

Comparison of the Visceral Antinociceptive Effects of Spinally Administered MPV-2426 (Fadolmidine) and Clonidine in the Rat

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Background: The authors determined the visceral antinociceptive effect induced by MPV-2426 (fadolmidine), a selective α_2 -adrenoceptor agonist, in rats with and without inflammation of the colon. They also determined whether the sympathetic nervous system or intact descending pathways are critical for the α_2 -adrenoceptor-induced visceral antinociception.

Methods: Spinal neuronal responses evoked by colorectal distension were recorded in pentobarbitone-anesthetized rats. MPV-2426 was administered onto the spinal cord. Clonidine was used as a reference α_2 -adrenoceptor agonist. Inflammation of the colon was induced by turpentine. Sympathectomy was induced by 6-hydroxydopamine. A midthoracic transection of the spinal cord was performed to study the role of descending pathways.

Results: Spinal administration of MPV-2426 produced a dose-dependent attenuation of responses evoked by colorectal distension, and this effect was of the same percentual magnitude in inflamed as in noninflamed animals. Clonidine and MPV-2426 induced equipotent visceral antinociception. The effect by spinally administered MPV-2426 was enhanced by a chemical sympathectomy but not influenced by spinal transection.

Conclusions: Spinally administered MPV-2426 produces a dose-dependent visceral antinociception as well in animals with an inflammation of the colon as in controls. The visceral antinociceptive effect induced by spinal MPV-2426 is equipotent to that of spinal clonidine. An intact sympathetic nervous system or intact brainstem–spinal pathway is not critical for the MPV-2426-induced visceral antinociception.

THERE is abundant evidence indicating that α_2 -adrenoceptor agonists suppress somatic pain.^{1,2} In addition, α_2 -adrenoceptor agonists have been shown to attenuate behavioral and neuronal responses induced by noxious visceral stimulation.^{3–6} Inflammation of the somatic structures leads to hyperalgesia and increases efficacy of α_2 -adrenoceptor agonists, and this increased efficacy is at least partly caused by spinal mechanisms.^{7–9} Inflammation of the viscera may also produce hyperalgesia.^{10–13} However, the efficacy of α_2 -adrenoceptor agonists in visceral inflammation has been only little studied.¹⁴

MPV-2426 (fadolmidine), or 3-(1H-Imidazol-4-ylmethyl)-indan-5-ol hydrochloride, is an α_2 -adrenoceptor agonist developed for spinal pain therapy.¹⁵ When administered intrathecally, it has proved a potent antinociceptive agent in various experimental models of somatic pathophysiology

as well as in controls.^{15–18} MPV-2426, like dexmedetomidine, another α_2 -adrenoceptor agonist with an imidazoline-structure, is a full agonist on all α_2 -adrenoceptor subtypes. However, MPV-2426 differs pharmacokinetically from dexmedetomidine and clonidine (a prototype α_2 -adrenoceptor agonist), since it only poorly crosses the blood–brain barrier.^{15,16} Also, when injected intrathecally, its pharmacologic effects are more dermatomally restricted than those of clonidine or dexmedetomidine.^{15,18,19,20}

In the current study we raised a hypothesis that, because of its pharmacokinetic properties, MPV-2426 administered spinally might provide a potent and also segmentally restricted treatment for some visceral pain and hyperalgesia conditions. To test this hypothesis, we assessed the visceral antinociceptive effects induced by spinally administered MPV-2426 in the inflamed and noninflamed rat. An exogenous drug administered spinally could induce α_2 -adrenergic antinociception directly on spinal α_2 -adrenoceptors; indirectly by activating at medullary or pontine levels, descending noradrenergic pathways, synapsing on spinal α_2 -adrenoceptors; or both. To test between these possibilities, we compared the visceral antinociceptive effects induced by spinal administration of MPV-2426 in animals with intact and transected spinal cords. Furthermore, it has been speculated that the antinociception induced by spinal administration of α_2 -adrenoceptor agonists might be, at least partly, caused by action on the sympathetic nervous system.²¹ To address the role of the sympathetic nervous system in visceral antinociception, we determined the effect of MPV-2426 also in chemically sympathectomized animals. Clonidine was used as a reference α_2 -adrenoceptor agonist. Determination of colorectal distension-induced behavioral and spinal neuronal responses has proved a sensitive and reproducible method for assessing the visceral antinociceptive effects induced by various compounds such as an *N*-methyl-D-aspartate receptor antagonist,¹¹ opioid receptor agonists,^{3,4,22–24} lidocaine,^{22,25} and also some α_2 -adrenoceptor agonists.^{3–6} In the current study, visceral antinociceptive and antihyperalgesic effects were assessed by determining colorectal distension-induced neuronal responses of nociceptive spinal dorsal horn neurons in anesthetized rats with and without experimental inflammation of the colon.

Materials and Methods

The study was performed with adult male Hannover-Wistar rats (The Finnish National Laboratory Animal Cen-

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ter, Kuopio, Finland; weight, 220–360 g). The study protocol was accepted by the Institutional Animal Care Committee of the University of Helsinki and by the Regional Government of Southern Finland.

Surgery

For surgery, the rats were anesthetized with pentobarbitone (initial dose of 50 mg/kg administered intraperitoneally, and 10–20 mg · kg⁻¹ · h⁻¹ for maintenance of anesthesia). The level of anesthesia was frequently monitored by observing the size of the pupils, the general muscle tone, and responses to noxious pinching. Supplemental doses of pentobarbitone (20 mg/kg) were administered as required. The rats were spontaneously breathing and the body temperature kept within physiologic range with a homeothermic blanket. A carotid arterial cannula was inserted for recording of blood pressure. A laminectomy was performed at the level of L5–S2, the dura was removed, and a pool of skin formed, which was filled with warm mineral oil. Two spinal clamps, one distal and one rostral to the laminectomy, were used to stabilize the preparation. In some of the experiments, an additional midthoracic laminectomy was performed through which the spinal cord was completely transected under visual control. To avoid the confounding effect induced by the spinal shock, the interval from the transection of the spinal cord to start of the recording of neuronal responses was 3 h.

Colorectal Stimulation and Recording of Neuronal Responses

It is well established that colorectal distension is a noxious visceral stimulus.³ Graded colorectal distension was produced by inflating with air a 7–8-cm flexible latex balloon inserted transanally into the descending colon and rectum. Spinal unit activity was recorded extracellularly with lacquer-coated tungsten microelectrodes (tip impedance 3–10 MΩ at 1 kHz) using standard techniques. The amplified and filtered signal was fed through an amplitude window discriminator to a rate monitor (bin width: 0.2 s) and timed counter. The rate meter recordings and integrated spike activity counts were observed on a storage oscilloscope screen, and hard copies of the data were printed for off-line analysis.

During a search for spinal units, the skin in the perianal area, tail, and proximal parts of the hind limbs was stimulated with a brush. After a neuron responding to brushing was found, its response to colorectal distension of short duration (5 s) at 80 mmHg was tested. If the neuron gave a sustained excitatory response to colorectal distension, its response to a series of graded colorectal distension (20, 40, 60, and 80 mmHg of 10-s duration at 2-min intervals) was quantitatively determined. Only neurons giving sustained and differential responses to colorectal distension within noxious range (40 vs. 80 mmHg) were studied further. The recording depth from the cord surface

was 0.4–1.0 mm (mean, 0.8 mm). Only one neuron was tested in each animal.

Induction of Visceral Hyperalgesia and Chemical Sympathectomy

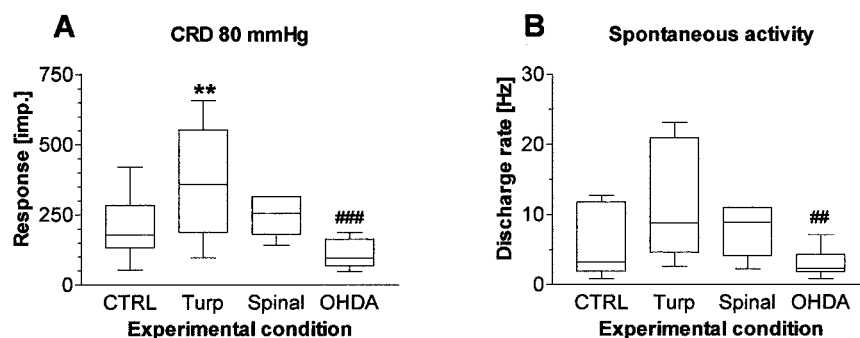
To produce inflammatory hyperalgesia, 1 ml of turpentine (25% in mineral oil) was administered 2 h before start of the recordings with a polyethylene catheter through the anus alongside the distending balloon.^{11–13,26} To produce chemical sympathectomy, rats were treated with 6-hydroxydopamine hydrobromide (6-OHDA; Sigma, St. Louis, MO; 50 mg/kg administered intraperitoneally for 2 days, followed by 100 mg/kg administered intraperitoneally for 3 days).²⁶ The experiments with 6-OHDA-treated animals were performed 3 to 7 days after the last injection of 6-OHDA. Our parallel study²⁶ indicates that this procedure produces a highly effective sympathetic denervation as verified by immunocytochemical methods. Treatment with 6-OHDA caused a weight loss by about 10%, but no marked change in behavior was observed.

Course of the Study

Drugs were administered either in a cumulative fashion or as a single dose. Cumulative administration of drugs was used to study dose dependence of drug-induced effects in a group with colonic inflammation, a group with chemical sympathectomy, and an intact control group. In these groups, the experiment started with spinal administration of saline, followed at 15-min intervals by spinal administration of MPV-2426 or clonidine at cumulative doses of 1, 3, and 10 μg. Atipamezole was injected systemically 15 min following the highest dose of MPV-2426. The mean spontaneous discharge rate during a 1-min observation period and, immediately after that, the response evoked by colorectal distension of 10-s duration at 80 mmHg were assessed at each measuring point. The measurements were performed before administration of each drug dose–saline and 15 min following the injections (immediately before the next dose). The effects of cumulative drug doses on visceral responses were tested at a time point (15 min) at which the maximum antinociceptive effect was not yet achieved. This early time point was used because the focus of this study was to find out possible spinal effects of drugs. It was presumed that a spinal action would take place earlier than a more rostral or peripheral action following administration of drugs onto the lumbo-sacral spinal cord. Moreover, the comparisons were made at the same time point between the different experimental groups.

A time course of visceral antinociception was studied in a spinalized group and in two controls groups. In these experiments, the spinalized group and one control group received a single 10-μg dose of MPV-2426 and one control group received saline. The spontaneous activity and the response evoked by colorectal distension of 10-s

Fig. 1. (A) The spinal neuronal responses evoked by colorectal distension (CRD) of 10-s duration at 80 mmHg before administration of drugs or saline. (B) Spontaneous activities of spinal neurons with visceral inputs before administration of drugs or saline. The boxes extend from the 25th percentile to the 75th percentile, and the whiskers extend from the smallest value to the largest. */# $P < 0.05$, **/## $P < 0.01$, ***/### $P < 0.005$ (Tukey test; * indicates that the reference is the control group; # indicates that the reference is the turpentine-induced inflammation group). CTRL = controls (n = 15); OHDA = 6-OHDA-induced chemical sympathectomy (n = 10); Spinal = spinalized animals (n = 6); Turp = turpentine-induced inflammation of the colon (n = 9).



duration at 80 mmHg were assessed before injections and at various time points (5, 15, and 30 min) following the injections. Only one experimental condition was tested in each animal. At the completion of the experiment, the animals were given a lethal dose of pentobarbitone.

Drugs

The α_2 -adrenoceptor agonists MPV-2426¹⁵ [also known as fadolmidine or 3-(1H-Imidazol-4-ylmethyl)-indan-5-ol hydrochloride; Orion Pharma, Turku, Finland] and clonidine (Sigma) were freshly dissolved in sterile water to obtain the volume of 5 μ l. This was mixed with 45 μ l of physiologic saline. Thus, drugs were injected with a 50- μ l Hamilton microsyringe onto the spinal cord in a volume of 50 μ l. Physiologic saline (50 μ l; Orion Pharma, Espoo, Finland) was used as a control. Atipamezole,²⁷ an α_2 -adrenoceptor antagonist (Orion Pharma), was administered subcutaneously (1 mg/kg) in an attempt to reverse the MPV-2426-induced effects.

Statistics

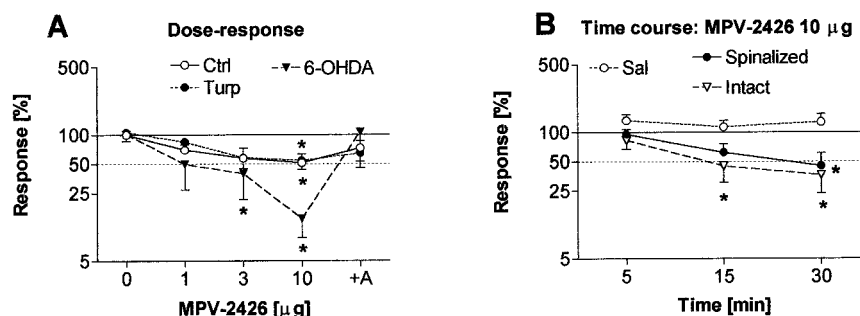
Statistical evaluation of the colorectal distension-evoked responses and spontaneous activity was performed using one- or two-way analysis of variance followed by Tukey test. $P < 0.05$ was considered to represent a significant difference.

Results

The baseline responses of spinal neurons evoked by colorectal distension at the noxious pressure of 80 mmHg were significantly different between the experimental groups ($F_{3,39} = 8.350$, $P < 0.0005$; fig. 1A). According to *post hoc* testing, the response evoked by colorectal distension was significantly enhanced in animals with a turpentine-induced inflammation. The weakest responses were evoked in chemically sympathectomized animals, although the difference between controls and sympathectomized animals was short of significance. The spontaneous activity of spinal neurons with nociceptive inputs from the colorectal region was also significantly different between the experimental groups ($F_{3,40} = 5.131$, $P < 0.005$; fig. 1B), the highest spontaneous activities being recorded in animals with a turpentine-induced inflammation.

Cumulative administration of MPV-2426 onto the spinal cord produced a dose-dependent attenuation of spinal neuronal responses to colorectal distension ($F_{3,61} = 10.94$, $P < 0.0001$; fig. 2A). The suppression of visceral responses by MPV-2426 was significantly different between the experimental groups ($F_{2,61} = 3.15$, $P < 0.05$), being strongest in the sympathectomized animals and of equal percentual magnitude in animals with inflammation of the colon as in controls, independent of the dose

Fig. 2. (A) The standardized mean response to colorectal distension at 80 mmHg following spinal administration of MPV-2426 in a cumulative fashion. On the x-axis, 1–10 is the cumulative doses of MPV-2426, 0 = saline, and +A = atipamezole (1 mg/kg, administered subcutaneously). (B) The standardized mean response to colorectal distension at 80 mmHg following a single spinal dose of 10 μ g of MPV-2426 or saline administered at time point 0. In both graphs, 100% on the y-axis represents the corresponding response before any drug or saline administration. Note the logarithmic scale in this and the following graphs. The error bars represent SD. * $P < 0.05$ (Tukey test; reference: the corresponding value before drug-saline administrations). Ctrl = control animals (n = 6); Intact = administration of MPV-2426 in control animals (n = 4); 6-OHDA = chemically sympathectomized animals (n = 7); Sal = administration of saline in control animals (n = 4); Spinalized = administration of MPV-2426 in spinalized animals (n = 4); Turp = animals with turpentine-induced inflammation of the colon (n = 7).



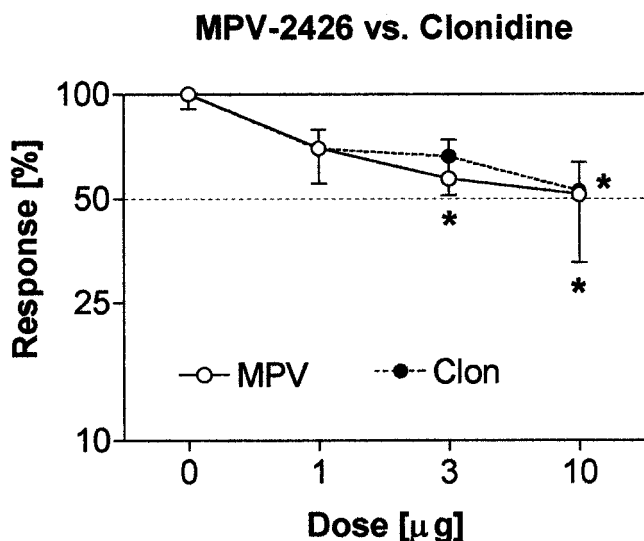


Fig. 3. The standardized mean response to colorectal distension at 80 mmHg following spinal administration of MPV-2426 (MPV; $n = 6$) or clonidine (Clon; $n = 4$) in control animals. On the y-axis, 100% represents the corresponding response before any drug administrations. On the x-axis, 1–10 represent cumulative doses of MPV-2426 or clonidine in micrograms, and 0 represents saline administration. The error bars represent SD. * $P < 0.05$ (Tukey test; reference: the corresponding value before drug-saline administrations).

($F_{6,61} = 0.46$). Atipamezole (1 mg/kg, administered subcutaneously), an α_2 -adrenoceptor antagonist, attenuated the visceral antinociception induced by MPV-2426 (fig. 2A). A time course of the visceral antinociception induced by spinal administration of 10 μ g of MPV-2426 versus saline was studied in animals with intact and transected spinal cords. Visceral nociceptive responses were significantly decreased following administration of 10 μ g of MPV-2426 ($F_{2,27} = 3.58$, $P < 0.05$; fig. 2B). In controls, the decrease of responses was significant within 15 min, and the maximum decrease of the response was obtained at the end of the 30-min observation period. The effect induced by MPV-2426 was significantly different from that of saline ($F_{2,27} = 14.23$, $P < 0.0001$) throughout the observation period following drug administration ($F_{4,27} = 0.57$). The visceral antinociceptive effect induced by spinal administration of MPV-2426 was of equal magnitude in animals with intact and transected spinal cords (fig. 2B). The visceral antinociceptive effect induced by MPV-2426 was not signifi-

cantly different from that of clonidine ($F_{1,42} = 0.07$; fig. 3). MPV-2426 produced a decrease of spontaneous activity both in controls and inflamed animals (fig. 4). Clonidine induced a decrease in spontaneous activity that was of equal magnitude as that induced by MPV-2426 (not shown). Following a dose of 10 μ g of clonidine or MPV-2426 the spontaneous discharge rate was about 50% lower than before drug administration.

Discussion

The spinal neurons recorded gave differential and sustained responses to colorectal distension at noxious intensities. This type of neuron has been described in a number of earlier studies, and they are supposed to have a role in mediating visceral nociception.^{4,13,28} Also in line with previous results, the evoked responses following turpentine treatment of the colon were enhanced in a population of spinal neurons that gave sustained responses to colorectal distension.^{12,13,26} This finding indicates that the turpentine-treated animals had a visceral hypersensitivity. Previous studies indicate that visceral responses of healthy animals are under descending control, which includes excitation as well as inhibition.²⁹ In particular, C fiber-evoked visceral responses are under tonic inhibitory control.³⁰ In the current study, the colorectal distension-induced responses or spontaneous activities of viscerosensitive spinal neurons were not significantly lower in animals with an intact versus a transected spinal cord. This finding suggests that, under the current experimental conditions, there was no marked net effect of tonic descending controls on visceral responses evoked from an uninflamed colon. However, the current sample of neurons recorded in spinalized animals was small, and a comparison of differences in neuronal response characteristics between different animals is not as sensitive a method as a comparison of changes in responses within neurons. Indeed, earlier results, in which the effect of a reversible block of descending pathways was studied within single neurons, indicated that descending control has predominantly a tonic inhibitory effect on responses evoked by distension of an uninflamed colon.²⁸ In contrast, in animals with visceral inflammation, the net effect of descending

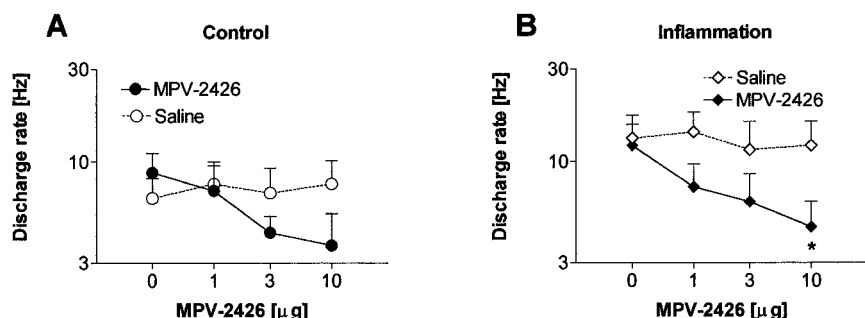


Fig. 4. (A) The mean spontaneous discharge rates of spinal neurons with visceral inputs in control animals following spinal administration of saline ($n = 4$) or MPV-2426 ($n = 6$) in a cumulative fashion. (B) The mean spontaneous discharge rates of spinal neurons in animals with a turpentine-induced inflammation of the colon following spinal administration of saline ($n = 5$) or MPV-2426 ($n = 7$) in a cumulative fashion. In both graphs the error bars represent SD. * $P < 0.05$ (Tukey test; reference: the corresponding value 15 min following saline administration = 0 on the x-axis).

control may be excitatory.³¹ As in our earlier study, animals with a chemical sympathectomy had the lowest baseline responses to colorectal distension, suggesting that sympathectomy may attenuate visceral pain induced by distension of the gut.²⁶

Spinal administration of an α_2 -adrenoceptor agonist, MPV-2426 or clonidine, dose-dependently attenuated neuronal responses induced by colorectal distension at a noxious pressure. This finding is in line with previous behavioral studies demonstrating that intrathecal administration of clonidine or ST-91 produces visceral antinociception.^{3,5,6} An earlier electrophysiologic study showed that systemic administration of clonidine attenuated both spontaneous activity and responses evoked by colorectal distension in nociceptive spinal neurons with visceral inputs,⁴ as spinal administration of MPV-2426 or clonidine did in the current study. The visceral antinociceptive doses of MPV-2426 were in the same range as spinally administered doses needed to attenuate somatically evoked nociceptive responses in earlier studies.¹⁵⁻²⁰

Visceral nociception was effectively attenuated by spinal administration of MPV-2426 also in rats with inflammation of the colon. This finding is in line with the result of an earlier behavioral study showing that visceral hypersensitivity is attenuated by orally administered clonidine in the rat.¹⁴ The MPV-2426-induced attenuation of visceral responses was of equal magnitude, percentually, in inflamed animals as in controls. In contrast, an enhanced antinociceptive efficacy by α_2 -adrenoceptor agonists has been reported in animals with an inflammation of cutaneous tissues.⁷⁻⁹ The difference in the antihyperalgesic efficacy of α_2 -adrenoceptor agonists in visceral *versus* somatic inflammatory conditions may reflect a corresponding difference in the plastic response of the spinal cord to visceral *versus* somatic inflammation. However, when considering this proposal, it should be noted that comparing responses with widely different baselines may provide a complicating factor. Indeed, since inflamed animals had higher baseline responses and the decrease of responses induced by MPV-2426 was of equal percentual magnitude in inflamed animals as in controls, the visceral antinociceptive effect counted as a decrease in the number of impulses was actually stronger in the inflammatory condition.

Acute spinalization had no effect on visceral antinociceptive effect induced by spinal administration of MPV-2426. This finding indicates that intact descending pathways or a spread of the drug from the injection site to a supraspinal site are not needed for the full visceral antinociceptive effect induced by MPV-2426. In line with this, earlier studies have shown that an acute spinalization does not modulate the efficacy of an α_2 -adrenoceptor agonist on somatically evoked spinal nociceptive responses.³² Unexpectedly, the visceral antinociceptive effect induced by spinal administration of MPV-2426 was

stronger in chemically sympathectomized animals than in controls. This finding suggests that chemical sympathectomy has sensitized α_2 -adrenoceptors leading to enhanced visceral antinociception. It remains to be studied whether a possible sensitization of α_2 -adrenoceptors may have taken place at the central terminals of primary afferent fibers, postsynaptic receptors of spinal interneurons, or elsewhere. Irrespective of the site of action, the strong effect of MPV-2426 in sympathectomized animals indicates that an intact sympathetic nervous system is not critical for visceral antinociception induced by spinal administration of an α_2 -adrenoceptor agonist.

In conclusion, spinal administration of MPV-2426, a selective α_2 -adrenoceptor agonist, attenuated visceral nociception in rats with and without inflammation of the colon. This visceral antinociceptive effect was independent of intact brainstem spinal pathways or an intact sympathetic nervous system. Intrathecal administration of MPV-2426 may be a useful alternative for treatment of some visceral pain conditions, particularly since previous studies suggest that, because of its pharmacokinetic properties, MPV-2426 provides a more targeted¹⁵⁻²⁰ and at least as potent treatment of segmentally restricted visceral pain conditions as clonidine, but with lesser cardiovascular side effects.¹⁵

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