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MINIREVIEW

ACTION OF PINAVERIUM BROMIDE, A CALCIUM-ANTAGONIST, ON GASTROINTESTINAL MOTILITY DISORDERS

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Abstract—1. The evidence reviewed here indicates that pinaverium bromide (Dicetel®) relaxes gastrointestinal (GI) structures primarily by inhibiting Ca^{2+} influx through potential-dependent channels of surface membranes of smooth muscle cells.

2. The *in vivo* selectivity of pinaverium bromide for the GI tract appears to be due mainly to its pharmacokinetic properties. Because of its low absorption (typical for quaternary ammonium compounds) and marked hepatobiliary excretion, most of the orally-administered dose of pinaverium bromide remains in the GI tract.

3. Orally-administered pinaverium bromide does not elicit adverse cardiovascular side-effects at doses that effectively relieve GI spasm, pain, transit disturbances and other symptoms related to motility disorders.

4. Pinaverium bromide is the only Ca^{2+}-antagonist with known therapeutic efficacy in the treatment of irritable bowel syndrome and certain other functional intestinal disorders.

INTRODUCTION

The most accepted approach for treating patients afflicted with digestive disorders, such as irritable bowel syndrome (IBS), esophageal spasm or chronic intestinal pseudo-obstruction, involves controlling gastrointestinal (GI) motility. IBS is the most common GI disorder (Flavell, 1985), and regardless of whether it results from a primary bowel dysfunction or from impaired brain–gut interactions, its therapeutic management can be envisaged upon considering that activation of Ca^{2+} channels represents the 'final common path' of all mechanisms that regulate GI motility. Thus, Ca^{2+}-antagonists that act selectively on the GI tract might well be expected to provide effective therapy.

Pinaverium bromide [N-(bromo-2-dimethoxy-4,5-benzyl)-N([(dimethyl-6,6 norpinanyl-2)-2 ethoxy]-2 ethyl)morpholinium bromide; Dicetel®], a quaternary ammonium compound synthesized by Baronnet *et al.* (1974), appears to be such a Ca^{2+}-antagonist that acts selectively on the GI tract. Pinaverium bromide is registered for the treatment of functional intestinal disorders. It effectively relieves GI spasm, pain, transit disturbances and other symptoms related to motility disorders and does not elicit adverse cardiovascular side-effects at therapeutic doses. Studies concerning its mechanism of action and clinically beneficial effects will be briefly reviewed.

RELAXATION OF SMOOTH MUSCLE BY PINAVERIUM BROMIDE

Pinaverium bromide at concentrations of $0.4–4.0 \times 10^{-6}$ *M* competitively antagonized $BaCl_2$-induced contractions of guinea pig isolated ileum and rat isolated duodenum; higher concentrations of the drug had additional non-competitive effects (Bretaudeau *et al.*, 1980).

Using smooth muscle preparations of guinea pig ileum and taenia coli, Droogmans *et al.* (1983) found a striking correlation between the concentrations of pinaverium bromide that inhibited mechanical activity (frequency and amplitude of contraction) and those that inhibited electrical activity (frequency of action potentials). Such effects became evident at 10^{-6} M, and spontaneous activity was abolished at 10^{-5} M in most preparations. Pinaverium bromide also inhibited the effects of electrical field stimulation, $BaCl_2$, acetylcholine or synthetic MET-enkephalin analogue FK33-824 on *in vitro* intraluminal pressure responses of rat colonic segments; IC_{50} values (concentrations that produced 50% inhibition) were 3.4×10^{-6} M for $BaCl_2$ stimulation, 5.2×10^{-6} M for acetylcholine stimulation, and 3.3×10^{-6} M for FK33-824 stimulation (Baumgartner *et al.*, 1985). Pinaverium bromide was about 30 times less potent than verapamil in this latter preparation, but both drugs had similar concentration–response characteristics and their inhibitory effects on pressure responses to field stimulation were antagonized to a similar extent by a 10-fold increase in external Ca^{2+} concentration ($[Ca^{2+}]_o$).

In rabbit ear artery, contractions induced by norepinephrine were much less sensitive to pinaverium bromide than those induced by K^+-depolarization, indicating that pinaverium bromide interferes with Ca^{2+} influx through potential-dependent channels (PDCs) and that it affects receptor-operated channels

(ROCs) to a much lesser extent (Droogmans *et al.*, 1983). Also, in this preparation pinaverium bromide did not prevent refilling of the norepinephrine-sensitive Ca^{2+} store after its depletion by stimulation with norepinephrine in Ca^{2+}-free medium.

Experiments with uterine strips prepared from pregnant rats further support the contention that pinaverium bromide acts as a Ca^{2+}-antagonist. In this preparation, both pinaverium bromide and D 600 (gallopamil) were more potent in inhibiting K^+-induced contractions than electrically-induced twitch contractions (Mironneau *et al.*, 1984). Pinaverium bromide inhibited electrically-induced twitches with $IC_{50} = 6.4 \times 10^{-7}$ M and K^+-induced contractions with $IC_{50} = 3 \times 10^{-7}$ M within 15–20 minutes; D 600 inhibited electrically-induced twitches with $IC_{50} = 3.7 \times 10^{-7}$ M and K^+-induced contractions with $IC_{50} = 1.4 \times 10^{-7}$ M. As such effects were overcome by increasing $[Ca^{2+}]_o$, both pinaverium bromide and D 600 most likely acted by interfering with Ca^{2+} entry into smooth muscle cells.

Collectively, these results provide strong evidence that pinaverium bromide acts mainly by interfering with Ca^{2+} influx through PDCs and that it exerts minimal effects on ROCs.

EFFECTS OF PINAVERIUM BROMIDE ON ION FLUXES

Droogmans *et al.* (1983) showed that neither pinaverium bromide (10^{-5} M) nor D 600 (10^{-6} M) affected $^{45}Ca^{2+}$ uptake by rabbit ear artery under resting conditions, but that the additional uptake of $^{45}Ca^{2+}$ elicited by K^+-depolarization was largely blocked by both agents. These findings correlated with the effects of both agents on the contractile response elicited under the same conditions (see above). These workers showed further that pinaverium bromide (10^{-5} M) inhibited K^+-depolarization-induced stimulation of $^{45}Ca^{2+}$ efflux rate in guinea pig taenia coli, and blocked the stimulatory effect of carbachol on $^{45}Ca^{2+}$ efflux. As such stimulation of $^{45}Ca^{2+}$ efflux rate is caused by an increase in Ca^{2+} entry which can be blocked by D 600, these findings indicate that pinaverium bromide acts like D 600 in inhibiting Ca^{2+} influx. Other experiments on rat uterine smooth muscle have shown that low concentrations of pinaverium bromide ($\leq 10^{-5}$ M) act directly on uterine membranes to inhibit Ca^{2+} inward current in a manner similar to that of D 600 (Mironneau *et al.*, 1984). With regard to intracellular processes involved in mediating contraction, pinaverium bromide ($< 10^{-5}$ M) did not inhibit calmodulin-dependent phosphodiesterase or Ca^{2+} transport ATP-ase (Wuytack *et al.*, 1985).

Taken together, these findings support the contention that pinaverium bromide acts primarily by blocking PDCs of smooth muscle membranes: direct effects on intracellular Ca^{2+} systems appear to be of lesser importance for its spasmolytic properties. Its action is similar to that of other calcium antagonists but presents some originality (see below).

COMPARISON OF THE ACTIONS OF PINAVERIUM BROMIDE AND CONVENTIONAL CALCIUM-ANTAGONISTS ON SINGLE INTESTINAL SMOOTH MUSCLE CELLS

Tissue-selectivity of Ca^{2+}-antagonists involves many factors, among which state-dependence is of particular importance. 'Resting', 'open' and 'inactivated' states of Ca^{2+} channels can each have different affinities for a given Ca^{2+}-antagonist (e.g. Triggle *et al.*, 1989). Ca^{2+} channel blockade may also show use-dependence. For example, with higher stimulation rates, or increased use of the channels, verapamil produces greater inhibition of the channels; i.e. the affinity of verapamil is increased when the channels are in the open state (see e.g. Janis and Triggle, 1983). In contrast, dihydropyridine Ca^{2+}-antagonists (DHPs) like nitrendipine show much less use-dependence than verapamil (Bayer *et al.*, 1975; Lee and Tsien, 1983).

Recent patch-clamp experiments conducted with single smooth muscle cells of the longitudinal muscle layer of rabbit jejunum have shown that the Ca^{2+} inward current is antagonized by pinaverium bromide. Pinaverium bromide inhibited Ca^{2+} inward current with $IC_{50} = 1.5\,\mu$M (Bolton *et al.*, 1989; Beech *et al.*, 1990), as compared with previously reported IC_{50} values of $0.2\,\mu$M for nicardipine, $1.3\,\mu$M for verapamil and $1.4\,\mu$M for diltiazem and flunarizine (Terada *et al.*, 1987a, b, c). Increasing concentrations of pinaverium bromide (to $10\,\mu$M) appreciably inhibited Ca^{2+} inward current, but with repetitive stimulation (increased use of the channels) no further increase occurred in this antagonism, indicating that pinaverium bromide, in contrast to verapamil, does not show use-dependence (Bolton *et al.*, 1989; Beech *et al.*, 1990).

In these experiments, the availability of the inward (Ca^{2+}) current in solution containing 1.5 mM Ca^{2+} was tested by measuring the absolute sizes of peak currents evoked by a test potential of +20 mV after holding for 2 sec (or 10 sec, in some cases) at various conditioning potentials. The potential at which the current was half-available, Vh, was −39 mV. Pinaverium bromide ($1\,\mu$M) reduced the peak current evoked at +20 mV from all potentials with little change in Vh (−40 mV). Similar results were obtained when the Ca^{2+} of the bathing solution was replaced by 110 mM Ba^{2+}; pinaverium bromide ($1\,\mu$M) produced only a small negative shift in the availability curve; i.e. Vh was changed very little by pinaverium bromide (Beech *et al.*, 1990). Under these conditions conventional Ca^{2+}-antagonists such as nifedipine, nitrendipine, flunarizine, verapamil and diltiazem produce marked negative shifts in the availability curve (Terada *et al.*, 1987a, c). The lack of shift in the availability curve with pinaverium bromide indicates that this drug has similar affinities for the closed available and the inactivated state of the Ca^{2+} channel.

Collectively, these results indicate that DHPs have little use-dependence, that gallopamil, verapamil, diltiazem and flunarizine have use-dependence, and that pinaverium bromide has no use-dependence. Hence, on these intestinal smooth muscle cells, DHPs act on the inactivated state of the "L-type" Ca^{2+} channel,

whereas gallopamil, verapamil, diltiazem and flunarizine block the channel when it is opened by activity, and pinaverium bromide acts on all states of the channel (Bolton *et al.*, 1989; Beech *et al.*, 1990). On this basis, pinaverium bromide appears to represent a new category of Ca^{2+}-antagonist possessing similar affinities for the various Ca^{2+} channel states.

CLINICAL STUDIES: TREATMENT OF GASTROINTESTINAL DISORDERS WITH PINAVERIUM BROMIDE

The spasmolytic effects of pinaverium bromide, first shown in lower mammals, have been confirmed in man, and it has been used clinically in treating functional colonopathies (e.g. IBS) and certain other GI disturbances (see e.g. Paris *et al.*, 1977; Dubarry and Quinton, 1977; Levy *et al.*, 1977; Drouillard *et al.*, 1978; Delmont, 1981; Barbara *et al.*, 1984; Galeone *et al.*, 1986; Di Somma *et al.*, 1986). Double-blind trials have shown that pinaverium bromide is effective at an oral dose of 50 mg (t.i.d.) in treating such disorders (see Table 1). It is significantly more effective than placebo and at least as effective as drugs commonly used in these indications (Dubarry and Quinton, 1977; Levy *et al.*, 1977; Delmont, 1981; Benvestito, 1983; Corazza *et al.*, 1983; Barbara *et al.*, 1984; see Table 1). Other Ca^{2+}-antagonists such as nifedipine, nicardipine, verapamil and diltiazem, can also influence colonic motility in patients with IBS (see e.g. Traube and McCallum, 1984; Prior *et al.*, 1987; Byrne, 1987). However, although studies with these cardiovascular drugs seem to provide some evidence for therapeutic efficacy in IBS patients, it should be noted that only small numbers of patients have been tested to date, and no orderly dose–response relationships could be established due to the occurrence of pronounced cardiovascular effects.

Pinaverium bromide (150 mg single oral dose, or 200 mg, b.i.d. for 3 days) relaxed Oddi's sphincter in patients with biliary dyskinesia (Paris *et al.*, 1977; Lamazza *et al.*, 1986). It also inhibited spasmodic reactions during barium enema 30 minutes after an oral dose of 200 mg (Paris *et al.*, 1977) or after local application (Drouillard *et al.*, 1978), and oral administration (e.g. 50 mg, t.i.d.) decreased the motor index in sigmoid and lower sigmoid colon after a test meal (Cargill *et al.*, 1985) and after neostigmine stimulation (Barbara *et al.*, 1984). Unlike nifedipine and verapamil, which decrease lower esophageal sphincter (LES) pressure in man and which can induce gastroesophageal reflux (Hongo *et al.*, 1984), administration of pinaverium bromide (50 mg, t.i.d. for 3 days, or single doses up to 200 mg) did not influence LES pressure (Heitz and Decourcelle, 1979; Denis and Colin, 1982). This lack of effect of pinaverium bromide on LES pressure can be explained by considering its pharmacokinetic properties and the pharmaceutical preparation in which it is orally administered (see below). Its administration in capsule or tablet form does not appreciably affect GI structures rostral to the stomach since the esophagus is by-passed and since systemic bioavailability is very limited.

Verapamil is known to retard GI transit, thereby producing constipation (e.g. Lewis, 1980; McGoon *et al.*, 1982; Zelis and Flaim, 1982; Schroeder, 1982). Constipation is a rare adverse effect associated with the therapeutic use of nifedipine (Zar and Gooptu, 1983), but disturbances of the upper GI tract occur in about 7% of patients (see Zelis, 1982; Ellrodt and Singh, 1983). Although constipation is the most frequently reported adverse side-effect of pinaverium bromide, its incidence is below 1% when the drug is administered at a dose of 150 mg/day. Using this dose, no reduction in GI transit time has been shown in man (Bertrand *et al.*, 1981; Alivisi *et al.*, 1983; Spivach *et al.*, 1983; Barbara *et al.*, 1984). However, administration of pinaverium bromide in a dose of 50 mg (t.i.d.) for 7 days did reduce transit time significantly in patients with chronic idiopathic constipation (Barbara *et al.*, 1984). Overdose with pinaverium bromide (single oral doses $\geq$600 mg/day) sporadically caused diarrhea in human volunteers; the mechanism underlying this effect has not been clarified.

Table 1. Double-blind studies performed with pinaverium bromide (PB)

Type of study	No. patients	Oral drug dose		Duration of study	Diagnosis	Action of PB	Ref.
		PB	Ref. drug				
DB, R	25, PB 25, plac.	50 mg, t.i.d.	plac.	15 day	FC	Reduced severity of symptoms and global activity	a
DB, SI	30, PB 30, plac.	50 mg t.i.d.	plac.	6 days	20 (eso.) 20 (stom.) 20 (col.)	Reduced severity of symptoms and global activity	b
DB, R	30, PB 30, plac.	50 mg t.i.d.	plac.	1 month	FC	Reduced severity of symptoms and global activity	c
DB, RC	8	50 mg t.i.d.	plac.	2 wks/sequence	Chronic constip.	Reduced symptoms, total transit time and contractile activity of sig. colon	d
DB, RPG	21, PB 20, Ref.	50 mg t.i.d.	NBH, 30 mg t.i.d.	30 day	IBS	As active as Ref. drug	e
DB, PG	13, PB 15, Ref.	50 mg t.i.d.	T, 150 mg t.i.d.	30 days	FC	As active as Ref. drug	f

All differences in placebo-controlled studies were significant ($P < 0.05$–$P < 0.001$); see original publications for further experimental details.

Abbreviations: DB, SI = double-blind, stratified by indication; DB, R = double-blind, randomized; DB, RC = double-blind, randomized crossover; DB, RPG = double-blind, randomized parallel groups; DB, PG = double-blind, parallel groups; NBH = N-butyl hyoscine bromide; T = trimebutine; FC = functional colonopathy; eso. = esophagus; stom. = stomach; col. = colon; IBS = irritable bowel syndrome; plac. = placebo.

References: a, Levy *et al.* (1977); b, Dubarry and Quinton (1977); c, Delmont (1981); d, Barbara *et al.* (1984); e, Benvestito (1983); f, Corazza *et al.* (1983).

SELECTIVITY OF PINAVERIUM BROMIDE FOR THE GASTROINTESTINAL TRACT: ROLE OF PHARMACOKINETIC FACTORS

In general, the activity of a Ca^{2+}-antagonist on a particular tissue is governed by diverse factors, among which are the physicochemical properties of the compound, the concentration of the compound at the relevant site of action, and the level of activation of the target tissue (e.g. Cauvin *et al.*, 1983; Triggle *et al.*, 1989). Contraction of all types of smooth muscle cells depends upon the availability of free Ca^{2+} (see Fleckenstein-Grün and Fleckenstein, 1980), but pronounced differences exist among various smooth muscle cells (e.g. Brading, 1981). Events that follow Ca^{2+} channel activation of different membranes also vary considerably (e.g. Brading, 1981; Hagiwara and Byerly, 1983; Triggle *et al.*, 1989). A family of Ca^{2+} channels differing in molecular structure might actually exist (see Hagiwara and Byerly, 1983). These considerations provide an explanation for the findings that the Ca^{2+}-antagonists, despite their common mode of action, show pronounced tissue-selectivity. As examples, verapamil, which acts on the myocardium, cardiac pacemakers and the vasculature with comparable potency, is a drug of choice in treating supraventricular arrhythmias, whereas nifedipine, which is more potent as a vasodilator than as an inhibitor of cardiac pacemaker activity, is used mainly in relieving anginal symptoms (see Fleckenstein, 1983). However, since these Ca^{2+}-antagonists were not developed for treating GI disturbances, the doses required to reduce intestinal contractile activity would be expected to produce adverse cardiovascular effects.

Such limitations have been overcome with the introduction of pinaverium bromide into clinical practice. Selectivity of pinaverium bromide for the GI tract seems likely to depend upon its pharmacokinetics after oral administration and this is related to its quaternary ammonium structure. In man, only about 5–10% of the administered dose of pinaverium bromide is absorbed, it is rapidly metabolized (via the liver), and about 95–98% of it becomes protein-bound (Jacquot *et al.*, 1989). Accumulation of the parent drug is therefore unlikely, and elimination is mainly via the stools.

The pharmacokinetic distribution parameters of pinaverium bromide in man and rat differ from those of cardiovascular Ca^{2+}-antagonists mainly due to its low absorption (Jacquot *et al.*, 1989). Due to this poor absorption, its pharmacological selectivity is governed, at least in part, by a tissue-specificity that is related to absorption kinetics.

The pharmacokinetic profile of pinaverium bromide is also useful in explaining why it does not elicit cardiovascular side-effects. In this regard, the amount of pinaverium bromide (i.e. 4 mg) which corresponds approximately to that amount absorbed after oral administration of a 50-mg unit dose, when administered by slow intravenous infusion to patients afflicted with various cardiac disorders, did not affect blood pressure, electrocardiogram or cardiac electrophysiology, even after electrical stimulation of the heart (Guerot *et al.*, 1988). Thus, although pinaverium bromide shares the general molecular mechanism of action of verapamil or D 600, i.e., acts mainly by blocking PDCs of smooth muscle membrane, it exerts effects selectively on GI organs and does not elicit cardiovascular effects under therapeutic conditions.

CONCLUDING COMMENTS

From the foregoing discussion, it appears that pinaverium bromide (Dicetel®) relaxes GI structures primarily by inhibiting Ca^{2+} influx through PDCs of smooth muscle cells. Its *in vivo* selectivity for the GI tract appears to be due mainly to its pharmacokinetic properties. Because of its low absorption and its marked hepatobiliary excretion, most of the orally-administered dose of pinaverium bromide remains in the GI tract. A major advantage of using pinaverium bromide is that it does not elicit cardiovascular side-effects at doses that effectively relieve GI spasm, pain, transit disturbances and other symptoms related to motility disorders.

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