[Letter to the Editor]

Dear Editor:

We read with great interest "Recommendations of the National Football League Physician Society Task Force on the Use of Toradol® Ketorolac in the National Football League" by Matthew Matava et al in your September/October 2012 issue.[5] We support the recommendations of the task force that ketorolac should be administered only under the direct supervision and order of a team physician and should not be used prophylactically. However, as the developers of the intranasal formulation SPRIX® (ketorolac tromethamine nasal spray),[8] we wish to point out some additional published data regarding the pharmacokinetics of the oral formulation as compared with the intranasal formulation. This additional information suggests that oral ketorolac is absorbed more slowly after eating a meal as compared with after a 12-hour fast and suggests that parenteral forms (including intranasal) will be absorbed more rapidly than the oral formulation in a patient who has not fasted recently.

The article by Matava et al reports a t_{max} of 0.33 hours (20 minutes) for oral ketorolac and cites a review article.[2] This review article is citing data from a study by Jallad et al[3] that compared the pharmacokinetics of 10 mg oral ketorolac taken by 8 subjects between the ages of 20 and 39 years with the pharmacokinetics of 30 mg intramuscular ketorolac taken by a different 8 subjects ages 20 to 39 years. The 8 subjects that took the oral ketorolac did so after a 12-hour fast and continued to fast for 2 hours after ingesting the ketorolac. Other published reports of the pharmacokinetics of oral ketorolac in fasted subjects report t_{max} values of 30 minutes (n = 12)[7] to 53 minutes (n = 15).[4] The pharmacokinetic parameters of oral ketorolac in these 3 studies are compared with that of parenteral ketorolac (intranasal and intramuscular) in Table 1.

Table 1. Pharmacokinetic parameters of ketorolac tromethamine after oral, intramuscular, and intranasal administration

Ketorolac tromethamine	N	C_{max} (SD), ng/mL	t_{max}, min	$AUC_{0-\infty}$ (SD), ng·h/mL	$t_{1/2}$ (SD), h	Reference
10 mg, oral tablet, fasted	8	860 (210)	20 (range, 20-20)	2840 (1110)	4.69 (1.11)	3
30 mg, IM	8	2990 (1030)	45 (range, 20-120)	11,300 (3490)	4.45 (0.39)	3
10 mg, oral tablet, fasted	12	1140 (310)	30 (SD, 10)	4920 (1280)	5.57 (0.88)	7
10 mg, oral tablet, fasted	15	810 (250)	53 (SD, 38)	4810 (1340)	5.07 (0.97)	4
15 mg, IM	15	1163 (280)	45 (range, 15-90)	5196 (2077)	5.00 (172)	6
31.5 mg, IN (SPRIX®) (2 × 100 µL of a 15% w/w solution)	15	1806 (883)	45 (range, 30-120)	7477 (3654)	5.24 (1.33)	6
30 mg, IM	15	2382 (433)	45 (range, 15-62)	11,153 (4260)	4.80 (1.18)	6

C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; AUC, area under the plasma concentration–time curve; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; IM, intramuscular; IN, intranasal.

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Table 2. Mean pharmacokinetic parameters of PO ketorolac tromethamine in fasted vs fed patients

	n	C_{max}, ng/mL	t_{max}, min	$AUC_{0-\infty}$, ng·h/mL	$t_{1/2}$, h	Reference
10 mg oral capsule, fasted	12	1140	30.0	4920	5.57	7
10 mg oral capsule, high-fat breakfast	12	570	91.7	4440	5.55	7

PO, orally; C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; AUC, area under the plasma concentration–time curve; $t_{1/2}$, terminal elimination half-life.

More importantly, the absorption kinetics of oral ketorolac were slowed in subjects after a high-fat breakfast. In the study by Mroszczak et al,[7] a single 10-mg oral dose of ketorolac was assessed when administered after an overnight fast or 1 hour after a high-fat breakfast (Table 2).

Clearly, the t_{max} was prolonged and the C_{max} reduced when the oral dose was administered 1 hour after the ingestion of a high-fat meal. This may translate into reduced or delayed pain relief when oral Toradol® is ingested with food, a situation likely to occur in real-life settings. This effect is not expected for injectable or intranasal formulations. For example, scintigraphic assessment of drug disposition of ketorolac following SPRIX® intranasal dosing demonstrated that most of the ketorolac was deposited in the nasal cavity and pharynx (70%-85%), with less than 20% deposited in the esophagus and stomach.[1]

Also, we point out that Toradol® 10 mg (PO) is not indicated by the FDA for first-line analgesic therapy, and such use would be off-label. Per the prescribing information, the use of Toradol® (PO) should not be given as an initial dose and is only indicated as continuation therapy following intravenous or intramuscular dosing of ketorolac tromethamine.[9] The recommended dosing guidelines are 10 mg (PO) every 4 to 6 hours as needed, not to exceed 40 mg per day.

A single dose of SPRIX® nasal spray (31.5 mg) may be administered as a first-line analgesic, with dosing every 6 to 8 hours, for a maximum daily dose of 126 mg in adults between the ages of 18 and 65 years in patients without renal impairment.[8]

Thus, in our opinion, SPRIX® (ketorolac tromethamine) nasal spray has several advantages over Toradol® 10 mg (PO). It rapidly reaches maximum serum concentration, which is expected to occur regardless of whether the patient has recently eaten. In addition, SPRIX® may be initiated without prior intramuscular or intravenous dosing of ketorolac tromethamine. Obviously, the ability to administer the intranasal formulation without an injection means less pain to the patient. Lastly, the indicated single and maximum daily doses of SPRIX® (31.5 mg and 126 mg, respectively, in adults without renal impairment) are significantly higher than those of oral Toradol® (10 mg and 40 mg, respectively).

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