

[2003 Fall A10] Spinal ketorolac combined with intrathecal analgesics to manage intractable cancer pain

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Background : Intrathecal (IT) analgesics are used to control cancer pain when other routes have failed. Morphine (MOR) and adjuvants, bupivacaine (BUPI) and clonidine (CLO), often are used in combination but the doses are limited by side effects. NSAIDs possess central analgesic effect especially in hyperalgesic states and also potentiate opioids (1). Recently, after FDA approval, phase I safety assessment of IT ketorolac, a non-selective COX inhibitor (KETO: doses up to 2 mg), has been realized in human volunteers without serious adverse events (2). We here report our preliminary experience with IT KETO to manage intractable pain in ambulatory cancer patients.

Material and Methods : After informed consent (ketorolac is not labelled for spinal injection and IT use of the drug is still under investigation), cancer patients requiring IT administration of analgesics were included (group KETO, K, n=7; group Controls, C, n=11). Spinal analgesics included an initial combination of MOR (correlated to oral doses), BUPI 15 mg/day and CLO 30 µg/day. Doses were regularly adapted to reach satisfactory pain relief (VAS <4/10) with acceptable side effects. MOR, BUPI and CLO daily doses were recorded from day(d)0 until d90. In group K, at d7, IT bolus KETO 2 mg was administered followed by addition of KETO 2 mg/d to IT analgesic mixture. Statistical analysis used ANOVA tests. P <0.05 was significant.

Results: Age (y) and sex ratio were respectively in C and K groups: 52±13 and 57±16; 6M/5F and 5M/2F. C/K groups included patients with: visceral pain 5/3; neuropathic pain 3/4 and nociceptive pain 3/0. Duration of spinal infusion (mean; min-max) was 47d (35-130) in C and 45d (22-90) in K group. At d0, IT MOR (mg/d) was similar in C and K groups: 2.2±1.6 and 1.5±1.2. KETO IT bolus was devoid of side effect except sedation and provided rapid (< 60 min) and very effective pain relief in all patients. No side effect resulted from KETO infusion which did not modify CLO requirements but significantly allowed to reduce BUPI consumption from d10 to d28 (7.5 - 9 instead of 15 - 18 mg/d). Some MOR sparing effect was observed and IT KETO reduced MOR doses escalation in some patients. At d21 and d60 MOR (mg/d) was in C group 5.5±2.8 and 9.0±5.3 versus 3.6±2.7 and 4.6±2.9 in K group (P>0.05).

Discussion: Spinal injection of KETO in terminal cancer patients (bolus dose and continuous infusion) was well tolerated. Although the small number of patients probably precluded an objective significant MOR sparing effect, IT KETO seems to reduce doses escalation in relation with disease progression and perhaps opioid tolerance. Spinal KETO deserves further investigation as an analgesic adjuvant to relieve intractable cancer pain.

References: (1) Malmberg and Yaksh, *Science* 1992; 257: 1276-79; (2) Eisenach et al, *Pain* 2002; 99: 599-604.