

META-ANALYSIS OF ANTIEPILEPTIC DRUGS INDUCED CHOREOATHETOSIS IN PAEDIATRIC PATIENTS

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ABSTRACT

BACKGROUND The safety profile of anti-epileptic drugs (AEDs) is an essential consideration for the regulatory bodies, owners and prescribing clinicians. Meta-analysis has increasingly been used to identify adverse effects of drugs. Efficacy studies are often too small to reliably assess risks that become important when a medication is in widespread use, so meta-analysis, which is a statistically efficient way to pool evidence from similar studies, seems like a natural approach. The safety profile of drugs is an important consideration, and it affects clinicians' decisions to prescribe specific AED(s), as serious adverse effects can lead to chronic complications or even death. Less serious, but significant, adverse effects can significantly impact quality of life, leading to systematic illness which may increase the overall cost of treatment. **METHODS** An electronic search was performed in using Pubmed, Paediatric journals of Neurology, MEDLINE. **RESULTS** The literature search identified 30 unduplicated papers. Of these 11 papers were excluded by reading the abstracts and titles. Another ten papers were excluded from reading their complete text. We selected nine papers which comprised of case studies and observational studies. **CONCLUSION** The combination of different antiepileptic drugs has resulted in drug-induced choreoathetosis. A mainly increased risk was seen with combinations that have phenytoin and lamotrigine. This could be due to an additive or a synergistic effect on central dopaminergic pathways.

KEYWORDS: choreoathetosis, antiepileptics, meta-analysis

Introduction

Adverse Drug Reaction (ADR) is defined as "Any noxious change, which is suspected to be due to the drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug".

Morbidity and mortality due to ADR are becoming a challenge to the healthcare system. Approximately 25% of ADRs have been reported in inpatients admitted to the hospital. This could be attributed to a multitude of factors like polypharmacy, drug interactions, lack of awareness, easy accessibility of drugs and increased co-morbid disease conditions. The unexpected ADRs for the new drugs are yet to be well documented; hence the ADR monitoring system will be beneficial for the treating physician. Some adverse drug reactions have been identified after use by a large number of people in the phase IV clinical trial, so the documentation of ADR is more emphasised. In India, ADR monitoring system is still primitive due to lack of awareness and interest in reporting by the healthcare professionals. A voluntary reporting system could do active ADR monitoring in a hospital set-up. Pharmacovigilance plays an essential role in providing information about adverse drug reactions and drug safety in a hospital. The safety of drug prescribing has become a highly

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visible topic in medicine, due in part to research suggesting that there are essential ADRs caused by commonly used medications. Paediatric patients constitute a vulnerable group about rational drug prescribing since many new drugs are released onto the market without the benefit of even limited experience in this age group. This deficiency causes paediatricians to prescribe children drugs in an 'off-label' manner often, thereby increasing the risk of drug toxicity. Adequate controlled clinical trials in children lack, mainly because of issues of cost and responsibility, and to regulations that frequently act as significant obstacles. Moreover, until recently, the few clinical trials that had been performed involving children focused on the efficacy of drugs and rarely monitored their safety. Chorea (Latin for "dance") is a hyperkinetic movement disorder usually due to basal ganglia injury or dysfunction. Movements are brief, irregular, unpredictable, and flow from one body part to another in a random fashion. Occasionally, they may be incorporated into a more purposeful movement to avoid social embarrassment. Chorea can occur in isolation, but usually appears in conjunction with slow, writhing, distal movements called athetosis (i.e., choreoathetosis). Athetosis is considered to be a hyperkinetic movement disorder characterised by involuntary writhing movements of the distal extremities and perioral muscles. Most athetosis is secondary to lesions in the basal ganglia, whether from cerebral palsy, ischemia, or trauma. In cerebral palsy, athetosis commonly coexists with chorea and is called choreoathetosis. Meta-analysis is already a well-established methodological approach for evaluating the effectiveness of therapies. However, in contrast to the published experience of using meta-analysis to assess drug efficacy, the use of this method to also quantify the risk of treatments remains limited to date. A recently published meta-analysis on the incidence of ADRs in hospitalised patients shows that ADRs represent a significant public health issue, making these reactions between the fourth and sixth leading cause of death in the USA, even when the drugs are used in proper doses and for approved indications.

Although paediatric pharmacotherapy has recently come to the fore, so far no meta-analytical review has been performed to assess the risk of drugs in the paediatric population. Recently published drug surveillance studies allow an estimation of the overall incidence of ADRs in different child health care settings. In this study, we systematically conduct a meta-analysis on drug-induced choreoathetosis in the paediatric population and provide a summary quantitative estimate of their occurrence.

Material and Method

INCLUSION CRITERIA

- Age (neonates-14 years),
- Seizure disorder,
- Combination of ant-epileptic drugs.

EXCLUSION CRITERIA

- Comorbid disease,
- Pseudoseizure,
- Age above 14 years.

LITERATURE RESEARCH

A sound meta-analysis is characterised by a thorough and disciplined literature search. A clear definition of hypotheses investigated provides the framework for an investigation. Typically, published papers and abstracts are identified by

a computerised literature search of electronic databases like PubMed (www.ncbi.nlm.nih.gov/entrez/query.fcgi), ScienceDirect (www.sciencedirect.com), Scirus (www.scirus.com/srsapp), ISI Web of Knowledge (<http://www.isiwebofknowledge.com>), Google Scholar (<http://scholar.google.com>).

Individual or Aggregated Data

A 3-year-old boy was admitted for treatment of recurrent minor motor seizures complicating a recent otitis media. At this admission, he was still having seizures on a combination of lamotrigine, clonazepam, felbamate and a ketogenic diet. He was started on phenytoin and discharged. Within a few weeks, he developed generalised choreoathetoid movements, which increased with activity and disappeared during sleep. On discontinuation of phenytoin, there was a significant improvement in his chorea. Chorea as a result of lamotrigine therapy was noted as a rare side effect in trials. Published reports describing new onset choreoathetosis in two young patients treated. With lamotrigine.

A study describes three patients with new-onset choreoathetosis that developed while receiving lamotrigine and phenytoin in combination therapy. The first patient developed transient chorea when her usual lamotrigine and carbamazepine, were supplemented with phenytoin, which was loaded intravenously shortly before chorea development. At the time chorea developed, her phenytoin levels were in the normal range ($16 \mu\text{ml}^{-1}$). The third patient experienced the onset of choreoathetosis on a combination of anticonvulsants which included phenytoin and lamotrigine, in addition to felbamate and topiramate. The abnormal movements started shortly after adding phenytoin and significantly improved when phenytoin was discontinued since this patient used phenytoin in monotherapy before this without any abnormal movements. Similar movement disorders developed in two 8-year-old mentally disabled children while they were receiving phenytoin. Seizures after a diphtheria-pertussis-tetanus immunisation had improved in each child at 1 to 2 months of age. A static encephalopathy ensued, characterised by mental retardation, ataxia, spasticity, and a mixed seizure disorder. Intermittent dystonia and choreoathetosis developed insidiously while serum phenytoin concentrations were in the therapeutic range. Sustained dystonia and choreoathetosis developed 2 hours after an oral provocation with phenytoin. The baseline abnormalities on the electroencephalogram remained unchanged during the choreoathetosis. Recognizable metabolic abnormalities known to be associated with similar movement disorders were excluded.

A study describes three patients with severe myoclonic epilepsy in infancy (SME) who suffer from choreoathetosis due to the adverse effect of phenytoin. Choreoathetosis appeared when these patients were 8, 19, and 21 years old, two days to 6 months after increasing the phenytoin dosage. Choreoathetosis disappeared when the phenytoin dosage was decreased. The two elder patients experienced the episodic and rather paroxysmal onset of long-lasting choreoathetosis, requiring the differential diagnosis of degenerative disease. In one of the patients, an ictal SPECT revealed decreased perfusion in the basal ganglia contralateral to the unilateral choreoathetosis. Polypharmacy, including carbamazepine and zonisamide, may have facilitated the onset of choreoathetosis. Phenytoin-induced choreoathetosis in the patients with SME is a vital differential diagnosis of degenerative disorders involving involuntary movements. The episodic and paroxysmal nature of this movement disorder can

delay its diagnosis and effective treatment.

Paroxysmal kinesigenic dyskinesia Paroxysmal kinesigenic dyskinesia (PKD) described three cases of brief dyskinesic episodes induced by sudden voluntary movements. Further descriptions followed and named the clinical entity paroxysmal kinesigenic choreoathetosis (PKC). As a subtype of the primary dystonias, it is also called DYT10. PKC is a rare neurologic condition, and most cases are sporadic. Only 27% have a family history with an autosomal dominant inheritance. The attacks last seconds to minutes and can start between 1 and 40 years of age. Up to 100 attacks per day of dystonic posturing, choreoathetosis, and ballism can occur. About 42% of patients have additional afebrile seizures in childhood. Infantile convulsions and paroxysmal choreoathetosis- age onset less than one-year Childhood –chromosome 16p12-q12. The rare adverse event of antiepileptic therapies includes choreoathetosis. polytherapy with antiepileptic drugs induces choreoathetosis. The commonly involved antiepileptic drugs include phenytoin, Phenobarbital, valproic acid, carbamazepine and also benzodiazepines. Non-psychotic drugs that produce choreoathetosis are Pheno-barbital, carbamazepine, benzodiazepines, valproic acid and phenytoin. A study report three patients who developed choreoathetoid movements on anticonvulsants. All those patients were using phenytoin and lamotrigine in combination as part of their anticonvulsant regimen when they developed chorea. No patient had these movements while on either phenytoin or lamotrigine monotherapy at normal, or toxic, concentrations. Drugs are causing chorea: There are many drugs which may cause choreoathetosis. Drug-induced chorea may be seen during the acute phase of treatment or may appear after some time. Antiparkinsonian and antiepileptic drugs are most important causes of chorea. Levodopa-induced chorea is the most common cause of chorea in adults. Treatment includes withdrawal of the offending drug. It may take days to months before patient is free from symptoms In this patient, it is also reasonable to conclude that neither lamotrigine nor phenytoin alone produced chorea, but the combination did. The third patient experienced the onset of choreoathetosis on a combination of anticonvulsants which included phenytoin and lamotrigine, in addition to felbamate and topiramate. The abnormal movements started shortly after adding phenytoin and significantly improved when phenytoin was discontinued since this patient used phenytoin in monotherapy before this without any unusual movements . Chorea is most likely due to the combination therapy. This patient has similar risk factors to other children described with drug-induced choreoathetosis. The mechanism by which these patients developed chorea is unknown. Pharmacokinetic interaction between anticonvulsants causing elevated high phenytoin levels is unlikely in our patients as lamotrigine is known not to elevate phenytoin levels.

Discussion

Anticonvulsant-induced choreoathetosis was first reported in 1962 with phenytoin. A literature search reveals about 80 cases. Reported patients are frequently young and have organic brain abnormalities including mental retardation. More than one-half of the cases have occurred in association with toxic drug levels. The use of phenytoin with other medications was reported to increase the risk of developing abnormal movements.

GABAergic mechanism.

The most consistent biochemical lesion in patients with Huntington chorea appears to be a loss of neurons in the basal ganglia that synthesise and contain GABA. The significance of this remains unknown. A variety of pharmacologic techniques have been attempted to increase CNS GABA levels. Valproic acid, which acts in part via a GABAergic mechanism, has, in a limited number of uncontrolled cases, ameliorated not only the agitation sometimes seen in persons with HD but also the movement problem. [17] However, no systematic studies have been conducted on the use of GABAergic agents to treat HD.

Pathophysiology

A simple model of basal ganglia function states that dopaminergic and GABAergic impulses from the substantia nigra and motor cortex, respectively, are funnelled through the pallidum into the motor thalamus and motor cortex. These impulses are modulated in the striatum via two segregated, parallel, direct and indirect loops through the medial pallidum and lateral pallidum/subthalamic nucleus. Subthalamic nucleus activity drives the medial pallidum to inhibit cortex-mediated impulses, thereby inducing parkinsonism. Absent subthalamic nucleus inhibition enhances motor activity through the motor thalamus, resulting in abnormal involuntary movements such as dystonia, chorea, and tics. VPA-induced chorea seems to require both high or toxic VPA serum concentrations and pre-existing brain injury. This case report highlights the importance of an accurate pharmacological history when approaching a patient with subacute onset of movement disorders because of the potential for recovery upon drug discontinuation. Moreover, the VPA, singly or in combination with phenytoin or carbamazepine should be used with caution in those with pre-existing basal ganglia injury. Pharmacokinetic interaction leading to increased free phenytoin level was suggested as a plausible explanation. Both generalised and focal movements have been described. Duration of dyskinesia has been variable but has often responded to discontinuation of the anticonvulsants. Chorea is most likely due to the combination therapy. This patient has similar risk factors to other children described with drug-induced chorea. In combination, the effects of lamotrigine and phenytoin appear to be additive or synergistic, resulting in sufficient enhancement of dopaminergic activity to provoke clinically apparent choreoathetosis, this is rather a pharmacodynamic interaction between both anticonvulsants. the movement disorder is secondary to phenytoin and can occur at therapeutic serum concentrations. Phenytoin is a central anticholinergic agent and a central stimulant of serotonin and may induce movement disorders as a result of altering these neurotransmitters in the brain. The variable expression of these movement disorders may relate to the nature of the preexisting striatal insult. Combined lamotrigine and phenytoin effects on central dopaminergic pathways might explain why our patients developed chorea when both anticonvulsants were present in combination. Neither direct enhancement of dopaminergic activity induced by phenytoin or indirect enhancement by lamotrigine alone was sufficient to provoke abnormal movements. In combination, the effects of lamotrigine and phenytoin appear to be additive or synergistic, resulting in sufficient enhancement of dopaminergic activity to provoke clinically apparent choreoathetosis, this is rather a pharmacodynamic interaction between both anticonvulsants. Removal of one of the medications was sufficient to ameliorate or eliminate the clinical symptoms. These reported cases sug-

gest that patients treated with a combination of lamotrigine and phenytoin may have an increased risk of developing dyskinetic movement disorders.

Conclusion

We conclude that drug-induced choreoathetosis may be seen during the acute phase of treatment or may appear after some time. Chorea is a rare side effect of anticonvulsants. The combination of different antiepileptic drugs has resulted in drug-induced choreoathetosis. Polytherapy with certain anticonvulsants may predispose patients to drug-induced choreoathetosis. It is essential for clinicians to evaluate both AEDs' effectiveness and safety on an individual basis before the selection of the appropriate monotherapy or adjunctive AED therapy.

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Authors' Statements

Competing Interests

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

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