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updating

Pharmacological treatment of psychosis in epilepsy

Tratamento farmacológico das psicoses na epilepsia

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Abstract Epilepsy is one of the main causes of functional disability, and it is usually associated to psychiatric comorbidity, such as psychosis of epilepsy (POE). POE requires more careful pharmacological treatment, considering the propensity of the antipsychotics (AP) to provoke seizures and the risk of pharmacokinetic interaction with antiepileptic drugs (AEDs). We discussed the classification and the main types of POE, as well as some characteristics of AP typical and atypical, its potential to decrease the epileptogenic threshold (ET) and possible interactions between AP and AED. Atypical AP, except clozapine, disclosed smaller influence on ET than typical AP. Regarding pharmacokinetic interactions, AEDs are related with a significant increase of the AP metabolism. Therefore, in spite of the risk for AP induced convulsions be dose-dependent, higher doses of AP can be necessary in the treatment of POE.

Keywords Psychotic disorder. Epilepsy. Antipsychotic agents. Therapeutics.

Resumo A epilepsia é uma das causas mais comuns de incapacidade funcional. Comorbidades psiquiátricas, como as psicoses, estão freqüentemente associadas à epilepsia. Psicoses na epilepsia (PNE) requerem tratamento farmacológico mais cuidadoso, levando-se em conta a propensão dos antipsicóticos (AP) em provocar crises convulsivas e o risco de interação farmacocinética com as drogas antiepilépticas (DAE). Após uma breve descrição da classificação e das principais características clínicas das PNE, foram discutidos alguns aspectos gerais do tratamento farmacológico das PNE e o uso de AP típicos e atípicos, destacando seu potencial para diminuir o limiar epileptogênico (LE), bem como possíveis interações AP/DAE. Os AP atípicos, à exceção da clozapina, demonstraram exercer menor influência sobre o LE. Quanto às interações farmacocinéticas, as principais DAE estiveram relacionadas com um aumento importante do metabolismo dos AP. Portanto, apesar do risco para convulsões por AP ser dose-dependente, doses mais elevadas de AP podem ser necessárias no tratamento das PNE.

Descritores Transtorno psicótico. Epilepsia. Agentes antipsicóticos. Terapêutica.

Introduction

Epilepsy is a chronic disease, with high rates of functional incapacitation and impairment. It's incidence ranges from 26 to 70/100,000 people/year and its prevalence between 4 to 8 cases/1000 inhabitants.[1] Nearly 30 to 50% of the epileptic population have some type of psychiatric comorbidity,[2] and the several psychosis of epilepsy (POE) are probably those that demand more medical attention. These psychosis differ from schizophrenia due to the relatively high nearly 7% prevalence among epileptic outpatients, reaching up to 27% in specialized centers for attention of epilepsy.[3]

We tried to present the main clinical manifestations of POE and the possibilities of pharmacological therapy, highlighting the influence of antipsychotics (AP) on seizures and their interactions with antiepileptic drugs (AED). Other questions, such as safeness, tolerability and cost of AP, were not dealt with.

Classification and clinical characteristics of POE

POE are classified according to the temporal relation of ictal events in ictal psychosis (IP), post-ictal psychosis PIP and

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interictal psychosis (IIP).[4] Among IIP, there are chronic IIP and brief IIP, and the latter can be a forced-normalization psychosis – FNP. Psychotic disorders secondary to some AED or with onset after epilepsy surgery, although important in the differential diagnosis, were not interpreted as psychosis directly related to the epileptic syndrome.

Ictal psychosis

IP occurs during an epileptic seizure or status, and EEG studies are mandatory for the diagnosis.[5] Usually it courses with irritability, aggressiveness, perceptual experiences, automatisms, paused speech or mutism.[6] Except for cases of simple partial status, the conscience is generally impaired.[7] Most PIP have epileptogenic focus on the temporal lobe. Extratemporal foci are present in 30% of the cases, mainly in the frontal cortex or cingulate.[8] The course is brief, from hours to days. Occasionally, psychosis may persist despite remission of the ictal event.[7]

Post ictal psychosis

Near to 25% of POE are PIP. Generally, PIP appear after an increase in the frequency of epileptic seizures. An interval of lucidity of 12 to 72 hours is common between the end of the seizure and the beginning of psychosis. Mean duration is nearly 70 hours.[9] Symptoms are variable, with auditive, visual or tactile hallucinations,[10] sexual indiscretions,[11] persecutory, religious or grandiose delusions.[9-11] Although being pleomorphic, there is a trend to persecutoriness, irritability, aggressiveness and depression.[9-12] PIP seems to correlate to the presence of bilateral ictal and interictal foci in the limbic temporal regions, lower verbal IQ, absence of febrile convulsions[12,13] and absence of temporal mesial sclerosis.[13]

Interictal psychosis

IIP are persistent psychotic states, characteristically paranoid, not associated with ictal events and without impairment of consciousness. Its incidence is approximately 9% in epileptic populations followed up in outpatient wards,[14] starting nearly at 30 years of age.[15] More common symptoms are persecutory and religious delusions, commonly with insidious onset, auditive hallucinations, mannerisms, lack of initiative, disorganized thought,[15] aggressiveness and suicidal ideation.[14,16] The duration is some weeks (brief IIP), and may last for more than 3 months (chronic IIP).[11] Compared to schizophrenia, IIP can show a lower intellectual impairment, better pre-morbid functioning, lower presence of negative symptoms and higher preservation of affection and personality.[5]

Forced-normalization psychosis is a type of brief IIP in which the psychotic state is triggered after the normalization of a previously altered EEG, remitting with the reappearance of electrographical abnormalities and epileptic seizures. This makes both conditions excludent or antagonic.[5] FNP has a low prevalence, estimated in 1% of POE.[5] Its manifestation is mainly through paranoid delusions, auditive hallucinations, restlessness, sadness and premonitory symptoms, such as insomnia and anxiety.[4]

Treatment

General aspects

Koch-Stoecker (2002) proposed the following therapeutic strategies for POE:

- All AP reduce the epileptogenic threshold (ET) and may cause epileptic seizures. This propensity varies between the different AP and seems to be dose-dependent;
- Pharmacokinetic interactions between AED and AP can alter the desired therapeutic effects;
- Side-effects, toxic effects and pharmacokinetic interactions of AED and AP may be additive;
- To keep attention on the choice and dose of drugs, avoiding sudden increases or decreases in AED, mainly when there is history of psychotic events; to assess the need of continuous use of AP, seeking always the lowest dose for the shortest time.[17]

Specific aspects: typical and atypical neuroleptics

AP provoke electroencephalographic alterations without clinical repercussions in approximately 7% of users without previous history of epilepsy, and seizures in 0.5 to 1.2% of these subjets.[17]

AP are traditionally classified as typical (or conventional) and atypical. In both classes, the most important pro-convulsant factors are their different pharmacodynamic proprieties such as the affinity profile for neuroreceptors and the specific sites of action, if predominantly cortical, nigro-striatal or hippocampal.[19]

Typical neuroleptics

Among typical neuroleptics, those with low potency, such as phenotiazines, have the higher propensity to decrease the ET. Phenotiazines are associated with higher anticholinergic effects, have low affinity with D_2 receptors and, therefore, lower risk of developing extrapiramidal symptoms (EPS). Logothetis[20] reported that 1.2% of non-epileptic patients hospitalized in a psychiatric hospital had seizures when treated with phenotiazines. With low doses of chlorpromazine (<200 mg/day) crises occurred among 0.3% of the patients; between 200 and 1000 mg/day, among 0.7% of the patients; and with doses above 1000 mg/day, among 9% of the patients. Among patients who received treatment with non-phenotiazinic AP, none had spontaneous seizures . Other factors positively related to the seizures were the presence of brain lesion and the rapid introduction of the drug.

Specifically for the cases of FNP, Trimble[21] has speculated that the use of low potency neuroleptics would reduce the ET, by inducing a kindling phenomenon – increase in the brain neurochemical excitability without provoking epileptic seizures, leading to the improvement of the psychotic picture.

Haloperidol is undoubtedly one of the safest AP to treat POE, as it hardly decreases the ET. Being a highly potent neuroleptic, haloperidol has high affinity with D_2 dopaminergic receptors, and, therefore, it needs low doses to have an antipsychotic action. However, it can provoke more EPS. It is particularly

indicated for acute and severe psychotic states, such as in protracted IP and PIP during video-monitoring, in which the abrupt withdrawal of AED demands rapidness of action and use for a brief period.[17]

Atypical neuroleptics

This new generation of neuroleptics shows low propensity to cause EPS, minimal effects in the serum concentration of prolactine, good action on the negative symptoms and lower incidence of tardive dyskinesia.[16,22]

Due to its action on the $5HT_2$ receptors, risperidone may have some influence on the dysphoric symptoms of epilepsy. As POE may be also accompanied by dysphoric symptoms, it is supposed that risperidone may be a good therapeutic indication. In these cases, Blumer et al (2000), in a non-controlled clinical study, suggest an association of low doses of risperidone with antidepressants.[23] Similarly, risperidone can be useful in cases of mental retardation or in personality disorders with aggressive symptoms and risk of psychosis.[24] In clinical tests, the incidence of seizures in non-epileptic subjects related to the use of risperidone was 0.3%.[25]

Olanzapine has affinity with D_2, 5HT, alpha-adrenergic, cholinergic and histaminergic receptors. The potential of olanzapine causing EPS is probably intermediate between clozapine and risperidone.[26] Clinical tests with olanzapine showed occurrence of seizures in 0.24% of patients without epilepsy.[27] The relative safeness of olanzapine regarding seizures can be originated in its action on some neurosteroids, particularly allopregnenolone, which has anxiolytic and anticonvulsant properties.[28]

No difference in the incidence of seizures was observed in non-epileptic subjects treated with quetiapine and placebo (0.4 and 0.5 respectively).[3] However, as for all AP, it is recommended greater attention in the cases of previous history of seizures.

Quetiapine and olanzapine, therefore, can be indicated for all types of psychoses in epilepsy. Nevertheless, side-effects such as weight gain and sedation should be taken into account in the choice of these drugs, mainly if used concomitantly with AED which can also provoke these effects, such as valproate and vigabatrine.

Amissulpride differs from other AP for having selective affinity for D_2 and D_3 dopaminergic receptors, and for not having affinity for other subtypes of dopaminergic, serotoninergic or cholinergic receptors. It has low incidence of EPS, although it can provoke hyperprolactinemia.[29] One of the benefits of using amissulpride in epilepsy is its essentially renal elimination (75 to 80% of the drug is eliminated through the renal route without transformations and 20%, through the biliary route), what could prevent some pharmacokinetic interactions related to the hepatic system.[18]

Clozapine is among the AP with the highest potential to provoke seizures, even in non-epileptic subjects. Its use in epilepsy is restricted to cases of severe psychosis which are refractory to the other neuroleptics. The occurrence of seizures seem to be triggered by a very rapid titration and for being dose-dependent (increasing by 0.7% at each 100 mg of the drug). Up to 300 mg/day, the risk of seizures is comparable to other AP. However, between 600 and 900 mg/day this risk reaches 5%.[30] Clozapine should be gradually raised, with electroencephalographic and hematological monitoring and orientations for patients regarding the possibility of increasing their epileptic seizures. Concomitant use of carbamazepine should be avoided, due to the risk of suppression of the bone marrow, in addition to the risk of clozapine-induced agranulocitosis. Valproate can be the safest and best-tolerated AED in these cases.[3]

Recently, Trimble (2002) proposed the administration of clobazam 10 mg every 6 hours for two consecutive days in order to prevent occasional psychotic states after episodes of cluster seizures.[31]

Pharmacokinetic interactions between AED and AP

Pharmacokinetic interactions can occur during the absorption, distribution, excretion and biotransformation. The latter seems to be the most affected step by the interactions of AED and AP, by means of a competition for the same metabolic route or inhibition/induction of the activity of the hepatic microsomal P450 cytocrome oxidase system (CYP).

The CYP system includes more than 30 enzymes, classified in three families (1 to 3) and five subfamilies (A to E). In human beings, most psychotropics are metabolized by 4 isoenzymes: CYP1A2, CYP2D6, CYP2C and CYP3A4. Nonetheless, genetic variations, such as polymorphisms, have been documented for CYP2C19, CYP2D6 and CYP2E1, contributing to the wide individual variability in the drug metabolism and clearance.[32]

Effects of AED on the pharmacokinetic of AP

Due to the potent effect in inducing the metabolism on different CYP, mainly CYP1A2 and CYP3A4, carbamazepine (CBZ) can cause significant reductions in the plasmatic concentrations of many AP.[33] The association of CBZ with haloperidol has shown a decrease from 50 to 60% in the plasmatic level of this AP, and can therefore compromise the psychiatric treatment.[32] As haloperidol is predominantly metabolized by CYP2D6 and CYP3A4, it is possible an induction mediated by CYP3A4. CBZ can also decrease the plasmatic concentration of clozapine (CYP1A2, CYP3A4), risperidone (CYP2D6, CYP3A4), olanzapine (CYP1A2), chlorpromazine and thioridazine.[33,34]

The co-administration with phenobarbital (PB) and/or diphenilhidantoine (DPH) can reduce the plasmatic levels of chlorpromazine,[35] haloperidol, mesoridazine and clozapine.[36,37] DPH can also increase the metabolism of quetiapine.[38]

Controversial findings were found regarding valproate (VPA), when associated with clozapine, indicating both an increase[39] and a decrease[40] in the plasmatic concentration of clozapine.

Effect of AP in the pharmacokinetic of AED

Through metabolic inhibition, thioridazine can provoke intoxication by DPH and PB, while chlorpromazine can raise the plasmatic levels of DPH.[33] Many patients, however, tolerate

the combination of phenotiazines and AED, without higher alterations in the plasmatic levels of PB, DPH and CBZ.[36] All novel AP are weak inhibitors of CYP and thus they are not expected to affect the metabolism of concomitantly administered AED.[33]

Conclusion

POE are essentially classified by their temporal relation with epileptic events, as the clinical presentation can be usually pleomorphic and hardly distinguishable. Regarding the pharmacological treatment, one of the limitations of this study was the non-controlled nature of the clinical observations. Therefore, recommendations to use this or that AP should always be interpreted cautiously. Other aspect was that almost all studies which assessed the risk of convulsions induced by AP were performed with psychiatric patients without epilepsy. Therefore, we believe that future investigations should include controlled studies and preferentially be performed with subjects with epilepsy and psychiatric comorbidity.

The pharmacological treatment of POE has particularities, not only due to the AP/AED interaction, but also because psychosis can suffer the influence of an epileptic syndrome. Therefore, a sudden change in the pharmacological treatment of epilepsy (reduction, increase or substitution of AED) should be avoided, mainly in cases in which there is history of psychoses. Although the AP/DAE interactions are not yet totally understood, mainly regarding novel drugs, the knowledge on some aspects of the utilization of AP in epilepsy, such as their propensity to alter the ET and interactions with the AED, can be reflected in the therapeutic success.

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