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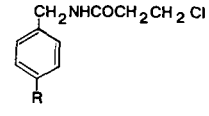
Comparison of the inhibitory action of aminobeclamide and beclamide on socially offensive behaviour

N. A. DARMANI*, R. D. E. SEWELL, M. Y. HASAN, P. J. NICHOLLS, *Pharmacology Division, The Welsh School of Pharmacy, UWCC, PO Box 13, Cardiff CF1 3XF, UK, *Department of Pharmacology, MCV, Box 613, Richmond, VA 23298, USA*

Abstract—The inhibitory effects of aminobeclamide (*N*-(*p*-aminobenzyl)-β-chloropropionamide) on socially offensive behaviour has been studied and compared with those of the parent drug beclamide (*N*-benzyl-β-chloropropionamide). Following oral administration in mice which had been individually housed for a 28 day period then paired with normal group-housed opponents, aminobeclamide and beclamide both produced significant and dose-related inhibition of socially offensive behaviour. Aminobeclamide (20–150 mg kg^{-1} p.o.) and beclamide (50–250 mg kg^{-1} p.o.) gave increased offense onset latency whilst at the same time they reduced the incidence of offense encounters/animal and decreased the group percentage of animals displaying offense behaviour. It is likely that both drugs have similar monoamine modifying effects though this animal study suggests that aminobeclamide is 1·5 to 2·7 times more potent than beclamide against socially offensive behaviour.

Along with the advent of new and more powerful anticonvulsant drugs, the clinical use of beclamide (Nydrane) as an antiepileptic agent has declined. However, in conditions where epilepsy is part of the diagnoses such as those occurring in mentally retarded patients, those with behavioural disorders and temporal lobe epilepsy, its use has continued (Delay et al 1958; Melin 1970; Sime & Easby 1974; Pavulans et al 1975; Puech et al 1962). In these reports, aggressive behaviour was part of the clinical diagnosis which was significantly reduced by beclamide. Moreover, the drug was found to be of benefit in stabilizing mood, reducing anxiety, ameliorating destructive antisocial conduct and improving impulsive and demanding behaviour in mentally handicapped patients with epilepsy.



R=H Beclamide
R=NH_2 Aminobeclamide

I. Structure of beclamide and aminobeclamide.

Recently, we reported the inhibitory properties of beclamide on isolation-induced offensive behaviour in mice, and hypothesized its mechanism of action partially through release of 5-hydroxytryptamine (5-HT) from presynaptic storage sites (Darmani et al 1988a) and via inhibition of GABA metabolism (Darmani et al 1988b). Beclamide was found to be eight times more potent in reducing offense encounters (IC50) in mice than reducing convulsive score in the maximal electroshock and leptazol seizure tests (Sehmbhi 1981). Moreover, the beclamide analogue aminobeclamide (*N*-(*p*-aminobenzyl)-β-chlorpropionamide, I) has been shown to be more potent than beclamide against chemical and electrically induced seizures 2 h after administration (Sehmbhi 1981). The purpose of this report therefore, was to assess any inhibitory activity versus offensive behaviour for aminobeclamide compared with beclamide, in the hope that an improved anticonvulsant activity would correlate with higher inhibitory propensity for aminobeclamide against socially offensive behaviour.

Correspondence to: R. D. E. Sewell, Pharmacology Division, The Welsh School of Pharmacy, UWCC, PO Box 13, Cardiff CF1 3XF, UK.

Materials and methods

Male albino mice of the ICI strain, bred in the animal facility of the Welsh School of Pharmacy, were used. After weaning (at 19–21 days) mice were grouped in tens in opaque wire-topped polypropylene cages, measuring 45 × 30 × 12 cm, with free access to food and water, under a 12/12 h light/dark cycle.

Isolation induced socially offensive behaviour. The isolation paradigm was similar to that described previously (Darmani et al 1988a). Briefly, after 7 days of grouped-housing, half the animals were housed individually in wire-topped polypropylene cages (30 × 12 × 11 cm) for a further 28 days. These test animals were then randomly assigned to a treatment group (n = 10) receiving either an oral (p.o.) vehicle (0·75% carboxymethylcellulose), beclamide (20, 50, 100, 250 mg kg^{-1}) or aminobeclamide (20, 50, 100, 150 mg kg^{-1}) suspended in vehicle. The remaining group-housed mice were designated "standard opponents" which were not inherently offensive and these animals were rendered anosmic by nasal perfusion with 4% $ZnSO_4$ solution under anaesthesia 72 and 24 h before testing. The tests were carried out under subdued red light during the dark phase (21.00–24.00 h). Isolated animals were pretreated with drug or vehicle 45 min before experimentation and each test involved the introduction of a "standard opponent" into the home cage of an isolated individual. Home cages were not cleaned for at least 24 h before the test to partially standardize olfactory conditions within the test arena.

The behavioural interactions between animal pairs were observed for 10 min and the following behaviours noted: normal social investigation and self-grooming, tail-rattling and direct offensive behaviour, characterized by biting or kicking often accompanied by vocalization (see Benton et al 1984). This behaviour was evaluated using the following individual measures described in detail by Benton (1981): latency(s) to onset of initial offensive encounter, percentage of animals displaying offensive behaviour and the total incidence of offensive encounters per animal. There was a negligible incidence of initiated attacks by standard partners and this was a consequence of the induced anosmia (Benton et al 1984). In the rare cases where there were episodes of agonistic encounters provoked by standards they were excluded from the assessment. Statistical comparisons between treated and untreated groups were made using Kruskal-Wallis one way analysis of variance.

Drugs. Beclamide (*N*-benzyl-β-chloropropionamide) was obtained from Rona, UK and aminobeclamide (*N*-(*p*-aminobenzyl)-β-chloro-propionamide) was synthesized in the Welsh School of Pharmacy. In both cases the compounds were suspended in 0·75% sodium carboxymethylcellulose for oral administration.

Table 1. Comparison of the dose-related inhibitory effects of beclamide and aminobeclamide against socially offensive behaviour as evaluated using the delay in offensive onset latency in mice. Values represented are medians (interquartile ranges).

	Beclamide dose (mg kg^{-1})				Aminobeclamide dose (mg kg^{-1})			
	Vehicle	50	100	250	Vehicle	50	100	150
Latency to onset of offensive behaviour (s)	60 (30–120)	180 (150–240)	210 (180–300)	570 (540–600)	60 (30–120)	420 (210–540)	480 (270–570)	600 (510–600)
Significance (P)		<0.05	<0.025	<0.005		<0.025	<0.01	<0.005

Results

Orally administered aminobeclamide did not produce any overt change in self grooming or socially investigative behaviour, although it increased the latency to onset of offense behaviour in a dose-dependent manner similar to that of the parent drug, beclamide (Table 1). Thus aminobeclamide caused a 3-fold increase in latency to onset at 20 mg kg^{-1} and a 4-fold increase at 50 mg kg^{-1} compared to vehicle controls. At 150 mg kg^{-1} aminobeclamide produced an equivalent increase in offense onset latency to beclamide at 250 mg kg^{-1} and in both cases the level of latency enhancement was highly significantly different from the corresponding vehicle-treated controls (Table 1).

The number of offensive encounters per animal in 10 min was significantly ($P<0.005$) decreased dose-dependently down to a value of 0·2 per animal (i.e. two encounters in 10 min) at the highest aminobeclamide dose (150 mg kg^{-1}). Beclamide also decreased the number of encounters per animal dose-dependently over the range 50–250 mg kg^{-1} (Fig. 1).

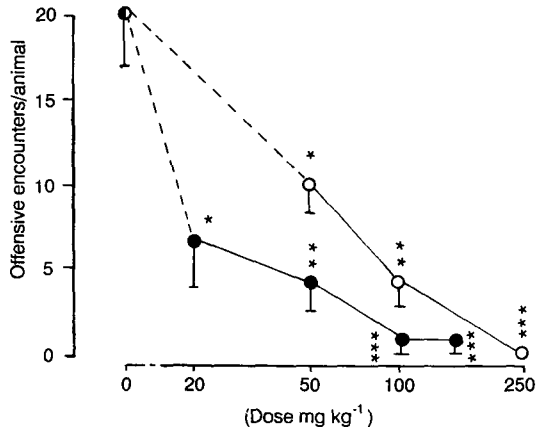


FIG. 1. Dose-response curves for orally administered aminobeclamide (●) and beclamide (○) inhibition of socially offensive behaviour (incidence of offensive encounters per animal in 10 min) induced following 28 day isolation of mice. Control animals (◐) were treated with carboxymethyl cellulose vehicle p.o. $*P<0.05$, $**P<0.01$, $***P<0.001$.

Similarly, the percentage of animals in the group displaying offensive behaviour was decreased in graded fashion over the above dose ranges of aminobeclamide and beclamide. The highest doses of the two compounds totally inhibited 80 and 90% of the animals, respectively, from displaying offensive behaviour (Fig. 2).

Discussion

While using beclamide as an epileptic agent, one of the first groups of authors to comment on the ability of the drug to improve behavioural disorders was Hoenig et al (1956). Similarly, Merlis & Martin (1956), and Sharpe et al (1958) had stressed the efficacy of beclamide in increasing co-operation and decreasing irritability in epileptic patients. Furthermore, Delay et al (1958) reported that beclamide treatment was of benefit in stabilizing mood, reducing temper tantrums and improving impulsive, excitable and demanding behaviour. Sime & Easby (1974) in a double blind study involving adults (25–50 years old) found a 65% improvement in aggressive patients who had been very difficult to manage. Another controlled double blind crossover trial (Pavulans et al 1975) showed that beclamide markedly improved disturbed behaviour in 65% of subnormal patients with severely disturbed behaviour even when epilepsy was absent. The best improvements were observed on aggressiveness, restlessness, pathological fear and anxiety.

Aggressive behaviour is sometimes associated with other central disorders such as schizophrenia and temporal lobe epilepsy in mentally subnormal patients and those with hyperkinetic syndromes. In these conditions a variety of drugs such as barbiturates, benzodiazepines, phenothiazines, carbamazepine, diphenylhydantoin, lithium and reserpine have been used (Dostal & Zvolsky 1970; Itil & Wadud 1975; Itil & Mukopadhyay 1978; Itil & Reisberg 1979) though their clinical value can be restricted by side effects. Beclamide usage has provided an approach attended by few side effects and a wide margin of safety (Hawkes 1952). Moreover, beclamide at effective doses lacks sedative effects (common to most anti-aggressive drugs) since it does not depress locomotor activity after continued dosage and actually enhances this behavioural parameter mildly in the acute situation (Darmani et al 1987b); at the same time beclamide has been found to be eight times more effective in reducing offensive encounters than decreasing convulsive score in animal studies (Darmani et al 1988a; Sehmbhi 1981). The daily dosage of beclamide as an antiepileptic agent recommended by the British National Formulary (1987) is between 3 and 4 g for adults. Thus it is reasonable to assume that much lower doses are required to produce its antiaggressive effects.

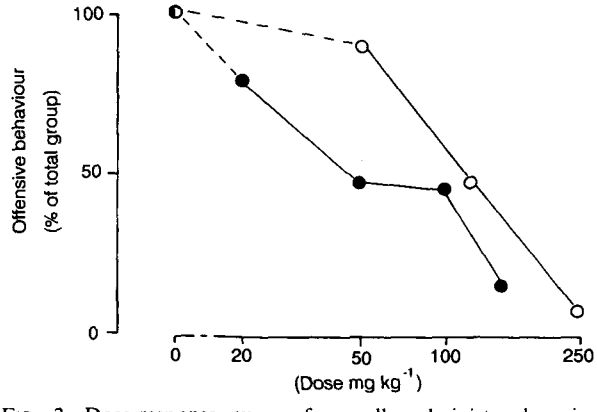


FIG. 2. Dose-response curves for orally administered aminobeclamide (●) and beclamide (○) against the percentage of 28 day isolated animals displaying offensive behaviour over a 10 min test period. Control animals (◐) were treated with carboxymethyl cellulose vehicle p.o.

The present study has investigated further the inhibitory properties of aminobeclamide, which was found on a dose for dose basis to be 1·5 to 2·7 times more potent than beclamide in reducing the number of encounters per animal by 50% (Fig. 2). Whether this improved potency of aminobeclamide compared with beclamide is reflective of enhanced antiaggressive efficacy devoid of sedative side effects is, as yet, not completely resolved since motor activity has not been examined in fine detail. It is highly pertinent, however, that aminobeclamide did not exhibit any observable changes in socially investigative behaviour during the offensive paradigm and this aspect is the subject of further investigation.

Several studies have provided evidence that biogenic amines are involved in aggressive behaviour in animals. In particular, both noradrenaline and 5-HT appear to play an important role in aggression (Garattini et al 1969) whereby a drug-induced reduction in central noradrenergic activity (Ross & Ögren 1976; Lassen 1978) or an increase in 5-HT function (Yen et al 1959) give rise to antiaggressive effects. Another inhibitory neurotransmitter of importance involved in aggressive behaviour is thought to be GABA, lower levels of which have been found in the striatum, hippocampus, amygdala and olfactory tubercle of isolated mice (Earley & Leonard 1977). De Feudis (1979) has shown that GABA's capacity for binding to heavy synaptosomal fractions was lower in brains of isolated mice than those of grouped mice. Furthermore, the GABA receptor agonist (muscimol) as well as inhibiting of GABA transaminase (γ-acetylenic-GABA) reduced the incidence of agonistic encounters in this species (Poshivalov 1986). The mechanism of action of aminobeclamide is highly likely to be similar to beclamide, firstly in that it lacks affinity for dopamine D_2, 5-HT_2, β- and α_2-receptor binding sites (Darmani et al 1987a; Darmani 1988). Secondly, it may be reasonable to assume that it produces its acute anti-offensive effects via presynaptic release of 5-HT from storage sites (Darmani et al 1986, 1988a). The GABA-ergic mechanism may also be involved since beclamide is a mild inhibitor of succinic semialdehyde dehydrogenase, a second enzyme involved in metabolism of GABA (Sawaya et al 1975).

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