Clarithromycin-Carbamazepine Interaction In A Clinical Setting

Nancy K. O'Connor, MD, and John Fris, RPh

Background: **Clarithromycin was used to treat lower respiratory tract infection in several developmentally disabled men who were also taking carbamazepine for seizure disorder.**

Methods: **We studied retrospectively the use of clarithromycin in 5 patients taking carbamazepine. Because a drug interaction was suspected, the carbamazepine dosage was decreased during treatment, and serum levels were measured 3 to 5 days after change in therapy. In this study, we compared these findings with the base-line pretreatment and posttreatment dosage and serum levels of carbamazepine.**

Results: **Despite decreasing the dosage of carbamazepine by 30 to 40 percent, the serum levels of this drug increased in all of our patients while taking clarithromycin, including 3 patients who developed toxic serum levels of carbamazepine.**

Conclusion: **There is a serious drug interaction between carbamazepine and clarithromycin. If possible, we believe that using clarithromycin should be avoided in patients taking carbamazepine. If clinical judgment suggests clarithromycin should be used, however, we suggest decreasing the dosage of carbamazepine by 30 to 50 percent, monitoring the serum drug levels closely, and warning the patient about the signs and symptoms of carbamazepine toxicity. (J Am Board Fam Pract 1994; 7:489-92.)**

In March 1993 our community experienced an epidemic of lower respiratory tract infections with signs and symptoms suggestive of *Mycoplasma pneumoniae*, including low-grade fever, malaise, and dry nonproductive cough associated with a low or normal white cell count and a positive cold agglutinin test in some of the patients during the 2nd week of symptoms.

Clarithromycin was chosen for some patients to treat the infection, because the drug has a low incidence of drug-associated gastrointestinal side effects and the twice-a-day dosage makes it easy to administer.[1]

Among those given medication for the infection were individuals who resided in a long-term training institution for the developmentally challenged (Intermediate Care Facility for Mental Retardation). Several of those prescribed clarithromycin also were being treated with carbamazepine (Tegretol) for epilepsy. In the institution involved, routine anticonvulsant serum levels are closely monitored when dehydration, poor compliance, or drug interactions are suspected. Because of biochemical similarities between erythromycin and clarithromycin, and because erythromycin is known to interfere with carbamazepine metabolism, the dosage of carbamazepine was reduced in these patients, and serum drug level measurements of carbamazepine were performed.

The following five cases summarize our experience of serious interaction between carbamazepine and clarithromycin.

Methods

This report is a retrospective study in which patient charts were examined with the aim of clarifying the extent of clarithromycin-carbamazepine interaction.

All charts of patients receiving carbamazepine for epilepsy who had received clarithromycin for lower respiratory tract infection were examined. One patient was eliminated from the study because of a concomitant illness (hepatic dysfunction) that could affect drug metabolism. The remaining five charts were examined to determine the dosage of carbamazepine and the serum drug levels of carbamazepine prior to treatment with clarithromycin, during the course of treatment, and following the discontinuance of the clarithromycin.

Subjects

The 5 individuals whose charts were chosen were men aged between 25 and 40 years who had developmental disabilities, cerebral palsy, and epilepsy. All were severely physically disabled, re-

quired a wheelchair for mobility, had limited verbal skills, and required assistance in many activities of daily living. Except for the disabilities and epilepsy, however, all 5 were in good health: they had good nutritional status, with no evidence of anemia, and had normal renal and hepatic functions when measured at a routine biannual screening earlier in the year.

Carbamazepine is a short-acting anticonvulsant medication. In the following cases, total daily dosages are noted, but this medication is usually divided into three daily doses.

Our findings are summarized in Table 1.

Patient 1 received no medications except 1200 mg of carbamazepine daily for seizures. Three weeks before his illness, a routine measurement of his serum level for carbamazepine was 10.5 μg/mL (normal being 4.0 to 12.0 μg/mL). When he was prescribed clarithromycin, his carbamazepine dosage was decreased to 800 mg daily; 3 days later, his carbamazepine level was 14.1 μg/mL, which is considered toxic; therefore, the daily dosage of carbamazepine was decreased to 600 mg. After the antibiotic course was finished, his carbamazepine dosage was increased to the pretreatment level of 1200 mg daily, and the drug level measured 5 days later was 8.1 μg/mL.

Patient 2 was prescribed 300 mg of carbamazepine daily. Three months before his acute illness, his serum drug level measured 5.3 μg/mL. When he began taking clarithromycin, his carbamazepine dosage was decreased to 200 mg daily; 3 days later, his serum drug level was 6.4 μg/mL. Two weeks after clarithromycin was discontinued and his original carbamazepine dosage restarted, his drug serum level was 4.9 μg/mL.

Patient 3, in addition to his developmental disabilities and epilepsy, had G6PD deficiency without any serious anemia. At the time of his illness,

his medication was being changed from phenytoin (Dilantin) to carbamazepine; therefore, his daily dosage of phenytoin was only 90 mg daily, and his daily dosage of carbamazepine was 500 mg. Two weeks before his illness, his carbamazepine serum level was 2.9 μg/mL; because of the unlikelihood of toxicity, his carbamazepine dosage was not changed when clarithromycin was started. Three days after starting clarithromycin, his carbamazepine serum level measured 6.6 μg/mL. Three weeks after his illness, his carbamazepine dosage was increased to 900 mg daily, and his carbamazepine serum level 2 weeks after this increase measured 6.0 μg/mL.

Patient 4 took 800 mg of carbamazepine and 150 mg of phenytoin daily. He also took 10 mg of metoclopramide (Reglan) at bedtime for chronic gastroesophageal reflux. Three months before his illness, his carbamazepine serum level measured 10.2 μg/mL. On starting clarithromycin therapy, his carbamazepine dosage was decreased to 500 mg daily. Despite this reduction, 5 days later his carbamazepine serum level measured 13.2 μg/mL, which was above the therapeutic range of 4.0 to 12 μg/mL. His carbamazepine dosage, therefore, was reduced to 300 mg daily. After the antibiotic was finished, his dosage of 800 mg daily was resumed. Ten days later his drug serum level was 8.5 μg/mL; 6 months later, it remained at 8.8 μg/mL on the same dosage.

Patient 5 took 800 mg of carbamazepine daily for epilepsy, 5 mg of diazepam (Valium) twice a day for spasticity, and 150 mg of ranitidine (Zantac) at bedtime for peptic ulcer disease. His serum carbamazepine level 2 months before his illness was 10.0 μg/mL. On starting clarithromycin therapy, his carbamazepine dosage was decreased to 500 mg. Three days later his serum drug level measured 14.7 μg/mL; the carbamazepine dosage was further decreased to 300 mg daily; a second

Table 1. Dose (mg/24 h) and Serum Levels (μg/mL) of Carbamazepine, Initially, During, and After Therapy in 5 Patients Receiving Clarithromycin for Lower Respiratory Tract Infections.

Patient	Initial		During		After	
	mg/24 h	μg/mL	mg/24 h	μg/mL	mg/24 h	μg/mL
1	1200	10.2	800	14.1	1200	8.1
2	300	5.3	200	6.4	300	4.9
3	500	2.9	500	6.6	900	6.1
4	800	10.2	500	13.2	800	8.5
5	800	10.0	500	14.7	700	8.5

drug serum measurement 2 days later was 11.0 μg/mL. After the antibiotic course was finished, his carbamazepine dosage was increased to 700 mg daily; a serum drug level measured 3 weeks later was 8.5 μg/mL.

Discussion

Deciding which antibiotic is appropriate to use in developmentally challenged individuals can depend on many factors, including the type of infection that is suspected, the efficacy of the antibiotic, how often the antibiotic must be taken, and any possible interaction with other medications being taken.

In such individuals the gastrointestinal side effects are especially important, because nausea or anorexia in a noncooperative individual with limited verbal skills could result in that person's refusal to take not only the antibiotic but also other medication needed for seizures or behavioral problems. If gastrointestinal side effects cause dehydration in patients who are taking anticonvulsant medications, marked increases can occur in anticonvulsant blood levels.

In this case clarithromycin was considered the drug of choice because it is associated with a low incidence of gastrointestinal side effects. Because none of the 5 patients developed signs of dehydration, we believe that the great increase in carbamazepine level was due to clarithromycin interfering with the metabolism of carbamazepine by the cytochrome P-450 oxidase system.[2]

Carbamazepine is an anticonvulsant medication that is useful in the treatment of tonic-clonic and complex partial seizures. Carbamazepine is also used to treat a variety of neuropathic pain syndromes and as an adjunct to treating schizophrenia and various affective disorders.[3]

Carbamazepine is usually well tolerated, but persons receiving carbamazepine should be monitored for signs of toxicity, such as drowsiness, blurred vision, transient diplopia, and ataxia, which can occur even at therapeutic levels of medication. Other problems include hematologic and hepatic toxicity, Stevens-Johnson syndrome, cardiac toxicity, and hypo-osmolality caused by an antidiuretic effect.[4]

Carbamazepine has a half-life of 14 to 27 hours and can take 3 to 4 days to reach a steady state.[5] The usual effective serum concentration range is 4 to 12 μg/mL, and blood specimens are usually drawn 12 hours after a dose is taken.[6] Finally, clinicians using the drug should be aware that conventional carbamazepine assays do not measure an active metabolite, carbamazepine 10,11 epoxide, which can also cause both therapeutic and toxic effects.[4,6]

Carbamazepine is a potent inducer of catabolic enzymes and thus decreases the plasma level of other medications, including warfarin, doxycycline, haloperidol, theophylline, and oral contraceptives. At the same time, the metabolism of carbamazepine is exclusively hepatic; therefore, other medications that induce or inhibit hepatic enzymes can cause a change in plasma carbamazepine levels. Drugs in this category include diltiazem, propoxyphene, and cimetidine, as well as several macrolide antibiotics including erythromycin.[2]

Antibiotics that can be used for *M. pneumoniae* include erythromycin and tetracycline. Although clinical experience in the use of azithromycin and clarithromycin is limited, they are also active against this type of infection.[7]

Erythromycin is the drug of choice for mycoplasma infections; however, up to 30 percent of patients will not be able to finish a 2-week course because of gastrointestinal side effects.[7]

Clarithromycin (Biaxin) is a new semisynthetic macrolide antibiotic that is biochemically related to erythromycin. It is indicated for mild-to-moderate infections of the upper and lower respiratory tracts caused by susceptible strains of *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*, including pneumonia caused by *M. pneumoniae* or *Streptococcus pneumoniae*. Clarithromycin also is indicated for mild-to-moderate skin infections caused by *Staphalococcus aureus* and *Streptococcus pyogenes*. Although not indicated for its clinical use, clarithromycin is active in vitro against many gram-positive and gram-negative anaerobes.[1]

Erythromycin has a well-documented interaction with other medications, including interference in terfenadine (Seldane)[8], theophylline[9], and carbamazepine[2] metabolisms through the cytochrome P-450 oxidase enzyme system, resulting in an increase in serum levels of these medications. There are few studies, however, that show a definite interaction between clarithromycin and carbamazepine.

Because both erythromycin and clarithromycin have a similar inhibitory effect on other drugs metabolized by the cytochrome P-450 oxidase enzyme system,[8] prescribing such medications concomitantly should be done only with caution.

Indeed, the package insert for clarithromycin suggests that serum levels of carbamazepine be monitored, inasmuch as single dose administration of clarithromycin has resulted in increased serum concentrations of carbamazepine.[1]

Tetracycline and doxycycline can also be used in *M. pneumoniae* infections. They have the advantage of being low cost. Tetracycline requires a multiple dosing schedule, it must be given on an empty stomach, and dairy products interfere with its absorption. It also is likely to cause gastrointestinal side effects[10] and is considered somewhat less effective than erythromycin for mycoplasma infections.[7]

Doxycycline is better tolerated in most patients and has the advantage of usually requiring only once-a-day dosing. The elimination half-life of doxycycline is reduced, however, to approximately 7 hours in patients receiving long-term therapy with phenobarbital, phenytoin, or carbamazepine.[9] This alteration in doxycycline pharmacokinetics in persons taking these anticonvulsant medications would require increased frequency of dosing, and there would be an associated uncertainty that satisfactory doxycycline tissue level concentrations would be maintained. Finally, the increase in dosage required would probably cause an increase in gastrointestinal side effects.

Azithromycin is another new antibiotic that is being used for community-acquired lower respiratory tract infections.[11] Azithromycin, however, must be taken 1 hour before meals or 2 hours after meals, which might increase noncompliance in the developmentally disabled patient, because some individuals might refuse to take medications except with meals or at the usually scheduled times. In addition, medications given on an empty stomach increase the possibility of gastrointestinal upset. Finally, azithromycin has a prolonged tissue half-life: in the event of an allergic reaction, one would see a prolonged dermatologic or anaphylaxis symptomatology.

Preliminary reports suggest that azithromycin does not seem to interact with carbamazepine.[12] Nevertheless, Pfizer promotional literature, revised in December 1992, advises careful monitoring of patients when azithromycin is prescribed in combination with carbamazepine,[13] and at least one article discussing terfenadine-erythromycin and terfenadine-clarithromycin interaction suggests that azithromycin can also have an inhibitory effect on the P-450 oxidase enzyme system.[8]

Conclusion

If a physician wishes to prescribe clarithromycin for a patient who is being treated with carbamazepine, we suggest that carbamazepine dosages be decreased by 30 to 50 percent during such treatment. We also suggest that serum levels of carbamazepine be monitored within 3 to 5 days of starting clarithromycin therapy and that patients be instructed to report to their physicians any signs of carbamazepine toxicity, including dizziness, diplopia, ataxia, or mental confusion. Finally, if further experience confirms a lack of interaction with carbamazepine, azithromycin could become the drug of choice for lower respiratory tract infections for persons taking carbamazepine.

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