

## Pilot Study of Nitric Oxide-Donating Aspirin in Patients With Pancreatic Cancer Pain

Adequate pain control in patients with pancreatic cancer improves quality of life (QOL) and may increase survival.<sup>1</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line medications in pancreatic cancer pain control, intended to keep patients comfortable without resorting to opioids. We explored the analgesic potential of the novel nitric oxide-donating aspirin (NO-ASA), which might be much safer than ASA.<sup>2</sup>

This single-center pilot study was conducted at the University Hospital, Patras Medical School, in Rion, Greece. Patients had inoperable pancreatic cancer; mild pain (a score of 1–4 on an 11-point Numeric Rating Scale [NRS]); Eastern Cooperative Oncology Group performance score > 2; life expectancy longer than 3 months; and required no opioids. Exclusion criteria were salicylate intolerance, renal or liver failure, prior treatment with opioids, or a peptic ulcer or gastrointestinal bleeding within the preceding 3 months. Research and ethics committees and the Greek Food and Drug Administration approved the study. All patients gave written informed consent.

NO-ASA was administered orally, 1 g every 8 hours for 4 weeks. At baseline and every week for 4 weeks, we performed a physical examination, blood count, and biochemistry and toxicity profile; determined pain intensity with the NRS; and

measured quality of sleep (QOS) using a single 5-point scale (0 = worst possible sleep, 5 = best possible sleep). At baseline and at weeks 2 and 4, we evaluated patients' self-reported QOL; raw scores were linearly transformed to values between 0–100.

In total, 9 men and 3 women (age 67 ± 8.6 years) entered the study; 4 non-compliant subjects were excluded from analysis. Admission pain (2.81 ± 0.38 [mean ± SEM], indicating mild pain) decreased gradually to 1.71 ± 0.57 by week 4 (Table 1). These changes were statistically significant for weeks 2–4 ( $P < 0.05$ ). QOS improved gradually from baseline to week 4; these differences failed to reach significance but represent an important trend. The better QOS was reflected in the increased hours of sleep from baseline to week 4. Global QOL improved from baseline to week 4 ( $P < 0.05$ ). As pain decreased, QOS increased ( $r = -0.75$  at week 4,  $P < 0.05$ ;  $r = -0.63$  for weeks 1–4 combined,  $P < 0.01$ ). This inverse association was also observed, but was less pronounced, between levels of pain and QOL and sleep duration.

All 12 subjects were analyzed for NO-ASA toxicity, which was acceptable and reversible: heartburn, grade 1 (n = 4); nausea, grade 1 (n = 2); vomiting, grade 1 (n = 1); somnolence, grade 1 (n = 1); headache, grade 1 (n = 1); blurred vision (n = 1); bone pain, grade 1 (n = 1).

Epigastric discomfort, grade 2; anorexia, grade 1; constipation, grade 1; bloating, grade 1; early satiety, grade 1; and insomnia, grade 1 were recorded in 2 patients.

Our data suggest that NO-ASA had a significant analgesic effect in patients with mild pancreatic cancer pain and that a total daily dose of 3 g was well tolerated. The result of this treatment was improved QOS and global QOL. The analgesic effect of NO-ASA may reflect that not all mechanisms of pancreatic cancer pain are responsive to a single agent; neuropathic pain due to celiac plexus infiltration is often resistant to anti-inflammatory analgesics.<sup>3</sup> The apparent safety of NO-ASA is important, since patients with cancer pain are a high-risk group when using NSAIDs, which may cause gastrointestinal bleeding and mask opportunistic infections related to their antipyretic effects.<sup>4</sup>

These desirable effects represent a potentially strong conclusion: In a condition as serious as advanced pancreatic cancer, NO-ASA improved patients' well-being and delayed switching to opioids or to invasive approaches. NO-ASA merits detailed future evaluation.

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**Table 1**

Mean (± SEM) Scores of Pain, Sleep, and Global Health Status/QOL

	PAIN <sup>a</sup>	QUALITY OF SLEEP <sup>b</sup>	SLEEP DURATION (hr) <sup>c</sup>	GLOBAL HEALTH STATUS/QOL
Baseline	2.81 ± 0.38	3.50 ± 0.46	6.19 ± 0.42	57.29 ± 7.29
Week 1	2.38 ± 0.65	4.38 ± 0.32	6.31 ± 0.71	ND
Week 2	1.21 ± 0.63 <sup>d</sup>	4.25 ± 0.37	6.13 ± 0.75	59.52 ± 7.37
Week 3	1.21 ± 0.63 <sup>d</sup>	4.13 ± 0.35	6.94 ± 0.57	ND
Week 4	1.71 ± 0.57 <sup>d</sup>	4.29 ± 0.36	6.44 ± 0.85	70.24 ± 7.47 <sup>d</sup>

<sup>a</sup> Measured on numeric rating scale from 0–10; higher values indicate more pain. <sup>b</sup> Measured on numeric rating scale from 1–5. <sup>c</sup> Higher values indicate better quality and longer duration of sleep and better global QOL, respectively. <sup>d</sup>  $P < 0.05$ . Abbreviations: QOL = quality of life; ND = not determined.

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