

Plasma levels of long-acting injectable antipsychotics in outpatient care: a retrospective analysis

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Abstract

Background

The antipsychotic efficacy in schizophrenia depends on its availability in the organism. Although therapeutic outcomes remain still far from satisfactory, therapeutic drug monitoring is not a common part of clinical practice during a treatment with long-acting injectable antipsychotics (LAI AP). The real effectiveness of LAI AP is thus uncertain.

Methods

We made a retrospective evaluation of plasma levels of LAI AP. Collection of blood samples was performed just before the drug application and one week later. Forty patients with a stabilized clinical condition and steady-state plasma levels were included.

Results

In the observed cohort of patients, flupentixol decanoate ($n = 23$) was the most often used drug, followed by fluphenazine decanoate ($n = 7$), haloperidol decanoate ($n = 5$), paliperidone palmitate ($n = 3$), and risperidone microspheres ($n = 2$). Just 5 of 40 patients were treated with a monotherapy. At the time before the application, 60% of the patients did not reach the therapeutic reference range (TRR) and 20% of the patients had an undetectable plasma level. At the time of collection of the second blood samples performed after 7 days, 24% of the patients were under the TRR.

Conclusion

We have found the surprisingly high incidence of plasma levels under the TRR in patients treated with LAI AP. Notwithstanding the individual variability in pharmacokinetics, it seems the LAI AP may be underdosed in the usual clinical practice.

Background

Therapeutic drug monitoring (TDM) is a method of optimization and individualization of pharmacotherapy, the use of which in psychiatry is encouraged by the frequent need of treatment not only of the acute stage of the illness but also of long-lasting effective prophylaxis. Schizophrenia is one of the most serious psychiatric disorders and antipsychotics remain first-choice drugs for its treatment.

However, there is a strong interindividual variability in plasma levels of the psychopharmaceuticals administered in similar doses that can reach up to the twentyfold differences (1). The fundamental recommendation for the use of TDM in psychiatry is based on the guidelines of "Arbeitsgemeinschaft für

Neuropsychopharmakologie und Pharmakopsychiatrie" (AGNP) published in 2017 (1). Generally, TDM is indicated in cases of the proven relation between the plasma level and the clinical effect; when there exists a distinctive variability in pharmacokinetics; in cases of a narrow therapeutic window; in patients with a suspicion of a poor adherence; when it is not possible to optimize the dose on the basis of clinical observation only; when the toxic symptoms are difficult to recognize; and in cases of an altered clearance of the drug (1).

Long-acting injectable antipsychotics (LAI AP) are used in the treatment of schizophrenia both for providing an effective antipsychotic treatment in non-adherent patients and for the reason of more advantageous pharmacokinetics – they avoid the "first-pass" effect and provide stable plasma levels during the continuous release of the drug from the muscle depot. Apart from these advantages, this galenic form excludes the risk of overdosing within a suicidal attempt; it generally reduces the risk of relapse and the number of rehospitalizations when compared to the oral forms (2). However, the advantages of the LAI forms were recently questioned by the results of an extensive meta-analysis (3) where neither better tolerance nor effectiveness was found for individual drugs when compared to the oral forms. Aripiprazol (reduced number of drop-outs for any reason) and risperidon (reduced incidence of hyperprolactinemia) were the only exceptions. On the other hand, it is not possible to change the dosing of LAI flexibly in an occurrence of adverse effects (4).

In outpatient care, LAI AP are perceived as a therapeutic tool that enhances the probability of effective prophylaxis because of their stable plasma levels, regardless of the therapeutic adherence level. Therefore, the aim of our study was to evaluate plasma levels of LAI AP as used in the common outpatient care in the usual recommended dosing, and the stability of them.

Methods

We conducted a retrospective evaluation of plasma levels of LAI AP in individuals treated in the outpatient ward of the psychiatric department of the University Hospital Ostrava.

The first inclusion criterion was obtaining a blood sample within the usual regimen of TDM in LAI AP at our department; it means the blood was taken twice within one cycle of the drug administration – on the day of administration (before administration) and 7 days later. We included the results of TDM in patients of both sexes, over 18 years of age, and with the diagnosis of schizophrenia and related disorders (F2x.x). The diagnosis was assessed by a fully qualified psychiatrist, according to the ICD-10 (5). The patients were examined within the year 2015. We evaluated plasma levels of all LAI AP available in the Czech Republic at that time. Other inclusion criteria were at least the three-month treatment with the agents, which is enough to reach the steady-state and the absence of any treatment changes during this period. The patients had to adhere to the dates of application with the tolerance of ± 2 days.

The patients using the same drug in both LAI and oral form concurrently were excluded. A concurrent long-term use of different psychopharmaceuticals was permissible.

After obtaining the blood samples, the specimens were immediately sent for the further processing to the Department of Clinical Pharmacology, where they were analysed by the method of the ultra-performance liquid chromatography-tandem mass spectrometry (6). This method has been fully validated and is used for routine analysis at the University Hospital Ostrava.

The assessment of the plasma levels according to the schedule described above was a part of the usual clinical practice for TDM in both LAI and oral antipsychotics, and was routinely used for the evaluation of adequate pharmacotherapy. All patients whose data were included in the study signed an informed consent at the time of their admission to outpatient care, in which they agreed with a processing of their data for research reasons. The use of anonymised data was approved by the Ethical Committee of the University Hospital Ostrava (1130/2019).

The methods of descriptive statistic were used for data processing. Patient representation was described by absolute and/or relative frequencies in each group, where 95% Clopper-Pearson confidence intervals (CI) were added.

Results

A total of 40 patients (23 men and 17 women), with the average age of 45 ± 13 years, fulfilled the inclusion criteria. The second blood taking was performed in 37 of them because 3 patients refused to have their blood sample collected, or did not show up.

The included individuals were most often treated with flupentixol decanoate (n=23), then fluphenazine decanoate (n=7), haloperidol decanoate (n=5), paliperidone palmitate (n=3), and risperidon microspheres (n=2). The average intervals of an application were 21 days in flupentixol, 24 days in fluphenazine, 18 days in paliperidone, and 14 days in risperidon.

Regarding the first blood samples obtained (just before the regular administration of LAI AP), the recommended therapeutic reference range (TRR) was not achieved in 24 (60.0%, CI 43.3 – 75.1%) patients and 8 of them (20.0%, CI 9.1 – 35.6%) had even undetectable plasma levels. In case of the second blood taking (1 week later) 9 patients (24.3%, CI 11.8 – 41.2%) did not achieve the TRR, no patient had an undetectable level, and in 1 patient, the plasma level exceeded the TRR (Table 1). Only 5 patients (12.5%, CI 4.2 – 26.8%) were treated with a monotherapy of LAI AP: flupentixol decanoate was given to 4 of them and haloperidol decanoate was given to 1 patient. The rest of the cohort was also treated with an oral AP with a different agent. The plasma levels of all 5 patients treated with the monotherapy were under the TRR at time of the first blood taking; in case of 1 patient treated with flupentixol decanoate and 1 patient with haloperidol decanoate, the levels were even undetectable (Table 2).

The vast majority of applied agents were indicated in accordance with the Summary of Product Characteristics. One diagnosis of acute and transient psychotic disorder and one of bipolar disorder were the only exceptions; however, we found an apparent development towards the paranoid schizophrenia and schizoaffective disorder when we re-examined these cases in more detail.

Discussion

In the presented study, we performed a retrospective analysis of plasma levels of LAI AP. The results of the patients treated at the outpatient psychiatric ward of the University Hospital Ostrava were included. The choice of a specific LAI AP depends on the clinical features of the patient as well as on experiences and preferences of individual physicians at outpatient or inpatient wards, because LAI AP are often administered for the first time during hospitalization.

The obtained results may be found surprising because the plasma levels before a regular administration did not reach the lower borderline of the TRR in more than a half of the patients, even though the recommended dosing was maintained. It is necessary to bear in mind the fact the TRR has been established for oral preparations. In one fifth of the patients, the levels were even undetectable, and so the administration of LAI AP most certainly does not fulfil its basic aim in these cases, i.e. to ensure a permanent presence of the effective agent in the patient's organism. Similar results have also been recently presented for oral antipsychotics (7), revealing a pseudo-resistance in patients with schizophrenia. However, the main reason of low concentrations of an oral medication, i.e. insufficient treatment adherence, can be excluded in case of LAI AP.

Nevertheless, even subtherapeutic plasma levels might be effective in some patients, what follows from the definition of TRR (1). But the TRRs have been defined for oral preparations with their pharmacokinetic properties, and it is possible that the TRR of LAI AP could be different (8). This is in accordance with the results of Marder et al. (9), who did not observe a connection between the plasma levels of fluphenazine decanoate and its clinical or adverse effects, and the authors assume that even the low (subtherapeutic) plasma levels of LAI fluphenazine may be effective. Also the effect of low doses of flupentixol in the treatment of anxiety and depressive disorders is well known (10).

Especially in cases of monotherapy associated with low levels of LAI AP it is possible to ask a question whether the stabilized clinical condition is a consequence of an effective prophylaxis or whether it is achieved because of the natural course of the disease. The self-evident need of chronic antipsychotic prophylaxis was called into question e.g. in the naturalistic observational study performed by Harrow et al. (11). On the other hand, regular visits to the outpatient department are considered to be one of the favourable factors in patients treated with LAI AP. During these regular visits, the medical staff is also able to recognize the first signs of possible worsening of the clinical condition.

The combined therapy using LAI AP and oral AP is used in a third to a half of the patients in the clinical practice (8, 12) and reached even 87.5% in our cohort. Despite general recommendations where the monotherapy is preferred because of the missing evidence regarding the combined treatment (13), a combination of LAI AP and oral AP does not necessarily have to be associated with more adverse events, and may even lead to a lower number of drop-outs (9). Considering a high rate of patients with combined treatment, we suppose a rather supportive role of LAI AP in a general treatment strategy, the aim of which is to reduce the risk of a complete non-adherence. But the frequent use of a combination with the oral AP might also indicate a therapeutic hesitation regarding determination of a specific dose of LAI AP in a

specific patient (if not using TDM), when relying on conversion recommendations only. This is contrary to the case of the short-acting agents, where the connection between the dose changes and the clinical effect is much more evident according to clinical practice. The more frequent use of the TDM in LAI AP treatment might help the physicians to overcome this therapeutic uncertainty in this way.

The deviations in plasma levels can be also associated with drug or food interactions. In our study, we considered the comedication in patients with the undetectable plasma levels only. We did not find the presence of any of the known inhibitors or inducers of the CYP 450 isoenzymes. Smoking as a well-known inducer of CYP1A2 was not relevant to any of the followed antipsychotics.

Interesting results were found in the case of haloperidol. Its plasma levels declined surprisingly in the second blood sample (obtained one week after the initial administration) in 3 of 4 patients; in one patient the plasma level was even on the lower limit of the TRR (1.0 µg/L). An inconstant absorption from the muscle depot can be a possible explanation. In case of fluphenazine, a subtherapeutic plasma level was observed in all patients even in the second blood samples, and so the overall dosing (including the single dose and interval of an application) should be considered insufficient with respect to all the above-mentioned limitations.

The study has several obvious limitations. The first one is the size of the cohort and its diagnostic heterogeneity. The collection of blood samples and their evaluations were performed analogically to the oral medication, and the established regimen of TDM at our department did not respect the pharmacokinetic differences of individual agents but fitted well for everyday clinical use. Also, we did not follow the body weight of the patients and did not analyse all possible interactions in the whole cohort.

Conclusions

LAI AP are primarily used to exclude non-adherence and they should guarantee a sustained therapeutic plasma level of the drug. However, our results show interindividual differences in pharmacokinetics of this antipsychotic medication and emphasize the importance of use of TDM in patients treated with LAI AP, especially in monotherapy. Despite the small size and heterogeneity of the cohort, the obtained results raise a question regarding a possible underdosing of LAI AP, even when adhering to the dosing recommendations. This finding should form a basis for future research aimed at the effective therapeutic plasma levels in LAI AP.

Declarations

Ethics approval and consent to participate

Approved by the local ethical committee (of University hospital Ostrava) under the reference number 1130/2019

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

None to declare. We have analyzed the data collected during regular treatment.

Author's contributions

MH, PŠ and TS extracted the appropriate data from the documentation and analyzed them. RU, IK and MG drafted the pharmacological part of the study. EČ revised the final form of the manuscript. All the authors read and approved the final manuscript.

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Tables

Table 1. Measured antipsychotics, dosing, number of patients, and number of patients with plasma levels under the therapeutic reference range.

	Dosing		First blood collection		Second blood collection	
	Interval of application (days) †	Dose (mg/week) †	Number of patients	Plasma levels under the TRR	Number of patients	Plasma levels under the TRR
Flupentixol decanoate	21 ± 6	14.5 ± 4	23	15	22	0‡
Fluphenazine decanoate	24 ± 4	7.4 ± 1	7	6	6	6
Haloperidol decanoate	18 ± 6	20.8 ± 6	5	1	4	1
Paliperidon palmitate	28 ± 0	22.9 ± 4	3	1	3	0
Risperion microspheres	14 ± 0	12.5 ± 0	2	1	2	1
Total	-	-	40	24§	37	9

TRR, therapeutic reference range

† data represent mean ± standard deviation

‡ in 1 case plasma level above the TRR

- in 8 cases undetectable plasma levels: fluphenazine 4, flupentixol 3, haloperidol 1

Table 2. Pharmacokinetically relevant characteristics of the patients with undetectable plasma levels.

Patient	LAI AP	Smoking	Other psychiatric medication
	Dose/Interval of application		
1.	Fluphenazine decanoate 25 mg i.m./3 weeks	Yes	quetiapine, tiapride, pregabalin, risperidon
2.	Fluphenazine decanoate 25 mg i.m./4 weeks	Yes	amisulprid, clozapine, olanzapine
3.	Fluphenazine decanoate 25 mg i.m./4 weeks	Yes	chlorprothixen, clozapine
4.	Fluphenazine decanoate 25 mg i.m./4 weeks	Yes	olanzapine, clozapine, aripiprazole
5.	Flupentixol decanoate 40 mg i.m./4 weeks	No	zotepine, clozapine
6.	Flupentixol decanoate 40 mg i.m./4 weeks	Yes	0
7.	Flupentixol decanoate 40 mg i.m./3 weeks	Yes	olanzapine, haloperidol, levomepromazine, clozapine
8.	Haloperidol decanoate 50 mg i.m./2 weeks	Yes	0

LAI AP, long-acting injectable antipsychotics