Pharmacovigilance

Predicting and managing adverse reactions of psychotropic drugs

Rosa Yu. Ilyina, Olga O. Pasynkova and Lilia E. Ziganshina

Department of Basic and Clinical Pharmacology, Kazan Federal University, Kazan, Russian Federation

Republican Psychiatric Clinical Hospital named after V.M. Bekhterev, Kazan, Russian Federation

Department of Dentistry, Kazan State Medical Academy, Kazan, Russian Federation

Received 21 October 2012
Accepted 22 February 2013

Abstract.

BACKGROUND: Neuroleptic induced extrapyramidal disorders are often presented in a form of orofacial hyperkinesias and dystonia. Rational use of neuroleptic drugs requires individualised approach to a patient, however simple criteria for determining individual, “personalised” dosage regimen have not been fully developed for routine practice in resource-limited hospital settings.

OBJECTIVE: To study the tonus of tongue muscles as a measure of orofacial dystonia and the total hepatic oxidative capacity as a potential predictor of excessive vulnerability to neuroleptic-induced dystonia in psychiatric patients.

METHODS: We measured the maximal force of the tongue manoeuvre (F, g/cm²), the total (integral) hepatic oxidative capacity by the antipyrine-test and used chlorpromazine equivalent to calculate the total daily neuroleptic load in 283 psychiatric patients and 30 healthy volunteers.

RESULTS: The tonus of tongue muscles depends on the total daily neuroleptic dose and the length of antipsychotic treatment. The higher the total daily neuroleptic dose and the longer the treatment history, the greater the tongue muscles' tonus is. The tongue muscles' tonus was greater in patients with low rate of oxidative antipyrine metabolism. Antidepressants contributed to the increased tonus of the tongue muscles in "slow metabolisers" of antipyrine.

CONCLUSIONS: The simple and cheap measurements of total hepatic oxidative capacity and of muscle tonus of the tongue could be used to predict and manage neuroleptic-induced adverse reactions.

Keywords: Neuroleptics, antidepressants, tongue muscle tonus, movement disorders, drug metabolism, hepatic oxidative capacity

1. Introduction

One of the problems of the modern psychopharmacotherapy is insufficient practice of individual approach to determining dosage regimen of psychotropic drugs. High frequency of adverse drug reactions is the result of indiscriminate use of psychotropic drugs of the same type in individual patients [7]. The total hepatic oxidative capacity is one of the parameters that could be used for prediction of individual responses to psychotropic drugs. Our previous studies showed that the total hepatic oxidative capacity could be used as a rough predictor of neuroleptic tolerability. Patients, both men and women, with low total
hepatic oxidative capacity have been shown to be excessively sensitive to neuroleptic-induced adverse reactions [16]. Fast “metabolisers” among schizophrenic patients were shown to be more resistant to adverse effects of neuroleptics, both men and women [14].

Rational use of psychotropic drugs is based on individualised approach to a patient and in particular on determining individual, personalised dosage regimen. Thus, thorough calculation of the total daily neuroleptic dose, the use of monotherapy with drugs of established efficacy; - these are the ways of minimizing risks of unwanted adverse effects. Movement disorders remain the most severe adverse reactions of neuroleptics [13] and result in social and mental disability [29]. Moreover, they grossly impair patients’ treatment compliance [4, 11].

Dystonia or dystonic syndrome presents with paroxysmal disorders in the form of muscle tension in the mouth, its bottom, neck, tongue, pharynx, masticatory muscles with forced tongue protrusion, sometimes with tongue injuries, primarily biting [1, 3, 23, 25, 26]. Orofacial syndrome often combines with respiratory distress, facial hyperemia, fear and feeling of threat, hypersalivation, etc. [17]. Researches describe tongue vibration and lower jaw vibration (“rabbit syndrome”) [8, 12, 18–20].

We proposed that measuring the tonus of the tongue muscle could reflect the extent of dystonia and that it would depend on the total neuroleptic exposure. The research questions were:

- Does the tonus of tongue muscles depend on the total daily neuroleptic dose?
- Does the tonus of tongue muscles depend on the length of antipsychotic treatment?
- Do antidepressants contribute to the increased tonus of the tongue muscles?
- Is there any interrelation between the total hepatic oxidative capacity and the extent of dystonia as measured by the tonus of the tongue muscles?

Our study presents the first attempt to answer these questions.

2. Material and methods

We examined 253 patients aged 15–85 years, who were admitted to the Republican Clinical Psychiatric Hospital in 2005–2008 with the diagnosis of paranoid schizophrenia (226 patients, 89%), organic and epileptic psychoses (15 patients, 6%); consequences of organic cerebral damage (9 patients, 3.6%); oligophrenia (3 patients; 1%). The control group consisted of 30 healthy volunteers aged 19–57 years (35 ± 13 years). Healthy volunteers were defined by history and physical examination. A separate comparison group comprised the patients with newly diagnosed mental illness (first episode), who had not taken any psychotropic drugs prior to our study (30 patients). Sex ratio of patients and volunteers of control group was approximately 50:50. The diagnosis of psychiatric illness was made by qualified psychiatrists as well as treatment decision and its initiation.

We grouped patients by the type of the used psychotropic drugs into 3 groups: the patients who were treated only by neuroleptics (90 patients); only by antidepressants (43 patients); or a combination of neuroleptics and antidepressants (90 patients).

The following psychotropic drugs were used: neuroleptics – chlorpromazine, levomepromazine, thioridazine, trifluoperazine, haloperidol, trifluoperidol, chlorprothixene, zuclopenthixol, clozapine, sulpiride, risperidone, quetiapine and olanzapine, and antidepressant amitriptyline. Psychiatric patients were not treated with anticholinergics for at least a month prior to inclusion into the study.

The rate of oxidative hepatic metabolism or the total (integral) hepatic oxidising capacity was determined by the antipyrine-test. Antipyrine concentration in saliva was determined by a simple
spectrophotometer-based procedure [15], saliva was taken before and after 3, 6, 9, 12 and 24 hours of antipyrine ingestion (500 mg by mouth). Antipyrine half-life was calculated by exponential regression method for single compartment pharmacokinetic model [21].

We grouped patients on the basis of their integral hepatic oxidative capacity into two groups – slow “metabolisers” (antipyrine $T_1/2 > 18$ hours, 101 patients) and fast “metabolisers” (antipyrine $T_1/2 < 18$ hours, 122 patients). For distribution curve see Figure 1.

We used the Dynamometric Analyser of Muscular Manoeuvre (DAMM) of tongue, developed and produced by the enterprise “Medphysprybore” (Kazan)\(^1\). We determined the maximal force of the tongue manoeuvre ($F$) measured in g/cm\(^2\) – the tongue pressure in grams per a unit of square of the olive-shaped disk of the DAMM in cm\(^2\) – as described in [10]. We used chlorpromazine equivalent to calculate the total daily neuroleptic load [6, 28].

2.1. Ethical approval

The study was approved by the Ethical committee of the Kazan State Medical Academy. Volunteers and psychiatric patients or their representatives singed informed consent form.

2.2. Statistics

We used SPSS 13.0 for data processing: since the distribution of values of the tongue muscle force ($F$) was normal, according to the Kolmogorov-Smirnov test (or to the Shapiro-Wilke test for subgroups with $N < 50$), and the dispersion was homogeneous (according to Levene test), statistical analysis of the data was performed using two-tailed $t$-test for multiple comparisons and homogeneous variances. Mean difference between subgroups was considered to be due to non-random causes with the $P$ values of less than 0.05.

\(^{1}\)We thank professor I.G. Yamashev for liaising with the enterprise and making the DAMM device available for our studies.
Table 1
Tongue muscle force (F) in healthy volunteers and psychiatric patients grouped by the type of psychotropic drugs used (M [95% CI])

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>N</th>
<th>Integral oxidative hepatic capacity (T 1/2&lt;18 hours)</th>
<th>Integral oxidative hepatic capacity (T 1/2&gt;18 hours)</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (healthy volunteers)</td>
<td>30</td>
<td>203 [105 to 301]</td>
<td>305 [205 to 405]</td>
<td>14</td>
</tr>
<tr>
<td>First episode psychiatric patients, not yet treated</td>
<td>30</td>
<td>224 [80 to 369]</td>
<td>346 [213 to 477]</td>
<td>13</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>90</td>
<td>432 [291 to 571]</td>
<td>522 [460 to 584]</td>
<td>28</td>
</tr>
<tr>
<td>Neuroleptics and antidepressants</td>
<td>90</td>
<td>424 [283 to 563]</td>
<td>569 [427 to 709]</td>
<td>31</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>43</td>
<td>316 [214 to 416]</td>
<td>452 [369 to 535]</td>
<td>13</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>283</td>
<td>99</td>
<td>184</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference when compared with control. **Statistically significant difference when compared between slow and fast “metabolisers”. NS – Statistically non-significant. CI – Confidence interval.

3. Results

Does the tonus of tongue muscles depend on the total daily neuroleptic dose?

The data presented in Table 1 show that psychiatric patients, treated with psychotropic drugs, had consistently higher indices of tongue muscle tonus as measured by the muscle force, than healthy volunteers (control group) or untreated psychiatric patients, admitted to the hospital for their first episode. There was no statistically significant difference in the tongue muscle force between healthy volunteers and psychiatric patients in their first episode, not treated yet with psychotropic drugs. These data showed that the use of psychotropic drugs was accompanied by the increase in tongue muscle tonus.

When we subdivided patients by the total daily neuroleptic dose into three groups of less that 800 conventional units (CU) of chlorpromazine, 800 to 1500 CU and over 1500 CU, we found that the tongue muscle force was consistently higher in patients treated with the total neuroleptic dose of over 1500 CU that with the dose of less than 800 CU over the years of treatment (Table 2).

Does the tonus of tongue muscles depend on the length of antipsychotic treatment?

When we grouped patients by the length of treatment with psychotropic drugs into three groups of treatment periods of less than 5 years, 5 to 10 years and over 10 years, we noted that the tongue muscle force was significantly higher in patients treated over 10 years compared to patients treated for less that 5 years with any total daily neuroleptic dose (Table 2). We found the same difference when grouping patients, treated with neuroleptics, by the length of treatment period and by therapeutic category (Table 3).
### Table 2

Tongue muscle force (F) in psychiatric patients grouped by length of psychotropic treatment and the total daily neuroleptic dose (M [95% CI])

<table>
<thead>
<tr>
<th>Total daily neuroleptic dose</th>
<th>N</th>
<th>Length of psychotropic treatment</th>
<th>5 to 10 years</th>
<th>Over 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Less than 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F [95% CI] g/cm²</td>
<td>p*</td>
<td>p**</td>
</tr>
<tr>
<td>&lt;800 CU</td>
<td>85</td>
<td>280 [237 to 324]</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>800 to 1500 CU</td>
<td>54</td>
<td>322 [277 to 367]</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>&gt;1500 CU</td>
<td>41</td>
<td>400 [334 to 464]</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Total numbers (N)</td>
<td>180</td>
<td>69</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference when compared with patients treated with daily neuroleptic dose <800 CU. **Statistically significant difference when compared with patients treated with daily neuroleptic dose 800 to 1500 CU. *Statistically significant difference when compared with patients treated for less than 5 years. NS – Statistically non-significant. CU – Conventional Unit.
Table 3

<table>
<thead>
<tr>
<th>Length of treatment</th>
<th>N</th>
<th>Type of psychotropic drugs</th>
<th>Neuroneptics</th>
<th>Neuroleptics and antidepressants</th>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F [95% CI] g/cm²</td>
<td>P*</td>
<td>P**</td>
</tr>
<tr>
<td>Less than 5 years</td>
<td>75</td>
<td>Neuroneptics</td>
<td>365 [350 to 489]</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroneptics and antidepressants</td>
<td>495 [379 to 609]</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>5–10 years</td>
<td>73</td>
<td>Neuroneptics</td>
<td>542 [403 to 681]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Over 10 years</td>
<td>75</td>
<td>Neuroneptics</td>
<td>596 [453 to 739]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference when compared with patients treated for less than 5 years. **Statistically significant difference when compared with patients treated for 5–10 years. NS – Statistically non-significant.

Do antidepressants contribute to the increased tonus of the tongue muscles?

Grouping treated psychiatric patients by therapeutic category and by the length of treatment, as presented in Table 3, showed that there was no statistically significant difference in the tongue muscles’ force between patients treated with antidepressants only at any time-point of treatment. In other words, these data showed that antidepressants did not significantly increase the tongue muscles’ tonus with years of treatment.

Is there any interrelation between the total hepatic oxidative capacity and the extent of dystonia as measured by the tonus of the tongue muscles?

We found the most pronounced statistical difference when grouping patients by the type of integral hepatic oxidative capacity. The tongue muscle force was consistently higher in patients with antipyrine half-life of over 18 hours (so called slow “metabolisers”) treated with neuroleptics only (by 21%), treated with combination of neuroleptics and antidepressants (by 34%) and treated with antidepressants only (by 43%), compared to “fast metabolisers” – patients with antipyrine half-life less than 18 hours (Table 1). These findings suggest that in “slow metabolisers” antidepressants contribute to a greater extent to the increase of the tongue muscles’ force as a measure of muscle dystonia.

4. Discussion and limitations of the study

Drug-induced dystonia for a long time has been described as a sensation of contraction in tongue muscles and gullet, numbness of the mouth, involuntary opening of the mouth and protrusion of the tongue, difficulties in swallowing and speaking. Muscle tension, forced head movements, seen on examination and with palpation, were also described [5]. Such conditions of hypertonus of orofacial muscles in psychiatry and neurology practice have been qualitatively described in every detail, however quantitative methodology of measuring the extent of dystonia has not been developed yet.
Our findings support the existing understanding that psychotropic drugs, and primarily neuroleptics, increase muscle tonus. We did not find significant difference in the tongue muscle tonus in psychiatric patients not treated with psychotropics yet compared to healthy volunteers, which suggested that the mental disease itself was not associated with the changes in tongue muscle tonus, at least in its onset. However our study was underpowered to generate evidence rejecting the possibility of tongue muscle tonus to be affected by the mental disease per se. However the numbers of patients were small and our findings should be interpreted with caution and used only as indicative parameters of the first pilot study. Small patient numbers reflect inherent methodology difficulties of the study. We did not predict the expected difference in tongue muscles’ force and did not set statistical difference thresholds in order to determine the required number of patients to reach statistical significance. We included all the patients according to the study objectives and design in the three year period.

The results confirmed that the increased tongue muscle tonus was associated with the use of neuroleptics. The higher was the total daily neuroleptic load and the longer was the treatment history, the greater were the increases in the force of tongue muscles. We suggest that this methodology could be used for early prediction of development of severe movement disorders in psychiatric patients in order to consider potentials for changing treatment options.

The use of antidepressants per se did not seem to adversely affect the tongue muscle tonus. Interestingly, theoretically it would seem that the indices of tongue muscle tonus would decreased in antidepressant treated patients due to the well established sedative and muscle-relaxing effects of conventional amitriptyline-like antidepressants [9], which were used in the in-patient psychiatric hospital setting studied. However rare cases of extrapyramidal symptoms in patients, treated by antidepressants only, have been described. The antidepressants included amitriptyline and SSRIs [30]. It was unexpected finding that the maximal force of the tongue manoeuvre increased in amitriptyline treated patients compared to controls both in slow and fast “metabolizers”. This is suggestive of the causative effect of amitriptyline; however, due to the limited number of observed cases, these results should be treated with caution because of high probability of various uncontrolled confounding factors. Confirmation of our findings in a larger study would have implications for research and for clinical practice: this would trigger much needed research of extrapyramidal system in patients taking antidepressants on one hand, and could help identifying the most vulnerable patients with the highest risk of development of adverse extrapyramidal effects. We think that the most important finding of our study was that the increase in tongue muscle tonus was greater in “slow metabolisers”. This offers potential predictive strategy in terms of rational management of psychiatric patients. Noteworthy is the fact that the difference in the tongue muscles’ tonus between “slow” and “fast metabolisers” were more prominent with inclusion of antidepressants in treatment regimen and particularly in patients treated solely with antidepressants. This is in agreement with well-documented dependence of amitriptyline-like antidepressants’ efficacy and safety on metabolic phenotype of patients [24, 27]. It has been shown that being a “slow metaboliser” led to the development of movement disorders and other neuroleptic adverse effects [15, 22].

However, since our study was a pilot one and the major limitation was the small number of patients studied (statistical power for all comparisons with nonsignificant – difference was less than 80%), we suggest that these studies be continued on larger patient populations.

Individual (personalised) approach to every psychiatric patient on the basis of phenotyping by the integral hepatic oxidative capacity and measurements of tongue muscle tonus could be used for ensuring more rational and safe psychotropic drug treatment. The use of these cheap and non-invasive methods could help to prevent and minimise adverse effects of psychotropic therapy.
5. Conclusions

The tonus of tongue muscles depends on the total daily neuroleptic dose and the length of antipsychotic treatment. The higher the total daily neuroleptic dose and the longer the treatment history, the greater the tongue muscles’ tonus is.

The total hepatic oxidative capacity influences the extent of psychotropic-induced dystonia as measured by the tonus of the tongue muscles: the slower the metabolic capacity, the greater the tongue muscles’ tonus is.

Antidepressants contribute to the increased tonus of the tongue muscles in “slow metabolisers” of antipyrine.

Conflict of interest

Authors declare that they have no conflict of interest.

References

[16] Ziganshina LE, Vedemikova OO. The oxidative hepatic capacity is one of the major determinants of the safety of neuroleptics in schizophrenic patients, Abstracts of the 8th World Congress on Clinical Pharmacology and Therapeutics, 1-6 August 2004, Brisbane; 2004 pp. 73-4.