Reporting rate of adverse drug reactions to the French pharmacovigilance system with three step 2 analgesic drugs: dextropropoxyphene, tramadol and codeine (in combination with paracetamol)

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Three 'weak' opioid analgesics are marketed in France and other European countries in association with paracetamol.
- They are very largely used, but to our knowledge there is no large study comparing the reporting rate of adverse drug reactions (ADRs) between these different step 2 analgesic combinations to determine the safest one.

WHAT THIS STUDY ADDS

- The aim of this study was to compare reporting rate of ADRs with three step 2 combinations according to their consumption in France.
- The results show that among these combinations, reporting rate and 'seriousness' of reported ADRs are the highest with tramadol/paracetamol (TRM+P) and the lowest with codeine/paracetamol.
- The safety of TRM+P needs to be urgently investigated with more methodologically rigorous studies.

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AIMS

Three 'weak' opioid analgesics in association with paracetamol are marketed in France as step 2 analgesics: dextropropoxyphene, tramadol and codeine. These combinations are involved in several adverse drug reactions (ADRs), but no data are available about their comparative reporting rate. The aim was to compare the reporting rate of ADRs between tramadol/paracetamol (TRM+P), codeine/paracetamol (COD+P) and dextropropoxyphene/paracetamol (DXP+P).

METHODS

All spontaneous reports submitted to the French Pharmacovigilance Database from 1 January 1987 to 31 December 2006 suspected to be induced by one of the three step 2 analgesic combinations (DXP+P, TRM+P, COD+P) were extracted. Their consumption for the same period was obtained from the French Drug Agency. The number of ADRs, serious ADRs and different organ classes of ADRs were compared according to their consumption. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable using DXP+P as reference.

RESULTS

The reporting rate of ADRs was calculated as 24.9/100 000 person-years for DXP+P, 44.5/100 000 person-years for TRM+P and 12.5/100 000 person-years for COD+P. The reporting rate (OR 0.56, 95% CI 0.50, 0.63) and 'seriousness' (OR 0.65, 95% CI 0.53, 0.80) of ADRs were significantly higher with TRM+P than with DXP+P. However, hepatobiliary ADRs were significantly more frequent with the DXP+P combination (OR 2.62, 95% CI 1.59, 4.37). In contrast, the reporting rate (OR 1.99, 95% CI 1.82, 2.18) and 'seriousness' (OR 2.64, 95% CI 2.24, 3.11) of ADRs were significantly higher with DXP+P than with COD+P.

CONCLUSIONS

Among the three step 2 analgesic combinations, reporting rate and 'seriousness' of ADRs are the highest with TRM+P and the lowest with COD+P. Our study suggests that the safety profile of DXP+P is worst than that of COD+P.

Introduction

Three 'weak' opioid analgesics are marketed in France in association with paracetamol as step 2 analgesics (according to the World Health Organization (WHO) classification) [1]: dextropropoxyphene, tramadol and codeine (Table 1). Their level of consumption is very high, especially dextropropoxyphene/paracetamol (DXP+P) (20 801 997 160 units in 2006), which belongs to the top 10 drugs in France [2].

Dextropropoxyphene is a 'weak' opioid analgesic, structurally related to methadone, acting through activation of μ -opioid receptors and producing analgesia and other central effects similar to those seen with other morphine-like compounds [3]. The association DXP+P has been marketed in France since 1974. It is involved in several serious adverse drug reactions (ADRs) (i.e. hepatic reactions, hallucinations, abuse, withdrawal symptoms, hypoglycaemia...) [1]. Moreover, plasma elimination half-life of dextropropoxyphene is long (15–34 h), in contrast to paracetamol (2 h), which increases the risk of accumulation in patients with renal failure or in elderly people [3]. Overdoses of dextropropoxyphene could lead to fatal respiratory depression or cardiac ADRs (such as severe bradycardia or atrioventricular dysfunction) [3, 4]. These observations have led some European countries (Switzerland, Sweden, UK,...) to remove approval of products containing DXP [5, 6]. In 2008, the European Medicines Agency decided to review all fixed combination analgesics containing DXP+P to determine whether they should have their product information changed to reflect safety concerns or be taken off the market altogether [7]. Recently, the Food and Drug Administration (FDA) review committee has voted against the Darvon (paracetamol + propoxyphene) combination, and it remains to be seen whether or not the FDA will implement a total ban [8].

Tramadol and codeine are two other 'weak' opioid analgesics also used in combination with paracetamol as step 2 analgesics. The combination of tramadol/paracetamol (TRM+P) has been marketed in France since 2002 and the combination of codeine/paracetamol (COD+P) since 1983.

They have the same ADR profile as opioid analgesics in general [3]. To our knowledge, there is no large study comparing the reporting rate of ADRs between these different step 2 analgesic combinations.

Thus the aim of this study was to compare the rate of ADRs reported with TRM+P, COD+P and DXP+P according to their consumption in France.

Methods

The French Pharmacovigilance System was first established in 1973 and consists of a network of 31 Regional Centres. The French Pharmacovigilance Database (FPD) was established in 1985 to record spontaneous reporting of ADRs [9, 10]. Furthermore, reporting 'serious' or 'unlabelled' ADRs to the French Regional Centres has been mandatory for any drug prescriber, physician, dentist or midwife in France since 1995 [11]. A 'serious' ADR is defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening [12]. An 'unlabelled' (or 'unexpected') ADR is defined as an ADR whose nature or severity is not consistent with data contained in domestic labelling or market authorization or expected from characteristics of the drug [12]. Case causality assessment is performed for all ADRs registered in the FPD according to the French method, which contains five intrinsic causality levels: I0, excluded; I1, dubious; I2, plausible; I3, likely; I4, very likely [13].

Spontaneous reports submitted to the FPD from 1 January 1987 to 31 December 2006, in which the products containing the combination of DXP+P, TRM+P or COD+P (whatever the dosage forms) were 'suspected' (I1, I2, I3 and I4 levels of causality assessment), were extracted. Consumption of the same products in France for the same period was obtained from the French Drug Agency [Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS)]. The number of ADRs, 'serious' ADRs and different organ classes of ADRs were compared according to their consumption expressed in person-years using the

Table 1

Dosage forms and defined daily doses (DDD) of dextropropoxyphene, tramadol and codeine, in combination with paracetamol

Combination	Main commercial products	Opioid dosage	Paracetamol dosage	DDDs
Dextropropoxyphene/paracetamol	Dextroref; Di-Dolko; Diadupsan; Dialgirex; Di-Antalvic; Propofan	27–30 mg	400 mg	4 pharmaceutical units
Tramadol/paracetamol	Ipgrim; Zaldiar	37.5 mg	325 mg	4 pharmaceutical units
Codeine/paracetamol	Algicalm; Algisedal; Claradol Codeine; Codoliprane; Compralgyl; Dafalgan Codeine; Efferalgan Codeine; Gaosedal Codeine; Gelumaline; Klipal Codeine; Lindilane; Migralgine; Panadol Codeine; Prontalgine; Salgydal; Sedarene; Supadol; Vegadeine	10–30 mg	250–600 mg	3–6 pharmaceutical units

defined daily dose of combination products according to the WHO (Table 1) [14].

Statistical analysis

Categorical variables were expressed as counts per 100 000 person-years and compared using the χ^2 test (if frequency <5 , Fisher's exact test was performed). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable using DXP+P as reference. Statistical analyses were performed using EPI-INFO. The significance threshold was 5%.

Results

Consumption was 14 247 943 person-years for DXP+P from 1 January 1987 to 31 December 2006, 655 746 person-years for TRM+P from 1 January 2003 to 31 December 2006 and 4 575 058 person-years for COD+P from 1 January 1987 to 31 December 2006 in France according to data provided by AFSSaPS. A total number of 4418 spontaneous notifications (i.e. 3553 with DXP+P, 292 with TRM+P and 573 with COD+P) were registered in the FPD during the same period. Thus, the rate of reported ADRs was calculated as 24.9/100 000 person-years for DXP+P, 44.5/100 000 person-years for TRM+P and 12.5/100 000 person-years for COD+P.

Comparison between DXP+P and TRM+P shows that rate and 'seriousness' of reported ADRs were significantly higher with the TRM+P combination (Table 2). However, the rate of deaths related to ADRs was not significantly different between the two groups ($P = 1.000$). The combination of TRM+P was involved in significantly more gastrointestinal, vascular, neurological, psychiatric and cutaneous ADRs ($P < 0.001$). Nevertheless, hepatobiliary ADRs were significantly more frequent with the DXP+P combination.

Results with DXP+P and COD+P are also shown in Table 2. Rate and 'seriousness' of reported ADRs were significantly higher with the DXP+P combination. The rate of deaths due to ADRs was more marked with DXP+P, even though not reaching the level of significance ($P = 0.082$). Gastrointestinal, neurological, hepatobiliary, cutaneous and metabolic ADRs were significantly more frequent with the DXP+P combination ($P < 0.001$). Among metabolic ADRs, it should be emphasized that no case of hyperglycaemia was reported with COD+P, contrary to a reporting rate of 0.8/100 000 person-years and 0.6/100 000 person-years with DXP+P and TRM+P, respectively.

Discussion

This study shows that between the three step 2 analgesic combinations, rate and 'seriousness' of reported ADRs are the highest with TRM+P and the lowest with COD+P. The

rough number of ADRs is the highest with DXP+P and the lowest with TRM+P. However, TRM+P has been marketed in France since 2003, whereas DXP+P and COD+P were marketed between 1970 and 1985.

To our knowledge, no large study has compared the safety profile of these three step 2 analgesics. However, a few studies have compared the efficacy and reporting rate of ADRs between two step 2 analgesics in some indications during short periods of use. For example, Mullican compared TRM+P and COD+P combinations in a 4-week, randomized, double-blind, multicentre trial for the management of nonmalignant low back pain or osteoarthritis pain in adults. The overall incidence of ADRs was comparable between the two groups [15]. Boissier *et al.*, in a double blind, randomized, parallel group trial, compared the acceptability and efficacy of COD+P and DXP+P for 1 week in 141 outpatients with active osteoarthritis of the knee or hip. They show that acceptability of COD+P was significantly worse than that of DXP+P: 53% failure with COD+P vs. 29% failure with DXP+P ($P = 0.005$) [16]. Nevertheless, in another study comparing DXP+P and COD+P in post-partum pain after episiotomy and/or rupture of perineum, the COD+P combination was shown to cause fewer ADRs than DXP+P [17]. Thus, study results differ according to the type of pain treated by analgesics. However, results from these small studies can not be extrapolated to the general population using step 2 analgesics in different indications. The present study is the first to compare the three step 2 analgesics in the general population, in all types of pain and in real life.

Comparison of different types of ADRs showed that for most organ classes, the TRM+P combination was significantly associated with the highest reporting rate. However, the reporting rate of hepatobiliary ADRs was significantly higher with DXP+P. These data are in accordance with previous studies. For example, Bergeron *et al.* reported four cases of hepatitis with the DXP+P combination [18]. They also found 29 cases of hepatic injuries in patients treated with dextropropoxyphene in international publications. It was suggested that the active dextropropoxyphene metabolite, norpropoxyphene, could induce these hepatic ADRs via an immunoallergic mechanism [19, 20].

Our study suffers from some unavoidable limitations. The first one is underreporting of ADRs to a national pharmacovigilance system. The reporting rate of ADRs in France was estimated to be about 5–10% for 'serious' ADRs [21]. However, Pierfitte *et al.*, in a study based on the FPD data, demonstrated that the magnitude of reporting rates is the same for several drugs from the same therapeutic class, supporting the methodology used in the present study and the results with three drugs belonging to the same pharmacotherapeutic class (step 2 analgesics) [22]. Second, the combination TRM+P was launched much more recently (2002). Healthcare professionals are probably much more likely to submit reports of suspected ADRs arising with new, unfamiliar agents, thus accounting for the

Table 2

Frequency of ADRs registered in the French Pharmacovigilance Database with dextropropoxyphene, tramadol and codeine in combination with paracetamol between 1 January 1987 and 31 December 2006

Parameters	DXP+P			TRM+P			COD+P		
	Number of case reports	Frequency per 10 ⁵ patient-years	Number of case reports	Frequency per 10 ⁵ patient-years	Number of case reports	Frequency per 10 ⁵ patient-years	OR (95% CI)	P	OR (95% CI)
Number of ADRs	3553	24.9	292	44.5	573	12.5			
Number of serious ADRs	1357	9.5	96	14.6	165	3.6			
Death due to ADRs	42	0.3	1	0.2	6	0.1			
Gastrointestinal ADRs	557	3.9	106	16.2	120	2.6			
Cardiac ADRs	56	0.4	6	0.9	14	0.3			
Vascular ADRs	83	0.6	16	2.4	19	0.4			
Neurological ADRs	385	2.7	65	9.9	80	1.7			
Seizure	23	0.2	7	1.1	2	0.0			
Peripheral neuropathy	16	0.1	0	0.0	1	0.0			
Abnormal movements	33	0.2	18	2.7	15	0.3			
Cephalalgia	106	0.7	6	0.9	19	0.4			
Psychiatric ADRs	222	1.6	35	5.3	53	1.2			
Delirium and confusion	106	0.7	19	2.9	12	0.3			
Behavioural disorders	58	0.4	15	2.3	5	0.1			
Hepatobiliary ADRs	967	6.8	17	2.6	79	1.7			
Cutaneous ADRs	852	6.0	61	9.3	183	4.0			
Metabolic disorders	189	1.3	12	1.8	6	0.1			
Hypoglycaemia	118	0.8	4	0.6	0	0.0			

DXP, dextropropoxyphene; ADR, adverse drug reaction; CI, confidence interval; COD, codeine; NA, not accurate; OR, odds ratio; P, paracetamol; TRM, tramadol.

*Significant results (p < 0.05).

differences in rates. The target population may also have been different. Patients from the 1980s and 1990s who have been taking DXP+P or COD+P may have different comorbidities from those on TRM+P.

Conclusion

Among the three step 2 analgesic combinations marketed in France (DXP+P, TRM+P, COD+P), the rate and 'seriousness' of reported ADRs were the highest with TRM+P and the lowest with COD+P. However, the rate of deaths due to ADRs did not differ among the three combinations. Concerning the different types of ADRs, TRM+P is associated with the greatest reporting rate of gastrointestinal, vascular, neurological, psychiatric and cutaneous ADRs and DXP+P with the greatest reporting rate of hepatobiliary ADRs. Thus, despite its intrinsic limitations, our study suggests that the safety profile of DXP+P is worst than that of COD+P. It is more difficult to draw conclusions about TRM+P. There is evidence concerning its high reporting rate of ADRs, but further systematic studies are necessary to confirm these results.

Competing interests

None to declare.

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