via the lipoxygenase pathway, inducing neutrophil adhesion to endothelium and vasoconstriction. The NSAIDs harbouring a carboxyl group also inhibit oxidative phosphorylation, lowering ATP generation leading to dysfunction of mucosal tight junctions and increased mucosal permeability.

As mentioned in the introduction, the tolerability profile of ketorolac parallels that of other NSAIDs, and effects of the drug on the gastrointestinal tract seem to follow this precept. It was not surprising that numerous case reports implicating ketorolac as the cause of gastrointestinal complications began to surface shortly after its initial marketing. However, there are far fewer well designed published studies that assist the clinician in understanding the incidence and cause of gastrointestinal dysfunction associated with the drug.

In a large study by Garcia-Rodriguez et al.,[34] over 1500 patients admitted for gastrointestinal bleeding and/or perforation were analysed. The adjusted relative risk for upper gastrointestinal tract bleeding in NSAID users compared with nonusers was 4.4. The risk increased with higher daily doses. Ketorolac was found to be 5 times more gastrotoxic than all other NSAIDs. The excess risk with ketorolac was observed after both oral and intramuscular administration. Their conclusion was that the excess risk of major upper gastrointestinal tract complications with outpatient use of ketorolac suggests an unfavourable risk–benefit assessment compared with other NSAIDs. They recommended use of the lowest effective dosage of any NSAID to reduce the burden of serious gastrointestinal tract complications.

A pair of well performed Italian studies revealed a significantly higher risk of occurrence of gastroduodenal lesions[35] and of hospitalisation attributable to gastrointestinal complications[36] from ketorolac than from other NSAIDs. The authors reiterated 'the need to adhere to the restrictions relating to the indications and duration of use of ketorolac.'

Strom et al.[29] published the results of a comprehensive multicentre study in which many thousands of courses of ketorolac were evaluated for incidence of gastrointestinal bleeding. The overall association between ketorolac use and gastrointestinal bleeding was small, with relatively little difference in the risk of gastrointestinal bleeding associated with the use of ketorolac versus opioids. The increased risk seemed to be limited to the elderly, those using the drug at high doses, or those using the drug for prolonged durations. Strom et al.[29] also concluded that the optimal dose of ketorolac is the lowest dose that can achieve the desired pain relief. The increased risk of gastrointestinal bleeding was apparent despite the relatively short courses of therapy used compared with outpatient use of oral NSAIDs. An increase in the duration of parenteral ketorolac treatment from less than 2 days to 3 to 5 days resulted in a marginally increased risk of gastrointestinal bleeding, whereas a treatment duration of more than 5 days was associated with a markedly increased risk.

Labelling for ketorolac in the US states that the drug is 'contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.'[26] The US label recommendation call-

ing for a maximum of 5 days of therapy was not based on any particular data indicating a higher risk with longer duration, but simply from the maximum duration of therapy that had been studied. Furthermore, there are also no data supporting the European label restricting use to a maximum of 2 days of therapy. But, given the findings of the studies discussed in this section and others,[37-39] it seems to be prudent to restrict ketorolac use to no more than 5 days, particularly in elderly patients.

1.3 Renal Effects

As with other NSAIDs, ketorolac can alter prostaglandin-mediated renal function.[3,40]

NSAIDs do not appear to compromise renal haemodynamics in patients with normal renal function, although patients with such conditions as congestive heart failure, hepatic cirrhosis, hypovolaemia or underlying renal disease are more susceptible to drug-induced nephrotoxicity.[41-43] There have been numerous case reports linking ketorolac treatment to renal failure, and renal toxicity has been reported in a small number of patients after only a single dose of ketorolac. Many of these reports deal with the elderly and patients with other risk factors. However, there are also reports of acute tubular necrosis and interstitial nephritis in otherwise healthy young patients receiving recommended doses of the drug.

There have also been several randomised controlled studies investigating the effect of the drug on renal function.[44,45] The study by Aitken et al.[44] was a randomised, double-blind, placebo-controlled trial involving patients undergoing upper abdominal surgery. Patients received ketorolac 60 mg/day (continuous intravenous or intermittent intramuscular administration) or placebo for 2 days postoperatively. The only relevant result was a decrease in potassium excretion in ketorolac recipients, with no change in urine output, urine osmolarity, creatinine and urea clearance or sodium output. In another study of 5 days of therapy with oral ketorolac 40 mg/day in 12 patients with rheumatological pain, the investigators reported increases in mean blood urea and serum potassium and creatinine levels from baseline.[46] Although the increases in these parameters were statistically significant, the values for all parameters remained within normal limits.

Since renal failure is such a rare complication, the randomised controlled study may not be the most reliable design because of the risk of a false negative result.[47] It may be more prudent to rely on cohort or case-control studies and, in the case of ketorolac, there has been one published by Strom and colleagues in the US.[29] The same group analysed the risk of renal failure and did not find an increase in risk from ketorolac.[48] However, it must again be noted that the study was not a randomised controlled study. Such epidemiological studies depend on the quality of the data, which are often collected for other reasons and may be inaccurate or incomplete.[49]

After a thorough review of the current literature regarding the renal effects of ketorolac, Myles and Power[47] concluded that if ketorolac causes renal failure, it is a rare event. Their best estimate of incidence or risk, based on epidemiological data, is approximately 1 in 1000 to 100 000. They suggest that this risk should be weighed against the many other causes of postoperative renal failure and the risks associated with alternative drugs and pain control methods.

The current US drug label carries the warning that 'ketorolac is contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.' In view of this warning and the published reports described above, close monitoring seems prudent even if patients do not receive long term treatment. Rao et al.[46] suggest that monitoring of renal parameters (such as blood urea, serum creatinine, and serum potassium) may be advisable during short term ketorolac therapy.

1.4 Hypersensitivity

Pulmonary reactions induced by aspirin (acetylsalicylic acid) have been described previously.[50-52] Such reactions have also been associated with NSAID usage.[53] Since the introduction of ke-

torolac, dozens of case reports describing bronchospastic reactions associated with its administration have been published.[54-57] To date, there are no prospective, randomised, placebo-controlled studies concerning the risk of pulmonary adverse events with ketorolac.

Patients who have a known hypersensitivity to NSAIDs or aspirin should not receive ketorolac. The drug is contraindicated for patients in whom aspirin or other NSAIDs precipitate a complete or partial syndrome of angioedema, bronchospasm and nasal polyps (Samter's triad).[56-58] The current ketorolac package insert states that administration of the drug is 'contraindicated in patients with previously demonstrated hypersensitivity to ketorolac, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs.'[26]

1.5 Hepatic Disease

Careful monitoring of liver function is suggested when using ketorolac in patients with hepatic disease.[59] Borderline elevations of liver function tests may occur in approximately 15% of patients. These changes may be transient, continue unchanged or progress with continued NSAID therapy. These elevations usually resolve after discontinuation of the NSAID therapy. Severe reactions, including jaundice and fatal hepatitis, are rare.[60] There is no evidence that ketorolac causes hepatic disease more frequently than do other NSAIDs.

In a study performed by Hennesey et al.,[61] several thousand courses of parenteral ketorolac versus parenteral opioid given in the hospital setting were analysed for hepatotoxic effects. Liver injury was defined by a modified national consensus definition that relied on liver function tests. The study failed to find evidence of a hepatotoxic effect of parenteral ketorolac and provided strong evidence against the existence of a clinically meaningful association between exposure to parenteral ketorolac and liver injury.

1.6 Perinatal Effects

As early as 1988, it was understood that ketorolac could cross the placenta and theoretically could have an adverse effect on the fetal circulation.[62] The same investigators discovered that maternal administration of ketorolac led to inhibited platelet aggregation in neonates.[63] Subsequent reports suggested that ketorolac produced uterine atonia and, in 1 study, the drug was recommended as an appropriate first-line tocolytic agent.[64,65]

The manufacturer's label includes a warning that ketorolac is contraindicated in labour and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus prolonging pregnancy and labour and increasing the risk of uterine haemorrhage.[26,66] Constriction of the ductus arteriosus, renal dysfunction and haemostatic abnormalities can occur in the fetus and neonate.[67] Furthermore, the warning label stresses that ketorolac should not be used in nursing mothers because of the potential adverse effects of prostaglandin inhibiting drugs on newborns. Ostensen and Ramsey-Goldman[66] suggest that most of these adverse events can be prevented by discontinuing NSAIDs 8 weeks prior to delivery.

1.7 Other Effects

Transient, reversible hearing loss with ketorolac has been noted in a few reports.[68,69] Acute bilateral sensorineural hearing loss occurred in 1 patient with polyarteritis nodosa who received a 30mg intravenous dose of ketorolac.[68] On admission, the patient reported taking methotrexate and prednisone which may have potentiated ototoxicity. Another patient who experienced hearing loss after ketorolac had pre-existing end-stage renal disease and was maintained on continuous ambulatory peritoneal dialysis.[69]

NSAIDs are believed to interfere with the renal elimination of lithium by inducing prostaglandin inhibition in the kidney. This produces renal vasoconstriction, increased proximal tubular reabsorption and decreased lithium excretion.[70] One report described an 80-year-old patient with manic depressive psychosis who experienced a marked increase in serum lithium concentrations after therapy with ketorolac.[71] The age of the patient probably played

Table II. Dosage guidelines for ketorolac in the US[26] and UK[73]

Patient characteristics	Intramuscular	Intravenous[a]	Oral[b]
United States			
Age <65 years	60mg (SD) or 30mg q6h	30mg q6h	20mg[c] SD then 10mg q4-6h
	NTE 120 mg/day for ≤5 days	NTE 120 mg/day for ≤5 days	NTE 40 mg/day
Age ≥65 years, renal impairment and/or bodyweight <50kg	30mg (SD) or 15mg q6h	15mg q6h	10mg q4-6h
	NTE 60 mg/day for ≤5 days	NTE 60 mg/day for ≤5 days	NTE 40 mg/day
United Kingdom			
Age >16 to <65 years[d]	10mg bolus then 10-30mg q4-6h	10mg bolus then 10-30mg q4-6h	10mg q4-6h
	NTE 90 mg/day for ≤2 days	NTE 90 mg/day for ≤2 days	NTE 40 mg/day for ≤7 days
Age >65 years	10mg bolus then 10-30mg q4-6h	10mg bolus then 10-30mg q4-6h	10mg q6-8h
	NTE 60 mg/day for ≤2 days	NTE 60 mg/day for ≤2 days	NTE 40 mg/day for ≤7 days

a Should be administered over ≥15 seconds.

b In the US, oral administration of ketorolac is indicated only as continuation therapy after intramuscular or intravenous administration; the duration of combined therapy should not exceed 5 days.

c 20mg may be administered as the first oral dose to patients who received a single dose of 60mg (intramuscular) or 30mg (intramuscular/intravenous) or multiple doses of 30mg.

d The dosage should be reduced in patients weighing <50kg and in those with mild renal impairment (creatinine clearance 1.2 to 3 L/h); avoid in patients with moderate or severe renal impairment.

NTE = not to exceed; **qxh** = every *x* hours; **SD** = single dose.

a role in the finding of elevated serum lithium. Another patient experienced lithium toxicity after taking oral ketorolac 60 mg/day for a period of 3 weeks.[72]

Sodium retention, possibly leading to oedema, has been reported in clinical trials with ketorolac. Advanced age is the most common risk factor for fluid retention from ketorolac, but hypertension and diuretic use also increase the risk.[26] Ketorolac should only be used very cautiously in patients with cardiac decompensation, hypertension or similar conditions.

2. Dosage and Administration Guidelines and Label Warnings

Concern over postmarketing reports of the frequency and severity of adverse events with ketorolac led to a number of revisions of dosage guidelines, and thus prescribing information is complex and often differs among countries. The current recommendations for the use of ketorolac in the US and the UK are summarised in table II.[26,73] In the US, ketorolac is packaged in unit dose syringes and ampoules containing 15 or 30mg for intravenous or intramuscular injection, and 60mg for intramuscular injection. In other countries, ketorolac is available for parenteral administration in ampoules containing 10 or 30mg of the drug. The oral form of ketorolac is available in 10mg tablets.

In the US, injectable ketorolac is indicated for the short term (less than 5 days) management of moderately severe acute pain that requires treatment at the opioid level, normally in a postoperative setting. It is not indicated for minor or chronic painful conditions. In the US, the manufacturer recommends that therapy should be initiated with ketorolac injection and the oral form used as continuation treatment.[26] In the UK, oral ketorolac can be administered for up to 7 days without prior parenteral therapy. In the US, combined use of the injectable and oral form exceeding 5 days is not recommended because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses.

The maximum recommended intramuscular dose of ketorolac for single-dose treatment in the US is 60mg. In both the US and UK, a dose of 10 to 30mg may be administered intravenously or in-

Table III. Summary of label contraindications for ketorolac

Contraindication	Reason for contraindication
Patients with peptic ulcer disease, recent GI bleeding or perforation, or a history of peptic ulcer disease or GI bleeding	Increased risk of GI bleeding or perforation
Patients with advanced renal impairment, at risk for renal failure due to volume depletion	Increased risk of renal failure due to alteration of prostaglandin-mediated renal function
Use in labour and delivery	Through prostaglandin inhibition, drug may adversely affect fetal circulation and inhibit uterine musculature
Nursing mothers	Potential adverse effects of prostaglandin-inhibiting drugs on neonates
Patients with previously demonstrated hypersensitivity to ketorolac or allergic manifestations to aspirin (acetylsalicylic acid) or other NSAIDs	Potential cross-allergy to aspirin and other NSAIDs
As a prophylactic analgesic before any major surgery, and intraoperatively when haemostasis is critical	Increased risk of bleeding
Patients with suspected or confirmed cerebrovascular bleeding, haemorrhagic diathesis, incomplete haemostasis and others at high risk of bleeding	Increased risk of bleeding or inability to achieve haemostasis
Patients currently receiving aspirin or NSAIDs	Cumulative risks of inducing serious NSAID-related adverse events
Neuraxial administration	Alcohol content of ketorolac can cause neural damage
Concomitant use with probenecid	Results in decreased clearance of ketorolac and increases serum ketorolac concentrations

GI = gastrointestinal; **NSAID** = nonsteroidal anti-inflammatory drug.

tramuscularly as a single dose or every 4 to 6 hours. The usual oral dosage is 10mg every 4 to 6 hours. Guidelines for total parenteral dosage include 90 mg/day in some countries (Italy, Spain, Belgium, Switzerland and the UK) and 120mg/day in others (Mexico, Canada, Finland, Sweden and the US). Maximum recommended duration of parenteral therapy varies from 2 days in the UK to 5 days in the US.

Dosage reduction is necessary in the elderly and in those with renal impairment.[26] Based on single-dose data, the half-life of ketorolac is increased from 5 to 7 hours in the elderly compared with young healthy volunteers. The mean half-life of ketorolac in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment.

Table III is a summary of the contraindications carried on US labelling for ketorolac. It is important for clinicians to understand that increasing the dosage of ketorolac beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

3. Conclusions

In a comprehensive article concerning the safety of ketorolac, officials of the Syntex Corporation made the following statement:[74]

'In assessing the risks and benefits of ketorolac injection, an important consideration is that of rational prescribing. It is not sensible to argue that all postoperative analgesia should be provided by opiates, nor is it sensible to suggest that the use of opiates should be replaced entirely by the use of injectable NSAIDs, such as ketorolac. Instead, it is important to realise the risks and benefits of each sort of postoperative analgesic treatment and thus to make the most appropriate use of each in its proper indications.'

Many of the reports of serious toxicity with ketorolac occurred prior to the revision of manufacturer's guidelines and occurred with high dosages, with prolonged therapy and in patients in whom ketorolac administration would not currently be recommended. Careful patient selection for ketorolac administration is vital to minimise the risk of adverse effects. Use of ketorolac in the elderly should be limited in dosage and duration, or restricted altogether. Those patients with current, or increased risk of, renal impairment should be closely monitored by serial creatinine and blood urea. Those with hepatic disease should have periodic measurements of hepatic function. Ketorolac administration should be avoided in those demonstrating hypersensitivity to NSAIDs or salicylates. Ketorolac is contraindicated in labour and delivery and should not be used in nursing mothers.

References

1. Council of International Organizations of Medical Sciences. Final report of CIOMS Working Group II. International reporting of periodic drug-safety update summaries. Geneva: Council of International Organizations of Medical Sciences, World Health Organization, 1992
2. Lewis S. Ketorolac in Europe [letter]. Lancet 1994; 343: 784
3. Gillis JC, Brogden RN. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs 1997; 53: 139-88
4. Anonymous. New ketorolac dosage recommendations. Pharm J 1993; 251: 49
5. Ketorolac: restrictions on parenteral dosage, WHO Drug Info 1993; 7 (2): 64
6. Bruno JJ, Yang D, Taylor LA. Differing effects of ticlopidine and two prostaglandins synthetase inhibitors on maximum rate of ADP-induce aggregation [abstract]. Thromb Haemost 1981; 46: 412
7. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81-106
8. Greer IA. Effects of ketorolac tromethamine on hemostasis. Pharmacotherapy 1990; 10 (6): 71S-6S
9. Conrad KA, Fagan TC, Mackie MJ, et al. Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther 1988; 43: 542-6
10. Concannon MJ, Meng L, Welsh CF, et al. Inhibition of perioperative platelet aggregation using toradol (ketorolac). Ann Plast Surg 1993; 30 (3): 264-6
11. Thwaites BK, Nigus D, Bouska GW, et al. Intravenous ketorolac tromethamine worsened platelet function during knee arthroscopy under spinal anesthesia. Anesth Analg 1996; 82: 1176-81
12. Thwaites BK, Nigus D, Bouska GW, et al. Intravenous ketorolac tromethamine does not worsen platelet function during knee arthroscopy under general anesthesia. Anesth Analg 1995; 81: 119-24
13. Weale AE, Durant N, Warwick DJ, et al. Is there a clinical interaction between low molecular weight heparin and nonsteroidal analgesics after total hip replacement? Ann R Coll Surg Engl 1995; 77: 35-7
14. Koh SCL, Pua HL, Tay DHB, et al. The effects of gynaecological surgery on coagulation activation, fibrinolysis and fibrinolytic inhibitor in patients with and without ketorolac infusion. Thromb Res 1995; 79: 501-14
15. Varrasi G, Panella L, Piroli A. The effects of perioperative ketorolac infusion on postoperative pain and endocrine-metabolic response. Anesth Analg 1994; 78: 514-9
16. Watcha MF, Ramirez-Ruiz M, White PF, et al. Perioperative effects of ketorolac and acetaminophen in children undergoing bilateral myringotomy. Can J Anaesth 1992; 39: 649-54
17. Watcha MF, Barry Jones M, Lagueruela RG, et al. Comparison of ketorolac and morphine as adjuvants during pediatric surgery. Anesthesiology 1992; 76: 368-72
18. Munro HM, Riegger LQ, Reynolds PI, et al. Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery. Br J Anaesth 1994; 72: 624-8
19. Hall SC. Tonsillectomies, ketorolac, and the march of progress. Can J Anaesth 1996; 43 6: 544-8
20. Gunter JB, Varughese AM, Harrington JF, et al. Recovery and complications after tonsillectomy in children: a comparison of ketorolac and morphine. Anesth Analg 1995; 81: 1136-41
21. Judkins JH, Dray TG, Hubbell RN. Intraoperative ketorolac and posttonsillectomy bleeding. Arch Otolaryngol Head Neck Surg 1996; 112: 937-40
22. Splinter WM, Rhine EJ, Roberts DW, et al. Preoperative ketorolac increases bleeding after tonsillectomy in children. An J Anaesth 1996; 43; 6: 560-3
23. Bailey R, Sinha C, Burgess PA. Ketorolac tromethamine and hemorrhage in tonsillectomy: a prospective, randomized, double-blind study. Laryngoscope 1997; 107: 166-9
24. Gallagher JE, Blauth J, Fornadley JA. Perioperative ketorolac tromethamine and postoperative hemorrhage in cases of tonsillectomy and adenoidectomy. Laryngoscope 1995; 105: 606-9
25. Sutters KA, Levine JD, Dibble S, et al. Analgesic efficacy and safety of single-dose intramuscular ketorolac for postoperative pain management in children following tonsillectomy. Pain 1995; 16: 145-53
26. Toradol package insert. Nutley, (NJ): Hoffman LaRoche, 1995
27. Buck M. Clinical experience with ketorolac in children. Ann Pharmacother 1994; 28: 1009-13

28. Rømsing J, Walther-Larsen S. Peri-operative use of nonsteroidal anti-inflammatory drugs in children: analgesic efficacy and bleeding. Anaesthesia 1997; 52: 673-83
29. Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. JAMA 1996 Feb; 275; 5: 376-82
30. Kehlet H, Dahl JB. Are perioperative nonsteroidal anti-inflammatory drugs ulceragenic in the short term? Drugs 1992; 44 Suppl. 5: S38-S41
31. Vane JR, Botting RM. The mode of action of anti-inflammatory drugs. Postgrad Med J 1990; 66 Suppl. 4: S2-S17
32. Bjaranason I, Thjodleifsson B. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. Rheumatology (Oxford) 1999; 38 Suppl. 1: 24-32
33. Fosslein E. Adverse effect of nonsteroidal anti-inflammatory drugs on the gastrointestinal system. Ann Clin Lab Sci 1998; 28 (2): 67-81
34. Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, et al. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998; 12: 33-9
35. Traversa G, Walker AM, Ippolito FM, et al. Gastroduodenal toxicity of different antiinflammatory drugs. Epidemiology 1995; 6 (1): 49-54
36. Menniti-Ippolito F, Maggini M, Raschetti R, et al. Ketorolac use in outpatients and gastrointestinal hospitalization: a comparison with other non-steroidal anti-inflammatory drugs in Italy. Eur J Clin Pharmacol 1998; 54 (5): 393-7
37. Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996; 312: 1563-6
38. Garcia Rodriguez LA, Jick H. The risk of upper gastrointestinal bleeding and/or perforation associated with individual nonsteroidal anti-inflammatory drugs. Lancet 1994; 343: 769-72
39. Cummings DM, Amadio P. A review of selected newer nonsteroidal anti-inflammatory drugs. Am Family Physician 1994 Apr; 49; 5: 1197-202
40. Kenny GN. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. Drugs 1992; 44 Suppl. 5: S31-S6
41. Murray MD, Brater DC. Adverse effects of nonsteroidal anti-inflammatory drugs on renal function. Ann Intern Med 1990; 112 (8): 559-60
42. Henrich WL, Agodoa LE, Barrett B, et al. National Kidney Foundation Position Paper: analgesics and the kidney: summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an Ad Hoc Committee of the National Kidney Foundation. Am J Kidney Dis 1996; 27: 162-5
43. DuBose Jr TD, Molony DA, Verani R, et al. Nephrotoxicity of non-steroidal anti-inflammatory drugs. Lancet 1994; 344: 515-8
44. Aitken HA, Burns JW, McArdle CS, et al. Effects of ketorolac trometamol on renal function. Br J Anaesth 1992; 68: 481-5
45. Ready LB, Bown CR, Stahigren LH, et al. Evaluation of intravenous ketorolac administered by bolus or infusion for treatment of postoperative pain. A double-blind, placebo-controlled, multicenter study. Anesthesiology 1994; 80: 1277-86
46. Rao TRK, Naidu MUR, Shobha JC, et al. Renal effects of oral ketorolac in patients with mild to moderate pain. Clin Drug Invest 1995; 9: 111-5
47. Myles PS, Power I. Does ketorolac cause postoperative renal failure: how do we assess the evidence? Br J Anaesth 1998; 80: 420-1
48. Feldman HL, Kinman JL, Berlin JA, et al. Parenteral ketorolac: the risk for acute renal failure. Ann Intern Med 1997; 126: 193-9
49. Sackett DL, Haynes RB, Guyatt GH, et al. Clinical epidemiology: a basic science for clinical medicine, 2nd ed. Boston: Little Brown, 1991: 283-302
50. Szezeklik A, Gryglewski RJ, Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. BMJ 1975; 1: 67-9
51. Szezeklik A. aspirin-induced asthma: new insights into pathogenesis and clinical presentation of drug intolerance. Int Arch Allergy Immunol 1989; 90: 70-5
52. Piado C, Castillo JA, Montserrat JM, et al. Aspirin intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. Eur Respir J 1989; 2: 127-9
53. Szezeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. J Allergy Clin Immunol 1977; 60: 276-84
54. Hebert WG, Scopelitis E. Ketorolac-precipitated asthma. South Med J 1994; 87; 2: 282-3
55. Vicks SD, Dean RJ, Tenholder MF. Ketorolac induced respiratory failure in an aspirin sensitive asthmatic. Immunol Allergy Pract 1991; 13: 23-5
56. Dias MA, Biedlingmaier JF. Ketorolac-induced status asthmaticus after endoscopic sinus surgery in a patient with Samter's triad. Arch Otolaryngol Head Neck Surg 1997; 117: S176-S8
57. Zikowski D, Hord AH, Haddox JD. Ketorolac-induced bronchospasm. Anesth Analg 1993; 76: 417-9
58. Haddow GR, Riley E, Isaacs R, et al. Ketorolac, nasal polyposis, and bronchial asthma: a cause for concern. Anesth Analg 1993; 76: 420-2
59. Hammonds WD, Donnigan D. Problems in anesthesia: clinical use of ketorolac tromethamine 1993; 3: 268-80
60. Litvak KM, McEvoy GK. Ketorolac: an injectable non-narcotic analgesic. Clin Pharm 1990; 9 (12): 912-35
61. Hennesey S, Kinman JL, Berlin JA, et al. Lack of hepatotoxic effects of parenteral ketorolac in the hospital setting. Arch Intern Med 1997; 157: 2510-4
62. Walker JJ, Johnstone J, Lloyd J, et al. The transfer of ketorolac tromethamine from maternal to foetal blood. Eur J Pharmacol 1988; 3495: 509-11
63. Greer IA, Johnstone J, Tulloch I, et al. Effect of maternal ketorolac administration on platelet function in the newborn. Eur J Obstet Gynecol Reprod Biol 1988; 29 (4): 257-60
64. Diemunsch P, Alt M, Diemunsch AM, et al. Post cesarean analgesia with ketorolac tromethamine and uterine atonia. Eur J Obstet Gynecol Reprod Biol 1997; 72 (2): 205-6
65. Schorr SJ, Ascarelli MH, Rust OA, et al. A comparative study of ketorolac (Toradol) and magnesium sulfate for arrest of preterm labor. South Med J 1998; 91 (11): 1028-32
66. Ostensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? Drug Saf 1998; 19 (5): 389-410
67. Ostensen M. Nonsteroidal anti-inflammatory drugs during pregnancy. Scand J Rheumatol 1998; 107 Suppl.: S128-S32

68. Schaab KC, Dickinson ET, Setzen G. Acute sensorineural hearing loss following intravenous ketorolac administration. J Emerg Med 1995; 13 (4): 509-13
69. Otti T, Weindel M, Bastani B. Ketorolac induced acute reversible hearing loss in a patient maintained on CAPD. Clin Nephrol 1997; 47; 3: 208-9
70. Ragheb M. The clinical significance of lithium-nonsteroidal anti-inflammatory drug interactions. J Clin Psychopharmacol 1990; 10: 350-4
71. Langlois R, Paquette D. Increased serum lithium levels due to ketorolac therapy. Can Med Assoc J 1994; 150 (9): 1455-6
72. Iyer V. Ketorolac (Toradol) induced lithium toxicity. Headache 1994 Jul/Aug: 442-4
73. British National Formulary. 36th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1998
74. Summers K, Wilson R. Ketorolac injection: a review of its safety and rational use in day case and major surgery. Pharmaceut Med 1994; 8; 115-34

Correspondence and offprints: Dr *Douglas Reinhart*, University of Utah, McKay-Dee Hospital, 3939 Harrison Blvd, Ogden, UT 84401, USA.
E-mail: dreinh3223@aol.com