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Off-label use of fixed-dose combination of tramadol and dexketoprofen in primary health care. Evidence-based or cause for concern?

Uso fuera de indicación de la combinación a dosis fija de tramadol/dexketoprofeno en atención primaria de salud: ¿Basado en la evidencia científica o motivo de preocupación?

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ABSTRACT

Introduction: The use of the fixed-dose combination of tramadol/dexketoprofen in Spain and in other countries has increased considerably. The authorized therapeutic indication for this medicinal product is the short-term symptomatic treatment of moderate to severe acute pain in adult patients. The objective of this study was to describe the pattern of use of tramadol/dexketoprofen in the field of primary health care.

Method: A cross-sectional, descriptive and multicenter study was carried out. The study population included all patients from a Primary Care Department (53 Primary Care teams) with an active prescription of tramadol/dexketoprofen on March 28, 2018. The target population was those patients who were prescribed tramadol/dexketoprofen. dexketoprofen for >20 days.

Results: A total of 176 patients had an active prescription for tramadol/dexketoprofen. All patients (100%) had a duration of treatment greater than 5 days and 72.7% (N=128) greater than 20 days. The mean duration of treatment was 14±160.9 days in patients who had less than 20 days of treatment and 224±160.8 days in patients who had more than 20 days of treatment. 35.1% of the patients were treated with >2 pain medications and concomitantly with tramadol/dexketoprofen. The general practitioner initiated 65.6% of the prescriptions.

Conclusions: The fixed-dose combination of tramadol/dexketoprofen was frequently used off-label, according to the product characteristics and the available scientific evidence. This study warns about the potential risks associated with the use of this drug in clinical practice, such as lack of effectiveness and/or the appearance of adverse effects.

Key Words: Off-label use; opioid; pharmacoepidemiology; primary health care; tramadol/dexketoprofen; drug combinations.

RESUMEN

Introducción: La utilización de la combinación a dosis fija de tramadol/dexketoprofeno en España y en otros países ha aumentado de forma considerable. La indicación terapéutica autorizada de este medicamento es el tratamiento sintomático a corto plazo del dolor agudo de moderado a intenso en pacientes adultos. El objetivo de este estudio fue describir el patrón de uso de tramadol/dexketoprofeno en el ámbito de la atención primaria de salud.

Método: Se realizó un estudio transversal, descriptivo y multicéntrico. La población de estudio incluyó a todos los pacientes de una Dirección de Atención Primaria (53 equipos de Atención Primaria) que tenían activa la prescripción de tramadol/dexketoprofeno el 28 de marzo de 2018. La población diana fueron aquellos pacientes a los que se les prescribió tramadol/dexketoprofeno durante más de 20 días.

Resultados: Un total de 176 pacientes tenía activa la prescripción de tramadol/dexketoprofeno. Todos los pacientes (100%) tuvieron una duración del tratamiento superior a 5 días y el 72,7% (N=128) superior a 20 días. La duración media del tratamiento fue de 14±160,9 días en pacientes que tenían menos de 20 días de tratamiento y de 224±160,8 días en pacientes que tenían más de 20 días de tratamiento. El 35,1% de los pacientes estaban tratados con más de 2 medicamentos para aliviar el dolor de forma concomitante con tramadol/dexketoprofeno. El médico de atención primaria inició un 65,6% de las prescripciones.

Conclusiones: La combinación a dosis fija de tramadol/dexketoprofeno se utilizó con frecuencia fuera de indicación, de acuerdo con la ficha técnica y la evidencia científica disponible. Este estudio alerta sobre los riesgos potenciales asociados a la utilización de este medicamento en la práctica clínica, como son la falta de efectividad y/o la aparición de efectos adversos..

Palabras clave: Uso fuera de indicación; opioide; farmacoepidemiología; atención primaria; tramadol/dexketoprofeno combinación de medicamentos.

Key points

Off-label use of the fixed-dose combination of tramadol and dexketoprofen is common, despite lacking evidence of efficacy and potentially increasing risk for adverse drug effects.

Tramadol/dexketoprofen should be prescribed with a diagnosis associated with acute pain and for the five days authorised according to the product characteristics.

Two thirds of the prescriptions came from the general practitioner and interventions directed at them are needed to promote an appropriate use.

Introduction

The estimated prevalence of chronic pain in the US is 11%[1] and 19% in Europe[2]. Not only the US[3] but also some European countries such as Germany[4] and United Kingdom[5] have shown a significant increase in the consumption of opioid analgesics and the trends in mortality due to opioid poisoning pointing out similarities to the US. So far, the key points of opioids that have raised are the increased risk of misuse (diversion), overdose, death, abuse, dependence, bone fractures, myocardial infarctions, constipation and sexual dysfunction[6].

A recent study about the prescribing patterns of opioids from 2013 to 2017 in one of the main health administrative regions in Portugal showed an increase approximately 1.5-fold over a 4-year period (2013-2017).[7] In Spain, the use of opioids for the period 2010-2021[8] went from 9.9 defined daily doses (DDD) per 1,000 inhabitants per day to 20.9 (DHD).

The appearance on the market of tramadol/dexketoprofen 75 mg/25 mg film-coated tablets in 2016 and the increase of consumption in 2017 are noteworthy.[9] In Spain this consumption has been growing and in 5 years it has gone from 0.22 DHD in 2017 to 0.42 DHD in 2021.[8] According to its summary of product characteristics (SmPC)[10] the authorised therapeutic indication is symptomatic short-term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen. The recommended dosage is one tablet with a minimum dosing interval of 8 hours, without exceeding three tablets per day and five days of treatment. Switching to a single agent analgesia should be considered according to pain intensity and response of the patient.[11]

Despite the progressive change and the increasing use observed that can impact of pain as a public health issue, there have not been published studies on the use of the combination tramadol/dexketoprofen in clinical practice. Thus, we aimed to describe the pattern of use of fixed-dose combination of

tramadol/dexketoprofen in the field of primary health care to examine potential off-label prescribing, warn about possible risks and suggest interventions.

Methods

A descriptive, cross-sectional and multicenter study was carried out between March 2017 and March 2018. It covered the 53 primary health care teams and 4 primary care services in the Department of Primary Care (DAP) *Costa de Ponent* of the Catalan Institute of Health (ICS), which provides health care for 1.3 million inhabitants in the southern Barcelona Metropolitan Area (Catalonia, Spain). ICS gives coverage to 42,374 professionals who provide health care to 80% of the Catalan population out of a total of 7,780,479 inhabitants. (12)

Total population in the study were patients covered by the DAP *Costa de Ponent* with an active prescription of tramadol/dexketoprofen on March 28, 2018 (cut-off date chosen as a cross sectional data to provide a snapshot of drug use at a day). Target population were those patients who were prescribed tramadol/dexketoprofen over 20 day's treatment, since it was considered 20 days as the limit for a short-term treatment of acute pain.

The computerized health records of patients with active tramadol/dexketoprofen prescription were selected from the e-CAP computer program and extracted from anonymized data. The analyses were performed on patients who had more than 20 days of treatment.

The variables studied were demographic (age, sex) and clinical (prescribers' specialty; characteristics of the study drug (combined tramadol/dexketoprofen) regarding indications, dosing and duration of treatment; diagnoses of target patients; previous analgesic treatment and concomitant analgesic treatment).

A descriptive statistical analysis of the data was carried out. Discrete variables were shown as proportions or frequencies and continuous variables as means and standard deviations.

Ethical approval was not required as it was made a secondary analysis in accordance with Spanish regulations at the moment of the study performed.

Results

On the cut-off date, there were 176 patients with active prescription of tramadol/dexketoprofen. All these patients (100%) had a treatment duration exceeding 5 days (average age: 54.7±13.4 years, 14.2% were women) and 72.7% (N=128) exceeding 20 days (average age: 54.7±13.5 years, 73.4% were women). The mean duration of treatment was 14±160.9 days in patients who

had less than 20 days of treatment and 224±160.8 days in patients who had more than 20 days of treatment. Figure 1 (a-d) shows the distribution of patients exceeding 20 days according to the origin of prescriptions, dosing, duration of treatment and diagnoses. Twelve patients did not have any diagnosis specified at e-CAP and they could not be included in Figure 1d (N=116).

Figure 1 (a-d). Distribution of patients according to the (a) origin of prescriptions, (b) dosing, (c) duration of treatment and (d) diagnoses.

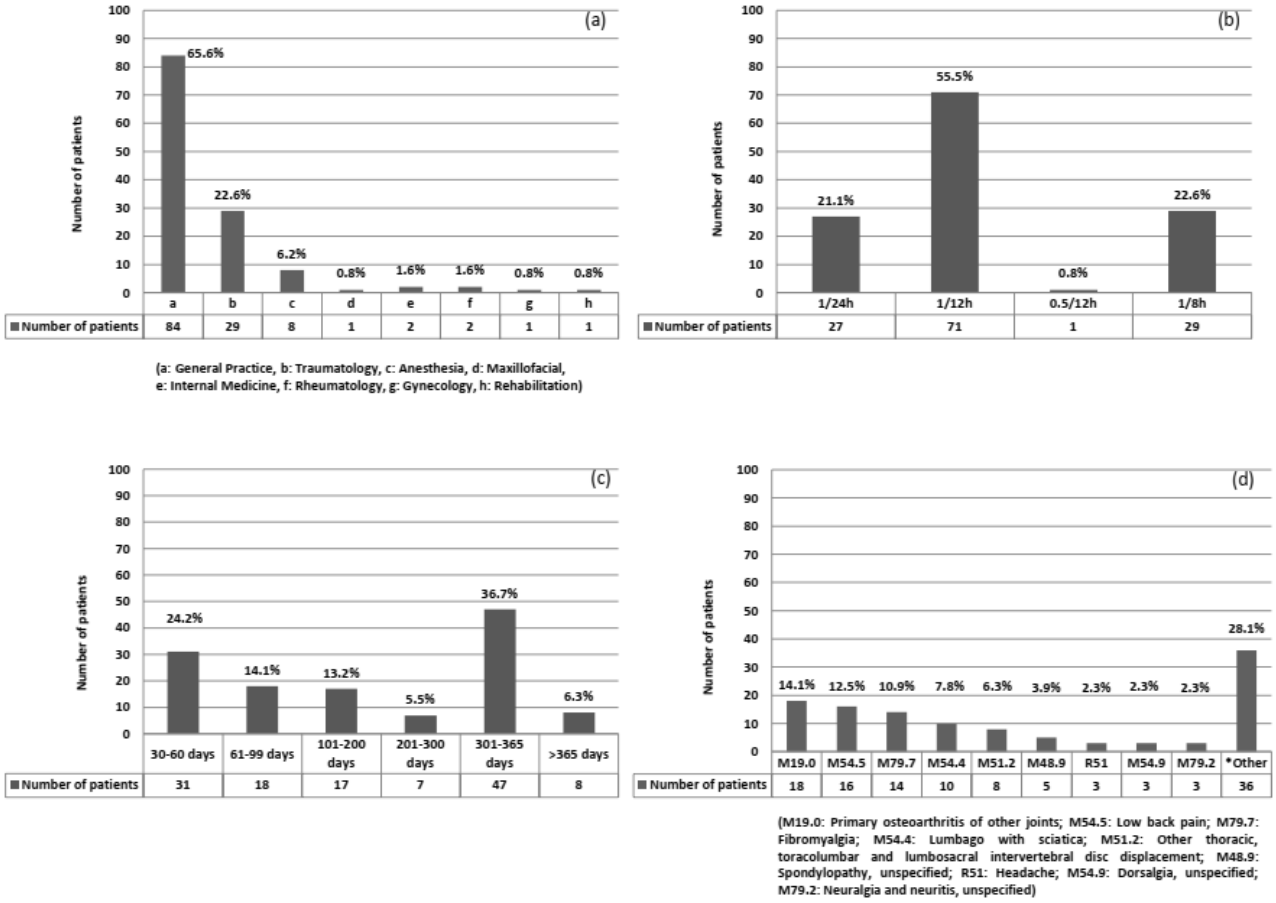

Table 1 shows in detail the diagnoses classified as “Other” in Figure 1d. Only three patients out of 128 (2.3%) had a treatment associated with an oncological diagnosis. The diagnoses of these patients were malignant neoplasm of cheek mucosa, osteochondroma and malignant neoplasm of ovary. Neither of them took the maximum prescribed daily dose (three tablets per day), nor of them took a longer treatment duration compared to the study population. In addition, the patient with osteochondroma was the only men and who did not take concomitant medication. The other two patients took acetaminophen.

Table 1. Diagnoses classified as "Other" (Figure 1d).

Sub-populations	ICD code	Other diagnoses	Number of patients (%)
Locomotor system	M25.5	Pain in joint	2 (1.6)
	M72.2	Plantar fascial fibromatosis	2 (1.6)
	M70.6	Trochanteric bursitis	2 (1.6)
	S43.001	Unspecified subluxation of right shoulder joint	1 (0.8)
	S42.0	Fracture of clavicle	1 (0.8)
	S12.0	Fracture of first cervical vertebra	1 (0.8)
	T07	Unspecified multiple injuries	1 (0.8)
	M06.9	Rheumatoid arthritis, unspecified	1 (0.8)
	Z96.69	Presence of other orthopedic joint implants	1 (0.8)
	M65.0	Abscess of tendon sheath	1 (0.8)
	M75.0	Adhesive capsulitis of shoulder	1 (0.8)
	M62.40	Contracture of muscle, unspecified site	1 (0.8)
	M65.2	Calcific tendinitis	1 (0.8)
	S52.502	Unspecified fracture of the lower end of left radius	1 (0.8)
	M80.9	Unspecified osteoporosis with pathological fracture	1 (0.8)
Neurological system	R53.82	Chronic fatigue, unspecified	1 (0.8)
	G43.1	Migraine with aura	1 (0.8)
	G93.3	Postviral fatigue syndrome	1 (0.8)
	M89.00	Algoneurodystrophy, unspecified site	1 (0.8)
	G62.9	Polyneuropathy, unspecified	1 (0.8)
	F32.2	Major depressive disorder, single episode, severe without psychotic features	1 (0.8)
	F90	Attention-deficit hyperactivity disorders	1 (0.8)
	F41.9	Anxiety disorder, unspecified	1 (0.8)
	M54.1	Radiculopathy	1 (0.8)
Internalist diagnoses	R10.3	Pain localized to other parts of lower abdomen	1 (0.8)
	E03.9	Hypothyroidism, unspecified	1 (0.8)
	E79.0	Hyperuricemia without signs of inflammatory arthritis and tophaceous disease	1 (0.8)
	N18.9	Chronic kidney disease, unspecified	1 (0.8)
	I87.2	Venous insufficiency (chronic) (peripheral)	1 (0.8)
	J31.1	Chronic nasopharyngitis	1 (0.8)

Sub-populations	ICD code	Other diagnoses	Number of patients (%)
Oncological	C56	Malignant neoplasm of ovary	1 (0.8)
	C06.0	Malignant neoplasm of cheek mucosa	1 (0.8)
	D16	Osteochondroma	1 (0.8)

Concerning medication prior to tramadol/dexketoprofen associated with the treatment of pain, 14.1% of patients (N=18) had not taken any medication for pain before. In contrast, 18.8% (N=24) had been previously treated with one medication for pain, 25.8% (N=33) had been previously treated with 2 drugs and 41.4% (N=53) had been previously treated with more than two drugs. Finally, 7.8% of total study population (N=10) had been previously treated with tramadol and dexketoprofen separately.

Regarding the associated pain medication prescribed concomitantly with tramadol/dexketoprofen, 14.1% of patients (N=18) had not ever taken any medicine for pain at any time during treatment with tramadol/dexketoprofen. The 26.6% of patients (N=34) had been treated with one medicine for pain in addition to tramadol/dexketoprofen, 24.2% (N=31) with two and 35.1% of patients (N=45) with more than two. There were 1.6% of patients (N=2) who took medication for migraine (sumatriptan, rizatriptan and clonazepam) concomitantly with tramadol/dexketoprofen. Table 2 shows the active substances and/or therapeutic groups that had been prescribed previously and concomitantly with tramadol/dexketoprofen.

Table 2. Drug treatment previous and in combination with tramadol/dexketoprofen.

Active substances and therapeutic groups	Number of drugs previous	%*	Number of drugs in combination	%*
Analgesics[a]	87	67.9	90	70.3
Weak opioids[b]	75	58.6	47	36.7
Antiepileptics/Analgesics[c]	32	25.0	46	35.9
NSAIDs[d]	79	61.7	42	33.1
Skeletal muscle relaxants[e]	13	10.2	24	18.8
Lidocaine	8	6.3	10	7.8
Corticosteroids[f]	7	5.5	9	7.0
Sumatriptan	0	0	2	1.6
Fentanyl	1	0.8	1	0.8

(*Since a patient may be associated with different products at once, total exceeds 100%; a-Acetaminophen, metamizole; b-Tramadol, tramadol/acetaminophen, oxicodone/naloxone, codeine/acetaminophen; c-Pregabalin, gabapentin, amitriptilyne, duloxetine; d-Etoricoxib, diclofenac, naproxen, dexketoprofen, ibuprofen; e-Cyclobenzaprine, diazepam; f-Prednisone, dexamethasone)

Discussion

Current evidence indicates that opioids should not be used as first line therapy, but only when all other treatment options have been tried and failed[11] The National Institute for Health and Care Excellence's (NICE) found no evidence of long-term effectiveness in chronic non-cancer pain treatment, despite its analgesic effect in the short-term.[13] Furthermore, prescribing of opioids for acute indications such as surgical pain in opioid-naïve patients can also lead to a transition to chronic opioid therapy.[5]

A higher percentage of women with active prescription and an average age of 54.7 years were expected data since the prevalence of pain for more than three months is more common in women and in people over 65 years old in Spain.

Exploring the origin of the prescriptions, most of them came from the general practitioner, when a prescription by a specialist would be advisable.[14] The influence of general practitioner on the dissemination of opioids is substantial to promote an appropriated use. Insufficient training and information about opioid management protocols, time pressure to assess patients properly and system-level constraints such as limited access to specialized and integrative care are some of the reasons that could explain the off-label prescription of opioids.[14]

About the duration of treatment, 36.7% of patients had a prescription with durations between 9.5 and 12 months. According to the SmPC of tramadol/dexketoprofen,[10] it is intended only for short-term use and treatment should be limited strictly to the symptomatic period (5 days). Although in our study, only three patients had post-surgical pain treatment and for 10 days, several studies of chronic postsurgical pain [14] showed that if postoperative pain is not managed properly, it could evolve in chronic pain, becoming a serious problem. In addition, in the absence of evidence on the efficacy and safety of long-term opioid use, it is recommended to re-evaluate at three months the opioid treatment.[11]

In relation to the diagnoses found, tramadol/dexketoprofen was hardly used in cancer pain management or in the context of palliative care what is a cause of concern considering the long-term treatment observed (more than 300 days) in 43% of patients. In reference to the most common diagnoses (primary osteoarthritis, low back pain, fibromyalgia and lumbago with sciatica), nociceptive pain was highly prevalent and should be treated with analgesics and anti-inflammatory drugs. Although long-term opioid treatment has not yet been widely studied on a population basis, many patients may tolerate and respond to this treatment, and it should not be denied to them, with a close follow-up in terms of effectiveness and safety.[15]

The first line use of tramadol/dexketoprofen in off-label indications would require more research. The combination of analgesic products in general should be avoided as first-line treatment, because it does not allow independent assessment of each drug.[16] There are no comparative studies with other associations of analgesics, but there is so in monotherapy, obtaining better results with the combination tramadol/dexketoprofen.[17,18]

In addition, the prescription of concurrent treatments given alongside tramadol/dexketoprofen was analyzed. Painkillers, NSAIDs, antiepileptics and weak opioids were found to be the most prescribed. This information was expected as the indications for the prescription of tramadol/dexketoprofen were bone and joint pain, fibromyalgia and low back pain with sciatica.

It was also found that 26.6% of patients prescribed with tramadol/dexketoprofen had been treated concomitantly with one of the two components of this drug, which was unable to account for.

Interventions to improve prescribing should be carried out since there are numerous contraindications and precautions related to tramadol/dexketoprofen, as well as risk of tolerance and addiction.[10] Therefore, some interventions were be realized and warnings have been introduced in the electronic primary care clinical station that alert of the inadequate duration of treatment during the prescription process (Prefasec program, safe pharmacological prescription module).[19] Additionally, prescribers have now the option of reviewing the safety of their patients' treatments of tramadol/dexketoprofen through a support tool (self-audit) that facilitates the systematic review of medication and detects inadequate treatments. Also, some interventions could be that patients had an assessment of their pain and their perspectives regarding the use of this drug (and opioids in general), and general practitioner considered them to promote their correct use, specially preventing their misuse.[11] Another possibility could be to make a reminder to general practitioners about the indications of tramadol/dexketoprofen and provide information about the inadequate diagnoses and/or prolonged use in chronic noncancer pain, and alternatives in such cases according to evidence.[5]

Our study has several limitations. This is a drug utilization study, focus on a specific region with a population with active prescription and in the context of new medicines available under the public financing system. Furthermore, the conclusions may not be directly applicable to other regions as the prescription may be influenced by different factors, including, among others, morbidity, characteristics of the prescribing physicians, or the number of specialists per inhabitant.

Conclusion

The present study points out that tramadol/dexketoprofen is frequently used off-label, as treatments were usually prescribed without a diagnosis associated with acute pain and were lengthened beyond the days authorised and in most cases 4 times longer than the time period indicated. These results warn about potential harmful or ineffective effects ("concern") of tramadol/dexketoprofen combination since no adequate evidence exists about its off-label use. Interventions to improve tramadol/dexketoprofen prescribing for the treatment of moderate-to-severe acute pain are needed.

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