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CONTENTS

ORIGINAL ARTICLE

Transdermal opioids for cancer pain control in patients with renal impairment

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ABSTRACT

Objectives: *As guidelines for opioid use in renal-impaired patients with cancer are limited, the authors sought to assess the efficacy, safety, and tolerability, of transdermal buprenorphine for moderate/severe cancer pain in renal-impaired outpatients.*

Methods: *In a prospective parallel-group active-controlled study, n = 42 consecutively recruited outpatients with or without renal impairment (serum creatinine ≥1.3 or ≤1.2 mg/dL, respectively) were treated with transdermal buprenorphine (group BUP) or fentanyl (group FEN), respectively. Patients were followed up, at home, by the nonprofit ANT-Italia-foundation physicians in Bologna, Italy. Measurements at 10 (T1), 30 (T2), and 90 (T3) days after enrollment (T0) were pain intensity (Numerical Rating Scale [NRS]), Karnofski score, opioid dose (μg/h), rescue-dose consumption, and occurrence of adverse effects. Patients recorded subjective measurements in a personal diary. Upon data analysis, investigators were blinded to the patient group.*

Results: *At T0, in groups BUP and FEN, median NRS score was 8.0 (CI, 7.4-8.4); its reduction over time (T3; NRS = 3.0; CI, 2.1-3.8 and 2.0-4.0, respectively) was significant and constant in both groups (t-test; T0-T1, T1-T2, and T2-T3; $p < 0.0001$, $p < 0.001$, and $p < 0.05$, respectively). At all times, there were no significant differences in pain scores between the groups. In all evaluations, adverse effects were reported n = 73/126 times (60.8 percent) and showed no significant association (χ^2, $p > 0.05$) with the study groups.*

Conclusions: *Transdermal buprenorphine, in outpatients with cancer and renal impairment, is as effective, safe, and tolerable as fentanyl in patients without such impairment. These results add further evidence to the notion that buprenorphine, with its peculiar pharmacokinetics, may be an appropriate choice for opioid treatment in patients with renal impairment.*

INTRODUCTION

Impairment of renal function is a major issue in cancer and noncancer pain treatment. In patients, such as those in palliative care, who have reduced renal function or who are undergoing hemodialysis, most opioids should be administered at reduced dosages, with increased intervals between the doses; or should not be used at all because of the risk of accumulation of the parent compound or its metabolites, and hence of increased adverse effects.[1,2] Some opioids may also precipitate or aggravate pre-existing renal and hepatic disease.[2,3] Understanding the relationship between opioids and renal function is mandatory for a tailored approach that will accommodate the individual responses in terms of pain relief, tolerance, and adverse effects experienced by patients with pain.[2]

The risk of opioid use in renal impairment is stratified according to the activity of opioid parent drug

or metabolites, potential for accumulation and reports of successful or harmful use.[4] It is known that the presence of renal failure affects the pharmacokinetics of opioids and their metabolites; this is due to the altered balance between renal and nonrenal plasma clearance of these compounds.[2,5] This effect may differ among individual opioids, and for some opioids it may differ between the parent compound and its metabolites. In patients receiving dialysis, other factors related to the physical and chemical features of the molecule to be cleared as well as to the dialysis technique may also affect opioid pharmacokinetics.[2,5]

Recommendations for using opioids in patients with cancer and renal failure are limited. Such recommendations are made on the basis of pharmacokinetic data, extrapolation from noncancer pain studies and from clinical experience.[4] Mercadante and Arcuri[2] reviewed the role of endogenous opioids on renal physiology and pathologic conditions and the clinical implications of using opioids in patients with renal impairment. They concluded that clinicians should be aware of the risks of administering opioids in patients with renal impairment and should pay attention to titrating the doses or should choose opioids with a more favorable renal profile, like methadone and alfentanil. Murphy[3] reviewed the evidence for acute pain management pharmacology for patients with renal impairment. He found that among opioids, those drugs which exhibit the safest pharmacological profile are alfentanil, buprenorphine, fentanyl, remifentanil, and sufentanil; none of these deliver a high active metabolite load or show significantly prolonged clearance. He further found that hydromorphone, methadone, morphine, oxycodone, and tramadol have been used in the presence of renal failure but do require specific precautions, usually dose reduction; and that dextropropoxyphene and pethidine should not be used in the presence of chronic renal failure due to the risk of significant toxicity. Dean[5] reviewed the literature relative to opioid metabolism and the influence of renal failure and dialysis upon the clinical effects of both the parent drugs and their metabolites. He recommended that in patients with renal failure or undergoing dialysis, because of the accumulation of their active metabolites, morphine and codeine should be avoided while hydromorphone or oxycodone should be used with caution and close monitoring. The author concluded that methadone, with apparently inactive metabolites, and fentanyl/sufentanil, although their parent compound may accumulate, "appear to be safe to use" in patients with renal failure.[5] However, in this review, buprenorphine was not considered. Another systematic review of the use of opioids for cancer pain in patients with renal impairment failed to find results for diamorphine, codeine, dihydrocodeine, buprenorphine, tramadol, dextropropoxyphene, methadone, or remifentanil; whereas fentanyl, alfentanil, and methadone were identified, with caveats, as the least likely to cause harm when used appropriately.[4] Nonetheless, the authors concluded that the overall evidence is of very low quality and that the direct clinical evidence in cancer-related pain and renal impairment is insufficient to allow formulation of guidelines, but that it is suggestive of significant differences in risk between opioids.[4]

It has been argued that buprenorphine, because it is mainly excreted through the liver, can be administered at normal doses in patients with renal dysfunction, chronic renal insufficiency, or undergoing dialysis.[1-3,6-8] Thus, it appears to be a safe choice when opioid treatment is initiated in such patients.[1] Although there is some evidence for clinically insignificant accumulation of buprenorphine metabolites,[2,9,10] evidence from data submitted to authorities upon drug registrations reveals that among the six clinically most often used World-Health-Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, and oxycodone), accumulation of these drugs or, when present, their active metabolites in renal failure has been reported for all opioids except for buprenorphine.[11]

In Europe, transdermal fentanyl and buprenorphine are common pharmacological preparations used for moderate/severe cancer pain control and the use of these preparations as a first-line approach has increased substantially.[11] Transdermal opioids may be preferred over oral therapies because of better patient adherence, fewer treatment-related adverse events; and for patients unable to swallow.[12,13] Of the two opioids that are available with transdermal formulation, fentanyl is the most investigated, but based on the published data both seem to be effective for moderate/severe pain control with low toxicity and good tolerability profiles, especially at low doses.[11-13]

Given the above and the lack of straightforward guidelines for the use of opioids in renal-impaired patients, we sought to compare the efficacy, tolerability, and safety, of transdermal buprenorphine and

fentanyl for moderate/severe cancer pain control in outpatients with and without renal dysfunction, respectively.

METHODS

Patients, study design, and procedures

This prospective and observational study included outpatients with cancer who were followed for homecare by ANT Italia Onlus Foundation in Bologna, Italy. The latter is a nonprofit Foundation which guarantees, free of charge, social and clinical assistance to patients with cancer and their families in nine regions of Italy. Clinical assistance, delivered by specialized physicians, psychologists, and nurses, includes all aspects of homecare for patient with advanced cancer from diagnosis to the treatment of symptoms.

The aim of this parallel active-controlled study was to evaluate the efficacy, safety, and tolerability of transdermal buprenorphine for moderate/severe pain control in patients with cancer and renal function impairment (group BUP) as compared to that of transdermal fentanyl in patients with cancer pain without such impairment (group FEN). Thus, group BUP was considered the test arm of the study, whereas group FEN was the active control arm, as transdermal fentanyl in patients with cancer pain may be considered, based on the literature,[11-13] as standard-of-care therapy. Indeed, the most basic form of the classic clinical trial design is the parallel-group assignment which concurrently exposes two treatment groups, test and control (or active concurrent control as in this study), to alternative interventions.[14] The purpose of a controlled study, such as this one, is to derive information of general validity regarding the risk-benefit ratio of two or more therapies on the basis of the study result which is reproducible at a specified probability. Thus, a parallel design study brings more supportive evidence than an uncontrolled one out of which no information of general validity may be derived. Active control trials can have two distinct objectives with respect to showing efficacy: 1) to show efficacy of the test treatment by showing it is as good as a known effective treatment (ie, standard-of-care therapy) or 2) to show efficacy by showing superiority of the test treatment to the active control. They may also be used with the primary objective of comparing the efficacy and/or safety of the two treatments.[15] In accordance with these objectives, we have hypothesized that if the test group of transdermal buprenorphine, with its more favorable renal profile,[1,2,11] is shown to be at least as effective, safe, and tolerable for moderate/severe pain control in patients with cancer and renal impairment as transdermal fentanyl in patients with cancer without renal impairment (the standard-of-care therapy), this result, better than an uncontrolled trial, can support the evidence for using buprenorphine in patients with cancer and renal impairment.

Consecutive patients were enrolled until n = 22 patients were accrued in each study group. Inclusion criteria for both groups were 1) outpatients with advanced cancer disease followed for homecare by ANT Italia in Bologna, Italy; 2) age ≥18 years; 3) persistent (>7 days) moderate/severe (Numerical Rating Scale [NRS] ≥ 5) cancer-related pain uncontrolled by oral NSAIDs and weak opioids; 4) patients for whom oral opioids are unsuitable (due to excessive nausea, heavy load of concomitant oral therapy, and patient's preference) supported by specialist advice; 5) Karnofsky Performance Status (KPS) ≥ 50/100; 6) signed informed consent for participating in the study. Additional inclusion criteria for group BUP was serum creatinine level ≥1.3 mg/dL and for group FEN ≤ 1.2. Exclusion criteria for both groups were cognitive deterioration before and during the study time frame.

Patients in group BUP were treated for pain control with transdermal buprenorphine at a starting dose of 17.5-35 μg/h and those of the FEN group with transdermal fentanyl at a starting dose of 25 μg/h. Patients were allowed to assume morphine sulfate 10-30 mg as a rescue dose up to six times a day. Daily rescue-dose consumption of more than 60 mg of morphine sulfate yielded dose escalation of 17.5-35 μg of transdermal buprenorphine or 12.5-25 μg/h of transdermal fentanyl. Dose increments were also influenced by the presence of opioid adverse effects. Each patient was thoroughly instructed to fill a daily diary self-reporting pain intensity, rescue-dose consumption, and the advent of opioid adverse effects. Transdermal opioid dose variation over time, when needed, was decided for each patient by the physician according to pain scores, side effects, and rescue-dose consumption reported in the patient's diary. Finally, during data analysis, investigators were blinded to the patient treatment group.

Measures

Although patients were seen by their ANT physician regularly once a week for care review, data for this study were recorded at 10 (T1), 30 (T2), and 90 (T3) days after enrollment (T0). At these times, we have recorded pain intensity, using 11-point NRS (0 = no pain to 10 = worst pain I can Imagine), KPS score (0-100), patch dose (μg/h), rescue-dose consumption in the past 24 hours, and presence of opioid adverse effects (nausea, constipation, cognitive impairment, and itching). At T0, we have also recorded patient demographics, disease characteristics, pain intensity, and type (nociceptive, neuropathic [the presence of long-lasting dysesthesias, spontaneous or evoked burning pain, with a superimposed lancinating component, hyperesthesia, hyperalgesia, allodynia, and hyperpathia] or mixed), pain therapy prior to the study, and serum creatinine level.

Ethics

The study was approved by the Institutional Investigational Review Board and conducted according to the Helsinki declaration and IASP guidelines for pain research in animals and humans. All participants were personally and thoroughly informed by the investigators on the aims of the study, its structure and the pain treatment alternatives (oral or transdermal) were discussed. Patients were informed that participation was voluntary, anonymous, and would not affect their ongoing therapy. An informed consent was obtained before the study.

Data presentation and statistical analysis

All analyses were conducted using StatView for Windows (SAS Institute Inc., Cary, NC). Continuous data are reported as the mean (±standard deviation) and ordinal data as the median (95% lower and upper CI, confidence intervals). Category data are expressed in percentages.

The study's primary endpoint was steady NRS score reduction over time in both groups. Secondary endpoints were rescue-dose consumption, opioid adverse effects, and study dropouts association with the study's group. We have assumed that the hypothesis of noninferiority of the test group may be accepted if the primary endpoint would be comparable for both groups and if there would be no significant associations between the secondary endpoints and the study's groups. Differences between NRS scores over time (T0-T1, T1-T2, and T2-T3) within and between the groups were analyzed using a paired t-test (differences between the study's groups were also tested by applying analysis of variance and Fisher's protected least significant difference [PLSD]). For the secondary endpoints, differences in frequencies and category data comparisons were determined using chi-square (χ^2) analysis. Statistical significance was defined as $p < 0.05$. When appropriate, $p < 0.01$ and $p < 0.001$ were reported.

RESULTS

Of the n = 44 patients enrolled, two deceased before T1 and thus were excluded from the study. The demographics, pain treatment prior to the study, and disease characteristics of the n = 42 patients enrolled in the study are summarized in Table 1. Mean age in the sample was 72.9 (±11.0) years and most patients were females (54.8 percent); more than half of the patients (57 percent) had mixed pain type, 41 percent had nociceptive pain, and only one patient had exclusively neuropathic pain. The two groups were generally homogeneous except for serum creatinine level and pain treatment.

Mean serum creatinine level among the n = 21 patients of group BUP was 2.4 (±1.8; range, 1.3-8.3) mg/dL. The latter group was treated for pain control with transdermal buprenorphine, whereas the n = 21 patients without renal impairment (group FEN) with transdermal fentanyl.

Table 2 summarizes the mean of transdermal opioid dose and morphine rescue dose in each group as well as the median scores and CIs of KPS and NRS from T1 to T3. At T0, KPS median score was in both groups 50/100 (CI for group BUP were 46.6-51.5 and for group FEN 43.5-48.9); NRS median score was 8.0 (CI, 7.4-8.4) in both groups. Mean dose of transdermal buprenorphine increased by 48 percent from T1 to T2 and by 26 percent from T2 to T3, whereas that of fentanyl by 34 percent and 38 percent, respectively. At all times, there were no statistically significant differences between the two groups for rescue-dose consumption. KPS median scores were roughly similar in both groups at all times except for T1 when KPS were significantly lower in group FEN (t-test, p = 0.0127).

Figure 1 shows box and whisker plots of the median, interquartile range, and range of NRS

Table 1. Demographics, pain treatment, and disease characteristics in the sample			
	Sample	**FEN**	**BUP**
Patients, n (percent)	42 (100.0)	21 (50.0)	21 (50.0)
Mean age, y (±SD)	72.9 (11.0)	75.7 (8.5)	70.1 (12.6)
Female/male, n (percent)	23/19 (54.8/45.2)	15/6 (71.4/28.6)	8/13 (38.1/61.9)
Mean treatment period, d (±SD)	68.2 (29.8)	60.8 (32.3)	75.6 (25.8)
Primary tumor site,* n (percent)			
GI tract	13 (31.0)	4 (19.0)	9 (30.8)
Lung	4 (9.5)	3 (14.3)	1 (4.8)
Uro-genital	14 (33.3)	9 (42.9)	5 (23.8)
Breast	5 (11.9)	2 (9.5)	3 (14.3)
Other	6 (14.3)	3 (14.3)	3(14.3)
Metastases, n (percent)	29 (69.1)	17 (81.0)	12 (57.1)
Pain type, n (percent)			
Nociceptive	17 (40.5)	10 (47.6)	7 (33.3)
Neuropathic	1 (2.4)	0 (0.0)	1 (4.8)
Mixed	24 (57.1)	11 (52.4)	13 (61.9)

*GI tract includes stomach, colon, liver, and pancreas; uro-genital includes kidney, bladder, prostate, and uterus; and others include hematological, bone marrow, brain, and skin tumors.

scores in both groups, from T0 to T3. Pain score reduction was significant and constant over time. Indeed, in both groups, statistically significant differences were found for NRS scores between T0 and T1 (t-test, group BUP: $p < 0.0001$; group FEN: $p < 0.0001$), T1-T2 (t-test, group BUP: $p < 0.0006$; group FEN: $p < 0.0006$) and T2-T3 (t-test, $p < 0.0083$, $p < 0.001$, and $p < 0.0194$, respectively). At all times, there were no significant differences in pain scores between BUP and FEN groups (Fisher's PLSD for NRS T0, $p = 0.6225$; T1, $p = 0.0639$; T2, $p = 0.7838$; and T3, $p = 0.9194$).

As shown in Table 2, the number of cases with adverse effect was similar in both groups and decreased over time. Of the n = 126 evaluations, adverse effect were reported n = 73 times (60.8 percent). Most common adverse effects detected, variably associated, were somnolence/confusion, nausea, constipation, and pruritus. All adverse effects were treated symptomatically and no patient required treatment interruption or dose reduction. At all times (T1, T2, and T3), no statistically significant association was found between the reported adverse effects and the treatment groups (χ^2 test: T1, $p = 0.2897$; T2, $p = 0.4252$; and T3, $p = 0.2220$).

DISCUSSION

Our data suggest that in patients with cancer and renal impairment, transdermal buprenorphine is as effective, safe, and tolerable for moderate/severe pain control as transdermal fentanyl in patients with cancer without renal impairment. Given the established evidence for the role of transdermal fentanyl in pain treatment[11-13] (ie, standard-of-care therapy), the equivalent effectiveness shown for transdermal buprenorphine in patients with renal impairment supports the indication for the use of the latter in such patients.

Opioids are of prevailing importance in the treatment of acute and chronic pain conditions. Changes

Table 2. Mean patch dose, scores of KPS and NRS, and number of adverse effects, from T1 to T3, in the study groups

	Group	TDS, µg/h, mean (±SD)	Rescue dose, mg, mean (±SD)	KPS, median (CI)	NRS, median (CI)	Adverse effects, n (percent)*			
						Somnolence/ confusion	Nausea/ vomiting	Constipation	Pruritus
T1	BUP	38.3 (14.2)	58.0 (34.2)	50.0 (43.9-50.4)	5.0 (4.6-6.6)	6 (28.6)	8 (38.1)	7 (33.3)	1 (4.8)
	FEN	45.2 (20.3)	81.3 (40.7)	40.0 (34.4-44.6)	5.0 (4.9-6.6)	12 (57.1)	7 (33.3)	14 (66.7)	1 (4.8)
T2	BUP	56.7 (28.7)	98.8 (52.8)	50.0 (41.2-49.3)	4.0 (3.2-4.6)	7 (33.3)	5 (23.8)	8 (38.1)	2 (9.5)
	FEN	60.9 (24.1)	81.7 (77.3)	40.0 (33.4-46.6)	4.0 (3.4-4.9)	8 (38.1)	3 (14.3)	10 (47.6)	1 (4.8)
T3	BUP	71.2 (39.9)	106.7 (50.1)	45.0 (37.4-48.9)	3.0 (2.1-3.8)	5 (23.8)	2 (9.5)	2 (9.5)	1 (4.8)
	FEN	84.1 (30.2)	92.5 (25.0)	40.0 (31.8-50.2)	3.0 (2.0-4.0)	5 (23.8)	2 (9.5)	5 (23.8)	1 (4.8)

*The total number of adverse effects in each group may rise above the number of patients due to the presence of more adverse effects in a single patient.

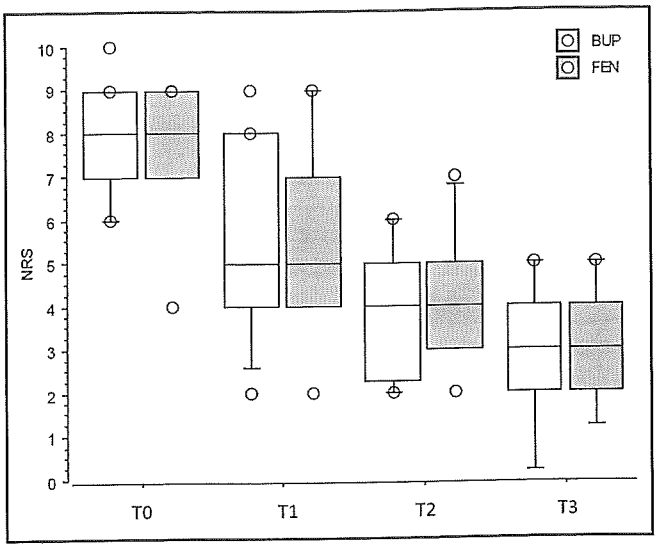

Figure 1. Box and whisker plots of the median, interquartile range, and range of both NRS scores in the sample groups, from t0 to t3. Differences among T0-T1, T1-T2, and T2-T3 were statistically significant (t-test, $p < 0.0001$, $p < 0.001$, and $p < 0.05$, respectively).

in renal function might strongly condition the use of opioids in the clinical setting.[1-5] Further, this class of drugs presents substantial physicochemical and pharmacokinetic differences, which explain the profound changes in the clinical effect in the presence of poor renal function.

Altered renal function is a major issue in drug treatment for patients with cancer. These patients often have preexisting comorbidities or risk factors that increase the probability of renal impairment before receiving potentially nephrotoxic therapies: patient age, preexisting renal dysfunction, and chronic comorbidities (eg, diabetes, kidney disease, hypertension, and cardiac insufficiency) all contribute to the risk of renal impairment. Further, both cancer and its therapies may lead to renal impairment.[2,11,16,17] A number of cancer therapy agents are nephrotoxic, including chemotherapy agents, molecular targeted agents, pain management agents, radiopharmaceuticals, contrast agents used in radiology, and antiresorptive agents.[16] Reduction in glomerular filtration rate can increase the half-life of parent drugs and metabolites that are mainly eliminated via the kidneys.[11] Further, in elderly patients, normal serum creatinine concentrations do not exclude renal impairment, and several commonly prescribed drugs require dose adjustments or should be avoided in the presence of renal insufficiency.[18] Other factors that might also affect pharmacokinetics, especially drug binding, in renal failure include hypoalbuminemia, abnormal albumin configuration, hyperlipoproteinemia, and displacement by accumulated endogenous and exogenous compounds including drug metabolites.[19] Accumulation of drug or active drug metabolites, when present, increases the risk of toxicity and the severity of drug-related adverse events.[1]

For patients with pain who have reduced renal function, such as those in palliative care, most opioids used for chronic pain treatment should be

administered with particular caution.[1,2,11] It has been reported that among clinical outcomes of the use of opioids in patients with impaired renal function, there may be increased active metabolites that may lead to long-lasting respiratory depression (morphine); reduced renal clearance of parent compound and metabolites (oxycodone); accumulation of metabolites (hydromorphone); and decreased renal clearance in the elderly (fentanyl).[1,5] Although the pharmacokinetics of buprenorphine, alfentanil, sufentanil, and remifentanil change little in patients with renal failure, the continuous administration of fentanyl can lead to prolonged sedation.[20]

In contrast, buprenorphine can be administered at normal doses in patients with renal dysfunction because it is mainly excreted through the liver.[1-3,6-8] Indeed, it is extensively metabolized into the active metabolite norbuprenorphine, primarily through cytochrome P450 (CYP) 3A4, into buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide.[21] Although both metabolites may contribute to the overall pharmacology of buprenorphine, little is known about their possible role in renal impaired humans. The fourfold rise in the plasma concentration of norbuprenorphine observed in patients with renal failure undergoing lower abdominal or peripheral body surface surgery[10] is unlikely to result in clinically significant effects.[2,9] Approximately two-thirds of buprenorphine is eliminated by the biliary system via the feces; the metabolites are eliminated via the biliary system and the kidneys. Nonetheless, the kidneys overall exposure to buprenorphine metabolites is very small.[11]

In patients undergoing regular hemodialysis, removal of an opioid during dialysis varies between individuals based on a number of factors including the dialysis technique used.[1] Morphine appears to be difficult to process in patients undergoing hemodialysis due to a possible "rebound" of metabolites between dialysis sessions. The pharmacokinetics of buprenorphine are unchanged in patients undergoing hemodialysis, which means that there is no need for dose adjustment with this drug.[1,7,22] Indeed, buprenorphine has a large volume of distribution and is highly protein bound (96 percent)[21]; these features reduce the likelihood of drug removal during dialysis.[5] Further, in cases of renal impairment, no clinically important accumulation of metabolites has been observed; therefore, a dose reduction is not necessary.[2,9,11] Thus, in patients with reduced renal function, chronic renal insufficiency, and hemodialysis, buprenorphine appears to have favorable characteristics when opioid treatment is initiated.[1,6,7]

Early guidelines recommend oral morphine as the "drug of choice" for moderate/severe cancer pain[17]; however, newer synthetic opioids can be given by a reliable and effective transdermal route.[13] Both buprenorphine and fentanyl possess ideal characteristics for transdermal delivery, both being small molecules with high lipophilicity. Transdermal fentanyl has been used for a longer period of time and has a larger body of evidence supporting its use, with data to suggest improved pain relief and reduced opioid side effects compared with sustained release oral morphine.[11-13] However, functional impairment of excretory organs, especially with respect to renal function, implies for all opioids except buprenorphine, dose reduction, a longer time interval between doses, and creatinine clearance to be monitored.[1-5] Patients who have used both oral morphine and transdermal fentanyl expressed a preference for the transdermal drug.[11-13]

Given the established value of transdermal buprenorphine and fentanyl for moderate/severe cancer pain, it is imperative to further tailor their application with respect to the risk of the presence of renal impairment. In this study, patients with or without renal impairment, treated with transdermal buprenorphine or fentanyl, respectively, showed good and long-lasting pain control with limited and acceptable opioid side effects.

Study limitations. 1) The study's sample size was relatively small and the issue of type II error may ensue. Because of the limited number of available patients and of similar trials in the literature, no power analysis could have been reported and no standards were prospectively considered to be equivalent. Indeed this study was designed as a first step toward a future trial in which efficacy, tolerability, and safety of both fentanyl and buprenorphine will be compared in renal impaired patients and where stratification will be based on serum creatinine values. Thus, the reported study was intended to convey exploratory analysis to gather clinical information, to validate the setup of the trial, and to figure out an estimate of the variability of the measurements. Based on this pilot study, a new randomized and controlled study can now be more carefully planned with satisfactory power analysis and adequate sample size. Given the consecutive nature of the screened cases and the lack of dropouts, the

sample realistically represents our daily practice. The external validity of this pilot report comes from its strong relevance to practice and the ability to highlight important clinical outcomes in daily clinical practice. 2) It can be argued that renal impairment is frequent despite normal serum creatinine levels[18] and that other methods to uncover renal dysfunction should have been used. Monitoring renal function in patients with solid tumors and hematologic malignancies is vital to the safe administration of therapeutic agents.[16] Because serum creatinine levels do not accurately reflect clearance rates, renal function should be estimated by calculation (either Cockcroft-Gault or abbreviated Modification of Diet in Renal Disease [aMDRD] equations) or by measuring creatinine clearance using a 24-hour urine collection.[23] Routinely, in our practice (ie, outpatient care setting), we use serum creatinine levels to monitor renal function. Nonetheless, post hoc calculations of renal function in the sample confirmed the appropriateness of the stratification of the patients in group BUP and FEN. Further, all patients in group BUP continued, throughout the study, to have abnormal serum levels, whereas those of the FEN group continued to show levels <1.2 mg/dL. In the future, we intend to shift our renal function monitoring to that of Cockcroft-Gault calculation. 3) Opioid titration in this study did not follow the EAPC recommendations for oral morphine titration.[17] Initial doses of buprenorphine and fentanyl patches were established on the basis of pain therapy prior to the study, whereas dose escalations were dictated by the amount of rescue doses used. We have adopted this method as opioid titration with morphine sulfate 4-hourly[17] is difficult to follow in our setting both for outpatients and for caregivers. Further, slow dose titration helps to reduce the incidence of typical initial adverse events such as nausea and vomiting; sustained release preparations, including transdermal formulations, increase patient compliance.[1,11,16]

In conclusion, the results of this study confirm that for moderate/severe pain control, transdermal buprenorphine, in outpatients with advanced stage cancer and abnormal serum creatinine levels, is as effective and tolerable as transdermal fentanyl in patients with cancer without renal impairment. These results add further evidence to the notion that buprenorphine with its peculiar pharmacokinetics appears to be an appropriate and a safe choice with respect to fentanyl, when opioid treatment is initiated in patients with cancer and renal impairment.

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REFERENCES

1. Boger RH: Renal impairment: A challenge for opioid treatment? The role of buprenorphine. *Palliat Med.* 2006; 20(Suppl 1): s17-s23.

2. Mercadante S, Arcuri E: Opioids and renal function. *J Pain.* 2004; 5(1): 2-19.

3. Murphy EJ: Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesth Intensive Care.* 2005; 33(3): 311-322.

4. King S, Forbes K, Hanks GW, et al.: A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: A European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med.* 2011; 25(5): 525-552.

5. Dean M: Opioids in renal failure and dialysis patients. *J Pain Symptom Manage.* 2004; 28(5): 497-504.

6. Davis MP: Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol.* 2012; 10(6): 209-219.

7. Filitz J, Griessinger N, Sittl R, et al.: Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *Eur J Pain.* 2006; 10(8): 743-748.

8. Pergolizzi J, Aloisi AM, Dahan A, et al.: Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract.* 2010; 10(5): 428-450.

9. Bennett WM, Aronoff GR, Morrison G, et al.: Drug prescribing in renal failure: Dosing guidelines for adults. *Am J Kidney Dis.* 1983; 3(3): 155-193.

10. Hand CW, Sear JW, Uppington J, et al.: Buprenorphine disposition in patients with renal impairment: Single and continuous dosing, with special reference to metabolites. *Br J Anaesth.* 1990; 64(3): 276-282.

11. Pergolizzi J, Boger RH, Budd K, et al.: Opioids and the management of chronic severe pain in the elderly: Consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract.* 2008; 8(4): 287-313.

12. Cachia E, Ahmedzai SH: Transdermal opioids for cancer pain. *Curr Opin Support Palliat Care.* 2011; 5(1): 15-19.

13. Caraceni A, Hanks G, Kaasa S, et al.: Use of opioid analgesics in the treatment of cancer pain: Evidence-based recommendations from the EAPC. *Lancet Oncol.* 2012; 13(2): e58-e68.

14. Husler J, Wernecke K: How to design trials/studies. In Zbinden AM, Thompson D (eds.): *Conducting Research in Anaesthesia and Intensive Care Medicine.* Oxford: Butterworth-Heinemann, 2001: 97-138.

15. European Medicines Agency: Choice of Control Group in Clinical Trials. Available at *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf.* Accessed July 4, 2013.

16. Aapro M, Launay-Vacher V: Importance of monitoring renal function in patients with cancer. *Cancer Treat Rev.* 2012; 38(3): 235-240.

17. Hanks GW, Conno F, Cherny N, et al.: Morphine and alternative opioids in cancer pain: The EAPC recommendations. *Br J Cancer.* 2001; 84(5): 587-593.

18. Wong NA, Jones HW: An analysis of discharge drug prescribing amongst elderly patients with renal impairment. *Postgrad Med J.* 1998; 74(873): 420-422.

19. Bower S: Plasma protein binding of fentanyl: The effect of hyperlipoproteinaemia and chronic renal failure. *J Pharm Pharmacol.* 1982; 34(2): 102-106.

20. Davies G, Kingswood C, Street M: Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet.* 1996;31(6):410-422.

21. Elkader A, Sproule B: Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet.* 2005; 44(7): 661-680.

22. Deng J, St Clair M, Everett C, et al.: Buprenorphine given after surgery does not alter renal ischemia/reperfusion injury. *Comp Med.* 2000; 50(6): 628-632.

23. Hudson JQ, Nyman HA: Use of estimated glomerular filtration rate for drug dosing in the chronic kidney disease patient. *Curr Opin Nephrol Hypertens.* 2011; 20(5): 482-491.