CASE REPORT

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Fatal Malignant Hyperthermia as a Result of Ingestion of Tranylcypromine (Parnate®) Combined with White Wine and Cheese

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ABSTRACT: Fatal malignant hyperthermia occurred in a patient who was taking tranylcypromine (Parnate®) and ingested wine and cheese. The case findings are presented along with a review of the literature concerning adverse interactions between monoamine oxidase (MAO) inhibitors and certain foods and beverages. Hyperthermia and its possible causative mechanisms and treatments are discussed. The facts suggest that the complicated dietary restrictions attending the use of MAO inhibitors and the possibility of severe and even catastrophic reactions resulting from violations of these restrictions make the use of these drugs fraught with danger and therefore not a first choice for the treatment of depression.

KEYWORDS: toxicology, tranylcypromine, hyperthermia

Tranylcypromine (Parnate®) is recommended for symptomatic relief of severe reactive or endogenous depression in hospitalized or closely supervised patients who have not responded to other antidepressant therapy. It causes serious side effects when ingested with certain foods with high tyramine content, other antidepressants, and alcohol [1-3]. Commonest side effect is hypertensive crisis, rarely leading to fatal intracranial hemorrhage. Also reported are a few cases of myoclonic fibrillation of skeletal muscles with hyperpyrexia, sometimes progressing to generalized rigidity and coma [*1*].

We are reporting a case of fatal malignant hyperthermia in a patient who was taking Parnate and ingested wine and cheese.

Case Report

A 26-year-old white woman, with a history of depression and nine previous suicide attempts (four times by cutting her wrists and five times by drug overdose) was brought to the local emergency room because of disorientation and hallucinations. For the past six months, she was prescribed tranylcypromine (Parnate), 10 mg three times a day, and supportive psycho-

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therapy. The night before this admission, she went to a party where she drank three glasses of white wine and ate an undisclosed quantity of cheese. She had been continuing her regular Parnate dosage according to given accounts. After she returned home, she became disoriented and began hallucinating and was brought to the hospital emergency room several hours later.

On examination, she was found to have rigid extremities, clenched teeth, cool skin, fixed and dilated pupils, a blood pressure of 110/40 mm Hg, and a rectal temperature of 97.6°C (107.7°F). She had a card that read "I am taking PARNATE." She was treated with intramuscular Haldol®, intravenous 5% dextrose in water, dopamine, lidocaine, atropine, sodium bicarbonate, Dantrium®, calcium chloride, epinephrine, and a hypothermia blanket; nevertheless, her blood pressure dropped quickly and she developed ventricular fibrillation progressing to asystole, while her rectal temperature rose to 44.4°C (112°F). Resuscitation failed and she was pronounced dead 1 h and 44 min after admission. The blood level of tranylcypromine (Parnate), collected in the hospital, was 0.102 mg/L. Laboratory data suggested hyperkalemia (potassium was 8.7 mg/dL, normal range 3.5 to 5.0) and hypocalcemia (calcium was 8.7 mg/dL, normal range 9 to 11).

Postmortem Findings

Postmortem examination was performed 24 h after death and revealed a well-developed white female, weighing 46 kg (102 lbs.) and measuring 157.5 cm (5 ft, 2 in.). Evidence of resuscitation attempts were present in the form of multiple subclavian punctures and needle puncture marks. Multiple recent, small, nondescript contusions were present on the knees, and a healed linear scar was noted on the right wrist. The brain was slightly swollen. The lungs showed minimal edema and congestion, and the tracheobronchial tree contained some frothy edematous fluid. The stomach contained a small amount of almost completely digested food material. The remainder of the postmortem examination showed no remarkable features. Samples of blood, stomach contents, liver, kidney, and bile were submitted for toxicological analysis, which were negative for alcohol, barbiturates, benzodiazepines, salicylate, opiates, and organic bases.

Discussion

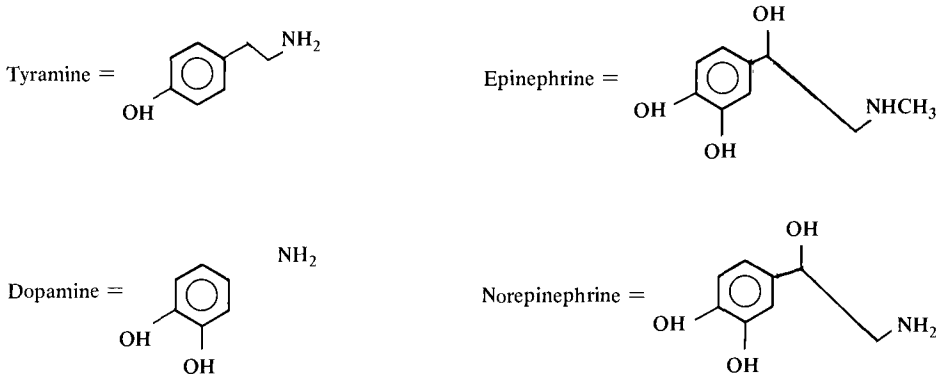
This case illustrates a fatal consequence of combining a monoamine oxidase (MAO) inhibitor, tranylcypromine (Parnate), with an alcoholic beverage and cheese. Cooper et al [*2*] have reported severe side effects suggestive of hypertensive crisis in 20% of patients treated with tranylcypromine, on an outpatient basis. Precipitating factors in some of these patients were ingestion of cheese, alcohol, or other antidepressants.

The blood level of Parnate in our patient was 0.102 mg/L after an unknown time interval between collection and ingestion of a regular dose of the drug. Correlation of blood level and the doses ingested is quite poor because of the time interval between ingestion and specimen collection has been variable. Baselt et al [*3*] have shown that in subjects receiving 10 to 30 mg on a chronic daily basis, serum concentrations averaged 0.005 to 0.010 mg/L 12 h after the last dose. They have also shown that an average peak serum concentration of 0.039 mg/L is found 1 h after the ingestion of 30 mg of the drug; the level declined with a half-life of 1.9 h to less than 0.008 mg/L by 24 h. Youdim et al [*4*] have reported a peak blood level of 1.0 mg/L in a nonfatal overdose involving the ingestion of 250 mg of tranylcypromine and Baselt et al [5] have reported a blood level of 3.7 mg/L after ingestion of 300 mg in a fatal case of Parnate overdose.

The mechanism of interaction of MAO inhibitors and alcohol is not fully known, but there is a definite increase in the incidence of reactions including severe headaches and hypertensive crises when alcohol is combined with these drugs [*6*] and for this reason patients are generally advised to abstain from alcohol while they are using these medications. The role of tyramine in provoking hypertensive crises in patients taking MAO inhibitors is well-known [*2*] and cheeses

are known sources of this agent [7,8]. White wine, of which the subject had reportedly consumed three glasses, has a relatively low tyramine content of 0.5 μg/mL [7], compared to cheeses which vary from 4 to 2170 μg/g with the highest content generally in aged cheeses rich in protein breakdown products [7]; however, tyrosine is normally present in all wines in concentrations of 22 to 29 μg/mL as a result of fermentation by yeast, and its decarboxylation product is tyramine. Thus, the ingestion of wines can indirectly lead to a buildup of tyramine in patients taking MAO inhibitors.

Less well understood is the mechanism of production of hyperthermia, from which the subject suffered [9]; there is no evidence of a hypertensive reaction in this case. Pollock and Watson [10] suggest that antidepressant drugs, including the MAO inhibitors, increase intracellular cyclic adenosine monophosphate (AMP) since they elevate the level of catecholamines which in turn stimulate adenyl cyclase resulting in the formation of cyclic AMP from AMP. Tyramine itself may simulate a catecholamine to produce the same result, since its molecular structure bears a striking resemblence to the catecholamines.



Cyclic AMP acts to stimulate numerous enzyme systems and alters cellular metabolism and permeability. This may explain the pattern of clenched teeth and muscle rigidity suggestive of extreme spasm caused by a hypermetabolic state which is seen in this subject. Muscle rigidity often does accompany the syndrome so aptly called malignant hyperthermia which can occur with overdosage of a single agent [11] or in combination with other drugs, especially imipramine [12]. In such cases, hypotension, rather than hypertension, is the rule, followed by coma and cardiac arrhythmias progressing to asystole.

In tranylcypromine-related hyperthermia treatment of the muscle rigidity through the use of tubocurarine [12,13] in paralytic doses or intravenous chlorpromazine [11,14], 25 to 50 mg combined with cooling, has been shown to reduce the body temperature to normal and permit recovery. Chlorpromazine, in moderate doses, does control muscle spasm and spasticity in tetanus and certain other neurological conditions, has an alpha-blocking action producing hypotension and peripheral vasodilatation (which aids cooling), and blocks response to epinephrine. It also has a quinidine-like action on the heart, which can guard against the arrhythmias that occur in malignant hyperthermia. In our case, Dantrium with hyperthermia blanket was used to control hyperthermia, however, the patient failed to respond.

The use of MAO inhibitors with proper attention to dietary restrictions is associated with no greater incidence of side effects than the use of tricyclics or electroconvulsive therapy (ECT) [15]. Unfortunately, the dietary restrictions required by the use of MAO inhibitors are rather complicated. Patients must be instructed to avoid rigorously cheese, sour cream, alcoholic beverages including beer and wine, pickled herring, liver, canned figs, raisins, bananas, avocados, chocolate, soy sauce, the pods of broad beans (fava beans), yeast extracts, yogurt, meat prepared with tenderizers, and excessive use of caffeine in any form. It is questionable whether

the MAO inhibitors are as effective as the tricyclics in the treatment of endogenous depression, and their use requires very high motivation on the part of the patients, who, because of their depression, may often be greatly lacking in motivation. Therefore, the American Medical Association [*16*] in its Drug Evaluations recommends that tranylcypromine (Parnate) and other MAO inhibitors (such as phenelzine and isocarboxazid) not be administered in those cases of severe endogenous depression in which other antidepressants or ECT may be effective.

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