Summary

In addition to their role in the treatment of infantile spasms, steroids have shown benefit in the management of various other epilepsies and seizure types. The present article briefly reviews these aspects, and summarizes the pathophysiological considerations at the basis of the use of steroids in these conditions.

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Key words: Steroids, infantile spasms, epilepsy, intractable seizures

Stéroïdes dans les épilepsies pédiatriques: spasmes infantiles et autres...

Outre leur rôle dans le traitement des spasmes infantiles, les stéroïdes peuvent apporter un bénéfice dans le traitement d'autres types d'épilepsies et de crises. Cet article décrit brièvement ces aspects, et résume les notions physiopathologiques à la base de l'utilisation des stéroïdes dans ces conditions.

Mots clés : Stéroïdes, épilepsie, spasmes infantiles

Introduction

Epilepsy is one of the most common neurological disorders in childhood, with multiple etiologies, acquired or congenital, symptomatic to previous central nervous system insults or resulting from genetic causes at the molecular level. The treatment of epilepsy has always aimed at eliminating or reducing the number of seizures, without necessarily influencing the pathophysiology of the disease itself. Several drugs with different mechanisms of action have been introduced over the last decades and used more or less successfully for seizure control. Among those, corticosteroids, known for their anti-inflammatory and anti-immune properties, have been used in different types of epilepsies and epileptic syndromes, which include West syndrome, Landau-Kleffner syndrome and electrical status epilepticus during sleep, Lennox-Gastaut syndrome, epilepsy with myoclonic-astatic seizures, as well as Rasmussen's encephalitis.

The use of steroids in the treatment of epilepsy beyond West syndrome has not been well defined, however, and is limited to a few studies. In this paper, we review the use of corticosteroids in the management of West syndrome and outline some of the proposed mechanisms of action of these drugs in this situation. We also discuss the use of steroids in the treatment of epilepsies other than those associated with infantile spasms.

1. Infantile spasms

Infantile spasms (IS) are age-dependent seizures characterized by a sudden flexion, extension or mixed flexion-extension of predominantly proximal and truncal muscles, usually more sustained than a myoclonic movement but not as sustained as a tonic seizure (~1-5 seconds). Although arms, legs and trunk are most commonly implicated, limited forms, such as grimacing and head nodding may occur. In addition to West syndrome (WS), a severe infantile seizure disorder presenting in the first year of life with IS, associated with a disorganized interictal EEG with slow background and multifocal high voltage spikes (hypsarrhythmia) and developmental arrest or regression, IS may be noted in epileptic encephalopathies of later onset [1, 2]. Most infants with IS exhibit some degree of cognitive impairment, and additional seizure types or epilepsy syndromes are frequently observed on evolution.
a) The treatment of infantile spasms

Infantile spasms are classically refractory to the usual antiepileptic drugs. Much effort has been directed over the past years to evaluate the role of available anticonvulsants in the management of IS. Unfortunately, valuable comparisons among the various studies published are difficult because the schemes applied vary, the patient groups are not comparable in terms of age at onset of the spasms and of treatment choices, the criteria for evaluation of the results are different or not indicated, and the distribution of factors capable of affecting the treatment are usually distributed differently among the groups. While the optimal therapy for IS based on an understanding of its pathophysiology remains elusive, the cardinal questions of which drugs to use, at what dosage, for what duration and how to evaluate their efficacy, remain unanswered. Since the 1990s, vigabatrin, an inhibitor of GABA transaminase, has been shown to be successful in the resolution of IS, especially for those associated with tuberous sclerosis [1-5] and has been widely used as first line therapy. Its potential association with irreversible visual field constriction, which requires perimetric visual field study to identify, has restricted its use in certain parts of the world, however. Alternative treatments, including valproate, nitrazepam, pyridoxine, topiramate, zonisamide, lamotrigine, tiagabine, sulthiam, intravenous immunoglobulins, and the ketogenic diet, have been used with variable success [6].

b) Steroids in the treatment of infantile spasms

The pioneering work of Sorel in 1958 [7] suggested that corticotropin, a neuropeptide acting directly within the brain, might suppress infantile spasms, and improve electroencephalogram findings and behavior. Early anecdotal treatment successes with ACTH were later confirmed by prospective studies, as well as randomized controlled clinical trials, in which the rate of efficacy varied from 40 to 80% [8]. The recommended doses of ACTH vary between 10 and 240 IU/kg/d of natural hormone, or 0.1 to 0.5 mg/kg of tetracosactride or tetracosactrin (synthetic analogue). Corticosteroids, including prednisolone at 2-10 mg/kg, hydrocortisone at 10 and 25 mg/kg/d and dexamethasone at 0.3-0.5 mg/kg/day, have been used alone or in various combinations with ACTH, for durations of two weeks to many months. Relapses occur in 20-35% of patients. There is reasonable evidence from prospective, retrospective, randomized and blinded controlled studies for the efficacy of ACTH or steroids [9-20]. A Cochrane review in 2008 suggested that hormonal therapy was better than vigabatrin in the short term [21]. However, there are insufficient data to show that treatment of IS with either ACTH or steroids, or any other approach, improves the long term prognosis for cognitive outcome or decreases the later incidence of epilepsy [17, 22]. The United Kingdom Infantile Spasms Study (UKISS), a collaborative multicentric approach comparing the effect of hormonal therapy including treatment with corticotropin or steroids with vigabatrin in the treatment of IS, reported that the cessation of spasms after 2 weeks of treatment in patients with no identified underlying etiology was more likely with hormonal treatment. However the proportion of infants free of spasms at the final clinical assessment (12-14 months after treatment onset) was similar in both treatment groups [23]. An international collaborative multicentre study (ICISS) is under way, designed to compare the efficacy of hormonal treatment and vigabatrin given together to hormonal treatment alone in controlling spasms and assessment of developmental progress at 18 months of age.

c) Suggested mechanisms of action of steroids in infantile spasms

The notion that ACTH and glucocorticoids share a hormonal action that alters immune, inflammatory and other derangements in infantile spasms is well accepted [24]. However, their precise mechanisms of action remain unclear, and evidence suggests that ACTH, frequently reported to be more efficient in the treatment of IS, may have direct neurobiological effects on brain function [25]. For instance, ACTH has been shown to increase dendritic sprouting and myelination in immature animals, to regulate the action and metabolism of certain neurotransmitters, and to alter membrane permeability and signal transduction properties [25]. In addition, ACTH may reduce neuronal excitability in infantile spasms by various means:

a) As a neuropeptide, it may have anticonvulsive properties by itself.

b) It may act through the hypothalamic-pituitary-adrenal axis to stimulate glucocorticoid synthesis. Glucocorticoids are thought to interact with central nervous system steroid receptors that act as transcriptional regulators [26] to influence voltage-dependent calcium channels [27].

C) A downregulation of the genetic expression of corticotropin-releasing hormone (CRH), an endogenous neuropeptide, was demonstrated in the amygdala of rats treated with high-dose ACTH. This steroid-independent effect, supposed to be exerted through the direct interaction of ACTH with melanocortin receptors (MCR) in limbic structures [25], may be of importance given the proconvulsant activity of CRH in the develop-
oping brain [28, 29]. An IS animal model based on this pathophysiological hypothesis has been developed.

d) It may stimulate neurosteroid synthesis in gli al cells and neurons, such as deoxycorticosterne (DOC), a precursor of dihydrodeoxy-corticoster-
one (DHDOC), and tetrahydrodeoxy-corticoster-
one (THDOC), both allosteric modulators of GABA_A receptors [30].

2. Steroids beyond infantile spasms

The use of steroids in epilepsy beyond infantile spasms has been less clearly defined; little is known about their efficacy, their mechanism of action and their safety in such cases [31]. Unlike for IS, steroids are typically used in conjunction with other antiepileptic drugs, depending on the specific syndrome, and often in the case of acute exacerbations complicating these syndromes, including episodes of nonconvulsive status epilepticus. The following examples, without being ex-
haustive, illustrate some of these epilepsies and seizure types, in which steroids were reported to be effective.

a) Epilepsies with intractable seizures other than IS

Snead et al. described their experience in 64 chil-
dren with intractable seizures other than IS: 74% of those treated with ACTH became seizure free, versus none of those treated with prednisone [11]. You et al. reported their experience with prednisolone in the treatment of 41 patients with cryptogenic epileptic encephalopathies other than those with IS: 32 had Lennox-Gastaut syndrome, 4 had Doose syndrome, 1 had Ohtahara syndrome, 2 had Landau-Kleffner syndrome, and 2 had other unspecified generalized 
epilepsies. After prednisolone treatment, 59% of pa-
tients became seizure free and 15% showed reduc-
tions in seizure frequency of >50% [32]. Velherst et al. reported their experience with steroids in treating 32 children with intractable epilepsy not including West syndrome: 47% had a decrease in seizure frequency, 25% became seizure free and 22% had re-
duction in seizure frequency [33]. Sinclair reported treating 28 children older than 1 year with intrac-
table epilepsy with prednisone: of the nine children with myoclonic epilepsy, five became seizure free, two showed reduction in seizures and the other two showed no response, while all of the seven children with absence epilepsy improved, and five became seizure free [34].

b) Doose syndrome

Doose syndrome, otherwise known as epilepsy with myoclonic-astatic seizures, is a difficult to treat general-
ed epilepsy of early childhood. Corticosteroids
have been reported as partially effective in control-
ling seizures in Doose syndrome [35], the major 
drawbacks of steroid use being seizure recurrence 
after discontinuation and significant side effects 
from long-term use.

c) Dravet syndrome

O’Regan and Brown observed no improvement in their single child with Dravet syndrome treated with ACTH [36]. Oguni et al. reported only a transient im-
provement in the myoclonic and absence seizures in five of their 84 patients treated with ACTH [37].

d) Epileptic syndromes with continuous spike waves during sleep

Epileptic syndromes with continuous spike waves in slow-wave sleep (CSWS), including electrical status epilepticus in sleep (ESES) and Landau-Kleffner syn-
drome, are true epileptic encephalopathies where sustained epileptic activity is related to cognitive and behavioral decline. Treatment extends beyond 
the control of the seizures; improvement of the con-
tinuous epileptiform discharges must occur to im-
prove neuropsychological outcome. It is recognized 
that the response to conventional antiepileptic 
drugs (AEDs) is often incomplete and transitory. Cor-\nticosteroids are an effective treatment for patients 
with Landau-Kleffner syndrome and CSWS [38-41]. 
Most reported patients exhibit improvement in lan-
guage, cognition, and behavior after treatment. Side 
effects are few and reversible, and benefits appear 
long lasting [40, 41]. The most recent recommenda-
tions in these syndromes include pulsatile intrave-

dalous dexamethasone [20], and high-dose long-term 
treatment with oral hydrocortisone [41].

e) Absence epilepsy

Intravenous methylprednisolone pulse therapy was recently reported to be successfully used in a young girl with refractory absence epilepsy [42].

f) Rasmussen’s encephalitis

Rasmussen’s encephalitis (RE) is a severe and pro-
gressive brain atrophy of unknown origin that leads 
to intractable focal epilepsy and deterioration of
motor and cognitive function. Hart et al. described a temporary improvement in seizure control in 10 of 17 patients with RE receiving corticosteroids [43], and Bahi-Buisson et al. reported the positive effect of high doses of steroids during the first year after the onset of RE, although long term relapse may occur among the good responders requiring delayed hemispheric surgical disconnection [44].

### g) Prolonged seizures

High dose corticosteroid treatment of epilepsy partialis continua in relation with anti-GAD antibodies, and a case of successful treatment using steroids in a 17 year old with status epilepticus have been reported [45, 46].

### h) Acute symptomatic seizures

Finally, corticosteroids, and specifically dexamethasone and methylprednisolone, are frequently used in the management of patients with acute symptomatic seizures complicating bacterial or viral meningitis/meningoencephalitis, demyelination (acute disseminated encephalomyelitis and multiple sclerosis), cerebral vasculitis, and brain tumors. In these situations the use of corticosteroids is largely targeted at the underlying disease process (specifically to shorten time to recovery and reduce the risk of secondary sequelae), rather than at the seizures themselves.

### 3. Neuroactive steroids and neurosteroid replacement epilepsy therapy

Endogenous steroid hormones, mainly synthesized in the adrenal glands, the gonads and the feto-placental unit, can easily cross the blood-brain barrier, due to their high lipid solubility, and act as neuroactive steroids. Estrogens exacerbate seizures, whereas progesterone is protective. The physiological premenstrual decrease of progesterone and its metabolites may cause catamenial seizures as well as psychic changes in the premenstrual period [47]. In vivo, progesterone may be converted into highly neuroactive compounds, in particular allopregnanolone. Allopregnanolone is a very potent positive-allosteric modulator and direct activator of the GABA<sub>A</sub> receptor complex. Like other GABA<sub>A</sub> receptor modulators, allopregnanolone is a powerful anticonvulsant. All of the enzymes required for neurosteroid synthesis are expressed in the brain. Cholesterol can be converted to allopregnanolone in human hippocampus, temporal lobe and other human brain regions [48]. Inhibitory neurosteroids, molecules generated in glia from circulating steroid hormones and de novo from cholesterol, keep seizures under control in epileptic animals because they can enhance inhibitory transmission mediated by GABA receptors [49], thus providing evidence that the availability of neurosteroids critically influences seizure propensity and supporting the concept that neurosteroid replacement may be useful in the treatment of seizures associated with neurosteroid fluctuations such as catamenial epilepsy [50, 51].

Naturally occurring neuroactive steroids undergo rapid biotransformation upon exogenous administration. Synthetic neurosteroids that exhibit better bioavailability and efficacy and drugs that enhance neurosteroid synthesis have therapeutic potential in epilepsy. Ganaxolone, a 3-beta-methylated synthetic analogue, is as potent as allopregnanolone in modulating GABA<sub>A</sub> receptors but has no hormonal function. In humans, ganaxolone has shown a promising pharmacokinetic profile and was well tolerated in a trial with 96 healthy volunteers [52]. The steroid proved to be well tolerated and effective in the first clinical studies with epilepsy patients, including children with and without IS [53-55].

### 4. Side effects of steroids

Further data are clearly required to assess not only the effectiveness, but also the relative efficacy of this potentially less “toxic” and more specific neuroactive steroid, compared to prednisolone, ACTH, or hydrocortisone and to establish the future role of ganaxolone in clinical practice. Analogs of ACTH that bind melanocortin receptors (MCR) but do not release steroids might eventually provide the best solution for therapy, free of the potentially severe systemic side effects of ACTH and high dose steroids. Indeed, prednisolone and ACTH may cause significant irritability, the development of Cush-}

ing syndrome, electrolyte disturbances (specifically hypokalaemia and hyperglycaemia), glucose intolerance, osteoporosis, infections, hypertension, and a usually reversible dilatation of the ventricular and extra-ventricular cerebrospinal fluid spaces [56]. However, the more serious side effects have been reported predominantly with ACTH, rather than prednisolone, and have included cardiac hypertrophy, gastrointestinal bleeding and severe sepsis resulting in death [57, 58]. Although these side effects are more likely to be associated, and become more marked, with prolonged use (over many weeks), they may still develop within days of administration. Synthetic rather than natural ACTH is also considered to be more frequently associated with more serious side effects [24, 59]. However, synthetic ACTH (tetracosactrin) is considered to be less antigenic than ACTH and is therefore less likely to cause allergic reactions than the natural molecule.
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Address for correspondence:
Dr. Mary Kurian
Neuropédiatrie
Hôpital des Enfants
6 Rue Willy Donzé
CH 1211 Genève 14
Tel. 0041 22 3824572
Fax 0041 22 3825489
mary.kurian@hcuge.ch