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Why Diazepam More than Other Benzodiazepines is Unsuitable for Neonates?

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Abstract

For a good number of years, physician has learnt about the contraindication of diazepam and perhaps benzodiazepines at large in the management of neonatal seizures. However, very few scientific publications give account about underlying pathophysiological and pharmacological insights of mechanism involved. As a result, a non or poorly understood categorization of neonatal anticonvulsants is sometimes observed in daily clinical pediatric practice in some settings, with each physician going by his own way of managing seizures in neonates. This with more or less success and consequent adverse effects. This review is intended to contribute to a better understanding of phenomena implicated in the unsuitable use of diazepam beyond other benzodiazepines in the management of neonatal seizures.

Keywords: *Diazepam, Benzodiazepine, Anticonvulsant, Antiepileptic, Neonatal seizure*

Introduction

Neonatal seizures are a spectacular but common sign in pediatrics which may be worrying for parents and preoccupying for the physician. Although there have been considerable advances in their symptomatic treatment, their etiological enquiry and the curative aspects of their management may be quite challenging [1,2]. In effect causative factors may be due to injuries that occur during the antepartum, peripartum or postpartum periods, with possible acute or chronic complications. This underlines the necessity for deep assessment and adequate management of such infants with manifestations that can negatively impact the psychological states parents [3-25].

Despite the fact that the development of various anticonvulsant drugs has led to improvements of therapeutic attitudes towards neonatal seizures, the safety of these medications with regards to systemic immaturity in neonates remains equivocal. Therefore, a judicious choice of the wright drug in adequate doses is often required, even though instantaneous cessation of convulsive fits with drug administration is not always guaranteed [26].

Actually, the recommended first line drug for the management of neonatal seizures is phenobarbital, which belongs to the pharmacological class of barbiturates. However, it may happen that phenobarbital alone does not suffice enough to stop the seizure, and a second or third line drug required [26-29]. Since their development, benzodiazepines have become popular in general medicine, and progressively adopted as second line anticonvulsant drugs in neonatal seizure. This is mainly due to their effective anticonvulsant properties. Moreover, their myorelaxation ability, anxiolytic effects, and low toxicity, especially when given on short term, at minimum effective doses have made them more useful [27,28]. Nevertheless, their use may be associated with a number of adverse effects such as sedation, amnesia, cognitive impairment, ataxia, and dependence, contraindicating their long-term prescription. Due to the predominance of their advantages over documented side effects, progressive long-term use of benzodiazepines has been noted [27,28]. This still often occurs in current clinical practice, but not without consequences. As a matter of fact, adverse effects and their severity may vary from one benzodiazepine to another, according to specific pharmacological characteristics that differentiate them [27].

All benzodiazepines fundamentally have the same mechanism of action and may only vary in few points from each other such as receptor binding sites or subunits, the time onset of action, duration of action and adverse effects [29]. However, diazepam is among the first discovered benzodiazepines. It's the most commonly used molecule of the kind, and seems to be the prototype of the pharmacological class, being involved in most clinical trials and experiments.

Recent research findings have led to better understanding of the mechanism of action of benzodiazepines and significant milestones in the explanation of reported side effects are being noted. In the following paragraphs, we will give a simplistic but essential description of current knowledge about benzodiazepine-receptors interaction. Emphasis will be laid on diazepam specificities and the reasons for its contraindication in neonates illustrated.

Mechanism of Action of Benzodiazepines

Benzodiazepine produces neurological effects through allosteric interaction with a particular receptor in the central nervous system known as $GABA_A$ receptor ($GABA_AR$) [29]. This appears to be the fastest inhibitory neurotransmitter system in the brain. The receptor

comprises five transmembrane-spanning subunits that combine to form a ligand-gated chloride channel [30]. Various subunits actually identified are α1−6, β1−3, γ1−3, δ, ε, θ, and π making $GABA_AR$ heterogeneous in constitution [31]. From an electrophysiological stand point, the combination of Gamma Amino Butyric Acid (GABA) with its natural receptor- $GABA_AR$ may occur through several patterns according to subunits involved. The involvement and combinations of these subunits generally yields a pentamer which somehow improves the functioning of the receptor. In effect, the most commonly described subunit combination is the pentamer with 2α, 2β, and 1γ subunits [32]. However, whatever the subunit pattern formed, there is neuronal action potential inhibitory effects produced. This involve increased chloride ions (Cl^-) flowing into the neuron, causing inhibitory postsynaptic signal (IPSP) through hyperpolarization of the cell membrane.

Over the years, studies have shown that $GABA_AR$ with specific subunits have particular distribution throughout the nervous system, producing various effects and functions according to their structural constitution and their anatomical location [30]. Indeed, diverse but specific GABAergic subunits concentrations have been identified in the cortex, hippocampus, and basal ganglia for example. This with a spectrum of complex neurological signaling depending on receptor subunits involvement [31,33] whereas, some other receptor subunits may have a random distribution throughout the central nervous system.

Benzodiazepines specifically increase by allosteric and agonistic means the affinity of $GABA_AR$ containing subunits located within the α to γ subunit interval. Contrarily, they may never interact with $GABA_AR$ that involve the α4- or α6-subunit. This selectivity permitted to understand that other drugs such as barbiturates and some antiepileptics, anesthetics, neurosteroids and ethanol, proven to affect $GABA_AR$ functioning may act through other subunits [33]. Moreover, within benzodiazepine-sensitive $GABA_AR$ subunits, different combinations or involvement may be responsible for distinct neurological effects. As such, processes derived from genetics and pharmacology permitted to improve on the selectivity of novel benzodiazepines molecules and anticonvulsants. These refined molecules are capable to produced majored distinct neurological impacts including sedative, anxiolytic, myorelaxative, or anticonvulsive effects with some precision [31]. This evolution marks the difference with conventional benzodiazepines such as diazepam which can produce intense stimulation of most $GABA_AR$, with consequent secondary and adverse effects.

Adverse and Side Effects of Benzodiazepines in Neonates

An adverse effect might be defined as an unintended pharmacologic outcome that occurs even though the drug is administered correctly, while a side effect may be considered as a secondary unwanted repercussion that occurs as a result of a drug therapy. As stated before, under normal circumstances the interaction between GABA and $GABA_AR$ leads to the intracellular influx of Cl^- which causes cell membrane hyperpolarization. This is in turn responsible for inhibitory signaling against eventual depolarization, action potential or nerve impulses [29,30].

However, during the neonatal period, nerve cells are believed to have high concentrations of Cl^- to the point that GABA-gated Cl^- efflux sets up, as well as potential GABA-mediated neuro-excitation. This phenomenon seems compatible with the development of the central nervous system in humans and predominates in the neocortex [34]. As a result of this process, the neocortex shows the most delayed establishment of neuronal Cl^- homeostasis during development, compared with other subcortical brain regions [34-36]. Although the phenomenon reverses during maturation as nerve cells Cl^- concentrations progressively decrease to render GABA actions inhibitory [37,38].

Therefore, when a benzodiazepine is administered to a neonate with seizure, neocortical enhancement of GABA-gated Cl^- efflux may occur with GABA-mediated neuro-excitation. This might produce paradoxical effects to those expected, with rather exacerbation of myoclonus, seizures, and abnormal movements [34-36]. This could mean that cessation of neonatal seizures after benzodiazepine administration might proceed through subcortical inhibition pathways. On the other hand, the persistence of seizure might be explained by paradoxical neuro-excitation or reduced anticonvulsant activity of benzodiazepines in neonates [38-41].

Contraindicating Specificities of Diazepam in Neonates

Beyond the above listed side effects and adverse effects that may be caused by the use of benzodiazepines in the management of neonatal seizures, diazepam has specific characteristics that makes it even less recommended in such instances. In effect, being one of the earliest benzodiazepines discovered, diazepam is one of the most conventional [38-41]. It has not benefited from novel pharmacological fashioning that procure refined benzodiazepines $GABA_AR$ subunit selectivity. Therefore, it lacks specificity of action and strongly modifies the functioning of most $GABA_A$ergic subunits and with equal affinity. This with consequent secondary and adverse effects including apnea and hypotension which are most fatal [38-41]. Moreover, diazepam has a longer duration of action with one of the most delayed half-life in the pharmacological class, making its various side and adverse effects even stronger and lasting compared with other benzodiazepines. Furthermore, the metabolism of diazepam as a benzodiazepine is one of the most complex with more biochemical transformations, yielding a greater number of active metabolites which multiply expected, side and adverse effects, in comparison with other class members [38-41].

Conclusion

Although some benzodiazepines such as clonazepam are recommended as second line anticonvulsants in neonatal seizure benzodiazepine should be avoided as much as possible in neonate infants as a general rule. They may be responsible for paradoxical effects with exacerbation of initial neurological signs and symptoms, or cause adverse effects that may be fatal in some cases. This phenomenon is more common with conventional, non-selective molecules such as diazepam which strongly stimulate a wide variety of $GABA_AR$, relatively over a longer duration. However, in case of necessity the choice of adequate benzodiazepine should consider selectivity, half-life, duration of action, availability and cost-prize effectiveness, as well as the risk-benefit adequacy.

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