

Retrospective analysis of opioid prescriptions in cancer patients in a northern Italian Region

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We evaluated patterns of use of opioids in palliative care across one region in Italy by cross-referencing a cancer registry with unique patient identifiers, with prescription databases. There were 90 803 patients in the registry, of whom 39 597 died during the study period. Only 8539 (21%) of these were prescribed opioids at the time of their death. Prescribed daily doses of oral morphine used (45 mg) and of buprenorphine (0.71 mg) were low compared with injected morphine (28.6 mg, equivalent to approximately 90 mg of oral morphine) and especially with doses of transdermal fentanyl (1.13 mg, equivalent to approximately 180 mg morphine). The reasons for this acceptance of transdermal fentanyl and reluctance to use oral morphine are unclear, but it seems that more effort in educating healthcare professionals and patients about the use of morphine would be useful. The use of more detailed prescribing data such as prescribed or received daily doses can add to our understanding of headline prescribing data.

Introduction

Opioids are safe, effective and essential analgesics in the treatment of cancer pain [1]. Pain in cancer patients is generally undertreated [2], due to factors such as insufficient education of healthcare professionals [3, 4], fear of adverse effects, exaggerated concerns about the risks of abuse and diversion, and complex and restrictive prescription regulations [5].

Until recently, Italian legislation was very restrictive concerning the use of opioids [6], making Italy one of the lowest users of medical opioids in Europe. In a previous survey of opioid prescriptions issued for cancer outpatients in one district of the Venetian Region between 1993 and 2000 [7], we found that the vast majority of terminally ill outpatients received inadequate opioid prescriptions in terms of either dose or

therapy duration. These findings closely reflected the general situation in Italy [8].

In 2001, the Italian government eased the law on opioid prescription [6] and introduced changes including: simplification of prescription forms; an increase in the amount of opioids that can be prescribed at one time; allowing physicians to prescribe two different opioids in the same prescription, instead of only one; and a reduction of sanctions for inadvertent prescription or dispensing errors. Although there was an increase in opioid use in Italy from 16 Defined Daily Doses (DDDs) per 100 000 inhabitants per day in 2000 to 45 in 2002, morphine and buprenorphine consumption remained unchanged, and the increase was entirely due to the introduction of transdermal fentanyl in the list of drugs reimbursed by the Italian National Health-Care System [9], and not to the change in legislation.

In the present study, we evaluated the doses of opioid analgesics in palliative care in the Venetian Region (north-east Italy) and examined whether patient age and gender influence opioid prescribing.

Methods

All cancer patients who died between 1 January 2000 and 31 December 2002 and had been on continuous therapy (i.e. who received at least one prescription per month) with opioids up to the time of their death were identified by cross-referencing the comprehensive prescription database of the 22 Local Health Authorities of the Venetian Region (about 4500 000 inhabitants) with the Regional Cancer Registry (Registro Tumori della Regione Veneto), using each patient's unique identifying number.

Three opioids (morphine oral and injectable; buprenorphine, sublingual tablets; and fentanyl, transdermal patches) were available at the time.

Opioid prescription adequacy was estimated by means of the following indicators:

- 1 DDD. The official opioid DDD values issued in 2002 by the World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology [10] were used: 100 and 30 mg for oral and parenteral morphine, respectively; 1.2 mg for buprenorphine; and 0.6 mg for transdermal fentanyl.
- 2 Prescribed Daily Dose (PDD), i.e. the average opioid dose (mg) prescribed, calculated according to the following equation:

$$\text{PDD} = \frac{\sum[\text{total dose prescribed per day} \times \text{days at that dose}]}{\text{length of therapy}}$$

- 3 Received Daily Dose (RDD) was the mean opioid dose (mg) actually received by a patient per day, calculated according to the following equation:

$$\text{RDD} = \frac{[(1\text{st received dose} \times \text{days}) + (2\text{nd received dose} \times \text{days}) + (3\text{rd received dose} \times \text{days}) + \dots]}{\text{total length of therapy}}$$

For each patient, the length of therapy was calculated from the date of the first prescription to the date of death.

Results

During the study period, 90 803 patients had a diagnosis of cancer, of whom 39 597 (43.6%) died (22 841 men and 16 756 women) in the same period. Of these, 8539 (21.5%) (4967 men and 3572 women) were treated with opioids at the time of death and therefore met the inclusion criteria for the study.

Opioid prescription

PDD and RDD values were lower than the DDDs for oral morphine and buprenorphine, whereas, for injectable morphine, the PDD was similar (Table 1). These doses were not affected by changes in legislation around opioid prescribing. Oral morphine RDD was 1.4-fold

Table 1

Opioid prescription to patients who died with cancer in the Venetian Region between 1 January 2000 and 31 December 2002

	Oral	Morphine Injectable	Transdermal fentanyl	Buprenorphine
Number of patients	5482	434	1929	694
DDD mg	100	30	0.6	1.2
PDD mg (95% CI)	45.6 (45.4, 45.7)	28.6 (28.4, 28.8)	1.1 (1.1, 1.1)	0.7 (0.7, 0.7)
RDD mg (95% CI)	62.8 (62.7, 62.8)	23.5 (23.2, 23.7)	1.2 (1.2, 1.2)	0.7 (0.7, 0.7)

DDD, Defined Daily Dose; PDD, Prescribed Daily Dose; RDD, Received Daily Dose.

Table 2

Morphine and transdermal fentanyl Prescribed Daily Doses (PDDs) by patient age and gender

Age (years)	n	Morphine PDD (95% CI)		Transdermal fentanyl PDD (95% CI)	
		Men	Women	Men	Women
0–44	350	ND	ND	ND	ND
45–54	910	57.7 (57.1, 58.3)	42.3 (41.7, 42.9)	ND	ND
55–64	1976	52.4 (52.4, 53.1)	49.1 (48.8, 49.4)	1.4 (1.3, 1.4)	0.9 (0.8, 0.9)
65–74	2924	53.9 (53.6, 54.1)	45.6 (45.3, 45.8)	1.5 (1.5, 1.5)	1.0 (1.0, 1.0)
≥ 75	2379	38.1 (37.9, 38.3)	34.4 (34.3, 34.6)	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)

ND, Not determined, because of the small number of patients.

higher than the PDD. In the case of transdermal fentanyl, both PDD and RDD values were higher than the DDD.

Older patients received lower doses of morphine than younger patients, but not of fentanyl. There were minor differences in the prescribed daily dose of morphine and fentanyl between men and women (Table 2). The mean duration of opioid therapy was 108 days [95% confidence interval (CI) 107.8, 108.2]: shorter for morphine (93 days; 95% CI 92.8, 93.2) than for either buprenorphine (128 days; 95% CI 125.8, 130.2) or transdermal fentanyl (115 days; 95% CI 114.5, 115.5).

Discussion

Only 21% of the patients who died of cancer in the region over the 3 years of the study were ever prescribed opioids. In most cases, the doses used were less than the WHO DDDs, though not when fentanyl was used. The DDD is not of course a recommended dose in an individual patient, nor does it imply therapeutic equivalence across a range of drugs; rather, it is based on the recommended dose in adult use across several countries and is intended to allow international comparisons of drug utilization. We cannot judge the adequacy of the pain relief therefore by examination of DDDs, but would need pain scores for the patients either treated or not treated with opioids. Nevertheless, in the absence of such data and based on evidence that in the late stages of their illness most cancer patients usually suffer moderate to severe pain, we hypothesize that there is inadequate use of opioid analgesics. We suggest that physician 'opiophobia' and insufficient patient knowledge and education could partly explain this.

To evaluate opioid consumption, we have used two indicators, i.e. PDD and RDD as well as the DDD. These add further explanatory value in that, for instance, for oral morphine, RDD is higher than PDD, indicating

that cancer patients take morphine at a higher dose than that prescribed by the physician. In contrast, for injectable morphine, the RDD is lower than PDD, suggesting use below prescribed levels, perhaps due to difficulties of administration, or patient or carer reluctance. For buprenorphine, both PDD and RDD are equal, suggesting good compliance with prescription and ease of use.

A completely different situation is observed in the use of transdermal fentanyl, whose PDD and RDD are similar but twice the DDD. This may suggest that the DDD is too low for adequate pain relief. This is supported by recent clinical trials [11] and by the recent decision of the WHO Collaborating Center for Drug Statistics Methodology in April 2005 [12] to raise the DDD of transdermal fentanyl from 0.6 to 1.2 mg day⁻¹.

The British National Formulary [13] defines transdermal fentanyl 0.6 mg day⁻¹ as equianalgesic to oral morphine 90 mg day⁻¹ and to approximately 30 mg of injectable morphine, in keeping with the older DDDs. It would seem therefore that doctors are willing to prescribe transdermal fentanyl in much higher doses (equivalent to approximately 180 mg oral morphine) and thereby greater analgesic effect than morphine. This may be the result of successful marketing, or patient acceptance. This may also be reflected in the duration of therapy, which is longer for fentanyl than for morphine. While this may be for patient benefit, it suggests that further education on the proper use of morphine would be useful.

There were differences in the dose of opioids prescribed for men and women – this may be explained by simple pharmacological influences such as body weight, or may relate to cultural and gender effects on perception of pain. The reasons for lower doses in the elderly may be similarly explained, but with the addition of greater sensitivity to opioids. Most other studies suggest

little effect of gender in palliative opioid use, but show the same decrease in dose in the elderly [14].

In summary, our data indicate that only a small proportion of cancer patients in the Venetian Region were treated with opioids during the 3-year period considered. In addition, oral morphine is generally used at low doses, well under the suggested DDD, while transdermal fentanyl is used at higher doses and would be expected therefore to have a greater analgesic effect. As a whole, our results outline some limitations in the use of opioid DDD by itself in drug use studies and indicate the value of other indicators such as PDD and RDD. Greater efforts to educate healthcare professionals, patients and family members are needed.

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