RESEARCH PAPER | Medical Science | Volume : 4 | Issue : 10 | October 2014 | ISSN - 2249-555X

Tofisopam: Does this old molecule hold a new promise?

KEYWORDS

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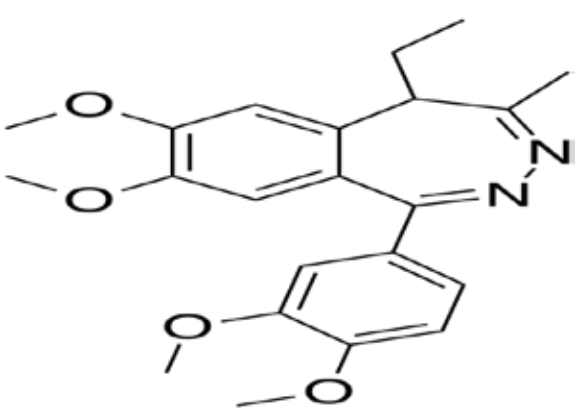
Introduction:

Despite of development of newer pharmaco-therapeutic options, in recent decade the focus of treatment in psychiatry is going back to older drug molecules. Older pharmacological agents like – opipramol, tofisopam, which were not in lime light for quite long time were gained focus now a days and it's time to watch whether these molecules establish themselves as efficacious pharmaco-therapeutic agents. Similarly antipsychotic clozapine was withdrawn due to serious side effects like – agranulocytosis but relaunched again and reached height for its efficacy in treatment refractory schizophrenia.

Tofisopam is a novel addition to class of anxiolytic in India though it was first introduce over three decades ago. Most of the studies related to Tofisopam were conducted in 1980s.

Chemically tofisopam considerably differ from other benzodiazepine derivatives because of different position of nitrogen molecule i.e. 2, 3 vicinal [1, 2]. This difference in spatial organization of nitrogen atoms could be the reason for considerably unique influencing the pharmacokinetic and pharmacodynamics of Tofisopam. It produces anxiolysis, without producing sedation [3]. It also does not possess the anticonvulsant and muscle relaxant property unlike other benzodiazepines [2].In addition to anxiolytic properties of Tofisopam antipsychotic effects are also reported. Its chemical structure is as follows:



Chemical formula of Tofisopam is 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine.

Pharmacodynamics:

The exact mechanism of anxiolytic action of Tofisopam is not known but its pharmacological action differs from 1, 4 benzodiazepine's actionwhich act through GABA receptors [4]. However Tofisopam enhances the binding of benzodiazepines to their binding sites. Apart from its anxiolytic property, Tofisopam produces sedation but only on higher dose. It lacksmuscle relaxant, anticonvulsive and hypnotic properties unlike classical benzodiazepines. Tofisopam has not been shown to cause psychomotor impairment and cognitive dysfunction; rather it has mild cognitive stimulatory effect.Rundfeldt et al (2010)in their study on Swiss albino mice that Tofisopam act by inhibiting an isoenzyme-phosphodiesterases (PDEs) with highest affinity to PDE-4A1 (0.42 μM) followed by PDE-10A1 (0.92 μM), PDE-3 (1.98 μM) and PDE-2A3 (2.11 μM) [4]. It has shown effectiveness in negative symptoms of psychosis. Tofisopam, facilitates the binding of 1, 4- benzodiazepineslike Flunitrazepam, Diazepam etc; to the GABA receptors [5, 6]. Only on higher doses Tofisopam produces sedation [7]. A higher dose of Tofisopam also potentiates the effect of barbiturates, alcohol and amphetamine[7]. Tolerance is not reported with the drug even after repeated use [7].

Pharmacokinetics: After oral administration tofisopam reach peak plasma level in approx. two hours [8]After absorption of Tofisopam, major metabolites of R-Tofisopam catalyze by CYP2C9 and metabolite of S-Tofisopam by CYP3A4. Tofisopam primarily eliminated from body by process of glucoronidation [9].

Tofisopam has property of inhibiting CYP3A4 , enzyme, one of the essential liver enzyme involve in metabolism of various drugs [10]. Because ofTofisopam property of inhibition of this potential enzyme it may cause serious drug interaction with the drugs metabolized by this enzyme [11, 12]. But clinical relevance related to these interactions still not clear.

Evidences from clinical studies:

Goldberg &Finnerty (1979), in their double blind, pacebo-control trial compared the efficacy of Tofisopam and found that it has prominent anxiolytic effect in patients with anxiety and depression [13]. In another study, Kanto et al (1982), tried Tofisopam and placebo as premedication immediately before surgery and did not found any difference between the two, however when Tofisopam and placebo were used in repeated doses (thrice daily) prior to surgery, Tofisopam group had shown significant reduction in arousal symptoms in comparison to placebo [14]. Tofisopam also lacks the side effect of cognitive disturbance unlike other benzodiazepines, rather it causes improvement of cognition [15].

Efficacy in animal trial:

In animal studies, it was found that Tofisopam, acts through central autonomic area of hypothalamus and re-

Volume : 4 | Issue : 10 | October 2014 | ISSN - 2249-555X

duces the stress induced autonomic changes [22].Tofisopam effectiveness has been shown in negative symptoms of psychosis in animal model study [20].Long duration immobility is consideredbeing equivalent to avolition (negative symptoms of psychosis). This study induce negative symptom of psychosis(immobility) in Swiss mice using drug dizocilpine which is a NMDA-receptor antagonist and has shown that Tofisopam lead to improvement of negative symptoms. Tofisopam increases the sensitivity of central dopaminergic receptors; hence have an enhancing effect on the dopaminergic drugs [2]. This property of Tofisopam is abolished by pretreatment with Lithium [2].Arushunian& Popov (2006), in a study on rats found that when Tofisopam was combined with melatonin, a pineal hormone, the stress induced changes in circardian rhythm were effectively prevented [16].

Therapeutic uses:

Tofisopam is as much as effective as classical benzodiazepines in the management of anxiety spectrum disorders. Various studies have been done in regard to anxiolytic effects of Tofisopam. One such study conducted by Molcan et al in 1981 on patients with anxious depressive syndrome of non-psychotic origin with dose range of 100-300 mg/day. Using Beck's scales this study concluded that Tofisopam has anxiolytic effect[17].

In another study done by fillip et al has shown that improvement in anxiety with tofisopam when compared to placebo [18]. Tofisopam also found to be effective in reducing anxiety in pre-operative patients when administered before night, however it is incapable of inducing sedation [15].

Banki CM (1983), in a study mentioned that Tofisopam is having equal potency with less sedating effect like benzodiazepines in patients of alcohol withdrawal syndrome [19]. Sasagawa I (1989), in a study found that Tofisopam was effective in treating lower urinary tract symptoms [20]. Tofisopam was having some efficacy in vertigo, dizziness, tinnitus, functional gastrointestinal disorders [23]. It also has immune-modulating activity and phosphodiasterase inhibiting activity [4, 21].

Dosage and precautions [21, 22]	
Recommended dose	50 – 300mg/day in three divided doses
Recommended duration of clinical use	12 weeks
Dependence potential	Minimal in comparison to Benzodiazepines
Contraindications	Known hypersensitivity reaction Pregnancy Psychosis Aggressive behavior Severe depression
Safety in pediatric population	Not studied adequately
Safety in hepatic impairment	Needs dose reduction; to be used with caution
Safety in renal impairment	Needs dose reduction; to be used with caution
Adverse effects	• Hypersensitivity reaction – Rashes, Itching • Gastrointestinal – Nausea, Dyspepsia, Epigastric pain • Psychological – Hyperactivity, Aggressive behavior, Sleep disturbances

Conclusion

Tofisopam is a safe option in management of anxiety with less sedation. It is well tolerated and the side effects are mostly benign. It can be a good alternative for long term use for control of the anxiety symptoms due to its good safety profile [4].Its' time to test the efficacy of the drug in different psychiatric disorders, due its diversity in mechanisms of action.

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