Abecarnil Shows Reduced Tolerance Development and Dependence Potential in Comparison to Diazepam: Animal Studies

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1 Introduction

Development of tolerance and dependence limits the therapeutic use of traditional benzodiazepine-(BZ) receptor agonists, such as diazepam (Owen and Tyrer 1983; Woods et al. 1987; Haefely et al. 1990). Recent reports have indicated that partial (low efficacy) BZ-receptor agonists, i.e., compounds which induce smaller fractional responses in their target cells than do full agonists at the same fractional receptor occupancy, may have advantages in this respect, because low-efficacy agonism prevents overstimulation of a receptor population, thereby reducing overdose problems, desensitization responses, and adaptation (Haigh and Feely 1988; Haefely et al. 1990). Indeed, repeated treatment of mice with the partial BZ-receptor agonist, bretazenil (Ro 16-6028), produced no significant tolerance to the anticonvulsant effect, in contrast to the effect of full agonists (Haigh and Feely 1988). Furthermore, again unlike full agonists, physical dependence could not be induced in squirrel monkeys after repeated very high doses of bretazenil as assessed by challenge with the BZ-receptor antagonist, flumazenil (Haefely et al. 1990). Although these data on bretazenil indicate that partial BZ-receptor agonism might have important practical consequences, there are also studies on other partial BZ-receptor agonists reporting less favorable data. Thus, during chronic treatment of dogs with clonazepam, which has a lower intrinsic efficacy than diazepam (Haefely et al. 1990), there was only a slight reduction in anticonvulsant potency during chronic treatment, but severe withdrawal symptoms, including seizures, were seen upon abrupt termination of treatment (Scherkl et al. 1985; Scherkl and Frey 1986). Similarly, during chronic treatment of dogs with clorazepate, a prodrug of desmethyldiazepam, which acts as a partial agonist at BZ receptors (Frey and Löscher 1982; Gobbi et al. 1987), no tolerance developed to the anticonvulsant effect, but again severe withdrawal symptoms were observed.
upon discontinuation of treatment (Scherkl et al. 1989). This clearly demonstrates that during treatment with BZs that act as partial BZ-receptor agonists, physical dependence may occur without obvious tolerance. This apparent separation of BZ tolerance and dependence has also been demonstrated in rodents (Wilson et al. 1989).

More recently, the preclinical pharmacological properties of abecarnil, an anxiolytic and anticonvulsant β-carboline with high affinity for central BZ receptors, have been described (Stephens et al. 1990; Turski et al. 1990). Like bretazenil, abecarnil is effective in lower doses than diazepam in tests predictive of anxiolytic and antiepileptic activity, but is clearly less potent than diazepam in tests of sedation and muscle relaxation and even antagonizes the motor-impairing effects of traditional BZs, a pharmacological profile characteristic of partial BZ-receptor agonism (Stephens et al. 1990; Turski et al. 1990). However, there are certain features of the pharmacology of abecarnil which are less consistent with a partial agonist classification but suggest a preference of abecarnil for subtypes of a heterogeneous BZ-receptor population (Turski et al. 1990; Stephens et al. 1990, 1991).

Irrespective of whether abecarnil is a selective or a partial agonist at central BZ receptors, chronic experiments in rodents have indicated that abecarnil might have advantages over BZs with respect to development of tolerance. In mice, repeated treatment with abecarnil (15 mg/kg i.p., twice daily for 12 days) led to a slight reduction in its potency to increase the threshold for induction of clonic seizures by pentylenetetrazol (PTZ; Schneider et al. 1990). However, abecarnil remained to exert significant anticonvulsant effects throughout the period of treatment (Schneider et al. 1990), and the reduction in its anticonvulsant potency in the PTZ seizure-threshold model was much less marked compared to full BZ-receptor agonists, such as diazepam, in the same model (Haigh and Feely 1988). Similarly, using amygdala-kindled rats as a model of complex partial seizures, abecarnil showed reduced tolerance development in comparison to standard benzodiazepines, such as clobazam (Löscher and Rundfeldt 1990; Löscher et al. 1991).

In order to obtain more information on tolerance development during longterm treatment with abecarnil, we used dogs as a model. This species offers the advantage that in addition to tolerance the dependence potential of BZ-receptor ligands can be studied in more detail than in rodents. Indeed, as shown previously by different groups, withdrawal symptoms precipitated in dogs by abrupt termination of chronic BZ treatment or by administration of BZ-receptor antagonists are similar to those observed in humans (McNicholas et al. 1983; Scherkl et al. 1985; Scherkl and Frey 1986; Löscher et al. 1989; Scherkl et al. 1989). The data which were obtained with abecarnil and diazepam in dogs (Löscher et al. 1989, 1990; Löscher and Hönack 1992) will be described and discussed in the present paper.