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Pre- and post-marketing safety profile of racecadotril capsules, a "new" antidiarrhoeal drug

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Introduction :

Racecadotril, an enkephalinase inhibitor, reinforces the physiological activity of endogenous enkephalins and shows intestinal antisecretory activity without motility inhibition. Among antidiarrhoeal drugs, racecadotril is known as effective to reduce stool output and duration of diarrhoea in adults, but published safety data is considered as insufficient.
Our aim was to report the overall experience with racecadotril tolerance from pre- and post-marketing data.

Methods :

The individual case safety reports (ICSRs) and the adverse events (AEs) from all the acute diarrhoea clinical trials performed in adults were collected. Periodic safety update reports were used for post-marketing analysis.

Results (1) :

During clinical trials,

The most frequent AEs were constipation and headache (see Table).

Withdrawals had similar frequency in racecadotril groups (5.0%) and placebo groups (7.8%).

Elderly : the frequency of AEs in elderly patients treated by racecadotril (4/27=14.8%) was not greater than those in patients treated by placebo (5/26=19.2%) and was significantly lower (P<0.05) than those in patients treated by loperamide (2/26=7.7% vs 10/34=29.4%). The odds ratio is 0.20 [0.04 – 1.01].
Among the patients treated by racecadotril, the frequency of AEs was not different in those aged 65 years at least (6/53=11.3%) than in those aged less than 65 years (113/960=11.8%).

Results (2) :

Post-marketing data,

From launch in March 1993 to March 2009, worldwide safety management (34 countries) reports 94 ICSRs (144 AEs) among 26.12 million patients, that is a frequency of about one for 278 000 patients.

The annual frequency of ICSRs was round between 0.0009% and 0.0011% during the first five years, then below 0.0006% (see Figure).

There were 62 serious and 32 non serious ICSRs. Half of these AEs belong to "skin and subcutaneous tissue disorders", mainly rash and urticaria.

Nature and frequency of AEs did not significantly differ between elderly and younger patients.

	placebo	loperamide	racecadotril	OR*
Number of treated patients	282	721	2,193	
Number of patients with AEs	32	163	212	
Patients with AEs : %	11.3%	22.6%	9.7%	0.37 [0.29 ; 0.46]
Constipation (%)	1.3 %	11.9 %	1.5 %	0.11 [0.07 ; 0.17]
Headache (%)	1.5 %	0.6 %	1.4 %	NS
Withdrawal due to AE	0 %	1.1 %	0.4 %	0.20 [0.07 ; 0.62]

* Odds Ratio [95% CI], racecadotril *versus* loperamide

Table : Safety during clinical trials (adult patients suffering from acute diarrhoea)

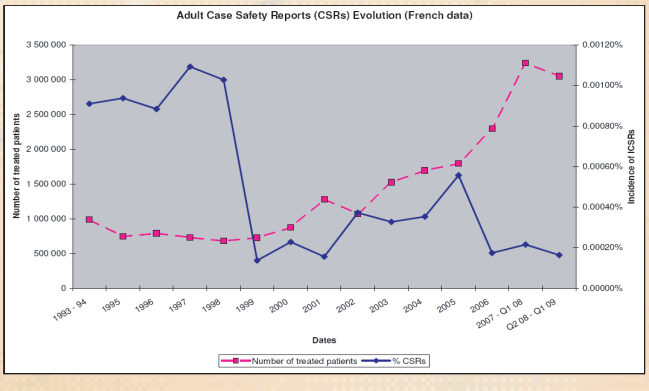

Figure : Evolution of Case Safety Reports (CSRs) frequency since racecadotril capsules launching in France.

Summary & Conclusion :

Racecadotril cumulative tolerance data are consistent with a safe profile, not different from placebo and better than loperamide.

Information disclosed for potential conflicts of interest :

Philippe Baumer : part-timer for Bioprojet Pharma, Yves Joulin : Qualified Person for PharmacoVigilance for Bioprojet Pharma.