Fixed combinations of neuroleptics with antidepressants: potential risks and estimation of use

Keywords pharmacogenetics drug utilization antidepressants neuroleptics

Several neuroleptics and antidepressants (i.e. haloperidol, perphenazine, nortriptyline, amitriptyline) are extensively metabolized by the same isoenzyme of the cytochrome P450 (CYP) family, CYP2D6 [1]. The activity of CYP2D6 is determined genetically and the capacity to metabolize the drug substrates of this enzyme is bimodally distributed in the population. About 7% of Caucasians have a low expression of CYP2D6 activity (so called 'poor metabolizers') and the use of standard doses in these patients results in higher than anticipated plasma concentrations of drugs which are substrates of the enzyme [1, 2, 3]. In the 'extensive metabolizer' phenotype CYP2D6 can be saturated, and thus is a potential site for a number of clinically important pharmacokinetic interactions [2]. Such interactions are most likely to arise when combination products are used in which both ingredients are substrates of the same enzyme (CYP2D6). Combination products of antidepressants and neuroleptics are available in several countries (e.g. USA, UK, Spain and Finland). Therefore, we have conducted a survey to estimate the frequency of use of fixed combination preparations in a defined population.

We studied drug use in the autonomous Spanish community of Extremadura (population 1.1 million), based on the statistics of the Spanish National Institute of Health. Drug sales for the years 1990–1992 were summarized, coded, classified and transformed into the number of defined daily doses (DDD) per 1000 inhabitants per day (DDD/1000/day). One DDD is the assumed average daily dose prescribed for the main indication in adults [4].

During the study period combination products of neuroleptics together with antidepressants, known to be metabolized by CYP2D6 [1, 2], were available in Spain in seven different preparations, containing either perphenazine plus amitriptyline, or perphenazine plus nortriptyline. The DDD of 3 tablets per day, used as a unit of measurement in this study for combination products, and expressed as the weighted average of the different strengths, was equivalent to a daily dose of 8 mg perphenazine plus 66 mg amitriptyline or nortriptyline. Virtually all (99.9%) of the combination products were used in out-patient care. The amount of perphenazine in the combination products accounted for 85% of all perphenazine available for use and the amount of antidepressants in these combinations accounted for 7% of the total use

of antidepressants in Extremadura. The total sales of the combination preparations had increased from 0.42 DDD/1000/day in 1990 to 0.48 DDD/1000/day in 1992. Extrapolating the data for 1992 to the whole Spanish population of approximately 40 million we estimate that as many as 19,000 patients may use such combination products daily. The number of patients exposed to these potentially hazardous compound preparations in other countries remains to be established. According to official statistics in Finland the total consumption of all combination products of antidepressants was 2.2 DDD/1000/day in 1991 [5]. This figure does not reveal the proportion of combinations containing two or more of the substrates of CYP2D6, as it includes all combinations with antidepressants.

Owing to inhibition of CYP2D6 the phenotype of 'extensive metabolizers' may be transformed to that of 'poor metabolizers' [2], and higher than anticipated plasma concentrations of either or both of the drugs in these preparations can occur in many of these patients, exposing them to the corresponding risks. Thus it is irrational and dangerous to use fixed combinations of drugs which are metabolized by the same enzyme, because metabolic interactions may be responsible for unpredictable therapeutic responses and adverse reactions.

The availability and use of fixed combination products of neuroleptics and antidepressants should be re-evaluated on the basis of contemporary pharmacogenetic knowledge, which calls for individualization of drug dosage schedules, especially of major psychotropic drugs. Finally, we would like to emphasize that the use of these problem-generating compound preparations of antidepressants with neuroleptics is not limited to only one country, as they are produced and marketed by international companies worldwide.

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Received 4 October 1993,
accepted 22 November 1993

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