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LETTER TO THE EDITORS

Flupentixol: relevance of stereoselective therapeutic drug monitoring

Pierre Baumann · Hartmut Kirchherr · Patricia Berney · Christoph Hiemke

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Positron emission tomography (PET) provides important information in studies centered on the drug plasma concentrations–clinical effectiveness relationship, as it directly allows measuring of drug binding to pharmacologically relevant receptors in the brain. Such studies have been carried out for many antipsychotics, the binding of which to central dopamine D2 receptors can be observed with PET (Grunder et al. 2011). A study showed a 50–70 % D2-receptor occupancy by therapeutic doses (4–10 mg/day; 5.7±1.4 mg/day [mean ± SD]) of the antipsychotic drug flupentixol, which reportedly lead to flupentixol plasma concentrations between 0 and 6 ng/ml (1.47±0.97 ng/ml) after oral administration of this drug to 13 patients (Reimold et al. 2007). Flupentixol is available as a 1:1 mixture of the geometric isomers *cis*- and *trans*-isomers (*Z*- and *E*-isomers, respectively) for oral administration, while the depot preparation flupentixol decanoate contains only *cis*-flupentixol. Only *cis*-flupentixol is considered to be pharmacologically active with regard to its affinity for dopamine (and serotonin) receptors, as also shown in clinical studies in which clinical efficacy of *cis*-flupentixol (α-flupentixol; *Z*-flupentixol) was found to be superior to that of trans-flupentixol (β-flupentixol; *E*-flupentixol) (Johnstone et al. 1978). An analysis of three-dimensional structures and molecular electrostatic potentials confirms the higher receptor affinities of *cis*-flupentixol in comparison to the *trans*-isomer (Sylte and Dahl 1991). In the already mentioned PET study with flupentixol, the presented drug plasma concentrations appear to be those of the sum of *cis*- and *trans*-flupentixol, as the standard analytical technique used by MDS Pharma Services (Fehraltorf, Switzerland) was not developed for the separation of these isomers (Reimold et al. 2007; and Petra Struwe, Celerion, Fehraltdorf, personal communication).

Recently, the AGNP-TDM group (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) (Hiemke et al. 2011) recommended published updated consensus guidelines for therapeutic drug monitoring in psychiatry: The therapeutic reference range (recommended plasma drug concentration) for the antipsychotic drug flupentixol (flupenthixol) was given as 1–10 ng/ml. This range is related to the sum of the *cis*- and the *trans*-isomers concentrations, and the recommended range is mainly based on 2 studies (Reimold et al. 2007; Balant-Gorgia et al. 1985). The question arises whether after analysis of the literature, which considers pharmacological and pharmacokinetic differences between the *cis*- and *trans*-isomers of flupentixol, the recommended plasma concentration range of flupentixol may still be considered as valid.

Only few studies considered the existence of two geometric isomers of flupentixol differing by their properties. In 1985, a lower threshold of 2 ng/ml flupentixol was reported for satisfactory antipsychotic effect (Balant-Gorgia et al. 1985). The authors did not use a stereoselective method,

P. Baumann, H. Kirchherr and C. Hiemke are members of the AGNP-TDM group (cf. Hiemke et al. 2011).

P. Baumann (✉)
Département de Psychiatrie, DP-CHUV,
Site de Cery,
CH-1008 Prilly-Lausanne, Switzerland
e-mail: pierre.baumann@chuv.ch

H. Kirchherr
Medizinisches Labor Bremen,
Bremen, Germany

P. Berney
Département de Psychiatrie, Hôpitaux Universitaires de Genève,
Chêne-Bourg, Switzerland

C. Hiemke
Department of Psychiatry and Psychotherapy,
University Medical Center Mainz,
Mainz, Germany

but divided the measured flupentixol concentration by 2 in order to consider only the concentration of *cis*-flupentixol, with the assumption, that *cis*- and *trans*-flupentixol plasma concentrations are equal in flupentixol treated patients. As a result, patients treated orally with 6–12 mg/day flupentixol achieved maximally 10 ng/ml *cis*- + *trans*-flupentixol concentrations. However, in 1987, the same group (Balant-Gorgia et al. 1987) developed a stereospecific assay which revealed that in a group of patients treated orally with flupentixol, 59 % of the patients had a *trans*-/*cis*-flupentixol ratio in plasma between 1.5 and 2.5 (range 0.77–6.0). In 93 % of the cases, the inactive *trans*-isomer concentration exceeded that of the active *cis*-isomer. A graphic presentation suggests that in patients treated orally with 4–15 mg/day flupentixol, *cis*-flupentixol concentrations vary between 0.5 and 5 ng/ml.

This suggests that in the PET study (Reimold et al. 2007), significantly lower concentrations than 0.5–2 ng/ml *cis*-flupentixol lead to 50–70 % D2-receptor occupancy.

Other authors developed stereoeselective methods of flupentixol in the blood of patients treated with flupentixol. Ulrich (1995) described disappearance of *cis*-flupentixol exposed to daylight and its *trans*-isomerization to *trans*-flupentixol until a 1:1 mixture of both isomers is reached. In the clinical part of his study, none of the few patients treated with 20 mg/day flupentixol p.os had *cis*-flupixol levels >10 ng/ml. After a treatment of dozens of patients with 2.5–40 mg/day oral flupentixol, *cis*-flupentixol levels were found to be <10 ng/ml in all but one patient. These authors carefully avoided exposition of the probes to daylight during drug analysis (Walter et al. 1998). In cocaine dependent patients treated with low doses (2.5 or 5 mg/day) of oral flupentixol, *cis*-flupentixol plasma trough levels as measured with a stereoselective method only reached 0.53 ± 0.2 ng/ml (means ± SEM) (Evans et al. 2001).

Several authors did not mention the existence of *cis*–*trans* isomerism of flupentixol in their publications, where they proposed non-stereoselective assays for therapeutic drug monitoring (Gutteck and Rentsch 2003; Kumazawa et al. 2000).

In conclusion, considering the pharmacological and pharmacokinetic differences between *cis*- and *trans*-flupentixol, therapeutic monitoring studies with oral flupentixol in psychiatric patients should include stereoselective assays in conditions protected from daylight. Moreover, more data are needed to clearly define an optimal therapeutic range for *cis*-flupentixol plasma levels, as almost all studies were performed in a limited number of patients treated with relatively low doses (2.5–20 mg/day) of flupentixol. Tentatively, a therapeutic reference range/recommended *cis*-flupentixol concentration range of 0.5–5 ng/ml is proposed.

Conflict of interest The authors have no competing interests

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