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Pinaverium Bromide: A Calcium Channel Blocker Acting Selectively on the Gastrointestinal Tract

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Evidence is reviewed which indicates that pinaverium bromide (PB) relaxes gastrointestinal (GI) structures mainly by specifically inhibiting Ca^{2+} influx through potential-dependent channels that exist on the surface membranes 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, typical for quaternary ammonium compounds, and its efficient hepato-biliary excretion, most of the orally-administered dose of PB remains in the GI tract. Other mechanisms possibly related to its selectivity, and comparisons between the actions of PB and those of other Ca^{2+}-antagonists, are also discussed. PB is the only Ca^{2+}-antagonist currently registered for treatment of functional intestinal disorders (e.g., irritable bowel syndrome). A major advantage of orally-administered PB is that it does not elicit adverse systemic (e.g., cardiovascular) side-effects at doses that effectively relieve GI spasm, pain, and abnormal motility.

Key words: calcium-antagonists, colonic disorders, irritable bowel syndrome, smooth muscle, gastrointestinal motility, pinaverium bromide

INTRODUCTION AND BASIC RATIONALE

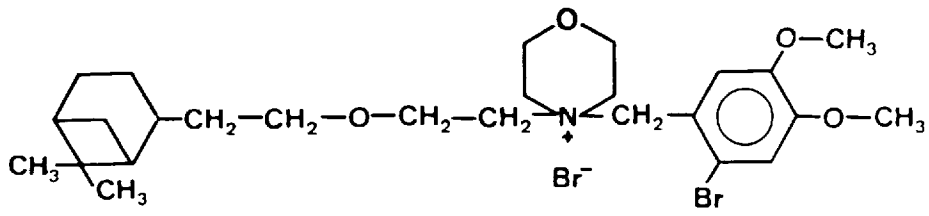
Smooth Muscle of the Gastrointestinal Tract

The human gastrointestinal (GI) tract may be viewed as a hollow tube having a grossly similar basic structure throughout its 5–7 meters of length. The inner mucosa is surrounded by a sub-mucosal compartment which in turn is surrounded by two perpendicular layers of smooth muscle cells, the inner circular layer being responsible for concentric contractions and segmentation (of the GI tract), the outer longitudinal layer being responsible mainly for the progression of intestinal contents. Together, these two muscular layers induce peristalsis, thereby ensuring intestinal transit.

The GI tract is divided into segments by sphincters and is analogous to other smooth muscle tubes such as bile ducts, glandular ducts, ureters, and particularly the blood vessels. However, smooth muscle of GI tissues differs both structurally and electrophysiologically from that of large arteries and, of course, from heart muscle. Smooth muscle of the GI tract is generally arranged in sheets or bundles, the cell membranes being in contact with each other at multiple points (gap-junctions) through which ions can flow freely. Thus, a functional syncytium exists and contracts synchronously in large areas. In contrast, many of the larger blood vessels possess smooth muscle tissue that is composed of discrete smooth muscle fibers, each fiber operating independently from the others and often being innervated by a single nerve ending. It is this difference between the smooth muscle of the GI tract and blood vessels that permits flexibility in designing pharmacological agents that will selectively modify GI function.

Gastrointestinal Motility Disorders

Motility disorders of the GI tract might be considered to involve primarily disturbances of smooth muscle function, but of course, are not related exclusively to smooth muscle dysfunction. Autonomic dysfunction is also an important cause of GI motility disorders that must be considered in efforts to provide therapy (see below). In any case, chronic alterations in GI motor activity, whether localized or diffuse, may interfere with normal propulsive function in the absence of anatomical impediment [see Malagelada, 1984]. Such abnormalities can involve the esophagus (e.g., achalasia and spasm), the stomach (nausea, vomiting, and stasis), small intestine (chronic intestinal pseudo-obstruction), or the large intestine (constipation and dilatation of the colon).



4-(2-Bromo-4,5 dimethoxybenzyl)-4- [2-[2-(6,6-diméthyl norpinan-2-yl) ethoxy] ethyl] morpholinium bromide (IUPAC)

Fig. 1. Chemical structure of pinaverium bromide.

The present article will be focussed on "irritable bowel syndrome" (IBS), the most common GI disorder in clinical practice [Flavell, 1985]. IBS is a functional disease characterized by pain, disturbed bowel movements, and bloating that are caused by altered intestinal motility [Lamonte and Isselbacher, 1987]. Patients afflicted with the spastic colon variant of IBS (pain and constipation) have increased resting colonic motility; those displaying mainly diarrhea have decreased resting colonic motility. Colonic motility may also be increased in association with psychological stress. The visceral input to the locus coeruleus (LC) of the brain might be associated with the mental symptoms (tension or anxiety) observed in IBS. Regardless of whether IBS is primarily a bowel disorder or an anxiety disorder, a vicious cycle of stress seems useful in explaining how the original cause (whether central or peripheral) may have similar behavioral consequences for the individual [see Svensson, 1987], and this provides strong rationale for therapeutically attacking IBS at the level of the viscera.

Therapeutic Rationale Based on Ca^{2+}-Antagonism

It is evident from the discussion provided above that a major issue in managing patients with digestive disorders is the control of GI motility. Thus, a great need exists for therapeutic agents that can serve this purpose. Upon considering that Ca^{2+} channel activation represents the "final common path" of all mechanisms that control GI motility, it becomes evident that motility disturbances might be controlled by Ca^{2+}-antagonists (also termed Ca^{2+} channel blockers or Ca^{2+} entry blockers). However, such drugs would inhibit not only GI hypermotility or spasm, but also other Ca^{2+}-dependent events (e.g., contraction of blood vessels), regardless of the nature of the hormonal or neuronal mechanism involved in their generation. Therefore, drugs that exhibit some degree of selectivity for the GI tract are required [see Traube and McCallum, 1984].

Pinaverium bromide (N-(bromo-2-dimethoxy-4,5-benzyl)-N([(dimethyl-6,6 norpinanyl-2)-2 ethoxy]-2 ethyl)morpholinium bromide; abbreviated PB), synthesized by Baronnet et al. [1974], does act selectively on the GI tract. This compound (see Fig. 1) has low toxicity and has been characterized as a spasmolytic agent with potent musculotropic action and very weak neurotropic activity [see e.g., Baronnet et al., 1974]. It has been used orally in the form of capsules and tablets as Dicetel® since 1977 for treating IBS and disturbances of the biliary tract [Levy et al., 1977; Paris et al., 1977; Delmont, 1981; see below]. Its spasmolytic action appears to be mediated by an effect on Ca^{2+} channels, it has no significant in vivo anticholinergic effect, and its antagonism of responses evoked by histamine or serotonin appears non-specific [Bretaudeau et al., 1975; Roux et al., 1980; Lab. Thér. Moderne, unpublished reports, 1977–1988; see below].

In this article, some clinical and in vitro actions of PB will be discussed in an attempt to explain its selective action on the GI tract.

TISSUE SELECTIVITY OF THE ACTIONS OF CALCIUM-ANTAGONISTS

Contractility of all types of smooth muscle cells depends upon the availability (concentration) of free ionized Ca^{2+} within the cells ($[Ca^{2+}]_i$) for activation of myofibrillar ATP-ase which catalyzes the conversion of phosphate bond energy into mechanical work [see Fleckenstein, 1977; Bolton, 1979; Fleckenstein-Grün and Fleckenstein, 1980; Loutzenhiser et al., 1985]. Ca^{2+} can enter smooth muscle cells through at least three different pathways—potential-dependent channels (PDCs), receptor-operated channels (ROCs), and a "leak pathway" [see e.g., Hof, 1984; see below]. In general, the activity of a Ca^{2+}-antagonist on a given tissue will depend upon the physicochemical properties of the drug, the drug's concentration at its site of action, and the mechanism and level of activation existing in the tissue [see Cauvin et al, 1983; Hof, 1984]. Also, as smooth muscle cells are present in a remarkably diverse group of tissues, the mechanisms by which drugs and neurotransmitters initiate contraction are also extremely varied [see Brading, 1981]. These differences provide flexibility for approaches aimed at developing tissue-selective drugs and a basis for using Ca^{2+}-antagonists.

Ca^{2+} channels are macromolecules that selectively allow Ca^{2+} to cross the membrane in response to a depolarization of the membrane. When the channel is open Ca^{2+} can enter the cell via a passive process driven by the Ca^{2+} electrochemical gradient since $[Ca^{2+}]_i$ is usually less than 1/10,000th of the external Ca^{2+} concentration ($[Ca^{2+}]_o$). As the events linked to Ca^{2+} channel activation of different membranes vary considerably, a family of Ca^{2+} channels of different molecular structure might exist [see Hagiwara and Byerly, 1983], providing another element of flexibility for synthesizing tissue-selective drugs.

Ca^{2+}-antagonists are a group of chemically unrelated molecules that specifically block Ca^{2+} entry *during muscle activation* without interfering with Ca^{2+} movements in resting preparations [see Fleckenstein, 1983; Godfraind et al., 1986]. Despite their common mode of action, important differences exist among Ca^{2+}-antagonists, and it is these differences that provide the basis for tissue selectivity. Selectivity for the GI tract might be achieved with Ca^{2+}-antagonists that bind selectively to Ca^{2+} channels typical of the GI tract, or distribute selectively in GI smooth muscle cells, or it might be achieved as a function of the administered dose.

According to Janis and Triggle [1983], selectivity of Ca^{2+}-antagonist action can be considered at *stimulant* and *tissue* levels. At the stimulant level, the specific actions of Ca^{2+}-antagonists would be governed by the type of stimulus selectivity that they exhibit. For example, in smooth muscle, depolarization-induced responses (involving PDCs) are usually very sensitive to these drugs, whereas agonist- (e.g., neurotransmitter-) induced responses (involving ROCs) usually vary markedly in sensitivity but are generally relatively insensitive to Ca^{2+}-antagonists [see Janis and Triggle, 1983; Hof, 1984]. At the tissue level, selectivity can arise from many sources; e.g., pharmacokinetic differences, relative agonist use of PDCs, Ca^{2+} channel differences and/or pathological state of the tissue [Janis and Triggle, 1983; see also above].

Consideration of this multiplicity of factors provides a sound basis for explaining the tissue selectivity of various Ca^{2+}-antagonists. Analysis of the actions of three classic Ca^{2+}-antagonists, verapamil (a phenylalkylamine), nifedipine (a 1,4-dihydropyridine), and diltiazem (a benzothiazepine), can be used as examples. Verapamil prolongs atrio-ventricular (A-V) conduction and is a drug of choice for treating re-entrant supraventricular arrhythmias [Fleckenstein, 1983]. Nifedipine preferentially suppresses vascular contractility and (at least in humans) has only a modest influence on cardiac pacemaker function [Fleckenstein, 1983], and is a potent long-acting vasodilator that is very useful in relieving anginal symptoms caused by coronary vasospasm. Diltiazem is also more potent as a vasodilator than as an inhibitor of

cardiac pacemakers [Fleckenstein, 1983], and is used mainly to treat angiospastic angina [see also Henry, 1980].

Considerable differences in tissue selectivity also exist within given chemical classes of Ca^{2+}-antagonists. For example, among the 1,4-dihydropyridines, nimodipine is more potent in relaxing cerebral blood vessels than peripheral arteries, whereas the reverse holds for nisoldipine [Hoffmeister et al., 1979; Kazda et al., 1980; Louis, 1981; Towart et al., 1982]. Considering the phenylalkylamine series, both verapamil and tiapamil are about equal in Ca^{2+}-antagonistic potency on coronary vascular smooth muscle, whereas verapamil is 5–10 times more potent on smooth muscle of other arterial beds and on cardiac muscle. Therefore, tiapamil exhibits selectivity for coronary arteries [see Eigenmann et al., 1981]. Such differences are reflected in clinical use.

CALCIUM-ANTAGONISTIC PROPERTIES OF PINAVERIUM BROMIDE: COMPARISON WITH OTHER CALCIUM-ANTAGONISTS

Clinical Studies

The spasmolytic effects of PB, first shown in lower mammals, have been confirmed in man [Paris et al., 1977; Drouillard et al., 1978], and PB has been used clinically in treating functional colonopathies [Dubarry and Quinton, 1977; Levy et al., 1977; Delmont, 1981; Barbara et al., 1984; Galeone et al., 1986]. Results of some double-blind studies conducted with PB are provided in Table 1. It is evident that PB is effective at an oral dose of 50 mg (t.i.d.) in a treating IBS. PB is significantly more effective than placebo and at least as effective as certain reference drugs (e.g., trimebutine, N-butyl hyoscine bromide; see Table 1).

PB has also been found useful for controlling certain other GI disturbances. In particular, like verapamil and nifedipine, PB has been used to control dyskinesia of Oddi's sphincter [e.g., Darnis, 1977; Simon and Kovacs, 1983]. In this case, verapamil and nifedipine could exert the same type of action as PB, but further controlled clinical studies are required to substantiate this view. At doses of 150 mg (single oral dose) or 200 mg (b.i.d.) for three days, PB relaxed Oddi's sphincter in patients with biliary dyskinesia [Paris et al., 1977; Di Somma et al., 1986; Lamazza et al., 1986]. This effect appears to be dose-related since a single intraduodenal dose of 75 mg PB produced only slight relaxation of the sphincter, whereas a single dose of 150 mg produced a potent effect beginning 10 min after drug administration and lasting for at least an hour [O. Bordalo, personal communication, 1988].

Other Ca^{2+}-antagonists (nifedipine, diltiazem, nicardipine, verapamil) have also been shown to influence colonic motility in patients suffering from IBS [see e.g., Traube and McCallum, 1984; Narducci et al., 1985; Perez-Mateo et al., 1986; Prior et al., 1987]. Nifedipine has been used only sporadically to treat IBS [Schuster, 1985; Fritsch, 1986], a suggested dose being about 10 mg (t.i.d.). Verapamil (e.g., 120 mg, t.i.d.) has also been used in isolated cases [Byrne, 1987]. However, these studies are limited since small populations of patients were examined, double-blind placebo-controlled conditions were not employed, and dose-response relationships were not established due to the pronounced cardiovascular effects of these drugs.

Both verapamil and nifedipine are known to retard GI transit, leading to constipation. Constipation is also the most frequently reported adverse effect of PB, but at doses of 150 mg/day the incidence is below 1%. Measurements of transit time in man at this dose have not shown any retardation [Bertrand et al., 1981; Alivisi et al., 1983; Spivach et al., 1983; Barbara et al., 1984]. However, PB reduced transit time significantly in patients with chronic idiopathic constipation at a dose of 50 mg (t.i.d.) for 7 days [Barbara et al., 1984]. Overdosage with PB (single oral doses $\geq$ 700 mg) may induce diarrhea in human volunteers, but the mechanism of action of such high doses has not been clarified.

Perhaps the most important properties of PB in relation to therapy for GI disorders is that unlike classic Ca^{2+}-antagonists, it has no clinically observed vasodilatatory effect and no

TABLE 1. Some Double-Blind Studies Conducted with Pinaverium Bromide (PB)*

Reference	Type of study	No. patients	Oral drug dose		Duration of study	Diagnosis	Result; comparison of PB and ref. drug
			PB	Ref. drug			
Dubarry and Quinton (1977)	DB, stratified by indication	30,PB 30, plac	50 mg tid	plac	6 days	20 (eso) 20 (stom) 20 (col)	Reduced severity of symptoms and global activity ($P < 0.01$)
Levy et al. (1977)	DB, randomized	25,PB 25, plac	50 mg tid	plac	15 days	FC	Reduced severity of symptoms and global activity ($P < 0.01$)
Delmont (1981)	DB, randomized	30,PB 30, plac	50 mg tid	plac	1 month	FC, painful constipation	Beneficial effects on course of symptoms; reduced global activity ($P < 0.05 - P < 0.001$)
Barbara et al. (1984)	DB, randomized crossover	8	50 mg tid	plac	2 wks/ sequence	Chronic constipation	Reduced symptoms ($P < 0.01$), total transit time ($P < 0.01$) and contractile activity of sigmoid colon ($P < 0.05$)
Benvestito (1983)	DB, randomized parallel groups	21,PB 20,Ref.	50 mg tid	N-butyl hyoscine bromide 30 mg, tid	30 days	IBS	PB as active as ref. drug but with more rapid onset of action
Corraza et al. (1983)	DB, parallel groups	13,PB 15,Ref.	50 mg tid	Trimebutine, 150 mg tid	30 days	FC	PB as active as ref. drug in reducing symptoms and on global activity

*Abbreviations: DB, double-blind; eso, esophagus; stom, stomach; col, colon; FC, functional colonopathy. For further experimental details, see original publications.

antiarrhythmic action. These observations are best explained by considering the very low plasma concentrations of PB that exist after its oral administration. Only about 5–10% of PB is absorbed. When the amount of PB that is absorbed after oral administration of a 50 mg unit dose (i.e., 4 mg) was administered by slow intravenous infusion to patients with various cardiac disorders, blood pressure, electrocardiogram, and cardiac electrophysiology were not affected, even after electrical stimulation of the heart [Guerot et al., 1988]. Thus, although PB acts mainly like verapamil by blocking PDCs of smooth muscle membrane (see below), it does not exert cardiovascular effects like verapamil (or other Ca^{2+}-antagonists) in therapeutic doses.

It should also be noted that PB has no atropine-like (anticholinergic) effects in man at therapeutic doses. In this regard, symptoms representative of such effects (e.g., dry mouth, blurred vision, dysuria, cardiac palpitations, mydriasis) have been systematically investigated and found to be absent (Lab. Thér. Moderne, Safety Pharmacology Studies, 1978–1988). Also, in contrast to anticholinergic drugs, PB does not elicit gastroesophageal reflux [Denis and Colin, 1982] and it has no untoward effects in patients with glaucoma when compared with placebo [Roux et al., 1980]. Although no well-defined animal model for IBS exists, it has been shown that administration of PB (10 mg/kg, i.d.) to dogs elicited a potent and prolonged spasmolytic action on the intestine and had no anticholinergic action [Grenier et al., 1983; see also Itoh and Takahashi, 1981].

In Vitro Studies With Various Smooth Muscle Preparations

At concentrations of $0.4–4 \times 10^{-6}$ M, PB produced an apparent competitive antagonism of contractions induced by $BaCl_2$ in guinea pig isolated ileum and in rat isolated duodenum [Bretaudeau and Foussard-Blanpin, 1980]. Higher concentrations of PB had an additional non-competitive effect. Inhibition produced by PB persisted in Ca^{2+}-free Tyrode's solution. Such findings indicate that PB exerts a polyvalent action in these GI preparations, with underlying mechanisms that might include its inhibition of Ba^{2+}-induced release of membrane-bound Ca^{2+} (competitive action) and its inhibition of a process that follows Ca^{2+} release from superficial membrane sites (non-competitive component).

Using smooth muscle preparations of guinea pig ileum and taenia coli, Droogmans et al. [1983] found a striking correlation between the concentrations at which PB inhibited the mechanical activity (frequency and amplitude of contractions) and those which inhibited electrical activity (e.g., frequency of action potentials). Such effects became manifest at 10^{-6} M PB and became more pronounced at 10^{-5} M, leading to complete inhibition of spontaneous activity in some preparations. PB also inhibited the effects of electrical field stimulation, $BaCl_2$, acetylcholine or synthetic MET-enkephalin analogue FK33-824 on in vitro intralumnal pressure responses of rat colon [Baumgartner et al., 1985; see Table 2]. Although PB was about 30 times less potent than verapamil in this preparation, both drugs had similar dose-response characteristics and their inhibitory effects on pressure responses to field stimulation were antagonized to a similar extent by a 10-fold increase in $[Ca^{2+}]_o$. Also, contractions induced by K^+-depolarization and by carbachol (10^{-5} M) were inhibited in both guinea pig taenia coli and ileum in a dose-dependent fashion by PB [Droogmans et al., 1983].

In rabbit ear artery, contractions induced by norepinephrine (NE) were much less sensitive to PB than those induced by K^+-depolarization, indicating that PB interferes with Ca^{2+} influx through PDCs and that it affects ROCs to a much lesser extent [Droogmans et al., 1983]. Also, PB did not prevent refilling of the NE-sensitive Ca^{2+} store after it had been depleted by stimulation with the agonist (NE) in Ca^{2+}-free medium.

Further support for an involvement of Ca^{2+} channels in PB's mechanism of action has been derived from studies conducted with rat uterine strips. Using uterine strips from pregnant rats, Mironneau et al. [1984] showed that PB ($10^{-7}–10^{-6}$ M) depressed electrically-induced twitch contractions and K^+-induced contractures within 15–20 min, whereas D 600 ($2 \times$

TABLE 2. Some In Vitro Effects of Pinaverium Bromide (PB); Comparison with Ca^{2+}-Antagonists

Reference	Test preparation	Parameter measured	IC_{50} (μM) PB	Verapamil	D 600	$MnCl_2$
Baumgartner et al. (1985)	Rat colonic segments, intraluminal pressure response	Inhibition of electrical field stimulation	6.8	0.28		
		Inhibiton of $BaCl_2$-induced stimulation	3.4	0.12		
		Inhibition of acetylcholine-induced stimulation	5.2	0.099		
		Inhibition of MET-enkephalin analogue FK33-824-induced stimulation	3.3	0.11		
Mironneau et al. (1984)	Rat uterine strip, isometric contraction	Inhibition of electrically-induced twitch contraction	0.64		0.37	400
		Inhibition of K^+-induced contracture	0.3		0.14	400

10^{-6} M) and $MnCl_2$ (10^{-3} M) abolished both types of contraction. Both PB and D 600 inhibited K^+-induced contractures to a greater extent than electrically-induced contractions (see Table 2). However, regardless of the inhibitor used, blockade of contractions could be overcome by increasing $[Ca^{2+}]_o$, indicating that all three inhibitors acted by competing with Ca^{2+}.

Taken together, the results provided above provide strong evidence that PB, like verapamil and D 600, acts mainly by interfering with Ca^{2+} influx through PDCs, and that it exerts minimal effects on ROCs or on intracellular Ca^{2+} stores.

In Vitro Studies at the Cellular/Molecular Level

Measurement of ion fluxes using radioisotopes is considered to provide direct evidence for the Ca^{2+} channel-blocking actions of various agents. Use of the rabbit ear artery preparation permits quantitative analysis of $^{45}Ca^{2+}$ fluxes. A comparison of the effects of PB (10^{-5} M) and D 600 (10^{-6} M) in this preparation indicated that neither agent affected $^{45}Ca^{2+}$ uptake under resting conditions, but that the additional uptake of $^{45}Ca^{2+}$ elicited by K^+-depolarization was largely blocked by both agents [Droogmans et al., 1983]. These findings correlated with the effects of PB and D 600 on the contractile response elicited under the same experimental conditions (see above). In guinea pig taenia coli, PB (10^{-5} M) largely inhibited the stimulation of $^{45}Ca^{2+}$ efflux rate induced by K^+-depolarization and also largely blocked the stimulatory effect of carbachol on $^{45}Ca^{2+}$ efflux. As both stimulations of the $^{45}Ca^{2+}$ efflux rate are known to be caused by increased Ca^{2+} entry, these findings indicate that PB inhibits K^+-depolarization- or carbachol-induced Ca^{2+} influx in exactly the same way

as D 600 [Droogmans et al., 1983]. Other experiments conducted with uterine smooth muscle showed that PB (10^{-5} M) decreased the amplitude of the net Ca^{2+} inward current over a wide range of depolarizing voltages in a manner similar to that of D 600 [Mironneau et al., 1984]. Most recently, voltage-clamp experiments have shown that PB inhibits Ca^{2+} inward current in single smooth muscle cells of rabbit jejunum [unpublished results of T. B. Bolton, 1988]. In one of these cells, the IC_{50} value for PB was between 10^{-6} and 3×10^{-6} M, and complete block of inward current occurred at 10^{-5}–10^{-4} M.

Certain studies discussed above indicate that therapeutically relevant doses of PB do not significantly affect the release of intracellularly-stored Ca^{2+}. With further regard to intracellular processes involved in mediating contraction, Wuytack et al. [1985] have shown that PB, at concentrations below 10^{-5} M, does not inhibit calmodulin-dependent enzymes such as phosphodiesterase or Ca^{2+} transport ATP-ase of plasma membrane. However, calmodulin-dependent activities of both of these enzymes could be inhibited by PB with $IC_{50} \cong 10^{-4}$ M, indicating very weak inhibition [Wuytack et al., 1985]. Thus, concentrations of PB higher than those which are therapeutically achieved could interact with calmodulin [Ronca-Testoni et al., 1985. Wuytack et al., 1985]. Verapamil also acts only at very high concentrations to inhibit calmodulin-dependent phosphodiesterase [Lugnier et al., 1984].

Taken together, these findings support the contention that PB acts primarily by blocking PDCs of smooth muscle membranes.

SELECTIVITY OF PINAVERIUM BROMIDE FOR THE GASTROINTESTINAL TRACT

As emphasized above, the most important property of orally-administered PB that can be used to explain its selectivity for the GI tract is its *local Ca^{2+}-antagonist action*, rendering it devoid of any effects on the cardiovascular system. The highly polar *quaternary ammonium group* of the PB molecule limits its passage across cell membranes. The pharmacokinetic profile of orally-administered PB is useful in explaining its local action on the GI tract. In man, only about 5–10% of the administered dose enters the circulation, and peak plasma levels are reached within 30–60 min. PB is rapidly and extensively metabolized, the absorbed fraction being handled mainly by the liver and partly by the kidneys. Administered PB is about 95–98% protein-bound and therefore accumulation of the parent drug does not likely occur. PB is eliminated essentially via the stools.

Autoradiographic studies with rats have confirmed that PB is only slightly absorbed. Radioactivity after enteral application remained localized to the GI tract. The liver was labelled, a finding that is related to an hepatic excretion of the small fraction of PB that is absorbed. High concentrations of radioactivity were found in the stomach and in the small and large intestines. Determination of radioactivity in combusted segments of these organs indicated that PB had penetrated the tissues.

The finding that constipation is the most common side-effect of orally-administered verapamil provides evidence that this Ca^{2+}-antagonist exerts potent actions on the GI tract. Verapamil reduces intestinal contractile activity and may enhance gut water and electrolyte transport, whereas nifedipine and diltiazem are relatively devoid of such effects [see e.g., Malagelada, 1984]. The problem with using verapamil to relax the GI tract is that the doses required would likely produce significant adverse cardiovascular effects. However, some encouraging preliminary results have been obtained using verapamil in treating IBS [see Traube and McCallum, 1984].

PB's mechanism of action appears very similar to those of other organic Ca^{2+}-antagonists (especially verapamil and D 600), since it blocks PDCs and affects ROCs and intracellular Ca^{2+} stores to a much lesser extent (see above). Selectivity, rather than potency, seems important with regard to PB's action, since PB is generally less potent than verapamil in inhibiting Ca^{2+} influx (see above).

CONCLUDING REMARKS

From the foregoing discussion, it seems evident that although PB shares a number of properties with other Ca^{2+}-antagonists, it acts selectively on the GI tract. This selectivity can be explained by considering the pharmacological properties of PB and its pharmacokinetic profile. PB is a quaternary ammonium derivative and therefore its passage across cell membranes is limited. PB is also rapidly metabolized. Due to these properties, oral therapeutic doses of PB do not influence cardiovascular mechanisms.

Future studies of PB might include examining: 1) its possible selective affinity for certain types of Ca^{2+} channels of the GI tract; 2) its action in relation to the differential dependence of phasic and tonic contractile components of GI segments on $[Ca^{2+}]_o$ versus $[Ca^{2+}]_i$ [e.g., Hillemeier et al., 1986]; and 3) its action in relation to the different dependence on $[Ca^{2+}]_o$ or $[Ca^{2+}]_i$ that might exist between inner (circular) and outer (longitudinal) smooth muscle layers of various segments of the GI tract [e.g., Grider et al., 1986].

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