Tramadol and hypoglycaemia: comparison with other step 2 analgesic drugs

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Whereas dextropropoxyphene (DXP) has been recognized as a possible cause of hypoglycaemia, only isolated reports have described a similar adverse effect with tramadol (TRM).
- To the best of our knowledge, there is no large study comparing the occurrence of hypoglycaemia in patients treated with these step 2 analgesics.

WHAT THIS STUDY ADDS

- The aim of this study was to describe spontaneous reports of hypoglycaemia associated with TRM and to compare these data with that of DXP-induced hypoglycaemia.
- The results show that the characteristics of hypoglycaemia in tramadol users are very similar to those described with DXP, with old age, diabetes and renal insufficiency as the main risk factors.
- Physicians and patients should be warned of this potential adverse effect.

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AIMS

The risk of hypoglycaemia with tramadol (TRM) is not well described. Our aim was to analyze spontaneous reports of hypoglycaemia registered in the French Pharmacovigilance database and to compare these data with two other step-2 analgesic drugs.

METHODS

Cases of hypoglycaemia associated with TRM, dextropropoxyphene (DXP) and codeine (COD) recorded between 1997 and November 2010 in the French pharmacovigilance database were compared.

RESULTS

Seventy-two cases of hypoglycaemia associated with DXP and 43 with TRM were retained for evaluation (the single case reported with COD was not further considered). Most patients were elderly people with no significant difference in age between DXP- and TRM-treated patients (71.2 ± 21 vs. 69.4 ± 22.5 years). Hypoglycaemia occurred after a median of 4 and 5 days with DXP and TRM treatment, respectively. The mean lowest serum glucose concentration was 2.1 ± 0.9 mmol L⁻¹ in the DXP group compared with 2.5 ± 1 mmol L⁻¹ in the TRM group ($P = 0.072$). At least, one risk factor of hypoglycaemia was found in most patients, with no significant difference between groups (58.3% in the DXP group and 58.1% in the TRM group). In particular, 31.9% patients from the DXP group had diabetes compared with 41.8 % from the TRM group ($P = 0.28$) and 18% of DXP patients had renal insufficiency compared with 16.3% of TRM patients ($P = 0.8$).

CONCLUSIONS

Our study confirms that TRM is associated with the occurrence of hypoglycaemia in elderly or predisposed patients, with characteristics similar to those previously reported with DXP.

Introduction

Tramadol (TRM) is a centrally acting weak opioid analgesic, which belongs to the step 2 analgesic classification according to the World Health Organization. It was marketed in France in 1997. TRM is used either alone or in association with paracetamol (acetaminophen) for the treatment of moderate to moderately severe pain. TRM acts through the activation of μ -opioid receptors and in addition inhibits the central re-uptake of serotonin and norepinephrine, which are both involved in central nociceptive transmission [1]. The most frequent adverse effects associated with TRM include gastrointestinal disorders (nausea, vomiting and constipation) and neuropsychiatric effects (sedation, confusion, dizziness, anxiety and sweating) [2].

As recommended by the European Medicines Agency in October 2009, all medicines containing DXP, another weak opioid analgesic, have been withdrawn from the European market in March 2011 because the benefits did not outweigh the risks, in particular in the case of overdoses [3]. Although several investigators have shown that DXP withdrawal from a French hospital was not associated with an increase in step 2 analgesic consumption [4], it is reasonable to anticipate an increase in TRM or codeine (COD) sales in the near future. It is therefore essential to carefully take into account all possible adverse effects associated with these drugs.

To date, only DXP has been clearly associated with the occurrence of hypoglycaemia [5–8]. The first report was published in 1967 [9]. This adverse effect has been mentioned in the summary of the product characteristics (SPC) of DXP for many years and is not mentioned in the SPC of either TRM or COD. Whereas no cases of hypoglycaemia associated with COD have been published so far despite many years of marketing, several isolated cases of TRM-induced hypoglycaemia have been reported in the literature [10–12]. Based on an analysis of spontaneous reports of hypoglycaemia associated with step 2 analgesics and recorded in the French pharmacovigilance database (FPD), the aim of the present study was to investigate whether TRM or COD could be associated with the occurrence of hypoglycaemia, and to compare the characteristics of these hypoglycaemias with those induced by DXP.

Methods

Spontaneous reports of hypoglycaemia or related terms submitted to the network of the 31 French regional pharmacovigilance centres and recorded in the FPD from 1 January 1997 to 30 November 2010 with drugs containing COD, DXP or TRM coded as suspected or interacting drugs were extracted. Because several cases of true hypoglycaemia were clearly mentioned in the narrative, but mistakenly coded with the clinical symptoms only, two complementary search strategies were performed. The

first involved the use of the Medical Dictionary for Regulatory Activities (MedDRA) high level terms containing 'hypoglycaemic conditions' in the coded adverse effect and the second was based on the presence of the strings "%lyc_mi%" in the case narrative (% for truncation and _ to ignore letter with accent).

All cases were carefully reviewed. Cases with insufficient data, unconfirmed hypoglycaemia in the narrative, serum glucose concentrations higher than 3.9 mmol l^{-1} , concomitant exposure to any of the selected drugs, obvious other causes such as severe malnutrition, rapid loss of weight, acute alcohol intake, occurrence of hypoglycaemia in a context of suicide attempt, absence of recovery despite drug discontinuation or a Naranjo probability scale indicating a doubtful score [13] were excluded for further analysis. Missing values of glucose concentrations in the narrative were not considered an exclusion criteria provided hypoglycaemia was coded as an adverse effect and suggestive symptoms of hypoglycaemia were associated. Data analyzed for the remaining cases were the patient's characteristics including underlying diseases, the dosage forms, the time to onset of hypoglycaemia after starting the suspected drug, the lowest recorded serum glucose concentration, the presence of clinical symptoms suggestive of hypoglycaemia and the presence of serious criteria defined as any case resulting in death, hospital admission or prolongation of existing hospital stay, persistent or significant disability/incapacity or life threatening. Diabetes and other risk factors known to be associated with hypoglycaemia, such as acute or chronic renal insufficiency, concomitant infection, hepatic insufficiency, alcohol intake, intestinal resection, dysthyroidism, cancer and hyperinsulinism, were also taken into account. Patients were considered to have diabetes if this was clearly mentioned in the narrative, coded in the relevant medical history field or when concomitant exposure included antidiabetic drugs. Regarding the possible presence of clinical symptoms, cases were classified as asymptomatic, minimally or moderately serious (malaise, visual disorders, paraesthesia . . .), or serious when neurological signs (coma, convulsions) were mentioned. Variables are compared using the χ^2 test and Student's *t*-test with a significance threshold at 5%.

Results

From 1 January 1997 to 30 November 2010 and whatever the severity criteria, 3025 cases computerized in the FPD involved DXP as a suspected or interacting drug, 3726 involved TRM and 2349 involved COD. Hypoglycaemia was coded as the main symptom or appeared in the narrative in 90 reports for DXP (2.98% of the total), 53 for TRM (1.42%) and two for COD (0.08%). As compared with other adverse effects, the reporting rate of hypoglycaemia associated with DXP was higher than that of TRM ($P < 0.001$). Of

Table 1

Characteristics of the patients and hypoglycaemia

	Dextropropoxyphene (n = 72)	Tramadol (n = 43)	P
Gender ratio (male : female)	0.6	0.65	0.828
Age (mean $\pm$ SD) (years)	71.2 $\pm$ 20.9 (n=70)	69.4 $\pm$ 22.5 (n=42)	0.667
Median time to onset of hypoglycaemia after treatment initiation (days)	4 (n = 44) [1 120]	5 (n = 40) [1 645]	0.614
Number of cases with hypoglycaemia occurring within 10 days of treatment	63% (28/44)	77% (31/40)	
Serum glucose concentration (mean $\pm$ SD) (mmol l ⁻¹)	2.1 $\pm$ 0.9 (n = 51)	2.5 $\pm$ 1 (n = 35)	0.072
Clinical symptoms			
No specified	31	16	
Asymptomatic	5/41 (12%)	5/27 (18.5%)	
Minor to moderate signs	22/41 (54%)	14/27(52%)	
Severe neurological signs (coma, convulsions)	14/41 (34%)	8/27 (29.5%)	
Presence of seriousness criteria	69.4%	53.5%	0.086
Outcome			
Complete recovery	68	38	
Death	2		
Recovery with neurological sequelae	1		
Unknown	1	5	
Number of cases with positive re-administration	6	2	

these reports and according to our criteria, 72 and 43 cases of hypoglycaemia associated with DXP and TRM, respectively, were retained for further analysis. As only one case of hypoglycaemia was associated with COD, only DXP and TRM were subsequently compared.

DXP was involved as a single component in three cases, in combination with paracetamol in 59 cases or with paracetamol and caffeine in 10 cases. TRM was involved alone in 36 cases (16 immediate-release forms, 15 sustained-release forms, five not stated) and in combination with paracetamol in seven cases. According to the Naranjo probability scale, the mean score in the 43 cases of tramadol associated with hypoglycaemia was 4.2 (range 3 to 8).

The main characteristics of the patients and hypoglycaemic events are presented in Table 1. Patients experiencing hypoglycaemia were generally elderly people. There was no significant difference between DXP- and TRM-treated patients (71.2 $\pm$ 20.9 years vs. 69.4 $\pm$ 22.5 years). Hypoglycaemia occurred after a median of 4 and 5 days after the initiation of DXP and TRM treatment, respectively, and most cases were observed within 10 days of treatment. The mean lowest serum glucose concentration was 2.1 $\pm$ 0.9 mmol l⁻¹ in the DXP group (n = 51) compared with 2.5 $\pm$ 1 mmol l⁻¹ in the TRM group (n = 35) (P = 0.072). When the presence or absence of symptoms were clearly mentioned in the narrative, clinically symptomatic hypoglycaemia was observed with similar frequency with DXP (36 of 41 cases, 87.8%) and TRM (22 of 27 cases, 81.5%) groups (P = 0.47), whatever the severity of the symptoms. Overall, severity criteria were coded in 69.4% in the DXP group and 53.5% in the TRM group (P = 0.086). Death occurred in two patients from the DXP group. A 95-year-old patient who experienced glucose-resistant hypoglycaemia with coma

died 4 days later from an infectious pneumonitis. Unfortunately, the cause of death was not detailed in another patient aged 86 years, who also experienced severe and glucose-resistant hypoglycaemia (1.1 mmol l⁻¹ at admission). Of note, six patients from the DXP group and two from the TRM group experienced recurring hypoglycaemia after subsequent exposure to the same drug.

As shown in Table 2, at least one predisposing or associated factor was reported in 58.3% of DXP-treated patients and 58.1% of TRM-treated patients with no significant difference between groups. Underlying diabetes was the most frequent risk factor reported in 31.9% of patients in the DXP group and 41.8 % in the TRM group (P = 0.283). Among diabetic patients, those from the DXP group were more likely to have non-insulin dependent or insulin requiring diabetes mellitus than those from the TRM group (P = 0.049), whereas insulin dependent diabetes was more frequently found in the TRM group (P = 0.019). Renal insufficiency was also found in 13 (18%) DXP-treated patients and seven (16.3%) TRM-treated patients (P = 0.808). After taking into account the presence of renal insufficiency and several known triggering factors of hypoglycaemia such as cancer, moderately reduced nutrition, sepsis, alcohol consumption, liver disease and thyroid disorders, concomitant risk factors were identified in 28 (38.9%) DXP users and in 15 (34.8%) TRM users (P = 0.668).

Discussion

This study suggests an association between TRM, either alone or combined with paracetamol and the occurrence of hypoglycaemia, without overt difference compared

Table 2

Predisposing factors

	Dextropropoxyphene (n = 72)	Tramadol (n = 43)	P
Diabetes	23 (31.9%)	18 (41.8%)	0.283
Insulin-dependent diabetes	4	10	0.019
Insulin-requiring diabetes	1	2	0.049
Non-insulin dependent diabetes	15	5	0.049
Not otherwise stated	3	1	
Other risks factors except diabetes (and/or)	28 (38.9%)	15 (34.8%)	0.668
Acute or severe chronic renal failure (creatinine clearance <30 ml min ⁻¹)	6	5	
Renal failure without precision	7	2	
Concomitant infection	2	5	
Hepatic failure		1	
Alcohol	3	2	
Enteric resection/anorexia	2	1	
Dysthyroidism	1	1	
Cancer	6		
Hyperinsulinism	1		
Both diabetes and other risk factors	58.3%	58.1%	0.936

with DXP. These results are in accordance with those of Tavassoli *et al.* who found a similar reporting rate of hypoglycaemia with DXP (0.8/100 000 person-years) and TRM (0.6/100 000 person-years) [2]. However, this study provided no details on the characteristics of hypoglycaemia. Five isolated case reports also detailed the occurrence of hypoglycaemia in TRM-treated patients, among whom three were over 80 years of age and two were young insulin-dependent diabetes mellitus patients [10–12]. In three of these cases, hypoglycaemia was noticed between 1 to 3 days of treatment and three patients had severe clinical symptoms. Very similar findings were evidenced in our study with hypoglycaemia being usually observed within the first 10 days of TRM treatment, particularly in elderly and predisposed patients, and marked by the presence of mild to severe symptoms in approximately half of the patients. All these characteristics were very close to those observed with DXP, another weak opioid analgesic well-known to be associated with hypoglycaemia [5–9], whereas no convincing cases have been reported with COD. A predisposing factor of hypoglycaemia was found in more than half of the cases, with age, renal insufficiency and diabetes mellitus being the most frequent factors. This suggests that prescribing TRM in such patients should be cautious. The number of patients with diabetes ranged from 32 to 42% in this study, a rate that appeared rather low given the fact that true hypoglycaemia without diabetes is rare. Unfortunately, and given the limitations of spontaneous notifications, it was not possible to confirm or

not the presence of diabetes in other cases. Although non-insulin-dependent diabetes mellitus was more frequently reported among diabetic patients from the DXP group compared with the TRM group, this finding was based on a small number of patients and could have been coincidental or resulting from multiple comparisons. Although a drug interaction might explain this finding, to the best of our knowledge, there are no data suggesting a possible pharmacokinetic interaction between DXP and oral hypoglycaemic drugs.

The mechanisms of TRM-induced hypoglycaemia are still hypothetical and at least two possible explanations based on TRM pharmacological effects can be discussed. A putative serotonergic-mediated mechanism is substantiated by experimental data showing that serotonin can increase insulin concentration in mice [14]. In rat models of diabetes, serotonin also induced β endorphin release and stimulated muscle glucose utilization through the activation of μ -opioid receptors by a mechanism, which is neither dose nor insulin dependent [15]. In addition, hypoglycaemia associated with selective serotonin re-uptake inhibitor treatment has also been reported, but the clinical evidence is limited to few case reports [16, 17].

Hypoglycaemia resulting from the activation of opioid μ -receptors by TRM is a more attractive hypothesis. Experimental data in streptozotocin-induced diabetic rats evidenced a dose-dependent lowering of plasma glucose concentrations shortly after intravenous TRM administration at doses ranging from 15 to 150 $\mu\text{g kg}^{-1}$ [18]. This hypoglycaemic effect of TRM was blocked by pre-treatment with opioid μ -receptor antagonists such as naloxone. By contrast, only a moderate effect on plasma glucose concentrations was found in normal rats receiving a much higher TRM dose (i.e. 1 to 5 mg kg^{-1}). The same authors had previously shown that opioid μ -receptors stimulation lowered plasma glucose in diabetic rats and that loperamide, another μ -receptor agonist, exerted the same effect as TRM [19]. Further investigations indicated that activation of these receptors could decrease plasma glucose concentrations by increasing glucose utilization in peripheral tissues, probably via an insulin-independent mechanism and/or by inhibiting hepatic gluconeogenesis [20]. Although no specific studies have been conducted with DXP, a similar mechanism can probably explain the rare reports of hypoglycaemia in these patients. Overall, these experimental data in diabetic rats are in accordance with our results suggesting that diabetes mellitus appeared as the main risk factor in DXP- or TRM-treated patients who experienced hypoglycaemic episodes.

In conclusion, despite the limitations of our study due to probable under-reporting and the lack of knowledge of the characteristics of the whole treated population, our data indicate that TRM can be associated with hypoglycaemia, particularly in elderly or diabetic patients, or in those with renal insufficiency, similar to what was previously described with DXP. Although further signal strengthening

studies need to be carried out for definite confirmation, physicians and patients should be warned of this potential adverse effect, which is not mentioned in the summary of the product characteristics.

Competing Interests

There are no competing interests to declare.

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