Chapter 55

Antiserotonin Drugs in Migraine Prophylaxis

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Antiserotonin drugs are the first group of effective agents available for migraine prophylaxis. Originally, these drugs were thought to act via antagonism at serotonin (5-hydroxytryptamine; 5-HT) D receptors (38), now classified as 5-HT_2 receptors (45). This view is, however, no longer tenable for several reasons. First, many selective and potent 5-HT_2 receptor antagonists, including ketanserin, ICI 169,369, sergolexole, and mianserin, are either ineffective or only weakly effective in migraine (83). Second, the antimigraine potency of these drugs does not correlate with their affinity at the 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors (89). Furthermore, the antimigraine drugs ergotamine and dihydroergotamine have an agonist (not antagonist) action at the 5-HT_{2C} receptor (11). Thus, although conceding that the title of this chapter may be a misnomer, from the outset we wish to emphasize that the prophylactic effect of antiserotonin drugs does not depend on their antiserotonin property. For further discussion of mechanisms, see the sections on individual drugs.

METHYSERGIDE

Methysergide is a semisynthetic compound derived from the ergot alkaloid methylergometrine by adding a methyl group at the indole nitrogen (Fig. 55-1). It was introduced in pharmacotherapy as a specific 5-HT receptor antagonist (29,87).

Pharmacokinetics

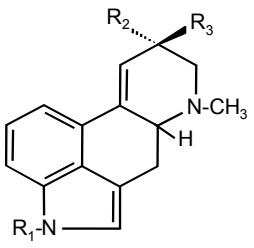
Pharmacokinetic studies in humans indicate that methysergide is probably a prodrug; its main metabolite is methylergometrine (10). After oral administration, the bioavailability of methysergide is about 13%, owing to a high degree of first-pass metabolic conversion to methylergometrine (see Fig. 55-1). Whereas the area under the plasma concentration curve (AUC) for methysergide and methylergometrine after intravenous administration of methysergide is in the same range, oral administration of methysergide results in 10 times greater AUC for methylergometrine than for the parent drug. The elimination half-lives of methysergide and methylergometrine are 60 and 220 minutes, respectively (10).

In contrast to methysergide, methylergometrine has dopaminergic activity (8). The metabolism of methysergide to methylergometrine probably explains why methysergide has little dopaminergic activity upon parenteral administration (8), but its oral administration can result in a significant decrease in the plasma prolactin level (32). Thus, when methysergide is used orally in humans, there are serotonergic effects both because of the parent drug and the metabolite methylergometrine, as well as some dopaminergic effects because of the metabolite methylergometrine.

Pharmacologic Background

It is well known that methysergide is a potent 5-HT_2 receptor antagonist, but it does not distinguish between the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes (45,89). Thus, methysergide antagonizes the contractile effects of 5-HT on vascular and nonvascular smooth muscles with a pA_2 of more than 8 (67). Indeed, in the human isolated temporal artery, which contains predominantly 5-HT_2 receptors (27), both methysergide and its active metabolite methylergometrine are potent antagonists; the latter compound is some 40 times more active than the parent drug (97).

In the early 1970s, Saxena et al. reported that the vasoconstrictor effect of 5-HT within the canine carotid vascular bed was not much modified by methysergide or by two other potent 5-HT_2 receptor antagonists, mianserin and cyproheptadine (Fig. 55-2) (78,80,84). Therefore, the receptors for 5-HT in the external carotid vascular bed



	Methysergide	Methylergonovine	Lisuride
R_1	$-CH_3$	-H	-H
R_2	$-CO-NH-CH(CH_2OH)-CH_2-CH_3$	$-CO-NH-CH(CH_2OH)-CH_2-CH_3$	-H
R_3	-H	-H	$-NH-CO-N(CH_2CH_3)_2$

FIGURE 55-1. Chemical structure of methysergide, its metabolite methylergometrine, and lisuride.

appeared to be of a novel type, which were later named 5-HT_1–like receptor (86). Interestingly, methysergide proved to be an agonist at these receptors (45) and selectively decreased carotid blood flow by constricting arteriovenous anastomoses (80,82). Although this effect of methysergide is much less marked than that of ergotamine or sumatriptan (23–25), its mediation by novel 5-HT_1–like receptors undeniably provided incentive for the development of sumatriptan, which at the time of its introduction was regarded as a selective 5-HT_1–like receptor agonist (48).

As recently argued (85), *5-HT_1–like receptor* is now redundant because the composition of this heterogeneous group has been delineated. This group comprises the sumatriptan-insensitive 5-HT_7 receptor mediating vasorelaxation (22,28), as well as sumatriptan-sensitive 5-HT_{1B}, 5-HT_{1D}, and, in some tissues, even 5-HT_{1F} receptors. Methysergide is a potent antagonist at the 5-HT_7 (and 5-HT_2) receptor and an agonist at 5-HT_{1B} and, possibly, also 5-HT_{1D} receptors. In vitro functional and radioligand studies confirm that methysergide is an agonist at the 5-HT_{1B} receptor (64–66).

The pharmacology of the metabolite methylergometrine has been investigated less thoroughly. However, it is a more potent vasoconstrictor than methysergide both in vivo (60) and in vitro on, for example, canine saphenous veins and human basilar (66) and coronary (59) arteries (Fig. 55-3). The last two effects may bestow efficacy in migraine (63) and coronary side effect potential (53,68) to methylergometrine.

Last, chronic but not acute treatment with methysergide has been reported to attenuate dural plasma extravasation following electrical stimulation of the trigeminal ganglion in the rat (77). The discrepancy between the effect of acute and chronic treatment with methysergide in this model is most likely because of the presence of methylergometrine during chronic administration of methysergide. Although Saito et al. have implied a presynaptic inhibition of the release of calcitonin gene-related peptide (CGRP) from perivascular sensory nerves, functional antagonism (via vasoconstriction) of the vasodilator effects of CGRP cannot be ruled out. Indeed, such a functional antagonism between methysergide and CGRP has recently been described in the rabbit eye (52) and should be investigated further with the use of methylergometrine.

Possible Mechanism of Antimigraine Action

The mechanism of action of methysergide in migraine is not well understood. The efficacy of methysergide has been ascribed to its 5-HT_2 receptor antagonist property, but this is unlikely because potent 5-HT_2 receptor antagonists such as mianserin, sergolexole, ketanserin, and ICI 169,369 have little or no prophylactic effect in migraine, and for cyproheptadine the claimed efficacy (67) has never been

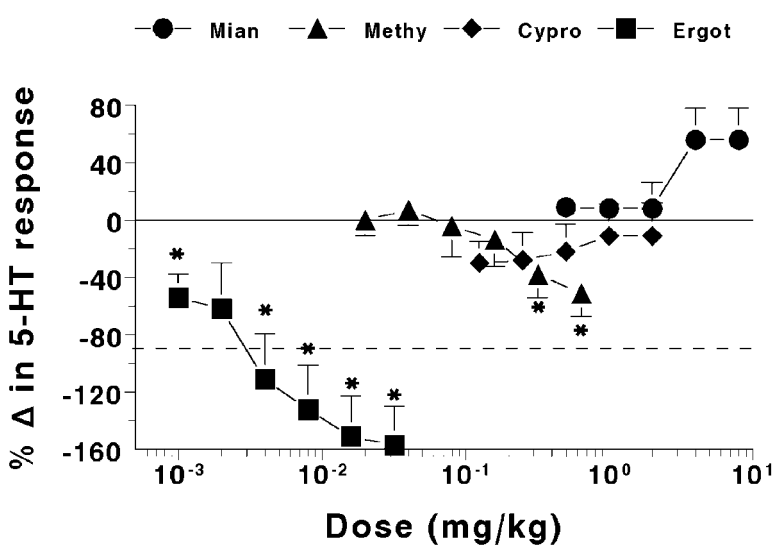


FIGURE 55-2. Dog external carotid vascular bed. Effect of mianserin (Mian), methysergide (Methy), cyproheptadine (Cypro), and ergotamine (Ergot) on the vasoconstrictor response to serotonin. Values below the interrupted line (i.e., change more than −100%) mean that serotonin caused vasodilatation instead of vasoconstriction. *Significant ($P < .05$) change compared with parallel administration of saline. Data from Saxena et al. (84) and Saxena (78).

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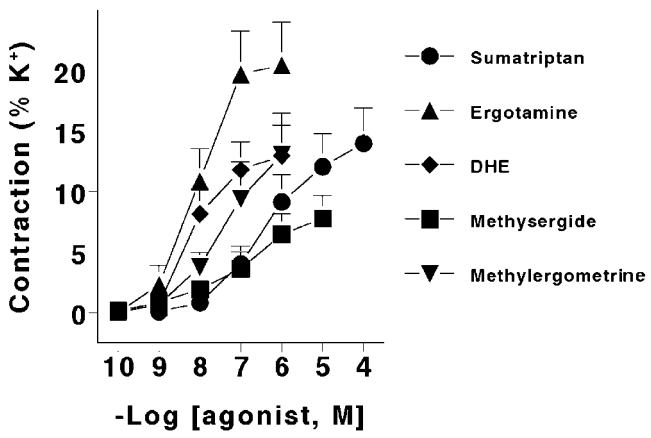

FIGURE 55-3. Concentration response (expressed as a percentage of the response to 100 mmol K^+) curves in human isolated coronary arteries ($n = 9$) obtained with ergotamine, dihydroergotamine (DHE), sumatriptan, methysergide, and its metabolite methylergometrine. Data, displayed as means ± SEM, are from MaassenVanDenBrink et al. (59).

confirmed in controlled clinical trials. Therefore, it is highly improbable that 5-HT_2 receptor antagonism plays any role in migraine prophylaxis (83,96). It should be noted that, in essence, these same arguments also apply against the advocated role of 5-HT_{2C} receptor antagonism (methysergide is a potent 5-HT_{2C} receptor antagonist [67]) in migraine (35,36).

We believe that the vasoconstrictor action of methysergide within the carotid vascular bed (79,82), which is mediated by the 5-HT_{1B} receptor (98), is most likely involved in the therapeutic efficacy. The carotid vasoconstrictor effect of methysergide is weaker, both in potency and efficacy, than that of ergotamine (24) or sumatriptan (23,25), which have the ability to abort migraine attacks (for more details, see Chapter 52). Thus, it is possible that methysergide owes its therapeutic effect in migraine to its metabolic product methylergometrine. Indeed, methylergometrine has a more potent vasoconstrictor action than methysergide (59,66).

Apart from 5-HT_{1B} receptors, the craniovascular effects of methysergide (and methylergometrine) are likely to involve 5-HT_7 receptor blockade (22,28,98). Also worth investigating is the involvement of dopamine receptors because Bell (6,7) has presented evidence that dilatation of arteriovenous anastomoses can be mediated by a neural release of dopamine.

Inhibition of peptide release from perivascular sensory nerve endings as well as neurogenic inflammation by methysergide, as demonstrated in the rat, also has been invoked as a mechanism of action in migraine (77). But, as argued elsewhere (21), there is considerable doubt whether inhibition of neurogenic inflammation in experimental animals is connected with antimigraine efficacy because several such compounds were found clinically ineffective in migraine.

Results of Clinical Trials

Open Trials

In open studies including approximately 1,400 migraine patients (18,37,39,55), methysergide was found to decrease migraine attack frequency in the majority of patients. However, about 10 (18,55) to 20% (37,39) of the patients had to stop the drug because of side effects. One case of ergotism was observed, and in one case angina pectoris was precipitated (37).

During the first years of clinical use of methysergide it became evident that continuous use of the drug for longer periods can induce retroperitoneal fibrosis, as well as pleural and heart valve fibrosis, with an estimated incidence of 1 in 5,000 treated patients (40,41). In most cases the fibrotic process regressed after discontinuation of methysergide (40). The metabolism of methysergide was unchanged in patients who had developed this side effect (9), and its mechanisms remain elusive. This side effect of methysergide limits its clinical use.

Controlled Clinical Trials

Methysergide has been compared with placebo or another drug in nine double-blind randomized clinical trials (2,5,33,43,71,74,75,91,95). The daily dosage of methysergide varied from 3 to 6 mg. In two trials methysergide was superior to placebo for either severe headaches (91) or frequency of attacks (71), but in one trial methysergide was not superior to placebo (75). In four trials (2,33,71,75), methysergide was found comparable with pizotifen (Table 55-1). Methysergide was also found comparable with lisuride (25 μg three times daily) (42), propranolol (40 mg tid) (5), and flunarizine (10 mg daily) (95).

The side effects reported in these trials were dizziness, nausea and vomiting, weight gain, epigastric pain, and psychic reactions. In some studies high drop-out rates of 20% (42) and 26% (91) occurred with a daily dosage of 6 mg methysergide, but apparently this dosage was tolerated in other studies (33,95).

Taken together, the controlled trials with methysergide show that the drug is efficacious in migraine prophylaxis. The problems with side effects also have been demonstrated for this potent drug.

Therapeutic Use

Because of potentially grave side effects, methysergide should be reserved for severe cases for which other attempts of migraine prophylaxis have not produced optimal results. The daily dosage of methysergide in migraine

TABLE 55-1 Controlled Double-Blind Trials Comparing Pizotifen With Placebo or Another Drug for Migraine Prophylaxis

Trial	*Drug Dosage (mg)*	*Study Design*	*No. of Patients (no. Evaluated) and Type of Migraine*	*Run-in and Duration of Treatment*	*Factors Evaluated*	*Investigators' Conclusions*
Lance and Anthony (54)	Pizotifen 1 tid Placebo tid	Parallel groups	50 ?	4 wk	Improvement	Pizotifen = placebo
Hughes and Foster (47)	Pizotifen 1 tid Placebo	Crossover	26 ?	2 mo × 2	Frequency, severity and preference	Pizotifen = placebo, Pizotifen > placebo
Ryan (76)	Pizotifen 1 tid Placebo	Parallel groups	60 (51) MO, MA	4 wk, 12 wk	Frequency, headache index[a]	Placebo > pizotifen, Placebo = pizotifen[b,c]
Arthur and Hornabrook (3)	Pizotifen 1 tid Placebo tid	Crossover	52 (41) MO, MA, CH	4 wk, 4 wk × 2	Frequency	Pizotifen > placebo
Carrol and Maclay (13)	Pizotifen 1 tid Placebo tid	Crossover	27 (14) MO, MA	4 wk,[d] 2 mo × 2	Headache index[a]	Pizotifen = placebo[a]
Lawrence et al. (57)	Pizotifen 1 tid Placebo	Parallel group	36 (28) ?	12 wk	Headache index[a]	Pizotifen > placebo
Cleland et al. (16)	Pizotifen 1.5 mg nightly Placebo nightly	Crossover	88 MO, MA	12 wk × 2, 4 wk washout	Frequency of attacks	Pizotifen > placebo (median attacks per month: 3.5 vs 3.9)
Ryan (75)	Pizotifen 2 bid Methysergide 2 bid Placebo bid	Crossover	62 MO, MA	4 wk × 3	Frequency, headache index[a]	Pizotifen > methysergide = placebo[f]
Presthus (74)	Pizotifen 0.5 tid Methysergide 1 tid	Crossover	21 (19) MO, MA	1 wk, 5 wk × 2, 1 wk washout	Frequency, severity, duration	Methysergide = pizotifen
Forssman et al. (33)	Pizotifen 1 tid Methysergide 2 tid	Crossover	22 (17) MO, MA	6 wk, 10 wk × 2	Frequency, headache index[a]	Methysergide = pizotifen
Andersson (2)	Pizotifen 0.5 qid Methysergide 1 qid	Crossover	73 (49) MO, MA	1 mo, 3 mo × 2	Frequency, headache index[a]	Pizotifen = methysergide both better than run-in
Hübbe (46)	Pizotifen 1 tid Perchlorperazine 5 tid	Crossover	43 (40) ?	8 wk × 2	Frequency	Pizotifen = perchlorperazine
Osterman (69)	Pizotifen 1 tid 1-Iso 5 tid Placebo tid	Crossover	30 (28) MO, MA	8 wk × 3	Frequency, headache index[a], preference	Pizotifen > 1-Iso = placebo
Kangasneimi (50)	Pizotifen 0.5 tid 1-Iso 5 tid	Crossover	50 (34) MO, MA	14 wk × 2, 4 wk washout	Frequency, headache index[a]	Pizotifen = 1-Iso = placebo[c]
Capildeo and Clifford Rose (12)	Pizotifen 0.5 tid Pizotifen 1.5 nightly	Crossover	17 MO, MA	2 months × 2	Headache index[a]	Pizotifen tid = pizotifen 1.5 nightly

For comparison with calcium blockers, see Chapter 58.
[a] Frequency times severity.
[b] In pretreatment period, more attacks in pizotifen group (12/4 weeks) than in placebo group (7/4 weeks).
[c] The opinion of the present reviewers.
[d] Pizotifen during run-in to determine optimal dosage (in most cases 3 mg/d).
[e] No statistics given, but Wilcoxon's test on raw data gives $P > .2$.
Abbreviations: 1-Iso, 1-isopropyl-3-hydroxy-5-semicarbazono-6-oxo-2.3.5.6-tetrahydroindol; bid, twice daily; tid, thrice daily; qid, four times daily; MO, migraine without aura; MA, migraine with aura; CH, cluster headache; =, no statistical significant difference; >, signifies more effective than.

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prophylaxis is 3 to 6 mg given in three divided doses. To minimize the acute side effect, the dosage should be increased gradually, starting with 1 mg per day and increasing with 1 mg every third day. Methysergide should not be taken continuously for long periods, which can result in retroperitoneal fibrosis (4,40,41). Instead, the drug should be given for 6 months, with a 2-month interruption before starting the drug again. When methysergide is stopped it should be weaned off gradually over 1 week to avoid rebound headache.

The side effects of methysergide are nausea and vomiting, dyspepsia, edema, dizziness, sedation, and depression. Long-term use may lead to retroperitoneal fibrosis, as well as heart valve (49) and pleural fibrosis. The starting symptoms of retroperitoneal fibrosis, in which the ureters are constricted, are low back pain, leg pain, and urologic disturbances (4,40,41). The drug should be discontinued immediately even on suspicion of retroperitoneal fibrosis.

Contraindications include cardiovascular diseases, severe hypertension, a history of thrombophlebitis, peptic ulcers, pregnancy, familial fibrotic disorders such as Dupuytren disease, lung diseases, collagenoses, and liver and kidney diseases.

PIZOTIFEN

Pizotifen was introduced in migraine prophylaxis as an anti-aminic drug based on the idea that not only 5-HT but also other biogenic amines might be involved in migraine (88,93). In controlled trials, the drug has been more effective than placebo. Its general use is hampered by its main side effects, weight gain and sedation.

Pharmacologic Background

Pizotifen is a potent 5-HT_2 receptor antagonist with a pA_2 value of around 9.2 (67). Pizotifen also has antihistaminic and weak anticholinergic actions and, in some animals, sedative and antidepressant properties (93). The antidepressant property has been confirmed in humans (94). Furthermore, in both dogs (64) and humans (1), a modest venoconstrictor activity of pizotifen has been demonstrated. It has been suggested that pizotifen acts as a calcium-channel blocker (73), but this is very unlikely in concentrations in plasma reached with therapeutic doses in humans (64). In our opinion, the diversity of pharmacologic properties of pizotifen precludes a meaningful hypothesis concerning its efficacy in migraine (70).

Pharmacokinetics

The pharmacokinetics of pizotifen has only been studied with [^{3}H]-labeled drug (61). Thus, measured concentrations in plasma (total radioactivity) include both parent drug and metabolites. The study indicated a maximal therapeutic plasma level of pizotifen of 9 ng/ml and an extensive metabolism of the drug, with less than 1% being excreted unchanged in the urine (61). Because of the method used, the study allows no conclusion about how often pizotifen should be administered.

Results of Clinical Trials

A summary of 15 randomized double-blind controlled clinical trials comparing pizotifen with placebo (3,13,16, 47,54,57,76) or other drugs (2,12,33,46,50,69,74,75) is given in Table 55-1. The daily dosage of pizotifen was 1.5 to 3 mg. In addition, pizotifen reportedly has been equally effective as the calcium blockers flunarizine (four trials) and nimodipine (two trials) (see Chapter 56).

Pizotifen was superior to placebo for frequency of attacks or headache index in several studies (3,16,57,69) and superior to placebo for severity of headaches in one study (47). In two trials with low power to detect a difference, no significant difference was found between pizotifen and placebo (13,54), and another trial (76) indicated that pizotifen was inferior to placebo, probably because of unsuccessful randomization (see Table 55-1).

In the comparative trials with methysergide, pizotifen was found to be as efficacious as methysergide (2,33,74), and in one trial pizotifen was reported to be superior to methysergide (75). Pizotifen was found comparable with prochlorperazine in one trial (46) and better than (69) or comparable with (50) 1-isopropyl-noradrenochrome-5-monosemicarbazono. In addition, one study indicated that pizotifen 1.5 mg at night was as effective as 0.5 mg three times daily (12). However, apart from one trial (75), these comparative trials with pizotifen lack a placebo control, and it is thus difficult to judge the significance of these results.

The side effects included drowsiness, increased appetite, and weight gain. Thus, in one placebo-controlled trial with pizotifen 3 mg per day in 30 patients, the drug induced drowsiness in 15, increased appetite in 12, and caused weight gain in 24 ($>$1.5 kg in 21 and $>$4 kg in 3) patients (69). Drowsiness, however, often diminished with time (69).

In conclusion, the controlled clinical trials demonstrated efficacy of pizotifen in migraine prophylaxis, but side effects, especially weight gain, were frequent and limit the use of the drug.

Therapeutic Use

Pizotifen is normally used in a daily dosage of 1.5 mg, which can either be taken as 0.5 mg three times daily or as one dose in the evening (12) to increase compliance and cause less sedation. The dosage should be increased gradually, starting with 0.5 mg once a day, increasing with 0.5 mg every third day to 0.5 mg three times daily or

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1.5 mg at night. In refractory cases, dosage up to 3 to 4.5 mg daily, taken in three divided doses, can be used.

Side effects include increase in appetite and weight gain, as well as sedation. Contraindications include obesity. Patients should refrain from driving at the start of the treatment.

LISURIDE

After its synthesis in 1959, the ergot alkaloid derivative lisuride (see Fig. 55-1) was first developed as a peripheral 5-HT receptor antagonist, and its similarity to methysergide led to its clinical use in migraine prophylaxis (44). Later, lisuride's dopaminergic effect was established, and it is now also used in higher doses in the treatment of Parkinson disease.

Pharmacologic Background

Lisuride is a dopamine D_2 receptor agonist, but it also a potent antagonist at 5-HT_2 (67) as well as at 5-HT_7 (22) receptors. In addition, lisuride may act as an agonist at CNS 5-HT receptors (44). The mode of action of lisuride in migraine prophylaxis remains elusive, but the doses used in migraine are probably without any dopaminergic effect (44).

Results of Clinical Trials

In open studies, success rates (more than 50% reduction in frequency of attacks) from 34% (56) to 61% (92) have been reported after lisuride (0.025 mg three times daily). In two double-blind placebo-controlled trials with lisuride (0.025 mg three times daily) was superior to placebo (42,90). In these trials (42,90), patients with up to 21 to 30 attacks per month were included, making the diagnosis of migraine, at least in some patients. In a double-blind trial, lisuride (0.025 mg three times daily) was found comparable with methysergide (2 mg three times daily) in 253 patients (43). In this study, 11 patients with cluster headache were included, and 40% of patients had more than 10 attacks per month, making it unlikely that only migraine attacks were treated. In one trial, there was no difference between lisuride in dosages of 0.025 and 0.05 mg three times daily (99).

The most common side effects of lisuride reported were nausea, gastrointestinal complaints, and dizziness.

In conclusion, the controlled clinical trials suggest that lisuride has some efficacy in migraine prophylaxis, but the selection of patients with uncertain diagnosis of migraine for these trials prevents a definitive statement.

Therapeutic Use

Lisuride can be tried in migraine prophylaxis in a dosage of 0.025 mg three times daily. Side effects include nausea, gastrointestinal complaints, and dizziness. Contraindications include peripheral vascular diseases, coronary artery disease, and psychosis.

CYPROHEPTADINE

Cyproheptadine is an antihistaminic drug that has been used in the past in migraine prophylaxis. The drug is a potent antagonist at 5-HT_2 receptors (pA_2 of around 8.8), but it also antagonizes responses mediated by histamine H_1 and muscarinic cholinergic receptors (67). In addition, cyproheptadine acts as a calcium-channel blocker in the canine basilar artery (72). The drug does not seem to act on 5-HT_1 receptors and is unable to block the 5-HT–induced vasoconstriction in the carotid vascular bed (Fig. 55-2) (78,81).

In open studies success rates (headache free or considerably improved) for cyproheptadine in migraine prophylaxis of 43% (56), 46% (18), and 65% (51) were reported. In one study cyproheptadine was found inferior to methysergide (18). Furthermore, the effect of cyproheptadine was not significantly different from that of placebo in another study (54). There are no double-blind randomized placebo-controlled trials with cyproheptadine, and the proof of its efficacy as a migraine prophylactic drug is virtually nonexistent.

Therapeutic Use

Cyproheptadine is sometimes used in migraine prophylaxis in a dosage of 8 to 32 mg daily, taken in three to four divided doses. The initial dose is 2 mg, increased by 2 mg every third day until beneficial effect is observed or side effects occur.

Side effects include drowsiness, dizziness, dry mouth, increased appetite, and weight gain. Contraindications include glaucoma.

OTHER 5-HT_2 RECEPTOR ANTAGONISTS

The antidepressant drug mianserin is a potent 5-HT_2 receptor antagonist with a pA_2 of 9.3 (67). Mianserin neither blocks the vasoconstrictor effects of 5-HT nor elicits vasoconstriction within the canine external carotid vascular bed (Fig. 55-2) (84). It has been claimed to be effective in migraine prophylaxis (26,62). However, this claim is based on two controlled studies that, even if they were double-blind and placebo-controlled, were full of methodologic faults (96). There were thus no clear indications for mianserin being better than placebo (96).

Sergolexole is a 5-HT_2 receptor antagonist with a pA_2 value of approximately 9 (17). The drug also can act as an antagonist at the 5-HT_7 receptor (19). Based on the

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possible involvement of 5-HT in migraine, it was investigated in one prophylactic migraine trial (14) and found no better than placebo.

In small open pilot studies, the selective 5-HT_2 antagonists ketanserin (100) and ICI 169,369 (20) were without convincing prophylactic effect in migraine.

Overall, these 5-HT_2 receptor antagonists seem to have no prophylactic effect in migraine.

5-HT_3 RECEPTOR ANTAGONISTS

It was hypothesized that 5-HT, released at perivascular nerve endings, causes migraine pain via activation of neuronal 5-HT_3 receptors on pain afferents present in cranial microvasculature (34). Initially, a small trial conducted with the 5-HT_3 receptor antagonist MDL 72222 in acute migraine attacks seemed to support this hypothesis (58).

The potent 5-HT_3 receptor antagonist tropisetron was evaluated in migraine prophylaxis in two double-blind placebo-controlled trials (31). The results with none of the doses of tropisetron (15 to 50 mg,) were different from those with placebo. As reviewed by Ferrari (30), the efficacy of 5-HT_3 receptor antagonists in migraine therapy remains hypothetical.

Another 5-HT_3 receptor antagonist, zatosetron, was also found ineffective in the treatment of migraine attacks (15).

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P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
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