Editorial

Chirality Counts?

Howard S. Smith, MD

aclofen is the P-chlorophenyl derivative of gamma-aminobutyric acid (GABA) derivative with an antispasmodic action and is used as a central acting muscle relaxant. GABA is a suppressive neurotransmitter widely distributed in the peripheral and central nervous systems (1). Baclofen [3-(p-Chlorophenyl)-4-aminobutanoic acid], is a GABA B agonist. Baclofen has both presynaptic and post synaptic actions. At the presynaptic site, baclofen decreases calcium conductance with resultant decreased excitatory amino acid release. At the postsynaptic site, baclofen increases potassium conductance, leading to neuronal hyperpolarization. Additionally, baclofen may inhibit the release of substance P.

Since 1975 baclofen has been reported to produce analgesic effects by systemic administration in various experimental pain models (2-5), It has been reported that low concentrations of baclofen depress synaptic transmission, primarily by a presynaptic action, because it occurs without any significant change in the passive membrane properties of the motoneuron (6, 7). Furthermore, this effect of baclofen was blocked by the two GABAB receptor antagonists, CGP 35348 and CGP 55845A (6), but not by phaclofen (7). Advokat and colleagues suggest that, at spinal doses below those that produce muscle relaxation (i.e., <1.2 μ g), baclofen may exert a slight antihyperalgesic/allodynic action (8).

Rats were pretreated 24 min earlier with 1 or 3 mg/kg of s.c. baclofen. Subsequently, microinjection of 0.5 or 3 micrograms of CGP 35348, a GABA antagonist, at sites in the VMM produced at best only a very modest attenuation of the antinociceptive effects of baclofen. These data suggest that systemically-administered baclofen acts at sites in both the spinal cord and the VMM, but that its antinociceptive effects are likely to be mediated to a greater extent by a spinal, rather than medullary site of action (9).

Baclofen hydrocholoride in addition to being used orally as a centrally acting muscle relaxant or to combat spasticity has also been reported to be clinically effective for the management of neuropathic pain such as trigeminal neuralgia (5, 10-15).

Twenty-five patients received 10 to 40 mg of baclofen for cancer pain relief (16). Twenty patients (80%) were thought to have neuropathic pain and complained of such as paroxysmal, lancing, sharp pain, or an electric shock-like pain. Baclofen was effective in 21 of 25 patients and significantly reduced Numeric Rating Scale (pain score, 0-10; P < .0001) (16).

Baclofen is available in the United States (US) as a tablet for oral administration and as a sterile preservativefree liquid for intrathecal administration. Intrathecal baclofen is largely utilized to combat spasticity (17-20),

but anecdotal reports exist for its use to help pain and dystonia (21-24). In the US both the oral and intrathecal formulations are racemates and consist of a 50:50 racemic mixture of R(+)-baclofen (also referred to by some authors as L-baclofen) and S(-)-baclofen (also referred to by some authors as D-baclofen).

Multiple studies have demonstrated that the more active isomer is R(+)- baclofen hydrochloride (25-27) Doses of R(+)-baclofen one fifth its From: Albany Medical College, Albany, NY;

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: None. equivalent racemic dosage produced a much greater enhancement of segmental inhibition in the cat trigeminal nucleus (28). S(-)-Baclofen, when given prior to R(+)-baclofen, blocked the effect of R(+)-baclofen on segmental inhibition and the unconditioned response at previously effective doses. Pretreatment with S(-)baclofen also blocked the effect of subsequent carbamazepine on segmental inhibition, but had no effect on the unconditioned response. Crystallographic evaluation of carbamazepine and the enantiomorphs of baclofen revealed a surprisingly good fit of baclofen isomers to moieties of the carbamazepine molecule. The results suggest that the baclofen enantiomorphs and carbamazepine may have a common mechanism of action in the cat spinal trigeminal nucleus, and that S(-)-baclofen, though relatively inactive, is capable of interfering with the effects of S(-)-baclofen and to a lesser extent with carbamazepine (28).

Terrence and colleagues first proposed that S(-)baclofen may antagonize the actions of R(+)-baclofen in 1983 (28). Following intrathecal administration into the spinal subarachnoid space, baclofen produced dose related increases in tail flick latency (29). R(+)-Baclofen was twice as potent as the RS-racemate and 100 times more potent than S(-)-baclofen. When S(-)baclofen was injected intrathecally 15 min prior to R(+)baclofen, the subsequent effect of R(+)-baclofen was markedly reduced. This reduction was dose-related for S(-)-baclofen in doses at least 20 times the R(+)-baclofen dose (29). These results indicate that R(+)-baclofen may antagonize the antinociceptive effect of R(+)-baclofen following intrathecal administration (29). Thus, antinociception produced by intrathecal administration of baclofen appears to result from activation of a receptor which is stereoselective for the R(+)-isomer and can be blocked by S(-)-baclofen in doses which have initial agonist activity (30).

Fromm and Terrence (31) compared R(+)-baclofen with racemic baclofen (Lioresal) in a double-blind crossover trial in 15 patients with typical trigeminal neural-

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gia. R(+)-Baclofen was more effective than five times as much racemic baclofen in nine patients, six of whom remained pain-free for 4 to 17 months (mean = 10 months). Also, R(+)-baclofen was better tolerated than the racemate (31).

Thus, studies or reports in human subjects using oral R(+)-baclofen (31) and in animal models using intrathecal R(+)-baclofen (28-30) all appear to support the higher potency/efficacy of R(+)-baclofen over the racemate or S(-)-baclofen.

A potential future option currently in clinical development is, arbaclofen placarbil, a novel transported prodrug of the pharmacologically active R(+)-isomer of baclofen designed to be absorbed throughout the intestine by both passive and active mechanisms via the monocarboxylate type 1 transporter (32). Arbaclofen placarbil is rapidly converted to R(+)-baclofen in human and animal tissues in vitro. This conversion seems to be primarily catalyzed in human tissues by human carboxylesterase-2, a major carboxylesterase expressed at high levels in various tissues including human intestinal cells. Arbaclofen placarbil was efficiently absorbed and rapidly converted to R(+)-baclofen after oral dosing in rats, dogs, and monkeys. Arbaclofen placarbil demonstrated enhanced colonic absorption, i.e., 5-fold higher R(+)-baclofen exposure in rats and 12-fold higher in monkeys compared with intracolonic administration of R(+)-baclofen. Sustained release formulations of arbaclofen placarbil demonstrated sustained R(+)-baclofen exposure in dogs with bioavailability up to 68%. In clinical use, arbaclofen placarbil may lead to potentially improved efficacy compared with racemic baclofen by prolonging exposure (e.g. greater duration of action) and decreasing the fluctuations in plasma levels of R(+)baclofen (32).

In view of the above, the author proposes the manufacture and appropriate testing of a sterile preservative-free injectable R(+)-baclofen, hopefully for eventual potential human intrathecal use.

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