Chapter 50

# Ergot Alkaloids in the Acute Treatment of Migraines

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He gently prevails on his patients to try
The magic effects of the ergot of rye.
Lord Alfred Tennyson (1809–1892) (71)

In the Middle Ages, grain contaminated with ergot (*Claviceps purpurea*) caused epidemics of gangrene known as the "Holy Fire" or "St. Anthony's Fire" (8,83,121). Ergotamine (Fig. 50-1), one of the ergot alkaloids mainly responsible for this effect, was isolated from ergot in 1918 (109) and found to have sympatholytic activity. Its introduction for the treatment of migraine in 1926 was based on the belief that migraine was caused by heightened sympathetic activity (80). In 1938, Graham and Wolff concluded that the efficacy of ergotamine was probably caused by vasoconstriction of the extracranial vasculature (41). Yet, soon afterward, in 1945, dihydroergotamine was introduced in migraine therapy as a more potent sympatholytic agent than ergotamine (54). The vasoconstrictor activity of these ergot alkaloids is most likely involved in their effect on migraine pain, although other possible mechanisms for the beneficial effect of ergotamine have been suggested, including an action on central serotonergic neurons (55,93) and an effect on neurogenic inflammation (81) (see Chapter 33).

## PHARMACOLOGIC BACKGROUND

### Receptor Binding Properties

The ergot alkaloids have a complex mode of action that involves interaction with a variety of receptors (86). Indeed, as shown in Table 50-1 (2,37,56,57,73,74), both ergotamine and dihydroergotamine have affinities for 5-hydroxytryptamine (5-HT), dopamine, and noradrenaline receptors. In contrast, sumatriptan is much more selective, showing high affinity for 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors and a moderate affinity for 5-$HT_{1A}$ and 5-$HT_{1F}$ receptors.

The $\alpha$-adrenoceptor blocking property of ergotamine, first described in 1906 (19), is textbook knowledge (53); however, this property is often overemphasized, in that it has been observed with high doses used in some animal models, which bears no relevance to therapeutic use in humans (32). In lower therapeutically relevant concentrations, ergotamine acts as an agonist at $\alpha$-adrenoceptors, 5-HT (particularly 5-$HT_{1B/1D}$) and dopamine $D_2$ receptors (22,85,86,101,129). In addition, there is evidence that both ergotamine and dihydroergotamine can activate novel, not yet characterized receptors (22).

### Vasoconstrictor Properties

The most important and conspicuous pharmacologic effect of ergot alkaloids is undeniably the vasoconstrictor action (85,86). Extensive studies in animal models have shown that this vasoconstrictor effect is particularly marked within the carotid vascular bed. This selectivity further extends to the arteriovenous anastomotic part of the carotid circulation; blood flow to a number of tissues, including that to the brain, is affected only minimally (22,63,128). Similar vasoconstrictor effects on cephalic arteriovenous anastomoses also have been observed with the use of sumatriptan as well as other triptans (102).

In humans, ergotamine can constrict several isolated blood vessels, including the pulmonary (16), cerebral (85), temporal (87), and coronary (79) arteries. The drug seems to be more active on large arteries (conducting vessels) than on arterioles (resistance vessels). Dihydroergotamine constricts veins as demonstrated locally by local infusion into hand veins (3) and its contractile effect on human basilar arteries is equipotent, but with a smaller maximal effect than ergotamine (85).

In humans, arterial blood pressure is transiently increased moderately after parenteral therapeutic doses of

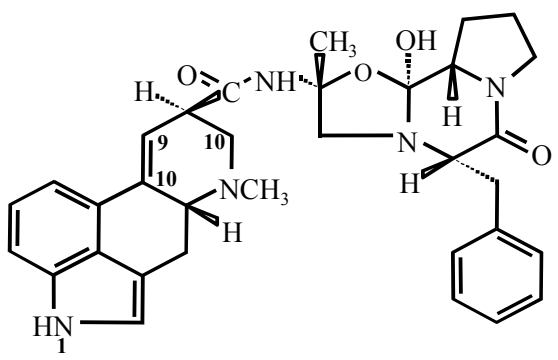

*FIGURE 50-1.*

ergotamine and dihydroergotamine (6,112,114). For ergotamine, the hypertensive response is caused by increased total peripheral resistance (116). Basal cerebral blood flow (CBF) and acetazolamide-stimulated CBF also is unchanged after both ergotamine and dihydroergotamine (6). Basal myocardial blood flow also is unchanged after intravenous ergotamine, but the coronary vasodilator reserve decreases, probably by an effect on the microcirculation (38). In contrast to the short-lasting (about 3 hours) effect on blood pressure, ergotamine causes a long-lasting (at least 24 hours) vasoconstriction of leg arteries (112,114,122). A similar long-lasting venoconstrictor effect (at least 8 hours) has been observed after a single dose of dihydroergotamine (5). For dihydroergotamine no effect on peripheral arteries was found (6). An important feature of ergotamine and dihydroergotamine, observed in vitro is that their effect on blood vessels is resistant to repeated wash (79,84,87), which appears to be caused mainly by slow diffusion from the receptor biophase; therefore,

**TABLE 50-1 Receptor Profile of Ergotamine and Dihydroergotamine as Compared to Sumatriptan**

| | *$pK_i$ Value on Human Cloned Receptors in Radioligand Binding Assay*[a] | | |
|---|---|---|---|
| ***Receptor Type*** | *Ergotamine* | *Dihydroergotamine* | *Sumatriptan* |
| 5-$HT_{1A}$ | 7.89[b] | 9.30[c] | 6.43[c] |
| 5-$HT_{1B}$ | 7.88[b] | 9.22[c] | 7.82[c] |
| 5-$HT_{1D}$ | 8.36[b] | 8.60[c] | 8.46[c] |
| 5-$HT_{1E}$ | 6.22[d] | 6.22[c] | 5.80[c] |
| 5-$HT_{1F}$ | 6.77[d] | 6.96[c] | 7.86[c] |
| 5-$HT_{2A}$ | 7.69[e] | 8.54[c] | <5.0 (pIC50)[c] |
| 5-$HT_{2B}$ | 8.17 ($pEC_{50}$, pig, functional)[f] | 7.70 ($pEC_{50}$, pig, functional)[f] | ND |
| 5-$HT_{2C}$ | 7.25 (pig, native)[e] | 7.43 (pig)[c] | <5.0 (pIC50, pig)[c] |
| 5-$HT_3$ | ND | <5.0 (pIC50, mouse)[c] | <5.0 (pIC50, mouse)[c] |
| 5-$HT_4$ | ND | 6.52 (guinea-pig)[c] | <5.0 (pIC50, guinea pig)[c] |
| 5-$HT_{5A}$ | 7.26[b] | 7.34[b] | 5.50[b] |
| 5-$HT_{5B}$ | 8.50 ($pK_d$, rat)[g] | ND | ND |
| 5-$HT_6$ | ND | 6.78[b] | 5.31[b] |
| 5-$HT_7$ | 7.49 ($pK_d$, rat)[g] | 7.17[b] | 6.51[b] |
| $\alpha_1$ Adrenoceptor | 8.00 (?)[h] | 8.00 (rat)[c] | <5.0 (pIC50, rat)[c] |
| $\alpha_2$ Adrenoceptor | 8.20 (?)[h] | 8.00 (rat)[c] | <5.0 (pIC50, rat)[c] |
| $\beta_1$ Adrenoceptor | ND | 5.27[c] | <5.0 (pIC50)[c] |
| $\beta_2$ Adrenoceptor | ND | <5.0 (pIC50)[c] | <5.0 (pIC50)[c] |
| Dopamine $D_1$ | ND | 5.32 (rat)[c] | <5.0 (pIC50, rat)[c] |
| Dopamine $D_2$ | 8.50 (?)[h] | 8.21[c] | <5.0 (pIC50)[c] |

?, species and test not specified; ND, not determined.
[a]Unless otherwise stated.
[b]Data from Pauwels PJ, personal communication.
[c]Data from Leyson JE, Gommeren W, Leylen L, et al. (74).
[d]Data from Adham N, Kao HT, Schecter LE, et al. (3).
[e]Data from Hoyer D (56).
[f]Data from Glusa E, Roos A (37).
[g]Data from Hoyer D, Clarke DE, Fozard JR, et al. (57).
[h]Data from Leysen JE, Gommeren W (73).

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their effects last far longer than can be expected from plasma concentrations (5,118).

### Neuronal Properties

Ergotamine and dihydroergotamine have been reported to inhibit dural plasma extravasation after stimulation of the trigeminal ganglion in rat (12,13,81) by a C-fiber–dependent mechanism, perhaps coupled to blockade of neuropeptide release from perivascular nerves (see Chapter 17). Furthermore, dihydroergotamine binds to receptors in the trigeminal nucleus caudalis and in the dorsal horn of the first and second cervical segments of the spinal cord in the cat (39), which, in turn, may inhibit activity in the central trigeminal neurons (55) (see Chapter 23). Probably, ergotamine has the same effect. Both the peripheral and central effects on the trigeminovascular system have been suggested to contribute to the antimigraine effect of ergot alkaloids.

## EFFECT ON THE CRANIAL VASCULATURE AND POSSIBLE MODE OF ACTION IN MIGRAINE

In the now classical study by Graham and Wolff (41), a parallel decrease in pulsation of the temporal artery and headache intensity was observed in 16 of 20 experiments after intravenous ergotamine. When the amplitude of pulsation decreased slowly, headache likewise diminished slowly. If the amplitude dropped precipitously, the headache ended promptly. Later, a similar decrease in pulsation of the temporal artery was found for dihydroergotamine (10). There was no evidence for changes in the diameter of intracranial arteries (41). This study apparently demonstrated an extracranial pain source, the dilated temporal artery, during migraine attacks, and also demonstrated that ergotamine acts by its vasoconstrictor effect. As pointed out subsequently by Brazil and Friedman (10), however, pulse-wave contour can vary considerably and depends not only on the tone in the arterial wall, but also on the pulse amplitude and the blood flow. Thus, an increase in amplitude does not necessarily imply vasodilatation nor does diminution of amplitude necessarily imply vasoconstriction. Furthermore, the likelihood of a specific vasoconstrictor effect on the extracranial arteries as being the effect solely responsible for the efficacy of ergot alkaloids has been weakened by the demonstration that only in one third of migraine patients is the pain arguably of extracranial vascular origin (27). In addition, the temporal artery was only relatively dilated to a small extent on the pain side during migraine attacks (62). Thus, the effect of ergot alkaloids may not be entirely from extracranial vasoconstriction.

The parallel decreases in pulse amplitude and headache still point to a vascular action of ergotamine, but this effect might have been brought about by actions of the drug on other parts of the cranial vascular bed. Thus, in male volunteers 0.5 mg ergotamine administered intravenously caused an increase in blood velocity in the middle cerebral artery (123). In another study, however, ergotamine (0.5 mg, administered intramuscularly) was effective in 9 of 10 migraine patients, but it did not affect blood velocity in the middle cerebral artery as would have been expected in case this artery dilated during the migraine attacks (24). This finding might suggest indirectly that some other action of ergot alkaloids, such as an effect on neurogenic inflammation (81) or central inhibition of trigeminovascular pathways (40,55), might be responsible for its antimigraine effect. Alternatively, a combination of effects may be necessary for the therapeutic effect.

## PHARMACOKINETICS OF ERGOTAMINE AND DIHYDROERGOTAMINE

### Ergotamine

With tritium-labeled ergotamine, 66% of the orally administered ergotamine was absorbed (4), but it was subsequently shown that the oral bioavailability of ergotamine was less than 1% (11,60). Thus, even if ergotamine is well absorbed, the majority of the drug is metabolized during the first pass through in the liver.

After intravenous injection, ergotamine is distributed quickly, with a half-life of 2 to 3 minutes and an elimination half-life of 2 hours (59). It is cleared extensively during its passage through the liver, with an extraction fraction of greater than 0.75 (116). The intramuscular bioavailability is about 50% and the peak plasma concentration is seen after 10 minutes (59). For other routes of administration, it is often impossible to detect ergotamine in plasma. Based on measurements with high-performance liquid chromatography (29) and mass spectrometry (99), the oral and sublingual bioavailability of ergotamine is estimated to be less than 1%, whereas the rectal and inhalational bioavailability are estimated to be 1 to 3% (11,31,59,60,99,119).

### Dihydroergotamine

Dihydroergotamine also has a low oral bioavailability (about 1%) as a result of extensive liver first-pass metabolism (77,132). Despite formation of an active metabolite 8′-hydroxydihydroergotamine with an area under the curve about seven times greater than the parent dihydroergotamine (82), the total oral bioavailability of dihydroergotamine is still quite low.

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After intravenous injection, dihydroergotamine is distributed quickly and eliminated, with a mean terminal half-life of 13 to 15 hours (226,132). The peak plasma concentration occurs 30 minutes after intramuscular injection (4) and 45 minutes after subcutaneous administration (75). Nasally administered dihydroergotamine becomes rapidly available to the systemic circulation, with peak plasma levels achieved in 0.75 (115) to 0.9 (58) hour. The bioavailability of intranasal dihydroergotamine is approximately 40% (58,115).

## RESULTS OF CLINICAL TRIALS WITH ERGOTAMINE AND DIHYDROERGOTAMINE

Ergotamine and dihydroergotamine have been in use for a very long time and, therefore, they did not undergo a controlled clinical trial program that would be expected of a new drug today. Not surprisingly, the number of good clinical trials incorporating such a widely used drugs as ergotamine is not great. In a recent review, it was stated that little evidence exists that ergotamine is significantly more effective than placebo (18). Despite the flaw that information from clinical trials with ergotamine is generally not up to date (61) (see Chapter 7), some evidence for the efficacy of ergotamine has been reported in the literature, which is briefly summarized below.

Oral ergotamine has been evaluated in 17 trials. Ergotamine (1 to 5 mg) was superior to placebo for some parameters in six trials (33,48,67,88,98,100), and no better than placebo in one study using a dose of 2 to 3 mg (130). In two comparative trials, ergotamine was superior to aspirin (500 mg) (46,47), and inferior to an isometheptene compound in one trial (133) and superior to it in another trial (1). Ergocristine, tolfenamic acid, dextropropoxyphene, naproxen sodium, and pirprofen were generally found to be comparable to ergotamine. In contrast, the triptans (100 mg sumatriptan, 10 mg rizatriptan, and 40 and 80 mg eletriptan) were superior to 2 mg of ergotamine plus 200 mg of caffeine (7,15,23,127). The combination of calcium carbasalate (equivalent to 900 aspirin) plus metoclopramide (10 mg) was superior to a rather small dose of 1 mg ergotamine plus 100 mg caffeine (72).

These trials of ergotamine, some placebo controlled, demonstrate that oral ergotamine is somewhat effective in the treatment of migraine; however, the clinical relevance of the different efficacy parameters used in the studies can be questioned, and no uniform picture of the effectiveness of oral ergotamine emerges from these trials. Other routes of administration of ergotamine, which from a kinetic point of view should be more efficacious, have scarcely been investigated. In one trial, inhaled ergotamine (maximum dose, 1.8 mg) was superior to sublingual ergotamine (maximum dose, 2 mg), and sublingual ergotamine did not produce better results than sublingual placebo (17). In one double-blind, placebo-controlled study, a suppository of ergotamine (2 mg) was no better than placebo, whereas ketoprofen (100 mg administered as a suppository) was superior to placebo (66). In a recent randomized, crossover, double-blind trial including 251 patients (110), suppositories containing ergotamine (2 mg) and caffeine (100 mg) administered once with an option another after 1 hour, were found superior to 25 mg sumatriptan suppositories with response rates of 73 and 63% after 2 hours, respectively. Because more side effects occurred after ergotamine suppositories, slightly but not significantly more patients preferred sumatriptan suppositories (44%) than ergotamine suppositories (36%).

Intranasal dihydroergotamine was compared with placebo in nine double-blind trials, but most of these trials were published in abstract form only and, therefore, are difficult to evaluate; results varied considerably. For a review of these trials and other open trials, see the first edition of this book and the review by Scott (103). Subsequently, intranasal dihydroergotamine was compared with placebo in three trials (25,36). In two studies reported in the same paper (25), 1 mg plus 1 mg dihydroergotamine was superior to placebo after 1 and 3 hours, respectively. In another trial (36), doses of 2 mg and 3 mg of dihydroergotamine had superior results than with placebo, as judged from the response rates. In contrast, in one small trial neither 0.5 mg nor 1 mg (plus optional 1 mg) of intranasal dihydroergotamine was superior to placebo (126). In one study, intranasal dihydroergotamine 1 mg (plus an optional dose of 1 mg after 30 minutes) was clearly inferior to 6 mg of subcutaneous sumatriptan up to 2 hours after intake (125), but recurrences were less.

In the three placebo-controlled trials (25,36), dihydroergotamine caused nasal congestion (21 and 50%) and taste disturbances (9 and 12%) more frequently than placebo. Also, nausea (4 and 17%) occurred more frequently with intranasal dihydroergotamine.

Subcutaneous dihydroergotamine 1 mg was inferior to 6 mg subcutaneous sumatriptan for the first 2 hours, but apparently comparable thereafter (131) and with fewer recurrences. The tendency of the effect of dihydroergotamine being less rapid but more long lasting than the effect of sumatriptan is theoretically interesting. It fits with the time–effect curve for the vasoconstrictor effect of ergot alkaloids, both in vitro as well as in vivo (118). A slow dissociation from the receptor site, in addition to a long-lasting effect, would result in a slow onset of action (112).

Intravenous dihydroergotamine was compared with placebo in one complicated crossover trial, where results indicated some superiority of dihydroergotamine (14).

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In one small double-blind trial ($n = 9$), the intravenous combination of dihydroergotamine and metoclopramide was superior to placebo (68). In children, oral dihydroergotamine (20 to 40 $\mu$g/kg) was marginally better than placebo ($P = .06$) in a crossover trial that evaluated 12 children (49). For trials comparing parenteral dihydroergotamine with other drugs or drug combinations, see Chapter 52.

## THERAPEUTIC USE OF ERGOTAMINE AND DIHYDROERGOTAMINE

### Ergotamine

Ergotamine still is widely used in some countries for the treatment of severe migraine attacks. It is generally regarded as a safe and useful drug when prescribed in the correct dose and in the absence of contraindications (91,92,106,113,120). For information about choosing between ergotamine and the triptans, which in many countries now are the drugs of first choice for severe attacks, if both are available and affordable, see Chapter 55.

#### *Dosages and Routes of Administration*

Ergotamine can be given, in ascending order of efficacy and side effects, as sublingual or oral tablets, and by suppository. The very low bioavailability results in marked interpatient variability with regard to the amounts of the drug reaching the circulation. Thus, there is no 'standard dose'; rather, the dose should be tailored to the individual patient. The safer option is to begin with a small dose and to increase it gradually, depending on efficacy and side effects, until the optimal dose for the individual patient has been achieved. Nausea is encountered in 10 to 20% of patients after oral or rectal administration of ergotamine. The frequent occurrence of this side effect most often limits the use of ergotamine. The drug has a direct effect on the chemoreceptor trigger zone in medulla (91). Ergotamine should be administered in the selected dose as soon as the patient is sure that a migraine attack is developing. The dose of ergotamine should not be divided, as is often recommended.

For oral ergotamine, sublingual and ordinary tablets and, in some countries, effervescent, tablets are available. The recommended starting dose is 2 mg, the maximum dose 6 mg. In tablets, 1 mg of ergotamine tartrate often is combined with 100 mg of caffeine, which increases the absorption of ergotamine. For rectal ergotamine, the recommended starting dose is 1 mg (half a suppository), and the recommended maximum dose is 4 mg (two suppositories). The rectal route is in clinical practice the most effective and is useful for attacks associated with severe nausea and or vomiting.

#### *Frequency of Dosing*

A persistent (at least 24 hours) vasoconstrictor effect occurs after a single therapeutic dose of ergotamine (114). Ergotamine thus should not be given daily, because this leads to chronic vasoconstriction or habituation (see Chapter 118); ideally, patients should not be allowed more than two doses per week (92).

#### *Can Ergotamine Be Used in Migraine With Aura?*

Because of its vasoconstrictor effect, it has long been debated whether ergotamine can be used safely in migraine with aura, where decreased CBF, continuing into the headache phase, occurs (see Chapter 35). Studies in migraine patients during attacks (44,107), nonmigrainous patients (45) as well as normal subjects (6) failed to show any effect of ergotamine on CBF. In large intravenous doses, however, ergotamine can cause a small constriction of cerebral arteries in volunteers (123) and may do so to a greater extent in susceptible persons, causing symptomatic arterial vasospasm, as has been confirmed angiographically (52). Therefore, ergotamine perhaps is best avoided in treating migraine attacks preceded by an aura lasting for more than 30 minutes.

#### *Side Effects*

The side effects of ergotamine are listed in Table 50-2. After a single dose, side effects include nausea (occurring in 10% after oral administration) (91) and vomiting, abdominal discomfort, acroparaesthesia, and leg cramps. After chronic daily intake, unwanted symptoms include those attributable to vasospasm (such as intermittent claudication) and ergotamine-induced headache (see Chapter 118).

Overt ergotism (34,50,83,121,134) is rare but should be treated early and vigorously with a direct-acting vasodilator for at least 24 hours (e.g., intravenous nitroglycerin in at starting dose of 0.5 $\mu$g/kg per minute) (117). Even if pregangrenous symptoms such as cyanosis are not present, treatment should be started if the patient has resting limb pain to avoid ischemic neuropathy (Tfelt-Hansen, personal observation). If the vasodilator treatment is ineffective and gangrene is imminent, mechanical intra-arterial dilatation with a balloon-tipped catheter may be necessary (105). Alternatively, prostacyclin infusion has been suggested (30).

In patients with ischemic heart disease, ergotamine, given in therapeutic doses, has in a few cases caused variant angina, myocardial infarction, and cardiac arrest (35,69,97). Even sudden death in a case without atherosclerosis has been described (9). Also, cerebral vasospasm may be caused by ergotamine (52). Anorectal ulcers,

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**TABLE 50-2 Side Effects of and Contraindications for Ergotamine[a]**

| | |
|---|---|
| **Side effects** | |
| Single dose | Nausea/vomiting, abdominal pain, acroparaesthesia, swollen fingers, leg cramps, diarrhea, tremor, syncope, globus feeling.[b] (In patients with ischemic heart disease: angina and myocardial infarction) |
| Chronic daily intake | Ergotamine-induced chronic headache,[c] ergotamine withdrawal headache,[c] intermittent claudication, acrocyanosis, constant nausea, acroparesthesia, anorectal ulcers, ischemic neuropathy, dorsal column lesion, fibrotic disorders involving the pleura, pericardium, and retroperitoneum, overt ergotism. |
| Contraindications | Cardiovascular disease, pregnancy, breast-feeding, liver and kidney disease, sepsis, concomitant use of triacetyloleandomycin, or erythromycin |
| Cautions | Concomitant use of methysergide, $\beta$-blockers and triptans (see text) |

[a]For references, see text.
[b]After parenteral use.
[c]See Chapter 115.

although usually reported after chronic use of ergotamine, also have been reported after a single rectal dose (64,65). A few cases of fibrotic disorders involving pleura, pericardium, heart valves, and retroperitoneum have been reported (51,96,108,111). Palsy of the peroneal nerve, probably caused by constriction of the vasa vasorum, also can be caused by ergotamine (83,90); and neurophysiologic investigations have demonstrated signs of peripheral neuropathy and dorsal column lesion after chronic use of ergotamine (43,78).

### *Contraindications*

As summarized in Table 50-2, ergotamine is contraindicated in cardiovascular disease, sepsis, liver and kidney disease, pregnancy (because of the prominent uterotonic action) (20,42,95) and breastfeeding. Ergotamine should not be used concomitantly with certain drugs, including triacetyloleandomycin and erythromycin, which decrease metabolism of ergotamine (28,70,89).

### *Precautions*

One half the normally effective dose of ergotamine should be tried in patients on methysergide because of the vasoconstrictor action of methysergide (35). Caution is advocated in patients on $\alpha$-adrenoceptor antagonists. Triptans have a minor peripheral vasoconstrictor effect (21,26,104, 122,124) and generally should not be used together with ergotamine.

## Dihydroergotamine

### *Dihydroergotamine Injections*

Dihydroergotamine can be injected in a dose of 1 mg subcutaneously or intramuscularly or in doses of 0.5 mg to 1 mg intravenously in the treatment of severe migraine attacks. Parenterally, 3 mg of dihydroergotamine is the recommended maximum daily dose (92,106,113,120). Concerning intravenous dihydroergotamine for status migrainosus, see Chapter 63.

### *Intranasal Dihydroergotamine*

The recommended initial dose for intranasal dihydroergotamine is 1 mg (one puff in each nostril). If needed, the patient can repeat the dose of 1 mg after 15 minutes. We recommend, however, that the patient be instructed to titrate the effective dose of intranasal dihydroergotamine between 1 and 2 mg, which then should be administered as a single dose.

### *Side Effects*

With parenteral dihydroergotamine, the most common side effect is nausea, and concomitant administration of an antiemetic is recommended for intravenous use (94). Leg pain, paraesthesia, and a few cases of angina and ergotism have been reported (94). With intranasal dihydroergotamine, the most common side effects are transient nasal congestion, nausea, and throat discomfort (76).

### *Contraindications*

Contraindications include known hypersensitivity to ergot alkaloids, pregnancy, breastfeeding, coronary arterial disease, and inadequately controlled hypertension.

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