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Review

Stiripentol. A novel antiepileptic drug

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Abstract:
Epilepsy is one of the most widespread pathologies of human brain, affecting approximately 1% of world population. Despite the development of new methods of seizure control, chronic administration of antiepileptic drugs (AEDs) remains the treatment of choice. Nevertheless, pharmacotherapy is not always effective. In the case of single drug treatment, the number of non-responding patients is as high as 30%. Moreover, chronic medication with currently available AEDs may result in severe side-effects and undesired drug interactions. That is why in recent years intensive research has been carried out aiming at the development of new therapeutic strategies in epilepsy. The goal of this review is to assemble current literature data on stiripentol (STP), a novel anticonvulsant unrelated to any other AEDs. STP potentiates central γ-aminobutyric acid (GABA) transmission and is characterized by nonlinear pharmacokinetics and inhibition of liver microsomal enzymes. STP has proved its anticonvulsant potency in different types of animal seizures, as well as in clinical trials. The drug seems a good candidate for adjunctive therapy in intractable epilepsy.

Key words:
stiripentol, antiepileptic drugs, seizures, refractory epilepsy

Abbreviations: AEDs – antiepileptic drugs, CBZ – carbamazepine, CBZE – carbamazepine-10,11-epoxide, CLB – clobazam, CYP 450 – cytochrome P450, DZP – diazepam, GABA – γ-aminobutyric acid, ip – intraperitoneal, iv – intravenous, MRT – mean residence time, NCLB – norclobazam, PB – phenobarbital, PHT – phenytoin, po – per os, PRM – primidone, PTZ – pentetrazole, SMEI – severe myoclonic epilepsy in infancy, STP – stiripentol, V_d – volume of distribution, VPA – valproic acid, valproate

Introduction

Epilepsy is considered one of the most common neurological disorders, affecting approximately 1% of world population [51, 52]. It constitutes a heterogeneous group of central nervous system pathologies characterized by periodic and unpredictable occurrence of seizures [34]. Even though the etiology and pathogenesis of epilepsy is complex, the pathology is believed to be a consequence of an imbalance between inhibitory and excitatory mechanisms within the brain [10].

Epilepsy requires long-term treatment, usually for the patient's entire life. Despite innovative methods of seizure control, such as neurosurgery or vagal stimulation, chronic administration of antiepileptic drugs (AEDs) remains the most common approach [50, 64]. The goal of therapy with AEDs is to make epileptic patients seizure-free with possibly no concomitant adverse effects [43]. Unfortunately, as many as one third of all treated patients do not respond to monotherapy

with first-line AEDs [17, 26]. Also polytherapy with 2 or more drugs does not guarantee the desired effects [11, 16]. Furthermore, chronic medication with currently available AEDs may result in a wide range of toxic and idiosyncratic reactions, teratogenesis, not to mention undesired pharmacokinetic interactions with other drugs [5, 8, 42].

That is why in recent years intensive effort has been undertaken aiming at the development of both new antiepileptic compounds as well as new formulations of the established ones [3, 36, 39, 60]. Despite the introduction of several new AEDs, the number of individuals failing to respond to the antiepileptic treatment has not markedly dropped since the introduction of sodium valproate in 1978 [4, 35]. As a result, there is still an urgent need for newer, better, both more efficacious and less toxic AEDs.

The aim of this review is to summarize current literature data on stiripentol (STP) – an AED which may turn out beneficial in the treatment of at least some forms of epilepsy.

Chemistry and mechanisms of action

STP is a novel anticonvulsant that is structurally unrelated to any other currently available AED. The compound has been under investigation since 1970s, when it was derived from a series of ethylene alcohols [2]. Chemically STP is a 4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol. The structural formula of the drug is depicted in Figure 1. The characteristic feature of the drug is the presence of chiral center at C-3. As a result, STP is a racemic mixture of two enantiomers: R(+)-STP and S(–)-STP [7]. There are marked differences in pharmacokinetics and antiepileptic potency between the two enantiomers.

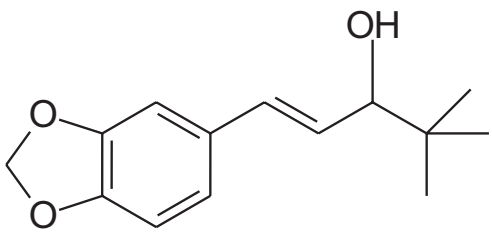

Fig. 1. The chemical structure of stiripentol

STP is easily soluble in acetone and alcohol, moderately soluble in chloroform and insoluble in water. STP is stable in the frozen state [4].

Although its precise mechanisms of action remain unknown, it has been demonstrated that STP may increase γ-aminobutyric acid (GABA) levels in brain tissue [47, 63]. Interestingly, in the study by Poisson et al. [47], STP showed no affinity for either $GABA_A$ or $GABA_B$ receptors. This would suggest that STP-induced increase in GABA concentration involves at least two independent neurochemical mechanisms: inhibition of synaptosomal uptake of GABA and inhibition of GABA transaminase [47, 63].

Animal studies

Numerous animal experiments have revealed STP's broad spectrum of anticonvulsant action in different models of experimental seizures. The antiepileptic activity of STP was first demonstrated in the early 1970s. The drug turned out to protect rats from seizures in the pentetrazole (PTZ) and supramaximal electroshock models [2].

In the acute experiments with PTZ-induced seizures in rats, a significant elevation of seizure threshold was observed after a single intraperitoneal (*ip*) STP dose of 300 mg/kg, which corresponded with plasma concentrations of above 35 mg/l. Maximal anticonvulsive response was reached with doses at or above 450 mg/kg or plasma levels at or above 120 mg/l, along with the appearance of neurotoxicity [55].

Chronic STP administration, however, led to the development of tolerance. To be more precise, subacute STP treatment with oral (*po*) doses resulted in about 40% loss of the drug's anticonvulsant potency. As tolerance to STP-induced neurotoxicity developed to the same extent, no changes in protective index were noted. It is suggested that the observed tolerance was of "functional", rather than "metabolic" type.

In the PTZ model in mice, the ED_{50} for STP was 200 mg/kg *ip*. At the same dose STP protected about 40% of animals against bicuculline- and 20% against strychnine-induced seizures [47].

In the study by Gąsior et al. [13], STP offered a dose-dependent protection against cocaine-induced clonic seizures in mice. The ED_{50} after *ip* administration was 68.3 mg/kg. STP was also effective in supra-

maximal electroshock-induced convulsions in mice with ED_{50} equal to 240 mg/kg *ip* [47].

Last but not least, protective properties of STP were confirmed in alumina-gel Rhesus monkeys. In the acute experiment, where convulsions were precipitated by 4-deoxypyridoxine, the activity of STP (150 mg/kg *ip*) was compared with standard AEDs. STP turned out to delay the onset of seizures similarly to valproate (VPA), but did not eliminate them, as did phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB) and diazepam (DZP) at their standard doses. Chronic administration of STP significantly reduced electroencephalographic interictal activity at mean plasma concentrations of 20–27 mg/l or 11–14 mg/l in another experiment [24, 25].

Clinical studies

Antiepileptic potency of STP has also been proven in different types of seizures in humans. The drug is currently undergoing phase III clinical trials. In Europe it has received an orphan drug status for the treatment of severe myoclonic epilepsy in infancy (SMEI) [57].

The pilot study of STP was carried out in the late 1980s and involved only 7 patients with complex partial seizures [48]. Co-administration of STP resulted in reduction of seizure frequency. In another study, as much as 66% of partial epilepsy patients demonstrated at least 50% improvement [31]. Equally impressive results were confirmed in trials assessing STP's efficacy in the management of refractory partial epilepsy, especially when the drug was given in combination with CBZ [9, 30]. For instance, 16 of 26 patients benefited from STP (1800–3000 mg/day) bitherapy in a long-term study [4]. STP was well-tolerated and no tolerance to the drug developed.

Nevertheless, results obtained by Martinez-Lange et al. [37] were not that much optimistic. Of 42 patients with refractory partial seizures participating in their trial, only 17 reached the final stage of the study. In the majority of cases, STP failed to be as efficacious as PB, PHT or CBZ, used in standard therapy. Only 12 individuals showed marked (50–75%) reduction in seizure frequency during a minimum of 3 months of follow-up. Interestingly, several subjects experienced exacerbation of seizures or even generalized convulsions.

Several trials focused on the use of STP in absence seizures [12, 29, 32]. In an open trial, STP was added to the standard antiepileptic therapy with PB, PHT, CBZ and VPA in 10 children (6–16 years of age) with atypical absence seizures. During a 20-week observation period all patients experienced a significant decrease in seizure frequency (mean reduction by 70%).

STP was also tested in a large group of 212 children in single-blind, placebo-controlled or open-label trials [44]. In the placebo-controlled study, 49% of patients responded to the drug, of whom 10% were seizure-free. STP was most efficacious in partial seizures. In the open study, STP was effective in 68% of the patients. Once again, partial epilepsy patients proved to have the highest response rate. Authors stressed that STP was particularly potent in combination with CBZ.

Perhaps the most desired property of STP is its potency in controlling SMEI – one of the most deleterious epilepsy syndromes among childhood epilepsies [6, 44, 48]. In a randomized placebo-controlled syndrome-dedicated trial in SMEI, 71% of children presented the reduction of seizure frequency after STP was added to VPA and clobazam (CLB) [6]. Nine of 41 children were seizure-free. No other AED has ever presented comparable efficacy in SMEI [14, 33, 62]. Even though these results necessitate further research on larger populations, STP has already received an orphan drug status for the treatment of SMEI in Europe [57].

Pharmacokinetics

STP presents a unique pharmacokinetic profile both in animals and humans. Its multiphase elimination curve was first discovered in rats after intravenous (*iv*) administration. In the first phase, ^{3}H-STP plasma concentrations dropped rapidly, with much slower decrease during the second phase [45]. Such atypical kinetic behavior had been described earlier for aminoglycosides [53, 54].

The same multiphasic pattern of STP disappearance from plasma was observed in monkeys following *iv* administration at three different dose levels [23]. The authors concluded that the prolonged, shallow phase of the curves did not represent elimination, but rather slow distribution process. It is worth noting that values of plasma clearance (Cl) obtained after 40,

80 and 120 mg of STP varied and amounted to 1.1, 0.92 and 0.86 l/h/kg, respectively. This decrease in Cl with dose proved to be statistically significant and provided evidence of nonlinearity, i.e. dose-dependence in elimination of the drug. However, there was no dose-dependence of the volume of distribution (V_d) or mean residence time (MRT). The average values were as follows: V_d = 1.03 l/kg and MRT = 1.09 h. The large V_d may indicate that STP is distributed extravascularly with a high degree of tissue binding [23].

It is emphasized that STP rapidly enters the brain, where it accumulates in the cerebellum and medulla [45]. In the Rhesus monkey, STP is eliminated mostly by metabolism and the fraction of the dose appearing unchanged in urine is very low. The main pathway of elimination is glucuronidation. Due to its insolubility in water and possible hepatic first-pass, STP's bioavailability is relatively low, with the 0.21 fraction of the dose absorbed after *po* and 0.25 or 0.28 fraction absorbed after *ip* administration. STP is highly bound to plasma proteins [23].

Pharmacologic profile of STP in humans seems very similar to that observed in primates and has been thoroughly investigated both in healthy and epileptic subjects [18, 20, 21, 41]. STP is well absorbed after oral administration, but is slowly distributed with a characteristic pattern of a multiphasic elimination curve [18, 61]. The decrease in its plasma concentration is much slower, especially 8 h after the administration. The average Cl and MRT values after single STP oral doses of 300, 600 and 1200 mg amount to: Cl = 1.83; 1.85; 1.36 l/h/kg and MRT = 4.02; 4.07; 4.30 h, respectively. There are no statistically significant differences between these parameters. However, STP does demonstrate nonlinear pharmacokinetics of the Michaelis-Menten type in humans. The phenomenon was confirmed in healthy volunteers after multiple STP dosage from 600 to 1800 mg daily, in whom the Cl ratio decreased from 1000 l/day at the lowest dose to 400 l/day at the highest one [20]. The fact that the per cent of STP dose excreted unchanged in urine increases significantly during chronic administration from day 1 to day 8 is another evidence for dose-dependence in STP pharmacokinetics [18]. In the study by Levy et al. [21], STP kinetics during oral therapy was assessed in 6 epileptic patients who were receiving concomitant antiepileptic treatment. STP concentrations achieved after 600, 1200 and 2400 mg/day doses once again increased in a nonlinear fashion. The Michaelis-Menten parameters were determined. The average velocity of conversion of STP to its metabolites (Vm) was 49.3 mg/day/kg, Michaelis constant (Km) was 1.35 mg/l and the Vm/Km ratio was 50.2 l/day/kg.

STP is very highly bound to human plasma proteins (approximately 99%) [18]. After a single oral dose of 1200 mg, 18% of the dose can be recovered from feces and 73% from urine over 12 h [41]. There are 5 different metabolic pathways of STP: conjugation with glucuronic acid, oxidative cleavage of the methylenedioxy ring system, O-methylation of catechol metabolites, hydroxylation of the t-butyl group and conversion of the allylic alcohol side-chain to the isomeric 3-pentanone structure. Overall, 13 metabolites have been identified so far. It is suggested that the most important pathway of STP transformation is the opening of the methylenedioxy ring to generate catechol derivates. The process is probably responsible for STP inhibitory effects on the oxidative metabolism and drug interactions [41].

Interactions

STP is associated with several drug interactions, which make it difficult to use it in clinical studies.

The metabolism of STP is significantly accelerated by enzyme-inducing AEDs. As reported by Levy et al. [21], CBZ, PHT or PB co-medication increases the Cl of a daily STP dose of 1200 mg by a factor of 3.

On the other hand, STP strongly inhibits the metabolism of other commonly prescribed AEDs, resulting in considerable increase in their serum concentrations.

The inhibition of PHT metabolism by STP is dose-dependent. PHT Cl is reduced by approximately 78% by 2400 mg/day of STP and by 38% by 1200 mg/day. There is, however, large interindividual variability in this respect [21, 28, 38].

Consequently, several studies indicated the necessity to reduce CBZ dose during concomitant use of STP [21, 32]. According to Kerr et al. [15], STP inhibits CBZ Cl by 50% and reduces CBZ transformation to its metabolite carbamazepine-10,11-epoxide (CBZE). Simultaneously, it has no significant effect on CBZE metabolism itself. It is worth stressing that the inhibitory effect of STP on CBZ metabolism rises gradually over 7–10 days of STP co-administration. The authors conclude that in clinical practice CBZ

dosage should be reduced stepwise after introduction of STP. CBZ doses of 4.3–8.7 mg/kg/day seem adequate to maintain CBZ therapeutic levels of 5–10 mg/l in humans.

Similarly, there is strong experimental and clinical evidence that STP decreases the metabolism of VPA, PB and primidone (PRM) [4, 19, 21, 28, 46]. There are also data suggesting that STP may inhibit the transformation of PRM to PB, resulting in the elevation of PRM concentrations [4]. Nevertheless, some authors indicate relative lack of interactions between STP and VPA [12, 22].

STP does significantly increase plasma concentrations of CLB in children with epilepsy [49]. Consequently, STP inhibits the hydroxylation of active metabolite of CLB norclobazam (NCLB) into hydroxy-NCLB [6]. This metabolic interaction could potentiate the antiepileptic activity of CLB and NCLB.

Most of the pharmacokinetic interactions listed above are of clinical importance and require dose adjustment during STP polytherapy. Monitoring of plasma concentrations of concomitant AEDs is recommended. Loiseau et al. [31] conclude that the doses of PHT, CBZ and PB should be reduced by 49%, 38% and 26%, respectively.

The inhibitory properties of STP on the metabolism of other drugs have been attributed to methylenedioxyphenyl ring system, a structural feature of the drug, known to inhibit cytochrome P450 (CYP 450) [15, 40, 41]. According to the study by Tran et al. [59], STP inhibits CYPs 1A2, 2C9, 2C19, 2D6, 3A4 *in vitro* and CYPs 1A2, 3A4 *in vivo*. Interestingly, the inhibition of CYP 3A4 is linearly related to STP plasma concentrations in patients with seizures.

Stereoselectivity

STP is usually supplied as racemic mixture and most available experimental and clinical data concern the racemic form of STP. There are, however, marked differences in the anticonvulsant potency and plasma Cl characteristics between the two STP enantiomers. As reported by Shen et al. [56], in the PTZ-seizure model in rats, the (+)-STP was eliminated much more rapidly than its antipode (Cl = 1.64 l/h/kg for (+)-STP *vs.* Cl = 0.557 l/h/kg for (–)-STP). No significant discrepancies in V_d values were observed. Furthermore, in the acute experiment, the (+)-STP showed 2.38 times higher anticonvulsant potency than the (–) enentiomer. The potency of the racemate was between the potency of (+)-STP and (–)-STP, suggesting additive action of the enantiomers. Nevertheless, an obvious metabolic interaction between the two enantiomers became apparent after racemic STP administration. The total STP plasma concentration was not in-between the levels obtained after administration of either enantiomer, as expected, but was markedly higher.

In the subacute study, a shift towards a higher accumulation of (–)-STP relative to (+)-STP was observed [1]. The reason was most probably the difference in plasma half-lives of the two enantiomers and the continual metabolic conversion of (+)-STP to (–)-STP during repetitive drug administration, as reported earlier [58, 65]. The authors conclude that the phenomenon may explain the development of tolerance to the anticonvulsant action of STP in the case of chronic administration of the drug.

Toxicity

The toxicity of STP is considerably lower than that of some usual AEDs, both in animals and humans.

Animal data point to a relatively good tolerance of STP. In the acute experiment, the LD_{50} values obtained after STP oral administration were above 5000 mg/kg for mice and above 3000 mg/kg for rats [47]. In another experiment, behavioral toxicity assessed in the inverted-screen test in mice appeared after *ip* dose of 364 mg/kg in half of the animals [13]. Also long-term toxicity studies in dogs proved good STP tolerance [27]. No evidence of teratogenicity or carcinogenicity has been available [27].

Currently available human data also suggest that the drug is generally well-tolerated. Even though the overall incidence of side-effects after STP administration is reported high, most of them result from the potentiation of adverse-effects of concomitant AEDs and can be avoided by reducing their dose [44, 57]. Discontinuation of STP therapy because of adverse-effects is uncommon. Predominant problems connected with STP therapy concern neurobehavioral and gastrointestinal disorders. The most common complaints include: drowsiness, tremor, ataxia, nausea, anorexia, weight loss or occasional vomiting. Transient aplastic anemia and leukopenia have also been reported [6, 44].

Final conclusions

STP is a novel potential AED with a structure unrelated to any currently available or experimental AEDs. It has proven its broad spectrum of antiepileptic activity in numerous models of animal seizures, as well as in clinical trials. STP's efficacy in partial and atypical absence seizures has been confirmed. Moreover, no other AED has ever shown to possess antiepileptic potency comparable to STP in SMEI. Last but not least, STP has good safety profile with relatively high therapeutic index. It is generally well tolerated, even in epileptic children. The aforementioned findings make STP a promising AED. Despite several stumbling blocks including nonlinearity or inhibition of microsomal enzymes, it seems a serious candidate for adjunctive therapy in refractory epilepsy. Needless to say, further research is necessary to determine STP efficacy in larger populations of epileptic patients.

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