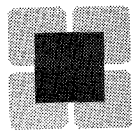

The use of benzodiazepines in epilepsy and febrile seizures

GREGORY L. HOLMES, MD

THE BENZODIAZEPINES are widely used in the treatment of epilepsy. Diazepam and lorazepam are primarily used in the treatment of status epilepticus, while clonazepam, nitrazepam, clobazam, and clorazepate are efficacious as chronic, oral antiepileptic agents. In addition, diazepam has been demonstrated to be of value in reducing recurrences of febrile seizures. Unfortunately, side effects and the development of drug tolerance have hindered greater use of this group of medications.

In the present review, the clinical efficacy of the benzodiazepines in the treatment of epilepsy will be discussed. The major emphasis will be on clonazepam, the drug most widely used as an oral antiepileptic agent in the United States.

CLONAZEPAM

Clonazepam (Klonopin—5-(2-chlorophenol)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one) was approved for use as an antiepileptic drug by the United States Food and Drug Administration in 1975.[1] Clonazepam is an antiepileptic drug with a wide clinical spectrum of efficacy,[1–18] even though animal studies had suggested that it would be of particular value in generalized seizure disorders. Microinjection of clonazepam bilaterally into the substantia nigra pars reticulata produces a 75% elevation of the generalized seizure threshold in the kindling rat model, suggesting that the substantia nigra is an area where the drug may have an effect.[19] Clonazepam is effective in reducing absence, generalized tonic-clonic, and myoclonic seizures. In addition, it is quite effective in suppressing the generalized discharges seen in absence and in photic-induced seizures and also helpful in the partial seizure disorders. While focal epileptiform discharges are not abolished by clonazepam, it does appear to prevent the propagation of seizures.[20]

From The Children's Hospital, Harvard Medical School, Boston, Mass.

Pharmacokinetics

It is beyond the scope of this article to review in detail the pharmacokinetics of clonazepam. The interested reader is referred to the article by David J. Greenblatt and Lawrence W. Miller in this issue ("Mechanism of the anticonvulsant action of benzodiazepines") as well as to Greenblatt et al, 1987.[21]

Clonazepam is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentration between 1 to 4 hours, but may occur as late as 8 hours.[1,22] The drug is 47% to 80% protein bound.[2] Its major hepatic metabolic pathway is reduction of the nitro group to form a 7-amino derivative, a metabolite with minimal antiepileptic properties.[4] Only a small percentage of clonazepam is excreted freely in the urine.[22] The half-life of the drug, in both children and adults, ranges between 20 and 46 hours.[1,3,4,23]

Clonazepam serum levels are of limited value in the management of children with seizure disorders. While most patients whose seizures are controlled have serum concentrations ranging between 20 and 80 ng/ml (0.02 to 0.08 ug/ml), a consistent relationship between serum level and either seizure control or toxicity has not been demonstrated.[1–3,24]

Clonazepam is available in 0.5-mg, 1-mg, and 2-mg scored tablets. The initial dose for infants and children (up to 10 years of age or 30 kg of body weight) is 0.01

to 0.03 mg/kg/day, usually administered in 2 to 4 daily doses. The daily dosage should be increased by 0.25 to 0.50 mg every 3 to 7 days until a maintenance dose of 0.1 to 0.2 mg/kg/day is achieved. In teenagers and adults, the drug can be started at 1.0 to 1.5 mg/day in 2 to 4 divided doses and increased in increments of 0.5 mg every 3 to 7 days until seizures are controlled. Although the maximum recommended daily dosage in adults is 20 mg, few patients can tolerate a dose this high. Patients generally tolerate the higher doses of clonazepam better when they are on monotherapy rather than on polytherapy.

Clonazepam should never be stopped suddenly, since abrupt cessation may precipitate status epilepticus.[4,25] Ideally, the drug should be tapered off over several months.

Adding clonazepam to other antiepileptic drugs does not usually result in significant changes in the serum levels of the ongoing drug regimen.[26,27] The drug interactions that have been observed appear to be variable. For example, serum phenytoin levels after the administration of clonazepam have been noted to either rise or fall.[1] The addition of phenytoin or of phenobarbital, on the other hand, may lower the steady-state serum concentration of clonazepam.[1,2,28]

Clinical indications

As already noted, clonazepam has a broad spectrum of action and has demonstrated at least some efficacy in all seizure types. Unfortunately, determining accurate figures on efficacy from published series is difficult. The majority of studies used clonazepam as an add-on agent to the ongoing regimen of patients with intractable seizures and methodological differences occurred in both the length of the follow-up and in the outcome analysis. Nevertheless, by combining the series, some indication of efficacy can be obtained.

The reader should be cautioned that, in the following tabulations of efficacy, not all published series were reviewed. Since the various authors classified outcome results differently, their outcome figures are only estimations. Unfortunately, many authors failed to reveal the number of patients that were seizure-free following the addition of clonazepam. In addition, some authors did not specify when clonazepam was used as monotherapy or add-on therapy. Other than for absence seizures, clonazepam has generally been used as add-on therapy. Although as a general rule children appear to fare better than adults on clonazepam, in the following figures results from both children and adults are combined.

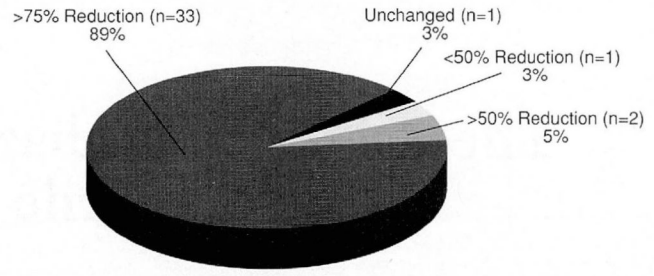

FIGURE 1. Efficacy of clonazepam used as *mono-*treatment in *absence seizures*: combined results from three studies totaling 37 patients.[23,25,29]

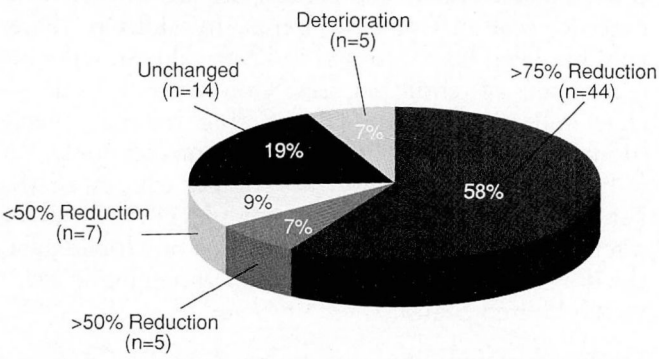

FIGURE 2. Efficacy of clonazepam used as *add-on* treatment to various regimens in *absence seizures*: combined results from nine studies (N = 75).[25,30–37]

Absence seizures

In three studies of absence seizures involving 37 patients, clonazepam was used as monotherapy.[23,25,29] As can be seen in *Figure 1*, clonazepam is highly efficacious in patients with absence seizures. In 9 studies in which clonazepam was used as add-on therapy, clonazepam reduced seizure frequency by greater than 75% in 59% of 75 patients (*Figure 2*).[25,30–37]

Generalized tonic-clonic seizures

The results from eight series in which clonazepam was primarily used as add-on therapy in generalized tonic-clonic seizures are given in *Figure 3*. While 59% of 109 patients had over a 50% reduction in

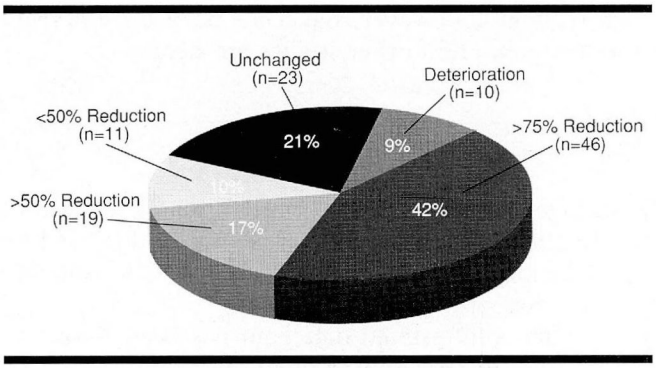

FIGURE 3. Efficacy of clonazepam, used primarily as treatment in *generalized tonic-clonic seizures*: combined results from eight studies (N = 109).[25,28,31,32,35–38]

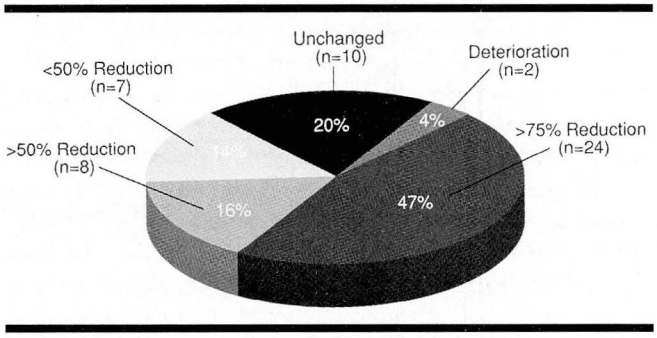

FIGURE 4. Efficacy of clonazepam used primarily as add-on treatment in *myoclonic seizures*: combined results from eight studies (N = 51).[25,28,31–34,37,39]

seizure frequency, deterioration was noted in 9%.[25,28,31,32,35–38]

Myoclonic seizures

In eight studies of myoclonic seizures, 47% of 51 patients had a 75% reduction in seizure frequency with clonazepam used as add-on therapy (*Figure 4*).[25,28,31,34,37,39]

Partial seizures

Outcome figures for treatment of partial simple (N = 92)[25,32,34–37,40] and for partial complex seizures (N = 183)[25,30,31,34–36,38,40,41] with clonazepam used primarily as add-on therapy are given in *Figures 5* and 6, respectively. As can be seen, outcome results were not as favorable as those for generalized seizures.

In addition to the above noted seizures, clonazepam—again used primarily as an add-on drug—has also been found to be useful in the treatment of other seizure types including atonic, tonic, and infantile spasms.[1]

Side effects

A major limiting factor in the use of clonazepam is its high incidence of toxicity. The three most common side effects are drowsiness, ataxia, and behavioral and personality changes.[2–4,6] In seven studies reviewed by Dreifuss and Sato,[6] side effects were observed in 16% to 90% of patients using clonazepam, leading to drug discontinuation in 10% to 35% of patients. In a double-blind study comparing clonazepam with ethosuximide in children with absence seizures, side effects occurred in 92% of the children treated with clonazepam and the drug was discontinued in 27%.[6] In some patients, both adults and children, the sedative side effects of clonazepam gradually resolve.

The behavioral disturbances in children can be quite marked and include hyperactivity, irritability, moodiness, and aggressive behavior.[4] While lowering the dose may reduce some of these disturbances, in many children the adverse effects of clonazepam persist. Additional central nervous system (CNS) depression may occur when clonazepam is given with any other drug that has similar action.

Clonazepam may bring about increased salivation and bronchial hypersecretion, leading to respiratory distress and pneumonia in some pediatric patients.[4] Carson and Gilden[42] recommend that amphetamines or methylphenidate not be administered with clonazepam because of the risk of producing CNS depression. Ethanol and barbiturates also potentiate the sedative actions of clonazepam. Increased seizure frequency has been reported in some patients.[2,6,25] Other rare side effects include leukopenia, thrombocytopenia, rashes, hair loss, and skin pigmentation.[6] Nonetheless, clonazepam does compare favorably to other antiepileptic drugs in regard to serious side effects.

The combination of clonazepam and valproic acid has been reported to precipitate absence seizures, including the possibility of absence status.[43] Unfortunately, the fear of absence status has limited this therapeutic combination. It now appears that the risk of absence status has been overestimated and that, in the vast majority of patients, clonazepam and valproic acid can be safely used together.

Tolerance is a well-known phenomenon in humans and has also been demonstrated in animals. Tolerance to clonazepam developed in dogs after 1 to 2 weeks of treatment,[44] in mice over a 72–hour period,[45] and in kindled rats after 5 days.[46]

Approximately a third of patients who initially respond to clonazepam develop a tolerance and experience recurrence of seizures, usually within 1 to 6

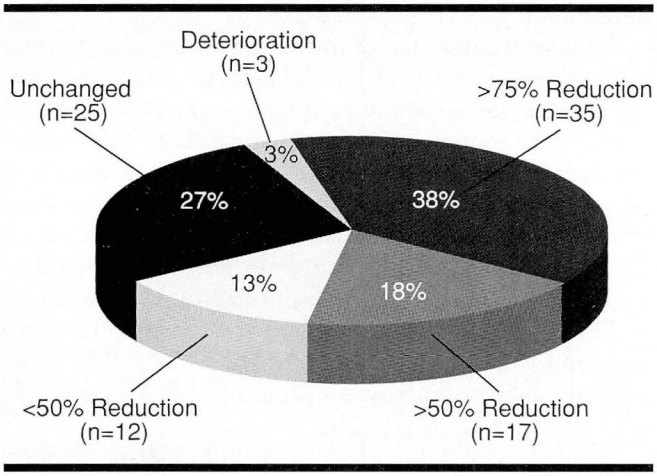

FIGURE 5. Efficacy of clonazepam used primarily as add-on treatment in *partial simple seizures*: combined results from seven studies (N = 92).[25,32,34–37,40]

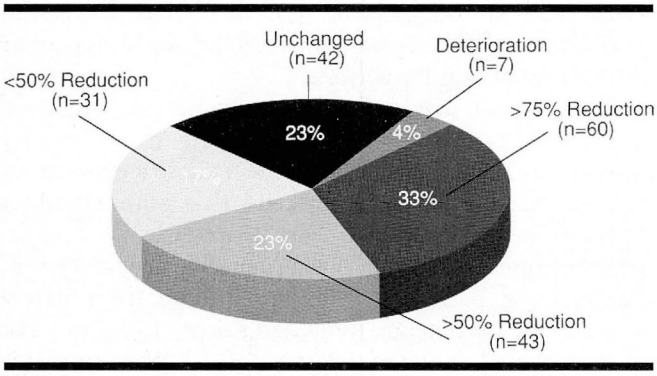

FIGURE 6. Efficacy of clonazepam, used primarily as treatment in *partial complex seizures*: combined results from nine studies (N = 183).[25,30,31,34–36,38,40,41]

months from starting the drug.[4,6,28] Some patients may respond to an increased dose, while others will no longer respond to clonazepam at any dosage. The tolerance may surface within weeks of starting the medication, with the following typical scenario: A child is started on clonazepam for absence seizures. Initially, there is a marked improvement. However, after several weeks or months, the child starts having "break-through" seizures. Initially these seizures respond to increasing doses of clonazepam; but then they begin to occur even when the dosage is increased to clinical toxicity.

Because of the development of tolerance to its antiepileptic effects, some authors have recommended alternate-day clonazepam therapy.[47] The advantages of such regimens, however, have not been convincingly demonstrated and further studies are necessary.

DIAZEPAM

Intravenous diazepam (Valium) has a major role in the treatment of status epilepticus and is discussed by Ilo E. Leppik in this issue ("Status epilepticus: the role of benzodiazepines").

Rectally administered diazepam has been shown to be effective in reducing the recurrence rate of febrile convulsions.[48–50] In a prospective study, children (N = 195) were randomized to either a group administered a 5-mg diazepam suppository every 8 hours when the rectal temperature was above 38.5°C or to continuous phenobarbital at a dose of 3.5 ± 1 mg/kg/day.[48] Results indicated that children receiving diazepam had a similar rate of recurrence (11%) as those receiving phenobarbital (9%). The authors concluded that long-term treatment with phenobarbital offered no advantages over intermittent diazepam therapy. In a prospective study conducted by Knudsen,[49] 289 children admitted consecutively to the hospital with their first febrile seizure were randomized to either a group receiving rectal diazepam whenever the temperature was 38.5°C or higher, or to a control group receiving the diazepam only for the acute treatment of seizures in progress. The recurrence rate of febrile children receiving rectal diazepam was 12% compared to 39% in the control group.

Thorn[50] also found that intermittent therapy with rectal diazepam was effective for the treatment of febrile seizures. The recurrence rate in the control group (N = 153), which received no therapy, was 40.5% compared to 12.1% in the children treated intermittently with diazepam (N = 207). In 68% of the children experiencing a recurrence in the diazepam group, the medicine had not been given either because the fever was not noticed or the parents did not feel it was necessary at the time. Side effects were not common, occurring in only 10% of the children treated. The primary side effect was slight sedation, usually lasting a few hours but occasionally persisting for up to 24 hours. Rectal diazepam has also been used to treat serial seizures and to prevent or abort status epilepticus.[51–53]

Oral diazepam has not been widely used as an antiepileptic. As noted by Schmidt,[54] prolonged exposure to oral diazepam is fraught with risk for overdose, dependence, and withdrawal symptoms. Oral diazepam is therefore not recommended for the long-term treat-

ment of chronic epilepsy. However, like rectal diazepam, intermittent oral treatment may be useful in preventing the recurrence of febrile seizures or in aborting prolonged seizures. Milligan and colleagues[52] found that a single 20-mg dose of oral diazepam significantly reduced the incidence of serial seizures.

CLORAZEPATE DIPOTASSIUM

Clorazepate dipotassium (Tranxene) was initially introduced in the mid-1960s as an antianxiety agent and is now also used as an antiepileptic agent.[55] Clorazepate is a pro-drug which is decarboxylated by acid in the stomach to N-desmethyldiazepam (DMD), an active metabolite. It is useful in selected patients with generalized or partial seizures.

N-desmethyldiazepam is well absorbed after oral administration, with maximum levels achieved within 0.5 to 2.0 hours. The drug has a long half-life, approximately 40 hours, but because of its rapid absorption the daily dosage should be divided into at least two daily doses to prevent clinical toxicity during absorption peaks. The starting dose in children is 0.3 mg/kg/day, with subsequent doses ranging from 0.4 to 3.0 mg/kg/day. In adults, the average dose is usually lower, ranging from 0.5 to 1.0 mg/kg/day. Serum clorazepate levels between 0.5 and 2.0 ug/ml are associated with the best responses in both adults and children, but the therapeutic range has not been firmly established.

Clinical studies have primarily used clorazepate as an add-on therapy, making the interpretations of these trials difficult. As noted by Wilensky and Friel,[55] for every study demonstrating a positive effect, an example of a study which does not show any effect can be cited. There is some evidence that clorazepate may be more effective in children than in adults.[55]

Berchou et al[56] added clorazepate to the drug treatment of 61 pediatric and adult patients with a variety of seizure types and reported that 23% improved. Graf and Rothman,[57] on the other hand, reported that 72% of children with refractory seizures had improved seizure control with clorazepate (N = 13). Booker[58] used clorazepate in 59 pediatric and adult patients with a variety of seizure types and noted that those with generalized seizures had better responses than patients with partial seizures. Of 14 patients with partial complex seizures, none improved. Conversely, Guggenheim et al,[59] in a study of the use of clorazepate in 131 primarily pediatric patients, found clorazepate to be more efficacious in patients with partial seizures. Mimaki et al[60] also reported improvement in seizure frequency in 74% (20/27) of children with generalized seizures with clorazepate therapy. Dasheiff et al,[61] on the other hand, found that 29% of 31 adult subjects with intractable partial complex seizures responded to clorazepate but that these results were not persistent.

In the only double-blind randomized cross-over study using clorazepate, Wilensky and colleagues[62] compared the antiepileptic effect of clorazepate-plus-phenytoin with phenobarbital-plus-phenytoin in 42 adult patients with partial seizures. While 30 of 42 (71%) subjects preferred the combination of clorazepate-plus-phenytoin to phenobarbital-plus-phenytoin, there was no statistically significant difference in seizure control between the two regimens. Patients on the phenobarbital-phenytoin combination had significantly more toxicity than those on the clorazepate-phenytoin regimen.

Based on a review of the literature, Wilensky and Friel[55] concluded that patients with partial seizures, particularly those with psychic symptomatology, as well as those with very frequent seizures (>20/month), respond best to clorazepate. *Figure 7* demonstrates, in graphic form, the efficacy of clorazepate in various types of seizure.

The primary adverse reaction of clorazepate is lethargy. However, lethargy usually improves with time, even when the dosage does not change. Occasionally, adverse behavioral changes occur, especially in children. Idiosyncratic and allergic reactions are rare. Although tolerance to clorazepate may develop, this problem is not as prominent as with the other benzodiazepines.

BENZODIAZEPINES NOT YET AVAILABLE IN USA

Two other benzodiazepines have been demonstrated to be of value in the treatment of epilepsy—nitrazepam and clobazam. Since neither is currently marketed in the United States, they will only be briefly discussed. The interested reader is referred to Baruzzi et al[63] and Shorvon.[64]

Nitrazepam

Nitrazepam is a widely used and safe hypnotic drug.[63] It is effective in the treatment of various types of epilepsy, infantile spasms, myoclonic seizures, and Lennox-Gastaut syndrome. Unfortunately, initial success may be followed by the development of drug tolerance.

The peak concentrations of nitrazepam occur 1 to 4

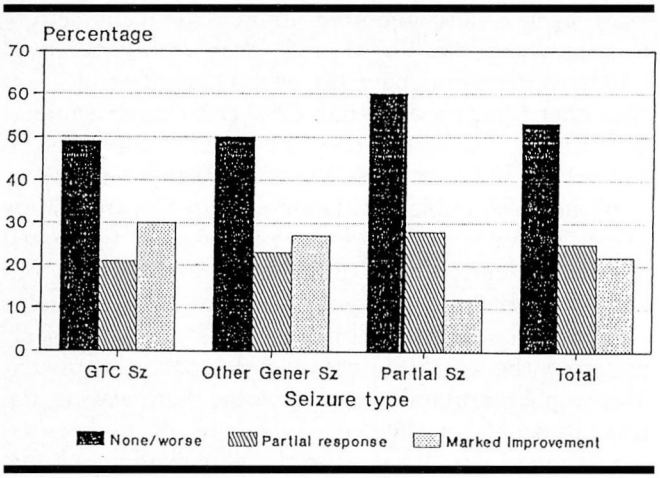

FIGURE 7. Efficacy of clorazepate dipotassium treatment in generalized tonic-clonic (GTC) seizures, in other generalized seizures, in partial seizures, or in all three types of seizures (N = 42). Modified from Wilensky and Friel,[55] with permission.

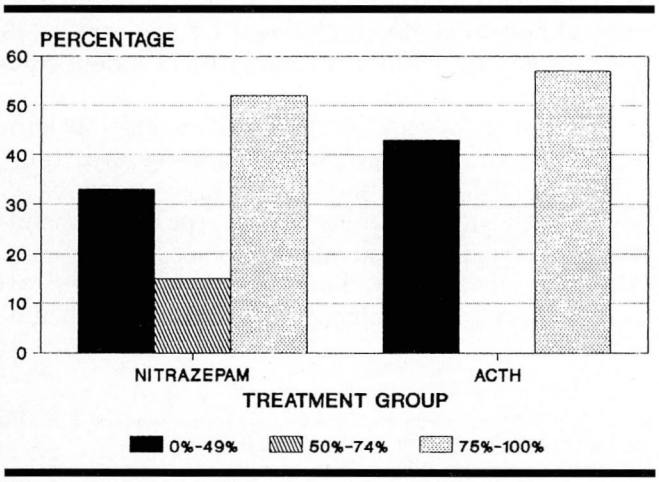

FIGURE 8. Comparison of nitrazepam (N = 27) and adrenocorticotropin (ACTH) (N = 21) in the treatment of new onset infantile spasms. From Dreifuss et al,[66] with permission.

hours after administration and its half-life ranges from 24 to 40 hours. The effective dose ranges from 0.25 to 3.0 mg/kg/day. The average daily dose is higher in children (around 1.0 mg/kg) than in adults (around 0.5 mg/kg). The therapeutic plasma levels of nitrazepam are quite variable and, consequently, of little relevance in clinical practice.[65]

Like clonazepam, nitrazepam has been found to be of value in a variety of seizure disorders.[5] Nitrazepam appears to be particularly valuable in the treatment of infantile spasms. Baruzzi et al[63] reviewed 137 cases of West syndrome and 93 of these (68%) responded satisfactorily to nitrazepam. A 4-week randomized, controlled study, by Dreifuss et al,[66] comparing the efficacy and safety of nitrazepam and of adrenocorticotropin (ACTH) demonstrated that 52% of patients in the nitrazepam group (N = 27) and 57% in the ACTH group (N = 21) achieved excellent control (*Figure* 8). The number of side effects was similar in both groups but those in the ACTH group were more severe.[66] Nitrazepam is also useful in the Lennox-Gastaut syndrome.[63]

Intermittent oral nitrazepam has also been used for the prophylactic treatment of febrile convulsions.[67] The rate of recurrence was 19.3% (N = 6), after a follow-up of 16 months, compared to 45.8% untreated children who had a high recurrence risk but whose parents refused the medication.

The side effects of nitrazepam include drowsiness, ataxia, impairment of psychomotor skills, hypotonia, increased salivary and bronchial secretion, and swallowing abnormalities.

Clobazam

Clobazam is a 1,5-benzodiazepine with marked antiepileptic action.[64] The metabolite N-desmethylclobazam contributes to the antiepileptic action. Time to peak concentration in healthy controls varies from 1 to 4 hours. The half-life of N-desmethylclobazam is much longer (mean 42 hours; range 36 to 46 hours) than that of clobazam (mean 18 hours; range 36 to 46 hours) and it also reaches higher plasma levels than those of clobazam. Since no therapeutic range has been established for the plasma levels of either clobazam or N-desmethylclobazam, there is no clinical rationale for routine measurements of these concentrations.

Clobazam is a broad-spectrum antiepileptic. It is thus beneficial in partial and in generalized seizures in all age groups[64] as well as in Lennox-Gastaut syndrome.[68] A major limitation to its long-term use, however, is the development of tolerance. Clobazam appears to be safe and its side effects, as with the other benzodiazepines, consist primarily of sedation, dizziness, and fatigue. Fortunately, these side effects are usually mild and transient.

GREGORY L. HOLMES, MD
Clinical Neurophysiology Laboratory
Hunnewell 2
The Children's Hospital
300 Longwood Avenue
Boston, Massachusetts 02115

REFERENCES

1. Sato S. Benzodiazepines: clonazepam. [In] Antiepileptic Drugs. Third Edition. Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE, eds. New York, Raven Press, 1989, pp. 765–784.
2. Browne TR. Benzodiazepines. [In] Browne TR, Feldman RG, eds. Epilepsy: Diagnosis and Management. Boston, Little Brown and Co., 1983, pp. 235–245.
3. Browne TR. Clonazepam. N Engl J Med 1978; **299:**812–816.
4. Browne TR. Clonazepam. A review of a new anticonvulsant drug. Arch Neurol 176; **33:**326–332.
5. Browne TR, Penry JK. Benzodiazepines in the treatment of epilepsy. Epilepsia 1973; **14:**277–310.
6. Dreifuss FE, Sato S. Benzodiazepines. [In] Antiepileptic Drugs. Second Edition. Woodbury DM, Penry JK, Pippenger CE, eds. New York, Raven Press. 1982, pp. 737–752.
7. Farrell K. Benzodiazepines in the treatment of children with epilepsy. Epilepsia 1986; **27(suppl 1):**S45–S51.
8. Bladin PF. The use of clonazepam as an anticonvulsant: clinical evaluation. Med J Aust 1973; **1:**683–688.
9. Hooshmand H. Intractable seizures; treatment with a new benzodiazepine anticonvulsant. Arch Neurol 1972; **27:**205–208.
10. Ishikawa A, Sakuma N, Nagashima T, et al. Clonazepam monotherapy for epilepsy in childhood. Brain Dev 1985; **7:**610–613.
11. Lambie DG, Johnson RH. Serum concentration of clonazepam and the therapeutic effect of the drug. Acta Neurol Scand 1983; **67:**97–102.
12. Lander CM, Donnan GA, Bladin PF, Vajda FJE. Some aspects of the clinical use of clonazepam in refractory epilepsy. Clin Exp Neurol 1979; **16:**325–332.
13. Mikkelsen B, Berggreen P, Joensen P, et al. Clonazepam (Rivotril) and carbamazepine (Tegretol) in psychomotor epilepsy: a randomized multicenter trial. Epilepsia 1981; **22:**415–420.
14. Mikkelsen B, Birket-Smith E. A clinical study of the benzodiazepine Ro 5-4023 (Clonazepam) in the treatment of epilepsy. Acta Neurol Scand 1973; **49(suppl 53):**91–96.
15. Nogen AG. The utility of clonazepam in epilepsy of various types: observations with 22 childhood cases. Clin Pediatr 1978; **17:**71–74.
16. Seki T, Kawahara Y, Yamawaki H, et al. The effect of clonazepam in children with typical absence. Brain Dev 1979; **3:**218–227.
17. Shakir RA, Nanda RN, Lambie DG, Johnson RH. Comparative trial of valproate sodium and clonazepam in chronic epilepsy. Arch Neurol 1979; **36:**301–304.
18. Naito H, Wachi M, Nishida M. Clinical effects and plasma concentrations of long-term clonazepam monotherapy in previously untreated epileptics. Acta Neurol Scand 1987; **76:**58–63.
19. King PH, Shin C, Mansbach HH, et al. Microinjection of a benzodiazepine into substantia nigra elevates kindled seizure threshold. Brain Res 1987; **423:**261–268.
20. Lockard JS, Levy RH, Congdon WC, et al. Clonazepam in a focal-motor monkey model: efficacy, tolerance, toxicity, withdrawal, and management. Epilepsia 1979; **20:**683–695.
21. Greenblatt DJ, Miller LG, Shader R. Clonazepam pharmacokinetics, brain uptake, and receptor interactions. J Clin Psychiatry 1987; **48(suppl 10):**4–11.
22. Kaplan SA, Alexander K, Jack ML, et al. Pharmacokinetic profiles of clonazepam in dog and humans and of flunitrazepam in dog. J Pharm Sci 1974; **63:**527–532.
23. Dreifuss FE, Penry JK, Rose SW, et al. Serum clonazepam concentrations in children with absence seizures. Neurology 1975; **25:**255–258.
24. Sjo O, Hvidber EF, Naestoft J, Lund M. Pharmacokinetics and side effects of clonazepam and its 7-amino-metabolite in man. Eur J Clin Pharmacol 1975; **8:**249–254.
25. Lund M, Trolle E. Clonazepam in the treatment of epilepsy. Acta Neurol Scand 1973; **49(suppl 53):**82–90.
26. Johannessen SI, Strandjord RE, Munthe-Kaas AW. Lack of effect of clonazepam on serum levels of diphenylhydantoin, phenobarbital and carbamazepine. Acta Neurol Scandinav 1977; **55:**506–512.
27. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. Acta Neurol Scand 1973; **49:**543–546.
28. Nanda RN, Johnson RH, Keogh HJ, et al. Treatment of epilepsy with clonazepam and its effect on other anticonvulsants. J Neurol Neurosurg Psychiatry 1977; **40:**538–543.
29. Chandra B. Clonazepam in the treatment of petit mal. Asian J Med 1973; **9:**433–435.
30. Birket-Smith E, Mikkelsen B. Preliminary observations on the effect of a new benzodiazepine (Ro 5-4023) in epilepsy. Acta Neurol Scand 1972; **48:**385–389.
31. Huang CY, McLeod JG, Sampson D, Hensley WJ. Clonazepam in the treatment of epilepsy. Med J Aust 1974; **2:**5–8.
32. Barnett AM. Treatment of epilepsy with clonazepam (Ro 5-4023). S Afr Med J 1973; **47:**1683–1686.
33. Mikkelsen B, Birket-Smith E, Brandt S, et al. Clonazepam in the treatment of epilepsy: a controlled clinical trial in simple absences, bilateral massive epileptic myoclonus, and atonic seizures. Arch Neurol 1976; **33:**322–325.
34. Lance JW, Anthony M. Sodium valproate and clonazepam in the treatment of intractable epilepsy. Arch Neurol 1977; **34:**14–17.
35. Fazio C, Manfredi M, Piccinelli A. Treatment of epileptic seizures with clonazepam: a reappraisal. Arch Neurol 1975; **32:**304–307.
36. Lehtovaara R. A clinical trial with clonazepam (Ro 5-4023). Acta Neurol Scand 1973; **49(suppl 53):**77–81.
37. Muntha-Kaas AW, Strandjord RE. Clonazepam in the treatment of epileptic seizures. Acta Neurol Scand 1973; **49(suppl 53):**97–102.
38. Bang F, Birket-Smith E, Mikkelsen B. Clonazepam in the treatment of epilepsy: a clinical long-term follow-up study. Epilepsia 1972; **17:**321–324.
39. Roussounis SH, de Rudolf J. Clonazepam in the treatment of children with intractable seizures. Dev Med Child Neurol 1977; **19:**326–334.
40. Scollo-Lavizzari G, Pralle W, DeLa Cruz N. Clinical experience with clonazepam (Rivotril) in the treatment of epilepsy in adults. Eur Neurol 1974; **11:**340–344.
41. Birket-Smith E, Lund M, Mikkelsen B, et al. A controlled trial on Ro 5-4023 (Clonazepam) in the treatment of psychomotor epilepsy. Acta Neurol Scand 1973; **49(suppl 53):**18–25.
42. Carson J Jr, Gilden C. Treatment of minor motor seizures with clonazepam. Dev Med Child Neurol 1975; **17:**306–310.
43. Jeavons RM, Clark JE, Maheshwari MC. Treatment of generalized epilepsies of childhood and adolescence with sodium valproate (Epilim). Dev Med Child Neurol 1977; **19:**9–25.
44. Sherkl R, Scheuler W, Frey HH. Anticonvulsant effect of clonazepam in the dog: development of tolerance and physical dependence. Arch Int Pharmacodyn Ther 1985; **278:**249–260.
45. Gent JP, Feely MP, Haigh JR. Differences between the tolerance characteristics of two anticonvulsant benzodiazepines. Life Sci 1985; **37:**849–856.
46. Vajda FJ, Lewis SJ, Harris QL, et al. Tolerance to the anticonvulsant effects of clonazepam and clobazam in the amygdaloid kindled rat. Clin Exp Neurol 1987; **23:**155–164.
47. Sher PK. Alternate-day clonazepam treatment of intractable seizures. Arch Neurol 1985; **42:**787–788.
48. Knudsen FU, Vestermark S. Prophylactic diazepam or phenobarbitone in febrile convulsions: a prospective, controlled study. Arch Dis Child 1978; **53:**660–663.
49. Knudsen FU. Effective short-term diazepam prophylaxis in febrile convulsions. J Pediatr 1985; **106:**487–490.
50. Thorn I. Prevention of recurrent febrile seizures: intermittent prophylaxis with diazepam compared with continuous treatment with phenobarbital. [In] Nelson KB, Ellenberg JH, eds. Febrile Seizures. New York, Raven Press, 1981, pp. 119–126.
51. Hoppu K, Santavuori P. Diazepam rectal solution for home treatment

of acute seizures in children. Acta Paediatr Scand 1981; **70**:369–372.
52. Milligan N, Dhillon S, Griffiths A, et al. A clinical trial of single dose rectal and oral administration of diazepam for the prevention of serial seizures in adult epileptic patients. J Neurol Neurosurg Psychiatry 1984; **47**:235–240.
53. Ventura A, Basso T, Bortolan G, et al. Home treatment of seizures as a strategy for the long-term management of febrile convulsions in children. Helv Paediatr Acta 1982; **37**:581–587.
54. Schmidt D. Benzodiazepines: diazepam. [In] Antiepileptic Drugs. Third edition. Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE, eds. New York, Raven Press, 1989, pp. 735–764.
55. Wilensky AJ, Friel PN. Benzodiazepines: clonazepam. [In] Antiepileptic Drugs. Third Edition. Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE, eds. New York, Raven Press, 1989, pp. 805–820.
56. Berchou RC, Rodin EA, Russell ME. Clorazepate therapy for refractory seizures. Neurology 1981; **31**:1483–1485.
57. Graf WD, Rothman SJ. Clorazepate therapy in children with refractory seizures. Epilepsia 1987; **28**:606.
58. Booker HE. Clorazepate dipotassium in the treatment of intractable epilepsy. JAMA 1981; **229**:552–555.
59. Guggenheim MA, Donaldson J, Hotvedt C. Clinical evaluation of clorazepate. Ann Neurol 1987; **22**:412–413.
60. Mimaki T, Tagawa T, Ono J, et al. Antiepileptic effect and serum levels of clorazepate on children with refractory seizures. Brain Dev 1984; **6**:539–544.
61. Dasheiff RM, McNamara D, Dickinson L. Efficacy of second line antiepileptic drugs in the treatment of patients with medically refractive complex partial seizures. Epilepsia 1986; **27**:124–127.
62. Wilensky AJ, Ojemann LM, Temkin NR, et al. Clorazepate and phenobarbital as antiepileptic drugs. A double-blind study. Neurology 1981; **31**:1271–1276.
63. Baruzzi A, Michelucci R, Tassinari CA. Benzodiazepine: nitrazepam. [In] Antiepileptic Drugs. Third Edition. Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE, eds. New York, Raven Press, 1989, pp. 785–804.
64. Shorvon SD. Benzodiazepines: clobazam. [In] Antiepileptic Drugs. Third Edition. Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE, eds. New York, Raven Press, 1989, pp. 821–840.
65. Jan JE, Riegl JA. Nitrazepam in the treatment of convulsive disorders. Clin Res 1970; **18**:220.
66. Dreifuss F, Farwell J, Holmes G, et al. Infantile spasms: comparative trial of nitrazepam and corticotropin. Arch Neurol 1986; **43**:1107–1110.
67. Vanasse M, Masson P, Geoffroy G, et al. Intermittent treatment of febrile seizures with nitrazepam. Can J Neurol Sci 1984; **11**:377–379.
68. Pechadre JC, Beudin P, Devoize JL, Gilbert J. Utilisation du clobazam comme anti-épileptique dans le syndrome de Lennox et Gastaut. L'Encéphale 1981; **7**:181–190.