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### Respiratory Failure After Clonazepam and Amobarbital

SIR: The case reported here is the first we know of to suggest that the combination of clonazepam and amobarbital can induce coma and central respiratory depression. Clonazepam appears to be safe when administered in combination with phenytoin, chlorpromazine, or phenobarbital, an anticonvulsant barbiturate (1). However, this does not apply to combination with all barbiturates.

Mr. A, a 49-year-old man with a chronic schizoaffective disorder, was seen for treatment after 3 weeks of manic behavior. Four months previously he had developed neuroleptic malignant syndrome while being treated with thiothixene in the hospital. His recovery was complete, and on discharge his psychosis was well controlled on a regimen of clonazepam, 1 mg b.i.d.

On each of his first 2 days in the hospital during the current admission, the patient received a total of 6 mg of clonazepam and two doses of 265 mg of amobarbital. The third day he received 3 mg of clonazepam at 8:00 a.m., 4 mg at 5:00 p.m., and 4 mg at 9:00 p.m., as well as 300 mg of lithium. His agitated behavior was treated with 265 mg of amobarbital at 9:30 p.m. and 10:30 p.m.

At 7:00 a.m. the next day, Mr. A was found to be unresponsive. His temperature was 37.9°C, his pulse 144 beats/minute, and his respirations 32/minute and shallow. His blood pressure was 150/74 mm Hg. His pupils measured 1.5 mm and were sluggishly reactive to light. His oculocephalic reflexes were absent, but his corneal and gag reflexes were present. His musculature was hypotonic; his tendon reflexes and plantar responses could not be elicited. Results of a general physical examination were unremarkable. His arterial blood gas levels on room air were pH, 7.23;  $\text{PaO}_2$ , 34 mm Hg; and  $\text{PaCO}_2$ , 84 mm Hg. The patient was intubated. His blood pressure on admission to the intensive care unit was 70 mm Hg systolic. Dopamine therapy and mechanical ventilation were started. The results of an ECG and blood chemistry and hematology studies were normal.

The patient was soon moving spontaneously and was off dopamine therapy within 24 hours. A mild aspiration pneumonitis developed, and he was not extubated for a further 48 hours. On transfer back to the psychiatric

service he remained manic and appeared to have suffered no permanent sequelae from the coma.

Respiratory depression secondary to anticonvulsant therapy generally occurs in the setting of intravenous administration of benzodiazepines in patients with seizures who are taking multiple oral anticonvulsants. In the case reported here, a coma occurred following commonly used doses of clonazepam and amobarbital. Overdoses of clonazepam generally cause drowsiness (2), and in one reported case a coma occurred (3). Sedation due to clonazepam has been reported to be potentiated by barbiturates; in these cases, phenobarbital is the usual supplemental agent (2).

The different effect with amobarbital in combination may relate to the different properties of various barbiturates at the  $\gamma$ -aminobutyric acid (GABA) receptor complex. Clonazepam is bound to the benzodiazepine site of this complex. Barbiturates bind to another site and can alter benzodiazepine and GABA binding. The anticonvulsant barbiturate phenobarbital, which has minimal clinical interactions with clonazepam, has no effect on benzodiazepine or GABA binding (4). In contrast, the sedative-hypnotic barbiturate amobarbital potentiates the binding of both benzodiazepines and GABA (4). This interaction may explain the observed clinical effects. Certainly, clonazepam and sedative-hypnotic barbiturates should be used in combination only with great caution.

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### Isocarboxazid in the Treatment of Bulimia

SIR: We read with interest the letter "Case Report of Successful Treatment of Bulimia With Isocarboxazid" (April 1986 issue) by Michael H. Kronig, M.D. He described a successful outcome in the treatment of a 24-year-old white woman who had an 8-year history of bulimia. The author noted that the patient, although dysphoric at times, did not meet criteria for a major depressive disorder.

We previously reported a successful response to isocarboxazid treatment in bulimic and anorexic patients (1) and have recently completed a double-blind, placebo-controlled crossover trial of the same drug. Of 29 patients who enrolled for our 12-week crossover study, 24 completed phase 1 and 18 completed both phases. All patients took 60 mg/day of isocarboxazid, and the mean enzyme inhibition rate was 86%. In addition to meeting *DSM-III* criteria for bulimia nervosa, a large number of our patients also met criteria for affective disorder and personality disorder diagnoses (seven