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Safety profile of enantiomers *vs.* racemic mixtures: it's the same?

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The physicochemical properties of racemates and stereoisomers of medicines can differ significantly, and this may affect the side-effect profile in addition to the pharmacokinetics and intended pharmacology.

WHAT THIS STUDY ADDS

- This is a study to investigate the profile of adverse drug reactions of racemic and enantiomeric forms of drugs. Our data suggest differences in the safety profile for ofloxacin and omeprazole.
- This area requires more work to investigate this for other compounds.

AIMS

The objective was to investigate the safety profile of four drugs marketed as racemic and enantiomeric forms in France.

METHODS

Data from the French PharmacoVigilance Data Base (January 2005 to June 2010) were analysed for four pairs of racemic/isomeric drugs. A case–noncase approach was used to measure the disproportionality of combination between adverse drug reaction (ADR) and exposure to drug.

RESULTS

No significant difference in the number of ADRs was observed between Rac-cetirizine/(*R*)-cetirizine or Rac-citalopram/(*S*)-citalopram pairs. (*S*)-Omeprazole induced more haematological effects than Rac-omeprazole. Rac-Ofloxacin induced more haematological, renal and neuropsychiatric ADRs than (*S*)-ofloxacin, whereas levofloxacin was associated with more reports of musculoskeletal ADRs.

CONCLUSIONS

The profile of ADRs could differ for some drugs marketed as racemic and enantiomeric forms. Further studies would be necessary to confirm these data.

Introduction

Isomers are compounds with the same molecular formula but a different structural formula or different spatial arrangement. Stereoisomers (spatial isomers) are compounds that share an identical molecular formula, but differ in their three-dimensional arrangement. Enantiomers are stereoisomers which are nonsuperimposable, mirror images. A mixture of equal amounts of two stereoisomers of an optically active substance is called a racemic mixture or racemate. Thus, in the environment where specific structure–activity relationships may be required for effect (e.g. receptors and transporters), the properties of a racemate and an enantiomer can differ significantly [1]. In drug development, enantiomeric selection to increase clinical effects or mitigate adverse drugs reactions (ADRs) has yielded both success and failure. The tragic example was thalidomide, introduced in the late 1950s as a sedative

drug and antiemetic in pregnant women, with a significant difference of profile between the two isomers; while (*R*)-thalidomide was effective against nausea, (*S*)-thalidomide appeared to be highly teratogenic in humans [2]. Since 1980, interest in enantiomic forms has increased. To get around the concurrence with generic drugs, pharmaceutical laboratories promote the enantiomer as a new drug with better efficacy. Concerning ADRs, preliminary data from Moachon *et al*. [3] suggested a difference in occurrence of haematological effects of (*S*)-omeprazole compared with rac-omeprazole. The aim of our study was to investigate the safety profile of four drugs marketed in racemic and enantiomeric forms, using the French PharmacoVigilance Database (FPVDB).

Methods

We used the FPVDB, including all ADRs reported to the 31 French Regional Pharmacovigilance Centers since 1985. The following four pairs of racemic/enantiomeric drugs were selected: rac-omeprazole/(*S*)-omeprazole, rac-citalopram/(*S*)-citalopram, rac-cetirizine/(*R*)-cetirizine (levocetirizine) and rac-ofloxacin/(*S*)-ofloxacin (levofloxacin). Adverse drug reactions were classed according to the Medical Dictionary for Regulatory activities classification [4]. The study period was 1 January 2005 to 15 June 2010. The case–noncase method was used to measure the disproportionality of combination between ADR and exposure to drug. Cases were defined as reports corresponding to the ADR of interest, while noncases were all reports of ADRs other than that being studied. Exposure was considered as the presence in a report of the drug of interest [5]. We compared the number of ADRs of the pair enantiomer/racemate reported for each system organ class (SOC) of interest with those reported for other SOCs, which allowed us to estimate a reporting odds ratio (ROR). We excluded case reports in which the causal relationship of the drug of interest was assessed as 'doubtful' or 'unlikely', according to the French method of assessment of causal relationship [6] and also suicide attempts leading to overdosage and drug error cases. Moreover, using data from the Health Insurance (MEDIC'AM) database from 2006 to 2008 [7], we also estimated the numbers of ADRs per million daily defined doses (DDDs) for each SOC for which a significant difference had been found between enantiomer/racemate in case–noncase analysis. The DDDs suggested for rac-omeprazole/(*S*)-omeprazole, rac-citalopram/(*S*)-citalopram, rac-cetirizine/(*R*)-cetirizine (levocetirizine) and rac-ofloxacin/(*S*)-ofloxacin (levofloxacin) are 20/30 mg, 20/10 mg, 10/5 mg and 0.4/0.5 g, respectively. Statistical analyses were done using Student's paired *t*-test for quantitative data (age), chi-squared and Fisher's exact test for qualitative data.

Results

Table 1 shows the number of case reports with corresponding ADRs and the characteristics (age and sex) of patients for each pair of enantiomeric/racemic drugs. No significant difference was found for age and sex between the case reports with racemates and their enantiomers.

No significant difference of ADR reports was observed between racemates and enantiomers for rac-cetirizine/(*R*)-cetirizine and rac-citalopram/(*S*)-citalopram pairs. Differences were found for two pairs of drugs, (*S*)-omeprazole/rac-omeprazole and (*S*)-ofloxacin/rac-ofloxacin. (*S*)-Omeprazole was associated with more reports of haematological effects ($n = 69$, 22.5%, corresponding to 66 ADRs per million DDDs) than rac-omeprazole ($n = 34$, 12.6%, corresponding to 25 ADRs per million DDDs), with ROR = 2.1 (1.4–3.3), $P < 0.001$. Table 2 shows the ROR of ADRs for which a significant difference was found between racemate and enantiomer and the corresponding estimations of ADRs per million DDDs for (*S*)-ofloxacin/rac-ofloxacin. Rac-Ofloxacin was associated with more haematological, renal and neuropsychiatric ADRs than (*S*)-ofloxacin, whereas (*S*)-ofloxacin was associated with more musculoskeletal reports.

Table 1

Descriptive data (number of cases and corresponding ADRs) and demographic data for four pairs of racemic/enantiomeric drugs

	Rac-CTM/(*S*)-CTM	Rac-CTZ/(*R*)-CTZ	Rac-OMR/(*S*)-OMR	Rac-OFX/(*S*)-OFX
Number of cases	116/126	25/20	162/206	331/280
Number of ADRs	189/212	41/40	282/307	500/467
Age [years (SD)]	62.1 (26.2)/58.2 (22.8)	44.4 (23.0)/44 (22.7)	59.4 (20.9)/61.0 (18.9)	65.4 (19.7)/63.8 (18.7)
Sex [*n* (%)]				
Male	34* (29.3)/37 (29.4)	12 (48.0)/7 (35.0)	68 (42.0)/98 (47.8)	157 (47.4)/129 (46.1)
Female	81* (69.8)/89 (70.6)	13 (52.0)/13 (65.0)	94 (58.0)/107 (52.2)	174 (52.6)/151 (53.9)

Abbreviations: ADRs, adverse drug reactions; CTM, citalopram; CTZ, cetirizine; OFX, ofloxacin; OMR, omeprazole; *R*, rectus (Latin for right); and *S*, sinister (Latin for left). *One missing value.

Table 2

Comparison of reporting odds ratio between rac-ofloxacin and (*S*)-ofloxacin and the corresponding number of ADRs per million DDDs

ADRs [*n* (%)]	Rac-OFX/(*S*)-OFX	ROR [95% CI]	*P* value	Number of ADRs per million DDDs, Rac-OFX/(*S*)-OFX
Haematological	51 (10.2)/20 (4.3)	2.5 [1.5–4.3]	0.0005	1634/998
Neuropsychiatric	55 (11.0)/34 (7.3)	1.9 [1.2–3.0]	0.0452	1040/499
Renal	16 (3.2)/4 (0.9)	3.8 [1.3–11.5]	0.0119	297/166
Musculoskeletal	66 (13.2)/94 (20.1)	1.7 [1.2–2.3]	0.0042	1585/4160

Abbreviations: ADRs, adverse drug reactions; CI, confidence interval; DDDs, daily defined doses, estimated with health insurance data (MEDIC'AM) 2006–2008; OFX, ofloxacin; OMR, omeprazole; and ROR, reporting odds ratio.

Discussion

In this study, quantitative differences were found for some ADRs between racemates and their enantiomeric forms. Our study was limited by some mandatory bias. First, underreporting of ADRs to the pharmacovigilance system is usual and may amount to 90% of cases [8]. Nonetheless, the underreporting rate was shown to be similar for several drugs from the same pharmacotherapeutic class [9]. However, a 'notoriety bias' cannot be excluded, because racemates were marketed before the enantiomeric forms. In France, the schedule of marketing of rac-omeprazole/(*S*)-omeprazole, rac-citalopram/(*S*)-citalopram, rac-cetirizine/(*R*)-cetirizine and rac-ofloxacin/(*S*)-ofloxacin is 1986/2000, 1994/2002, 1987/2002 and 1986/1998, respectively. The choice of the period (2005–2010) for our study (at least 3 years after the last marking of the drug studied) could minimize the notoriety biases. Second, data quality of the cases could be variable in spontaneous reporting. Selection of cases with at least a 'probable' causal relationship allowed the exclusion of all reports with a low level of quality of the data. Third, previous studies using the disproportionality approach in a spontaneous reporting database (FPVDB or VigiBase) suggested its usefulness for detecting a signal concerning drug safety in the context of real life [10]**.** Finally, data interpretation could be limited by the fact that several SOCs were investigated in our analysis, leading to multiple testing.

These data indicate that (*S*)-omeprazole induces more haematological disorders than rac-omeprazole. Formation of a larger quantity of the sulphone derivative from the metabolism of (*S*)-omeprazole compared with that of rac-omeprazole could explain the difference in haematological ADRs between these drugs. Indeed, *in vitro* experiments in human liver microsomes [11] suggested that the formation of the hydroxy- and 5-*O*-desmethyl metabolites of (*S*)-omeprazole is via cytochrome CYP3A4, whereas that of the sulphone metabolite is via CYP2C19. Moreover, (*S*)-omeprazole is preferentially metabolized by CYP2C19, whereas rac-omeprazole is metabolized by CYP3A4. The difference of 'dose' between racemate and enantiomer could be another explanation of the profile of ADRs; for example, in gastro-oesophageal reflux, the DDD is 20 mg for rac-omeprazole, which theoretically contains 10 mg of (*S*)-omeprazole, and 30 mg for (*S*)-omeprazole. Thus, the quantity of (*S*)-omeprazole involved in haematological ADRs is threefold higher in the enantiomeric than the racemic form. For (*S*)-ofloxacin, which is the active form of ofloxacin, although the difference in the pharmacokinetic parameters of the enantiomers was small, their disposition was found to be stereoselective in a species-related manner. In monkeys and humans, in contrast to rats and dogs, serum concentrations of (*S*)-ofloxacin predominated over (*R*)-ofloxacin levels, which could be explained by competition between the enantiomers for renal excretion. Thus, administration of rac-ofloxacin leads to production of more (*S*)-ofloxacin than administration of (*S*)-ofloxacin. This hypothesis could explain the higher frequency of ADR reports for rac-ofloxacin than for (*S*)-ofloxacin, which is the active form of ofloxacin [12, 13].

Conclusion

According to our data extracted from FPVDB, the profile of ADRs could differ for racemic and enantiomeric forms of omeprazole and ofloxacine. Further studies would be necessary to confirm these data.

Competing Interests

There are no competing interests to declare.

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