Stiripentol

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Summary: Stiripentol (STP) is a new antiepileptic compound made by Biocodex. It recently proved to increase the GABAergic transmission *in vitro* in an experimental model of immature rat. Clinical studies were based on the fact that STP also acts as an inhibitor of CYP3A4, CYP1A2, and CYP2C19 *in vivo* in epileptic patients. Whereas the studies in adult patients were disappointing, the trials conducted in pediatric populations demonstrated a specific efficacy of STP in severe myoclonic epilepsy in infancy, Dravet syndrome, when combined with valproate and clobazam. Based on these results, STP was granted orphan drug status in the European Union for the treatment of Dravet syndrome. The French experience in compassionate use suggests that STP might also be of benefit when combined with carbamazepine in pediatric patients with pharmacoresistant partial epilepsy. The interactions of STP with a large number of drugs need to be carefully taken into account, with doses of the combined antiepileptic drugs adjusted to improve the tolerability of the therapeutic association. **Key Words:** Stiripentol, antiepileptic drugs, childhood epilepsy, severe myoclonic epilepsy, cytochrome P450 interactions.

INTRODUCTION

Stiripentol (STP) is an antiepileptic drug (AED) made by Biocodex (Gentilly, France), structurally unrelated to all currently marketed antiepileptic products, and belonging to the aromatic allylic alcohols. It has been studied and used in France and Canada for more than 10 years, but the clinical development of the drug was delayed due to its inhibitory effect on hepatic cytochrome P450 (CYP). Nevertheless, pediatric studies have yielded positive results such that STP was granted orphan drug status in the European Union for the treatment of severe myoclonic epilepsy in infancy (SMEI, or Dravet syndrome).

PHARMACOLOGY

The anticonvulsant properties of STP were assessed in animal models *in vitro*, and the results suggest that STP possesses an antiepileptic effect by itself. In addition to inhibiting the synaptosomal uptake of GABA,[1] STP was recently shown in patch-clamp studies to enhance central GABAergic transmission in CA3 pyramidal neurons of immature rats.[2] At clinically relevant concentrations, STP increases both the release of GABA and the duration of the activation of $GABA_A$ receptors in a concentration-dependent manner and through a barbiturate-like effect.

Drug interactions and dosing

Most of the actions of STP during adjunctive therapy *in vivo* are probably indirect and mediated by inhibition of cytochrome P450 enzymes, namely CYP3A4, CYP1A2, and CYP2C19.[3] As a result, STP increases the plasma concentrations of a wide variety of AEDs, including phenytoin, carbamazepine (CBZ), phenobarbital, valproate (VPA), and clobazam (CLB)[3–5] and decreases plasma concentrations of their metabolites (including the toxic ones). Such drug interactions may partially explain the antiepileptic effects of STP in humans as well as the surprisingly good tolerability of high plasma concentrations of CBZ and CLB. Nevertheless, the dosage of the AEDs associated with STP must be decreased simultaneously.

When STP is coadministered with CBZ, the ratio of CBZ epoxide to CBZ markedly decreases, but the dosage of CBZ must be decreased simultaneously by approximately 50% to ensure adequate tolerability.[6] When associated with CLB, STP inhibits the hydroxylation of the active metabolite of CLB, desmethylclobazam,[4] through CYP2C19,[7] and CLB should be dosed not more than 0.5

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(mg/kg)/day to minimize side effects. The necessity of decreasing the dose by 50% when associated with STP also applies to all the drugs eliminated through cytochrome P450, such as drugs used for anesthesia, hypertension, diabetes, or asthma. Combining STP with antivitamin K medications is prohibited, a situation exceptionally observed in children.

The advised dose of STP in pediatric epileptic patients is 50 (mg/kg)/day with a maximum of 3500 mg/day, 2 or 3 times a day, preferably during meals.[4,8] STP is available as capsules and as sachets for preparing an oral suspension, both at 250 mg and 500 mg.

Efficacy

Studies in adults have been interrupted since 1995 due to lack of significant efficacy in a trial of STP associated with CBZ. By contrast, pediatric studies were conclusive.

In a large open-label adjunctive therapy study in more than 200 children aged from 1 month to 20.5 years, combining STP with CBZ or CLB resulted in a decrease of seizure frequency by more than 50% in two epilepsy syndromes: 1) partial epilepsy, in which two thirds of children were responsive and 20% became seizure-free, and 2) SMEI (Dravet syndrome), in which 10 of 20 children were responsive and 3 became seizure-free—although no other AEDs have ever controlled seizures in this syndrome.[8] To confirm these results, three placebo-controlled adjunctive-therapy trials were performed.

In the first two trials, independently conducted in France and Italy in children with Dravet syndrome aged from 3 to 18 years and receiving concomitant therapy with CLB and VPA, STP was similarly found to be superior to placebo despite a relatively small sample size in both trials (41 patients in France and 23 patients in Italy).[4] Of the patients on STP, 15/21 (71%) in the French trial and 8/12 (67%) in the Italian trial were responders (more than 50% reduction in the frequency of [tonic]–clonic seizures), with a respective 9 and 3 patients who became seizure-free; on placebo, only 1/20 (5%) in the French trial and 1/11 (9%) in the Italian trial were responders, and none were seizure-free ($p < 0.000002$ and $p = 0.009$ for the French and Italian trials, respectively).

The relatively small number of patients needed to demonstrate a significant difference between STP and placebo is remarkable in these two studies focused on a nosologically and etiologically homogeneous syndrome; in more heterogeneous populations, such as patients with partial onset epilepsy or patients with Lennox–Gastaut syndrome, 100 patients or more were needed.[9,10] The practice of dedicating trials specifically to a given homogeneous population of patients represents a more rational strategy for the development of new antiepileptic drugs in children than testing such drugs on the whole population of refractory epilepsies. Controlled data can be obtained relatively rapidly on limited samples of patients, thus improving ethical acceptability of antiepileptic drug trials in a pediatric population.[4]

In a third trial, STP was associated with CBZ in children with partial epilepsy using an enrichment and withdrawal design in order to limit the number of patients included.[11] Among the 67 children entered in a 3-month open add-on STP study after a 1-month single-blind placebo baseline, the 32 responders were randomized for 2 months either to continue STP ($n = 17$) or to withdraw to placebo ($n = 15$). If seizures increased by at least 50% after randomization compared to baseline, patients dropped out: this escape criterion was selected as the primary endpoint for this trial for ethical reasons. There were fewer seizures on STP (−75%) than on placebo (−22%) ($p < 0.025$) (secondary endpoint), but the number of patients exiting during the double-blind phase (6 on STP, 8 on placebo) failed to reach statistical significance difference. In addition, the incidence of adverse events prevented the obtaining of similar CBZ plasma concentrations in both groups, as had been planned in the protocol. This study illustrates the difficulties of performing double-blind placebo-controlled adjunctive-therapy trials with STP and of separating the effects of STP from those resulting from changes in the plasma concentration of concomitantly given AEDs.

Data on long-term STP administration are available from the extension studies of the previous trials and the compassionate use experience in France. Altogether, a total of approximately 1000 patients have been exposed to STP.

In the open study,[8] 50% of patients continued to receive STP long term, and efficacy was sustained in 74% of those patients for a mean of 30 months of follow-up. In the French SMEI trial, 90% of the patients previously included received STP for a mean of 25 months of follow-up, and 57% of them were responders. Among the nine patients who were seizure-free in the double-blind STP group, five remained seizure-free, three developed rare febrile seizures, and one relapsed.

In the compassionate use trial, 155 children received STP as adjunctive therapy for either SMEI (45 cases), partial epilepsy (81 cases), or other epilepsies (29 cases), with up to a 13-year follow-up; STP withdrawal rates were 22, 38, and 34%, respectively (Biocodex data). Although efficacy data are limited, compassionate use does show that 25% of patients have at least a 65% reduction in the number of monthly seizures. Improvements in epilepsy are consistently reported to be the best in the SMEI group, compared with the other two subgroups.

In a retrospective long-term study of 46 patients with SMEI receiving STP combined with VPA and CLB for a median of 3 years of follow-up, the frequency and the

duration of seizures was significantly reduced ($p < 0.001$), as well as the number of episodes of convulsive status. Efficacy was better in the youngest patients, especially under the age of 2 years, whereas the tolerability of STP was poor when initiated over the age of 12 years [12].

Tolerability

In the trials just described, adverse events (AEs) were reported in about half of the patients but could be minimized by optimizing the dose of comedication. The most frequently reported AEs included drowsiness, slowing of mental function, ataxia, diplopia, loss of appetite resulting in weight loss, nausea, and abdominal pain. Asymptomatic neutropenia was also occasionally observed. In the French controlled trial on SMEI, AEs were reported in the 21 patients on STP (100%) *versus* 5 (25%) on placebo.[4] AEs were considered severe in 5 patients on STP (drowsiness in 3, loss of weight in 2) and in 1 on placebo (drowsiness). Some AEs led to a decrease of the comedication dose (in 17 patients) as planned by the protocol, and then these effects later disappeared. Only a single patient, who was on placebo, was withdrawn from the study for adverse effects. In the controlled trial for partial epilepsy with STP–CBZ combination,[11] 12 patients (71%) experienced at least one adverse event on STP, compared with 4 (27%) on placebo during the double-blind period; 9 patients (53%) experienced at least one neurological AE (drowsiness, intellectual slowness, ataxia, diplopia) *versus* 3 (20%) on placebo; 6 (35%) had a digestive AE (nausea, abdominal pain) on STP, but none did on placebo.

The protracted experience in compassionate use in France now provides 400 patient-years of tolerability data. It confirms loss of appetite as the first side effect reported, provided that interactions with STP are carefully taken into account, with doses of the combined AEDs adjusted accordingly.

STP proved to be useful when combined with VPA and CLB in Dravet syndrome, a rare but highly deleterious and pharmacoresistant form of childhood epilepsy. Preliminary data also showed promising results with zonisamide[13] and topiramate,[14–16] but those are open studies. The usefulness of STP in Dravet patients first led to widespread compassionate use in France and other countries, and also to the granting of European Union orphan status. By contrast, the efficacy of STP in other epilepsy syndromes has yet to be demonstrated, although its compassionate use suggests that it might be of benefit when combined with CBZ in pediatric patients with pharmacoresistant partial epilepsy.

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